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## Is scientific assessment a scientific discipline?

### A reflection paper on EFSA, the European Food Safety Authority

Hubert Deluyker

#### Abstract

EFSA, the European Food Safety Authority, was established in 2002 as the EU's independent risk assessment body for food and feed safety. This paper takes stock of what has been achieved and what challenges lie ahead. To do so, it first reviews scientific assessments conducted by EFSA from the perspective of a scientific experiment. This includes a hypothesis that is examined by scientific experts using existing evidence and employing agreed-upon assessment methods, the results of which are made public. Next, it considers a number of characteristics legitimising this work: quality, consistency, independence and impartiality, as well as transparency and openness. Other key considerations are relevance, evolving expectations and innovations, fitness-for-purpose and efficiency, along with sustainability of the system. By and large, the scientific assessment process in place at EFSA can be understood to mimic the conduct of a scientific experiment. However, being a regulatory support mechanism, it has some distinct characteristics. Therefore, its legitimising characteristics are not necessarily identical to those used in academic research. In conclusion, since its creation 15 years ago, EFSA has very much delivered on its mission. Whatever the achievements, the EU cannot rest on its laurels though.

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## Foreword

When establishing a new model for European food safety at the turn of the century, the EU placed EFSA in a unique position: at arm's length from the risk manager and free from undue influence be it national, commercial or otherwise. In the intervening years, EFSA has built a strong portfolio of scientific advice, methodologies, standards, data and expertise which continue to serve European citizens well and is recognised internationally.

Regulatory science is a distinct discipline which straddles the domains of science and policy making. EFSA has been fortunate over the years to have the highest level expertise at its disposal: in its Panels, Working Groups and networks on the one hand and among its own staff on the other. In this paper, Hubert Deluyker, who has recently retired from the position of Scientific Advisor at EFSA, takes the opportunity to reflect on the institutional development of EFSA and the evolution of 'assessment science'. While analysis of the broader legal, institutional and societal framework of scientific advice is not lacking, the 'bottoms up' contribution of scientific agencies such as EFSA that are tasked with delivery of that advice is not as well documented. That makes the current paper interesting and worthwhile. While its review of the status quo of assessment science is in itself a valuable addition to the field, the analysis of key forward-looking topics - such as the evolving expectation of EFSA stakeholders and organisational sustainability - raises important and timely questions.

While ultimately the paper reflects the views of one person, all actors in European regulatory science - and particular those engaged in food and feed safety - will identify to one extent or another with the challenges identified. The paper will no doubt stimulate further reflection and, while the author enjoys a well-earned retirement, it is important to address those future challenges to ensure that collectively we can continue to offer our consumers the highest level of protection. Therefore, I very much welcome comments on this paper to [efsajournal@efsa.europa.eu](mailto:efsajournal@efsa.europa.eu)

EFSA is grateful to Hubert for taking the opportunity of capturing his considerable experience so effectively.

Bernhard Url,  
Executive Director EFSA

## Summary

### Introduction and remit of EFSA

EFSA, the European Food Safety Authority, is one of the EU's agencies for scientific advice. It was established in 2002, along with national agencies in Member States, as the EU's independent risk assessment body for food and feed safety. The remit of EFSA concerns the entire food chain covering aspects of human, animal and plant health, and sometimes environmental protection. Its focus in human health is on food safety and its scientific advice may contribute to various phases in the policy cycle: reflection, regulation, verification and review.

The question posed in this paper is whether providing scientific advice delivered for regulatory purposes can be considered a scientific discipline and, if so, whether this process can be strengthened further. In the section Processes and Achievements the current state of 'assessment science' at EFSA is reviewed. It does so through the perspective of the conduct of a scientific experiment, reviewing its various components and considering whether they are present in a scientific assessment carried out by EFSA. Next, in the section Legitimising Characteristics, the paper reflects on what works well and what could be improved by assessing EFSA's scientific processes against a number of characteristics that are relevant to make EFSA the 'authority' it was conceived to become.

### Processes and achievements

Consistent with the model described by Popper, in a research project one translates the objective(s) of the study into a concrete hypothesis which can be tested. To do so, one designs an experiment to test it using a defined methodology; generates the data and analyses this information; and reports and discusses the results in a scientific journal. How similar is this to scientific experts in EFSA's Scientific Panels and Scientific Committee EFSA addressing a mandate using existing evidence and employing agreed-upon assessment methods; the results of which are made public?

**Objectives.** In food safety risk assessment, the aim is not to come to a conclusion that a food, a feed, a single microorganism or chemical compound or a mixture thereof, is perfectly safe under any circumstances. Rather the objective is to estimate the upper limit below which exposure to a hazard does not constitute a risk.

**Methods.** Over the years, 'cross-cutting' guidances have been developed by EFSA's Scientific Committee. These serve as harmonised scientific methodologies across multiple fields within EFSA's remit. For example, assessment of scientific evidence is carried out at several levels of aggregation: the level of an individual study, the combination of several studies on the same endpoint, combining different strands of evidence, integrating evidence from other compounds and the overall risk assessment which brings together all the steps of the process. In addition, topic-specific guidance has been developed by the Scientific Committee and individual Scientific Panels.

As EFSA has matured, the concept of guidance development has evolved from the initial need for guidance creation towards a need to maintain the growing body of existing guidelines so as to make sure it remains up-to-date.

**Evidence.** EFSA does not generally conduct primary research, but rather assesses existing scientific evidence. For scientific assessment advice to be delivered prior to market authorisation, the data requirements to be fulfilled are typically stated in sector-specific legislations. To meet these data requirements, evidence is to be generated through studies funded by the applicant. In contrast, for food chain contaminants, the burden for funding applied research assessing their impact on human safety and environmental protection reverts to public institutions.

The pre-authorisation approach aims to predict the maximum doses at and below which no adverse health effects are anticipated. Being dependent on the information available at a particular time, such predictions may be subject to revision as and when new evidence emerges. The review of a previous scientific assessment, post-market approval, can entail both the re-assessment based on more safety information of the same nature as in the initial assessment, e.g. additional laboratory animal studies or a new method to assess available information. In addition, new types of evidence may be collected and become available only after market authorisation was granted, e.g. human and environmental exposure and health events.

**Scientific expertise.** The appointment of Panel members concerns the nomination of individuals in their personal capacity. The exception to this model is the scientific assessment of the active ingredient of pesticides, also called plant protection products, which is carried out by staff in Member State institutions and finalised by EFSA staff.

The Panels are supported by working groups and EFSA scientific staff. Over the years, EFSA has also established a set of networks for information exchange with Member States. In recent years, EFSA has explored a series of cooperation initiatives with public organisations in Member States through the multi-annual framework partnerships.

### Legitimising characteristics

Process Quality and the monitoring thereof. Over time, EFSA has developed several approaches to ascertain quality. Initially, this focused on the process quality of individual outputs taken in isolation. Rather than continuing to focus solely on *post hoc* peer review of a sample of outputs, EFSA has more recently opted for an overall quality assurance system of the process to produce its scientific assessments.

Consistency. Unless justified otherwise, there is a need for consistency not only within but also across scientific opinions, both within and between Scientific Panels. Standing working groups, i.e. those with a mandate that is of a continuous nature, supporting several Scientific Panels may provide not only opportunities for guidance harmonisation and fora to discuss consistency in the assessment of specific cases, but they may also end up routinely supporting the review of specific sections of individual dossiers.

Equally, justification for the diversity of data requirements, as laid down in sectorial legislations across different areas of the food chain, may merit further consideration.

Independence and impartiality. The term independence is frequently used in the General Food Law Regulation and is also a topic of much debate. Hence, it merits reflection as to what it means and what purpose it is to serve in the context of EFSA.

First, EU Agencies do not operate as totally independent organisations; rather they are firmly embedded in the legal provisions for the governance of EU institutions. Next, the independence of the advice can be viewed to reside with the independence of the constituent parts of a scientific opinion. Indeed, independent scientific advice is the result of how the objectives of the advice are determined, how it is carried out (expertise, data and methods) and how it is communicated.

As to aspect of the evidence, a number of issues merit careful consideration: the roles and relative merits of (Good Laboratory Practice (GLP)) studies carried out upon request of the applicant as compared to those originating from peer-reviewed literature or open data sources; the dossier completeness; the inclusion of the raw data and the format in which they are submitted to EFSA; and the desirability of a structured dialogue between EFSA and the applicant prior to the submission of a dossier.

In summary, it is argued that all of these aspects therefore deserve attention and the debate should not solely be focused on the independence of the expertise.

Transparency and openness. Transparency is a key condition to be able to reproduce results and has thus been the subject of guidance development by the EFSA Scientific Committee.

Currently, a transformation of EFSA into an Open Science organisation is being carried out through the Transparency and Engagement in Risk Assessment (TERA) Project. It aims at enhancing both the openness and transparency of EFSA's operations at various stages of the scientific assessment process.

Much of the interest regarding transparency remains focused on publication of the outcome of the scientific assessment. The extent to which this aspect of independence is addressed depends very much on the when, what, and how of the publication process.

Relevance. Both guidance documents and individual scientific opinions have a finite 'shelf life'. In general, assessment methods need to be managed following the principles of a quality circle (plan, do, check, act). This also includes testing the potential impact of a new guidance during its development, piloting implementation, organising training on newly developed guidance and allowing for sufficient lead time prior to making it mandatory.

The continued relevance of individual scientific opinions is determined by the duration of the relevance of the components that constitute the opinion, such as the question posed, the evidence and the methods used to address it, and the expertise available.

Evolving expectations and innovation. The credibility of the scientific advice given by EFSA also depends on it meeting evolving societal expectations that can be addressed through scientific methods. A number of different developments can be envisaged.

The nature of the hypothesis tested may evolve from a risk-only assessment to a risk-risk or a risk-benefit assessment.

The scope of the mandate may broaden. For example, environmental protection aspects are already considered in the assessment of the potential direct impact of genetically modified organisms

(GMOs), pesticides and feed additives on the environment, but this is not the case for other areas. It may also evolve from the assessment of a single compound to the evaluation of mixtures.

The scientific assessment framework will also continue to evolve. Unlike in medicines, in food safety assessment, there is no expectation to conduct a pre-market safety study in humans to confirm that the proposed dose is safe. The *in vivo* safety testing is instead carried out in laboratory animal species and safety (or uncertainty) factors are introduced to extrapolate results from the most sensitive animal species to humans. The field of toxicology testing is in the middle of a major evolution whereby evidence on safety gradually accumulates through a sequence of steps. A hypothesis-driven approach is to be based on the prior elucidation of the mode of action (MoA) and the possible identification of the adverse outcome pathway (AOP) through various screening systems that have been and are being developed. Their adoption obviously also requires adaptation of the data requirements and the assessment methods used. The structures to support this transformation require collaboration with centres of excellence. In this regard, the concept of 'laboratory' needs to be extended to include 'software labs' to ensure that data modelling and bioinformatics capabilities are kept up-to-date.

EFSA's budget does not permit to fund research and development to fill information gaps, be it on specific compounds or on research underpinning the development and implementation of new assessment methods. Hence, data gaps are identified and highlighted to organisations that are responsible to fund such research.

Another dimension concerns verification of the prediction that the exposure levels and the no-adverse-health effects at a level that is considered safe, proves to be correct. For this verification to happen routinely, i.e. beyond dedicated research projects, it may be necessary that the market authorisation of a chemical be made dependent on providing with the dossier a validated biomarker to be able to assess exposure through various routes. Provided exposure is identified or likely to take place, it is also suggested to monitor the occurrence of adverse health effects following such exposure in groups that are potentially at high risk. This raises questions as to who is responsible to conduct this work and how it is to be funded.

Fitness-for-purpose and efficiency. Scientific excellence is not necessarily a goal in itself but rather the scientific advice has to address the needs for information of those who will use the opinion for decision-making, i.e. be 'fit for purpose', and thus be refined to the extent necessary to meet this aim.

It is essential that the time spent by Panel experts be used in the most efficient way. Scientific staff employed by EFSA ensure smooth functioning of the system and do much of the preparatory work, such as putting together the 'materials and methods'. This allows the discussions of the Panel experts to focus on the key, non-routine scientific aspects that emerge in the assessment process. There are EFSA units (or teams thereof) that directly provide scientific support dedicated to individual Scientific Panels and their working groups, and some units that provide 'cross-cutting' support to several Panels; which approach is most appropriate may vary.

Another aspect of efficiency concerns the fact that EFSA is gradually building an ever-more elaborate system to conduct its scientific evaluations. This has resource implications for the time spent on the conduct of a scientific assessment. Irrespective of the fitness-for-purpose aspect, it would seem that newly developed assessment approaches need to be optimally integrated so as not to reduce efficiency. This is a challenge.

Furthermore, as is the case with other EU institutions, the human resources available within EFSA have actually been decreasing. Hence, efficiency gains are necessary even if no new facets would be added to the risk assessment process. The MATRIX project that EFSA has embarked on is a key multi-annual transformational initiative. It represents a big push towards optimisation of the flow of data and work processes during a regulatory dossier review, through the development of an electronic platform. This will affect all aspects of and steps in these scientific assessment processes. It may gradually develop into the backbone through which efficiency gains can be achieved.

Sustainability. The EU Agencies that give scientific advice put the main responsibility for this advice on a variety of potential actors: their own staff, external experts who represent the public Member State organisations they are employed by or – as is the case with EFSA – experts who, while also employed by scientific institutions in EU Member States, do not represent them, i.e. are considered independent vis-a-vis their employers' view on the matter at hand. The EFSA model has proven to be both effective, delivering some 500 scientific opinions a year, and also to be flexible enough to be able to deal with sizable fluctuations, i.e. peaks, in workload. Credit for this goes in no small measure to the numerous scientists in Europe who have been willing to devote time to serve the common good. Credit also goes to their employers who have supported them to take on these tasks.

The continued availability of qualified experts for these Scientific Panels is obviously key to enable EFSA to continue to function. A recent survey of experts' employers shows their commitment to support EFSA, but conditional on proper financial compensation being given for the important time commitment Panel membership entails. It would also be highly desirable if the appointment of Panel members could be for a five-year period (instead of the current three-year term) and be renewable at least once.

A related key issue is how to ensure that the EU maintains adequate future expert capacity for scientific assessments. This requires on the one hand that training is offered and on the other that there are adequate opportunities to gain experience.

### **Discussion and conclusions**

By and large, the scientific assessment process in place at EFSA can be understood to mimic the conduct of a scientific experiment. However, being a regulatory support mechanism it has some very distinct characteristics and therefore its legitimising characteristics are not necessarily identical to those used in academic research.

This paper has not very much reflected on the importance of cooperation at the international level. Clearly though, collaboration with various international bodies is considered key for EFSA. Equally, the paper says little on communication, particularly to the public at large, another issue of key importance to EFSA. Indeed, successful communication can be considered as one condition to be recognised as an 'authority'. The reason why this is not discussed in depth here is rather that it probably merits a separate reflection.

In conclusion, since its creation 15 years ago, EFSA has very much delivered on its mission. However, whatever the achievements, the EU cannot rest on its laurels. It could even be argued that what has been achieved thus far represents harvesting of the 'low hanging fruit' and that EFSA is now in the position to face other important and challenging issues. These include becoming a more transparent and open organisation (TERA project), modernising the regulatory evaluation process (MATRIX project), moving into 21st century toxicity testing approaches, accepting evidence collected pro-actively post-market not only as a source of compliance monitoring but also as a different source of scientific information, and building a body of EU scientific assessment expertise that is sustainable. Taken together, these challenges form a unique opportunity to prepare the future for an effective, efficient, and internationally recognised organisation that is well equipped to serve EU citizens in this 21st century. Pro-actively addressing these challenges shows responsibility.

To meet these challenges this paper also calls for further reflection on what may currently be considered established practices, e.g. arms-length relationship with industry, the consideration of risks only, the desirability of sector-specific differences in data requirements and assessment methods, and embracing big data and artificial intelligence-based approaches. A critical success factor concerns the generation of scientific evidence and the development of assessment approaches through publicly funded applied research and development to underpin EFSA's and other scientific agencies' needs.

For EFSA to progress towards meeting these challenges and opportunities, continued close cooperation with the European Commission, as well as other stakeholders, will be essential.

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## 1. Introduction

Scientific advice is used in a number of areas for EU policy development. For this purpose, also the European Parliament and the Council of the European Union (EU) have set up a number of decentralised Agencies to carry out specific legal, technical or scientific tasks within the EU (Everson et al., 2014). Societal areas covered by scientific advice through these decentralised agencies include both the natural sciences and the social sciences.<sup>1</sup>

One of these agencies is the European Food Safety Authority (EFSA). Its roots lie in the food scares of the 1990s and early 2000s, resulting from the contamination of feed by prions, causing bovine spongiform encephalopathy ((BSE), also known as 'mad cow disease') and dioxins. These led to a number of negative consequences (see insert). To restore public confidence in the European food safety system and as part of a wide-ranging reform of European food safety policy in response to these food crises, EFSA was established in 2002, along with national agencies, as the EU's independent risk assessment body for food and feed safety.<sup>2</sup>

- Food scares (e.g. BSE, dioxins) with
  - ✓ Loss of consumer trust in food safety
  - ✓ Loss of confidence in EU food trade
  - ✓ Damaged trust in public authorities
- General Food Law Regulation (Reg. (EC) 178/2002): creation of
 

**EFSA as independent source of scientific advice and communication**

The mission of EFSA within this framework is to provide independent scientific advice to Europe's risk managers and communicate this promptly. In this paper, the term scientific assessment is meant to include various types of scientific evaluation. One of those is a risk assessment which may be, e.g. a human or an environmental safety assessment. Other types being a benefit assessment or a combination of the assessment of risks and benefits.

EFSA's founding regulation, the General Food Law Regulation, (Regulation (EC) No 178/2002)<sup>3</sup> introduced the functional separation of risk assessment and risk management in the risk analysis process, with each being responsible for the communication of aspects that fall within their respective remit (Figure 1). Article 29 of the General Food Law Regulation states that EFSA shall issue scientific opinions in response to questions posed by those risk managers, while it may also initiate self-tasks.<sup>4</sup> The intention of the legislator was that scientific advice should be independent from undue influence by risk managers. The concept of risk manager is understood to include the legislative and the executive branches of government, i.e. the European Commission, the European Parliament, and the executive and legislative branches of the Member States.



**Figure 1:** Risk analysis components

<sup>1</sup> [http://bookshop.europa.eu/is-bin/INTERSHOP.enfinity/WFS/EU-Bookshop-Site/en\\_GB/-/EUR/ViewPublication-Start?PublicationKey=TM0115491](http://bookshop.europa.eu/is-bin/INTERSHOP.enfinity/WFS/EU-Bookshop-Site/en_GB/-/EUR/ViewPublication-Start?PublicationKey=TM0115491)

<sup>2</sup> [http://ec.europa.eu/dgs/health\\_food-safety/library/pub/pub06\\_en.pdf](http://ec.europa.eu/dgs/health_food-safety/library/pub/pub06_en.pdf)

<sup>3</sup> Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, OJ L 31, 1.2.2002, p. 1–24, as last amended: <http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1507719904763&uri=CELEX:02002R0178-20140630>



Much has been published about scientific advice. Academic researchers have studied the legal, institutional and societal framework of scientific advice delivery (Jasanoff, 2005; Millstone, 2007; Vos and Everson, 2016), the role of scientists (Pielke, 2007) and the impact of science on policy (Nowotny et al., 2001; Doubleday and Wilsdon, 2013). Also, senior scientists who, at some point in their career hold a position of senior governmental scientific adviser<sup>4</sup> (Walport and Craig, 2014), as well as science academies (The National Academies of Sciences, Engineering and Medicine, 2017) have contributed much to broad reflections concerning delivery of scientific advice. Much less has been contributed to the public debate from the 'bottom-up' perspective of agencies that have been set up to provide scientific advice in specific domains. Fifteen years after the advent of the General Food Law Regulation, this paper is a contribution from the latter perspective, using EFSA as a case study.

The question posed in this paper is whether providing scientific advice delivered for regulatory purposes can be considered a scientific discipline and, if so, whether this process can be strengthened further. After a brief description of the remit of EFSA, in the section Processes and Achievements, the current state of 'assessment science' at EFSA is reviewed. It does so through the perspective of the conduct of a scientific experiment, reviewing its various components to ascertain whether they are present in a scientific assessment carried out by EFSA. Next, in the section called Legitimising Characteristics, the paper reflects on what works well and what could be improved by assessing EFSA's scientific processes against a number of characteristics that are relevant to make it the 'authority' it was conceived to become.

The opinions expressed in the paper are those of the author and not EFSA's. They are based on experience gained as an EFSA staff member as well as through membership of the EU Agencies Network for Scientific Advice (EU ANSA).<sup>2</sup>

## 2. Remit of EFSA

The remit of EFSA concerns the entire food chain covering aspects of human, animal, plant and sometimes environmental protection. Its focus in human health is on food safety (see insert below).

What aspects of **human health** are assessed?

- ✓ *focus on food safety*
- ✓ *less on benefits (cfr. European Medicines Agency, EMA), except for health claims*
- ✓ *nothing on cost-benefit analyses (cfr. European Chemicals Agency, ECHA)*

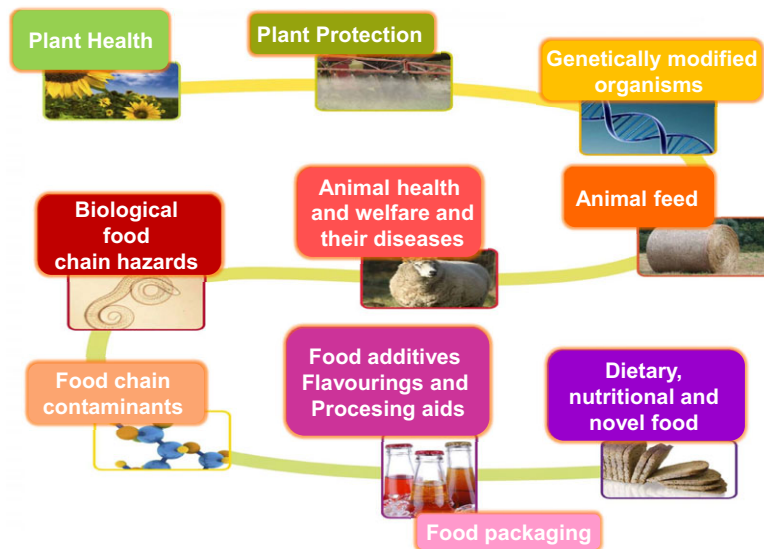
In human public health, EFSA's remit includes aspects of nutrition, substantiation of health claims, the safety of 'novel foods' (i.e. a food traditional consumed outside the EU but consumed to a significant degree in the EU prior to 1997), chemicals and organisms that are deliberately added to or modified in food and feed as well as those that may be present as contaminants in food or materials in contact with food. The food chain being typically long and global, introduction as well as transformation (e.g. growth of microorganisms) may take place at various stages of production and processing of food and feed. In addition, chemicals are not only introduced externally but can also be generated internally, e.g. as a result of processing, as is the case with acrylamide.<sup>5</sup>

EFSA's remit also includes the scientific assessments plant diseases, their genetic modification (GM) and their treatment with pesticides; as well as animal diseases, their welfare, and compounds added to their feed. Finally, aspects of environmental protection may be examined as well, i.e. for pesticides, genetically modified organisms (GMOs) and feed additives.

With the creation of EFSA, the legislator decided (Art. 28 General Food Law Regulation) that the bodies ultimately responsible for EFSA's scientific advice would be its Scientific Panels, plus an overarching Scientific Committee (Figure 2).<sup>4</sup> The Scientific Committee is composed of the chairs of the Scientific Panels plus 'six independent scientific experts who do not belong to any of the Scientific Panels'.

<sup>4</sup> <http://www.pmcsa.org.nz/wp-content/uploads/The-role-of-evidence-in-policy-formation-and-implementation-report.pdf>

<sup>5</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/4104>



**Figure 2:** EFSA's remit: spread over 10 Scientific Panels

While the notion of separation of risk management and risk assessment may suggest that these two functions operate separately from each other, they may rather be intertwined in the sense that scientific advice may contribute to various phases in the policy cycle. In this regard, the legislative frameworks within which EFSA operates can be viewed as consisting in principle of a number of steps that can be represented schematically as the following successive phases of a policy cycle (Table 1), akin to the plan, do, check, act quality cycle:

- **Monitoring and reflection.** Article 22 of the General Food Law Regulation states that one of EFSA's missions is 'to undertake action to identify and characterise emerging risks, in the fields within its mission'<sup>4,6</sup> EFSA may in addition be asked to contribute to this phase by providing technical support to the Commission; which may feed into legislative initiatives. An example is the development of legislation on the control of zoonoses such as *Salmonella*<sup>7</sup> and of metal(oid)s, such as arsenic,<sup>8</sup> for which EFSA produced a series of risk assessments and scientific reports.
- **Regulate and implement.** As a first step, this typically concerns the establishment of sector-specific regulations that define the subject of the assessment. Where it concerns compounds for which pre-market authorisation is required, it also generally describes the areas to be assessed and setting out the data requirements which applicants seeking a market authorisation need to adhere to. EFSA may provide key input into this process by issuing guidance on the preparation and presentation of a dossier, e.g. on health claims<sup>9</sup> or on novel foods<sup>10</sup> and guidance (Table 2) on how to assess what may be a large number of scientific opinions on, e.g. individual chemical compounds in foods which fall under a specific legislation. On the other hand, for food chain contaminants, existing international risk assessment standards may be applied (WHO, 2009).
- **Check.** An agency such as EFSA may also be tasked to contribute to elements of the Check phase. For example, EFSA is often cooperating with Member States' agencies and European partner agencies such as the European Centre for Disease Prevention and Control (ECDC) and the EMA, in the monitoring of the implementation of the legislative initiatives. This is particularly the case for exposure to food-borne zoonoses,<sup>11</sup> antimicrobial resistance<sup>12</sup> and chemical contaminants and residues<sup>13</sup> present in food, whereby EFSA collates data that generated by Member State public organisations. The monitoring programmes on the prevalence of *Salmonella* in animals and food-animal products offer examples of how disease

<sup>6</sup> <https://www.efsa.europa.eu/en/supporting/pub/1100e>

<sup>7</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/2017>

<sup>8</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/3597>

<sup>9</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/530>

<sup>10</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/4594>

<sup>11</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/4634>

<sup>12</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/4694>

<sup>13</sup> [https://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/161215chemicalsinfoodreport.pdf](https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/161215chemicalsinfoodreport.pdf)

incidence can be gradually reduced through the setting of reduction targets and subsequent intensive monitoring of whether these expectations have been met.<sup>12</sup>

- The Review aspect is a reminder that any legislative initiative (and the science it may be based on) can be viewed as having a life cycle. It creates the opportunity to learn from experience gained, in a manner which is preplanned. This can in principle take on two forms which have been described as either single-loop learning or double-loop learning (Dunlop, 2009). The former concerns a review which intends to remain within the boundaries of the established legislative framework. For example, the regular scientific review of chemicals that have been granted market authorisation usually takes place every 5 or 10 years, depending on the legislative framework. In contrast, double loop learning, is an event whereby the entire regulatory framework is reconsidered. An example of this is the Commission's Better Regulation initiative, in particular the REFIT process. Agencies can contribute to such a reflection, most efficiently if this is part of a pre-planned process. Also, a body such as the High Level Group (HLG) supported by the European Commission's Scientific Advice Mechanisms (SAM) unit may be well suited to support the scientific aspects of this type of review.<sup>14</sup>

**Table 1:** Successive steps in the cycle of policy initiatives

	<b>Plan</b>	<b>Do</b>	<b>Check and review</b>
Activity	White paper and impact assessment	Legislative initiative and its implementation	Verification and re-assessment of legislative decisions

<sup>14</sup> <https://ec.europa.eu/research/sam/index.cfm?pg=hlg>

**Table 2:** Guidance by Scientific Panel: domain, subject, and number of guidance topics

Scientific panel domain	Dossier general RA	Subject of scientific review										
		Proposed use	Composition and/or characterisation	Manufacturing process	Human (food) or animal (feed) safety assessment					Efficacy	Environm. safety	Other aspects
					General	Kinetics	Toxicology	Microbial	Exposure			
<b>PPR pesticides</b>						1 <sup>(a)</sup>			3 <sup>(b)</sup>		10 <sup>(c)</sup>	
<b>GMO GMOs</b>	6 <sup>(d)</sup>		1 <sup>(e)</sup>					2 <sup>(f)</sup>			3 <sup>(g)</sup>	3 <sup>(h)</sup>
<b>Feedap feed additives</b>	9 <sup>(i)</sup>				2 <sup>(j)</sup>				6 <sup>(k)</sup>	1 <sup>(l)</sup>	1 <sup>(m)</sup>	1 <sup>(n)</sup>
<b>ANS additives, colorants, nutrient sources</b>	1 <sup>(o)</sup>				2 <sup>(p)</sup>	2 <sup>(p)</sup>	2 <sup>(p)</sup>		2 <sup>(p)</sup>			
<b>CEF packaging materials, enzymes, flavourings, smoke flavourings, processing aids</b>	6 <sup>(q)</sup>				6 <sup>(q)</sup>		6 <sup>(q)</sup>		2 <sup>(q)</sup>			
<b>BIOHAZ decontamination substances, use of animal by-products</b>							1 <sup>(q)</sup>	1 <sup>(r)</sup>		1 <sup>(q)</sup>		
<b>CONTAM</b>												1 <sup>(s)</sup>
<b>NDA health claims, novel foods and traditional foods from 3rd countries, foods for special groups, allergens</b>	4 <sup>(t)</sup>						1 <sup>(u)</sup>			7 <sup>(v)</sup>		
<b>AHAW</b>					1 <sup>(w)</sup>							1 <sup>(x)</sup>

Scientific panel domain	Dossier general RA	Subject of scientific review											
		Proposed use	Composition and/or characterisation	Manufacturing process	Human (food) or animal (feed) safety assessment					Efficacy	Environm. safety	Other aspects	
					General	Kinetics	Toxicology	Microbial	Exposure				
<b>PHL</b>						3 <sup>(y)</sup>						1 <sup>(z)</sup>	1 <sup>(aa)</sup>

- (a): Dermal absorption <https://www.efsa.europa.eu/en/efsajournal/pub/2665>
- (b): Modeling dietary exposure <https://www.efsa.europa.eu/en/efsajournal/pub/2839>, Exposure of operators, workers, residents and bystanders <https://www.efsa.europa.eu/en/efsajournal/pub/3874>, Residue definition <https://www.efsa.europa.eu/en/efsajournal/pub/4549>
- (c): Aquatic organisms <https://www.efsa.europa.eu/en/efsajournal/pub/3290>, Transformation in soil <https://www.efsa.europa.eu/en/efsajournal/pub/4093>, Dissipation in soil <https://www.efsa.europa.eu/en/efsajournal/pub/3662>, Emissions from protected crops <https://www.efsa.europa.eu/en/efsajournal/pub/3615>, Bees <https://www.efsa.europa.eu/en/efsajournal/pub/3295>, Birds and mammals <https://www.efsa.europa.eu/en/efsajournal/pub/1438>, Non-target arthropods <https://www.efsa.europa.eu/en/efsajournal/pub/3996>, In-soil organisms <https://www.efsa.europa.eu/sites/default/files/consultation/160503.pdf>, Non-target terrestrial plants <https://www.efsa.europa.eu/en/efsajournal/pub/3800>, Amphibians and reptiles <https://www.efsa.europa.eu/en/consultations/call/170410>
- (d): RA GM plants <https://www.efsa.europa.eu/en/efsajournal/pub/99>, GM-derived food and feed <https://www.efsa.europa.eu/en/efsajournal/pub/2150>, GM micro-organisms and their products <https://www.efsa.europa.eu/en/efsajournal/pub/2193>, GM animals <https://www.efsa.europa.eu/en/efsajournal/pub/2501>, Dossier GM plants <https://www.efsa.europa.eu/en/efsajournal/pub/3491>, Renewal application food and feed <https://www.efsa.europa.eu/en/efsajournal/pub/4129>
- (e): Agronomic and phenotypic characterisation GM plant <https://www.efsa.europa.eu/en/efsajournal/pub/4128>
- (f): Allergenicity <https://www.efsa.europa.eu/en/efsajournal/pub/1700>, <https://www.efsa.europa.eu/en/efsajournal/pub/4862>
- (g): GM plants <https://www.efsa.europa.eu/en/efsajournal/pub/1879>, Post-market environmental monitoring <https://www.efsa.europa.eu/en/efsajournal/pub/2316>, GM animals <https://www.efsa.europa.eu/en/efsajournal/pub/3200>
- (h): Stacked events <https://www.efsa.europa.eu/en/efsajournal/pub/512>, Choice of comparators <https://www.efsa.europa.eu/en/efsajournal/pub/2149>, Low GM levels in food and feed <https://www.efsa.europa.eu/en/consultations/call/170502>
- (i): Technological additives <https://www.efsa.europa.eu/en/efsajournal/pub/774>, <https://www.efsa.europa.eu/en/efsajournal/pub/2528>, Nutritional additives <https://www.efsa.europa.eu/en/efsajournal/pub/775>, <https://www.efsa.europa.eu/en/efsajournal/pub/2535>, Zootechnical additives <https://www.efsa.europa.eu/en/efsajournal/pub/776>, <https://www.efsa.europa.eu/en/efsajournal/pub/2536>, Coccidiostats and histomonostats <https://www.efsa.europa.eu/en/efsajournal/pub/777>, <https://www.efsa.europa.eu/en/efsajournal/pub/2174>, Re-evaluation <https://www.efsa.europa.eu/en/efsajournal/pub/779>, Already authorised in food <https://www.efsa.europa.eu/en/efsajournal/pub/800>, <https://www.efsa.europa.eu/en/efsajournal/pub/2538>, Sensory additives <https://www.efsa.europa.eu/en/efsajournal/pub/1352>, <https://www.efsa.europa.eu/en/efsajournal/pub/2534>, Additives in non-food producing animals <https://www.efsa.europa.eu/en/efsajournal/pub/2012>, Renewal <https://www.efsa.europa.eu/en/efsajournal/pub/3431>
- (j): Human safety <https://www.efsa.europa.eu/en/efsajournal/pub/801>, <https://www.efsa.europa.eu/en/efsajournal/pub/2537>, Users and workers <https://www.efsa.europa.eu/en/efsajournal/pub/802>, <https://www.efsa.europa.eu/en/efsajournal/pub/2539>
- (k): Compatibility of microbial additives with other additives showing antimicrobial activity <https://www.efsa.europa.eu/en/efsajournal/pub/658>, Antimicrobial susceptibility <https://www.efsa.europa.eu/en/efsajournal/pub/732>, <https://www.efsa.europa.eu/en/efsajournal/pub/2740>, Microbial studies <https://www.efsa.europa.eu/en/efsajournal/pub/836>, Microbial biomasses <https://www.efsa.europa.eu/en/efsajournal/pub/2117>, Bacillus sp. <https://www.efsa.europa.eu/en/efsajournal/pub/2445>, <https://www.efsa.europa.eu/en/efsajournal/pub/3665>, Enterococcus faecium <https://www.efsa.europa.eu/en/efsajournal/pub/2682>
- (l): Efficacy and tolerance <https://www.efsa.europa.eu/en/efsajournal/pub/778>, <https://www.efsa.europa.eu/en/efsajournal/pub/2175>
- (m): Environmental RA <https://www.efsa.europa.eu/en/efsajournal/pub/842>
- (n): Extrapolation from major to minor species <https://www.efsa.europa.eu/en/efsajournal/pub/803>
- (o): Sources of nutrients and other added ingredients, European Commission, Food additive submission <https://www.efsa.europa.eu/en/efsajournal/pub/2760>
- (p): Guidance for submission for food additive evaluations <https://www.efsa.europa.eu/it/efsajournal/pub/2760>, Conceptual framework approach for the re-evaluation of food additives <https://www.efsa.europa.eu/it/efsajournal/pub/3697>

- (q): Smoke flavouring submission <https://www.efsa.europa.eu/en/efsajournal/pub/492>, Food contact materials submission <https://www.efsa.europa.eu/en/efsajournal/pub/rn-21> Recycled plastics submission <https://www.efsa.europa.eu/en/efsajournal/pub/717>, Active or intelligent substances <https://www.efsa.europa.eu/en/efsajournal/pub/1208>, Data for flavourings <https://www.efsa.europa.eu/en/efsajournal/pub/1623>, Food enzymes <https://www.efsa.europa.eu/en/efsajournal/pub/1305>
- (r): Microbial decontamination <https://www.efsa.europa.eu/en/efsajournal/pub/1544>
- (s): Non-allowed pharmacologically active compounds <https://www.efsa.europa.eu/en/efsajournal/pub/3195>
- (t): Application health claims <https://www.efsa.europa.eu/en/efsajournal/pub/2170>, Application guidance stakeholders <https://www.efsa.europa.eu/en/efsajournal/pub/4367>, Foods for special medical purposes <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4300/epdf>, Infant formula manufactured from protein hydrolysates <https://www.efsa.europa.eu/en/efsajournal/pub/4779>
- (u): Novel foods <https://www.efsa.europa.eu/en/efsajournal/pub/4594>
- (v): Various health areas <https://www.efsa.europa.eu/en/efsajournal/pub/2474>, <https://www.efsa.europa.eu/en/efsajournal/pub/2604>, <https://www.efsa.europa.eu/en/efsajournal/pub/2702>, <https://www.efsa.europa.eu/en/efsajournal/pub/2816>, <https://www.efsa.europa.eu/en/efsajournal/pub/2817>, <https://www.efsa.europa.eu/en/efsajournal/pub/4369>, <https://www.efsa.europa.eu/en/efsajournal/pub/4590>
- (w): Animal health modelling <https://www.efsa.europa.eu/en/efsajournal/pub/1419>
- (x): Animal welfare <https://www.efsa.europa.eu/en/efsajournal/pub/2513>, <https://www.efsa.europa.eu/en/efsajournal/pub/3486>
- (y): RA and risk management <https://www.efsa.europa.eu/en/efsajournal/pub/1194>, <https://www.efsa.europa.eu/en/efsajournal/pub/1495>, <https://www.efsa.europa.eu/en/efsajournal/pub/2755>
- (z): Environmental RA <https://www.efsa.europa.eu/en/efsajournal/pub/3417>
- (aa): Import RA, under development <http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2016.EN-1062/pdf>

### 3. Processes and Achievements

Experimental research aims to uncover new knowledge or replicate (and possibly invalidate) previously reported findings. Consistent with the model described by Popper,<sup>15</sup> in a research project one translates the objective(s) of the study into a concrete hypothesis which can be tested; designs an experiment to test it using a defined methodology; generates the data and analyses this information; and reports and discusses the results which are then communicated. All this is to be done while adhering to a set of predefined quality standards. It is a bit analogous to... preparing a 'good' meal (see insert).

*The conduct of a 'good' risk assessment is a bit like preparing a good meal...*

- Mandate – *What dish does the customer request, that can be delivered?*
- Information – *What are the ingredients to be used?*
- Methods – *What is the 'best' recipe to prepare this meal?*
- Expertise – *Who are good cooks?*
- Output – *How do you serve it?*

What are its quality attributes?

How similar is this to EFSA scientific experts addressing a mandate using existing evidence and employing agreed-upon assessment methods; the results of which are made public? This section sets out to examine each of those aspects in the conduct of scientific assessments by EFSA.

#### 3.1. Objectives

The outcome of a scientific assessment depends first and foremost on the precise hypothesis to be tested to address the needs of the risk manager (Figure 3; WHO (2009)).



**Figure 3:** Responsibilities of risk assessors and risk managers

While the roots of EFSA may lie in matters relating to chemical and microbiological contaminants of the food chain, it currently devotes most of its resources to providing scientific advice on regulated products, reviewing dossiers submitted as pre-market applications or renewals. In general terms, for pre-market risk assessment such scientific advice aims to make a prediction about the (un-)likelihood of future adverse health events after a market authorisation would have been granted under the conditions stipulated in the authorisation. More specifically, the objective is to ascertain at what dose a chemical or a microorganism may safely enter the food chain by assessing under which scenarios of dose and exposure the risk of adverse health effects will be essentially absent.

Unlike pre-market scientific assessments, the evaluation of contaminants typically concerns ongoing exposure. This means that in principle for contaminants the safety question is not only what levels of potential exposure are safe but also to ascertain whether current levels of exposures constitute a problem.

<sup>15</sup> [https://en.wikipedia.org/wiki/Karl\\_Popper](https://en.wikipedia.org/wiki/Karl_Popper)

### 3.2. Methods

At the time of its creation, EFSA Panels started their work based on the internationally accepted methods as well as guidance that had already been developed by pre-existing Panels that were operating under the auspices of the European Commission.

For human food safety risk assessment, the classic internationally accepted paradigm (WHO, 2009) is not to come to a conclusion that a food, a feed, a single microorganism or chemical compound or a mixture thereof, is perfectly safe under any circumstances. Rather, the objective is to estimate the upper limit below which exposure to a hazard does not constitute a safety concern. This requires clarity on

- which is (are) the most relevant hazard(s) and at what doses they occur. This information is used to estimate the no-observed-adverse-effect-level (NOAEL) or the lowest-observed-adverse-effect-level (LOAEL) based on the most critical effect of a substance.
- They in turn form the reference point for deriving a health-based guidance value (HBGV) known as acceptable daily intake (ADI), acute reference dose (ARfD) or tolerable daily intake (TDI). They express the amount that can be ingested over a defined period of time without appreciable health risk. They are generally derived by dividing the NOAEL by safety factors (or uncertainty factors) to account for variability within the laboratory animal species and extrapolate results from the most sensitive animal species to humans.<sup>16</sup>
- Finally, an estimation is made whether exposure is likely to occur under the proposed use conditions and, if so, whether the anticipated exposure can be expected to generally remain below these HBGVs (Figure 3).

Starting from this and other international guidance, EFSA has further refined its assessment methods. These are described in guidance documents that are either of a general nature or have a more narrow topic-specific scope, as further discussed below.

#### 3.2.1. Overall guidance on the conduct of the scientific assessment

According to Article 28 of the General Food Law Regulation,<sup>4</sup> EFSA's Scientific Committee is 'to ensure the consistency of the scientific opinion procedure, in particular to the adoption of working procedures and harmonisation of working methods [...]'. In this, EFSA's Scientific Committee has developed or endorsed the development of a number of 'cross-cutting' guidance documents, i.e. harmonised methodologies on scientific matters across multiple fields within EFSA's remit. These various guidance documents and the issues they address are briefly reviewed below.

An essential element of consistency concerns standardisation, wherever justified, including use of common terminology<sup>17</sup> and a common structure of a scientific opinion.<sup>18</sup>

Assessment of scientific evidence is carried out at several levels of aggregation (see insert). Over the years, guidance has been developed in all these areas.

- Interpretation of a single study
- Combining results of several studies of the same substance on the same endpoint
- Combining different strands of evidence on the same substance
- Integrating evidence from other compounds
- Overall risk assessment

Guidance from EFSA on the design and interpretation of a single study concerns the distinction between statistical significance and biological relevance,<sup>19</sup> standards for statistical reporting<sup>20</sup> and guidance on biological relevance distinguishing between normal, adaptive and adverse responses.<sup>21</sup>

In its guidance on statistical significance and biological relevance,<sup>20</sup> the Scientific Committee notes that the nature and size of biological changes or differences seen in a study that would be considered

<sup>16</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/2579>

<sup>17</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/2664>

<sup>18</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/3808>

<sup>19</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/2372>

<sup>20</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/3908>

<sup>21</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/4970>



relevant should be defined before studies are initiated. The size of such changes should be used to design studies with sufficient statistical power to be able to detect effects of such size, if they truly occurred. This ensures that the absence of evidence of adverse health effects is not wrongly used as evidence of the absence thereof. For the presentation and interpretation of the outcomes, the Scientific Committee recommended that less emphasis be placed upon the reporting of statistical significance and more on statistical point estimation and associated interval estimations, e.g. a confidence interval, as more information can be presented using the latter.

For chemicals that have been on the market for a while, there often are several studies in which the same end-point has been studied. These elements of evidence need to be combined in a way that is meaningful and reproducible. EFSA has invested substantially in the area of systematic literature review<sup>22</sup> (possibly with meta-analysis) and in particular in adapting the methodology for use in food safety<sup>23</sup> and then testing and implementing it in specific cases.<sup>24</sup>

A next level of complexity concerns the aggregation of different strands of evidence. Taking the aspect of the hazard characterisation of chemical substances as an example, this requires the integration of distinct lines of evidence (*in vivo*, *in vitro*, *in silico* studies). The challenge is to weigh these types of evidence in a systematic, consistent and transparent way (Gocht et al., 2017; The National Academies of Sciences, Engineering and Medicine, 2017). This is the topic of a recent EFSA weight-of-evidence guidance.<sup>25</sup> Particularly, interesting aspects concern the use of epidemiological evidence<sup>26</sup> and the history of safe use in novel food.

Similarly, there may be a need to address exposure to a single chemical via different routes. Generally, consistent with its mandate, EFSA focuses on the oral route of intake, with ingestion of food and beverages as the main vehicles. The potential for exposure via other routes has been considered, in particular via dermal and inhalation exposure.<sup>27</sup> However, if several routes have to be considered jointly, then the safe dose needs to be expressed as the 'internal dose', allowing the exposure through various routes to be taken into account.<sup>28</sup>

In addition to considering evidence generated on a specific substance, evidence from related substances might also be considered relevant. This could be done by using the so-called read-across approach.<sup>29</sup> It is an area for which EFSA has however not developed guidance, with one exception, i.e. the threshold of toxicological concern (TTC).<sup>30</sup> Its use is limited to cases where there is a paucity of data.

Finally, as with any scientific evaluation, a risk assessment encompasses a number of steps which are to be integrated into one overall risk characterisation. These 'building blocks' each bring evidence, which needs to be characterised both in terms of the type of evidence it provides and the uncertainty and variability that accompanies that evidence, both of which feed into the overall risk characterisation. Uncertainty is defined as referring to all types of limitations in the knowledge available to assessors at the time an assessment is conducted (and within the time and resources available for the assessment), including assumptions and simplifications. This was first addressed by EFSA's Scientific Committee for the exposure assessment<sup>31</sup> and most recently expanded to cover all parts of the risk assessment.<sup>32</sup>

Where the source of some information (e.g. assumptions) may be expert opinion, it is important to make sure that the expert knowledge elicitation (EKE) is based on a reproducible process,<sup>33</sup> especially as their accuracy may vary.<sup>34</sup> The same is true for safety (or uncertainty) factors.<sup>17</sup>

Further reflections on this have been presented by Hardy et al.<sup>35</sup>

<sup>22</sup> [http://ph.cochrane.org/sites/ph.cochrane.org/files/public/uploads/Guide%20for%20PH%20protocol\\_Nov%202011\\_final%20for%20website.pdf](http://ph.cochrane.org/sites/ph.cochrane.org/files/public/uploads/Guide%20for%20PH%20protocol_Nov%202011_final%20for%20website.pdf)

<sup>23</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/1637>

<sup>24</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/2092>

<sup>25</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/4971>

<sup>26</sup> <https://www.efsa.europa.eu/en/press/news/170612>

<sup>27</sup> <http://www.efsa.europa.eu/en/supporting/pub/en-637>

<sup>28</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/4525>

<sup>29</sup> [https://echa.europa.eu/documents/10162/13628/raaf\\_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a](https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a), [https://echa.europa.eu/documents/10162/13630/raaf\\_uvcb\\_report\\_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316](https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316)

<sup>30</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/2750>

<sup>31</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/438>

<sup>32</sup> <https://www.efsa.europa.eu/sites/default/files/consultation/150618.pdf>

<sup>33</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/3734>

<sup>34</sup> <http://www.nature.com/nature/journal/v463/n7279/full/463294a.html?foxtrotcallback=true>

<sup>35</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/e13031>

### 3.2.2. Topic-specific guidance

Topic-specific guidance has been developed by either the Scientific Committee or individual Scientific Panels. The contribution from the former is reviewed first.

Safety data needs are generally addressed through specific experimental studies. For various such studies, the OECD offers internationally agreed guidance describing the design, conduct, analysis and interpretation of various rodent studies. There has only rarely been a need for EFSA itself to issue additional guidance on such studies.<sup>36,37</sup>

The Scientific Committee has developed topic-specific guidance on various aspects of chemical safety relating to:

- elements of hazard identification, such as on genotoxicity<sup>38</sup>;
- hazard characterisation, such as the Benchmark Dose (BMD)<sup>39</sup> to make fullest use of the available dose–response data to estimate the point of departure for an endpoint. This results in a more consistent estimation of a NOAEL or LOAEL and the derived HBGV and provides a quantification of the uncertainties in these data for the effect that is the most critical. Following the development and implementation of this guidance and based on the experience gained, it has been subsequently further refined<sup>40</sup>;
- aspects of exposure assessment<sup>41</sup> and
- risk characterisation, such as the margin of exposure (MOE) concept.<sup>42</sup>

Differences in the assessment approaches between various age groups of consumers have also been recognised.<sup>43</sup>

On microorganisms to be deliberately released in the food or feed chain, the work of the Scientific Committee was focused on qualified presumption of safety (QPS).<sup>44</sup> This concept was subsequently expanded to botanicals.<sup>45</sup>

More recently, aspects of environmental protection assessment were also addressed. These include the guidance on the development of specific environmental protection goals in relation to biodiversity and ecosystem services,<sup>46</sup> guidance on how to measure recovery<sup>47</sup> and a position paper on the coverage of endangered species in environmental risk assessments.<sup>48</sup>

Finally, the Scientific Committee has also developed guidance on emerging food safety topics such as on botanicals and botanical preparations<sup>49</sup> and the application of nanotechnology<sup>50</sup> and next generation sequencing in the food chain.

EFSA guidance developed by Scientific Panels (Table 2) may concern broad areas, such as environmental risk assessment methods (Panel on Plant Protection Products and their Residues (PPR Panel)), demonstration of beneficial effects (health claims, Panel on Dietetic Products, Nutrition and Allergies (NDA Panel)), assessment of risk management options and import risk assessment (Panel on Plant Health, (PLH Panel)).<sup>51</sup> Guidance can also be more topic-specific, such as animal welfare (Panel on Animal Health and Welfare (AHAW Panel)), extrapolation of evidence from major species to minor species (Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel)), low levels of contamination of chemicals (Panel on Contaminants in the Food Chain (CONTAM Panel)).

### 3.2.3. Guidance life cycle

As EFSA has matured, the concept of guidance development has evolved from the initial need for guidance creation towards a need to maintain the growing body of existing guidelines so as to make

<sup>36</sup> [http://www.oecd-ilibrary.org/environment/test-no-408-repeated-dose-90-day-oral-toxicity-study-in-rodents\\_9789264070707-en](http://www.oecd-ilibrary.org/environment/test-no-408-repeated-dose-90-day-oral-toxicity-study-in-rodents_9789264070707-en)

<sup>37</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/2438>, <https://www.efsa.europa.eu/en/efsajournal/pub/3871>

<sup>38</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/282>, <http://www.efsa.europa.eu/en/efsajournal/pub/2379>

<sup>39</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/1150>

<sup>40</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/4658>

<sup>41</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/249>

<sup>42</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/2578>

<sup>43</sup> <https://www.efsa.europa.eu/sites/default/files/consultation/170220.pdf>

<sup>44</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/587>

<sup>45</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/3593>

<sup>46</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/4499>

<sup>47</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/4313>

<sup>48</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/4312>

<sup>49</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/1249>

<sup>50</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/2140>

<sup>51</sup> <http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2016.EN-1062/pdf>

sure it remains up-to-date, i.e. keeps up with scientific developments. The Scientific Committee has recognised this necessity to regularly evaluate EFSA's guidance documents and recommended that they should be screened every 3 years for their scientific relevance and to identify any needs for revision.<sup>52</sup> To support this process, a working group has been established under the Scientific Committee.<sup>53</sup>

### 3.3. Evidence

EFSA does not generally conduct primary research, but rather assesses existing scientific evidence. Scientific advice needs to take all available information that is relevant into account and weigh the evidence using a pre-established and transparent process. The available evidence may not allow any prediction to be made with a reasonable degree of certainty and, in any case, always carries a degree of uncertainty.<sup>33</sup>

#### 3.3.1. Data requirements for assessment prior to market introduction

Before a food, feed or ingredient, e.g. an enzyme, that is intended to be deliberately added to the food chain is authorised for such use, sector-specific regulations require that the applicant carries out a battery of studies to examine their safety and/or efficacy and then requests EFSA to carry out a scientific evaluation of the available evidence.

For human food safety, the types of data required are shown in the insert below. There may be exceptions however, such as for novel foods, where sometimes more general evidence is considered adequate by the legislator, dependent on the substance and prior knowledge.

Evidence generally used for human food safety assessment of deliberately introduced <i>new micro-organism or chemical</i>
<ul style="list-style-type: none"> <li>• <b>Hazard Identification and Characterisation:</b> <ul style="list-style-type: none"> <li>➤ GLP studies in <u>lab animals</u>, along with <i>in vitro</i> and <i>in silico</i> studies, supplied by <u>applicant</u>,</li> <li>➤ <u>Extrapolation</u> to man using uncertainty factors</li> </ul> </li> <li>• <b>Exposure Assessment:</b> <ul style="list-style-type: none"> <li>➤ Based on <u>use assumptions</u> submitted by <u>applicant</u></li> <li>➤ Food (and feed) <u>consumption data</u> from the EFSA database</li> </ul> </li> </ul>

In EFSA, the two phases of dossier generation and the assessment thereof by EFSA are successive and separate.

- First, as is also the case in other regulated areas, e.g. medicines (EMA) and in other jurisdictions, the applicant is responsible for generating the necessary information. This means to pay for the studies to be carried out and put the resulting evidence in a dossier which is to meet the regulatory requirements, including relevant EFSA guidance documents. The services EFSA provides in this regard can be found on the EFSA website.<sup>54</sup>
- Next, when considered complete, the applicant submits the dossier for scientific review to EFSA directly, via a Member State or via the European Commission, depending on the relevant regulation.

As indicated, for scientific assessment advice to be delivered prior to market authorisation, the data requirements to be fulfilled are typically stated in sector-specific legislations.<sup>55</sup> Thus, within EFSA's remit, a set of different legislations exist for compounds or organisms that are to be deliberately introduced in the food chain, depending on the intended use of the compound or organism. These lay out the study requirements that an applicant that wishes to bring, e.g. a chemical to market needs to comply with. Data requirements vary both with regard to the areas to be covered (Table 3), as well as the actual data requirements, i.e. the types of studies to be conducted within a given area.

<sup>52</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/4080>

<sup>53</sup> [https://www.efsa.europa.eu/sites/default/files/wgs/methodology/GuidanceReview\\_mandate\\_2015.pdf](https://www.efsa.europa.eu/sites/default/files/wgs/methodology/GuidanceReview_mandate_2015.pdf)

<sup>54</sup> <https://www.efsa.europa.eu/en/supporting/pub/1025e>

<sup>55</sup> <http://www.efsa.europa.eu/sites/default/files/assets/apdeskhov.pdf>

**Table 3:** Pre-marketing dossier data requirements for compounds to which food or feed is intentionally exposed

Domain	Subject of scientific review							
	Proposed use	Composition	Manufacturing process	Human (food) or animal (feed) safety assessment			Efficacy	Environmental safety
				Kinetics	Toxicology	Exposure		
<b>Pesticides</b>			+		+	+	+	+
<b>GMOs</b>	+	+	+		+	+	-	+
<b>Feed additives</b>			+		+	+	+	+
<b>Food additives</b>	+	+	+	+	+	+	+	
<b>Food enzymes</b>	+	+	+		+	+		
<b>Food flavourings</b>	+	+	+		+(b)	+		
<b>Smoke flavourings</b>	+	+	+		+			
<b>Food packaging materials<sup>(g)</sup></b>	+	+	+	+(e)	+(f)			
<b>Nutrient sources<sup>(a)</sup></b>					+/- <sup>(d)</sup>			
<b>Health claims</b>							+	
<b>Decontamination substances<sup>(c)</sup></b>		+			+		+	+
<b>Use of animal by-products</b>								

(a): Concerns generally supplementation with minerals or vitamins.

(b): When considered applicable.

(c): Substances, other than potable water, that are used for the removal of microbial surface contamination of foods of animal origin require prior authorisation.

(d): No dossier submitted, review of available information by EFSA.

(e): Migration test and residual concentration in food.

(f): Test requirements vary with the degree of migration of the food contact material in the food.

(g): Additional requirements for recycling processes and for intelligent and active packaging materials.

### Applicant-sponsored studies

To meet these data requirements, evidence is to be generated through studies funded by the applicant. In fact, for new chemicals or microorganisms to be deliberately added to food or feed or whose residues potentially enter the food chain, only the organisation submitting the dossier may have access to the product at the stage of initial development.

Nowadays, the laboratory studies that are submitted generally need to be carried out under the requirements of Good Laboratory Practices<sup>56</sup> (GLP) and in a GLP-certified testing facility or by an organisation accredited under a relevant standard of the International Organization for Standardisation (ISO). For example, for feed-additives Annex II to Commission Regulation 429/2008<sup>57</sup> states that the description of the methods of analysis in feed or water shall be in conformity with the rules of GLP as laid down in Directive 2004/10/EC<sup>58</sup> and/or EN ISO/IEC 17025.

The testing facility's study director has the responsibility to ensure compliance of a study to GLP requirements. Verification of the adherence of a study facility to GLP processes is the responsibility of the EU Member States' or third countries' competent authorities. While GLP represents therefore only one of the possibly relevant quality standards, this one is a standard that is commonly required across various regulations.<sup>59</sup>

Beyond the laboratory in which the study is carried out, the techniques or methods of analysis used in the study must also be certified.

### The dossier submitted to EFSA

A regulatory dossier is not to be viewed as a mere compilation of a set of studies that are to be carried out according to a set of defined protocols. Instead, it is to be a scientific document putting together various strands of evidence that are gradually generated during the study of the safety and, where required, efficacy profiles, typically starting from the elementary (molecular and cellular characteristics) to the more complex levels (tissue and whole body). Burden of proof, i.e. the responsibility for demonstrating safety resides with the applicant submitting the dossier. For example, Article 5 (5) of Commission Regulation (EU) No 234/2011 on food additives, flavourings, enzymes illustrates this point.<sup>60</sup> It states as a dossier requirement: 'The safety evaluation strategy and the corresponding testing strategy shall be described and justified with rationales for inclusion and exclusion of specific studies and/or information'.

### Studies to be included in the dossier

With differences in data requirements between different sector-specific legislations also comes some variation in the legislative requirements with regard to the information to be included in a dossier.

The applicant is generally obliged to submit all information they have generated themselves and the relevant literature; but it is not always explicitly stated that all studies that were initiated by the applicant himself or on his behalf or that were published by third parties have to be included in the dossier. Of course, for a novel compound there might not yet be many, if any, studies in the scientific literature at the time the dossier is evaluated.

### Information gathering by EFSA

For the purpose of the gathering of all pertinent information, already in 2010 EFSA embraced the principles of systematic review of the evidence pertinent to address specific questions.<sup>24</sup> This approach uses prespecified and standardised methods to identify relevant research and to collect, report, analyse and critically appraise the data from the studies that are included in the reviews.

<sup>56</sup> [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem\(98\)17&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem(98)17&doclanguage=en)

<sup>57</sup> Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives, OJ L 133, 22.5.2008, p. 1–65. Available online: <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R0429&from=EN>

<sup>58</sup> Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances, OJ L 50, 20.2.2004, p. 44–59.

<sup>59</sup> [http://ec.europa.eu/growth/sectors/chemicals/legislation/index\\_en.htm](http://ec.europa.eu/growth/sectors/chemicals/legislation/index_en.htm)

<sup>60</sup> Commission Regulation (EU) No 234/2011 of 10 March 2011 implementing Regulation (EC) No 1331/2008 of the European Parliament and of the Council establishing a common authorisation procedure for food additives, food enzymes and food flavourings, OJ L 64, 11.3.2011, p. 15–24. Available online: <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R0234&from=EN>

For regulated products, there currently are no provisions in any of the regulatory processes for a systematic search to be conducted by EFSA itself to identify information from peer-reviewed literature for the particular Scientific Panel to consider. The scientific assessment will thus start from the data package submitted by the applicant. While this assessment may take into consideration other information the experts are aware of, EFSA Panels assessing regulated products do not generally (re-) do a systematic search for literature themselves.

### 3.3.2. Data requirements for food chain contaminants

Responsibility for conducting research on food chain contaminants, e.g. environmental pollutants is not typically 'claimed' by entities (private or public) causing the pollution. The burden for funding applied research assessing their impact on human safety and environmental protection then reverts to public institutions.

In addition in this area, specific regulatory frameworks as to what such studies should entail in order to usefully feed into a subsequent scientific assessment very often do not exist.

When EFSA receives a request for scientific advice that does not concern a regulated product that is submitted by an applicant, this is usually not accompanied by a set of studies to be assessed. The relevant Scientific Panels therefore have to first gather all potential information. For the identification and characterisation of these hazards, this mostly originates from published research (see insert). These may or may not have been designed to be useful for such an assessment. Scientific Panels may thus be faced with a paucity of relevant evidence on which to base their assessment.

**Data used for human food safety assessment of micro-organism or chemical already present in the food chain**

- **Hazard Identification and Characterisation:**
  - Peer-reviewed *in silico*, *in vitro*, experimental and observational studies
  - With or without GLP lab-animal studies
- **Exposure:**
  - Based on existing monitoring programmes or collected ad hoc
  - Food (and feed) consumption data from the EFSA database

### 3.3.3. Post-approval monitoring and re-assessment

The pre-authorisation approach aims to predict the maximum doses at and below which no adverse health effects are anticipated. Being dependent on the information available at a particular time, such predictions may be subject to revision as and when new evidence emerges.

The review of a previous scientific assessment, post-market approval, can entail both the re-assessment of a HBGV, based on more safety information of the same nature as in the initial assessment, e.g. additional laboratory animal studies or a new method to assess available information. The use of the weigh-of-evidence approach and the description of the uncertainty of a scientific assessment should allow for a determination to what extent a new publication shifts the entire evidence base in a given area.

In addition, new types of evidence may be collected and become available only after market authorisation was granted. This is discussed next.

#### Exposure

Following market introduction, programmes may be put in place by the risk managers to measure compliance with the license conditions. A distinction can be made between on the one hand the detection of fraudulent violative levels of chemicals present in food and on the other hand health effects due to (long-term) excessive exposure. In the latter case, the actual exposure is estimated and compared with what was assumed would take place, based on the data provided in the dossier.

To estimate chemical exposure of humans through food, data on food consumption are combined with data on concentrations of various contaminants, residues, and deliberately added ingredients in foods. EFSA has established a repository of such data as well as of microbiological contaminants. These originate from and are made available through collaborations with Member State scientific

assessment and public research organisations. They have resulted in the standardisation of various aspects such as standards for sample description<sup>61</sup> and data transmission protocols<sup>62</sup> for chemical and microbiological contaminants, various types of residues, such as from pesticides and veterinary medicines, and food additives.

For food consumption guidance has been agreed for the conduct of dietary surveys<sup>63</sup> and use of these data in the EFSA Comprehensive Food Consumption database for exposure assessments.<sup>64</sup> Table 4 provides an overview of all the standards that have been developed, agreed with and implemented by data providers and which are regularly updated. Crucially, a guidance for cross-domain sample description has been agreed upon and will be fully implemented by 2020.<sup>65</sup>

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<sup>61</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/1457>, <http://www.efsa.europa.eu/en/efsajournal/pub/3424>

<sup>62</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/1895>, <https://www.efsa.europa.eu/en/efsajournal/pub/3945>

<sup>63</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/1435>, <https://www.efsa.europa.eu/en/efsajournal/pub/2450>, <https://www.efsa.europa.eu/en/efsajournal/pub/3944>

<sup>64</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/2097>

<sup>65</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/3424>

**Table 4:** EFSA guidelines on data collection, reporting, transfer and analysis of chemical and biological hazards

Type of data	Data collection/reporting	Data transfer	Data analysis
<b>Chemical hazards<sup>(a)</sup></b>	1, 3, 4, 5, 16, 17	1,2, 17	9
<b>Food consumption</b>	6, 7, 16, 17	2,7, 17	6
<b>Biological hazards</b>	8, 10, 11, 12, 13, 14, 16, 17	2, 8, 13, 14, 15, 16, 17	8, 13

(a): Chemical contaminants, food additives, pesticide residues, veterinary medicinal product residues.

1: Standard sample description version 2.0.

2: Guidance on data exchange version 2.

3: Specific reporting requirements for contaminants and food additives occurrence data submission in SSD2.

4: Guidelines for reporting data on residues of veterinary medicinal products.

5: Guidance for reporting data on pesticide residues in food and feed according to Regulation (EC) No 396/2005 (2016 data collection).

6: Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment.

7: Guidance on the EU menu methodology.

8: Technical specifications for the pilot on the collection of data on molecular testing of food-borne pathogens from food, feed and animal samples.

9: Statement on approach followed for the refined exposure assessment as part of the safety assessment of food additives under re-evaluation.

10: Manual for reporting on zoonoses and zoonotic agents, within the framework of Directive 2003/99/EC, and on some other pathogenic microbiological agents for information deriving from the year 2016.

11: Manual for reporting on food-borne outbreaks in accordance with Directive 2003/99/EC for information deriving from the year 2016. EFSA supporting publication 2017.

12: Manual for reporting on antimicrobial resistance within the framework of Directive 2003/99/EC and Decision 2013/652/EU for information deriving from the year 2016.

13: Technical specifications on the collection, management and analysis of data on the surveillance of transmissible spongiform encephalopathies (TSEs) in ruminants in the EU.

14: Data dictionaries—guidelines for reporting data on zoonoses, antimicrobial resistance and food-borne outbreaks using the EFSA data models for the Data Collection Framework (DCF) to be used in 2017, for 2016 data.

15: User manual for data providers for mapping Member State standard terminology to EFSA standard terminology.

16: The food classification and description system FoodEx2 (revision 2).

17: FoodEx2 Browser – user's guide.



Based on such information generated by the Member States, EFSA will assess whether actual exposures, through all commodities combined, does not exceed the ADI or TDI.

### Health effects

When human exposure does take place, the absence of adverse health effects at these known exposure levels can, in principle, be monitored through epidemiological studies which aim to uncover causes of what truly makes people ill. This is the customary approach in microbiological risk assessment, where exposure to a microbiological contaminant can be rather readily identified, the time lag between exposure and disease occurrence is often short, and the resulting disease is clinical.<sup>66</sup>

## 3.4. Scientific Expertise

### 3.4.1. Scientific Panels

The appointment of Panel members concerns the nomination of individuals in their personal capacity. Among the experts that have applied to serve on an EFSA Panel, an evaluation of the candidates is made based on their scientific expertise, independence and a commitment to devote adequate time to this function. Gender and geographical balance are also considered, where possible. The assessment of expertise, among the individuals who volunteer to join a Panel, considers their scientific experience in general as well as the topic-specific competences that are needed for the particular Panel.<sup>67</sup> Panel members are nominated for a period of 3 years by the EFSA Management Board to one of the (currently) ten Scientific Panels or the Scientific Committee, based upon a list proposed by the Executive Director. They can serve up to 9 years on the same Panel.

Panel members have no employment agreement with EFSA. Rather, these experts are most often full-time employees of public organisations in Member States that volunteer to also join an EFSA Panel. The financial compensation that Panel members receive currently consists of a *per diem* for attendance of the meetings of Panels or working groups, as well as reimbursement of travel and accommodation expenses. It does not compensate for the preparatory time necessary to author an EFSA scientific assessment.

While this is the system in place for most of EFSA's activities, it is not the only one. Legislative provisions may foresee particular aspects of the scientific assessment to be carried by organisations in Member States.<sup>68</sup> It is particularly the assessment of pesticides that operates under a different model. In particular, the focus of the PPR Panel is to develop the basis for scientific assessment guidance, whereas the scientific assessment of the active ingredient of pesticides is carried out by staff in Member State institutions, where one of these institutions serves as rapporteur. This model is more akin to the model in place in the assessment of medicines by the EMA and of chemicals by the European Chemicals Agency. To carry out this work, fees may have to be paid by the applicant upon submission of a dossier for regulatory review.

To bring a pesticide to market in the EU currently requires in fact two successive assessment cycles.<sup>69</sup> In the first one, the applicant submits a dossier to the rapporteur Member State to assess the active ingredient only. EFSA and the other Member States' designated organisations perform a peer review of the rapporteur's report. EFSA, then issues an opinion based on the input of the rapporteur and its comments as well as those from the other Member States' assessors. This serves as an input for the European Commission and national risk managers to make a decision on the active ingredient only. The next cycle then concerns the assessment of specific uses concerning the formulated product (active ingredients and co-formulants) by Member State assessment bodies, whereby EFSA proposes maximum residue limits for these uses, and the subsequent approval of those uses at the national level. The adequacy of this system is currently the subject of a reflection.<sup>70</sup>

### 3.4.2. Support mechanisms

The Panels are supported by working groups and EFSA scientific staff, who carry out preparatory tasks. Working groups have a mandate that is either continuous ('standing' working group) or is

<sup>66</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/2390>

<sup>67</sup> Call for expressions of interest for membership of the Scientific Panels and the Scientific Committee of the European Food Safety Authority (EFSA): <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:C2017/174/08&from=IT>

<sup>68</sup> [http://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0004.02/DOC\\_1&format=PDF](http://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0004.02/DOC_1&format=PDF)

<sup>69</sup> [http://www.efsa.europa.eu/interactive\\_pages/pesticides\\_authorisation/PesticidesAuthorisation](http://www.efsa.europa.eu/interactive_pages/pesticides_authorisation/PesticidesAuthorisation)

<sup>70</sup> <https://ec.europa.eu/research/sam/index.cfm?pg=pesticides>

concerns just a single mandate and thus limited in time ('ad hoc' working group) (Table 5). These standing working groups are a common feature for Panels which conduct reviews of regulated products either pre-market or for license renewal. Their tasks may be either to conduct the full review of a particular type of compound, as is e.g. the case for the FEEDAP Panel, or they may primarily focus on the assessment of one particular section of the dossier as is, e.g. the case for the Panel on Genetically Modified Organisms (GMO Panel) and for the review of pesticide active substances.

**Table 5:** Roles of EFSA Panels' working groups: Panel and type of working group

Scientific Panel	Standing working groups <sup>(1)</sup>				Ad hoc working groups <sup>(2)</sup>		
	Guidance	Individual assessments			Guidance	Individual scientific assessments	
		Overall assessment	By compound/ organism type	By scientific area		By compound/ organism type	Individual assessments
<b>Scientific Committee</b>	1 <sup>(a)</sup>	1			5 <sup>(b)</sup>	1	
<b>Animal feed<sup>(c)</sup></b>	1 <sup>(d)</sup>		11		1 <sup>(e)</sup>		
<b>Food ingredients &amp; packaging<sup>(f)</sup></b>		1	5	1 <sup>(g)</sup>	1 <sup>(i)</sup>	1	1
<b>ANS Panel</b>			4	1 <sup>(h)</sup>			
<b>CEF Panel</b>							
<b>Genetically modified organisms<sup>(j)</sup></b>				4 <sup>(k)</sup>	2 <sup>(l)</sup>		
<b>Nutrition<sup>(m)</sup></b>			4	2 <sup>(n)</sup>		1	
<b>Pesticides<sup>(o)</sup></b>			1	5 <sup>(p)</sup>	9 <sup>(q)</sup>		
<b>Animal health and welfare<sup>(r)</sup></b>							8
<b>Biological hazards<sup>(s)</sup></b>							9
<b>Chemical contaminants<sup>(t)</sup></b>		2					11
<b>Plant health<sup>(u)</sup></b>					1 <sup>(v)</sup>	7	4

(1): With a mandate of a continuous nature

(2): With a single, temporary mandate

(a): Guidance review [http://www.efsa.europa.eu/sites/default/files/GuidanceReview\\_mandate\\_2015.pdf](http://www.efsa.europa.eu/sites/default/files/GuidanceReview_mandate_2015.pdf), Genotoxicity [http://www.efsa.europa.eu/sites/default/files/assets/scafgentox\\_mandate.pdf](http://www.efsa.europa.eu/sites/default/files/assets/scafgentox_mandate.pdf)

(b): Biological relevance, Uncertainty, Weight of evidence, Chemical mixtures, Nanotechnology.

(c): <https://www.efsa.europa.eu/en/animal-feed/working-groups>

(d): Guidance review <https://www.efsa.europa.eu/sites/default/files/guidanceupdatemandate.pdf>

(e): Environmental risk assessment.

(f): <https://www.efsa.europa.eu/en/food-ingredients-and-packaging/working-groups>

(g): Exposure assessment. <https://www.efsa.europa.eu/sites/default/files/expassessmentmandate.pdf>

(h): Genotoxicity of flavourings. <https://www.efsa.europa.eu/sites/default/files/FLAVReevaluation-mandate-genotoxicity.pdf>

(i): Nutrient sources.

(j): <https://www.efsa.europa.eu/en/gmo/working-groups>

(k): Molecular characterisation <https://www.efsa.europa.eu/sites/default/files/assets/gmowgimolchar.pdf>, Environment <https://www.efsa.europa.eu/sites/default/files/assets/gmowgimera.pdf>, Food/feed <https://www.efsa.europa.eu/sites/default/files/assets/gmowgimfoodfeed.pdf>, Post-marketing monitoring <https://www.efsa.europa.eu/sites/default/files/assets/gmowgimpmem.pdf>

(l): Low level presence of GM, Allergenicity of GM plants.

(m): <https://www.efsa.europa.eu/en/nutrition/working-groups>.

(n): Claims <https://www.efsa.europa.eu/sites/default/files/assets/nutriwgimclaims.pdf>, Food allergy <https://www.efsa.europa.eu/sites/default/files/assets/nutriwgimfoodallergy.pdf>

(o): <http://www.efsa.europa.eu/en/pesticides/working-groups>

(p): Physical & Chemical Properties, Mammalian Toxicology, Residues, Fate and Behaviour, Ecotoxicology <http://www.efsa.europa.eu/en/pesticidespeerreview/peerreviewexpertsmeetings>

- (q): Amphibians reptiles, Cumulative assessment, soil concentrations, dermal absorption, epidemiological studies, surface water repair, endocrine disruption, foods for infants and children, models for aquatic organisms.
- (r): <https://www.efsa.europa.eu/en/animal-health-and-welfare/working-groups>
- (s): <https://www.efsa.europa.eu/en/biological-hazards/working-groups>
- (t): <https://www.efsa.europa.eu/en/chemical-contaminants/working-groups>
- (u): <http://www.efsa.europa.eu/en/plant-health/working-groups>
- (v): Plant pest risk assessment method. [http://www.efsa.europa.eu/sites/default/files/assets/Dir%202000\\_29\\_Methods\\_wg\\_minutes.pdf](http://www.efsa.europa.eu/sites/default/files/assets/Dir%202000_29_Methods_wg_minutes.pdf)

Over the years, EFSA has also established a set of networks for information exchange with Member States. These now cover most areas in which EFSA gives scientific advice or provides technical support to the Commission.<sup>71</sup> Beyond the networks and within budgetary limits, over the years specific scientific tasks have also been carried out by and in collaboration with other scientific institutes. These have taken the form of grants<sup>72</sup> or contracts.<sup>73</sup> It concerns – in the area of scientific assessment – preliminary work, exploration of emerging topics of mutual interest and, at times, support with a standardised process when that represents a large body of work. In recent years, EFSA has explored a series of cooperation initiatives with public organisations in Member States through the multi-annual framework partnerships.<sup>74</sup> Examples concern the development of software for outbreak investigations,<sup>75</sup> a project led by the BfR in Germany; the study of Ciguatera food poisoning in Europe, led by the AECOSAN in Spain<sup>76</sup> or the study of cumulative risk assessment of chemicals with the RIVM in the Netherlands.<sup>77</sup>

## 4. Legitimising characteristics

Below, a number of legitimising characteristics are reviewed. They are characteristics that influence the scientific credibility of an individual output, of EFSA as an organisation, or the long-term trust in the EU system of food safety as a whole.

### 4.1. Process quality and the monitoring thereof

Reflections on assessing scientific quality of academic research<sup>78</sup> and criteria for scientific assessment in the framework of food safety<sup>79</sup> are not new. While peer review may seem a key element to verify transparency, necessary to allow reproducibility, the classic peer review system of scientific journals is one that does not fit the outputs of EU Agencies that provide scientific advice. The EU ANSA has issued a reflection paper on peer review<sup>80</sup> proposing a set of key principles applicable to the use of peer review approaches within the context of EU agencies providing scientific advice and technical support. It differs in a number of ways from the classical peer review in academic publishing.<sup>81</sup> Particularly, it is proposed that the process be transparent, i.e. the reviewers be identified and their comments and how they are addressed be made public.

Over time, EFSA has developed several approaches to ascertain quality. These have included public consultations on draft outputs,<sup>82</sup> in particular for guidance documents. As for process quality, EFSA has also developed a system of *post hoc* evaluations of a sample of EFSA outputs by peer scientists. These opinions are assessed as stand-alone documents. This addresses questions such as, whether the objectives were clear, the materials and methods were properly described and adhered to, and the results address the mandate. Over the years, these regular evaluations have shown an ever higher level of compliance.<sup>83</sup> More recently, EFSA has also sought feedback from its main customer, the European Commission, as to whether its outputs address their needs.

Rather than continuing to focus solely on *post hoc* peer review of a sample of outputs, EFSA has opted for an overall process quality assurance system for its scientific assessments. This overarching approach that EFSA is aiming at in its scientific assessment process is spelled out in the so-called PROMETHEUS (PROmoting METHods for Evidence Use in Scientific assessments) approach.<sup>84</sup> It includes essentially the following phases:

<sup>71</sup> <https://www.efsa.europa.eu/en/partnersnetworks/eumembers>

<sup>72</sup> <https://www.efsa.europa.eu/sites/default/files/art36grantsagreementsprevious.pdf>

<sup>73</sup> <https://www.efsa.europa.eu/sites/default/files/efsacontractorsprevious.pdf>

<sup>74</sup> [https://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/scientificcooperation16ar.pdf](https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/scientificcooperation16ar.pdf)

<sup>75</sup> <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0151977>

<sup>76</sup> [https://www.efsa.europa.eu/sites/default/files/event/AF170608/AF170608-p4.2\\_Spain\\_Ciguatera%20AF%20JUNE.final.%202017.pdf](https://www.efsa.europa.eu/sites/default/files/event/AF170608/AF170608-p4.2_Spain_Ciguatera%20AF%20JUNE.final.%202017.pdf)

<sup>77</sup> <https://www.efsa.europa.eu/en/press/news/160127>

<sup>78</sup> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3386428/>

<sup>79</sup> [http://www.foodsafety.govt.nz/elibrary/industry/Evidence\\_Based-Answer\\_Question.pdf](http://www.foodsafety.govt.nz/elibrary/industry/Evidence_Based-Answer_Question.pdf)

<sup>80</sup> <http://bookshop.europa.eu/en/-peer-review-by-eu-ansa-agencies-pbTE0215981/>

<sup>81</sup> <http://www.nature.com/nature/journal/v531/n7594/full/531305c.html>

<sup>82</sup> <https://www.efsa.europa.eu/en/calls/consultations>

<sup>83</sup> [https://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/qmr16.pdf](https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/qmr16.pdf)

<sup>84</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/4121>

- Define the assessment protocol beforehand, thereby specifying upfront the objectives of the assessment, defining the hypothesis to be tested, which evidence is to be collected for that purpose and the methods that are to be applied to appraise and synthesise the evidence.
- Carry out the assessment in line with this protocol. Document the process (including any deviations from the protocol) and report the results, results and conclusions, and ensure accessibility of methods and data.
- In a quality assurance section, review the compliance with the plan and discuss the impact of any deviations.

These phases are consistent with the principles for a systematic literature review or the overall approach used with the conduct of studies under GLP conditions. It considers a scientific assessment to be similar to a scientific study and implies that a scientific assessment therefore typically includes a protocol, a report and a section documenting compliance. In this, the report is the main study document with materials, methods and results, and it forms the core of the scientific opinion; whereas the protocol, details of the process documentation and the compliance verification are annexes to this publication.

In 2016, EFSA has been certified as having an ISO-9000 compliant quality-assurance system resulting in ISO 9001/2015 certification.<sup>84</sup> This means there is one single coherent system throughout the organisation based on an integrated and transparent management system designed to deliver accountability, management of risks in process errors and drive continuous improvement. Aspects of this quality management system include:

- description of the key parameters to describe quality;
- definition of the types of scientific outputs and the workflows that lead to those outputs;
- creation of a repository of EFSA's Governance and Management documents;
- development of a compliance monitoring system consisting of:
  - control and reporting of non-conformities;
  - implementation of measures to assess the quality of EFSA's scientific outputs;
  - feedback system; and
- a quality function created and operational in all concerned units.

## 4.2. Consistency

Besides internal consistency within a single opinion, as discussed above under Process Quality, there is also a need for consistency across scientific assessments. This is to say, will a same question, e.g. 'Is a particular chemical safe for human consumption at the proposed dose?' be addressed in a consistent manner both with regard to data required, the assessment methods considered, and how these are being applied?

First, there is the aspect of consistency in the assessment of individual compounds that are considered similar from a safety perspective. Should existing evidence on closely related compounds not be formally be taken into account? If so, how is this best done? As indicated, thus far EFSA seldom makes explicit use of information on closely related compounds, e.g. present in other dossiers. This merits further reflection from the perspective of developing a transparent scientific process on how to do this and from a legal perspective.

This issue is not only relevant within a single domain, say food additives, but also between different domains within EFSA e.g. between feed additives and food additives and – possibly – between EU Agencies, such as the European Chemical Agency (ECHA), EFSA and EMA.

While differences in assessment methods between EFSA Panels may be justified, for reasons of consistency but also transparency and efficiency, it is equally important to otherwise use approaches that are consistent.

As reviewed earlier (Table 2), since its creation the Scientific Committee and the Scientific Panels have developed extensive guidance on scientific assessment. This includes a substantial proportion of guidance on dossier requirements which often contain a mixture of data requirements as well as a description as to how this information will be assessed. When comparing the data requirements (Table 3) with the areas of guidance development (Table 2), there is currently little in the way of cross-cutting guidance as to how elements of a dossier that are common to various Panels are to be assessed. Examples include assessment of proposed use, composition, and aspects of human safety assessment (Table 2).

Panels have to address numerous and widely varied issues. Due to the width of EFSA's remit, it covers a large area of expertise, i.e. genetics, ecology, plant sciences, veterinary science, zoology, toxicology, nutrition, human medicine, biology, chemistry, mathematics/statistics/biostatistics, food/feed technology, pharmacology, exposure assessment, epidemiology and regulatory science.<sup>85</sup> Also within a Panel, an expert is not expected to be specialised in all areas under that Panel's remit. Rather, it is the collective body of experts selected to cover all of a Panel's areas of expertise that is needed to come to a collegial conclusion. However, this also means that the expertise on a very specific topic may be thinly spread within a Panel. This may be equally challenging if this same expertise is needed in several working groups of the same or of different Panels.

Within EFSA, working groups have generally served a single Panel. However, this is no obligation and cross-cutting working groups serving several Scientific Panels are emerging. First, guidance consistency is currently within the remit of the aforementioned standing working group on guidance review of the EFSA Scientific Committee.<sup>54</sup> This approach has also proven to be helpful for the development or revision of guidance as well as their consistent implementation, e.g. on genotoxicity<sup>86</sup> and BMD approaches,<sup>87</sup> areas which are relevant for multiple Panels.

This harmonisation merits further effort in the years to come. Standing working groups, with specialist experts from those different Panels and supported by specialised EFSA staff can in principle serve several Panels for the assessment of a specific component of a scientific assessment. Standing working groups with experts from different Panels may thus serve as a useful platform for multiple Panels offering not only opportunities for guidance harmonisation and fora to discuss consistency in the assessment of specific cases, but they may also end up routinely supporting the review of specific sections of individual dossiers. This is envisaged to potentially increase efficiency of reviews along with consistency and diligence in the implementation of guidance. This is already in place for the conduct of exposure assessments, which are most often prepared by EFSA staff for the benefit of different Panels. To further expand this approach would require some changes. First, it necessitates the alignment of the remit of the (standing) working groups with the parts of the dossier across concerned Panels, as is already largely the case today e.g. with GMOs and pesticides (Table 5). Second, it potentially means creating teams or units (real or virtual) of EFSA staff covering the same specialised competencies.

While harmonisation in addressing a same issue across different areas of the food chain may be highly desirable, it is also the case that diversity in methods used to address a scientific question may be enriching. When there is congruence, this strengthens the conclusions. When it leads to different answers, it provides an opportunity to understand why these differences have emerged, which in turn may lead to new scientific insights.

Equally, justification for the diversity of data requirements in the various areas of the food chain, as laid down in sectorial legislations, may also merit further consideration. EFSA could support the European Commission to review data requirements and study strategies across the various parts of the food chain that are covered by different legislations, including the use of tiered approaches. Where differences exist, it may be useful to take stock of the scientific basis for their justification.

### 4.3. Independence and Impartiality

The term independence is frequently used in the General Food Law Regulation and is also a topic of much debate. Hence it merits reflection as to what it means and what purpose it is to serve in the context of EFSA.

First, EU Agencies do not operate as totally independent organisations; rather they are firmly embedded in the legal provisions for the governance of EU institutions. As an example, the box below shows a number of EU bodies which impact the governance of EFSA.

<sup>85</sup> <https://www.efsa.europa.eu/en/press/news/170601>

<sup>86</sup> [https://www.efsa.europa.eu/sites/default/files/wgs/cross-cutting-science/scafgentox\\_mandate.pdf](https://www.efsa.europa.eu/sites/default/files/wgs/cross-cutting-science/scafgentox_mandate.pdf)

<sup>87</sup> <https://www.efsa.europa.eu/en/methodology/working-groups>

- DG Sante, the partner Directorate General (DG) at the European Commission
- Various other Commission DGs, such as DG Personnel, DG Budget, and European Commission Audit Services
- European Parliament and its Committees
- European Court of auditors
- European Ombudsman
- European Data Protection Supervisor
- European Court of Justice

The General Food Law Regulation<sup>4</sup> states that EFSA is to give advice that is independent. The independence of that advice can be viewed to reside with the independence of the constituent parts of a scientific opinion. Indeed, independent scientific advice is the result of how the objectives of the advice are determined; how it is carried out: selection of experts and recruitment of staff, data required and working methods and processes; and how the outcome is communicated. It would seem that each of these aspects affects this goal of independence, as further discussed below.

A first aspect concerns the hypothesis being tested. The task at hand for a specific scientific assessment is typically the result of a dialogue between the risk manager seeking scientific advice and the risk assessor, who is to independently provide the advice resulting from the agreed-upon hypothesis. This is documented in the mandate which forms the basis for initiating the assessment process and mimics the hypothesis to be tested or the objectives of a research project. The quality of this mandate, e.g. is it clear and is it achievable, largely impacts the relevance of the subsequent assessment (NRC, 2009).

When it concerns an individual routine assessment which derives directly from the implementation of a regulatory review process, the objectives have been defined previously in the regulatory framework and the dialogue would have taken place at that stage, where EFSA would be consulted. This legislation usually states the scope of the assessment, e.g. are environmental aspects to be assessed or not and, if so, to what extent. In the case of individual assessments for regulatory approval that fall under such a regulation, what may be the subject of negotiation is rather the planning, e.g. the prioritisation and the timing of delivery of the task at hand. This is typically the case where it concerns a large number of re-evaluations of products which are already on the market. Outside these set frameworks for pre-market regulatory review, requests may require and often are the subject of prior dialogue between risk manager (most often the European Commission) and EFSA.

A second aspect concerns where the responsibility resides for deciding on the assessment methods and approaches to be used. It would seem that the assessment guidance is a core responsibility of EFSA and a key feature of its independence and therefore should fall under the responsibility of EFSA. This is addressed in two places in the General Food Law Regulation.<sup>4</sup>

According to Article 28, cross-cutting guidance is to be issued by the Scientific Committee 'to ensure the consistency of the scientific opinion procedure, in particular to the adoption of working procedures and harmonisation of working methods [...]'.<sup>88</sup>

However, assessment guidance for specific sectors of the food chain seems to represent an exception to this principle. In this regard, Article 6 of the General Food Law Regulation<sup>4</sup> states that: 'The implementing rules for the application of this Article [which relates to scientific advice by EFSA] shall be established by the Commission after consulting the Authority [...]. These rules shall specify in particular: [...] '(b) the guidelines governing the scientific evaluation of substances or processes which are subject under Union legislation to a system of prior authorisation or entry on a positive list, in particular where Community legislation makes provision for, or authorises, a dossier to be presented for this purpose by the applicant'. Such rules are to be implemented through sectorial legislation as described in Article 58. In this process, the Commission shall be assisted by a Standing Committee on Plants, Animals, Food and Feed (PAFF Committee)<sup>88</sup> which is composed of representatives of the Member States and chaired by the representative of the Commission. In other words these decisions are to be made by risk managers.

This may affect, for example whether and when new EFSA guidance becomes a legal standard for Member States' risk assessments of a pesticide active substance. If this were systematically the case, the independence of EFSA could be viewed as being quite limited as it could only give advice on the very assessment procedures it considers to be appropriate to carry out its mandate rather than being

<sup>88</sup> Previously the Committee on the Food Chain and Animal Health



responsible for how it carries out its independent assessment. It also raises the question, which is not explored here further, to what extent scientific guidance issued by EFSA's Scientific Committee is considered binding for the evaluation of "substances or processes which are subject under Community legislation to a system of prior authorisation or entry on a positive list".

It is also noted that specific sectorial legislation may deviate and supersede the provision of Article 6 of the General Food Law Regulation. As an example, the legislation on food contact materials states in Article 9 that the dossier that is submitted by the applicant should contain 'the information specified in the guidelines for the safety assessment of a substance to be published by the Authority'.<sup>89</sup>

A third element concerns EFSA's independence with regard to the evidence used in the assessment. As mentioned previously, the data requirements are generally stated explicitly in sectorial legislation. It can be argued that the scope of the assessment, e.g. does it need to include environmental protection or not and to what degree of certainty one wishes this to be addressed, is within the remit of the risk manager who poses the question. It would seem that the data requirements to achieve this, along with the assessment methods used, are the responsibility of the risk assessor. Evidence and methods may be intertwined. As an example, when using a tiered approach the data needs depend on the assessment of the outcome of studies conducted at a lower level.<sup>90</sup> Also, it is the responsibility of EFSA to characterise the uncertainty that accompanies an assessment, considering the particular evidence that is available.

For the data use, the roles and relative merits of studies carried out upon request of the applicant as compared to those originating from peer-reviewed literature or open data sources merit careful consideration. Scientific assessment is to be based on an evaluation and weighing of all available scientific evidence that is pertinent. Such information may have been published or not, peer-reviewed or not, produced under various systems of quality assurance, and performed according to official test guidelines tailored to investigate specific endpoints or not.

Irrespective of these characteristics, in a scientific assessment, each study needs to be evaluated as to its suitability for the assessment at hand. If the study objectives and its design are considered adequate, it is considered pertinent information and it can be used and weighed as part of the overall scientific evidence. If a study is not considered pertinent, for the reasons stated, it cannot be used in the weighing of the evidence.

As to the relative merits of GLP studies vs non-GLP academic studies, the following considerations are offered.

- GLP studies are generally applicant-sponsored, but very often carried out in independent specialised facilities. Should they be sponsored by public organisations, they may need to revert to the same GLP-accredited organisations.
- Whereas the purpose of a GLP study is to ensure process transparency, this of course in itself does not mean that the study objectives are relevant and the study design was the appropriate one for the purpose under consideration.
- Whereas this quality assurance system is helpful as concerns 'procedural quality', i.e. operational correctness, the retrievability and reproducibility of results, it does not ensure 'scientific quality', i.e. the scientific soundness of the tests and the resulting data to address the question at hand.

In summary, if a particular legislation requires that data are produced under a quality assurance system, e.g. GLP, then the dossier should contain such data, but relevant data not produced under this quality assurance system should not be disregarded solely on that basis, even when relevant GLP studies are available. The fact that non-compliance with GLP does not imply study irrelevance and compliance with GLP standards is not necessarily a guarantee of scientific reliability, is also stated and supported in the EFSA guidance on 'Submission of scientific peer-reviewed open literature for the approval of pesticide active substances'<sup>25</sup> under Regulation (EC) No 1107/2009<sup>91</sup> 'and the EFSA systematic review guidance it was built on'.<sup>24</sup>

Scientific studies underpinning a pre-market scientific assessment must be developed, paid for, and carried out for or by the applicant. Given that the applicant of the study has a direct commercial

<sup>89</sup> <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004R1935&from=en>

<sup>90</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/3295>

<sup>91</sup> Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC, OJ L 309, 24.11.2009, p. 1–50. Available online: <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R1107&from=EN>

interest in the outcome of the study, the potential for a conflict of interest justifies the imposition of a GLP or equivalent standard. The upholding of this standard is indeed critical. In contrast to the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) in the USA, which have their own inspection services, in the EU the verification of the upholding of quality standards of GLP studies is not the responsibility of the concerned EU Agencies. Instead, EFSA relies on the GLP inspection services in EU Member States and third countries to carry out this task. EU-level coordination of their activities resides with the European Commission's DG Internal Market, Industry, Entrepreneurship and SMEs (DG GROW).<sup>92</sup> On collaboration DG GROW, EFSA is requesting the Member States a number of regulatory studies to be audited.<sup>93</sup>

For peer-reviewed literature, there is variation in the expectations for the regulatory dossiers with regard to the full inclusion of such literature, both whether and how. With the exceptions of feed additives and food contact materials, peer-reviewed literature is expected to be included. For example, for health claims the key responsibility of the applicant to collect and submit all pertinent published information has been clearly established.<sup>94</sup>

As to the exact process on how to gather such information, as mentioned – the requirements are very explicit for pesticides. Such explicit criteria, requiring systematic literature review, now also exist in other,<sup>95</sup> but not yet in all areas. Undertaking a systematic literature review is a labour-intensive process which needs to be carried out separately for every end-point under consideration. For any safety assessment, the *a priori* number of endpoints then equals the number of numerous outcomes being considered in the safety studies. Much also depends on how voluminous the literature might be, which in turn depends on whether and how long a food, feed microorganisms or compound has been on the market and the research it has generated during that period. In summary, it would seem reasonable that, at least with a focus on the critical endpoint(s), the EFSA guidance for conduct of a systematic literature review be mandatory and the process to carry it out be therefore consistent,<sup>24</sup> i.e. aligned with what is already in place for pesticides. Evidently, there is no point in demanding a systematic literature review if there is nothing to review, as may be the case with novel compounds.

Studies published in peer-reviewed journals can equally be unsatisfactory.<sup>96</sup> Hence, one cannot assume that the peer-review system is able to systematically identify and prevent studies that are not repeatable, from being published in scientific journals. In addition, there may be a bias if original research is favoured over acceptance of studies that aim to replicate previous studies and when studies with (statistically) significant findings are favoured over those showing no statistically significant differences between study groups. Regardless of where a (key) study originates from, its repeatability remains a key feature that merits checking.

If the applicant already has the responsibility for submitting published information, is there any benefit for EFSA to duplicate this effort? In the above example, in order to evaluate a health claim application, the Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) should not be expected to undertake any additional literature reviews (nor to assemble or process such data) as this responsibility already explicitly resides with the applicant. Provided the literature review that was submitted remains up-to-date at the time the scientific assessment is conducted, the added value that EFSA can rather bring is to provide clarity on the guidance that needs to be adhered to by the applicant and to conduct proper verification to confirm the guidance has been adhered to. This allows EFSA, in collaboration with Member States scientific assessment organisations, to concentrate on its task to monitor the literature on other topics of public health importance such as contaminants and nutrition as well as the assessment of potential emerging risks.<sup>97</sup>

A separate aspect concerns completeness of the dossier. Obviously, it is legitimate to expect the applicant to submit all the studies that are of potential relevance with regard to the data requirements – regardless of whether the outcome is favourable or unfavourable, whether they were completed or aborted, and whether deemed relevant or not by the applicant. The applicant is indeed often expected to submit all the evidence generated by himself or on his behalf. However, the wording in the legislation for these requirements varies, being explicit in some areas (e.g. GMO and

<sup>92</sup> [https://ec.europa.eu/growth/sectors/chemicals/good-laboratory-practice\\_en](https://ec.europa.eu/growth/sectors/chemicals/good-laboratory-practice_en)

<sup>93</sup> [http://www.ssa.it/phocadownload/Presentazioni\\_2016/XXV\\_Congresso\\_GIAR/3\\_RADULESCU.pdf](http://www.ssa.it/phocadownload/Presentazioni_2016/XXV_Congresso_GIAR/3_RADULESCU.pdf)

<sup>94</sup> <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1924&qid=1487676646592&from=EN>

<sup>95</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/4969>, <https://www.efsa.europa.eu/en/supporting/pub/1207e>

<sup>96</sup> <https://www.economist.com/news/leaders/21588069-scientific-research-has-changed-world-now-it-needs-change-itself-how-science-goes-wrong>

<sup>97</sup> <http://www.efsa.europa.eu/sites/default/files/Mandate.pdf>, [http://www.efsa.europa.eu/sites/default/files/wg\\_RASFF.pdf](http://www.efsa.europa.eu/sites/default/files/wg_RASFF.pdf)

pesticides) while being far less so in other areas, leaving margin for the applicant to decide on what information is submitted to EFSA.

With regard to the completeness of the data provided, EFSA may therefore wish to make it very clear (via its guidance documents) to all applicants that it expects them to adhere to the same standards as expected for pesticides and GMOs. This could be done through a standardised form in which the applicant explicitly declares having adhered to this requirement. To make it legally binding, this declaration should be signed by or on behalf of the legal representative of the organisation seeking market authorisation.

Human trials of medicines in humans are registered in a database hosted by the European Commission.<sup>98</sup> In its guidance on health claims, the NDA Panel nevertheless recommended doing so also for these studies in humans.<sup>99</sup> Unlike for clinical studies conducted on medicines in humans, there is no legal basis available to set up a database of the studies for human nutrition studies, let alone for the experimental studies in laboratory animals. Hence, even when the legislation/guidance clearly obliges the applicant to submit everything available, there is no control mechanism to check if this has been done. In light of this, it should be beneficial to consider, in cooperation with other concerned agencies, the establishment of a register on the key laboratory animal studies carried out inside and outside the EU. This would allow verification that all key GLP studies initiated on a compound subject to regulatory approval in the EU were indeed submitted. It would include studies that were initiated but later aborted. It could be done through notification by GLP labs located inside and outside the EU into either an EU or an international electronic database, similar to the one managed by the Commission on human studies.

Currently there is no structured dialogue between an individual applicant and EFSA prior to initiation of the studies, except for possible clarifications provided in response to EFSA webform queries.<sup>100</sup> This is not a legal provision, but rather a governance choice. Also, unlike with EMA, the current EFSA scientific review process does not include pre-submission meetings,<sup>101</sup> nor for a phased reviews allowing submission and assessment of one part of the dossier for review before proceeding with the next group of studies. This lack of interaction may have been viewed as being beneficial to EFSA's independence. However, it comes at a cost. For example, when identifying data gaps, EFSA may provide the applicant the opportunity to submit additional information and this information needs to be submitted within a reasonable timeframe.<sup>102</sup> There is a risk that this then results in an *ad hoc* phased assessment, in lieu of a pre-planned process. This current limited dialogue between EFSA and the applicant prior to the stage of submission of a full dossier also means there is no notification of (let alone prior authorisation by) EFSA of the planned studies. It thus takes away another possibility to monitor upcoming submissions and which studies are planned or being conducted when and where, a tool which other regulatory bodies such as the FDA do have.<sup>103</sup>

Another element is the inclusion of the raw data and the format in which raw data are submitted to EFSA. Currently, this is not done in an electronic format that permits their upload in standard databases or programmes for statistical (re-)analysis. This means that, in practice, it is very labour-intensive and thus impractical to run verifications on these raw data. The submission of the raw data can be seen first and foremost as a business need of EFSA, one that enables it to fulfil its mandate and hence merits an initiative towards the electronic submission of the raw data, in its own right, as is the case with other regulatory agencies. This is independent of the merits and the legality of the disclosure of such raw data to a larger public (discussed in the next section). To achieve this objective:

- there must be an obligation to submit the full study, including the raw data. For example, Commission Regulation (EC) 234/2011<sup>104</sup>, states in Art (5) that: 'The application dossier shall include all the available data relevant for the purpose of the risk assessment (i.e. full published papers of all references cited or *full copies of the original unpublished studies*)' and
- the submission needs to be in a computer-readable format such that the data can be (re-)analysed without requiring their manual re-entry.

<sup>98</sup> <https://www.clinicaltrialsregister.eu/ctr-search/search>

<sup>99</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/4680>

<sup>100</sup> <http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2016.EN-1025/pdf>

<sup>101</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/10/WC500004069.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf)

<sup>102</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/3553>

<sup>103</sup> <https://www.gpo.gov/fdsys/pkg/FR-1998-12-14/pdf/98-33029.pdf>

<sup>104</sup> <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R0234&rid=1>

Fourth, there is the independence of the experts. According to Article 37 of the General Food Law Regulation<sup>4</sup>, the members of the Scientific Committee and the Scientific Panels are to 'act independently of any external influence'. The BSE crisis was accompanied by divergence of opinion between experts, where individuals that were giving advice might have been under undue influence of Member States' risk managers. EFSA's Scientific Panels were not to be composed of experts that are representatives of Member States' competent authorities. This is also the case for its Management Board whose members do not represent the Member States but are instead appointed in their personal capacity. Furthermore and crucially, within EFSA the scientific advice from the Scientific Panels is issued free from interference by the EFSA Management Board and the EFSA management.

As EFSA's Panel members are individuals who are employed outside EFSA and volunteer some of their time as Panel members, there is a potential risk that their main activities may lead to conflicts of interest. The procedures EFSA uses for assessing experts' independence have gone through a set of cycles, whereby a procedure is developed, implemented, assessed and, learning from this experience, the existing procedure is then further refined.<sup>105</sup> A new policy has been adopted in 2017.<sup>106</sup> It covers experts, EFSA staff, and other parties that may contribute to the scientific assessment process.

The essence of the independence evaluation that EFSA has put in place for its experts consists of an assessment as to whether the (direct or indirect) connections an expert may have with stakeholders are of such a nature that they may influence the credibility of the expert for the matter under consideration. Obviously, this will always remain a matter of judgement. Experts live in the real world whereby contacts with industry or NGOs cannot be excluded. The issue of independence of the experts should in any case not be used as a way to try and discredit a Scientific Opinion, when it does not fit one's ideological position. Bringing arguments relating to the substance of the scientific assessment cannot be substituted by attempts to publicly discredit the integrity of the expert (*argumentum ad hominem*<sup>107</sup>) or even attempting to cause physical harm<sup>108</sup> and attempting to disrupt the process by generating fear.

One risk of an overemphasis on the facet of independence of experts is that it may obscure the other key elements that impact the delivery of scientific advice that is independent, i.e. the hypothesis to be tested, the data requirements, the assessment methods and the transparent reporting of the outcome. The latter is discussed in the next section.

#### 4.4. Transparency and Openness

Transparency and openness are different concepts, even though they can be viewed as two sides of the same coin. Transparency shows how the assessment process is conducted and openness considers how the stakeholder can contribute to this very process. Currently, a transformation of EFSA into an Open Science organisation is being carried out through the Transparency and Engagement in Risk Assessment (TERA) Project. It aims at enhancing both the openness and transparency of EFSA's operations.<sup>109</sup> This has resulted in a number of measures one of which is the Knowledge Junction.<sup>110</sup> This is an open repository of curated data and tools that EFSA has used.

Being a key condition to be able to reproduce results, early on the Scientific Committee set out key elements of transparency to be adhered to in risk assessments conducted at EFSA.<sup>111,112</sup> It requires *inter alia*, that beyond variability (natural variation) also the uncertainty be reported. The latter is the topic of a new EFSA guidance document that has been the subject of a public consultation and is being trialled at the moment.<sup>113</sup> Uncertainty, also serves as a key basis for prioritising further research.

Both openness and transparency are to cover the various stages of the scientific assessment process, i.e. not only the publication of the outcome but also its initiation and conduct. Mechanisms to seek input at the time of the mandate formulation and during the risk assessment process proper are therefore being sought. For example, the drafting of a mandate may include a public consultation step prior to its finalisation. If this results in a broad consensus on the aims of the planned assessment, it

<sup>105</sup> <https://www.efsa.europa.eu/en/howwework/independentscience>

<sup>106</sup> [https://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/policy\\_independence.pdf](https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf)

<sup>107</sup> [https://en.wikipedia.org/wiki/Ad\\_hominem](https://en.wikipedia.org/wiki/Ad_hominem)

<sup>108</sup> <http://www.sciencemag.org/news/2016/06/italy-investigates-explosive-letter-sent-european-food-safety-agency>

<sup>109</sup> [http://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/openefsadiscussionpaper14.pdf](http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/openefsadiscussionpaper14.pdf)

<sup>110</sup> <https://zenodo.org/communities/efsa-kj?page=1&size=20>

<sup>111</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/353>

<sup>112</sup> <http://www.efsa.europa.eu/en/efsajournal/pub/1051>

<sup>113</sup> <http://www.efsa.europa.eu/sites/default/files/160321DraftGDUncertaintyInScientificAssessment.pdf>

may pre-empt debate that would otherwise take place at the end of the process, particularly where it concerns issues for which there is a high interest.<sup>114</sup>

Also, the possibility for stakeholders to contribute at various other stages of the process may help focus input on adding to the quality of the content. In this regard, human and environmental exposure data and health information may be key.

Much of the interest regarding transparency remains focused on publication of the outcome of the scientific assessment, which the remainder of this section considers further. Preamble 54 of the General Food Law Regulation<sup>4</sup> states that: 'The independence of the Authority and its role in informing the public mean that it should be able to communicate autonomously in the fields falling within its competence, its purpose being to provide objective, reliable and easily understandable information'. This represents a crucial aspect of EFSA's independence.

As to the responsibility for the content, the Panels own the Scientific Opinions whereas the EFSA Executive Director and staff largely own the communication about these opinions. There is an expectation that any communication by EFSA staff about a Panel's scientific opinion must be fully in line with that document and not add its own interpretations. The Panels and EFSA staff are thus both guardians of the independence of EFSA's scientific advice.

Article 40 of the General Food Law Regulation describes some of the expectations: 'The Authority shall ensure that the public and any interested parties are rapidly given objective, reliable, and easily accessible information, in particular with regard to the results of its work. In order to achieve these objectives, the Authority shall develop and disseminate information material for the general public'. The General Food Law Regulation thus has an expectation, both of transparent communication of the scientific output as well as the dissemination of its content to a larger public of non-scientists. The former are published in the EFSA Journal by Wiley, a professional scientific publisher; whereas the latter takes place via the EFSA website and through social media.<sup>115</sup>

Much of the interest regarding transparency remains focused on publication of the outcome of the scientific assessment. The extent to which this aspect of independence is addressed depends very much on the when, what, and how of the publication process. First, the speed with which results are released is crucial and therefore remains a subject of attention.<sup>116</sup> There is also the issue of the level of detail that is communicated and the degree of access that is given to such details. What information is not to be published? Article 38 of Regulation 178/2002<sup>4</sup> on transparency states *inter alia*, that the Authority shall make available the information on which its opinions are based, but without prejudice to Articles 39 and 41. Article 39 states that the Authority shall not divulge to third parties information that it receives and for which confidential treatment has been requested and is justified. Article 41 concerns requests for access to documents for which the Management Board is responsible to, adopt practical arrangements for implementing Regulation (EC) No 1049/2001 on public access to documents which becomes applicable to EFSA by way of this provision<sup>117</sup> taking into account the general principles governing the right of access to the Union institutions' documents. The interpretation of the latter is subject to rulings of the Court of Justice of the European Union (CJEU).<sup>118</sup> The procedure of the EFSA Board states<sup>119</sup> in Article 3 that EFSA shall refuse access to certain documents in application of one of the exceptions mentioned in Article 4 of Regulation (EC) No 1049/2001 as interpreted by the CJEU, and in particular where the disclosure would undermine *inter alia*:

- Article 4(1)(b): the privacy and integrity of the individual, in particular in accordance with Community legislation regarding the protection of personal data;
- Article 4(2): commercial interests of a natural or legal person, including intellectual property, court proceedings and legal advice and the purpose of inspections, investigations and audits, unless there is an overriding public interest in disclosure; and
- Article 4(3): the disclosure of a document would seriously undermine the EFSA's decision-making process.

<sup>114</sup> <https://www.efsa.europa.eu/en/consultations/call/161024a>, <https://www.efsa.europa.eu/en/consultations/call/170630>

<sup>115</sup> [https://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/ar2016.pdf](https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/ar2016.pdf)

<sup>116</sup> <http://www.efsa.europa.eu/sites/default/files/mb161005-i1.pdf>

<sup>117</sup> Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents, OJ L 145, 31.5.2001, p. 43–48.

<sup>118</sup> [https://www.ashurst.com/publication-item.aspx?id\\_Content=12296](https://www.ashurst.com/publication-item.aspx?id_Content=12296)

<sup>119</sup> <http://www.efsa.europa.eu/sites/default/files/assets/docsaccess.pdf>

Other critical aspects here are timing of the release of documents and the level of detail that is published. In regard to the latter, there are two separate levels: the dossier with its studies and the raw data of each of these studies.

Currently, EFSA does not generally publish the dossier studies received from applicants. Certain parts of the dossier are published when defined as such in the legislation or released to third parties upon request. In an access to documents request relating to an application dossier, the information is only made available to the requestor and confidential and commercially sensitive information, as identified by the applicant, following consultation, is removed (blackened) beforehand by EFSA if EFSA considers the disclosure of such information will certainly undermine the commercial interest of the applicant. Such a case-by-case approach creates an enormous amount of work – even to the point of blocking the normal functioning of the organisation, while hardly serving the goal of transparency.

In addition, release of raw data may be requested by stakeholders. The EMA is already doing this where this is dictated by specific legislation<sup>120</sup> (and even beyond).

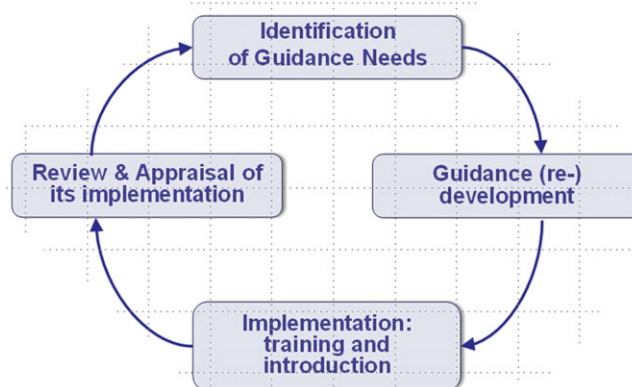
Upon completion of a scientific assessment, EFSA could similarly strive to pro-actively and systematically disclose the scientific studies underpinning the opinion. This could be done to the same level of detail as in a peer-reviewed scientific journal, thereby ensuring that the study is reproducible.

In summary, a key strength of EFSA is that it systematically and publicly communicates the outcome of its assessments<sup>121</sup> and it does so shortly after their completion. For this, it is necessary that EFSA determines, publishes and implements its own operational criteria for what it accepts to be confidential information and commercially sensitive information, consistent with what qualifies as confidential and commercially sensitive information for other EU Agencies and the Commission.

#### 4.5. Relevance

Both guidance documents and individual scientific opinions have a finite 'shelf life'. The former is discussed first and individual opinions next.

The very process of developing and implementing a guidance document is evolving in a number of ways. In general, assessment methods need to be managed following the principles of a quality circle (Figure 4).



**Figure 4:** Cycle of continuous guidance development

During the guidance development phase, EFSA can, in principle, make use of its body of over 4,000 assessments to test the potential impact of a new guidance through case studies selected from this body of existing opinions.<sup>122</sup> Next, prior to adoption and publication, finalisation may require a piloting phase to assess how it can best be incorporated in the work processes.

For proper implementation, there is also the necessity to organise training so as to make sure there is sufficient expertise to implement it. This is one reason why there is often a need for a transition period before guidance becomes effective. Independently, a formal decision is always required as to when a guidance becomes binding for new assessments and from when on it will lead to re-assessment of previous opinions, e.g. for compounds that are currently already on the market, i.e.

<sup>120</sup> <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN>

<sup>121</sup> <https://www.efsa.europa.eu/efsajournal/scdocdefinitions>

<sup>122</sup> <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.e15011/epdf>

either immediately or, for compounds subject to market authorisation, upon their re-assessment every 5 or 10 years. This is particularly relevant for food chain contaminants for which there generally is no preplanned review cycle. Also, transparency and dialogue throughout this process with institutional and other concerned stakeholders is obviously highly desirable for smooth implementation.

Equally, individual scientific opinions have a finite 'shelf life', which is determined by the relevance of the components that constitute the opinion such as the question posed, the evidence and the methods used to address it, and the expertise available. This is further addressed in the section Evolving Expectations and Innovations.

#### 4.6. Evolving Expectations and Innovation

As discussed, individual scientific assessments may be subject to single-loop learning, i.e. be re-assessed within the current regulatory framework. For example, while a market license is usually valid for 5 or 10 years, there is a need to prepare for the next evaluation and collect evidence which may affect the current variability and uncertainty estimates and possibly reveal biases in the original opinion.

The credibility of the scientific advice given by EFSA and trust in the EU food system, also depends on double-loop learning (Dunlop, 2009). First and foremost, changes will be determined by the needs of the risk managers. These may evolve due to very broad developments, such the impact of global warming on food safety or more topical issues such as the potential health impact of food fraud.

As discussed, scientific opinions also need to keep up with scientific and technological developments, where they can be addressed through scientific methods. In contrast to the above examples, the discussion below focuses on the scientific assessment process as such. It is difficult, at best, to anticipate what key trends may emerge over time and will require most resources, a few potential trends are presented for reflection below.

##### 4.6.1. Nature of the hypothesis tested

The current regulatory framework for pre-market authorisations is one based on the assessment of the safety of one chemical or a microorganism in isolation and based on an applicant's dossier, which includes the results of a set of mandatory studies. Undoubtedly this is and will remain the cornerstone of any such pre-market evaluation. It assumes:

- That there is consensus on when an observed effect is to be considered an adverse health effect. EFSA has recently explored this issue further in a scientific opinion on biological relevance.<sup>22</sup>
- That safety, e.g. in humans is to be assessed against a yardstick set by the risk manager and to be taken into account by the risk assessor.

This can imply either a zero risk concept – which is a theoretical concept but not a practical yardstick or, alternatively, a 'negligible risk' concept, which necessitates explicit definition. What level of risk is determined to be no different from zero risk for humans, and is thus acceptable to society, is however rarely explicitly defined, let alone harmonised.<sup>18</sup> For example, can an annual increase in lifetime cancer rate of 1 out of 1,000,000 million people be considered negligible, as has been used by the EPA<sup>123</sup>? Against a backdrop of an annual age-standardised incidence rate of some 300 cases per 100,000 inhabitants in many EU member States, or an annual rate of 3,000 per one million inhabitants, can an increase in the lifetime rate between zero and one additional case per million persons also be considered 'negligible' in the EU?

Building on the risk assessment of single compounds or organisms, one can ask additional questions. One of these is risk-risk assessment. For example, will banning one product lead to its replacement by another product that carries a lower risk or not? What is the impact on ill-health of a food chain contaminant as compared to other known risk factors for ill health?

Also, unlike in medicines, in the scientific evaluation of foods there is generally no explicit assessment of the claimed health or other benefits versus the risks. The risks and benefits of

<sup>123</sup> Office of Pesticides Programs. Environmental Fact Sheet: the Delaney Paradox and Negligible Risk. 1990. <https://nepis.epa.gov/Exe/ZyNET.exe/9100CFQV.txt?ZyActionD=ZyDocument&Client=EPA&Index=1986%20Thru%201990&Docs=&Query=&Time=&EndTime=&SearchMethod=1&TocRestrict=n&Toc=&TocEntry=&QField=&QFieldYear=&QFieldMonth=&QFieldDay=&UseQField=&IntQFieldOp=0&ExtQFieldOp=0&XmlQuery=&File=D%3A%5CZYFILES%5CINDEX%20DATA%5C86THRU90%5CTXT%5C0000020%5C9100CFQV.txt&User=ANONYMOUS&Password=anonymous&SortMethod=h%7C-&MaximumDocuments=1&FuzzyDegree=0&ImageQuality=r75g8/r75g8/x150y150g16/i425&Display=hpfr&DefSeekPage=x&SearchBack=ZyActionL&Back=ZyActionS&BackDesc=Results%20page&MaximumPages=1&ZyEntry=4>

medicines concern the health of one and the same patient. The equivalent in food may concern the weighing of the benefits of fish as a source of omega-3 fatty acids against the accumulation of contaminants, such as heavy metals.<sup>124</sup> Even if legislation does not explicitly require beneficial aspects to be assessed, there may be an implicit expectation that EFSA demands and does take evidence on effectiveness into consideration. For example, there would be little point in assessing the safety of a food colourant or a botanical preparation, if one does not have the evidence at which concentration or dose it will need to be used to exert its desired effect. Conversely, it may be questionable to assess the benefit of a health claim<sup>100</sup> if no assurance can be given that this food is safe at the proposed dosage regime?

In the food chain, the benefits and the risks may be much more diffuse and even concern very different aspects. For example, the benefits of pesticides concern agricultural production, and thus, ultimately the price and availability of food, while the risks may most directly concern the environment, the consumers, and the safety of workers. To compare these aspects both within and outside the food chain, the risk manager may thus wish to consider socio-economic aspects to formally, consistently and transparently assess and weigh these aspects. In the area of medicines, for example a cost-effectiveness evaluation might underpin a decision as to the level of reimbursement the insured patient will receive, as compared to other medicines with similar claims. Also, ECHA conducts economic assessments.<sup>125</sup> In contrast, whereas there clearly are socioeconomic if not cultural debates regarding, for example GMOs or pesticides, in food the risk management decision-process does not typically include an examination of such socioeconomic aspects.

These issues also merit reflection when it comes to discerning lack of impact on ecosystems. It raises, for example societal questions of what we are we trying to protect, and, next, how to assess this, for example when the environment may have already been modified by human activity to begin with.

However relevant it is in its own right, ultimately the natural sciences perspective can be viewed as merely one – albeit an important – input into the societal debate of whether to allow a (type of) product on the market. There are additional perspectives that risk managers may face when prioritising the allocation of scarce resources. For example, how to weigh the impact of poverty on ill-health:

- what proportion of it can be explained by classic natural science risk factors, e.g. smoking, obesity;
- what proportion cannot be explained by known risk factors; and
- what are the likely cause-effect relationships.

As such, a question like this also falls outside EFSA's remit. However, a partnership of scientific advice agencies could make an important contribution to addressing such a question.

#### 4.6.2. Scope

There may also be a broadening of the scope of the mandates. For example, environmental protection aspects are already considered in the assessment of the potential direct impact of GMOs, pesticides, and feed additives on the environment, but this is not the case for the potential environmental impact of food waste and the potential impact of food contact materials.

Another dimension of scientific assessment that is and may continue to evolve concerns the level of complexity of the material being studied.<sup>126</sup> For example, does it concern a single chemical (with various impurities); a fixed mixture of well-specified chemicals, e.g. a pesticide which is a formulated product containing one or several active ingredients along with a number of co-formulants; a variable mixture of chemicals such as residues present in foods; a unicellular or multicellular organism – genetically uniform or not and genetically modified or not; a mixture of different organisms; a single food (novel or not); or a diet. With increasing levels of aggregation, the nature of the questions posed and the answers that can be sought may differ.

#### 4.6.3. Scientific assessment framework

A risk assessment has to identify both, which are the critical (most sensitive) endpoints and what levels of exposure are safe to humans. How does one design studies to address both issues? This may currently be more challenging than is, e.g. the case when aiming to demonstrate efficacy of a medicine.

<sup>124</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/1673>

<sup>125</sup> <https://echa.europa.eu/support/socio-economic-analysis-in-reach>

<sup>126</sup> [http://www.rivm.nl/en/Topics/F/Food\\_safety/EFSA\\_RIVM\\_Symposium/Report\\_EFSA\\_RIVM\\_Symposium](http://www.rivm.nl/en/Topics/F/Food_safety/EFSA_RIVM_Symposium/Report_EFSA_RIVM_Symposium)



Typically in medicines the efficacy claim is derived from evidence which gradually accumulates throughout the development of the medicine.<sup>127</sup> It culminates in the testing of a very specific hypothesis in one or more studies in humans (or in the animal target species) representative of the groups in which the medicine will eventually be used. These studies have to be designed to have adequate power to be able to demonstrate for a well-defined endpoint that a statistically significant difference (or equivalence) between the group treated with, e.g. a new medicine and the control group which remained untreated (or was treated with a relevant comparator). This means one is able to reject the null hypothesis of no treatment effect, if such a difference truly exists. In testing the safety of a food the null hypothesis to be rejected by the applicant is the opposite, i.e. that there is an effect.

Unlike in medicines, in food safety assessment, there is expectation there is no pre-market safety study in humans to confirm that the proposed dose is safe, as this is considered to be unethical.<sup>128</sup> The *in vivo* safety testing is instead carried out in other animal species. As mentioned, safety (or uncertainty) factors are introduced to extrapolate results from the most sensitive animal species to humans. For example, for food additives, these factors intend to account for the uncertainty and are applied to extrapolate from the NOAEL in the test species to account for 'the inherent uncertainties in extrapolating toxicity data from experimental animal studies to potential effects in humans as well as variation within the human species' (WHO, 2009). It is possible that they may represent at times excessive or insufficient caution.

The extrapolation also implies that the lab animal model is predictive of what happens in humans. However, the lab animal species might not always display the disease that is of most concern (i.e. occurs at the lowest dose) to humans. This has for example been the subject of an EFSA Scientific Opinion on Parkinson's disease.<sup>129</sup> It has also been noted in the development of human medicines that the animal safety studies too often fail to reveal safety issues which then only appear late into the drug development process (Sistare et al., 2016). Not surprisingly, this is an area of active research by medicines manufacturers, also outside the EU e.g. in cardiac safety assessment.<sup>130</sup>

For safety testing in food traditionally, there has been no prior decision on which effect, among the traditional set of endpoints that is being tested, the hypothesis is to specifically focus on. In other words, there is no *a priori* determination of what is likely to be the most relevant endpoint and study design such that it has adequate power to detect a biologically relevant increase in the occurrence of the incidence rate for such an event. This matters greatly as caution is required in the interpretation of study results, such that the absence of evidence is not confused with evidence of absence.<sup>20</sup> This is to say, the incidence of an adverse event may not be shown to be statistically significantly different between treated and controls because the power to do so is inadequate rather than because a biologically meaningful effect does not exist.

Lack of a pre-established hypothesis also affects other aspects of the study design such as the proper study period and study duration so as to make sure that the proper age group is exposed (e.g. embryos) and the effects whose expression is delayed until later in the same or in the next generation are taken into consideration. What is also not yet always explicitly dealt with is how to make best use of prior evidence on the same or related chemicals,<sup>30</sup> even though it is common evaluation practice to include prior knowledge.

The field of toxicology testing is in the middle of a major evolution whereby evidence on safety gradually accumulates through a sequence of steps.<sup>131</sup> A hypothesis-driven approach is to be based on the prior elucidation of the mode of action (MoA) and the possible identification of the adverse outcome pathway (AOP) through various screening systems that have and are being developed.<sup>132</sup> This does not necessarily eliminate the need for confirmatory studies in laboratory animals but rather it increases their relevance if they are designed such that they are powered adequately to detect these effects that are hypothesised to be most relevant, based on the evidence that has emerged from preceding *in silico* and *in vitro* studies. This may include the decision on which lab animal strain is most suitable. These developments represent a major shift whose development and implementation will

<sup>127</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/special\\_topics/general/general\\_content\\_000489.jsp&mid=WC0b01ac058060676f](http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000489.jsp&mid=WC0b01ac058060676f)

<sup>128</sup> It is noted that for novel foods existing studies in humans can be used

<sup>129</sup> <http://www.efsa.europa.eu/en/supporting/pub/955e>

<sup>130</sup> <http://www.sciencedirect.com/science/article/pii/S1056871916301095>, <http://www.tandfonline.com/doi/full/10.1517/14740338.2014.915311?scroll=top&needAccess=true&>

<sup>131</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/3638>

<sup>132</sup> <http://publications.jrc.ec.europa.eu/repository/bitstream/JRC103522/eurl%20ecvam%20status%20report%20oct%202016%20online.pdf>

continue to require considerable resources from EFSA, as well as from other concerned agencies. It also requires adaption of the data requirements and the assessment methods used.

The assessment methods may also be expected to evolve with the advent of new technologies such as bioinformatics.<sup>133</sup> Alternatively, technological developments such as nanotechnology require re-assessment of existing tests and assessment methods for use on nanomaterials.<sup>51,134</sup>

To support all these developments requires partnerships. Already today, not all information used in a scientific assessment will have either been generated by (or on behalf of) the applicant or be accessible through peer-reviewed literature. For example, geographic information systems are key to be able to carry out environmental risk assessments or model the spread of plant diseases. This requires consultation of publicly accessible databases hosted by public organisations that are thus assumed to be kept up-to-date and be accessible, as is the case, e.g. for the European Bioinformatics Institute (EMBL-EBI).<sup>135</sup>

The concerted multi-annual effort towards development and validation of non-animal based screening methods, as well as their efficient implementation, to meet the needs of a variety of EU scientific advisory bodies remains in this regard a key priority.<sup>136</sup> This requires sustained structural EU funding for centres of excellence to carry out tasks which are highly specialised and would merit to be maintained by one or a small cluster of institutions. It potentially includes projects addressing emerging needs which may not currently be covered by the EU Reference Laboratories system.<sup>137</sup> Also, the concept of 'laboratory' needs to be extended to include 'software labs' to ensure that data modelling and bioinformatics capabilities are kept up-to-date.

EFSA's budget does not permit to fund research and development to fill information gaps be they on specific compounds or on research underpinning the development and implementation of new assessment methods. Hence, data gaps are identified and highlighted to organisations that are responsible to fund such research.<sup>138</sup> EFSA relies on this publicly funded research to continually inform the knowledge base which the scientific advice agencies use to keep their assessment methods and their scientific advice up to date.

#### 4.6.4. Verification

Another dimension concerns verification of the prediction that the exposure levels and the non-deleterious-effects at a level that is considered safe, proves to be correct. As much as may be known about a compound or organism prior to its market authorisation, its actual introduction in the food chain offers the opportunity to collect further information, for example, upon human exposure, which – in food safety pre-market assessment – is not available beforehand. It can thus be argued that a market authorisation represents the start of a new phase in the assessment process in which all who consume food constituents residues, contaminants or are otherwise exposed become part of a post-authorisation monitoring experiment (equivalent to Phase 4 in medicines).

Already, considerable resources are being invested in some areas to monitor potential exposure through food to verifying that exposure has been taking place at levels that were considered safe. For example, as described, once a pesticide is approved, compliance monitoring for residues in food is initiated by EU Member States and these data are assessed by EFSA every year. At EU level, there is no equivalent system to monitor human exposure through routes other than food for those at highest risk, such as may be the case for workers and bystanders.<sup>139</sup> For this verification to happen routinely, i.e. beyond dedicated research projects,<sup>140</sup> it may be necessary that the market authorisation of a chemical be made dependent on providing with the dossier a validated biomarker to be able to assess exposure through various routes.

Provided exposure is identified or likely to take place, it is also suggested to monitor the occurrence of deleterious effects following such exposure, in groups that are potentially at high risk of exceeding the HBGV. This requires a pro-active approach, similar to what is the case, e.g. in aviation safety where any failure is investigated in-depth as it is considered a major learning opportunity. While the classical predictive pre-market safety assessment approach tends to focus on identifying conditions under which no deleterious effect is anticipated, the focus of (post-authorisation) epidemiology studies is on the

<sup>133</sup> <https://www.ncbi.nlm.nih.gov/pubmed/27208439>

<sup>134</sup> <https://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/WhatWeDo/ucm334155.htm>

<sup>135</sup> <http://www.ebi.ac.uk/services>

<sup>136</sup> <https://eurl-ecvam.jrc.ec.europa.eu/> <https://www.epa.gov/chemical-research/toxicity-forecasting>

<sup>137</sup> [https://ec.europa.eu/food/safety/official\\_controls/legislation/ref-labs\\_en](https://ec.europa.eu/food/safety/official_controls/legislation/ref-labs_en)

<sup>138</sup> <https://www.efsa.europa.eu/en/supporting/pub/1166e>

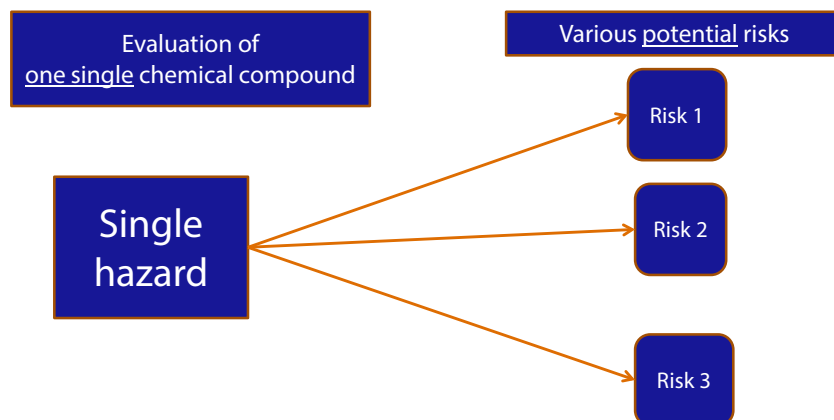
<sup>139</sup> <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data>

<sup>140</sup> <https://www.hbm4eu.eu/>

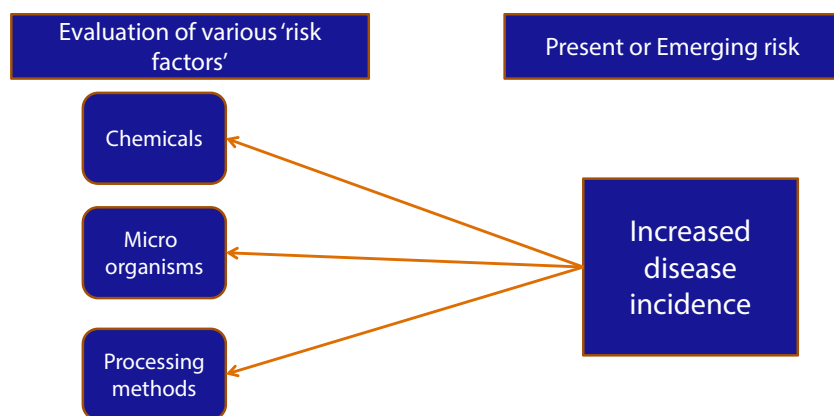
identification of risk factors shown to increase the incidence of human, animal, plant or environmental ill-health; thereby addressing the question: what makes people ill (Figure 6). As mentioned, use of epidemiological evidence is customary in areas within EFSA's remit when the lag time between exposure and disease occurrence is short, as is often the case with infections by microorganisms.<sup>141</sup> For chemicals, this information often needs to come from long term epidemiological studies designed to uncover effects of chemicals and other risk factors within and outside the food chain.<sup>142</sup> This not only requires the use of biomarkers of exposure but probably also those indicating deleterious effects.

Similar monitoring systems could be put in place for potential environmental effects, for example with regard to cultivation of GMOs, pesticide treatment, along with other contaminants. Ad hoc data collections have been envisioned to address specific issues, such as multiple stressors in bees.<sup>143</sup>

Conceptually, the objective of this scientific inquiry may be considered to be different between these two approaches (Figures 5 and 6). Rather than predicting how to avoid risk, it rather aims to uncover the key risk factors that effectively make people ill. These complementary approaches may improve the validity, the precision or the relevance of the available evidence.



**Figure 5:** Classic predictive approach to risk assessment: avoid illness



**Figure 6:** Epidemiological approach: what makes people ill?

The risk factors studied can be a single stressor or a combination thereof. Co-occurrence of chemicals is then not limited to simultaneous presence in the same formulation, but rather it means that exposure through food (e.g. multiple pesticide residues) or other routes has taken place, most likely in the same time period. For example, co-occurrence of different pesticide residues may be the result of different pesticides being utilised on the same crop. In addition, this is not limited to one type of hazard. For example, bee health might be affected by a combination of different stressors such as

<sup>141</sup> <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.s0507/full>

<sup>142</sup> <https://www.efsa.europa.eu/en/consultations/call/170612>

<sup>143</sup> <http://www.efsa.europa.eu/sites/default/files/assets/scmustb.pdf>

parasitic diseases, climatic conditions and exposure to chemicals that in combination could have a different effect than would be expected from each stressor separately.

Who has the responsibility to monitor for the emergence of new evidence in the period the product is on the market? The answer to this question probably depends on the nature of the information, how it is currently already being collected and what is the most efficient way to proceed.

It would seem that monitoring for and the assessment of the emergence of new scientific studies resides in first instance with the applicant. If this task is to be carried out in the public sector, as is *de facto* the case for contaminants, can responsibility for this activity then be shared between EFSA and its partner organisations in the Member States? Currently, residue occurrence measurements and exposure assessments thereof are typically carried out and reported by public institutions. The ill-health data potentially concern the collection of acute and chronic adverse effects. Acute (vigilance) data are typically centralised by public bodies in the Member States, such as Poison Centres; whereas epidemiology studies are often done by academic institutions. On the other hand, in the area of GMOs, the legislator has given the responsibility for the post-market environmental monitoring to the applicant who has to submit an annual report to the European Commission which it requests EFSA to assess.<sup>144</sup> The Commission may also launch ad hoc monitoring studies, as is the case for lycopene and which also needs to be prepared and submitted by the applicant.<sup>145</sup>

The creation of a plethora of parallel monitoring systems and epidemiology studies by a range of EU Agencies, let alone individual applicants, would not be an efficient use of resources. It could rather be a missed opportunity. For example, since there is already an extensive pharmacovigilance system in place for the monitoring of acute adverse effects in medicines, this raises the question to what extent this needs to be duplicated for other hazards that humans could be exposed to. As mentioned previously, there are already other such collaborations taking place between EU Agencies in areas such as zoonoses and antimicrobial resistance monitoring.

There is also merit in reflecting which agency is best placed to take the lead in any monitoring that serves different sectors. For example, can the European Agency for Health and Safety at Work (OSHA) be the hub for worker safety data collection systems which cover the needs of EFSA (and other EU Agencies and Commission DGs). Similarly, it would seem that the European Environmental Agency (EEA) can be the natural hub for environmental data collection needs that fall in the remit of agencies such as EFSA (see insert).

- **a conditional temporary license, based on the information available at that time &**
- **subject to** post-market monitoring of
  - ✓ Consumer safety
    - 'nutrivigilance' (part of pharmacovigilance – EMA)
    - exposure monitoring in food (EFSA)
    - biomonitoring
  - ✓ Occupational safety
    - exposure monitoring
    - worker safety (OSHA)
    - epidemiology
  - ✓ Environmental protection (EEA)

The fact that the responsibility for the monitoring of safety often reverts to public bodies once a compound is on the market, does not of course relieve the applicant of any responsibility to actively contribute data, as is for example already the case with medicines through the pharmacovigilance system.<sup>146</sup>

The consistent, regular monitoring for new information on exposure and possibly ill health through a transparent system is one that contributes to the credibility and consumer trust in the EU food safety system. However, to be credible, this requires a legislative framework and proper funding. This in turn raises the question where this funding has to come from. If it is to be (co-)funded by industry, then a system of contribution to the funding of studies might be envisaged.

<sup>144</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/4805>

<sup>145</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/3955>

<sup>146</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000199.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000199.jsp)

## 4.7. Fitness-for-purpose and Efficiency

### 4.7.1. Fitness-for-purpose

As stated in Article 29 of the General Food Law Regulation, a scientific opinion addressing the issue at hand needs to be delivered within the requested or the otherwise agreed-upon timeframe.<sup>4</sup> Also, as discussed previously,<sup>147</sup> for EFSA to be relevant it is essential that it is responsive and uses its resources judiciously. Scientific excellence is therefore not a goal in itself but rather the scientific advice has to address the needs for information of those who will use the opinion for decision-making i.e. be 'fit for purpose' and thus be refined to the extent necessary to meet this aim. In describing the intended approach for conducting an assessment, it is therefore necessary to make sure that the agreed mandate is addressed and does not go into one of a number of other areas that may be scientifically very interesting but are not part of the particular mandate. At the level of individual opinions, a reasonable balance thus needs to be struck between scientific excellence (minimising bias and uncertainty) and on the other hand the necessity to be responsive and deliver an assessment that is fit-for-purpose.

### 4.7.2. Efficiency

It is essential that the time spent by Panel experts be used in the most efficient way. This raises the question about the roles of scientific staff, from EFSA and partner organisations in Member States, can play to support the process.

Scientific staff employed by EFSA ensure smooth functioning of the system and do much of the preparatory work, such as putting together the 'materials and methods'. This allows the discussions of the Panel experts to focus on the key, non-routine scientific aspects that emerge in the assessment process. This support is organised through different functions. There are EFSA units (or teams thereof) that directly provide scientific support dedicated to individual Scientific Panels and their working groups, and some units that provide 'cross-cutting' support to several Panels. The latter includes for example centralised handling of dossiers and the specialised support of specific aspects of the assessment such as exposure assessment.<sup>148</sup> Such cross-cutting groups can consist of physical units or be virtual units operating in a matrix organisational structure; which approach is most appropriate may vary.

To reflect further on who takes on which responsibilities it is useful to consider other possible options. One of them, already discussed, concerns the organisation of the scientific assessment of individual pesticides which operates under a different model than the other Panels. On the one hand the PPR Panel is responsible for scientific opinions concerning guidance on the science and assessment methodology. On the other hand, the evaluation of individual active compounds operates along the lines of a model based on scientific assessment by Member State organisations. Provided there is a sustained and predictable workload, an advantage of such a system is that it allows building and maintaining institutional capacity in the concerned Member State organisations. An important difference with most of EMA's processes is that EFSA's scientific staff have the responsibility to finalise the scientific opinion (EFSA Conclusion) on a pesticide active compound. The current pesticide system is thus flexible in that it allows EFSA to build and draw on expertise for the scientific assessment of individual dossiers from national food safety assessment organisations as well as EFSA's scientific staff, while also being able to rely on expertise from a wide range of research institutions for membership of the PPR Panel and its working groups.

Can and should this model be copied to all other areas within EFSA's remit? Trying to do so systematically may create inefficiencies, when compared to the current 'lean' (and inexpensive) model. The model may be worth exploring further though for areas that also would have a predictable and sustained high workload, where there is a necessity to make sure adequate capacity is built and maintained, and provided there is proper and sustained financial compensation to support this process.

Another aspect of efficiency concerns the fact that EFSA is gradually building an ever-more elaborate system to conduct its scientific evaluations. This has resource implications for the time spent on the conduct of a scientific assessment. Irrespective of the fitness-for-purpose aspect, it would seem that newly developed assessment approaches need to be optimally integrated so as not to reduce efficiency. This is a challenge.

<sup>147</sup> [https://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/sciencestrategy12.pdf](https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/sciencestrategy12.pdf)

<sup>148</sup> <https://www.efsa.europa.eu/sites/default/files/assets/orgchart.pdf>

Furthermore, the human resources available within EFSA have actually been decreasing. Hence, efficiency gains are necessary even if no new facets would be added to the risk assessment process. In this, the MATRIX project that EFSA has embarked on is a key multi-annual transformational initiative. It represents a big push towards optimisation of the flow of data and work processes during a regulatory dossier review, through the development of an electronic platform.<sup>149</sup> This will affect all aspects of and steps in these scientific assessment processes:

- starting with the electronic submission of the dossier whose structure is to be harmonised through standardised submission manuals;
- the electronic management of the workflows, including the verification of its completeness (structured data submission and curation of meta-data), the assessment of individual studies, the inclusion of additional information from the literature, the consultation of the assessments conducted previously on related compounds; and
- the communication between EFSA and the applicants, as well as with other stakeholders, including on the administrative aspects and the standardisation of the publication of non-confidential parts of the dossier.

It may gradually develop into a backbone through which efficiency gains can be achieved. If properly structured and harmonised across regulatory areas, the evaluation of the applicant's submission can be the subject of data analytics to support the process including:

- an initial computer-aided verification of completeness and probing;
- support the risk assessment proper, based on and compliant with EFSA guidance that cover all aspects of the scientific assessment.

This also allows for digital collaboration on standardised parts of dossiers and helps experts to focus the evaluation on the key elements in a dossier that merit particular attention. Obviously, the MATRIX project represents a substantial multi-annual investment.

Building on this, there can be little doubt that public organisations such as EFSA will also wish to develop capabilities and take advantage of artificial intelligence approaches, especially given the wealth of 'big data' it has accumulated<sup>150</sup> both pre-market and post-market. Finding pattern also represents a huge opportunity in food safety. Detection algorithms are very powerful and may outperform humans. It is a topic that EFSA has recently begun to explore.<sup>151</sup> This being said, model transparency is an issue with machine learning approaches that will need to be addressed.

#### 4.8. Sustainability

The EU Agencies that give scientific advice put the main responsibility for this advice with a variety of potential actors<sup>152</sup>: their own staff, external experts that represent the public Member State organisation they are employed by or – as is the case with EFSA – experts who, while also employed by scientific institutions in EU Member States, do not represent them, i.e. are considered independent *vis-a-vis* their employer's view on the matter at hand.

All approaches have their strengths and weaknesses. The rationale for the choice that was made in the case of EFSA for putting the ultimate responsibility with external experts in Scientific Panels that do not represent their organisation is probably historic. During the BSE crisis, which led to the establishment of EFSA and scientific assessment organisations in Member States, there was considerable divergence in scientific opinion between Member State experts. Furthermore, the EFSA Scientific Panel model very much represents a continuation of the model that was already in place at the European Commission prior to the creation of EFSA. In this model, the key responsibility for content resided with external experts and staff supporting the Panels were considered to have a 'secretariat' role.

In light of over a decade of operation of EFSA, a few reflections can be made. First and foremost is the realisation that the EFSA system, based on volunteer experts, has worked remarkably well. In the various areas within EFSA's remit it has proven to be both effective, delivering some 500 scientific opinions a year, and also to be flexible enough to be able to deal with sizable fluctuations, i.e. peaks, in workload. Credit for this goes in no small measure to the numerous scientists in Europe who have

<sup>149</sup> <https://www.efsa.europa.eu/sites/default/files/shpESubmissionToR.pdf>

<sup>150</sup> <https://www.economist.com/news/science-and-technology/21621704-new-type-software-helps-researchers-decide-what-they-should-be-looking>

<sup>151</sup> <http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2017.EN-1254/epdf>

<sup>152</sup> [https://www.efsa.europa.eu/sites/default/files/corporate\\_publications/euansa150809en.pdf](https://www.efsa.europa.eu/sites/default/files/corporate_publications/euansa150809en.pdf)

been willing to devote time to serve the common good. Credit also goes to their employers who have supported them to take on these tasks. EFSA has regularly sought feedback from its Panel members and used these comments as a basis to systematically improve the support to its experts. Time and again, the expert surveys have indicated that EFSA's mission is indeed a key motivator and that the experts are highly committed to their role at EFSA because of the impact they can have to protect the health of European citizens and their environment. Also, they indicate that the experience they gain helps them grow professionally, including through networking opportunities.<sup>153</sup> However, this does not mean that this system cannot be improved. What are some of the challenges?

The continued availability of qualified experts for these Scientific Panels is obviously key to enable EFSA to continue to function. Expert surveys have highlighted aspects that may hamper their continued availability. These include the time available to devote to EFSA, time needed for travel, and employer support. To serve as a Panel member does indeed represent an important time commitment on the part of the expert and thus a key aspect is the expert's availability to effectively contribute to the Panel's work. As Panel members generally already have a full-time employment, time devoted during office hours to EFSA obviously cannot be spent on other tasks. Hence, while the expert's employer is not involved in the selection and nomination of an expert, there is at the very least a tacit agreement by the expert's employer to allow him/her to devote some of that time to EFSA Panel membership, as part of his or her position at the home institution. Hence, a survey was recently conducted to seek feedback from experts' employers.<sup>154</sup> It showed their commitment to support EFSA, but conditional on proper financial compensation being given commensurate with the expected effort for the important time commitment, during working hours, Panel membership entails. The above survey does provide cost estimates.

A related key issue is how to ensure that the EU maintains adequate future expert capacity for scientific assessments in the various areas within EFSA's remit. This requires on the one hand that training is offered and on the other that there are adequate opportunities to gain experience. While the selection of Panel members is based on their expertise, it should be noted that in the EU only few programmes offer M.Sc. training in scientific assessment.<sup>155</sup> With the growing worldwide needs for scientific assessment, training initiatives at the MSc level or continuing education level should not only be encouraged but also actively supported, similar to what has been initiated in the area of medicines.<sup>156</sup> For this the EMA has set up an EU Network Training Centre together with the Member States' National Competent Authorities.<sup>157</sup> This is an interesting model as it is a joint endeavour with its partner organisations in Member States who often also already regularly organise training in aspects of scientific assessment.

Currently, when joining as a new EFSA Panel member, there may be a need to learn about and be proficient in existing and new assessment guidance to be used by the concerned Panel. These experts may indeed previously not have had specific training on the scientific assessment methods covered in the EFSA guidance documents. EFSA already provides training to its staff and experts on new guidance.<sup>158</sup> Nevertheless, participation is currently on a voluntary basis. In other words, when joining as Panel members (or as EFSA staff), there is no formal follow-up on the assessment that took place at the time of selection, i.e. there is no assessment of, nor agreement on, what the selected expert's training needs are and no assessment at the end of the 3-year mandate as to whether these were addressed. The system of scientific advice is based on experts who volunteer some of their time for a period of 3 years, without assurances that their mandate will be renewed. Such a lack of predictability makes it hard for all parties concerned to justify investment in training. An important aspect is therefore that experts and institutions in Member States that do decide to support EFSA by allowing some of their staff to apply for Panel membership, have assurances that this commitment exceeds the current 3-year time horizon. Thus, it would be highly desirable, if the appointment of Panel members could be for a five-year period and be renewable (at least) once. In this regard, it is noteworthy that European Commission Scientific Panels have been switched from 3-year to 5-year mandates,<sup>159</sup> while EFSA's is stuck with the inefficient 3-year renewal cycle, as required in Article 28(5) of the General Food Law Regulation.<sup>4</sup>

<sup>153</sup> <https://www.efsa.europa.eu/de/node/871501>

<sup>154</sup> <https://www.efsa.europa.eu/en/supporting/pub/15091e>

<sup>155</sup> [https://www.efsa.europa.eu/sites/default/files/160112\\_3\\_KNEIFEL.pdf](https://www.efsa.europa.eu/sites/default/files/160112_3_KNEIFEL.pdf)

<sup>156</sup> [https://www.efsa.europa.eu/sites/default/files/20150914b\\_EFSAJournal-Supplement\\_web.pdf](https://www.efsa.europa.eu/sites/default/files/20150914b_EFSAJournal-Supplement_web.pdf)

<sup>157</sup> <http://www.hma.eu/otsg.html>

<sup>158</sup> <http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2016.EN-1009/pdf>

<sup>159</sup> [https://ec.europa.eu/health/scientific\\_committees/consumer\\_safety\\_en](https://ec.europa.eu/health/scientific_committees/consumer_safety_en)

Besides formal training, there is – as mentioned – also the need to provide a new generation of potential experts opportunities to gain experience, for which EFSA has launched a fellowship programme.<sup>160</sup> In this regard, it would seem sensible that interested scientists be encouraged to also join working groups as observers so they can gradually gain such experience. In fact, this opportunity does already exist in the system of pesticides review and is being used by Member State Competent Authorities when they send staff to join working groups organised by EFSA. Equally, M.Sc. training may offer an opportunity to gain direct experience in risk assessment organisations through, e.g. participation in working groups, in an observer role.

## 5. Discussion and conclusions

This paper first reviewed the various components of a scientific experiment to ascertain whether they are present in a scientific assessment carried out by EFSA and, if so, how they might differ from it. By and large, the scientific assessment process in place at EFSA can be understood to mimic the conduct of a scientific experiment. However, being a regulatory support mechanism, what has been termed ‘regulatory science’,<sup>161</sup> has some very distinct features and therefore its legitimising characteristics are not necessarily identical to those used in academic research. For example, EFSA’s scientific assessments being done within a legal framework, an outcome has to be delivered within a set time frame and in such a manner that it can feed into the risk manager’s decision-making process. The latter may require that one goes beyond just testing whether a hypothesis can or cannot be rejected but also makes sure that the uncertainties around it are properly described.

As to whether ‘regulatory science’ is (yet) a separate scientific discipline, this is a matter for debate. It is already considered of high scientific interest (The National Academies of Sciences, Engineering and Medicine, 2017) and, given its potential impact on society, it is also of high public interest.

This review has considered the roles of risk managers and risk assessors in this process. Separation of risk assessment and risk management represents separation between scientific assessment and the legislative and executive branches of government, who request this advice. EFSA’s advice should be given free from their political influence, as well as from others. This makes for a complex relationship. As an example, the scientific assessments within EFSA’s remit are carried out through the implementation of a detailed legislative framework regarding, e.g. the evaluation of a food additive. Such legislation often defines the data requirements and even the methods to be used by the risk assessor and the authorisation is the subject of a decision by risk managers for each and every compound on which advice was given. It indicates that the major concern of the regulator is to make sure that, when taking management measures, risk managers can rely on scientific advice that is not influenced by stakeholder interests, including those of the risk managers themselves; while leaving open the possibility to bring in other potential considerations in the decision-making process. The legislator may thus decide on alternative approaches than proposed by EFSA. For example, throughout EFSA’s existence, its Scientific Committee and Panels have maintained a position whereby the objective of the scientific risk-assessment is a full risk characterisation consisting of identifying deleterious effects, characterising the doses at which they occur, and the likelihood of exposure to such a dose. This may not prevent the risk manager from deciding that a hazard-based precautionary approach be used. It is indeed the prerogative of the legislator to decide when and why i.e. under what circumstances such a policy of ‘no exposure under any circumstances’ should be adopted.<sup>162</sup>

This paper has not very much reflected on the importance of cooperation at the international level. Clearly though, collaboration with relevant international bodies is considered key for EFSA.<sup>163</sup> For example, EFSA, along with other Agencies, wants to assist the Commission to help establish and support activities on international guidance development or study protocols with international bodies such as the Organisation for Economic Co-operation and Development (OECD), the secretariat of the Plant Protection Convention (IPPC) at the FAO, the Office International des Epizooties (OIE) and joint WHO/FAO bodies. In addition, there are other emerging fora, including for example the Global Coalition on Regulatory Science Research (GCRSR),<sup>164</sup> to discuss the impact of new technologies on the assessment of foods and medicines.

<sup>160</sup> <https://www.efsa.europa.eu/en/engage/fellowship>

<sup>161</sup> <https://www.fda.gov/scienceresearch/specialtopics/regulatoryscience/default.htm>

<sup>162</sup> <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R1107&from=EN>

<sup>163</sup> [https://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/strategy2020.pdf](https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/strategy2020.pdf)

<sup>164</sup> <https://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/WhatWeDo/ucm289679.htm>



Equally, the paper says little on communication, particularly to the public at large, another issue of key importance. Indeed, successful communication can be considered as one condition to be recognised as an 'authority'. The reason why this is not discussed in depth here is that it merits a separate reflection. For example, what are the routes and formats of communication that are most relevant and accessible to the individual consumer? Does EFSA have to become a Wikipedia on safety aspects of food? Does openness not ultimately mean empowerment? This may require that information is made available in a format that is directly relevant to the consumer. This has already been explored for the interactive analysis of the likelihood of the introduction of vector-borne diseases.<sup>165</sup> It may be taken further by EFSA or other stakeholders, for example to enable the consumer to make his/her own dietary exposure estimations and to assess whether this 'personalised' nutrition carries any longterm risks?

The paper has focused essentially on the human health responsibilities of EFSA in relation to food safety, at the expense of its role in providing scientific advice on animal health and plant health. These areas are not only important in their own right but they also impact human health, food security and environmental protection.<sup>144</sup> The reason for not further developing these areas is that the assessment framework in animal and plant health may be different since the hypothesis that is tested is different. For example, the question posed may be what is the risk for plant pathogen being imported and becoming established in the EU?

As is the case for most any organisation, EFSA needs to strike a proper balance between on the one hand delivering the 'here and now' of the core business and on the other hand making sure that the organisation keeps up with evolving science so as to remain relevant. This may represent a tension between various characteristics affecting EFSA's credibility at the level of the organisation where the scientific assessment data, methods, and expertise need to continue to evolve, while at the same time making sure that this does not unduly hamper ongoing work. For example, while providing support on training and future research are highly desirable, these may also become time consuming and resource-intensive. It requires strategic decision-making by EFSA management to define priorities and the resources to be devoted to it. To aid the EFSA in this process, it may be worth reflecting whether the Scientific Committee, in close cooperation with EFSA's Chief Scientist, could help steer strategic change, beyond the development of guidance per se. In particular, the six members of the Scientific Committee who do not belong to any of the Scientific Panels could help to take stock of upcoming and required scientific developments and how they can be taken on board at EFSA. Ad hoc groups of specialists may be able to assist with this and it can be supported by specialised scientific-assessment institutions.<sup>166</sup>

Besides striking a balance between the short term and the medium term needs, there is also the consideration of the adequacy of EFSA's overall resources to be a sustainable organisation. Is it reasonable to assume that EFSA's operation is sustainable with a budget that is 25% the magnitude of the budget EMA has at its disposal and 50% of EMA's staffing? The difference in staffing ( $\times 2$ ) explains 25% of the budget difference. The remaining 50% difference can largely be attributed to the fact that almost half of EMA's budget goes to risk assessment bodies in the Member States. This fourfold difference in resources impacts the ability to fund proper reimbursement of experts and thus the maintenance of current and the development of new assessment expertise in relevant Member State institutions to support EFSA. It also affects the ability of EFSA to keep up its assessment methods and develop key new initiatives, such as the streamlining of dossier assessment processes through the MATRIX project.<sup>150</sup>

In conclusion, since its creation 15 years ago, EFSA has very much delivered on its mission to provide scientific assessments, while at the same time gradually building an assessment system. To illustrate the latter, much has been achieved in the setting of standards for exposure data collection and data exchange between EFSA and competent public organisations in Europe to assess human dietary exposure across food components, microbiological and chemical residues and contaminants. It has taken about 10 years to achieve this.

Whatever the achievements, the EU cannot rest on its laurels though. It could even be argued that what has been achieved thus far represents harvesting of the 'low hanging fruit' and that EFSA is now in the position to face other important and challenging issues. These include becoming a more transparent and open organisation (TERA project), modernising the assessment of regulatory evaluation process (MATRIX project), moving into 21st century toxicity testing approaches, accepting

<sup>165</sup> <https://www.efsa.europa.eu/en/efsajournal/pub/4793>

<sup>166</sup> <http://qanu.nl/en/mission>

evidence collected pro-actively post-market not only as a source of compliance monitoring but also as a different source of scientific information, and building a body of EU scientific assessment expertise that is funded sustainably. Taken together, these challenges form a unique opportunity to prepare for the future by further developing an effective, efficient, and internationally recognised organisation that is well equipped to serve EU citizens in this 21st century.

Pro-actively addressing these challenges shows responsibility. To do so, this paper also calls for further reflection on what may currently be considered established practices, e.g. arms-length relationship with industry, the consideration of risks only, the desirability of sector-specific differences in data requirements and assessment methods, and embracing big data and artificial intelligence-based approaches. A critical success factor is the generation of scientific evidence and the development of assessment approaches through publicly funded applied research and development to underpin EFSA's and other scientific agencies' needs to support public policy development.<sup>167</sup>

For EFSA to progress towards meeting these challenges and opportunities, continued close cooperation with the European Commission, as well as other stakeholders, will be essential.

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## Abbreviations

ADI	acceptable daily intake
AECOSAN	Agencia española de Consumo, Seguridad alimentaria y Nutrición
AHAW Panel	Scientific Panel on Animal health and Welfare
AOP	adverse outcome pathway
ARfD	acute reference dose
BfR	German Federal Institute for risk assessment
BMD	Benchmark Dose
BSE	bovine spongiform encephalopathy
CJEU	Court of Justice of the European Union
CONTAM Panel	Scientific Panel on Contaminants in the food chain

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DG	Directorate General
ECDC	European Centre for Disease Prevention
ECHA	European Chemical Agency
EEA	European Environmental Agency
EKE	expert knowledge elicitation
EMA	European Medicines Agency
EMBL-EBI	European Bioinformatics Institute
EPA	Environmental Protection Agency
EU-ANSA	EU Agencies sub-Network for Scientific Advice
OSHA	European Agency for health and Safety at Work
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
FEEDAP Panel	Scientific Panel on Additives and Products or Substances used in Animal Feed
GCRSR	Global Coalition on Regulatory Science Research
GLP	Good Laboratory Practices
GM	genetic modification
GMO	genetically modified organisms
GMO Panel	Scientific Panel on Genetically Modified Organisms
HBGV	Health-based Guidance Value
HLG	High Level Group
IPPC	secretariat of the Plant Protection Convention (IPPC) at the FAO
ISO	International Organization for Standardisation
LOAEL	lowest-observed-adverse-effect-level
MoA	mode of action
MOE	Margin of Exposure
MATRIX project	system for the electronic management of regulated products dossiers
NOAEL	no-observed-adverse-effect-level
NDA Panel	Scientific Panel on Dietary Products, Nutrition, and Allergens
NGO	Non-governmental Organisation
OECD	Organisation for Economic Co-operation and Development,
OIE	Office International des Epizooties
PAFF Committee	Standing Committee on Plants, Animals, Food and Feed
PLH Panel	Scientific Panel on Plant Health
PPR Panel	Scientific Panel of Plant Protection Products and their Residues
PROMETHEUS	Promoting methods for evidence use in scientific assessments
QPS	qualified presumption of safety
RIVM	Rijksinstituut voor Volksgezondheid en Milieu
SAM	Scientific advice mechanism
TDI	tolerable daily intake
TERA	Transparency and Engagement in Risk Assessment
TTC	Threshold of Toxicological Concern
WHO	World Health Organization