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Microbiological risk assessment

Alessandro Cassini[1], Steve Hathaway[2], Arie Havelaar[3], Marion Koopmans[4], Kostas Koutsoumanis[5], Winy Messens[6], Gordon Müller-Seitz[7], Birgit Nørrung[8], Valentina Rizzi[6] and Flemming Scheutz[9]

Abstract

Microbiological risk assessment is defined by the CODEX Alimentarius Commission as 'a scientifically based process consisting of the following steps: (i) hazard identification; (ii) hazard characterisation; (iii) exposure assessment; and (iv) risk characterisation'. It is one of the components of microbiological risk analysis, which has the overall objective to minimise food-borne risks to consumers. It is a complex discipline that continues to evolve and challenges and new opportunities were discussed during the breakout session 'Microbiological risk assessment' held at the EFSA 2nd Scientific Conference 'Shaping the Future of Food Safety, Together' (Milan, Italy, 14–16 October 2015). Discussions focussed on the estimation of the global burden of food-borne disease, the prioritisation of microbiological risks taking into account uncertainty, the challenges in risk assessment when dealing with viruses, the contribution of typing methods to risk assessment and approaches to deal with uncertainty in risk assessment in emergency situations. It was concluded that the results of the global burden of food-borne disease study provide, for the first time, a comprehensive comparison of risks due to different hazards and this will be an important input to food safety strategies at the global, regional and national levels. Risk ranking methodologies are an important tool for priority setting. It is important to consider the underestimation (e.g. due to bias in reporting). Typing methods for microbial hazards inevitably impact on risk assessment and can have an important influence on the accuracy of source attribution studies. Due to their high genetic diversity and the limitations of current diagnostic methods, it is still challenging to obtain robust evidence for food-borne outbreaks caused by viruses and more research is needed on the use of whole genome sequencing in this area. The lessons learnt from the recent enterohaemorrhagic *Escherichia coli* (EHEC) outbreak in Germany include the need for more effective and timely connections within and between institutions as responses unfold.

Keywords: microbial risk assessment, burden of disease, risk ranking, *Escherichia coli*, viruses, outbreaks, typing methods

Correspondence: editor-in-chief.efsajournal@efsa.europa.eu

Author affiliations: [1] European Centre for Disease Prevention and Control (ECDC), Sweden; [2] Ministry for Primary Industries, New Zealand; [3] University of Florida, USA; [4] Erasmus MC, The Netherlands; [5] Aristotle University of Thessaloniki, Greece; [6] European Food Safety Authority (EFSA), Parma, Italy; [7] Technical University Kaiserslautern, Germany; [8] University of Copenhagen, Denmark; [9] Statens Serum Institut, Denmark.

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1. Introduction

Microbiological risk assessment (MRA) is defined by the CODEX Alimentarius Commission (CODEX, 2007) as 'a scientifically based process consisting of the following steps: (i) hazard identification; (ii) hazard characterisation; (iii) exposure assessment; and (iv) risk characterisation'. This clear and short definition 'hides' a complex discipline with a broad spectrum of approaches; from qualitative to quantitative assessments, focused on part (or specific step) of the food chain to the whole chain (or farm-to-fork). In addition, the outcome of the MRA may take many forms, ranging from number of human cases in a specific population to the economic impact of the disease.

This complexity is also reflected in the number and diversity of risk assessment tools currently available. The European Food Safety Authority (EFSA) has conducted several MRAs for which a model was designed to fit the needs of the particular risk assessment question (Romero-Barrios et al., 2013), whereas other models consist of more generic tools that can be used for a variety of purposes. In parallel to this, efforts have been made to better measure the impact of food-borne diseases on the human population and to use this information for prioritising risks (EFSA BIOHAZ Panel, 2012, 2015). Work is also being undertaken to bring a more structured approach to dealing with uncertainty in these MRAs (EFSA Scientific Committee, 2015), something that is particularly challenging when communicating risk estimates to risk managers and the general public. Examples of challenges and opportunities when applying risk assessment are provided here, covering issues, such as the estimation of the burden of disease in a global context, how to prioritise microbiological risks and deal with uncertainty, the difficulties of risk assessment when dealing with viruses, the contribution of typing methods to risk assessment and the approaches to deal with uncertainty in emergency assessments.

This publication builds upon presentations made and discussions held during the breakout session 'Microbiological risk assessment' at the EFSA 2nd Scientific Conference 'Shaping the Future of Food Safety, Together' (Milan, Italy, 14–16 October 2015).[1]

2. Summary of presentations, discussions and outcomes

2.1. Key messages of the speakers' presentations

2.1.1. World Health Organization estimates of the global burden of food-borne disease, 2010

Food-borne diseases are common throughout the world and are a constant threat to public health (PH). Recognising the absence of global and regional estimates of these food-borne diseases and the need for such estimates to guide PH policy, the World Health Organization (WHO) launched the 'Initiative to Estimate the Global Burden of Foodborne Diseases' in 2006 and established the Foodborne Disease Burden Epidemiology Reference Group (FERG). Burden of disease is a measure of population health that summarises the impact of mortality and morbidity in one single metric, the disability-adjusted life year (DALY). The DALY is calculated by adding the number of years of life lost (YLL) due to mortality and the number of years lived with disability (YLD) due to morbidity. The FERG provided the first estimates of the global food-borne disease incidence, mortality and disease burden in DALYs caused by 31 global food-borne hazards, comprising 11 diarrhoeal disease agents, seven invasive infectious disease agents, 10 helminths and three chemicals. A hazard- and incidence-based approach was used. For the 19 hazards that were not considered 100% food-borne, the proportion of the disease burden caused by food-borne transmission was estimated through expert elicitation. Specific estimates for each subregion were used. By the time of the presentation, the results were not yet available. Some building blocks of the global estimates were described. Diarrhoea was the global cause of 11% of the 7.6 million deaths among children under 5 years of age in 2010; neonatal deaths being 1%. It was estimated that, globally, 18% of all diarrhoeal cases is due to norovirus (NoV). Diarrhoeal illness was estimated to cause 582 million cases and 351,000 deaths in 2010; 40% of the cases were in children under 5 years of age. Most deaths were caused by *Salmonella* Typhi, enteropathogenic *Escherichia coli* and NoV. The highest disease burden is in African and South-east Asian regions. For toxoplasmosis, various sequelae were taken into account in the estimate leading to

[1] The scientific programme of the conference is available at http://www.efsaexpo2015.eu/programme/. All the conference material of the break-out session (including briefing notes, presentations and videos) is available at http://www.efsaexpo2015.eu/show-session/?idsession=10

a loss in DALYs of approximately 1.2 million per year. In this case, there is a high burden at the population level in Latin America and also in Eastern Europe. Many diarrhoeal diseases are linked to poverty, although this is not the case for *Toxoplasma*. The latter continues to be a problem in the developed countries across the world, such as *Salmonella* and *Campylobacter*. The global burden of trichinellosis in 2010 was only 523 DALYs, likely resulting from a better meat inspection. Annually, there are 550,000–600,000 cases of hepatocellular carcinoma, of which 4.6–28.2% may be attributable to aflatoxin. A 'top-down' approach was used for aflatoxin to correct for the background rate in the study population. Using the 'bottom-up' or risk assessment approach gives fourfold higher estimates when compared to the 'top-down' approach. To promote the use of burden of food-borne disease estimates, country studies were performed to strengthen the capacity of countries to conduct burden of food-borne disease assessments. To conclude, food-borne hazards cause a wide variety of diseases, ranging from relatively mild to severe and life-threatening. Many data gaps were identified, creating the need for imputation, assumptions and expert elicitation. Food production in general is linked to human disease via mechanisms other than the direct transmission of pathogens through food. The total burden of food-related diseases is therefore higher than these estimated for the food-borne diseases. The FERG results will help to focus control activities to reduce the burden of food-borne disease, although the burden and priorities vary by region. The current results provide a basis for strategies at the global, regional and national levels, although the national studies are needed to refine current regional insights. Concerted effort is needed by all stakeholders in the food chain, from primary production to consumers. All results became available on the WHO website in December 2015.[2] It contains the WHO report (WHO, 2015), the online interactive tool and the country study toolkit. Results are also available in a series of scientific papers (http://collections.plos.org/ferg2015 e.g. Havelaar et al., 2015).

2.1.2. Methodology and uncertainty impact on risk ranking of microbiological hazards: present and future

Risk ranking is a proper starting point for risk-based priority setting and resource allocation. It permits policy-makers to focus attention on the most significant PH problems. Because risk ranking aims to compare the comparative risk and not the actual risk, alternative approaches can be applied which could raise issues related to their consistency and transparency. A standardised risk ranking conceptual framework was developed consisting of nine steps (EFSA BIOHAZ Panel, 2012). Because the outcome of risk ranking depends on the risk metrics chosen (e.g. the probability of illness versus PH burden such as DALYs), the risk manager needs to define the risk metrics. When considering various hazards, common metrics need to be used that allow comparison of the severity of the health outcomes, such as the DALY. The two approaches for risk ranking, namely the 'bottom-up approach' ('normal' risk assessment approach) and the 'top-down approach' (based on epidemiological data), were recommended to be combined. The most important steps in risk ranking are the choice of the model type and the data integration. The first ranges from qualitative, semiquantitative to quantitative (deterministic or stochastic) models with increased resource and data needs but also with increased decision-making utility. The qualitative approach (decision tree) has very limited discrimination power for risk ranking and the arbitrary outcome (e.g. low risk) is considered problematic. A generic risk assessment model applying virtual data (EFSA BIOHAZ Panel, 2015) was build and run using various ways (e.g. deterministic, stochastic), with the stochastic way being the reference approach. This showed that deterministic models that ignores variability may result in risk ranking errors, which may be greater for the food–pathogen combinations with the highest risk. The selection of the point estimate in this approach can affect the risk ranking. Among different point estimates, the use of a high percentile provides, in general, risk ranking results that are most similar to a stochastic model. Semiquantitative models with ordinal scoring may lead to food–pathogen combinations classified into broad sets of categories with little discrimination. There are considerable differences using this semiquantitative models in risk ranking compared to a stochastic model and it results in more errors than the deterministic approaches. Uncertainty needs to be carefully addressed in risk ranking and communicated to decision-makers. Uncertainty in rank orders cannot be formally quantified using qualitative or semiquantitative ranking methods even though these are often applied in situations where data are limited. Expert elicitation procedures to incorporate diffuse information into the

[2] http://www.euro.who.int/en/health-topics/disease-prevention/food-safety/news/news/2015/12/more-than-23-million-people-in-the-who-european-region-fall-ill-from-unsafe-food-every-year

corresponding probability distributions may be adopted. It was recommended to combine the FDA-iRISK[3] and Burden of Communicable Diseases in Europe (BCoDE) software tools (see Section 2.1.3). The latter can be used for an initial priority ranking and then the first to further rank a selection of hazard-food combinations.

2.1.3. Improving the usability and communicability of burden of disease methods and outputs: the BCoDE toolkit application

To estimate the burden of and prioritise food-borne (and, in general, infectious) diseases and their impact on population health, various approaches can be used, ranging from qualitative to quantitative methods. The most robust input into ranking these risks is by estimating and expressing the burden of disease through quantitative composite health measures such as DALYs. The European Centre for Disease Prevention and Control (ECDC) has initiated the BCoDE study to assess the comparative impact of infectious diseases in Europe and estimate their burden in DALYs, including food-borne diseases. Objectives of the BCoDE project include fostering an evidence-based approach to health status description across Europe (extensive literature reviews assessing the acute phase and sequelae of diseases), providing decision-makers with tools for planning and prioritisation, facilitating the communication of complex epidemiological information, and supporting an overview of surveillance data availability and quality (Kretzschmar et al., 2012; Mangen et al., 2013). Surveillance systems often underestimate the number of cases at two levels of the surveillance pyramid: detection in the community because not all cases seek healthcare (under-ascertainment), and when symptomatic cases seeking medical attention are not adequately reported (healthcare level, underreporting). For example, the BCoDE 2015 study, which had the aim of estimating the burden of 32 communicable diseases and six healthcare-associated infections, multipliers adjusting for under-ascertainment and underreporting were applied to notification data, appraising surveillance systems across the European Union (EU). Ranking diseases and risks according to their impact on population health, in an evidence-based and quantitative approach, as well as considering the extent of disease under-notification, helps risk managers in their decision-making process. As a result of the BCoDE project work, a user-friendly and ready-to-use toolkit has been released on ECDCs website.[4] The toolkit is a standalone software application that allows calculation of DALYs for a selection of 32 communicable diseases and six healthcare-associated infections. This tool facilitates the complex calculation of DALYs by simply inputting age-, gender- and population-specific incidence data and adjustment values for underestimation. The BCoDE toolkit also focuses on user-friendly outputs for more effective communication, at the same time as providing meaningful detailed information on incidence, mortality and population stratification. The software aims at assisting users with applying the proposed BCoDE evidence-based approach to estimation of the burden of infectious diseases, for risk ranking purposes and disease prioritisation. EU Member States and European Economic Area (EEA) countries are encouraged to employ the toolkit to estimate their national burden of communicable diseases. Eventually, choices concerning data input allow national experts to assess availability and quality of data, identify gaps and generate additional information potentially useful for national surveillance systems. Moreover, multiple visualisation options focus on facilitating communication between data generators and users in support of health policy formulation.

2.1.4. The contribution of typing methods to risk assessment

To illustrate the contribution of typing methods to risk assessment of *E. coli* pathotypes and the types of methods that can be applied, the example of verocytotoxin-(Shiga toxin) producing *E. coli* (VTEC/STEC)[5] is provided. This organism is responsible for haemolytic uraemic syndrome (HUS), a life-threatening disease with severe sequelae characterised by acute renal failure, microangiopathic haemololytic anaemia and thrombocytopenia. Thirty years ago, the haemorrhagic colitis was associated with a rare of *E. coli* serotype called O157. Recently, it was shown that non-O157 serotypes share the same scene with O157 serotype. There are reports of many different serotypes

[3] Food and Drug Administration Center for Food Safety and Applied Nutrition (FDA/CFSAN), Joint Institute for Food Safety and Applied Nutrition (JIFSAN) and Risk Sciences International (RSI) 2015. FDA-iRISK version 2.0. FDA CFSAN. College Park, Maryland. Available at https://irisk.foodrisk.org/

[4] ECDC BCoDE toolkit [software application]. Version 1.1 Stockholm: European Centre for Disease Prevention and Control; 2015. Available from: http://ecdc.europa.eu/en/healthtopics/burden_of_communicable_diseases/Pages/Tool.aspx

[5] Also known as verotoxigenic *E. coli*, verocytotoxigenic *E. coli*, verotoxin-producing *E. coli* and Shiga toxin-producing *E. coli* (STEC).

from HUS cases. VTEC/STEC strains have two main features: the intimin-encoding gene (*eae* gene) encoded on a pathogenicity island (LEE PAI) that allows the bacteria to attach to the epithelium cells in the gut, and the capability to produce potent toxins, verocytotoxins 1 and 2 (VT1 and VT2) (or Shiga toxin 1 and 2 (Stx1 and Stx2)). There are many different types and variants of these toxins but, at present, only *vtx2a* and *vtx2d* are found in VTEC-associated HUS cases (Scheutz et al., 2012). The toxins are encoded by bacteriophages differing in size and morphology. These bacteriophages have been found in healthy individuals and in foods and are resistant in the environment where they can persist for very long periods. Next generation sequencing (NGS) or whole genome sequencing (WGS) are used for typing these strains (Joensen et al., 2015) and, to date, more than 2,324 different genomes of *E. coli* representing different serotypes have been identified. The analysis of single nucleotide polymorphism addresses through WGS has shown the global dispersion of VTEC O157 and the regional expansion in the cattle reservoir in several countries (in the UK, USA, Australia and Argentina) (Dallman et al., 2015). In the past, ground beef was deemed the primary source of human infection with VTEC O157 strains. Some studies have demonstrated that other foods are now implicated as well, such as fresh produce, and that risk factors (e.g. swimming, contact with ruminants, contact with other individuals with diarrhoea, visiting farms) and host factors (e.g. antacids, cardiovascular diseases, gastrointestinal infections) play an important role.

2.1.5. Challenges in risk assessment for viruses

The recent estimate from the WHO (see Section 2.1.1) has recognised that priority food-borne viruses are NoV and hepatitis A virus (HAV), although additional viruses continue to be detected. Different ways of transmission are identified for NoV and HAV, and quantifying the contribution of these different modes of transmission is challenging. NoV show a high genetic diversity and different lineages have been identified, although few genotypes are involved in most clinical cases. This reflects the transmissibility of these NoV genotypes among individuals, leading to outbreaks in, for instance, healthcare settings and schools. A recently recognised problem is the impact in a healthcare setting, which increasingly includes patients that are hospitalised with (severe) comorbidity. NoV persist in the population through evolution, as is common in viruses with an RNA genome. The sloppy replication of these viruses allows for incorporation of mutations that, together with the contribution of selection forces when such mutant genomes infect a new individual, may result in the selection of new antigenic variants that escape the protective immunity of the host. Another mechanism is the recombination that can occur in case of infection of a single cell with more than one strain; in this case, the final outcome is a progeny virus with mixed genome. Recombination is quite common in the evolution of NoV, and can have an impact on the circulation of current dominant strains. In food-borne outbreaks, as a result of the nature of the contamination, which could be sewage-related or irrigation-related, exposure of humans to multiple viruses increases the risk of emergence of recombinant strains. Other viruses are considered as source of food-borne infection (e.g. hepatitis E virus), and the potential for food-borne introduction or dissemination should be considered within each emerging viral disease outbreak. Despite the advancement of molecular typing, it is still challenging to obtain robust evidence for food-borne outbreaks caused by viruses and more research is need on the use of molecular typing. An EU-funded project (COMPARE[6]) is ongoing to capture the development in WGS on these types of questions for viruses as well as other pathogens.

2.1.6. Approaches to deal with uncertainty in emergency assessments: the case of the EHEC outbreak in 2011 in Germany

Every crisis is a distinct event at a certain extent but, frequently, response actions have common errors. These errors include a lack of preparedness of organisations that do not see crisis preparation necessary for daily operations (e.g. organisational cultural anomalies that rely on standard procedures for routine situations that are not appropriate in cases of crisis), a lack of knowledge transfer, wrong managerial mantras that miss efficiency and oriented indicators or ignorance of interdependencies between organisations. The example of the EHEC outbreak in Germany in 2011 was given (Berthod et al., 2014; Müller-Seitz, 2014). Several barriers hindered a swift solution of the crisis; first, the zoonotic nature of the incident required the sharing of responsibilities between the Federal Veterinary and Public Health Ministries; second, the federal organisation did not facilitate the collaboration between Federal Ministries; and, finally, the outbreak investigation was hampered by the uncertainties

[6] http://www.compare-europe.eu/

around the food vehicle, source of contamination, strain involved and role of the media. But other aspects worked well: a common frame of reference for actions was identified, driven by the time pressure and the need to act. An emergent leeway where actors found motivation in the opportunities for increasing academic reputation and for gaining new funds from public institutions was observed; new managerial ideas were shared across organisations and led to the creation of an EHEC Task Force across institutions, constituting a *de novo* cooperation form in this context. The knowledge of existing infrastructures supported the investigation. In crisis situations, transparency could be ambiguous, in particular, if there is uncertainty in identifying the source of infection. Lessons learnt include intraorganisational implications (e.g. making use of leeways during crisis to make changes) and interconnections with other organisations (e.g. making use of external experts to legitimate actions and working across levels – at national/European Union/global levels).

2.2. Outcomes/recommendations

It is recommended:

- to conduct national studies on the burden of food-borne illness where more information than that available in the FERG study is needed to inform food safety strategies;
- to encourage the EU Member States and EEA countries to employ the BCoDE toolkit when estimating their national burden of communicable diseases;
- to combine a 'bottom-up approach' and a 'top-down approach', in risk ranking methodologies that are applied to inform risk management priority setting and resource allocation; for example, using the FDA-iRISK and BCoDE software tools;
- to determine uncertainties in risk estimates of risk ranking studies to the greatest extent practicable and to effectively communicate such uncertainty to risk management decision-makers;
- to increasingly focus on epidemiological approaches and tools when applying new diagnostic methods in risk assessment;
- to use molecular typing methods, such as NGS and WGS, to characterise the hazards(s) involved where a cocktail of genes is implicated in food-borne diseases;
- to develop increased technical capability in national institutions to accurately determine the burden of (emerging) food-borne illnesses due to viruses and to understand how to take the genetic diversity of viruses into account in risk assessment studies and priority setting;
- to clearly establish risk assessment, risk management and risk communication responsibilities by national institutions and governments in the case of outbreaks of food-borne disease and to foster collaboration across institutions within institutions and cooperation across institutions.

3. Conclusions

The results of the FERG global burden of food-borne disease study provide, for the first time, a comprehensive comparison of risks due to different hazards and this provides an important resource to inform food safety strategies at the global, regional and national levels. However, national studies on the burden of food-borne illness should be conducted where more information than that available in the FERG study is needed to inform food safety strategies. Risk ranking is an important tool for risk-based priority setting and resource allocation. Risk ranking enables decision-makers to focus attention on the most significant food-borne illness problems and it is recommended that the 'bottom-up approach' ('normal' risk assessment approach) and the 'top-down approach' (based on epidemiological data) be combined in risk ranking; for example, by combining the FDA-iRISK and BCoDE software tools. Both tools are currently available online. The latter tool can be used for an initial priority ranking and then the first to further rank a selection of hazard–food combinations. It is important to consider underestimation (e.g. due to bias in reporting). Typing methods can contribute to risk assessment by providing information on the genetic traits of strains and their distribution, and can have an important influence on the accuracy of source attribution studies aiming to identify the primary source of human infection, as was the case for the EHEC outbreak in Germany in 2011. NoV and HAV have been recognised as priority food-borne viruses with a high burden of disease, as shown by the FERG studies. Due to their high genetic diversity, it remains challenging to obtain robust evidence for food-borne outbreaks caused by viruses and more research is needed on the use

of WGS in this area. The EHEC outbreak in Germany showed that some errors were made, whereas other aspects worked well. The lessons learnt from the recent EHEC outbreak in Germany include the need for more effective and timely connections within and between institutions as responses unfold.

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Abbreviations

BCoDE	Burden of Communicable Diseases in Europe
CD	communicable disease
DALY	disability-adjusted life year
eae gene	intimin-encoding gene
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EHEC	enterohaemorrhagic *E. coli*
FDA/CFSAN	Food and Drug Administration Center for Food Safety and Applied Nutrition
FERG	Foodborne Disease Burden Epidemiology Reference Group
HAV	hepatitis A virus
HUS	haemolytic uraemic syndrome
JIFSAN	Joint Institute for Food Safety and Applied Nutrition
MRA	microbiological risk assessment

NGS	next generation sequencing
NoV	norovirus
PH	public health
RSI	Risk Sciences International
Stx	Shiga toxin
STEC	Shiga toxin-producing *E. coli*
VT	verocytotoxin
VTEC	verocytotoxin-producing *E. coli*, also known as verotoxigenic *E. coli*, verocytotoxigenic *E. coli*, verotoxin-producing *E. coli*
WGS	whole genome sequencing
WHO	World Health Organization
YLD	years lived with disability
YLL	years of life lost