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Editorial: Exploring the need to include microbiomes into EFSA's scientific assessments

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The communities of microorganisms and their genomes in a defined environment are collectively referred to as microbiomes (Marchesi and Ravel, 2015). They include representatives from the Bacteria, Archaea, lower and higher Eukarya, and viruses, and are found in most environments such as soils, aquatic habitats, surfaces and specific lumen of plants, animals and humans. According to ongoing studies, microbiome structures and dynamics across the food system can have both direct and indirect effects on human and animal health, in addition to their impact on food quality, safety and sustainability (CNBBSV concept paper, 2019). Moreover, recent research projects have offered new insights into the associations between microbiomes and a wide range of human diseases as well as their possible impact in modulating the exposure to environmental chemicals. As one of the core tasks of EFSA is to assess risks to human and animal health and/or the environment from substances linked to food and feed production, the increasing understanding of the role of microbiomes in health calls for a prospective mapping of their roles into regulatory scientific assessment processes with a view to understanding their potential health impact.

Introduction

In the absence of explicit legal requirements under the food law to account for microbiomes in risk assessment, there is no guidance or methodology in place to systematically assess for possible effects on the microbiomes or by the microbiomes on human, animal or plant health. So far, potential effects on microbiomes are mentioned under various activities across the European Food Safety Authority

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(EFSA) without being addressed systematically in a harmonised way: e.g. (1) During the re-evaluation of the food additives, EFSA outsourced a project to monitor information on the potential impact of specific food additives on gut microbiome; (2) Under the health claim legislation (Regulation (EC) No 1924/2006), food constituents are assessed for their effects through the changes in the composition of the gut microbiome in humans, among other outcome variables; (3) Antimicrobial resistance is already being investigated in EFSA including the role that microbiomes could play in the wider environment as reservoirs for antimicrobial genes; (4) The efficacy of digestibility enhancers as feed additives is evaluated for their impact on the animal gut microbiome. However, microbiomes could also play an important role in other areas of EFSA's scientific assessments. The rhizosphere microbiome can have a potential relevance when assessing plant health, plant protection products (PPP) or genetically modified organisms. Animal gut microbiomes could have potential relevance when evaluating animal health and food/feed contaminants. More generally, animal and human gut microbiomes could have potential relevance for all risk assessments of oral exposure to chemicals. Due to their functional potential, microbiomes could play a central role in the 'One Health' framework, which approaches human, animal and plant health from an integrated perspective.

In anticipation of the new EFSA strategy (2021–2027) and related strategic objectives to develop knowledge and capacity for regulatory science, there is the opportunity for EFSA to embark on a thematic area of microbiomes. Such an initiative would be aimed at addressing the following questions: How to evaluate the impact on microbiomes by various substances under EFSA assessment, and How to evaluate the impact of microbiomes on human, animal and plant health?

EFSA organised a thematic discussion on Microbiomes with its Scientific Committee (see plenary meeting minutes[1] of February 2020) to start exploring the underlying elements of these questions. This discussion that took place, captured and further elaborated in the paragraphs below, also raised awareness in order to start building EFSA-wide capacity on microbiomes in scientific assessment.

The microbiome's role in human and animal health

The microorganisms (and their collective genomes) inhabiting the gut are thought to co-evolve with the host and develop a mutualistic relationship that benefits both the host and microorganisms. The human gut microbiome resides at the interphase between the inner and outer worlds. It interacts with the host, orchestrating an array of bodily functions (metabolic, immune, neural, etc.) and modulating the impact of adverse environmental exposure (nutrition through poor diets, chemicals, for example food contaminants and pharmaceuticals including antibiotics, biological hazards, etc.) on host physiology. Extreme and sustained adverse exposure can lead to profound ecological disruptions and a breakdown in the host–microbiome partnership, contributing to adverse health outcomes. The properties of the gut microbiome are considered to influence our response to external stresses (e.g. diet-related hazards) and, therefore, our vulnerability to diseases.

The profile and functions of the microbiome in food-producing animals have been investigated in several species. Although different species seem to partly share their microbiome, monogastric (e.g. pigs, chicken), ruminant (e.g. dairy cows, sheep) and lagomorph (e.g. rabbits) animals have well distinguished ecosystems that have co-evolved with their own microbiome and are characterised by species-specific enterotypes (Milani et al., 2017). The manipulation of animal microbiomes may contribute to a more sustainable production of high-quality foods by modulating animal growth, controlling their physiological development, boosting their defences against pathogens, improving nutrient quality and impacting on resistance to stress. Available data suggests that livestock microbiota play a significant part in health, production efficiency and behaviour of animals (Hooper et al., 2012; Shabat et al., 2016; CNBBSV, 2019).

The gut microbiome is currently viewed as an additional mediator of both beneficial and adverse effects of environmental exposure (namely diet, chemicals, pathogens, etc.). Research has indicated that the gut microbiome can modulate exposure to environmental chemicals. The idea that the gut microbiome can contribute to host metabolism is deeply rooted in the field of drug metabolism for which it is critical to investigate how the activities encoded by the human microbiome influence the dose of toxicologically active chemicals at the ultimate target site (tissue, cell, or molecule). Knowledge of how the human microbiome modulates the pharmacokinetics and metabolism of environmental chemicals has lagged behind knowledge of how the microbiome modulates drugs. Still, there is compelling evidence of gut microbiome involvement in the metabolic transformation of environmental

[1] 97th Scientific Committee Plenary on 19 February 2020.

chemicals in broad chemical classes, including metals, polycyclic aromatic hydrocarbons (PAHs), pesticides and persistent organochlorines, nitrosamines and aromatic amines, and other toxicant classes. Research suggests that the human microbiome might modulate the dose–response relationships of chemicals through a few general mechanisms, which might directly or indirectly influence the pharmacokinetics of the chemicals. The mechanisms include direct metabolic transformation of the chemicals and various secondary transformations such as deconjugation of host-generated metabolites, regulation of epithelial-barrier permeability with implications for transport or excretion of chemicals, and regulation of the expression or activity of endogenous host metabolic pathways (e.g. in the host liver) via signalling processes that involve microbial products (NASEM, 2018).

The challenge to define a compromised gut microbiome and its effects for its host

Human studies have shown that intestinal microbial communities are inherently dynamic and can fluctuate between different states over time. These fluctuations are closely linked to the person's age and diet and are compatible with the maintenance of a mutualistic relationship between the microbiome and its human host, which is essential for health. The maintenance of this beneficial host–microbiome interaction is particularly relevant during the first 2–3 years of life when strong disturbances of the gut microbiome over this period can eventually increase the risk for infections and non-communicable disorders at a later stage. Recent extensive surveys and meta-analyses exploring variations in the human gut microbiome in health and disease have revealed that microbiome changes are highly personalised and follow distinctive temporal changes. Studies characterising the gut microbiome in thousands of people, in parallel with covariates assessing health status, diet, lifestyle, medication, biomedical parameters and genetics, have demonstrated that these determinants explain only a small fraction of the total gut microbiome variation and that we are still missing important covariates when assessing drivers of this variation (Falony et al., 2016; Wang et al., 2016; Rothschild et al., 2018; CNBBSV, 2019). All those factors and others – such as socioeconomic status, geography, pregnancy status and environmental exposures – appear to play roles in shaping the composition and function of microbial communities (NASEM 2018). The same may apply to the different domestic animal species and various rearing or environmental conditions to which they are exposed.

Although most current knowledge on gut microbiomes concerns bacteria, other microorganism such as archaea, viruses and phage and fungi are assumed to play a role and remain largely unstudied.

Considering these uncertainties, it remains questionable whether it is useful for EFSA to attempt characterising a 'healthy microbiome'. Risk assessment of food and chemicals incorporating the gut microbiome intends to provide answers about what changes are induced by the chemical on the human gut microbiome, as well as the impact of the gut microbiome on the chemical. The final goal is to identify a causal relationship between those changes and adverse health effects in the host. In past EFSA assessments, a decrease in microbiome diversity has been observed when seeking to evaluate a possible effect of naturally occurring contaminants on the microbiome (EFSA CONTAM Panel, 2020). There is a challenge in translating this observation into a functional consequence as there are as yet no standards to define a healthy microbiome. Therefore, more data are required for a better understanding of covariates driving the human and animal gut microbiome variation within ranges not leading to adverse effects. This knowledge is needed to further assess when a change in the microbiome profile either in structure and/or function goes beyond those variations and translates into an adverse biological effect on the host.

Although several reports have shown that a chemical challenge can be sufficient to alter host physiology and microbiome composition and function, the reported experiments alone do not clearly distinguish between direct causal effects of the chemical on the microbiome and indirect effects of the chemical acting first on the host and altering selective pressures that drive changes in microbiome composition or function (NASEM, 2018). A related relevant question for risk assessment is: When does the observed change become adverse? (see also the work on biological relevance of the EFSA Scientific Committee, 2017). The causal effect could be studied in various ways. One possibility could be to look at evidence from human epidemiological studies, using multi-omic techniques to deeply phenotype the subjects and map the various disease states to certain microbiome configurations and to try to validate the mapping with *in vitro* and *in vivo* experiments. Alternatively, a more bottom up approach could investigate observed changes in microbiome and link them to microbiome metabolic

pathways responsible for adverse effects in specific endpoints. However, it may be difficult to establish criteria to differentiate when the activity of certain metabolic pathways is adverse for specific endpoints in the host.

Models to study the gut microbiome in risk assessment

In order to profile microbiome community structure, many studies have used amplicon-based sequencing of 16S ribosomal RNA (rRNA) genes of bacteria. Recently, high-throughput methods based on sequencing of untargeted DNA of the whole microbiome genome content in combination with newly expanded microbial gene catalogues, have dominated the field of microbiome analysis allowing microbiome species-strain-level resolution and functional gene assignment. Furthermore, multi-omic approaches including metatranscriptomics and metabolomics can be combined to help identify phenotypic microbial changes complementary to those observed by metagenomics and understand the dynamics of transcriptional regulation and metabolite production. Furthermore, the use of machine-learning algorithms is also helping to identify microbial gene or taxon-based signatures as disease biomarkers and as predictors of health outcomes (Rojo et al., 2017).

Although there is enormous potential of multi-omic approaches to unravel links between a compromised microbiome and disease status, there is still a need for experimental work. *In vitro* and *ex vivo* models are useful tools allowing for control of conditions when studying the complex interplay between food/chemicals, the gut microbiome and host physiology and confirm causality (Costa and Ahluwalia, 2019). Flow dynamic simulators mimicking the gastrointestinal tract are based around the partitioned cultivation of gut microbiota in dedicated bioreactors connected in series. They are highly reliable for microbial–chemical interaction studies, but they typically lack human cells. There have been recent developments on polarised epithelial cell lines grown on 3D scaffolds or microfluidic devices, which allows fluid flows and cyclic mechanical deformations like intestine peristalsis to be experienced and have the ability to facilitate co-culture of human intestinal cells with commensal microbiota for extended times (Bein et al., 2018).

Results of *in vitro* experiments, however, still need to be validated by further *in vivo* experiments. One model to study causality linking a compromised microbiome with human diseases is the germ-free murine model transplanted with human microbiota (Arrieta et al., 2016; Clavel et al., 2016). However, a potential drawback of this model is the lack of co-evolution between host and microbes of the donor and, consequently, the existence of functional deficits (e.g. affecting the immune system), which limits the extrapolation of results to humans. Alternatively, rodents with depleted microbiotas (by treatments with antimicrobials or chemicals e.g. polyethylene glycol), then re-colonised with the study microbiotas, are used (Le Roy et al., 2019).

Most of the research study models developed to explore the biological role of microbiomes may still need some adaptation before becoming useful for risk assessment. In the long term, models and methods for integration into future testing strategies for regulatory science will need to be standardised and adopted by the OECD and their members.

The understanding of the microbiome may also impact future interpretations of the results from animal models used in toxicity testing where the metabolic pathways and functions of the gut microbiome of laboratory animals may be significantly different from that of human microbiomes. This may support the understanding of some of the variability observed between toxicological animal studies and results in humans. This may reveal the need of using alternative or more complex study models, considering the microbiome variability between animals and humans. Also, in the light of the current trend to reduce animal testing for generating data on the safety of chemicals in the food chain, and moving towards more mechanistic data derived increasingly from *in vitro* testing and extrapolated from *in silico* models, it is important that the role of the gut microbiome is not overlooked. Devising complementary *in vitro* and *in silico* approaches for assessing the impact on and role of microbiome in chemical risk assessment may thus also be an important future avenue of research.

Soil microbiome and its relationship with plants and agriculture ecosystems

The soil microbial community represents the greatest reservoir of biological diversity in the world. The rhizosphere is the soil region in which microorganisms are most abundant, because of the richness in plant photosynthates as well as secondary metabolites such as flavonoids that inhibit or stimulate

targeted microorganisms. Plants may also secrete quorum sensing-interfering compounds that manipulate gene expression in the soil community. The collective genome of the rhizosphere microbiome is referred to as 'the plant second genome', and has crucial function for the plant, ranging from the recruitment of essential nutrients to boosting the defensive capacity against pathogens. The functions of the rhizosphere microbiome and its relationship with plants resemble those that the gut microbiome has with its animal host. The rhizosphere microbiome is composed not only of bacteria and fungi, which are the dominant population, but also of Archaea, Protists and viruses.

The balance within soil microorganisms is directly related to plant health and soil fertility. This balance may be impaired by several anthropogenic factors, such as antibiotics, heavy metals and plant protection products (PPP). Antibiotics and antibiotic-resistance bacteria can be found in soil mainly through irrigation with reclaimed wastewater and organic fertilisers. Antibiotics can have a microbiocidal effect on organisms in soil. Moreover, antibiotic resistance genes can be transferred to soil bacteria and vice versa, but our knowledge on the ecology of antibiotic resistance in soil needs to be improved (Christou et al., 2017). Heavy metals and metal nanoparticles have adverse effect on the soil microbiome causing reduction of its biodiversity, a slower decomposition of the organic matter and a selection of metal-tolerant microorganisms. Several studies have shown that PPP can be degraded in controlled conditions, but in agricultural soil this process is slow. It has been shown that some PPP affect the soil nitrification pathway thus impairing soil functionality (Zhang et al., 2015). One debated factor in the evaluation of the potential risks posed by GM plants is the effect on the diversity and abundance of soil microbial communities. Several studies have shown that gene transfer from GM plants is less prevalent than natural transformation and may not have a significant impact on the soil microbiome structure and activity, although further studies are necessary (Guan et al., 2016).

Therefore, the soil microbiome is crucial for the conservation of soil health particularly under changing environmental and/or management conditions and the preservation of its integrity is important under environmental risk assessment. It remains to be clarified how current environmental risk assessments could capture possible indirect effects of plant and soil microbiomes on soil fertility and plant health. There are no standardised approaches to characterise a healthy soil from a microbiome perspective but targeted microbial groups useful for this purpose can be defined and selected as the starting point for a protocol to study the links with microbial biodiversity, metabolic functions and interaction with anthropogenic factors. Links to the protection goals for risk assessment based on biodiversity and ecosystem services (EFSA Scientific Committee, 2016) remain to be established. This vast diversity could be studied by using advanced sequencing tools. These tools can also support further identification of the fungal, viral and archaeal diversity as ideally the microbiome should be evaluated in its integrity. Moreover, a lot of considerations relevant to the gut microbiome could also be extrapolated to soil microbiome, in particular in relation to methodological approaches to evaluate microbiome function.

Currently, several Horizon 2020 EU initiatives are investigating systems-level microbiome effects on the whole food chain (plant/soil, terrestrial and marine ecosystems) from a wider perspective, applying similar principles and methodologies to those used in human microbiome research. Among these, the Microbiome Support Action is mapping all the microbiome actions in the EU and beyond, identifying knowledge gaps and opportunities to delineate the future research agenda in this field, encompassing all ecosystems and their cross-links. EFSA can contribute to the Horizon 2020 microbiome program by identifying needs from a risk assessment perspective.

Conclusions

Gut microbiome research is expected to play a relevant role in regulatory science with potential implications for future risk assessments and predictive risk models. Considering that the gut microbiome is a biological component directly and indirectly involved in the metabolism of food/feed components and chemicals and in the protection of the host against adverse environmental exposure, it would be useful to establish criteria on how to evaluate the potential adverse impacts of perturbators on this defensive barrier, and consequently, on human/animal health. Furthermore, research is needed to enhance our understanding of the toxicological significance of microbiome-mediated metabolism of chemicals, with the aim to propose strategies that include the microbiome as an integrated part of a multi-organ host response.

Sequencing-based tools and multi-omic approaches for risk assessment still need considerable work to refine and integrate them into study design as well as analytical standardisation. Synthetic communities are also a promising research tool to test the role of specific microbes and microbial genes in model

systems. All in all, these powerful tools will contribute to understanding the complexity of microbial communities and their interaction with the environment and the host and their health consequences.

Preservation of the integrity of the soil microbiome, crucial for soil health and functionality, is an important consideration in environmental risk assessment. For this purpose, target microbial groups essential for soil functionality could be selected and monitored, in addition to whole microbiome richness and diversity through advanced sequencing tools.

Microbiomes are highly relevant to the health status of their hosts. Therefore, it is desirable to understand the importance of their role in risk assessment. These are opportune times for EFSA to start preparatory work on microbiomes for future scientific assessment challenges. To start building this capacity, EFSA launched a thematic grant[2] in March 2020 on this topic to collaborate with EU Member States. The outcome will provide indications for future EU research agendas with a focus on specific needs from a risk assessment perspective.

As microbiome assessment lies at the very heart of the intersection of chemical and biological risk assessment, it will provide ample opportunities in the future for these two disciplines to collaborate and foster mutual understanding on their respective risk evaluations.

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Abbreviations

CNBBSV	Comitato Nazionale per la Biosicurezza, le Biotecnologie e le Scienze della Vita
NASEM	National Academies of Sciences, Engineering, and Medicine
PAH	polycyclic aromatic hydrocarbon
PPP	plant protection products