Towards a sustainable and circular, microbiome-based bioeconomy

Call for action to foster microbiome research: a driver for future-proof food systems & circular economy innovations

Microbiomes (a.k.a. microbial communities) consist of trillions of bacteria, viruses and fungi. They exist within and on humans, animals and plants in both terrestrial and aquatic environments, and play a key role in shaping life on our planet. Microbiome research will significantly influence innovations in health and disease management, food system safety and productivity, and ecosystem health. Therefore, microbiomes have the potential to play a crucial part in the 21st century's circular economy. Despite this, awareness and support for this promising field are still to be enhanced.

Globally, knowledge about the microbiome is expanding rapidly. Europe is taking part in a worldwide race to unearth the best available discoveries and develop scientific techniques for understanding and managing the microbiome for the benefit of society. These gains in knowledge reveal that microbiome-based solutions may be key for the development of a modern circular economy and a sustainable, fair and healthy food system. For instance, microbial communities might play a leading role in fighting diseases and infections with microbiome modulation through pro- or prebiotics, potentially increasing health benefits; they may better control plant pests through bio-based agents, or degrade and revalourise waste and wastewater through catalytic bioprocesses and protect environments by acting as bio-sensors. Overall, innovative microbiome applications have the potential to create sustainable high-value alternatives to conventional approaches in health and food system management whilst reducing burdens on soils and waters and decreasing greenhouse gas emissions.

To support and encourage this upcoming field, microbiome researchers are asking for the engagement of decision-makers in governments, parliaments and funding institutions. By now, the human microbiome has been characterised in great depth; however, considering the whole food system from primary production to waste management, as described under the FOOD 2030 policy[1], the potential of microbes to improve environments benefitting health and well-being is still mostly untapped.

Priority improvements suggested

- **Better regulation:** A One Microbiome concept comparable to the One Health approach (protecting the integrity of human, animal, plant, soil, food, feed and environmental health) is suggested as an appropriate policy vision to provide guiding principles for safety and registration rules — ideally, a single microbiome-based food law.
- **More, and more coherent, research funding:** Microbiome research needs to become a research field on its own. Aligned funding programmes in the fields of food, agriculture and the environment (e.g. within the upcoming Horizon Europe programme), will avoid costly duplication. EU funding should include large infrastructures such as biobanks and easy-to-use open science platforms.
- **Harmonised rules:** Concise safety standards and evaluation requirements (including the clarification of legal frameworks) concerning different microbes used in food, feed, biocontrol and biopreserving are a prerequisite for the safe production, application and consumption of microbiome-based products. These should also be communicated to the public to build their trust.

Microbiome research attracts great interest

The microbiome is a hot topic in both national and international media. Though much of what we know about microbiomes remains relativel obscure, the ongoing discovery of the microbial potential to provide societal challenge-oriented solutions is seen as a chance by key global players.

Bill Gates, the founder of Microsoft and co-chair of the Bill & Melinda Gates Foundation, points to the microbiome as central to solving the challenge of malnutrition, obesity and many inflammatory diseases. Funding from the foundation may, in the future, target a better understanding of nutrition for the gut microbiome that could help, within the next 10-20 years, to save the lives of millions. According to Gates, 'that deeper understanding is why I predict we're going to solve malnutrition.'[2]

The Organisation for Economic Cooperation and Development (OECD) characterises microbiome research as a most promising scientific field that can help solve major challenges. Yet to have real impact, advances are required in five areas: science policy, the enabling of applied science, public–private cooperation, regulatory frameworks, and skills, communication and public awareness.[3]

The **International Bioeconomy Forum**, a worldwide platform for scientific and governmental exchange on bioeconomic developments, regards the microbiome and the knowledge about it as one of the key factors in the fight against climate change and ensuring food and nutrition security as well as global health.[4]

The policy brief presented here, issued by the EU-funded project **MicrobiomeSupport** and its **Innovation Actions** (see fact sheet), aims at bringing attention to the needs of, and deficiencies and bottlenecks in, microbiome research and innovation (R&I).

This paper can be used to raise awareness amongst private funders, stakeholders in higher education, science communicators, associations and citizens that are affected by the outcomes of microbiome research activities. Above all, the publication is a call for political decision-makers at various levels to improve regulations so that they consider the complexity of microbial communities and emphasise microbiomes as an integral part in research funding — and an appeal for investment in both the necessary infrastructure and the relevant start-ups working on efficient, innovative efforts. This is elaborated on in the 'Action is needed!' section below.

Several legislative proposals that will affect the future starting position of microbiome-related discoveries and developments are underway at EU and at national levels. This paper provides an **overview of the opportunities and challenges** involved, with an emphasis on food systems and the circular economy. **The initial improvements suggested** are listed in the current brief, and more details are to be provided as the projects develop.

The challenges: widespread fragmentation

Microbiome R&I is widely fragmented, not only across scientific disciplines but also within regulatory contexts, which is posing barriers to the efficient deployment of viable microbiome products and therapies. Currently, microbiome research is a sub-set of, or an appendix to, research within the fields of agriculture, food, health and the environment. Rarely is the microbiome considered as an active and prominent member of the environment.

Within funding programmes, food safety legislation or other management cycles the microbiome is usually not taken into consideration at a top level. This leads to dispersed and often incomplete results, leaving microbiome research in a disadvantaged position compared to major research sectors.

Research fragmentation that needs to be overcome

- Different research languages, methods, protocols and technologies and incoherent or inexistent rules for data sampling, collection, use and storage hinders the comparison of research results across disciplines, labs and fields.
- There are no standardised classifications and definitions for microbiome-based products and processes.
- Microbiome issues are dispersed across various policy fields (intellectual property rights; registration procedures, including data requirements for product applications; safety protocols in production processes and end-user safety).

To validate research, and concurrently foster the development of regulations that facilitate the commercialisation of applications, common standard operating practices need to be defined. They need to be robust and flexible, leaving provision for adaptation in response to the rapid advances in technology.

The industry will not implement methods and protocols if they are not standardised. Research may not advance if basic EU research infrastructures (such as biobanks or IT-infrastructure including support for, and retainment of highly qualified and trained personal are not established.

Regulative gaps to be avoided

Trusted relationships among researchers, industry, suppliers, consumers and the public are the *sine qua non* condition for introducing innovative microbiome-based medical and nutritional applications. This is equally true for improving the performance of the food system, which may imply microbial release into environment.

- Clarity in safety and efficacy standards, therefore, is crucial. However, divergent standards between the coverage and scope of the evaluation of food microbes, for example of those traditionally used as probiotics (*lactobacilli* or *bifidobacteria*), and those for major commensal bacteria living with us, are confusing.
- Classifications and definitions of new microbiome products are not harmonised. Sometimes they are even contradictory, as is the case with, for example, probiotics, and biocontrol and biopreserving products.
- Every second new pesticide registered in the EU is a biopesticide. However, the registration procedures for what are known as 'biocontrol agents' (including both pest and soil control), are expensive and unclear. They also vary across individual countries. Current data requirements for their registration are often still designed for conventional chemicals and are unfit to be applied to new microbiome-based product protocols. This leads to expensive and time-consuming procedures. In the US the time to register a biocontrol agent does not exceed one year, while in the EU it takes more than five.

Overall, this is resulting in uncertainty for entrepreneurs and investors, and consequently causes fragmented marketplaces within the same classes of produce or within classes of biocontrol agents while being non-compliant to the EU's internal market rules. Guidelines need to be updated and assessment bodies must integrate microbiome considerations within their work.

Action is needed!

Policy and funding coherence: Modernising existing policies, such as the Common Agricultural Policy (CAP), is needed to support the transition towards a sustainable agri-food sector that can integrate the principles of a circular economy. This in turn is expected to stimulate microbiome R&I, which is fragmented across disciplines.

A coherent and aligned policy approach considering the interdependencies between different microbiomes in humans, animals, plants and environments demands a **One Microbiome concept** (protecting the integrity of human and other microbiomes) as a guiding principle in law and as a policy vision (comparable to the One Health approach). This would allow more coherent policymaking within the CAP, food laws, and feed additive regulations and innovation policies, as it would also result in a more integrated and coherent funding of microbiome research in the fields of agriculture, health, food and the circular economy, particularly in the light of the HorizonEurope research programme (2021-27). The EU should take a front-runner role in pursuing an integrated approach, to end confusion and uncertainty for all actors.

Better research coordination: To support the urgently needed transformation of food systems, microbiome research requires upgrading and alignment on an international level, including more long-term funding for large-scale trials, better infrastructures (e.g. biobanks for storing samples and isolates, bioinformatic databases, computing power for large-scale analyses of microbiome data as well as for storing and sharing data efficiently and transparently), human resource and maintenance support. Excellent and collaborative microbiome research under HorizonEurope demands the completion of initiatives, such as thematic networks within the European Research Area (the ERA-Nets Cofund scheme) and the Joint Programming Initiatives, to coordinate national funding and programming with that on an EU level.

Consistent food microbes' legislation: One single source of food microbe laws for food (production, processing and consumption) might overcome the current incoherencies and gaps. The same applies for probiotic legislation and legislation regarding biocontrol agents. There is a demand for minimum requirements to legally define a probiotic or prebiotic in the microbiome context to advance innovation.

Common standards: The coverage and scope of the safety assessment of taxonomic microbe units used in food, feed, biocontrol and biopreserving agents lack the harmonisation needed to ensure the overall safe production, application and consumption of microbiome-based produce across the EU. Pre-product-launch safety and efficacy data provisions should be updated regularly to reflect new technologies and food safety techniques. Registration procedures for biocontrol products need to be simplified and harmonised.

Microbiome research and the Nagoya Protocol: Existing concerns about the Diversity Nagoya Protocol on Access and Benefit Sharing may lead to issues around securing intellectual property and conducting research that will adversely affect investment and translation. European countries have highly diverse practices in applying this protocol: from very restrictive to no application at all. International agreement should be sought on the implementation of the Nagoya Protocol in relation to microbiome research. The rising loss of biodiversity also affects the microbiome and may lead to considerations and dialogues about whether key elements of human (maybe also animal, plant and soil microbiomes in the context of specific cultures) should be recognised as part of our global heritage.

Platforms: EU-wide knowledge exchange platforms need to be established through workshops, expert

panels and clear, transparent and openly available reference documents (facilitating coordination between industry stakeholders or associations and policy institutions) about regulatory needs and adaptations of, among other things, safety standards and registration rules. Academia needs to be actively involved via coordination and support actions, which have, alongside other initiatives, a responsibility to contribute to the future strategic programming of agri-food microbiome research and innovative actions. They can also ensure better coordinated feedback from microbiome research to policy.

Microbiome literacy and technology assessment: Microbiome literacy efforts require clear public-awareness messages about the benefits, risks and misconceptions of microbiome innovations. Serious investment is demanded for adequate school and adult education as well as for science communication to ensure microbiome literacy. Given the current hype on the microbiome in the mediam there is a danger of overselling the scope of microbial innovation. Unexpected detrimental consequences (or side effects) and long-term impacts of optimising microbiomes need to be carefully investigated, as do the GMO aspects of microbiome R&I. Improved technology assessment capacities at national and EU-level can help manage expectations.

Consumer rights and citizen participation: To ensure transparency for consumers, microbiome products must be clearly labelled. Further, models of citizen participation, allowing co-creation for addressing potential risks and issues, need to be adopted for microbiome applications that may influence lifestyles and food consumption patterns through new forms of environmental management or waste and wastewater treatments. Both, labelling and participation will enable informed choices and democratic decisions for citizens. Public authorities and scientists need to initiate and lead the process of education, communication, expectation management and participation to foster trust.

The rewards: healthy guts, nutritious food, clean and sustainable environments

According to the OECD, a global food increase of 70 %, especially for protein and fibre, is needed by 2050[3]. This raise in agricultural productivity needs to be obtained under changing climate conditions and with declining soil and water quality. At the same time there is a strong need to improve European food systems in terms of sustainability, quality, nutritional value, safety and international competitiveness.

MicrobiomeSupport project partners are currently mapping all ongoing microbiome research internationally, from basic to applied research (i.e. product development activities) including available infrastructures and facilities in the field of food- and health-related microbiome research. The goal is to gain a clearer picture of potential future funding pathways in Europe and beyond.

According to the **Microbiology Society**,[5] current general approaches to managing and modulating the microbiome for increased benefits range from introducing beneficial microbes into existing microbiomes, to promoting beneficial microbiome diversity and functionality by managing environmental conditions. Other approaches include the development of diagnostics, predictive models and biomarkers (incl. applications for the prediction of diseases, enhancing food safety and monitoring environments), the prospecting of microbiomes as sources for new products, and the design of synthetic microbiomes with particular function(s).

Advancements will aim at the best available applications for better health and well-being, clean and sustainable environments, disease-resistant crops and soils, the degradation and revalourisation of waste and wastewater, climate mitigation and multi-billion-euro markets.

MicrobiomeSupport: projects, partners and stakeholders

The Horizon 2020-funded coordination and support action MicrobiomeSupport (www.microbiomesupport.eu) has been financed with EUR 3.5 m for 36 months (2018-2021). The action is a close collaboration of 36 academic and governmental partners (including two associated partners) from 13 EU countries and 7 international partners from non-EU countries. The consortium is working together with over 100 Advisory Group members, ranging from government agencies to academic institutions and industry stakeholders (including the support of the IBF working group Food System Microbiome).

MicrobiomeSupport's objectives are to:

- Harmonise the methods, approaches and standards used in microbiome research in different environments (e.g. soil, plants, aquatic, animals, humans, etc.) to ensure robust data for economic and public health;
- Support international efforts to align funding (to avoid the unnecessary duplication of research and maximise existing/previous projects and data, specifically through coordinating with the IBF's working group Food Microbiomes);
- Raise public awareness on the potential of microbiome applications;
- Map ongoing international research and facilities to draft a joint R&I strategy and agenda in the context of the wider bioeconomy and circular economy research.

Four Innovation Actions (IAs), funded under Horizon 2020 and including academic and industrial partners, are focused on applied research to trigger innovative development. They collaborate with MicrobiomeSupport.

The four Innovation Actions are:

MASTER (www.master-h2020.eu): Development of knowledge and commercial products for the safety of food across multiple food chains, to include marine, plant, soil, rumen, meat, brewing, vegetable waste, and fermented foods. The focus is on technologies and enterprise.

SIMBA (www.simbaproject.eu): Development of microbial product solutions, including viable terrestrial and aquatic microbiomes for soils, plants and waters to foster food security through sustainable agro- and aquacultures.

CIRCLES (www.circlesproject.eu): Development of knowledge of food system microbiomes to implement a vast panel of smart microbiome modulators (SMMs), such as pro/prebiotics, fermentative agents, and energy and waste management cultures.

HOLOFOOD (www.holofood.eu): The focus is on understanding the host (animal) and associated microbiome interplay and impact in response to natural feed additives within two popular food systems, salmon and chicken, resulting in optimised and sustainable food production systems.

Selection of governments, councils & research agencies as advisors to MicrobiomeSupport

Federal Ministry for Sustainability and Tourism (previously BMLFUW), Austria
Council for Agricultural Research and Analysis of Agricultural Economics, Italy
Ministry of Higher Education and Science, Denmark
Department of Agriculture, Food and the Marine, Ireland
Estonian Research Council, Estonia
Ministry of Higher Learning, Research and Innovation, France
Standing Committee on Agricultural Research, France
International Scientific and Technological Cooperation Directorate at the General Secretariat for Research and Technology, Greece
Spanish Foundation for Science and Technology, Spain
National Centre for Research and Development, Poland
Microbial Research Resource Infrastructure, MIRRI, Portugal

References

[1]European Commission (2018) FOOD 2030: Future-proofing our food systems through research and innovation. DOI: 10.2777/188064.

[2]Paul Brackley (2019) Bill Gates makes two big predictions for global healthcare in Cambridge Union speech. Cambridge Independent, 7 October.

[3]OECD (2017) The microbiome, diet and health: Towards a science and innovation agenda. OECD Science, Technology & Innovation Policy Paper 42.

[4]Agriculture and Agri-Food Canada (2019) International Bioeconomy Forum. Website.

[5]Microbiology Society (2017) Unlocking the microbiome: opportunities and challenges of microbiome research for health and agriculture. Website.