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OPINION

Concepts and criteria defining emerging microbiome applications

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Abstract

In recent years, microbiomes and their potential applications for human, animal or plant health, food production and environmental management came into the spotlight of major national and international policies and strategies. This has been accompanied by substantial R&D investments in both public and private sectors, with an increasing number of products entering the market. Despite widespread agreement on the potential of microbiomes and their uses across disciplines, stakeholders and countries, there is no consensus on what defines a microbiome application. This often results in non-comprehensive communication or insufficient documentation making commercialisation and acceptance of the novel products challenging. To showcase the complexity of this issue we discuss two selected, well-established applications and propose criteria defining a microbiome application and their conditions of use for clear communication, facilitating suitable regulatory frameworks and building trust among stakeholders.

MICROBIOME FUNCTIONS RAISE OPPORTUNITIES FOR NOVEL APPLICATIONS TO ENABLE SUSTAINABLE AGRI-FOOD PRODUCTION AND TO IMPROVE HUMAN AND ENVIRONMENTAL HEALTH

Microbiomes are defined as characteristic communities of microorganisms occupying well-defined habitats with distinct physico-chemical properties. The microbiome consists of an assembly of microorganisms, including bacteria, archaea, fungi, protists and algae, and their "theatre of activity", including structural and mobile elements, enzymes, metabolites, signal molecules, and the surrounding environmental conditions (Berg et al., 2020). Microbiomes "are in, on and all around us" and have a crucial role in maintaining life on Earth (Małyska et al., 2019). Recent data demonstrates that all higher eukaryotes depend on specific interactions with "their" microbiome and the related functional traits. Animals and humans have established a symbiotic relationship with microbial communities that substantially influence their physical and mental health, nutrition and behaviour (Ogunrinola et al., 2020; Peixoto et al., 2021; Sessitsch et al., 2023; Simon et al., 2019). Similarly, the plant microbiome is key to abiotic and biotic stress resilience, health and growth of plants (Chepsergon & Moleleki, 2023; De Mandal & Jeon, 2023; Hassani et al., 2018; Sessitsch et al., 2023). This high importance of microbiomes for the health of their particular host has been acknowledged in the term metaorganism or holobiont (Rosenberg & Zilber-Rosenberg, 2016). Consequently, microbiome innovations can potentially bring benefits to all fields of life, enabling the production of more sustainable food, feed and biobased products, as well as improving the health of humans, animals, plants, and the environment, while underpinning the principles of circularity (D'Hondt et al., 2021). For example, microorganisms have been exploited for plastic degradation, lowering CO_2 emissions or treating and recycling wastewater (Antranikian & Streit, 2022). This potential has been acknowledged by policymakers (EC, 2020; FAO, 2019), and substantial public and private funds have been invested in the development of microbiome applications (Eisenstein, 2022; Hadrich, 2020), with products starting to enter the market (Olmo et al., 2022). The ongoing transition from R&D to product development has raised various issues/questions that must be addressed to ensure the successful implementation of these novel applications. Therefore, an extensive exchange between diverse stakeholder groups is needed to improve public awareness of microbiomes and acceptance of microbiome applications, as well as to manage expectations. To facilitate this, more coherent communication is essential. At the same time, there is no clear concept of what a microbiome application is, with different fields and sectors following different rationales and employing different concepts. End-users, e.g., consumers, farmers and healthcare professionals, must understand the concept of current and upcoming microbiome applications, their benefits, current limitations and potential risks or downsides. Unclear communication can result in misperception and mistrust, but also in overly optimistic and unrealistic expectations among non-expert end-users, policymakers, funders and regulators. Raising expectations and not delivering on them could jeopardise trust and consequently negatively affect the development of the microbiome field through reduced funding and private investment, diminished policy support and consumer acceptance, and thus prevent full exploration and exploitation of these valuable natural resources. This disparity also poses a significant challenge to the establishment of an appropriate and unified regulatory framework, with the current legislative landscape being fragmented over different fields of applications. Even though regulatory organisations have recognised the need to include microbiomes in the regulatory scientific assessment of risks and benefits (Cordaillat-Simmons et al., 2020; Merten et al., 2020; Trivedi et al., 2021), the development of regulatory guidelines for assessing the risk and benefits of microbial strains and consortia is still in progress.

CATEGORISING AND DEFINING MICROBIOME APPLICATIONS

Tremendous advances in microbiome research in the last decade have led to the development of diverse microbiome solutions. Currently, many of these solutions are based on the application of single microbial strains, such as probiotic strains in the food industry or microbial inoculants used to improve crop production, and/or microbial modulation approaches like prebiotics. However, more complex and diverse solutions are in development, including, for example the application of more complex microbial consortia (Qian et al., 2020; Shayanthan et al., 2022), precision microbiome-modulating compounds (Silva et al., 2022; Tian et al., 2020) or microbiome prediction tools and diagnostics (Marcos-Zambrano et al., 2021; Wilhelm et al., 2022). Considering the increasing complexity of microbiome applications, it is even more important to consider natural microbiome fluctuations, such as those caused by changes in management practices, lifestyle or environmental factors, as well as the growing understanding of the functioning and interconnectedness of microbiomes throughout different systems (Sessitsch et al., 2023).

Several concepts related to microbiome applications have been elaborated. Foo et al. (2017) defined microbiome engineering as altering the microbial composition to improve host phenotypes and ecosystem quality. They presented a range of microbiome engineering strategies, including enzymes, prebiotics, probiotics, microbiome transfer, signalling molecules, drugs, agricultural management, and synthetic biology approaches. Additional strategies include the application of synbiotics (Swanson et al., 2020) or phages (Federici et al., 2021; Khan Mirzaei & Deng, 2022) and genetic improvement (Arnold et al., 2023). A somewhat different perspective focuses on the ecological principles of microbiome engineering that could be used to design and control microbiomes (Bernstein, 2019). Although it is indisputable that all strategies will affect microbial composition and/or function, the question arises of whether all these strategies can be categorised as microbiome applications. Debatable issues include how to categorise the use of individual microbial strains versus more complex microbial communities or how to address different management practices, such as specific soil fertilising or dietary/feeding regimes or the use of specific antibiotics, that are known to affect microbiome composition and/or function. Here, we have not considered approaches wiping out a major part of the microbiome, like detergents or broad-spectrum antibiotics.

We propose that a microbiome application is knowledge-based and/or microbiome data-driven, with measurable and predictable effects on the microbiome (function, diversity), thereby also having beneficial effects on the targeted host or (eco)system. Ideally, the mode of action is understood. Within these criteria, microbiome applications can comprise highly complex microbial communities, strain combinations or individual strains. Also, specific microbiome modulators and data-driven approaches, e.g., diagnostics, are included in the proposed concept (Table 1). With the upcoming deluge of increasingly comprehensive datasets on microbiomes and their interactions with the environment and within the holobiont, it can be expected that an increasing number of precision microbiome applications will reach the market. According to these criteria, we propose that a microbiome application is either (i) the direct use of microorganisms, microbial consortia, metabolites, or enzymes, or (ii) the manipulation of environmental or process variables to achieve a desired, beneficial functional effect on a targeted system.

Overall, we consider it important to distinguish between natural microbiome fluctuations (representing untargeted microbiome effects) or black box approaches, semi-understood and precision interventions (Figure 1). The composition, functionality and activity of microbiomes are affected by a wide range of factors, including environmental factors (e.g., temperature, oxygen content, nutrient availability, pH, humidity, host genotype) and, where relevant, lifestyle of the host (e.g., diet, physical activity, stress). Natural or induced changes in these factors will inadvertently affect the composition and/or function of the microbiome; however, they have no target. We suggest explicitly excluding untargeted microbiome modulations, like different diets or fertilisation regimes, from the concept of microbiome applications. Notwithstanding, these correlations should be addressed in communication activities to raise awareness about the dynamic nature of microbiomes.

Microbiome applications that are currently commercialised or in more advanced stages of R&D (Table 1) can be classified as semi-understood microbiome applications. Based on their nature, we can distinguish between applications containing microorganism(s) that provide a direct service and microbiome modulators, i.e., applications that modulate the naturally occurring microbiome in a way that results in the targeted beneficial effect. Both types are based on the knowledge of the microbial activities but do not consider the individual interaction with the particular holobiont or environment to which they are applied and the other influencing factors. Examples would include microbial inocula or microbiome-directed foods altering the composition of a microbiome in a desired way (Hibberd et al., 2024; Silverstein et al., 2023).

Emerging applications of well-understood microorganisms or microbiome modulations could be defined as precision applications if the mode of action and effects on the environment or the targeted microorganism are clearly understood. Such comprehensive knowledge will provide the basis for very specific fine-tuning, adjustment and improvement of any application. The understanding of the interactions between microbiomes and their environments (including holobionts) deepens, and there are efforts to integrate microbiome data with other "big data" from the targeted (eco)system, (e.g., environmental/lifestyle data, genotypic and phenotypic data of the host) to develop data-driven and tailor-made ("personalised") precision microbiome applications (French et al., 2021; Zhang et al., 2023). For instance, microbiome, -omics and environmental data might be used to predict which type of microorganism will best perform in a specific environment or holobiont, or multiple data can be used to clearly define the environmental parameters to yield a desirable microbiome exhibiting certain functions. The integration of artificial intelligence approaches is expected to further advance development of the precision microbiome applications (Kumar et al., 2022; Xiong et al., 2024). While also semi-understood microbiome applications might yield the expected effects, we expect that precision applications, based on the holistic understanding of the targeted (eco)system and utilising prediction models, will have a high probability of eliciting the expected beneficial effects. Furthermore, corresponding microbiome diagnostics can be used to reinforce the link between applications and effects. The implications and potential impact of such comprehensive and interdisciplinary/systemic approaches were highlighted by Zhang et al. (2023) who advocated for the establishment of

TABLE 1 Overview, assessment and categorisation of different microbiome applications.

Microbiome application characteristics	Application examples	Knowledge base	Precision level examples (semi-understood ⇒ precision application)	Current status of technology & key regulatory aspects
Application of microorganisms, microbial consortia or metabolites and enzymes				
Single strains	Probiotics improving human, animal and plant health and resilience; Microbial biocontrol strains (e.g., against a plant disease or insect damage); Starter cultures (e.g., to improve food flavour)	Well-defined taxonomy and proven, beneficial, targeted effects; Ideally, mode of action is known	Randomly selected universal probiotic mix used by the healthy individual (low probability of eliciting desired beneficial effect) ⇓ Universal probiotic mix used after, e.g. antibiotic use or illness causing dysbiosis in the gut microflora (higher probability of eliciting desired beneficial effect) ⇓ “Personalised” probiotic mix prescribed to an individual patient after establishing the exact nature of gut microflora dysbiosis via microbiome analysis (highest probability of eliciting desired beneficial effect)	Well-established, broadly used; regulatory requirements widely ranging depending on use, e.g., EU 2019/1009 and national fertiliser laws for biofertilisers, EU 284/2013 for microbial biocontrol strains
Synthetic microbial communities (“SynComs”) (of different complexities)	“SynComs” able to compete/establish well in receiving environment (e.g., soil or plant) and have targeted effects such as disease prevention	Well-defined composition; selected based on a comprehensive microbiome dataset and elaborated bioinformatic analysis; Measurable effect; Ideally, mode of action is known	SynCom of all organisms known for their plant growth-promoting activities applied to different plants under various environmental conditions (e.g., nutrient availability, presence/absence of biotic and abiotic stressors) (low probability of eliciting desired beneficial effect) ⇓ SynCom of selected organisms that are applied to defined plant species under defined environmental conditions (e.g., lack of specific nutrient or presence of specific abiotic or biotic stressor) (higher probability of eliciting desired beneficial effect) ⇓ SynCom of selected organisms that are applied to defined plant species under defined environmental conditions (e.g., lack of specific nutrient or presence of specific abiotic or biotic stressor and considering the naturally present microbiome) (highest probability of eliciting desired beneficial effect)	Mostly tested and applied in research; high interest of the industry; Regulatory issues unresolved, regulation partly strain-based and not-community-based (see above)

TABLE 1 (Continued)

Microbiome application characteristics	Application examples	Knowledge base	Precision level examples (semi-understood ⇒ precision application)	Current status of technology & key regulatory aspects
Enriched microbiomes	Enrichment cultures, e.g., for bioremediation applications	Defined composition; selected based on beneficial, desired effects (e.g., degradation of xenobiotics); Measurable effect; Ideally, degradation genes/pathways are known	Universal bioremediation consortium documented to promote degradation of defined contaminants applied to any site contaminated with this contaminant ⇓ Tailored bioremediation consortium adjusted to the specific characteristics of the contaminated site (e.g., composition of naturally occurring microbiome, availability of nutrients, oxygen)	Emerging use; Loose regulation
Natural, complex microbiomes	Faecal and vaginal microbiota transplantation; Rumen transfaunation; Soil transplantation	Selected based on proven, beneficial effects; Measurable effect; Ideally, microbiome composition is defined, and donor microbiome is selected based on a comprehensive dataset	Transplantation from any healthy donor to any sick recipient ⇓ Targeted matching of donor and recipient based on a set of defined parameters (e.g., microbiome composition, fitness, genotype)	Emerging use (particularly faecal microbiota transplantation (FMT) against *Clostridium difficile*); Regulatory issues unresolved; Requirements depending on use
Microbiome-modulating microorganisms and phages	Currently researched, e.g., for enhancing plant stress tolerance	Measurable, targeted effects; Well-defined taxonomy; Microbiome-modulating effect defined	Microbiome modulating organism or compound added to any targeted system (e.g., plants under drought stress)	Subject of R&D
Microbiome-modulating metabolites/compounds; enzymes	Prebiotics; Signalling compounds; Quorum sensing molecules; Synbiotics; etc.	Measurable, targeted effects; Microbiome-modulating effect defined	⇓ Microbiome modulating organism or compound added to the targeted system after pre-selection based on a set of defined parameters (e.g., the composition of naturally occurring microbiome)	Prebiotics are broadly used; Many other applications are the subject of R&D
Data-driven microbiome applications				
Environmental parameters/technical settings known to modulate microbiomes in a desired manner	Wastewater treatment; Biorefineries; Biological production	Measurable, targeted effects; Microbiome-modulating effect defined	Standard processing settings based on empirical knowledge of biological- or chemical-engineering principles ⇓ Modified processing settings depending, e.g., on the microbiome composition of the incoming material and current environmental conditions	Mostly empirical knowledge available; Underlying mechanisms subject of R&D
Management practices known to modulate microbiomes in a desired manner prediction of best practices	Specific crop management practices (crop rotation, mixed cropping etc.)	Measurable, targeted effects; Microbiome-modulating effect defined	Standard crop rotation/intercropping based on empirical knowledge/experience ⇓ Targeted selection of the crops based on the, e.g., soil microbiome composition, environmental conditions and planned subsequent crop	Mostly empirical knowledge available; Microbiome effects and functions poorly understood; Increasing amount of data will lead to a better knowledge base and data-driven approaches

(Continues)

TABLE 1 (Continued)

Microbiome application characteristics	Application examples	Knowledge base	Precision level examples (semi-understood ⇒ precision application)	Current status of technology & key regulatory aspects
Nutritional practices known to modulate microbiomes in a desired manner	Therapeutic foods	Measurable, targeted effects; Microbiome-modulating effect defined	Special diet for all individuals suffering specific health conditions ⇒ Personalised diet for the individual suffering specific health condition or fitness improvement (based on, e.g., individual genotype and gut microbiome composition)	Emerging use, still mostly in R&D phase; Increasing amount of data will lead to a better knowledge base and data-driven approaches
Diagnostics	Microbiome indicators of (human, animal, plant) diseases	Established database and data-driven identification of diagnostic indicators/markers	Precision application per definition	Emerging use

microbiota medicine as a new branch of modern clinical medicine that would include the study of the interaction between microbiome and the host, development of microbiome diagnostic techniques and therapies, conservation of human microbiome diversity and development of appropriate healthcare policies and medical education.

The importance and impact of the proposed definition criteria are indicated in Table 1. Below we elaborate our concept in more detail on two widely recognised and used microbiome applications: probiotics for human/animal use (example 1) and microbial bioremediation solutions (example 2).

Microbiome application example 1: Probiotics for human/animal use

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (Hill et al., 2014). Different probiotics are widely available on the market, and consumer acceptance is high. There is clinical evidence supporting some probiotic health benefits (Sanders et al., 2016). However, the evidence for their effectiveness in reducing disease risk factors in healthy populations is still lacking (Kristensen et al., 2016). The International Scientific Association for Probiotics and Prebiotics (ISAPP; https://isappscience.org/) strongly advocates for high-quality research to deepen the understanding of this microbiome application and enable evidence-based communication, development of applicable regulatory frameworks and improvement of end-user trust (Hill et al., 2014; Jackson et al., 2019).

Fermented foods are a (re-)emerging food trend, rising in popularity due to the widely perceived health benefits (Ibrahim et al., 2023; Soemarie et al., 2021). There is evidence that fermented foods can affect the gut microbiome (Leeuwendaal et al., 2022; Mukherjee et al., 2023; Stiemsma et al., 2020), however, these effects are currently neither targeted nor predictable. Even though some specific types of fermented animal feed, have been shown to have a targeted, lasting positive effect on the gut microbiome that is even more pronounced if the change of feed regime is initiated prior to animal insemination (Olmo et al., 2022). Still, according to the proposed microbiome application definition criteria, the consumption of fermented foods would be seen as an untargeted application. This is in agreement with the recent opinion of the ISAPP that comprehensively elaborates on the potential and the limitations of fermented foods and calls for the application of stringent criteria, i.e., documented health benefit, sufficient product characterisation and testing, for the classification as probiotics (Vinderola et al., 2023).

Probiotic supplements with known composition (strain designations and quantities) and ideally

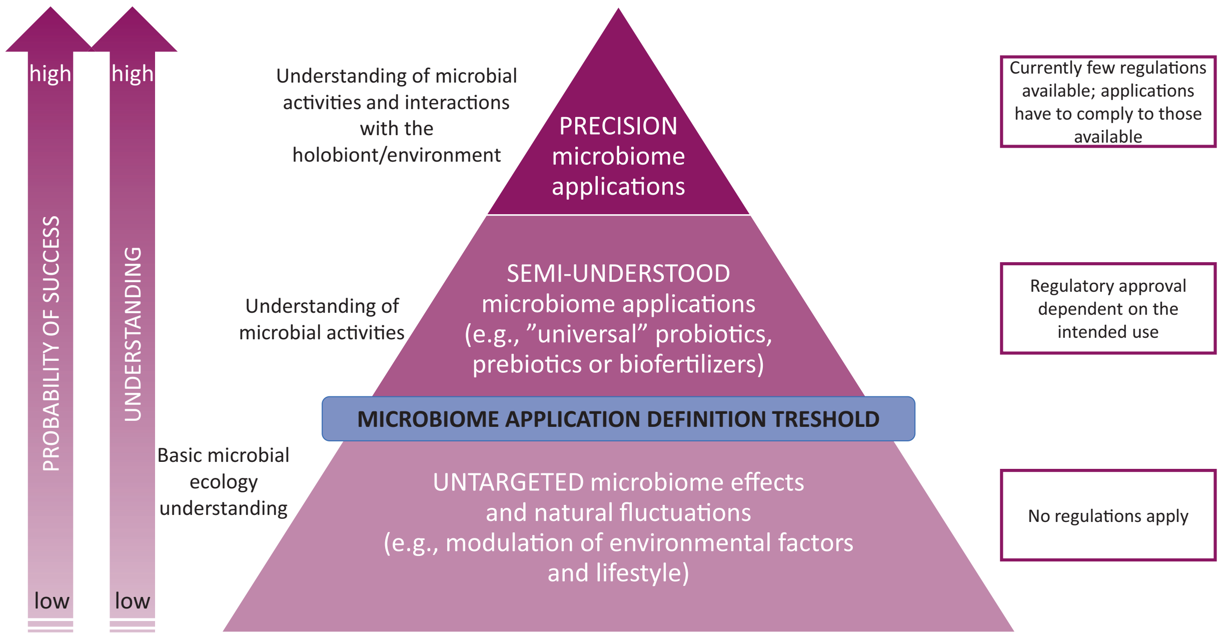

FIGURE 1 Overview of different microbiome approaches in relation to the underlying knowledge and probability of success (i.e., the probability to reproducibly elicit a targeted beneficial effect). The proposed threshold for defining microbiome applications is based on the current level of knowledge and selected to distinguish between natural fluctuations or black box approaches and targeted, knowledge-based interventions. It is to be expected that some of the microbiome applications, listed in Table 1 as semi-targeted, within the next few years may move to the category of precision microbiome applications for the benefit of people, animals, plants and soil.

evidence-based benefit claims would fulfil the proposed criteria and could thus be classified as microbiome applications. Nevertheless, how these are applied would differentiate between semi-understood and precision applications. Currently, there is insufficient scientific evidence to inform the determination of intake recommendations for the general population (Kristensen et al., 2016; Marco et al., 2020). Accordingly, the use of a randomly selected universal probiotic mix by the healthy individual would be classified as a semi-understood microbiome application. The beneficial effects of probiotic supplements for alleviating specific conditions are, on the other hand, better documented (Hutchinson et al., 2021; Sanders et al., 2016). Based on the growing scientific evidence, knowledge-based decision-making tools are emerging. For example, the Alliance for Education on Probiotics (AEProbio; https://aeprobio.com/) provides the Clinical Guide to Probiotic Products (https://aeprobio.com/get-the-guide/). This guide is based on the annual extensive, systematic literature review to evaluate and provide an unbiased summary of the scientific evidence for specific brands of probiotics. It enables healthcare providers to select the appropriate product, dose, and formulation for a specific condition and clearly indicates the level of evidence on which this recommendation is based. Accordingly, the occurrence of desired and targeted beneficial effects is more probable. This was also showcased in several recent reviews assessing the effects of single- or multi-strain probiotic formulations on Parkinson's disease patients (Chu et al., 2023; Leta et al., 2021; Tan et al., 2021). Most prominently, positive effects on constipation were demonstrated through supplementation with *Lactobacillus casei* Shirota, a mix of *Streptococcus salivarius* subsp. *thermophilus*, *Enterococcus faecium*, *Lacticaseibacillus rhamnosus* GG, *L. paracasei*, *Lactobacillus acidophilus*, *L. delbrueckii* subsp. *bulgaricus*, *Lactiplantibacillus plantarum*, *Bifidobacterium breve* and *B. animalis* subsp. *lactis* or a mix of *Lactobacillus acidophilus*, *L. reuteri*, *L. gasseri*, *L. rhamnosus*, *Bifidobacterium bifidum*, *B. longum*, *Enterococcus faecalis* and *E. faecium* (Tan et al., 2021). This approach is thus fully compliant with the proposed criteria for the precision microbiome application.

Microbiome application example 2: Microbial bioremediation

Microbial bioremediation is making use of microorganisms and/or their derivatives to clean up contaminants (Tekere, 2019). The potential of microorganisms for bioremediation is well documented (Ayilara & Babalola, 2023; Kour et al., 2022). However, it is often a complex process and, accordingly, challenging to optimise and control, esp. in situ, i.e., in the natural environment (Tekere, 2019). The bioremediation efficiency depends on the suitability of the selected microorganism(s) and environmental parameters, such as concentration of the contaminants, nutrient and oxygen availability, pH and temperature.

For example, members of the genus *Dehalococcoides* are well-known as key dechlorinating bacteria in sites contaminated with chlorinated ethene (Saiyari et al., 2018). The first described member of this genus was *Dehalococcoides mccartyi* strain 195, which was reported in 1997 to reductively dechlorinates tetrachloroethene to ethene (Maymó-Gatell et al., 1997). Even though available literature does not provide evidence of failed bioremediation application attempts, considering the underlying complexity of *Dehalococcoides* spp.-based bioremediation, it is safe to hypothesise that the semi-understood application of *Dehalococcoides* spp. would have a low probability of success. The genome analysis of *D. mccartyi* strain 195 (published in 2005) revealed the organism's complex nutrient requirements and provided a foundation for developing assays for environmental detection and monitoring of this organism (Seshadri et al., 2005). In their comprehensive review published in 2018, Saiyari et al. (2018) showed the progress made in the understanding of the system and its critical parameters, i.e., the concentration of *Dehalococcoides* sp. in the targeted environment and composition of the microbial community, presence of specific metabolic pathways, environmental conditions. They exemplified that the development of precision applications necessitates a fully integrated approach and the establishment of a broad knowledge base which is in agreement with the proposed criteria for defining microbiome applications. The successful use of *D. mccartyi* in bioremediation is nowadays evident in the availability of commercialised products such as SDC-9™ (RNAS Remediation Products) or KB-1® (SiREM) bioaugmentation cultures that are characterised through known product composition, cell concentration and targeted application guidelines.

DEFINING MICROBIOME APPLICATIONS FOR THE BENEFIT OF DIFFERENT STAKEHOLDERS

Depending on the intended use and applicable regulations, microbiome products have to fulfil different criteria regarding their safety and efficacy. Existing regulations do not specifically consider upcoming microbiome applications like complex microbiomes, specific microbiome modulators or microbiome-based diagnostics. Furthermore, the regulatory landscape is highly complex and greatly depends on the geography of approval or application and, most importantly, on the claims made. For example, the safety assessment of probiotics considered to be novel foods, i.e., strains that have not been consumed to a significant degree by humans before 15 May 1997, is performed according to the principles outlined in the EU Regulation 2020/1824 on Novel Foods. At the same time, probiotics belonging to species with a history of safe consumption and QPS (qualified presumption of safety) compliance are commercialised without additional safety assessments. The use of specific health claims requires, however, an additional assessment under the EU Health Claims Regulation 1924/2006, while the use of the term probiotic as a generic nutritional claim depends on national laws. Also, in the United States, the Food and Drug Administration's (FDA) regulation of products containing probiotics is complex and largely depends on the claims that are made for the product. They can be regulated as foods, dietary supplements, cosmetics, or drugs/biologics. Plant protection products with microorganisms as active ingredients are regulated in the EU according to the Regulation 1107/2009, whereas microbial fertilisers are regulated in the EU Fertilising Products Regulation. Microorganisms used for bioremediation are rarely regulated. Currently, most regulations consider the application of individual microorganisms or a limited number of strains, and more complex products or applications need to be implemented. A general framework on different types of microbiome applications will help to identify common issues related to assessing the safety and potential risks of microbiome applications and will help to overcome the fragmented regulatory landscape. Furthermore, considering that precision microbiome applications are based on increasingly comprehensive and multi-disciplinary datasets, it can be expected that risk assessment, function and efficacy prediction and validation will become key components of product development and will facilitate regulatory approval.

We need to acknowledge that microbiome applications are slowly, but surely leaving the "scientific ecosystem" and entering the realm of other stakeholders that have different expertise, expectations and needs. Therefore, it is essential to establish accurate and evidence-based communication anchored in a coherent and precise understanding of key concepts. This is in line with the concept recently proposed by the International Microbiology Literacy Initiative (Timmis et al., 2024).

We believe that establishing coherent criteria, such as those proposed here, for defining microbiome applications is essential as it would provide common understanding, facilitate acceptance by stakeholders and end-users through consistent and evidence-based communication and ensure that emerging regulations are suitable and knowledge-based. The needs and benefits of a clear framework for different stakeholder groups are shown in Box 1. Furthermore, a precise categorisation (Table 1, Figure 1) will also help to develop consensual, efficient and effective procedures required for licensing, registration and bringing microbiome applications to the market, ultimately strengthening microbiome research, use and impact at large.

Finally, we would like to emphasise that the proposed categorisation of current and upcoming microbiome

BOX 1 Needs and benefits of different stakeholder groups from a framework defining microbiome applications

The **General Public,** including consumers and potential users of microbiome applications, aims to not only have access to safe, efficient and sustainable products or applications, but also should have the knowledge basis to make good product choices. Literacy on beneficial microorganisms is still poor and microorganisms are frequently considered as detrimental. Therefore, there is a need to communicate both the principles of microbiology and microbiome applications, their potential benefits and risks to the general public in an understandable and non-misleading way. A framework laying out the different application types and creating awareness of different applications, e.g., being either microorganisms, certain metabolites or prebiotics, will help consumers/users understand the basic principles and how to distinguish from untargeted microbiome modulations, e.g., through diet or agricultural management.

Policymakers and Regulatory authorities have the responsibility to pave the path for the market introduction of new products, based on their benefits for the consumer and the society, and after careful risk assessment. The policy sector needs to develop suitable policies and strategies to assess the safety of new products. For an emerging technology, such as that based on microbiomes, a framework categorising different microbiome application types will help to frame risk assessment strategies according to the target but also to the type of application.

The **industry** aims to exploit the potential of microbiome-based (or microbiome modulating) applications and needs to develop safe, efficient and (economically and environmentally) sustainable products. Regulatory approval procedure(s) and timing will greatly influence the costs of a product and determine the time to market entry. A regulatory framework and clear guidelines will inform companies on the needed data for approval and enable them to deal efficiently with regulatory issues. The industry will also benefit from educated users and consumers being able to make qualified product choices.

applications and the threshold for implementation (Figure 1) are based on the current level of knowledge and represent the first effort to address this issue coherently. With future advancements in knowledge and data availability, the microbiome application concept will evolve, and more restrictive thresholds might become applicable.

AUTHOR CONTRIBUTIONS

Tanja Kostic: Conceptualization; writing – original draft; funding acquisition; project administration. **Michael Schloter:** Conceptualization; writing – review and editing. **Paulo Arruda:** Conceptualization; writing – review and editing. **Gabriele Berg:** Conceptualization; writing – review and editing. **Trevor C. Charles:** Conceptualization; writing – review and editing. **Paul D. Cotter:** Conceptualization; writing – review and editing. **George Seghal Kiran:** Conceptualization; writing – review and editing. **Lene Lange:** Conceptualization; writing – review and editing. **Emmanuelle Maguin:** Conceptualization; writing – review and editing. **Annelein Meisner:** Conceptualization; writing – review and editing. **Leo van Overbeek:** Conceptualization; writing – review and editing. **Yolanda Sanz:** Conceptualization; writing – review and editing. **Inga Sarand:** Conceptualization; writing – review and editing. **Joseph Selvin:** Conceptualization; writing – review and editing. **Effie Tsakalidou:** Conceptualization; writing – review and editing. **Hauke Smidt:** Conceptualization; writing – review and editing. **Martin Wagner:** Conceptualization; writing – review and editing. **Angela Sessitsch:** Conceptualization; writing – original draft; funding acquisition; project administration.

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The authors declare no competing interests.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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