Perspective

Received: 29 September 2020 Revised: 6 November 2020 Accepted article published: 17 November 2020 Published online in Wiley Online Library: 11 December 2020

(wileyonlinelibrary.com) DOI 10.1002/ps.6177

Why has the authorization of microbial biological control agents been slower in the EU than in comparable jurisdictions?

Ingvar Sundh[a]* and Jørgen Eilenberg[b]

Abstract

The aim of this study was to identify reasons why the authorization of microbial pest control agents is lengthier under regulatory frameworks of the European Union (EU) than in comparable jurisdictions. A main conclusion is that although the EU's regulatory processes have strong scientific foundations, the most appropriate scientific concepts, knowledge and expertise have not been applied in the safety assessment of microorganisms and biological control. Tradition and conceptual legacies from assessments of conventional chemical pesticides have likely contributed to this by steering the evaluations of microorganisms in less appropriate directions. According to our investigation, the current framework for microbial plant protection products complies poorly with the principles that legislation should have legal predictability, proportionality, and that it should be non-discriminative, for instance in comparison to corresponding regulations in comparable jurisdictions. We also found that existing possibilities to take non-safety and ethical considerations into account can probably be used more. To rationalize the EU's authorization of microbial control products, both the basic legislation and the evaluations of agents and products need stronger rooting in fundamental microbiological science.

Supporting information may be found in the online version of this article.

Keywords: microbial control agents; regulatory framework; legislation; biological control; biocontrol; plant protection products; integrated pest management; IPM; European Union

1 INTRODUCTION: THE NEED TO EXPAND USE OF MICROBIAL PEST AND DISEASE CONTROL

With anticipated increases in the human global population, the protection of food crops from pests (including plant diseases) is likely to be a high priority for the foreseeable future. Accordingly, the United Nations declared 2020 as the International Year of Plant Health (http://www.fao.org/3/ca0324en/CA0324EN.pdf). The dependence on conventional chemical active substances for crop protection that has prevailed since the middle of the 20th century is now challenged by ambitions to increase use of alternative crop protection measures with less adverse side effects on humans and the environment. In the European Union (EU), the sustainable pesticide use Directive[1] stated that by 2014 all EU countries should have implemented integrated pest management (IPM), in which alternative approaches not involving application of conventional chemical active substances should be the first choices, if available. Stricter legislation has led to withdrawal from the market of many chemical pesticides that do not meet current safety standards, adding to a shortage of available control solutions to farmers.[2,3] One alternative approach is biological control, where 'natural enemies' are used to control pest organisms. Antagonistic or insect pathogenic microorganisms (fungi, bacteria, viruses and other), insect parasitic nematodes, and arthropod predators and parasitoids, have all been successfully applied in biological control.[4] Moreover, new microbial strains that are promising biological control agents are continuously being isolated and characterized.[5]

A report from the EU Parliament expressed concern over poor implementation of the provisions of the sustainable pesticide use Directive and of IPM, and concluded that little progress has been made in promoting alternative techniques.[6] However, in the 'Farm to Fork Strategy',[7] the EU Commission recently identified actions to further promote use of alternative approaches for crop protection and facilitate the placing of products containing biological active substances on the market.

2 THE PROBLEM: SLOW IMPLEMENTATION OF MICROBIAL CONTROL

In many jurisdictions, rules concerning microbial pest control agents (MCAs) and products have been incorporated in the regulatory framework covering production and use of pesticides.[8,9]

* *Correspondence to: I Sundh, Swedish University of Agricultural Sciences, Department of Molecular Sciences, PO Box 7015, 750 07 Uppsala, Sweden. E-mail: ingvar.sundh@slu.se*

[Corrections added on 11 January 2021, after first online publication: Minor typographical errors were corrected in Section 4.]

a *Department of Molecular Sciences, Swedish University of Agricultural Sciences, Uppsala, Sweden*

b *Department of Plant and Environmental Sciences, University of Copenhagen, Frederiksberg C, Denmark*

Regulatory provisions for MCAs is a global phenomenon, and not restricted to Western countries or any particular geographic region.[8] In the EU, MCAs are categorized either as plant protection products (PPPs) or biocides (all pesticides that are not PPPs). Thus, they are approved (active agents) and authorized (formulated products) according to the systems initially developed for chemical pesticides (see Table 1 for basic features of the regulatory process). Our focus is on the regulation of PPPs, but many of the issues and principles we address are also relevant for the regulation of microbial biocides.

From a societal policy perspective, regulatory measures for any products should be tailored to the specific potential hazards and risks they pose. Unnecessarily strict regulations can discourage innovation, retard scientific and technological progress,[19,20] and lead to waste of resources.[21] In contrast, excessively permissive policy can leave the public and environment exposed to unpredictable, potentially severe, risks.

Many studies published in recent decades have stressed that regulatory frameworks for MCAs have been significant barriers to the implementation of microbial control of pests in practice.[22-28] Moreover, the average time for authorization of an MCA-product has been substantially longer in the EU than in comparable jurisdictions.[13,15,24] Recent studies have confirmed that the EU is lagging behind other countries when it comes to practical implementation of MCAs, and that this is due to the complex and lengthy authorization processes.[16,29] This implies that suboptimal regulatory frameworks have slowed transition towards IPM in pest management and regulation of pest populations through exploitation of ecological interactions between pests and their natural enemies.[23,30,31] It has been shown that the performance of approval processes can have strong effects on the economic incentives to make investments in new technologies and products.[32] Thus, improved authorization processes for MCAs in the EU are likely to have a positive impact on investments and market release of new MCA-products.

3 OBJECTIVES AND OUTLINE

The objectives of this study are to:

Table 1. Basic features of the regulatory framework for plant protection products (PPPs) in the EU, with emphasis on microbial active agents

Feature	Specifications	References
A pan-European framework	Before the beginning of the 1990s, any regulation of MCAs for plant protection was under national oversight and regulatory policies differed among countries. This situation changed with the introduction of the common European regulation for plant protection products (Directive 91/414). Directive 91/414 was subsequently replaced by Regulation 1107/2009. Several review articles provide further details on the historical developments of regulatory policies for MCAs.	*Quinlan 1990*[10] *EU 1991*[11] (first common EU regulation of PPPs) *EU 2009*[12] (Regulation 1107/2009 for PPPs) *Ravensberg 2011*,[13] *Sundh & Goettel 2013*[14] (historical development of regulatory policies for microbial PPPs)
Authorization in two steps	Microbial PPPs are registered in EU in two steps: (i) the so-called 'active substance' (i.e. the microorganism) is approved at EU level; and (ii) formulated products are authorized at member state level. Note than even though an MCA is a live, biological entity, it is referred to as a 'substance', in line with the terminology for pesticides. The basic criteria for evaluating MCAs and their corresponding formulated products are that they should be: (i) safe (for the human public and the environment); and (ii) efficacious.	*Hauschild et al. 2011*,[15] *Frederiks & Wesseler 2019*[16] (more details on authorization procedures for microbial PPPs)
Two categories of active 'substances'	An 'active substance' of a PPP can be either a 'chemical' or a 'microorganism'. Microorganisms include bacteria, fungi, protozoans, viruses and viroids. The chemicals category of PPPs includes, apart from traditional chemical actives, semiochemicals and other biologically produced compounds, and extracts from plants or other organisms.	Although they are categorized as chemical active substances, specific guidance has been developed for semiochemicals (https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app-proc_guide_doss_semiochemicals-201605.pdf) and botanical active substances (https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app-proc_guide_doss_botanicals-rev-8.pdf).
Legal documents for microbial PPPs	The same framework and procedures as for chemical PPPs (overarching Regulation 1107/2009) are applied. However, specific data requirements (Directive 2001/36) and uniform evaluation principles (Directive 2005/25) for microbial agents and products have been developed. These define the information that has to be provided with the application dossier, thus defining the topics that will form the basis for the risk assessment.	*EU 2001*[17] (data requirements microbial PPPs) *EU 2005*[18] (uniform evaluation principles microbial PPPs) For the purpose of legal and administrative adjustments to the updated PPP regulation (1107/2009), the data requirements and uniform principles were subsequently re-published (but not updated) together with the corresponding requirements for chemicals in Regulation 283/284/2013 and Regulation 546/2011, respectively.

Pest Management Science published by John Wiley & Sons Ltd on behalf of Society of Chemical Industry.

• Briefly consider what can reasonably be expected from a scientific and a legal perspective of regulatory frameworks for MCAs.

• Identify attributes of the regulatory frameworks that might have contributed to the slower uptake of MCAs in the EU than in other jurisdictions.

• Recommend actions that may lead to simpler and more appropriate evaluation processes in the future.

We examined the functionality of the current regulatory system according to three categories of principles and criteria (adapted from Zetterberg & Edvardsson Björnberg 2017[33]). The first is the suitability of the current regulatory framework's scientific foundations in terms of relevance and utility for assessing the safety of microbial pest and disease control measures and in terms of scientific adaptability, i.e. the ability to adjust the regulations in accordance with scientific progress and developments.[20,34]

The second category of principles includes legal certainty, non-discrimination and proportionality. Legal certainty refers to regulations' precision and understandability of both their clauses and the clauses' implications, especially for those to whom they apply. According to the principle of non-discrimination like risks should be treated alike,[35] i.e. a regulatory policy should not favor or disfavor any type of products over others that pose similar risks, without sound, explicit reasons. According to the principle of proportionality, governmental regulatory measures (for protecting humans or the environment) should be effective, necessary and balanced,[36] i.e. they should serve public interests and not be replaceable by equally effective but less intrusive measures. These three factors (legal certainty, non-discrimination and proportionality) partly overlap and should not be considered in isolation.[33]

The third category of principles concerns the extent that current frameworks allow non-safety and ethical considerations. Here we addressed the role of the efficacy requirement for authorization of new microbial products. We also examined whether the framework leaves room for considering sustainability arguments (e.g. that MCAs may be less harmful to humans and the environment than chemicals they can replace) and socio-economic benefits.

Procedural and bureaucratic factors can also have impacts on the performance of the evaluation and authorization processes. For instance, in contrast to the EU, in the USA MCAs are evaluated by a dedicated unit for evaluations of 'biopesticides', but still under the general pesticide regulatory framework (FIFRA). However, such procedural factors are not the subject of this study.

4 ARE CURRENT SYSTEMS ADEQUATE FOR REGULATING MICROBIAL CONTROL AGENTS?

4.1 Scientific foundations

4.1.1 Relevance of the science

For several decades, the legal frameworks and evaluations of MCAs in the EU and USA have been recurrently criticized for placing too much emphasis on chemical toxicology and ecotoxicology, and hence chemical risks, rather than the biological and ecological properties and specific potential risks associated with microorganisms.[13,14,25,27,29,37–43] For example, a review published 40 years ago of the first, national registration in Europe (France) during the 1970s of an MCA against plant diseases included the following comment: 'However, a major problem is that existing rules were designed for new chemical compounds, not microorganisms, so that a granting of a sales permit calls for a rational interpretation of these rules by competent authorities'.[37] Remarkably, today, after implementation in the early 1990s of Directive 91/414 for PPPs (the first EU-wide framework to include both chemical active substances and microorganisms), the EU's process for evaluating MCAs is still not well adapted for microorganisms.[42,43] However, since control of MCAs was incorporated into a new, precautionary framework intended to cover risks associated with production and use of xenobiotic chemical pesticides, it is perhaps not entirely surprising that this system has been suboptimal, or even poor, for evaluating potential risks associated with living microorganisms.

Suboptimal legislation and evaluations of MCAs could conceivably have been due to generally low levels of scientific progress and experience in microbiological safety assessment and biological pest control. However, we find this explanation unlikely, since the practical possibility of microbial pest control was established in the first half of the 20th century, with the commercial introduction of products based on *Bacillus thuringiensis* against insects in the 1930s.[44] Moreover, by the beginning of the 1980s, the concept of microbial control of both insects and plant diseases had been developed and presented, together with well-reasoned guidelines for risk analysis, safety testing and registration of bacterial MCAs.[45–47] For example, in 1980 Burges 'concluded that the basis for risk analysis of pesticidal bacteria is now well established'.[45]

Thus, we conclude that the problems in incorporating MCAs in the EU's PPP regulations and subsequent development of specific regulatory documents for MCAs were not due to a general lack of scientific knowledge. Instead it was due to a lack of sufficient attention to available, relevant biological knowledge regarding microbiological safety assessment and microbial pest control.

The data requirements (DRs) and uniform evaluation principles (UPs) regarding MCAs provide foundations and guidelines of the EU's risk assessment regime and steer the risk assessors and evaluations to certain topics. However, although the legislation was developed specifically for microorganisms, some of the requirements seem to have little relevance, or even be impossible to fulfill, for microorganisms.[14,15,42,43] We also note that neither the DRs nor the UPs treat MCAs as the live biological control agents they are, but instead as 'active substances' of pesticides. Each document mentions 'biological control' or 'biocontrol' only once, and does not refer to the microorganisms actually evaluated as biological control agents, but to potential negative effects of the microbial PPP on any resident natural enemies exerting macrobiological pest control. Thus, the current legislation appears to promote a view that the potential risks of MCAs are best assessed within a chemical paradigm.

The available resources and expertise of the agencies involved influence the time it takes to complete an authorization process for a new MCA.[48] In the EU, responsibility for assessments of all PPPs, chemical or microbiological, is allocated to the same regulatory institutions and units. Since chemical pesticides have dominated the PPP market for decades, allocation of resources for recruitment of microbiological expertise to assess the specific potential risks posed by microorganisms may have been neglected. Moreover, experience and expertise related to MCAs can vary among the national authorities.[49]

We conclude that inadequate attention by the regulatory institutions to recruitment of microbiological expertise has likely contributed to the EU's slower authorization of MCAs.

Pest Management Science published by John Wiley & Sons Ltd on behalf of Society of Chemical Industry.

4.1.2 *Scientific adaptability*

Regulatory systems should ideally have scientific adaptability, i.e. ability to take new scientific and technical findings into account.[20,34] If new risks are identified, additional precautionary measures may be needed. Conversely, if scientific progress shows that suspected risks are unrealistic, regulatory demands can be relaxed. Clearly, for example, as the EU currently includes 28 member-countries with potentially different views and priorities, the PPP Regulation, DRs or UPs for evaluation are unlikely to be updated particularly often. However, the DRs providing foundations for the evaluations of MCAs were developed during the 1990s, as an Annex to the previous PPP Directive 91/414. Since then there have been huge advances in understanding of the phylogeny, ecology and molecular biology of microorganisms. Thus, the regulations have not been aligned with current microbiological knowledge. As an alternative to updating the basic legislation, a more efficient strategy might be to produce and update, on a more regular basis, documents providing guidance for applying the DRs and performing the assessments in practice. We note that while the European Food Safety Authority (EFSA) supported two systematic reviews on environmental and human safety assessment of microbial PPPs,[50,51] and regularly provide updated guidance on various scientific aspects of risk assessment and authorization of microorganisms in, for example, animal feed,[52] and of chemical PPPs,[53] EFSA do not develop guidance for evaluations of microbial PPPs.

4.2 Legal certainty, non-discrimination and proportionality

4.2.1 *Legal certainty*

According to the principle of legal certainty, a law should be precise and understandable by those to whom it applies. Factors that raise legal uncertainty include the long (in international terms) and unpredictable registration times of MCAs in the EU, which have putatively discouraged companies from registering their products for the EU market (presentation by P. Marrone of Marrone Bio Innovations at Informa Ag-Bio Congress in Amsterdam December 2015; IBMA White Paper[54]). It should be noted that following introduction of the first common EU regulation with Directive 91/414, the time required for approval of an active agent gradually declined from 6–8 to 3.5–4 years.[16] Increasing experience with evaluations of MCAs at the regulatory institutions probably played a major role in this reduction.[15] However, the EU time spans still compare very unfavorably with those in the USA, which were on average 1.5 to 2 years.[16]

Another uncertainty factor is the likelihood of MCAs fulfilling the criteria for low-risk category of PPPs introduced with regulation 1107/2009.[12] This regulation stipulates that when an 'active substance' of a PPP meets certain criteria, it can be approved as a low-risk substance, and thus approved for 15 years instead of the normal 10 years, and that national product authorizations should have a stricter timeline (at most 120 days). However, criteria for categorizing active agents as low-risk were not published until 2017,[55] and practical guidance for interpreting the criterion for microorganisms (that they should not have 'multiple resistance to anti-microbials used in human or veterinary medicine') was posted on the EU Commission website in November 2020. Nevertheless, it is anticipated that most MCAs will comply with these criteria and the EU Commission has published a list of MCAs that are considered likely to become low-risk.[56] While implementation of the low-risk concept has been slow and unpredictable to date, the assignment of MCAs to the low-risk category should enable rationalization and acceleration of their registration in the near future.

4.2.2 *Non-discrimination*

According to the principle of non-discrimination, like risks should be treated alike. Since, globally, authorization of MCAs is often incorporated in existing regulations of chemical pesticides,[8,9] we compared how some key aspects are treated in DRs of the EU and other countries (Supporting Information, Supplementary material S1). The comparison shows that some issues receive less attention and/or are treated more straightforwardly in other countries. A striking difference is in the attention to potential risks posed by 'metabolites', a word mentioned 83 times in total in the DRs and UPs of the EU, but only two, one and six times in corresponding Australian, USA and Canadian documents, respectively (Supporting Information, Supplementary material S1). It has been noted that the remarkable emphasis on 'metabolites' in the EU DRs is a legacy of the DRs for chemical PPPs, and that the DRs for microorganisms mix up secondary metabolites produced by microorganisms with degradation products (referred to as 'metabolites') of organo-chemical pesticides.[43] This lack of clarity in the DRs has probably contributed to complications and delays in evaluations. This is because for regulatory experts familiar with evaluating chemical PPPs, the word 'metabolite' (when used in either context) may be a risk alert. This example shows that the EU framework can be said to 'discriminate' more against MCAs than the legislation of other countries.

4.2.3 *Proportionality*

According to the proportionality principle, regulatory measures for MCAs should be reasonably aligned with those for other types of microbes' applications in agriculture, food production and processing, or the environment. However, comparative analyses have demonstrated that regulations are substantially stricter for MCAs than for non-MCA beneficial (non-genetically modified) microorganisms used (for example) in plant growth stimulation, animal feed additives, fermentation of foodstuffs, novel foods, or environmental biotechnology, e.g. bioremediation).[57] An overview of other regulatory approaches taken for beneficial microorganisms is given in Table 2.

A comparison with the EU policy for microorganisms that stimulate plant growth and development by mechanisms other than pest or disease control is particularly interesting. Currently, such use of microorganisms is solely under national oversight within the EU, and the regulations vary strongly among the member states.[61,62] This will change with implementation of the new common EU Regulation 2019/1009 for fertilisers,[63] which includes provisions for 'biostimulants', including the product function category PFC 6A Microbial Plant Biostimulant (Supporting Information, Supplementary material S2). Before the new system is usable in practice, further guidance and criteria regarding the CE marking of microbial biostimulants need to be developed. Nevertheless, the limited information requirements and absence of a formal product authorization process for microbial biostimulants in Regulation 2019/1009 (Supporting Information, Supplementary material S2) is in contrast to the extensive DRs for MCAs of PPPs. Moreover, a single microorganism (e.g. a strain of *Bacillus* or *Trichoderma*) may be capable of interacting with plants in several ways, and organisms with pest or disease control and/or growth

Pest Management Science published by John Wiley & Sons Ltd on behalf of Society of Chemical Industry.

stimulation activities may be closely related.[64,65] This supports the view that the regulatory demands for MCAs in the EU are not proportional to the actual risks, and thus that MCAs might be considered 'overregulated'.

4.3 Inclusion of non-safety, ethical and socioeconomic considerations

Apart from potential risks, the EU legislation and evaluations of PPPs consider product efficacy, although it is evaluated during

Table 2. Overview of regulatory approaches for use of beneficial microorganisms in indicated sectors, relevant in view of the examination of the regulatory framework for microbial plant protection products in the EU

Framework	Basic features	Legislation	Comments, guidance documents etc.
EU feed additives regulation	Five product categories: - Technological additives - Sensory additives - Nutritional additives - Zootechnical additives - Coccidiostats and histomonostats	Regulation EC 1831/2003 on use of additives in animal nutrition (https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1551787423473&uri=CELEX:32003R1831). Regulation EC 429/2008 on rules for implementation of 1831/2003, including DR (https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1551787483183&uri=CELEX:32008R0429).	The DRs for all types of feed additives are given in Annexes to Regulation 429/2008. Several guidance documents have been produced and are available at EFSA´s website. (https://www.efsa.europa.eu/en/applications/feedadditives/regulationsandguidance).
EU novel foods regulation	- Definition: Any (type of) food that was not used for human consumption to a significant degree before 15 May 1997. - Covers MOs, as one of 10 categories. - Includes, with separate DRs, traditional food from a third country	Regulation EU 2015/2283 on novel foods (https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1551790766574&uri=CELEX:32015R2283). Implementing Regulation EU 2017/2469 with administrative and scientific requirements (https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1551790766574&uri=CELEX:32015R2283).	EFSA has produced several guidance documents concerning these regulations, available at: (http://www.efsa.europa.eu/en/applications/nutrition/regulationsandguidance). DRs for MO and other novel food categories are given in a guidance document by EFSA: Guidance on the preparation and presentation of an application for authorization of a novel food in the context of Regulation (EU) 2015/2283. (http://www.efsa.europa.eu/en/efsajournal/pub/4594).
EU food cultures	Microbial food fermentations (spontaneous or by addition of starter cultures) contribute unique, beneficial properties to food	The use of microorganisms in food fermentations does not require authorization, as long as it is considered as 'traditional use'.	Regulatory aspects of food fermentations have been reviewed by Bourdichon *et al.*[58]
EU biocides regulation	Specific DRs for MO, as for PPPs.	Regulation EC 528/2012 on authorization of biocides (https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1551789278401&uri=CELEX:32012R0528).	The DRs for MO in biocides are given in Annex II in 528/2012. A guidance document on microbial biocides has been developed by ECHA: (https://echa.europa.eu/documents/10162/23036412/biocides_guidance_micro_organisms_en.pdf/4d028d38-6d3c-4f2d-80f7-3aa2118ca49a).
New EU regulation for fertilizers	Covers microbial 'biostimulants', i.e. MO applied in crop production to improve: - nutrient use efficiency, - tolerance to abiotic stress, - crop quality	Regulation (EU) 2019/1009 on EU fertilizing products (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R1009&rid=1).	The new regulation stipulates that when the MO and the corresponding product fulfil two criteria, they can be added to a positive list, obtain CE marking and then be sold in the entire EU (see Suppl. material 2). Pre-market authorization not required.

Table 2. Continued

Framework	Basic features	Legislation	Comments, guidance documents etc.
National regulations for biostimulants in the EU	E.g. microbial plant strengtheners, plant growth-promoting rhizobacteria, diazotrophic bacteria in legumes	Some countries have systems for authorization of plant beneficial MO which are not classified as PPPs, others have not.	Microbial biostimulants that have not obtained CE marking according to the new fertilizers regulation can still be marketed in the EU, provided that any national regulations are respected. Overviews of regulations and DRs in different countries are presented in reviews by Traon *et al.*[59] and Caradonia *et al.*[60]
National regulations for 'microbial pesticides' outside EU	Categorization and evaluation procedures for what EU defines as microbial plant protection products vary among countries	International overviews have been given by Kabaluk *et al.*[8] and in an ARCHE/IBMA report (http://www.ibma-global.org/upload/documents/20180924archeibmaregulatoryframeworkreview.pdf).	DRs for 'microbial pesticides' in some comparable (to the EU) jurisdictions can be found at: **USA:** https://www.ecfr.gov/cgi-bin/text-idx?SID=738c16c85042ce20aec41a65fa12977e&node=40:24.0.1.1.9&rgn=div5#sp40.26.158.v **Australia:** https://apvma.gov.au/node/11196 **Canada:** https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/policies-guidelines/regulatory-directive/2001/registration-microbial-pest-control-agents-products-dir2001-02.html
EU legislation for use of MO in environmental or biotechnical applications (other than as agents of pest control), e.g. bioremediation	No common EU framework, but national legislation can be applicable	As an example, Sweden has an Environmental Act, containing provisions for 'Biotechnical organisms'. These state that anyone importing, producing, marketing or using a biotechnical organism is responsible for the safety of the operations. There are no actual data requirements, since there is no requirement for authorization.	

MO, microorganism; DR, data requirement; EFSA, European Food Safety Authority; ECHA, European Chemicals Agency.

the national authorization of the formulated products. MCAs may in some cases (but certainly not all) have lower efficacy than conventional pesticides, but they have several other benefits related to their potential replacement of more hazardous chemical pesticides. For instance, long-term adverse effects in e.g. groundwater or on human health due to persistence of harmful chemicals is not a significant issue with MCAs. It has been calculated that biocontrol of a wireworm in maize production in six European countries would provide an annual socioeconomic welfare gain, in monetary terms, of €190 million.[66] Another benefit of many MCAs is that since their mode of action is more complex than that of a single chemical, the targeted pests are less likely to evolve resistance to them, and if resistance evolves it can be countered by using other microbial strains.[67,68] Current EU legislation enables consideration of such benefits during the efficacy evaluation (see also EPPO guidance on evaluation of microbial PPPs[69]) and an expert group of the EU Council has proposed that for low-risk PPPs, such as many MCAs, there is scope within IPM for taking such benefits more into account.[48] Similarly, one outcome of an OECD workshop on strategies for implementation of IPM was a recommendation that so-called 'facilitative' policies should play a significant role in the move towards more sustainable agriculture.[70] We strongly encourage such approaches, as laid out in two sets of practical guidelines,[71,72] since stronger emphasis on the potential benefits of MCAs should further clarify their importance for the transition towards IPM.

5 CONCLUSIONS AND RECOMMENDATIONS

- As a starting point for discussion, it may appear logical to extend regulatory frameworks for pesticides to the regulation of microorganisms for biological control of harmful organisms. However, those frameworks were developed to address risks posed by xenobiotic chemicals, and were strongly influenced by tradition and conceptual legacies. Thus, they are unsuitable for regulation of live microorganisms. The traditions and expertise rooted in the science underlying the regulation of chemical pesticides have steered the DRs and evaluations of MCAs in less

Pest Management Science published by John Wiley & Sons Ltd on behalf of Society of Chemical Industry.

appropriate directions, thereby contributing to confusing evaluations and retarding implementation of microbial pest control in IPM, particularly in the EU.

- We have not found support for the idea that a general lack of scientific knowledge and progress has contributed significantly to the pesticide frameworks' functionality for authorization of MCAs. Rather, relevant knowledge regarding biological pest control, microbial ecology, and microbiological safety assessment has been available for several decades, but has not been sufficiently applied. Inexperience with MCAs and shortage of microbiological expertise at regulatory institutions have probably contributed to lengthy and complicated evaluations.
  We therefore emphasize that all responsible authorities involved in MCA assessment must possess appropriate in-house competence in microbiological sciences. For this, more resources might have to be allocated for recruitment of personnel with expertise in relevant aspects of microbiological sciences.
- Our investigation indicates that the amounts of resources, including time, devoted to EU authorizations of MCAs are not commensurate with the hazards associated with microorganisms for humans or the environment, or with more pertinent regulatory policies regarding their use in food, feed or other types of environmental applications. Thus, MCAs exemplify the principle that the primary focus of regulatory frameworks for any organisms or substances of biological origin should be on the intrinsic hazards and corresponding risks.

We therefore recommend that EU legislators intensify efforts to formulate and implement more resource-efficient regulation of MCAs, e.g. actions proposed in the Farm to Fork strategy. A revised framework should be better tailored to the specific properties and hazards of microorganisms and less to traditions associated with regulations of chemical pesticides. It should also be helpful to increase the awareness of all involved institutions about the undesirable consequences for evaluations of MCAs of the 'chemical' legacy of the PPP regulation, to avoid that such effects unnecessarily complicate authorizations of MCAs in the future.

As long as MCAs are evaluated within the PPP framework in the EU, we propose that the most strongly prioritized objectives should be to: (i) develop more adequate DRs and accompanying guidance; (ii) increase the number of dedicated microbiology experts at responsible institutions; and (iii) ensure that the simplification offered by the (likely) categorization of MCAs as low-risk 'substances' is realized.

ACKNOWLEDGEMENTS

Ingvar Sundh acknowledges support from the SLU Centre for Biological Control (CBC) at the Swedish University of Agricultural Sciences (https://www.slu.se/en/Collaborative-Centres-and-Projects/centre-for-biological-control-cbc/) and the EU Horizon 2020 project 'EcoStack - Stacking of ecosystem services: mechanisms and interactions for optimal crop protection, pollination enhancement, and productivity' (grant agreement number: 773554).

CONFLICT OF INTEREST

The authors declare that they have no involvements with companies or commercial interests that could be interpreted as a conflict of interest.

SUPPORTING INFORMATION

Supporting information may be found in the online version of this article.

REFERENCES

1 EU. Directive 2009/128/EC of the European Parliament and of the Council establishing a framework for Community action to achieve the sustainable use of pesticides. (2009). Available: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1598946978213&uri=CELEX:32009L0128 [1 September 2020].
2 Hillocks RJ, Farming with fewer pesticides: EU pesticide review and resulting challenges for UK agriculture. *Crop Prot* **31**:85–93 (2012).
3 Jactel H, Verheggen F, Thiery D, Escobar-Gutierrez AJ, Gachet E, Desneux N *et al*., Alternatives to neonicotinoids. *Environ Int* **129**: 423–429 (2019).
4 Van Lenteren JC, Bolckmans K, Köhl J, Ravensberg WJ and Urbaneja A, Biological control using invertebrates and microorganisms: plenty of new opportunities. *BioControl* **63**:39–59 (2018).
5 Bruisson S, Zufferey M, L'Haridon F, Trutmann E, Anand A, Dutartre A *et al*., Endophytes and epiphytes from the grapevine leaf microbiome as potential biocontrol agents against phytopathogens. *Front Microbiol* **10**:2726 (2019).
6 European Parliament. Report on the implementation of Directive 2009/128/EC on the sustainable use of pesticides. A8-0045/2019 (2019). Available: https://www.europarl.europa.eu/doceo/document/A-8-2019-0045_EN.html [29 October 2020].
7 EU 2020, A farm to fork strategy for a fair, healthy and environmentally-friendly food system. Communication from the EU Commission, COM(2020) 381. Available: https://ec.europa.eu/food/sites/food/files/safety/docs/f2f_action-plan_2020_strategy-info_en.pdf [30 October 2020].
8 Kabaluk JT, Goettel MS, Svircev AM and Woo SG, Use and regulation of microbial pesticides in representative jurisdictions worldwide. IOBC Global, 99 pp. (2010). Available: http://iobc-global.org/download/Microbial_Regulation_Book_Kabaluk_et_al_2010.pdf [1 September 2020].
9 FAO/WHO. Guidelines for the Registration of Microbial, Botanical and Semiochemical Pest Control Agents for Plant Protection and Public Health Uses. International Code of Conduct on Pesticide Management (2017). Available: https://apps.who.int/iris/bitstream/handle/10665/259601/WHO-HTM-NTD-WHOPES-2017.05-eng.pdf;jsessionid=788A594BE8EF2065644ED707EAD796C0?sequence=1 [1 September 2020]
10 Quinlan RJ, Registration requirements and safety considerations for microbial pest control agents in the European Economic Community, in *Safety of Microbial Insecticides*, ed. by Laird M, Lacey LA and Davidson EW. CRC Press, Boca Raton, pp. 11–18 (1990).
11 EU. Council Directive 91/414/EEC concerning the placing of plant protection products on the market. (1991). Available: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1598946600225&uri=CELEX:31991L0414 [1 September 2020].
12 EU. Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. (2009). Available: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1598947060441&uri=CELEX:32009R1107 [1 September 2020].
13 Ravensberg WJ, *A Roadmap to the Successful Development and Commercialization of Microbial Pest Control Products for Control of Arthropods*. Progress in Biological Control, Vol. **10**. Springer, Dordrecht, The Netherlands (2011).
14 Sundh I and Goettel MS, Regulating biocontrol agents: a historical perspective and a critical examination comparing microbial and macrobial agents. *BioControl* **58**:575–593 (2013).
15 Hauschild R, Speiser B and Tamm L, Regulation according to EU Directive 91/414: Data requirements and procedure compared with regulation practice in other OECD countries, in *Regulation of Biological Control Agents*, ed. by Ehlers R-U. Springer, Dordrecht, Heidelberg, London, New York, pp. 25–77 (2011).
16 Frederiks C and Wesseler JHH, A comparison of the EU and the US regulatory frameworks for the active substance registration of microbial biological control agents. *Pest Manag Sci* **75**:87–103 (2019).

17 EU. Commission Directive 2001/36/EC amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. (2001). Available: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1598946743456&uri=CELEX:32001L0036 [1 September 2020].
18 EU. Council Directive 2005/25/EC amending Annex VI to Directive 91/414/EEC as regards plant protection products containing micro-organisms. (2005). Available: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1598946836102&uri=CELEX:32005L0025 [1 September 2020].
19 Medley TL, Regulations: facilitating advancement or serving as a barrier – a shared responsibility, in *Nanotechnology: Delivering on the Promise Volume 1*, ACS Symposium Series, ed. by Cheng HN, Doemeny LJ, Geraci CL and Grob Schmidt D. American Chemical Society, Washington, DC, pp. 75–84 (2016).
20 Hansson SO, How to be cautious but open to learning: time to update biotechnology and GMO legislation. *Risk Anal* **36**:1513–1517 (2017).
21 Arrow KJ, Cropper ML, Eads GC, Hahn RW, Lave LB, Noll RG *et al*., Is there a role for benefit-cost analysis in environmental, health, and safety regulation? *Science* **272**:221–222 (1996).
22 Cook RJ, Assuring the safe use of microbial biocontrol agents: a need for policy based on real rather than perceived risks. *Can J Plant Pathol* **18**:439–445 (1996).
23 Waage JK, Biopesticides at the crossroads: IPM products or chemical clones? in *BCPC Symposium Proceedings No. 68: Microbial Insecticides. Novelty or Necessity?* British Crop Protection Council, Farnham, UK (1997).
24 Kiewnick S, Practicalities of developing and registering microbial biological control agents. *CAB Rev* **2**:1–11 (2007).
25 Chandler D, Davidson G, Grant WP, Greaves J and Tatchell GM, Microbial biopesticides for integrated crop management: an assessment of environmental and regulatory sustainability. *Trends Food Sci Technol* **19**:275–283 (2008).
26 Cuddeford V and Kabaluk JT, Alternative regulatory models for microbial pesticides, in *Use and Regulation of Microbial Pesticides in Representative Jurisdictions Worldwide*, ed. by Kabaluk JT, Goettel MS, Svircev AM and Woo SG. IOBC Global, pp. 94–98 (2010). Available: http://iobc-global.org/download/Microbial_Regulation_Book_Kabaluk_et_al_2010.pdf [1 September 2020].
27 Ehlers R-U, Regulation of biological control agents and the EU policy support action REBECA, in *Regulation of Biological Control Agents*, ed. by Ehlers R-U. Springer, Dordrecht, Heidelberg, London, New York, pp. 3–23 (2011).
28 Brodeur J, Abram PK, Heimpel GE and Messing RH, Trends in biological control: public interest, international networking and research direction. *BioControl* **63**:11–26 (2018).
29 Balog A, Hartel T, Loxdale HD and Wilson K, Differences in the progress of the biopesticide revolution between the EU and other major crop-growing regions. *Pest Manag Sci* **73**:2203–2208 (2017).
30 Hajek AE and Eilenberg J, *Natural Enemies: An Introduction to Biological Control*, 2nd edn. Cambridge University Press, Cambridge, United Kingdom, p. 454 (2018).
31 Togni PHB, Venzon M, Lagôa ACG and Sujii ER, Brazilian legislation leaning towards fast registration of biological control agents to benefit organic agriculture. *Neotrop Entomol* **48**:175–185 (2019).
32 Purnhagen KP and Wesseler JHH, Maximum vs minimum harmonization: what to expect from the institutional and legal battles in the EU on gene editing technologies. *Pest Manag Sci* **75**:2310–2315 (2019).
33 Zetterberg C and Edvardsson Björnberg K, Time for a new EU regulatory framework for GM crops? *J Agric Environ Ethics* **30**:325–347 (2017).
34 Jaffe G, Regulating transgenic crops: a comparative analysis of different regulatory processes. *Transgenic Res* **13**:5–19 (2004).
35 Miller HI, The regulation of agricultural biotechnology: science shows a better way. *N Biotechnol* **27**:628–634 (2010).
36 Winter G, Ecological proportionality: an emerging principle of law for nature? in *Rule of Law for Nature: New Dimensions and Ideas in Environmental Law*, ed. by Voigt C. Cambridge University Press, New York, pp. 111–129 (2013).
37 Corke ATK and Rishbeth J, Use of microorganisms to control plant diseases, in *Microbial Control of Pests and Plant Diseases 1970–1980*, ed. by Burges HD. Academic Press, London, pp. 717–736 (1981).
38 Cook RJ, Making greater use of introduced microorganisms for biological control of plant pathogens. *Annu Rev Phytopathol* **31**:53–80 (1993).
39 Jaronski ST, Goettel MS and Lomer CJ, Regulatory requirements for ecotoxicological assessments of microbial insecticides – how relevant are they? in *Environmental Impacts of Microbial Insecticides*, ed. by Hokkanen HMT and Hajek AE. Kluwer Academic Publishers, Dordrecht, The Netherlands, pp. 236–260 (2003).
40 Mensink BJWG and Scheepmaker JWA, How to evaluate the environmental safety of microbial plant protection products: a proposal. *Biocontrol Sci Technol* **17**:3–20 (2007).
41 Glare T, Caradus J, Gelernter W, Jackson T, Keyhani N, Köhl J *et al*., Have biopesticides come of age? *Trends Biotechnol* **30**:250–258 (2012).
42 Köhl J, Booij K, Kolnaar R and Ravensberg WJ, Ecological arguments to reconsider data requirements regarding the environmental fate of microbial biocontrol agents in the registration procedure in the European Union. *BioControl* **64**:469–487 (2019).
43 Scheepmaker JWA, Busschers M, Sundh I, Eilenberg J and Butt TM, Sense and nonsense of the secondary metabolites data requirements in the EU for beneficial microbial control agents. *Biol Control* **136**:104005 (2019).
44 Lord JC, From Metchnikoff to Monsanto and beyond: the path of microbial control. *J Invertebr Pathol* **89**:19–29 (2005).
45 Burges HD, Risk analysis in the registration of pesticidal bacteria: pathogenicity and toxicological aspects. *Ecol Bull (Stockholm)* **31**:81–90 (1980).
46 Burges HD, Krieg A, Lüthy P and de Barjac H, Guidelines for safety tests and registration of bacterial pesticides. *Entomophaga* **27**:225–236 (1982).
47 Cook RJ and Baker KF, *The Nature and Practice of Biological Control of Plant Pathogens*. American Phytopathological Society, St. Paul, MN, p. 539 (1983).
48 EU. Implementation plan on increasing low-risk plant protection product availability and accelerating integrated pest management implementation in Member States. Council of the European Union, Expert Group on Sustainable Plant Protection. (2016). Available: http://data.consilium.europa.eu/doc/document/ST-10041-2016-REV-1/en/pdf [1 September 2020].
49 Kvakkestad V, Sundbye A, Gwynn R and Klingen I, Authorization of microbial plant protection products in the Scandinavian countries: a comparative analysis. *Environ Sci Policy* **106**:115–124 (2020).
50 Mudgal S, De Toni A, Tostivint C, Hokkanen H and Chandler D, Scientific support, literature review and data collection and analysis for risk assessment on microbial organisms used as active substance in plant protection products–Lot 1 Environmental Risk characterisation. *EFSA Support Pub* **10**:518E (2013).
51 Hackl E, Pacher-Zavisin M, Sedman L, Arthaber S, Bernkopf U, Brader G *et al*., Literature search and data collection on RA for human health for microorganisms used as plant protection products. *EFSA Support Pub* **12**:801E (2015).
52 Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G *et al*., Guidance on the characterisation of microorganisms used as feed additives or as production organisms. *EFSA J* **16**:e05206 (2018).
53 Ockleford C, Adriaanse P, Berny P, Brock T, Duquesne S, Grilli S *et al*., Scientific opinion addressing the state of the science on risk assessment of plant protection products for in-soil organisms. *EFSA J* **15**:e04690 (2017).
54 IBMA. IBMA White Paper – New EU Regulatory Framework For Bioprotection Agents. (2018). Available: https://www.ibma-global.org/upload/attach-document/ibma-white-paper-web-final-a5-spreads.pdf [1 September 2020].
55 EU. Commission Regulation (EU) 2017/1432 amending Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market as regards the criteria for the approval of low-risk active substances. (2017). Available: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1598947372819&uri=CELEX:32017R1432 [1 September 2020].
56 EU. Commission Notice concerning a list of potentially low-risk active substances approved for use in plant protection, (2018/C 265/02). (2018). Available: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52018XC0727(01)&rid=7 [1 September 2020].
57 Sundh I, Wilcks A and Goettel MS eds, *Beneficial Microorganisms in Agriculture, Food and the Environment: Safety Assessment and Regulation*. CAB International Publishing, Wallingford, UK, p. 343 (2012).

58 Bourdichon F, Casaregola S, Farrokh C, Frisvad JC, Gerds ML, Hammes WP *et al.*, Food fermentations: microorganisms with technological beneficial use. *Int J Food Microbiol* **154**:87–97 (2012).
59 Traon D, Amat L, Zotz F and du Jardin P, A legal framework for plant biostimulants and agronomic fertilizer additives in the EU. Arcadia International Report. (2014). Available: https://publications.europa.eu/en/publication-detail/-/publication/dbeffd43-98a5-4e39-a930-7dfa21816f8c [1 September 2020].
60 Caradonia F, Battaglia V, Righi L, Pascali G and La Torre A, Plant biostimulant regulatory framework: prospects in Europe and current situation at international level. *J Plant Growth Regul* **38**:438–448 (2018).
61 Du Jardin P, Plant biostimulants: definition, concept, main categories and regulation. *Sci Hortic* **196**:3–14 (2015).
62 Ricci M, Tilbury L, Daridon B and Sukalac K, General principles to justify plant biostimulant claims. *Front Plant Sci* **10**:494 (2019).
63 EU. Regulation (EU) 2019/1009 of the European Parliament and of the Council laying down rules on making available on the market of EU fertilizing products and amending Regulations (EC) No 1069/2009 and (EC) No 1107/2009 and repealing Regulation (EC) No 2003/2003. (2019). Available: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R1009&rid=1 [1 September 2020].
64 López-Bucio J, Pelagio-Flores R and Herrera-Estrella A, *Trichoderma* as biostimulant: exploiting the multilevel properties of a plant beneficial fungus. *Sci Hortic* **196**:109–123 (2015).
65 Parnell JJ, Berka R, Young HA, Sturino JM, Kang Y, Barnhart DM *et al.*, From the lab to the farm: an industrial perspective of plant beneficial microorganisms. *Front Plant Sci* **7**:1110 (2016).
66 Benjamin EO, Grabenweger G, Strasser H and Wesseler J, The socioeconomic benefits of biological control of western corn rootworm *Diabrotica virgifera virgifera* and wireworms *Agriotes* spp. in maize and potatoes for selected European countries. *J Plant Dis Prot* **125**:273–285 (2018).
67 Bardin M, Ajouz S, Comby M, Lopez-Ferber M, Graillot B, Siegwart M *et al.*, Is the efficacy of biological control against plant diseases likely to be more durable than that of chemical pesticides? *Front Plant Sci* **6**:566 (2015).
68 Crickmore N, *Bacillus thuringiensis* resistance in *Plutella* – too many trees? *Curr Opin Insect Sci* **15**:84–88 (2016).
69 EPPO (European and Mediterranean Plant Protection Organization), Principles of efficacy evaluation for low-risk plant protection products. *Bull OEPP/EPPO* **47**:297–304 (2017).
70 OECD 2012, Report of the OECD workshop on Integrated Pest Management (IPM) strategies for the adoption and implementation of IPM in agriculture contributing to the sustainable use of pesticides and to pesticide risk reduction. OECD Environment, Health and Safety Publications, Series on Pesticides No. 70. Available: https://www.oecd-ilibrary.org/docserver/9789264221635-en.pdf?expires=1579097753&id=id&accname=oid053050&checksum=8119E795E1138BFE61FE056137C032A5 [1 September 2020].
71 Bigler F and Kölliker-Ott UM, Balancing environmental risks and benefits: a basic approach, in *Environmental Impact of Invertebrates for Biological Control of Arthropods*, ed. by Bigler F, Babendreier D and Kuhlmann U. CABI Publishing, Oxon, pp. 273–286 (2006).
72 Heimpel GE and Cock MJW, Shifting paradigms in the history of classical biological control. *BioControl* **63**:27–37 (2018).

