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Overview of approaches used by member countries to handle the issue of antimicrobial resistance potentially related to application of microbial pesticides

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Foreword

This document aims to provide an overview on how OECD member countries assess antimicrobial resistance (AMR) of microorganisms used as biopesticides and summarise the available approaches. The document also highlights the main issues to be considered during the evaluation of the AMR potential of microorganisms used as plant protection products.

This Guidance Document is an output of the OECD Expert Group on BioPesticides (EGBP), formerly known as BioPesticides Steering Group (BPSG), established by the Working Party on Pesticides in 1999 to help member countries to harmonise methods and approaches used to assess biological pesticides and to improve the efficiency of regulatory procedures. The first tasks the EGBP undertook were: (i) reviewing the regulatory data requirements for three categories of biopesticide (microbials, pheromones and invertebrates); and (ii) developing formats for dossiers and monographs for microbials, pheromones, and other semiochemicals. After tasks were concluded, the EGBP concentrated efforts on addressing the scientific and technical issues that act as barriers to the efficient regulation of biological pesticides by organising seminars and following up on the resulting recommendations.

The initial draft of this document was developed by the Secretariat and received input from members of the EGBP.

The document was sent to the EGBP for comments on three occasions: June 2020, 2021 and 2022. The draft guidance was revised, based on comments received. The final draft was sent to the Working Party on Pesticides for comments and subsequent approval in December 2022. The document was approved by the Working Party on Pesticides in August 2023.

This document is being published under the responsibility of the Chemicals and Biotechnology Committee (CBC), which has agreed that it be declassified and made available to the public.

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1 Introduction

1. Antimicrobial resistance (AMR) has become, in the last two decades, a global threat that poses potentially dramatic health and economic consequences. AMR is referring to antibacterial, antiviral and antifungal resistance. Although it remains a complex issue, antibacterial resistance is, presently, of greatest concern and the main drivers of AMR are antimicrobial overuse and misuse in human, animal, agricultural and environmental sectors and the spread of resistant bacteria and resistance determinants within and between these sectors and across countries.

2. AMR may lead to the acquisition of antimicrobial resistance genes (ARGs) by pathogenic bacteria. Overuse and misuse of antibiotics, among other reasons, are considered responsible for selecting and spreading these genes in microbial populations, which makes antibiotics ineffective against a growing number of bacterial pathogens. Exposure to antibiotics applied in clinical and agricultural settings leads to ARGs in environmental reservoirs that can be transmitted to human pathogens. The excretion into the environment of antibiotics used in medicine and agriculture promotes selection of naturally occurring resistant bacteria and their accompanying ARGs.

3. Having recognised this threat and its global nature, in 2015 the World Health Organization, together with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE), developed a Global Action Plan (GAP) to control the increasing trend in AMR. The GAP provided a guide to member countries as they were starting to develop their country-specific National Action Plans (NAPs) to combat AMR. The majority of these NAPs were developed to be compatible with the One Health framework and rely on multiple measures or solutions to address the challenges posed by AMR.

4. Based on the GAP, national regulations and surveillance systems relevant to AMR were established in a number of member countries. The OECD is involved in this process by providing a forum for discussion in order to facilitate the implementation of cost-effective policies to address AMR (OECD Health policies and Data). Additional work performed under the auspices of the OECD is focused on AMR and agriculture, and based on this work, an assessment of NAPS on AMR in animal production was recently published (Ryan, 2021).

5. However, no OECD activities related to potential AMR from the application of microorganisms as pesticides were undertaken until recently when the European Commission developed and published a guidance on this issue. The guidance explains how to assess AMR of microorganisms used as plant protection products in relation to the approval criteria and the low risk criteria set under Regulation (EC) No 1107/2009 (EC, 2020). At the EGBP meetings in June 2019, 2020, and 2021, the progress on the EC Guidance document on approval and low-risk criteria linked to AMR of microbials was presented and there was a request to compile information on how OECD member countries handle AMR of microbials.

6. This document aims to provide an overview of how OECD member countries assess AMR of microorganisms used as biopesticides and summarise the available approaches. The aspiration is that the document also highlights the main issues to be considered during the evaluation of the AMR potential of microorganisms used as plant protection products.

2 Issues to consider when the AMR potential of microorganisms used as plant protection products is evaluated

Category of microorganisms

7. As microorganisms become exposed to antimicrobial substances, adaptation might occur leading to AMR. This adaptation mechanism enables microorganisms to survive and overcome host strategies that threaten them.

8. According to WHO, AMR concerns all categories of microorganisms and involves bacteria, viruses and fungi that change over time and no longer respond to medicines, making infections harder to treat and increasing the risk of disease spread, severe illness and death.

9. Bacteria are more prone to acquire AMR than viruses and fungi. In the EC Guidance document on approval and low-risk criteria linked to AMR of microbials (EC, 2020), fungi and viruses are not addressed for the following reasons:

- Viruses as such are not susceptible or resistant to antibiotics. Most viruses are not considered major contributors to the AMR concern based on scientific literature (with the exception of temperate bacteriophages)
- Transfer of AMR genes between fungi rarely occurs because it involves a multigenic process, (i.e., involving several genes) and is not associated with the transfer of a single gene like in the case of bacteria (i.e., through plasmid exchange) (Morogovsky et al., 2022).

10. Compared to bacteria, the assessment of antimicrobial resistance genes for fungi and viruses is not considered relevant (see above paragraph). Nevertheless, sufficient treatment options in case of the unlikely occurrence of opportunistic infection with the microorganism (including fungi) should be listed by the applicants. It is worth noting that AMR in fungi is an emerging concern from a human health perspective although different mechanisms are involved than horizontal gene transfer and it appears to be related to agricultural chemical-based fungicide use (NAS, 2023).

11. In the case of bacteriophages (bacterial viruses), specific OECD guidance is available, which addresses this issue [ENV/CBC/MONO(2022)40].

AMR Mechanisms

12. Antimicrobial resistance refers to the ability of a microorganism to multiply in the presence of an antimicrobial agent at concentrations which are relevant for therapeutic measures in human or veterinary medicine, making that substance therapeutically ineffective. Resistance to an antibiotic is considered to be dose-dependent. Resistance can be on a scale where a microorganism is said to be either susceptible or tolerant to an antimicrobial compound until a pre-determined critical value of effect (e.g., Minimum Inhibitory Concentration, MIC) is passed, at which point it is said to be resistant. The genetic basis for AMR are different and AMR manifested by microorganisms can be intrinsic, acquired, or adaptive (Joon-Hee, 2019).

13. *Intrinsic resistance*: relies on inherent properties of the microorganisms and is a common characteristic in all microorganisms. The level of intrinsic resistance varies naturally between species and strains. Usually, the target structure of the antibiotic does not exist in the microorganism. One example is Gram-negative bacteria resistant to glycopeptide antibiotics due to the lack of permeability of the outer membrane.

14. Intrinsic resistance is governed by genes located in the genome. An ARG is considered intrinsic if it is located on a chromosome in the absence of mobile genetic element and shared by the majority of wild-type strains of the same species. Transfer of such genes is a very rare event and is not considered to be relevant for microorganisms used in plant protection.

15. *Acquired resistance*: relies on a mutation or the acquisition of new genetic material from an exogenous source (horizontal gene transfer) that occurs in a previously sensitive bacterium. Three main mechanisms are responsible for horizontal gene transfer.

- Transformation: involves the entrance of free DNA fragments from a dead bacterium in a recipient bacterium and incorporation into its chromosome. Natural transformations exist but are limited in number.
- Transduction: is temperate bacteriophage mediated transfer of genetic material between two microorganisms (donor and recipient).
- Conjugation: is considered the most important mechanism of horizontal gene transfer. It relies on the transfer of genetic material from one bacterium to another through physical contact between genetically compatible and physiologically competent cells, using a plasmid. Multiple resistance genes are often present on a single plasmid enabling the transfer of multidrug resistance in a single conjugation event.

16. In summary, plasmids, bacteriophages and extracellular DNA are the three primary drivers of horizontal gene transfer through the process of conjugation, transduction and natural transformation, respectively. The acquisition of naturally occurring ARGs by pathogenic bacteria might also occur by mutation.

17. *Adaptive resistance*: is induced by a specific environmental signal (e.g., stress, growth state, pH, concentrations of ions, nutrient conditions, etc.). Adaptive resistance is transient and is considered the result of modulations in gene expression as a response to environmental changes.

18. Underdosing, using the wrong antibiotic, or stopping a course of treatment can promote selection of antibiotic resistance. In the presence of an antibiotic only resistant cells can survive. If the concentration is too low (underdosing) or the antibiotic exposure is too short (interrupted treatment), cells can adapt and develop resistance. Similarly, resistant cells can transfer genetic elements to cells previously susceptible. If the treatment is sufficiently long or the concentrations are high enough, cells would be killed before resistance mechanisms can spread in the bacterial population. Rational use of antibiotics is considered one of the main approaches being taken worldwide to reduce AMR.

3 OECD member countries' approaches to assessing AMR of microorganisms used as biopesticides

Australia

19. Microbial pest control agents may survive and reproduce in the environment and may infect other living organisms. Therefore, the APVMA's basic testing requirements are designed to specifically detect the potential of a microbial pest control agent to exhibit any of these characteristics. While the APVMA does not routinely require submission of data on susceptibility to, or tolerance of, microbial pesticides to antimicrobial agents, these data may be required on a case-by-case basis.

20. Furthermore, in Australia, all new pesticide active constituents, including biopesticides, must go through the Poison Scheduling process before they can be approved for use in a registered end-use product. If there are AMR concerns associated with a new biopesticide, these will be considered as part of the Scheduling process.

Canada

21. The *Product Characterization and Analysis* requirements for a new microbial pest control agent (MPCA) include a discussion on the biological properties of the MPCA that addresses a number of topics related to AMR (see Section 6.0, Part M2.7.2 in GUI2021-Guidance Registration of MPCAs https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/policies-guidelines/guidance-registration-microbial-pest-control-agent-products.html).

22. Applicants must conduct testing to determine the susceptibility or tolerance of the MPCA to antimicrobial agents used in human or veterinary medicine. If resistance is observed, additional information, including but not limited to the relatedness of the MPCA to known pathogens, susceptibility of the MPCA to environmental factors, whether cross-resistance or co-resistance would be expected, as well as alternative treatment options would be used to assess the risks posed by AMR.

23. Applicants must also identify any secondary metabolites that are produced by the MPCA, particularly those that are related to antimicrobial agents used in human or veterinary medicine. If such metabolites are produced, information on the mode of action of the metabolite, the route of exposure to the metabolite, the level of the metabolite present in the product, potentially produced post-application and, where applicable, present in the edible portions of plants at the time of harvest would be required. Pest

Management Regulatory Agency's *Considerations for Pesticidal Uses of Antimicrobial Drugs* (https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management/registrants-applicants/product-application/memo/considerations-pesticidal-uses-antimicrobial-drugs.html) would also be triggered and used in conjunction with the aforementioned information on the metabolite of concern to evaluate the AMR transfer risks.

Chile

24. Chile is addressing the issue of ARG transfer from microorganisms used as biopesticides to bacterial pathogens from its participation in the Ad hoc Codex Intergovernmental Task Force on Antimicrobial Resistance.

European Union (EU)

25. Applying microorganisms in the environment as plant protection products might potentially contribute to the AMR concern. This is due to the potential for transferring, from microbial pest control agents to environmentally-occurring pathogenic bacteria, of ARGs encoding for relevant antimicrobials used in human and animal medicine if these genes are associated to mobile genetic elements. However, based on the available body of knowledge, potential long-term consequences of releasing in the environment microorganisms provided with ARGs remain not fully understood; hence, a precautionary approach in assessing related risks is required.

26. EU data requirements and Uniform principles for approval require evaluation of "the possibility for transfer of genes that code for resistance to antimicrobial agents used in human and animal medicine".

27. Microorganisms used in plant protection must not have relevant transferable resistance genes which are located on mobile genetic elements. To address AMR, there is a guidance document published by the European Commission (https://ec.europa.eu/food/system/files/2020-11/pesticides_ppp_app-proc_guide_180652_microorganism-amr_202011.pdf) that explains how to assess AMR of microorganism, as well as the risk of increasing the spread of ARGs of human and veterinary concern, in relation to the approval criteria and the low risk criteria set under Regulation (EC) No 1107/2009 (EC, 2020) and referring to the EFSA "Guidance on the characterisation of micro-organisms used as feed additives or as production organisms" (EFSA Journal 2018;16(3):5206, 24 pp. https://doi.org/10.2903/j.efsa.2018.5206).

28. The EU Guidance document, finalised in the Standing Committee on Plants, Animals, Food and Feed on 23/10/2020, applies to all applications for microorganisms as plant protection products submitted from 01/05/2021 onwards.

29. The guidance document proposes a two-step approach. Briefly, data on the presence of known relevant resistance genes in the genome of the microorganism needs to be provided, considering both the chromosome and mobile genetic elements such as plasmids. If resistance genes are detected, their localisation on the bacterial chromosome or on mobile genetic elements (e.g., plasmids) needs to be determined. The respective resistance shall then be tested phenotypically.

30. The phenotypic test shall include antibiotics for which a known AMR gene is detected in the genome screening. This analysis is performed to verify possible functionality of the relevant detected genes. The phenotypic test shall also include other groups of antibiotics to ensure that the microorganism is susceptible to antibiotics in case an opportunistic infection needs to be treated. According to the guidance document SANTE/2020/12260, phenotypic susceptibility of the bacterium to at least two classes of antimicrobial agents of the CIA or HIA groups in the WHO list has to be demonstrated in order to approve it.

31. The susceptibility test to antimicrobial agents is conducted with a series of different concentrations with the aim to determine a MIC to decide whether the strain is considered susceptible or resistant.

32. Microorganisms used in plant protection shall not have any relevant transferable resistance gene located on mobile genetic elements. As regards AMR transfer hazard, only these relevant resistance genes located on mobile genetic elements are exclusion criteria for approval of a microorganism as an active substance in the EU. Resistance genes located on the chromosome are considered non-transferable in the absence of mobile genetic elements, and confer "intrinsic" resistance.

33. Microorganisms can be approved as low risk active substances, in accordance to point 5.2.1 of the Annex II to Regulation (EC) No 1107/2009, only if susceptibility to at least two classes of antimicrobial agents has been demonstrated.

New Zealand

34. In 2017 a five-year National Action Plan on management of Antimicrobial Resistance was published. It takes a One Health approach in that it covers both human, animal, plants and food safety aspects in relation to management of antimicrobial resistance.

35. In New Zealand, there is specific guidance on Microbial Agricultural Chemicals that contains application information for registration under the Agricultural Compounds and Veterinary Medicines Act 1997 - https://www.mpi.govt.nz/dmsdocument/19484-microbial-agricultural-chemicals.

36. For antimicrobial resistance assessment, the following guidance is used https://www.mpi.govt.nz/processing/agricultural-compounds-and-vet-medicines/antimicrobial-resistance/. Although the main focus of this document is on veterinary medicines and animals, it does include information relevant to plant health.

Switzerland

37. There is a national strategy on antibiotic resistance and a strategy related to agriculture and is focused on animal production.

38. An evaluation of antibiotic resistance is necessary for the authorisation of a new microbial active substance. In the Swiss ordinance this aspect is regulated as follows: "various microorganisms produce antibiotic substances, which provoke normal interferences in the microbial community. The resistance to antimicrobial agents that are important for human and animal medicine should be evaluated. The possibility of a transfer of genes coding for resistance to antimicrobial agents should be evaluated." (Note: this part of the ordinance is not an official English translation).

United Kingdom

39. Currently, the UK has no guidance on AMR for microorganisms used as plant protection products. Before leaving the EU, the UK was participating in the development of the guidance that explains how to assess AMR of microorganism used as plant protection products in relation to the approval criteria and the low risk criteria set under Regulation (EC) No 1107/2009 (EC, 2020).

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