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Secondary metabolites in microbial agents used as plant protection products: a regulatory overview

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Introduction

Definitions

Microbials

- IBMA definition of microbials:
  ‘Microbials are based on microorganisms, including but not limited to bacteria, fungi, protozoa, viruses, viroids, mycoplasmas, living and dead cells, any associated microbials metabolites, fermentation materials and cell fragments’

- They are used as biological control agents in plant protection products for sustainable pest control

Primary metabolites

- Primary metabolites of microbials are essential compounds produced by microorganisms during normal growth and development, and are crucial for survival and reproduction

Secondary metabolites

- Secondary metabolites are bioactive compounds produced by microorganisms that influence interactions with other organisms beyond growth functions

Role of secondary metabolites

Ecological functions

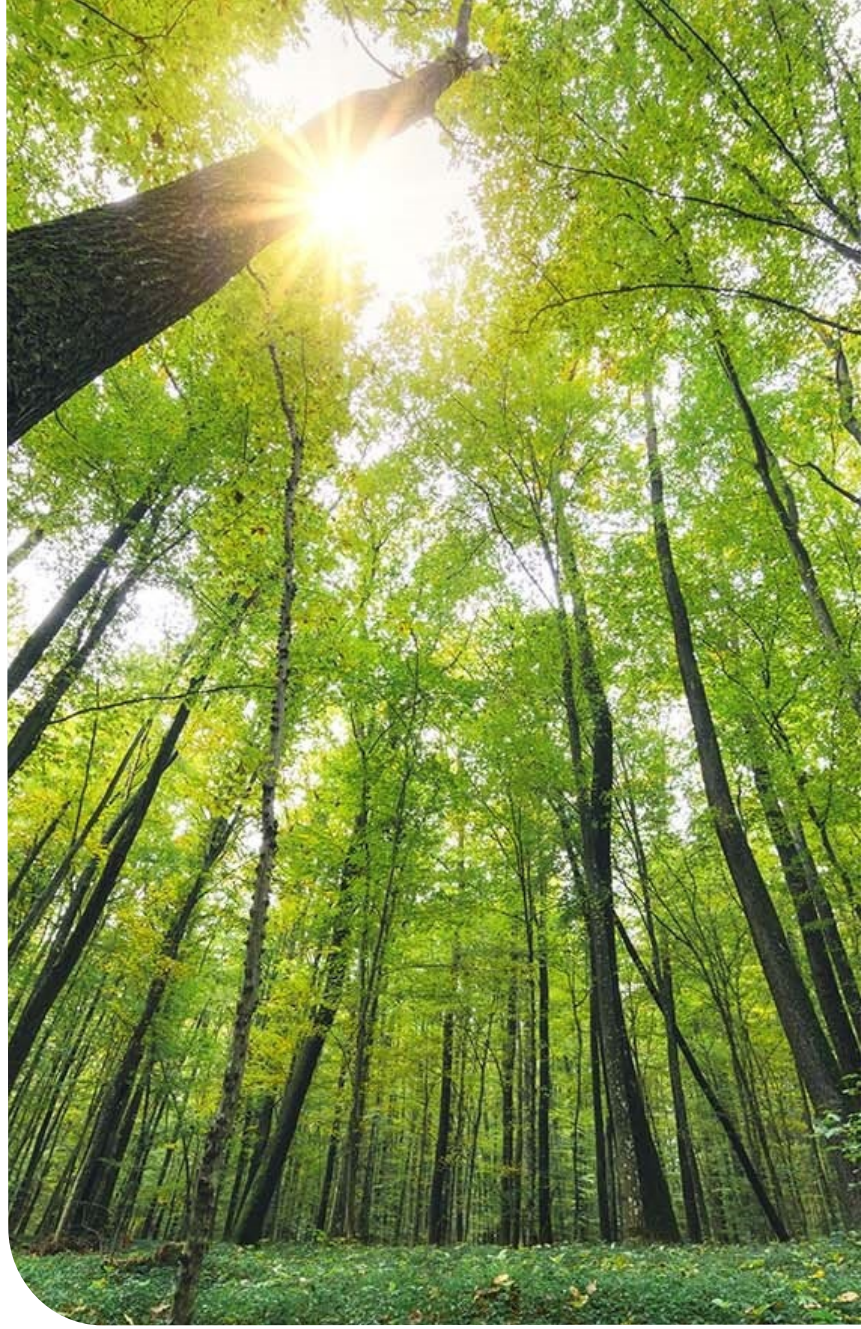
- Secondary metabolites are produced by microorganisms and are involved in functions beyond basic metabolism, such as roles in defence, signalling, interactions and competition in the ecosystem

Impact

- Some secondary metabolites may adversely affect or harm non-target organisms and exhibit biological effects

Regulatory oversight

- Regulatory frameworks ensure the identification, characterisation, and safe use of microorganisms that may produce secondary metabolites of potential concern



Regulatory context

EU and UK regulatory frameworks

EU framework

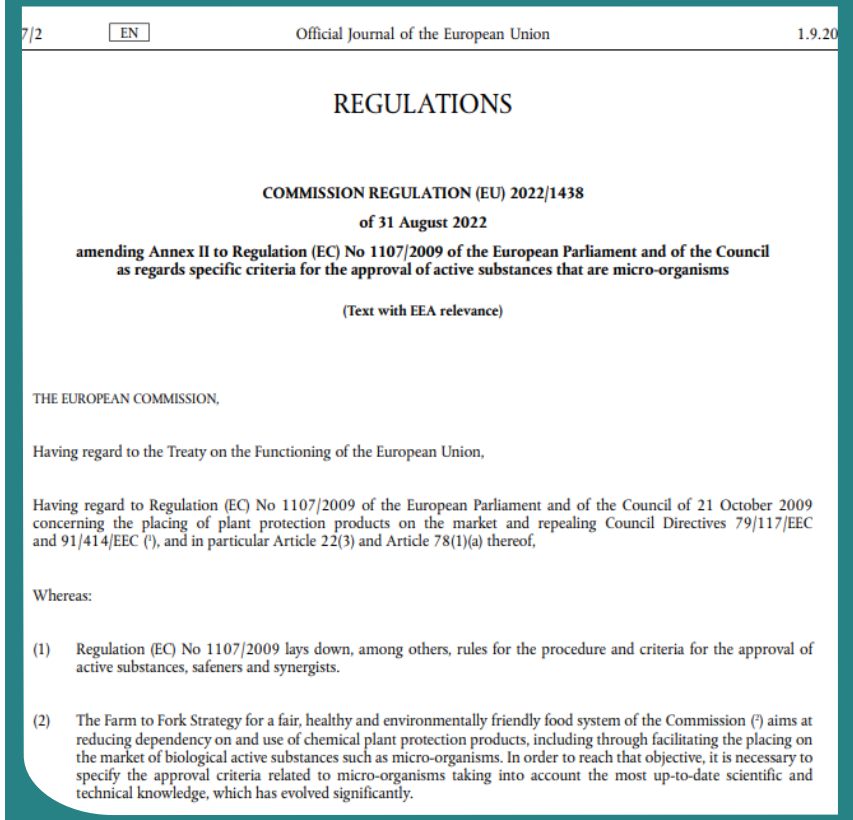
- EU Regulation (EC) No 1107/2009, as amended by Regulation (EU) No 2022/1438, provides the framework for plant protection products containing a microbial active substance
- Evaluation by Rapporteur Member States for active substances, with EFSA taking a key role to ensure safety and environmental protection in the EU, and by zonal RMS for authorisation of plant protection products at Member State level
- Microbial specific data requirements laid down under Regulations (EU) 2022/1439 and 2022/1440, amended to include latest scientific knowledge
- SANCO/2020/12258 rev.1 guidance alongside the Explanatory notes from the Commission (PAFF-PPL-October 2023-Doc.A.07.01 12 October 2023) with complementary advice from EFSA/Ctgb to address microbial secondary metabolites of concern

UK (Post-Brexit) framework

- The UK maintains similar regulatory principles under the GB Plant Protection Products Regulation (GB PPPR), with oversight by HSE/CRD for plant protection products
- Case by case approach to evaluation of secondary metabolites based on latest scientific knowledge

Safety and efficacy assessments

- Detailed assessments on microbial strains and secondary metabolites ensure adherence to safety and efficacy standards in both regions
- Regulatory bodies ensure latest scientific advances lead to updated guidelines and the adoption of emerging technologies



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REGULATIONS

COMMISSION REGULATION (EU) 2022/1438

of 31 August 2022

amending Annex II to Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards specific criteria for the approval of active substances that are micro-organisms

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC [1], and in particular Article 22(3) and Article 78(1)(a) thereof,

Whereas:

(1) Regulation (EC) No 1107/2009 lays down, among others, rules for the procedure and criteria for the approval of active substances, safeners and synergists.

(2) The Farm to Fork Strategy for a fair, healthy and environmentally friendly food system of the Commission [2] aims at reducing dependency on and use of chemical plant protection products, including through facilitating the placing on the market of biological active substances such as micro-organisms. In order to reach that objective, it is necessary to specify the approval criteria related to micro-organisms taking into account the most up-to-date scientific and technical knowledge, which has evolved significantly.

Sustainability goals

General trend of an increase in microorganisms under evaluation leads to necessity for innovative evaluation approaches to ensure continued rigorous standard of risk assessment

- Farm to Fork EU strategy
  - Aims to reduce chemical pesticide use by 50% by 2030, with microbial plant protection products seen as key substitutes
- UK Pesticides National Action Plan (NAP) 2025
  - Views microbial agents, as part of biopesticides and Integrated Pest Management (IPM), as important tools for reducing reliance on conventional chemical pesticides and promoting sustainable agriculture
  - Part of the broader strategy to reduce pesticide risks and impacts
- Sustainability supported by biological innovation
- Positive public perception…

Characterisation & secondary metabolites

Microbial strain characterisation

A key challenge in regulatory evaluations is strain characterisation

- Applicants need to show unambiguous characterisation of their strain to avoid regulatory uncertainty

Gold standard is Whole Genome Sequencing (WGS)

- Also supports secondary metabolite production determination

Leading on to identification of secondary metabolites following strain characterisation

- Key questions around identifying, quantifying and assessing potential impact of secondary metabolites

Secondary metabolites – a step wise approach

SANCO/2020/12258 rev.1 guidance developed in the EU follows a structured approach in a step wise manner to clarify risk assessment and hazard evaluation steps

1. Identification of potential secondary metabolites of concern
    - Comprehensive list of possible secondary metabolites of concern for the strain and related strains is compiled from a literature search
2. Genomic refinement
    - Initial list is refined using genomic data specific to the characterised strain. This refinement identifies which metabolites can be produced by that strain
3. Hazard data collection
    - Toxicological and ecotoxicological data for possible metabolites after genomic refinement
4. Risk characterisation
    - Potential exposure and risk assessments of identified metabolites, evaluated in context of their use profile

Challenges in risk assessment of secondary metabolites

Regulatory challenges for both the applicant and evaluator

- Literature searches for available information on similar strains and similar secondary metabolites, weight of evidence approach, can be complex
- Can production of secondary metabolites be robustly discounted, *i.e.* do biosynthetic gene cluster (BGC) data show no possibility of production?
- If secondary metabolites can be produced, can they be measured, *i.e.* sufficient analytical methodology to quantify levels?
- Regulatory pathways and step wise approach may exclude secondary metabolites, otherwise hazard assessment is required to address any concern around environmental or toxicological risk
- Clear interpretation of data is key, as is close liaison with regulators

Complexity in risk assessment of secondary metabolites

Complexity of secondary metabolite diversity

- Complicates risk assessment due to limited toxicological data for many compounds
- Attempts to counter this by focussed papers on specific secondary metabolites encountered, *e.g.* collective position on interpretation within ‘Consensus document on *Beauveria bassiana* strains as microbial plant protection product’ OECD, 2025
- Enables widely accepted points of reference and increased certainty for applicants and regulators to support a coherent approach to evaluation

Analytical detection difficulties

- Typically low concentrations and varied chemical properties makes detecting and quantifying secondary metabolites challenging
- Leads to potential data gaps hindering conclusive evaluations

Advances in characterisation

Advances in strain and secondary metabolite characterisation

New approach methodologies (NAMs) and technologies are emerging to improve the accuracy and comprehensiveness of risk assessments

- ‘Omics’ technologies
    - Genomics and metabolomics, *e.g.* WGS, enable detailed profiling of microbial strains and their metabolic outputs
- *In silico* prediction tools
    - Computational tools to identify biosynthetic gene clusters (BCGs) linked to metabolite production (BLAST, SMaSH)
- Analytical methods
    - LC-MS and NMR techniques provide precise identification and quantification
- Regulatory impact
    - New technologies are supporting improved safety assessment and streamlining the approval and authorisation process – reducing uncertainty with improved data and precision

Case study | regulatory evaluations

- *Beauveria bassiana* – Beauvericin
  - Production of beauvericin, an insecticidal compound, raising potential toxicity concerns in regulatory evaluation
    - OECD paper to address *Beauveria bassiana* evaluation as a standalone document for applicant reference
- *Metarhizium anisopliae* – Destruxins
  - Destruxins are produced which exhibit immunosuppressive effects, adding challenge to risk assessments as a potential secondary metabolite of concern
- Regulatory impact – data gaps
  - Regulatory assessments can reveal data gaps requiring further data generation and assessment, prolonging and complicating submissions
- Robust regulatory frameworks
  - Robust risk assessment frameworks and data requirements are essential to support applicants and evaluators in navigating secondary metabolite uncertainties

Looking to the future

Next Generation Risk Assessment (NGRA) & future direction

- Concepts to support risk assessment are evolving
- Adverse Outcome Pathways
  - Aim to link molecular events to adverse effects at organism or population levels, supporting risk understanding
- Integration of data approaches
  - Combines ‘omics’, *in vitro*, *in silico* and existing toxicology expertise for enhancement of quality of secondary metabolite evaluations
- Streamline approval process goals
  - Efficient regulatory pathways will support biological innovation and confidence in safe uses

Conclusions

- Secondary metabolites in microbial evaluations
  - Identification and robust assessment of secondary metabolites are key to smooth evaluation and regulatory control
- Regulatory framework evolution
  - EU and UK(GB) regulations adapted to address challenges posed by secondary metabolites in microbial products
- Advances in characterisation and evaluation
  - Emerging characterisation technologies feeding into enhanced risk assessment methods are supporting ever safer and more comprehensive evaluation outcomes
- Innovation continues, striving for sustainability
  - Regulatory adaptation to meet scientific challenges in cutting edge risk assessment to support sustainable plant protection options for agriculture in the real world

Thank you

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