GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT

BfR
Bundesinstitut für Risikobewertung

Regulatory aspects and risk assessment in the biopesticide approval process

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„Zero pollution ambition“

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

DIRECTIVE 2009/128/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 21 October 2009

establishing a framework for Community action to achieve the sustainable use of pesticides

- Reduce dependency on chemical pesticides
- Facilitate market access of non-chemical alternatives and low risk substances
- Biological, physical and other non-chemical methods to be preferred to chemical methods

Biopesticides

Microorganisms (bacteria, fungi, viruses)

Botanicals

Semiochemicals/Pheromones

Invertebrates

Active substances with new MoA (e. g. RNAi)

Plant incorporated pesticides

Microbial Biopesticides

Mode of action

- Direct interaction with target pest
  - Hyperparasitism
  - Antibiosis
  - Toxin production

- Indirect interaction with target pest
  - Competition (e. g. for nutrients, habitat)
  - Induction of plant resistance

Microbial biopesticides can have several advantages compared to conventional chemical pesticides

- Environmentally friendly
- Less toxic than conventional pesticides
- Target pest specificity
- Self-sustaining control
- Anti-resistance strategies due to various modes of action

… but also disadvantages

- Potential to act as opportunistic pathogens
- Production of secondary metabolites (toxins/antimicrobial substances)
- Microorganisms can cause sensitisation on repeated exposure

Legal framework for the assessment of microbial active substances and products containing microorganisms

Active substances must be approved under **Regulation (EC) No 1107/2009** before they can be used in plant protection products.

Technical data requirements

- Reg (EC) No 283/2013 (data requirements active substances), Part B
- Reg (EC) No 284/2013 (data requirements plant protection products), Part B

Criteria for evaluation and decision making on the authorisation

- Reg (EC) No 546/2011 (uniform principles), Part II

Need for revision of the data requirements and uniform principles

- Increased numbers of applications for new active substances and plant protection products
- Partially mimicking data requirements for chemical active substances
- Lack of guidance/interpretation issues/inconsistency
- Evolution of knowledge

Reg (EC) No 283/2013, data requirements for active substances

Effects on human health

Basic information

- Medical data
- Medical surveillance
- Sensitisation/allergenicity observations
- Direct observation, e.g. clinical cases

Basic studies

- Sensitisation
- Acute toxicity, pathogenicity, infectiveness
- Genotoxicity testing in vitro/in vivo
- Cell culture study
- Short-term toxicity and pathogenicity
- First aid measures, medical treatment
- Specific toxicity, pathogenicity and infectiveness
- In vivo studies in somatic cells

(Microbial) Pesticide Test Guidelines

- Microbial Pesticide Test Guidelines
  US EPA OPPTS Series 885

Group C – Toxicology Test Guidelines
885.3000 - Background – Mammalian Toxicity/Pathogenicity/Infectivity
885.3050 - Acute Oral Toxicity/Pathogenicity
885.3100 - Acute Dermal Toxicity/Pathology
885.3150 - Acute Pulmonary Toxicity/Pathogenicity
885.3200 - Acute Injection Toxicity/Pathogenicity
885.3400 - Hypersensitivity Incidents
885.3500 - Cell Culture
885.3550 - Acute Toxicology, Tier II, isolated toxins
885.3600 - Subchronic Toxicity/Pathogenicity
885.3650 - Reproductive/Fertility Effects

- OECD Test Guidelines for Chemicals

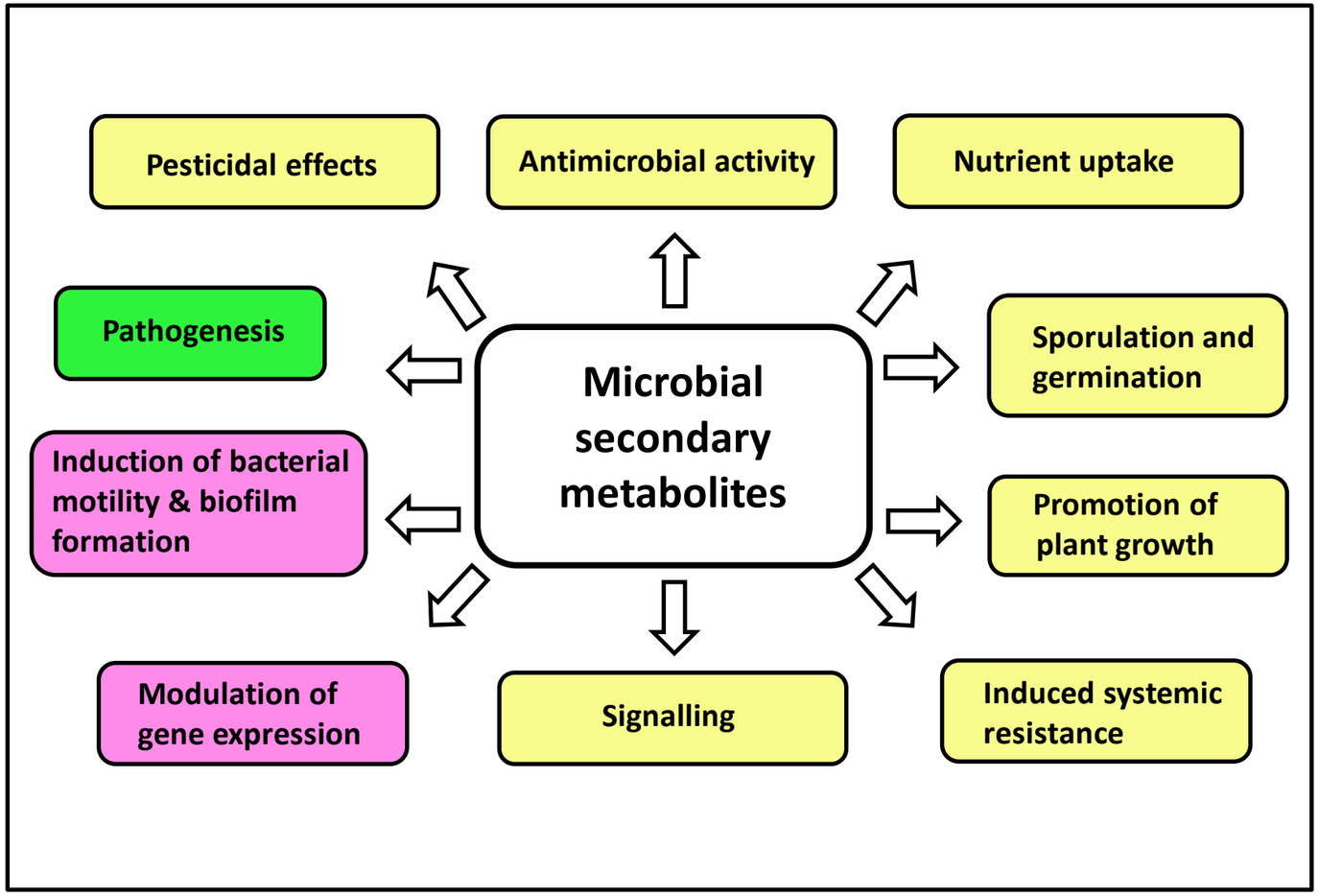
- Partially outdatet
- Not detailed enough
- OPPTS Series 885 not binding for EU
- No validated test guidelines for
  - Sensitisation testing
  - Genotoxicity testing

  of microorganisms

Secondary metabolites produced by microorganisms

Bacteria and fungi may produce secondary metabolites that can pose a risk to human and animal health or the environment.

Functions of microbial secondary metabolites



Fungi and bacteria

More specific to entomopathogenic fungi (EPF)

More specific to bacteria

Adapted from:
J. W. A. Scheepmaker et al., 2019
Sense and nonsense of the secondary metabolites data requirements in the EU for beneficial microbial control agents
Biological Control 136 (2019) 104005

Secondary metabolite production

Microbial Pest Control Agent		Secondary Metabolite
Fungi	*Beauveria bassiana*	Beauvericin
Bacteria	*Bacillus thuringiensis*	Enterotoxins
	Pseudomonas chlororaphis	DDR
	Bacillus subtilis	Lipopeptides

Bacillus thuringiensis

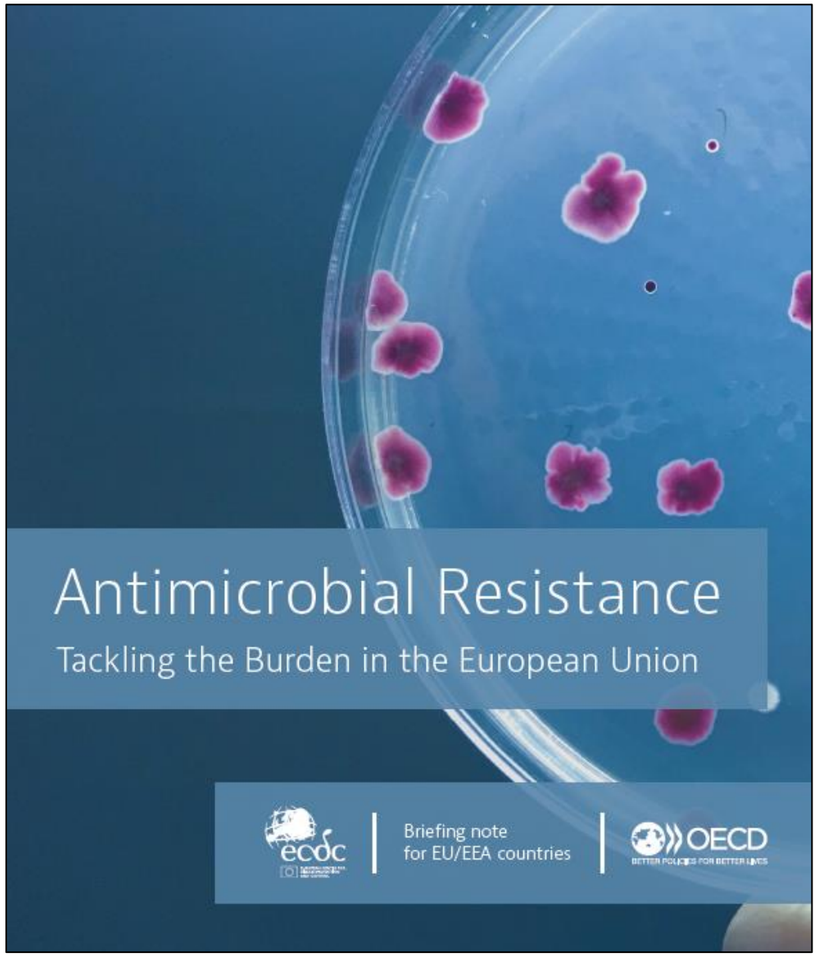
- **BfR Opinion No. 035/2019 of 16 September 2019**
  (*Bacillus cereus group* bacteria in foodstuffs may cause gastrointestinal diseases)
- **EFSA BIOHAZ Panel (2016)**

- *B. cereus* (*s. l.*) strains have the potential to form enterotoxins
- 10^5 cfu/g food might generate clinically relevant quantities of toxins
- Gastrointestinal diseases after consuming contaminated and incorrectly stored food
- Only very limited information on potential residues in treated commodities
- Only very limited information on degradation rate of spore in the absence of UV light
- Conservative assumptions based on the amount applied, empiric residue data and typical yield rates

Issues regarding risk assessment of microbial secondary metabolites

Risk = hazard + exposure

- Production in contact with the host/target organism
- Might be part of the mode of action
- Production influenced by biotic or abiotic factors
- Endophytic growth and translocation
- Literature on metabolite production is often incomplete
- Genomic data can confirm the presence/absence of relevant genes


Antimicrobial Resistance
Tackling the Burden in the European Union
ecdc
Briefing note
for EU/EEA countries
OECD


European Commission
A European One Health Action Plan against Antimicrobial Resistance (AMR)


GLOBAL ACTION PLAN
ON ANTIMICROBIAL RESISTANCE
World Health Organization

Antimicrobial resistance (AMR)

- Around **670 000 infections** with antibiotic-resistant bacteria in 2015 in the EU/EEA
- **33 000 attributable deaths**
- Impairment of medical procedures (transplantation, chemotherapy, …)
- Health burden of infections with antibiotic-resistant bacteria similar to the cumulative burden of influenza, tuberculosis and HIV (comparing disability-adjusted life-years, DALYs)
- Economic impact

Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

*Alessandro Cassini, Liselotte Diaz Högberg, Diamantis Plachouras, Annalisa Quattrocchi, Ana Hoxha, Gunnar Skov Simonsen, Mélanie Colomb-Cotinat, Mirjam E Kretzschmar, Brecht Devleesschauwer, Michele Cecchini, Driss Ait Ouakrim, Tiago Cravo Oliveira, Marc J Struelens, Carl Suetens, Dominique L Monnet, and the Burden of AMR Collaborative Group**

Lancet Infect Dis 2019; 19: 56–66

Approval criteria for microorganisms regarding AMR

If resistance to antimicrobials **can be transferred** to other microorganisms, including human and animal pathogens, the microorganism should **not be approved**.

Regulation (EC) 283/2013, Data Requirements for the active substance
Regulation (EC) 546/2011, Uniform Principles

Issues regarding the risk assessment of microorganisms and AMR

- Currently there is no defined list of antibiotics to be tested
  (WHO list of critically important antimicrobials? Fungi?)
- Is the identified resistance intrinsic or acquired?
- Added genes are a safety concern due to horizontal gene transfer.
- Microbial cut-off values are a pragmatic tool to distinguish between strains with acquired resistance and susceptible strains but cut-off values are often not available for strains used in PPP.

Issues regarding the risk assessment of microorganisms and AMR

- Horizontal gene transfer of AMR genes in fungi?
- Literature information on species level is not suitable for evaluation at strain level.
- Whole genome sequence data are not included in the data requirements.
- Available treatment options are not defined as an approval criterion.

Resistance pattern of *Bacillus amyloliquefaciens* MBI 600

Drug	Antimicrobial class	WHO ranking of medically important antimicrobials
Ampicillin Amoxicillin	Aminopenicillins	Critically important antimicrobials
Kanamycin	Aminoglycosides	Critically important antimicrobials
Tetracycline	Tetracyclines	Highly important antimicrobials
Cefotaxime	Cephalosporins (3rd, 4th and 5th generation)	Important antimicrobials
Metronidazole	Nitroimidazoles	Important antimicrobials

"The assessment of potential transfer of genetic material (e.g. responsible of antibiotic resistance) from *Bacillus amyloliquefaciens* strain MBI 600 to other organisms could not be finalised." EFSA Journal 2016;14(1):4359

Criteria for the approval of microbial low risk active substances

COMMISSION REGULATION (EU) 2017/1432

of 7 August 2017

amending Regulation (EC) No 1107/2009 of the European Parliament and the Council concerning the placing of plant protection products on the market as regards the criteria for the approval of low-risk active substances

Regulation (EU) 2017/1432 amends Point 5 of Annex II of Regulation (EC) No 1107/2009

"An active substance which is a micro-organism may be considered as being of low-risk **unless at strain level it has demonstrated multiple resistance to anti-microbials used in human or veterinary medicine**."

Approval of microbial low risk active substances

- No guidance exists so far for the interpretation of this definition.
- What is meant by “multiple”?
- Resistance to antimicrobials from different antimicrobial classes?
- Does the low risk criterion refer to intrinsic AND acquired resistances?
- Intrinsic resistances relevant for risk assessment?
- Products containing only low risk substances can - but not necessarily have to - be authorized as low risk plant protection products.

Microorganisms in Plant Strengtheners and Biostimulants

§45, German Plant Protection Act, Plant Strengtheners

… placing on the market can be prohibited for plant strengtheners if there are indications that the product has **harmful effects on human and animal health**.

PFC 6(A), Regulation (EU) 2019/1009, Microbial Plant Biostimulants

- CMC 7: Azotobacter spp., Mycorrhizal fungi, Rhizobium spp., Azospirillum spp.
- "… placed on the market only if they are sufficiently effective and **do not present a risk to human, animal or plant health, to safety or to the environment** […]"

Health risk assessment for plant strengtheners

Mutual assistance for health risk assessment of plant strengtheners
→ 5 products, 4 different strains

Pathogenicity	• No literature search on clinical cases submitted • 2 strains described in connection with clinical cases (brain abscess) • 1 strain classified “risk group 2” (TRBA 466, BAuA)
Production of secondary metabolites	• WGS screening limited to „troublesome agricultural toxins“ • No information about production of antimicrobial substances • For 1 strain production of a heat-stable toxin has been shown
Antimicrobial resistance	• No information on resistance/sensitivity pattern (and potential transferability of AMR) • No information about treatment options in case of opportunistic infections
Sensitisation	• Labelling according to PPP with precautionary sentence? (“Microorganisms may have the potential to provoke sensitizing reactions.”)

→ **Health risk assessment could not be finalised**

Summary

- Microbial biopesticides, plant strengtheners or biostimulants can be a valuable contribution to IPM programmes (crop protection, stimulating plant nutrition and tolerance to abiotic stress).

- Sufficient information to finalise risk assessment is essential to exclude harmful effects on human or animal health and the environment.

Outlook

- BfR supports OECD and EU/COM efforts to ensure harmonized procedures for the approval of microbial active substances and the authorisation of the respective plant protection products.

- This includes the revision of the current data requirements and uniform principles as well as the development of new test guidelines/guidance documents for human health and environmental risk assessment.

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Thank you for your attention

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