Biopesticides: towards ambitious and fit-for-purpose EU policies

CropLife Europe contribution on the assessment of innovative Biochemicals

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EU COM / SANTE E4 presentation at ABIM 2022

Road to 2030!

Micro-organisms (MO)
- New Reg on MO
- EC Communications
- Explanatory notes
- OECD activities
- Test methods for MO
- Consensus documents on MO
- Other initiatives

Biological control
- Semiochemicals etc.
- Waiving (point 1.5 introduction data requirements)
- Other biological control agents

Strengthen MS capacity
- BTSF
- Relevant expertise (grants)

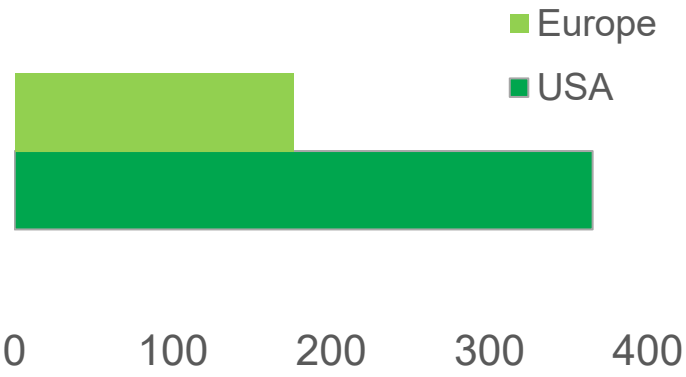
2030

European Commission

Biochemicals would represent those innovative biologicals control agents

Case studies conclusions

- **Innovation** is **not limited** to these case studies.
- Exciting new technologies such as peptides and fermentation products are being developed. But because of the **lack of a clear regulatory framework**, **this innovation is currently not reaching the farmers in the EU**.
- For the industry, **the ability to secure registration in Europe is uncertain** (reliability on regulatory timelines), and **EU farmers suffer because they are at a competitive disadvantage** compared to other regions of the world where those technologies are supported.

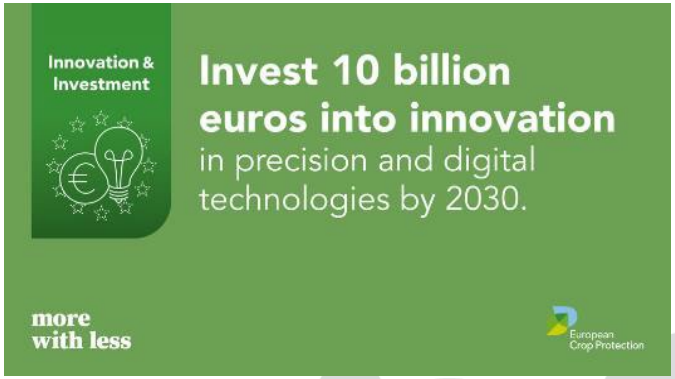


- Number of natural substances (analysis IBMA 2022)

Innovative biopesticides can be made accessible to farmers, what is needed is a science-based guidance to ensure timely approvals of innovative biopesticides

Innovation, our goal

- **Industry responsibility to develop solutions that are:**
  - Innovative
  - Effective
  - Sustainable
- **CLE member companies are actively developing new solutions:**
  - Conventional chemistry
  - Classical biopesticides
  - Novel biopesticides
- **Our 2030 Commitments support the European Green Deal policy initiative.**



We are an ambitious Industry committed to the development of novel solutions for agriculture.

EU Developments

1) *nEUROSTRESSPEP is a Horizon 2020 Research and Innovation Programme, funded by the European Commission*

- A consortium of 14 collaborators **dedicated to identifying new** and 'greener' ways of **controlling pest insect populations** in the context of IPM.
- Biopesticide development based on cutting-edge technologies **focused on the insects' own peptide hormones and their synthetic mimetics**, to **selectively control insect** pests of agriculture, horticulture and forestry, while preserving beneficial insects such as honeybees (http://www.neurostresspep.eu/home)

2) *Innovative technology identifies industrially useful enzymes*

EU-funded researchers using **innovative genomic** and microfluidic technologies to identify **useful enzymes** in nature …and boost the overall sustainability of a **range of industries, from agriculture** to pharmaceuticals (Innovative technology EU funded)

3) *Novel Pesticides for a Sustainable Agriculture*

The **NoPest project** is harnessing nature, to find a better solution, by **identifying the small molecules that inhibit enzymes vital to oomycetes**' survival and finding others that mimic their activity, **NoPest will deliver a safe and effective solution** …considering the pressures of climate change on our food supply (Novel Pesticides EU funded)

https://cordis.europa.eu/docs

Case-studies on exemplary biopesticide innovation with unclear defined regulatory requirements

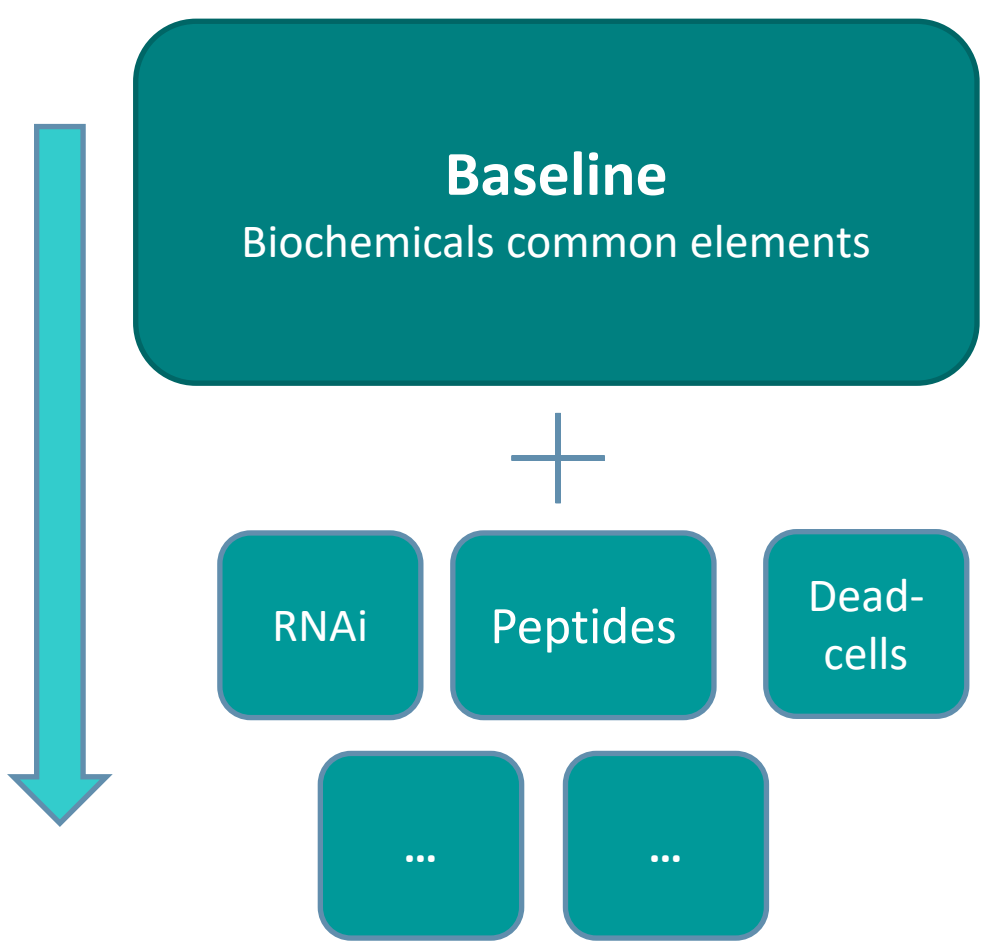
	Classical biopesticides			Biochemicals		
	Micro-organism (living)	Semiochemicals	Botanicals	Dead-cell and Fermentation material	RNA-based PPP	Peptide-based PPP
Definition	Any microbiological entity, including lower fungi and viruses, cellular or non-cellular, capable of replication or of transferring genetic material	Substances emitted by plants, animals and other organisms for purpose of intra- or inter-species communication	one or more components found in plants	Dead microbes containing the same components as the living product or broth/extract with the substances without vegetative cells or spores	Based on RNA interference, a naturally-occurring process that takes place in the cells of plants, animals, and humans.	Peptide-based PPP that selectively disrupt specific physiological processes in target species, and by this reduce survival and /or reproduction
How regulated (EU)	EC Reg. 1107/2009 & Reg. 283/2013, Part B	EC Reg. 1107/2009 & Reg. 283/2013, Part A But mainly guidance documents		EC Regulation 1107/2009 & Regulation 283/2013, Part A		
Environmental exposure	Based on literature data and environmental factors	Background level comparable		Identical to 'current' microorganisms containing products	Rapid degradation rates	Expected low due instability
Manufacturing pathway	Fermentation	Synthetic or biological		Biological: Identical to "living version"	Synthetic or biological	Synthetic or biological
Mode of action & specificity	Multiple	Botanicals: multiple Semiochemicals: specific		Multiple and almost identical to microorganism.	Species-specific alteration of a vital function	Species-specific alteration of a vital function
Fit-for-purpose	Yes fit-for-purpose Execution can be better	Yes fit-for-purpose Execution can be better		Not fit-for-purpose		

Partly, unclear how to register innovative actives of some of our case-studies!

What should a Biochemicals Guidance deliver?

- **Fit the current regulatory system (EC Regulation 283/284) to a fit for purpose data set**– no adaptations needed, can be delivered quickly and should as much as possible be based on existing guidance documents (EU, OECD,…)
- Certainty on **what is needed** as a *science-based guidance* to ensure timely approvals for these innovative biopesticides.
- Cover a **wide range of biochemical active substances** with low human and environmental impact such as plant/animal extracts, peptides, proteins, RNA, dead-cell and fermentation material, metabolites from microorganisms, …
- provide regulatory clarity to address ca. **90% of new biological innovation beyond micro-organisms and viruses (Baseline).**

Assessment structure



Main part: "*inspired*" by existing EU COM guidance documents introducing general principles for "**biochemical AS based on purified substances**" and "**biochemical AS based on complex mixtures**"

Topped by complementary modules: adding specific elements linked a to technology category. Could be developed over time, using partially experience from other regions

Case studies: Proteins[§] are already used as Pesticides

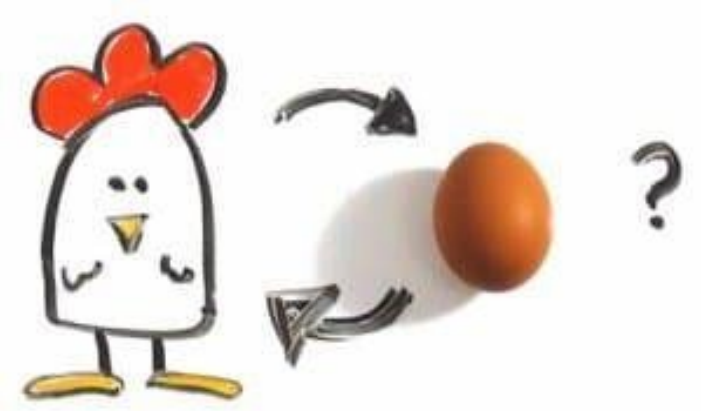
Table 1: Different proteins registered in USA (Status: September 2022)

Active Ingredient Name[§]	Year First Registration in USA
Ea peptide 91398 (3rd generation harpin protein) (71771-RE; 8F8698)	2020
Harpin Protein (Harpin Alpha Beta Protein)	2005
Harpin Protein	**2000**

Harpin protein initiates a complex set of metabolic responses in the treated plant, causing natural gene expression and eliciting a plant's natural defense and growth systems. **In USA**, it is classified as a **biochemical pesticide**, it is a broad-spectrum **fungicide** alternative with efficacy against a wide variety of fungal, bacterial, and viral diseases. **The product** also aids in the **suppression of certain insect, mite, and nematode** pests and enhances plant growth.

[§] Biopesticide Active Ingredients: https://www.epa.gov/ingredients-used-pesticide-products/biopesticide-active-ingredients

What comes first?



http://www.hungryforpurpose.com/wp-content/uploads/2015/10/chicken-or-the-egg.jpg

Biochemicals in the EU

EU citizens & EU Farmers demand novel low risk PPP products

Startup and pioneering Industry

(*knocking doors*)

Industry to invest in **novel technologies** (***registrability analysis***, DGA)

Long, unclear and complex regulatory process with **Authorities**

Impact on decision to invest on novel PPPs - **return of investment**

Conclusion: fit for purpose Regulatory framework for biochemicals is needed

http://www.hungryforpurpose.com/wp-content/uploads/2015/10/chicken-or-the-egg.jpg

What are the key points of CLE's technical contribution document?

Overall structure

- 1. Introduction
- 2. Scope
- 3. Definitions
- 4. Approval of biochemicals active substances and legal framework
- 5. Documented uses and exposure
- 6. Identity, physical and chemicals properties
- 7. Biological properties
- 8. Analytical methods
- 9. Mammalian toxicology
- 10. Operator, worker, bystander, resident safety
- 11. Residues
- 12. Environmental fate
- 13. Effects on non-target species
- 14. Efficacy
- ANNEX

Main part: "inspired" by existing COM guidance documents introducing general principles for "biochemical AS based on purified substances" and "biochemical AS based on complex mixtures"

Annex: case studies on how to apply the guidance on specific technologies (e.g., proteins, microbial extract, RNA,…)

Definitions

Definitions mostly taken over from existing EU guidance documents, but specific definitions developed e.g., for:

- Biochemical active substances based on purified substances
- Biochemical active substances based on complex mixtures
- Nature-identical substance
- Nature-derived substance
- Structural similarity
- Functional identity
- Dead cells and fermentation products
- …

Scope

Biochemicals are substances that may originate from nature or that are synthetically produced provided they are structurally similar and/or functionally identical to their naturally occurring counterparts. The biochemicals category may include but is not limited to:

- Nature-identical synthetic plant extracts / nature-derived but functionally identical
- Extracts from animal tissues
- RNA
- Peptides and proteins, including enzymes and antibodies
- Hormones
- Dead cell, fermentation material, microbial extracts
- Metabolites from micro-organisms (purified)

For all these technologies, **case studies** will be prepared and included in the Annex.

Tiered data requirements

Tier I

Public information, safe use history, weight o evidence approach…

Tier II

		al Grade gredient GAI)	Formulated product
		x	x
Acute dermal toxicity	402	x	x
Acute inhalation toxicity		x	x
Acute Eye Irritation		x	x
Dermal Irritation		x	x
Dermal Sensitization	429	x	x
28-day repeated dose study in rats[1]	407	x	-
In vitro test for gene mutation in mammalian cells	476	x	-
In vitro Micronucleus Test	487	x	-

Tier III

d Tier 2 Data Requirements for B cal Substances

*	OECD Guideline	Technical Grade Active Ingredient (TGAI)
duction /Developmental ty	421	x
ic oral - rodent and dent	452	x
ogenicity - two species - r ouse preferred	451	x
malian spermatogonial osome aberration test		x
y oral (one species)		x
y dermal - rat	411	Note 1
90-day inhalation - rat	413	Note 2

*Potential studies to address findings in Tier 1 (not-exhaustive)

Defining what data is relevant for certain technologies

So, there are some challenges…

- **How to address** an **impact assessment** (**market analysis**) requested by **EU authorities**:
  - The "**impact**" depends on the **size** of companies**, risk affordable?**
  - Can the **industry** decide on **acquiring a new technology** without knowing **how much** to **invest** to place the **biochemical as PPP**?
  - Can the industry "**predict**" what novel technology will be available (knocking doors) as PPP to provide **number of products**?
  - Will **institutions** working **to develop new technologies survive** without "**transferring**" their technologies **to the industry**?

- **Balance** between using **existing Guidance Documents** *vs.* considering **specificities of biochemical technologies**

- Provide **a baseline scope** that does not exclude future innovative technologies.

What are milestones and next steps?

- **To liaise with other industry associations within the EU, as key stakeholders**, to find common grounds on defining a proposal to authorities
- **A market analysis including all interested parties (industry)** to continues discussions with authorities.
- **Evaluation of the wide range of technologies**, to assess if prioritization is a suitable approach
- **To take lessons learnt from other regulatory regions (Australia, Brazil, USA)** on scopes for data requirements and risk assessment of biochemical technologies where those technologies are already placed as PPP.
- **To follow up** with DG SANTE Biopesticides WG, MS agree on the way forward **to support the development** of this initiative – **Europe needs novel Biopesticides!**

Many thanks for your attention!