IBMA Members Questionnaire - Natural Substances Regulatory Challenges

BPWG, Brussels, 10-11 June 2024

IBMA
INTERNATIONAL BIOCONTROL MANUFACTURERS ASSOCIATION

Introduction

- **IBMA** is the association of the biocontrol industry with **experienced members on natural substances registration** on the european market.

- IBMA is a key stakeholder involved in different forums to **support problem formulation** approaches and **fit for purpose data requirements for natural substances.**

- **Aim of the Survey : assess the ongoing regulatory challenges (technical, approval process)**, explore **areas of improvement** and propose **recommendations to streamline the risk assessment of natural substances**.

- From **15/05/2024 to 30/05/2024**, the survey was communicated to IBMA Members companies following the activities of the IBMA Natural Substances Professional Group.

- A total of **31 participants** filled out the survey of **21 questions**.

Introduction (cont.)

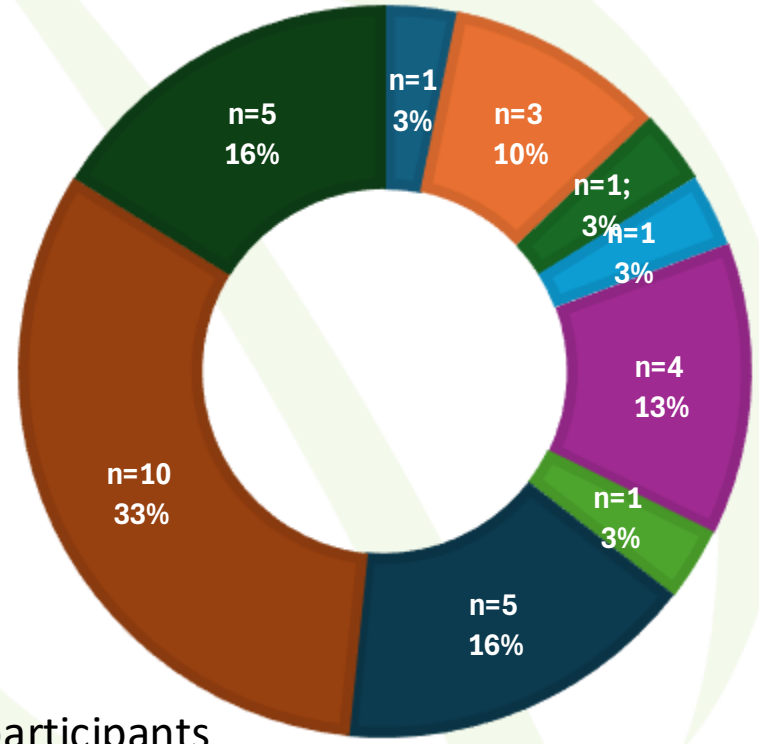
Natural substances categories according to IBMA's definition*

Category	Description	Examples
Inorganic/Mineral Mixtures	Milled mineral mixtures obtained from mining or other inorganic source	Paraffinic oil
Inorganic/Mineral Single Entities	'Pure' minerals obtained from mining/refineries/other inorganic source	Sulphur, kaoline, ferric phosphate, bicarbonate
Plant Mixtures	Natural extracts from plant origin	cinnamon oil, orange oil, garlic extract, pyrethrins
Plant Single Entities	Purified plant extracts or nature-identical synthetics	Terpenes, azadirachtin, cinnamaldehyde, citric acid, abamectin, Dodecan-1-ol, pelargonic acid
Animal Mixtures	Natural extracts from animal origin	Blood meal
Animal Single Entities	Purified Animal extracts or nature-identical synthetics	Pelargonic acid, chitosan
Micro-Organism Mixtures	Extracts of, and metabolites from micro-organisms (dead microbes)	yeast cell walls, ABE-IT 56 Chromobacterium subtsugae strain PRAA4-1T + Fermentation media
Micro-Organism Single Entities	Purified extracts of, and metabolites from micro-organisms or nature-identical synthetics	Gibberellins, microbial sourced sulphur
Nature-Identical Mixtures	Including Fermentation based extracts	To date, fermentation in which the micro-organism is a bio-factory, is always accompanied by purification to create an active substance Example *S.cerevisae* extract
Nature-Identical Single Entities	- Purified fermentation-based extracts or nature-identical synthetic s - Purified or nature-identical synthetic (poly)peptide/protein	6-benzyladenine Harpe protein Antibodies Enzymes Peptides

* "Substances that consist of one or more components that originate from nature, including but not limited to: plants, algae/micro algae, animals, minerals, bacteria, fungi, protozoans, viruses, viroids and mycoplasmas. They can either be sourced from nature or are nature identical if synthetized. This definition excludes Semiochemical and microbials.

Natural substances categories in the EU

What category of Natural Substance you have registered in the EU, or you would like to register in the EU ?



N=31 participants

- Animal Mixtures
- 4 Inorganic/Mineral Mixtures — 'Pure' minerals obtained from mining/refineries/other inorganic source
- Inorganic/Mineral Single Entities
- Micro-Organism Mixtures
- 3 Micro-Organism Single Entities — Purified extracts of, and metabolites from micro-organisms or nature-identical synthetics
- Nature-Identical Mixtures
- 2 Nature-Identical Single Entities — - Purified fermentation-based extracts or nature-identical synthetic s; - Purified or nature-identical synthetic (poly)peptide/protein
- 1 Plant Mixtures — Natural extracts from plant origin
- 2 Plant Single Entities — Purified plant extracts or nature-identical synthetics

~ 50%

50 % of the respondents shared that they registered or would like to register plant “extracts” and 30% of the population is working on ‘Natural-Identical Single Entities’/’micro-organisms Single entities’

Natural substances categories in the EU

Referring to the previous question, what is the regulatory status of your active substance (a.s.) in the EU?

Regulatory status:

19% (n=6) - approved

19% (n=6) - planned submission

26% (n=8) - ongoing renewal

35% (n=11) - ongoing submission

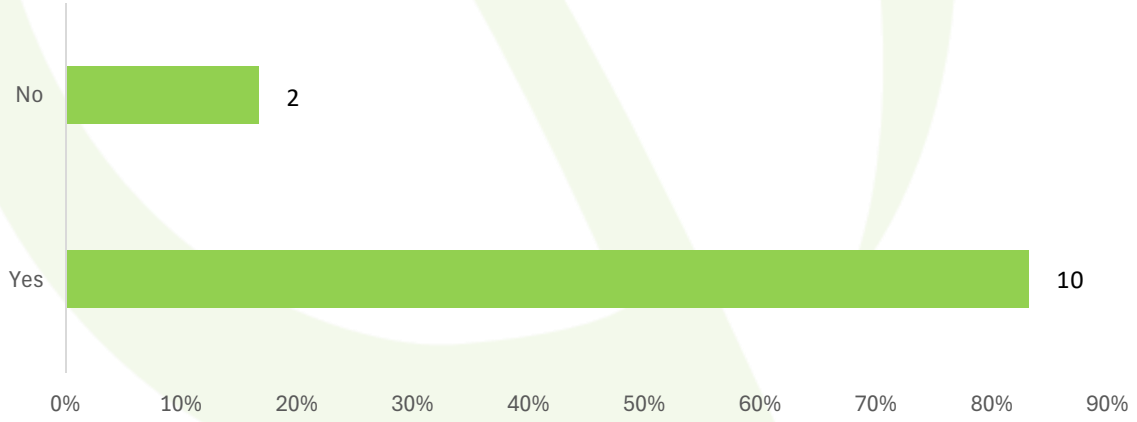
80 % of the a.s. dossier submissions of the respondents are planned or ongoing

Renewal process

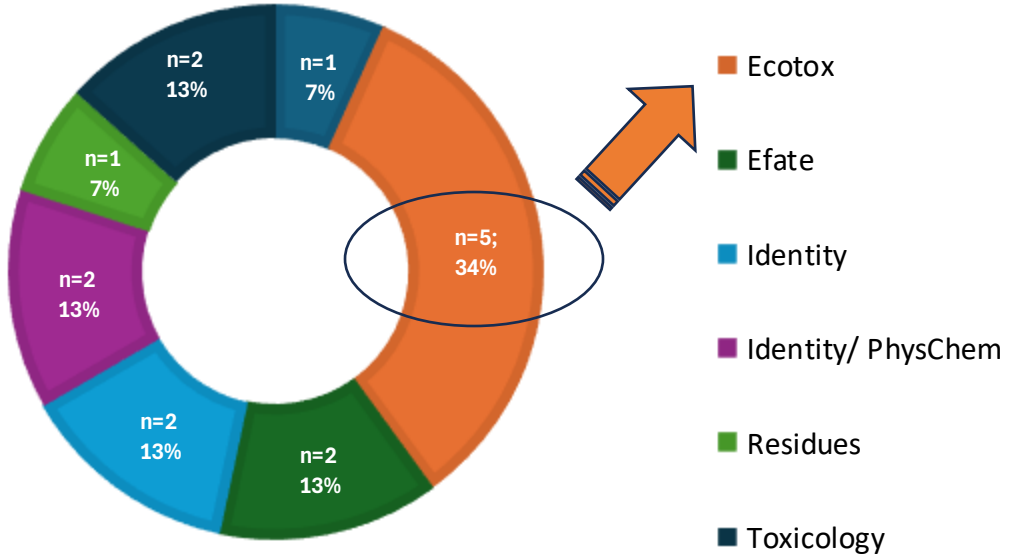
In the case of a renewal: How many times did your active substance (a.s.) go through the renewal process (including the ongoing renewal)?

- 58% of the participants stated their a.s. never underwent a renewal (n =18)
- 29% - once (n= 9)
- 28% - twice (n= 4)

During the last renewal, did you experience more data requests than in previous assessment(s) of the substance?



NATURE OF ADDITIONAL REQUESTS (DURING LAST RENEWAL)



Biggest challenges in the approval of the active substance

Identity/PhysChem/Methods

- 5 batch analysis
- Define lead component
- Method development
- Choice of reliable endpoint

22%

Ecotoxicology

- Aquatic risk assessment – solubility
- Higher tier studies
- Little persistence
- Test item concentration
- Define lead component

27%

Environmental Fate

- Radiolabeling
- Limited literature available
- Metabolism
- Ready biodegradability criteria not applicable

16%

21%

Human Toxicology

- 90-d study
- ED determination on extracts
- Historical control data
- Worker, residents, bystander exposure difficult to assess
- Dermal absorption could not be determined
- Limited literature available

15%

Residues

- Definition
- Further studies required
- Determine background levels
- Naturally occurring components

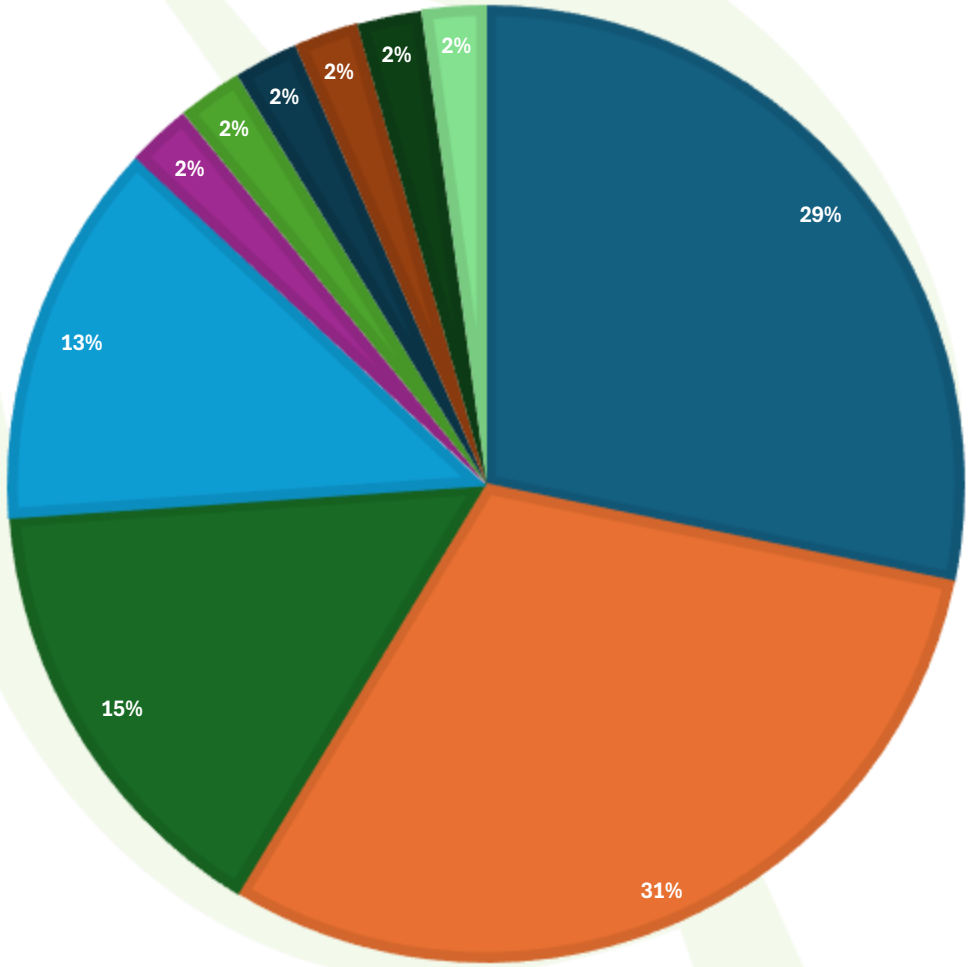
4%

Efficacy

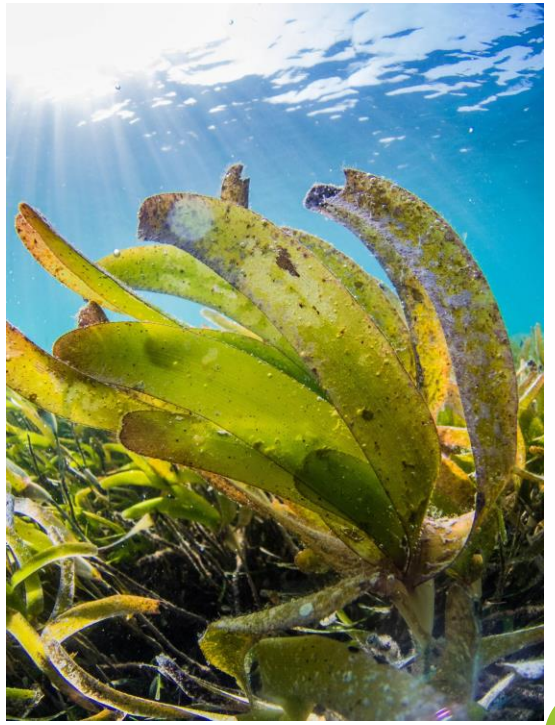
- Compared to synthetic standards
- Elevated cost due to required testing in all 3 zones

Highlight on Ecotoxicology- challenges

What challenges have you encountered in the area of ecotoxicology (i.e. background levels) during the registration of natural substances? (more than one answer possible)

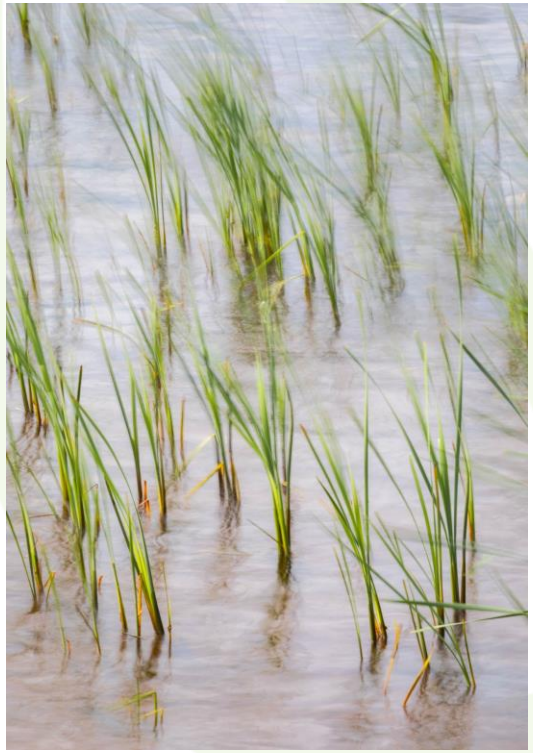


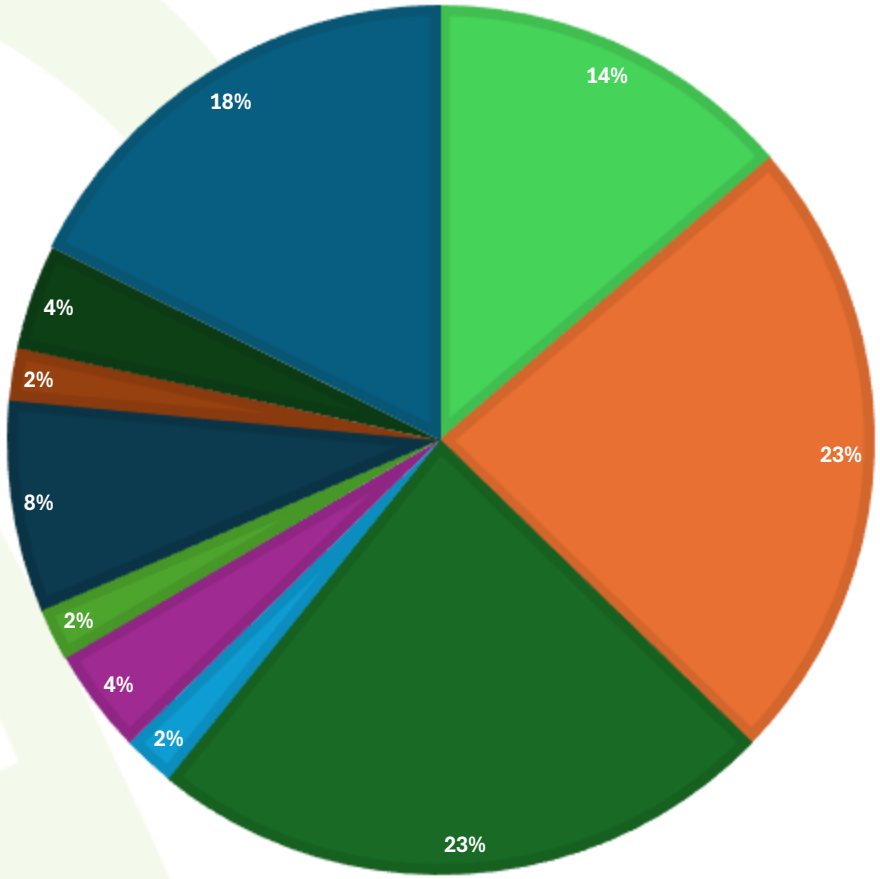
- Analytical verification of test concentrations - uncertainty on which compounds to analyse in a complex mixture
- Analytical verification of test concentrations - unstable test item
- Available literature on effects on non-target organisms was not accepted
- No response
- Other challenges - analytical verification (other reasons - NS)
- Other challenges - NS compared to synthetical chemicals
- Other challenges - higher tier studies needed
- Other challenges - issues with solubility of the extracts for chronic aquatic studies
- Other challenges - limited literature available
- Other challenges - perform studies with TGAI due to inherent properties of the a.i.



Highlight on Environmental fate - challenges

What challenges have you encountered in the area of environmental fate during the registration of natural substances? (more than one answer possible)





- Data on persistence, transformation and mobility in the environment could not be waived based on nature of the compound.
- Difficulty to show biodegradability – standard tests (e.g. OECD 301D Closed Bottle test) not appropriate for complex mixtures.
- No response
- Other challenges - approached as a synthetic chemical by the regulations
- Other challenges - Guidelines OECD 307, 308 and 309 not adapted to complexe mixtures
- Other challenges - high costs associated with testing five individual lead components
- Other challenges - issues with radiolabelling
- Other challenges - little consideration by the authorities in MRL setting for a compound that naturally exists in the environment
- Other challenges - no data published on background levels
- Published data on naturally occurring background levels not accepted.

Further information on regulatory challenges

Please provide any further information on regulatory challenges that may be of interest and relevance to natural substances.

14 replies

Regulatory challenges

- A simplified process for NS for organic farming certification
- Consistent methodology for UVCBs
- Disagreement between different authorities
- ED assessment
- Mixtures assessment

Suggestions for improvement

- Simplified process and more flexible data requirements for natural substances (n=7)
- Differentiate natural substances from chemical requirements (n=3)

General conclusion

- Regulatory activity is significant, and will grow with dossier submissions, e.g. new submissions and renewals.
- Natural substances categories are diverse with new technologies coming, e.g. natural identical single entities
- The request for additional data is increasing. Generating these additional data could be challenging for applicants.
- IBMA will continue its analysis of the survey results. We propose to communicate the full analysis to the BPWG along with a proposal for recommendations. These recommendations could also be shared in relevant forums for the development and implementation of fit-for-purpose data requirements for natural substances.

Thank you

IBMA Natural Substances Professional Group

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