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Current regulation system and data requirements within the EU

REBECA workshop:
Potential risks of microbials
Innsbruck 12-13 April 2006

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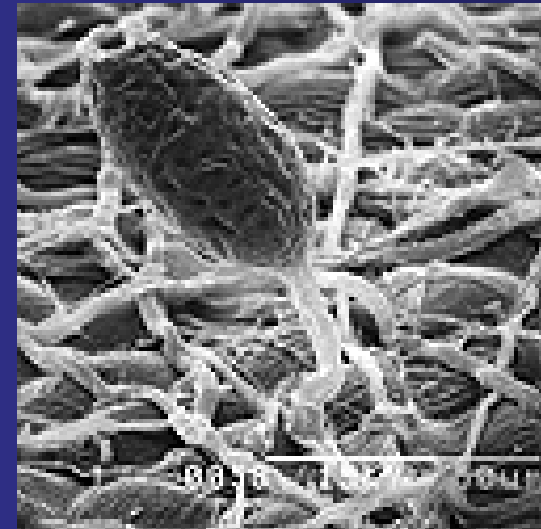


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Outline

- EU directive
- History
- Existing active substances
- EU evaluation process
- New active substances
- EU workshop 1998
- Data requirements Dir. 2001/36
- Conclusion





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Why so few microbials at the EU market compared to the USA?

- Regulation process
- Difference in risk perception/definition in EU and USA (e.g. GMO)
- Difference in legal system
- Small market
- Some of the big producers give low priority to microbials compared to their chemical ppp
- Low efficacy/reliability of some products
- Some chemical products easier to apply



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Microbial products authorised

EU

34 microbial strains
57 products

USA

76 microbial strains
225 products (145 Bt. products)

Canada

21 microbial strains
45 products (36 Bt. products)



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Fees

Sweden: 220.000 €
Denmark: 100.000 €
Germany: 86.000 €



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Microbial products authorised

“The PMRA does not charge any cost-recovery fees for evaluating microbial submissions. This is viewed as necessary to provide incentive to foreign registrants/manufacturers to consider the Canadian marketplace”

acts)

Canada

21 mikrobiel stains

45 products (36 Bt. products)

How should the authorities decide on the size of the fee?

Should the fee be equal to the amount of resources spent on the evaluation?

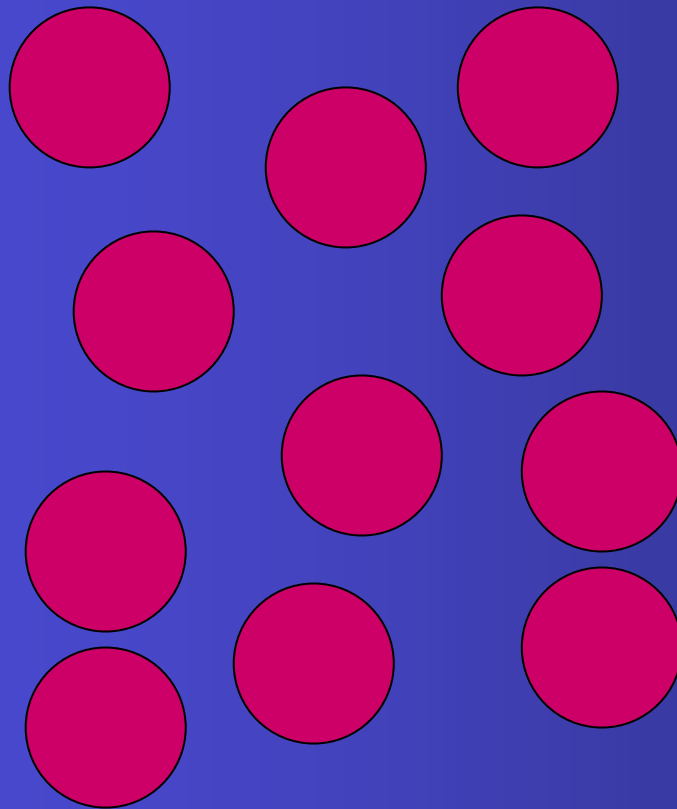
Should the fee be low due to the small market for these kind of products?

Should the fee be a result of the political interests in increasing the use of microbial products?

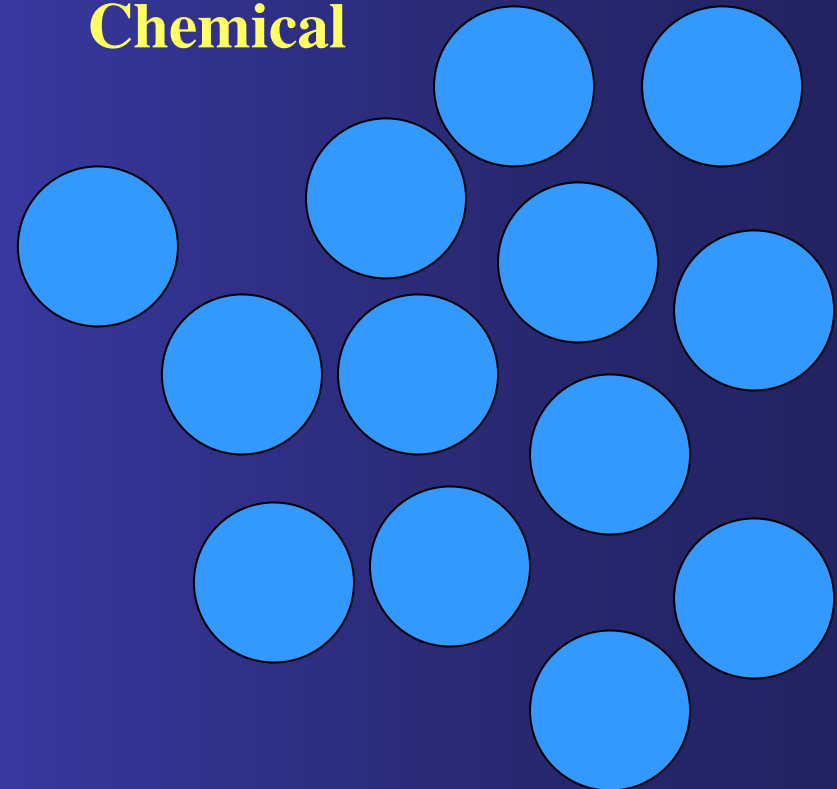
Then we have to divide products into *high risk* and *low risk* products?

High risk / low risk products

Microbial



Chemical



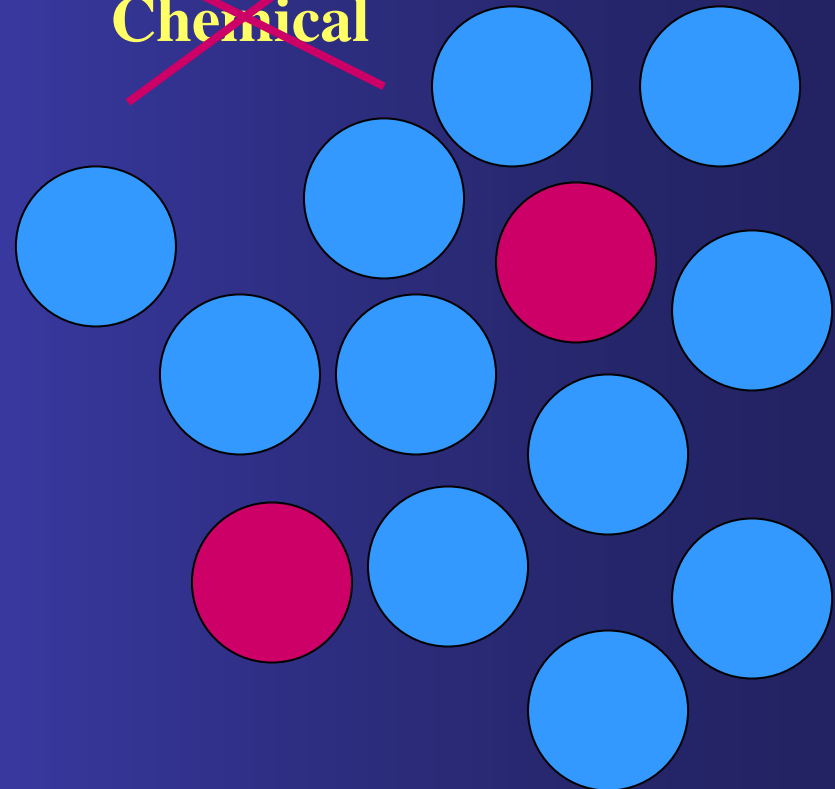
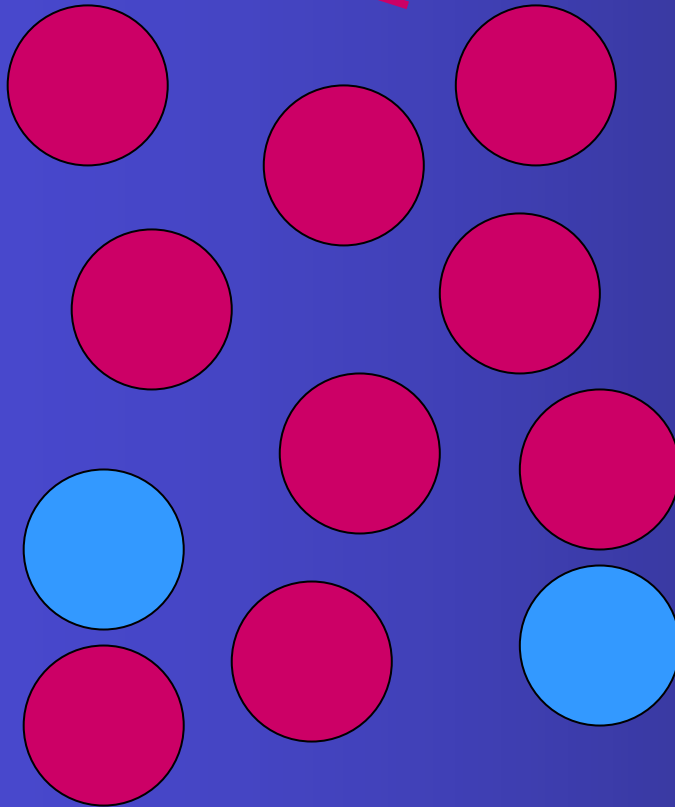
High risk



High risk / low risk products

~~Microbial~~

~~Chemical~~



High risk

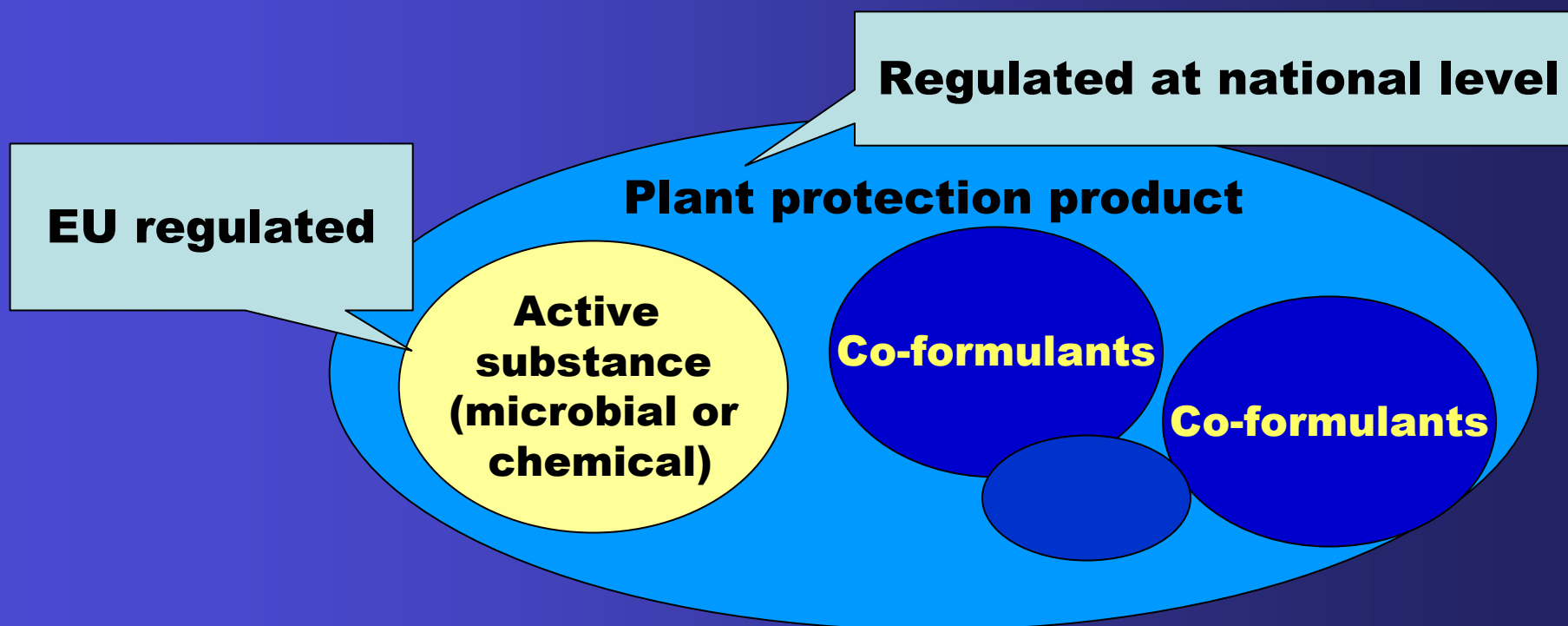




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National or EU regulation





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EU Directive 91/414/EEC

The EU directive contains 6 Annexes

I
Table with
active substances
100 chemicals
5-6 micro-organisms

II
Data
requirements
A: Chemical subst.
B: Micro-organism

III
Data
requirements
A: Chemical prod.
B: Microbial prod.

IV
Risk
phrases

V
Safety
phrases

VI
Uniform principles
A: Chemical pr.
B: Microbial pr.



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History - 1

- 1991
EU directive 91/414/EC on plant protection products.
- 1998
 - 7 applications for Annex I inclusion
 - EU workshop in Sweden on 26-28 October 1998 to revise data requirements. Attended by IBMA, US-EPA, PMRA - Canada, OECD, EU Commission, EU regulators and many experts



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History - 2

- 2001
EU directive 2001/36/EC with new data requirements on micro-organisms and products – Annex IIB and IIIB
- 2002-2003
4th list re-evaluation process started.
Notification of existing active substances
21 species (40-50 strains) notified
4 species not notified



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History - 3

- 2004
Commission regulation 2229/2004
Who had notified which organisms
Who was going to be Rapporteur MS
Deadline (30th November 2005), process, ...
- 2004
OECD harmonisation on dossier submission
and numbering system
- 2005
EU directive 2005/25/EC with Uniform
Principles of national evaluation of microbial
plant protection products



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History - 4

- 2005
Dossiers for 17 species - 29 strains submitted to RMS, however no dossiers submitted for 17 strains that had been notified (may be identical to the notified strains)
- 2006
Average EU evaluation period until Annex I inclusion 7 years. REBECA Action started
The Commission will finalise a revised draft of Dir. 91/414/EC – negotiations in 2006-2007



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Strains from 17 Microbial species
applied included in Annex I in Nov. 05

Bacillus thuringiensis - aizawai

Bacillus thuringiensis - israelensis

Bacillus thuringiensis - kurstaki

Bacillus thuringiensis - tenebrionis

Beauveria bassiana

Beauveria brongniartii

Cydia pomonella granulosis virus

Metarhizium anisopliae

Phlebiopsis gigantea

Pythium oligandrum

Streptomyces griseoviridis

Trichoderma harzianum

Trichoderma polysporum

Trichoderma viride

Verticillium dahliae

Verticillium lecanii

(*Lecanicillium longisporum*
and *L. muscarium*)



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8 Species not notified or dossiers not submitted in November 2005

Agrobacterium radiobacter

Aschersonia aleyrodis

Agrotis segetum granulosis virus

Bacillus sphaericus

Bacillus subtilis

Mamestra brassica NPV

Neodiprion sertifer NPV

Tomato Mosaic Virus



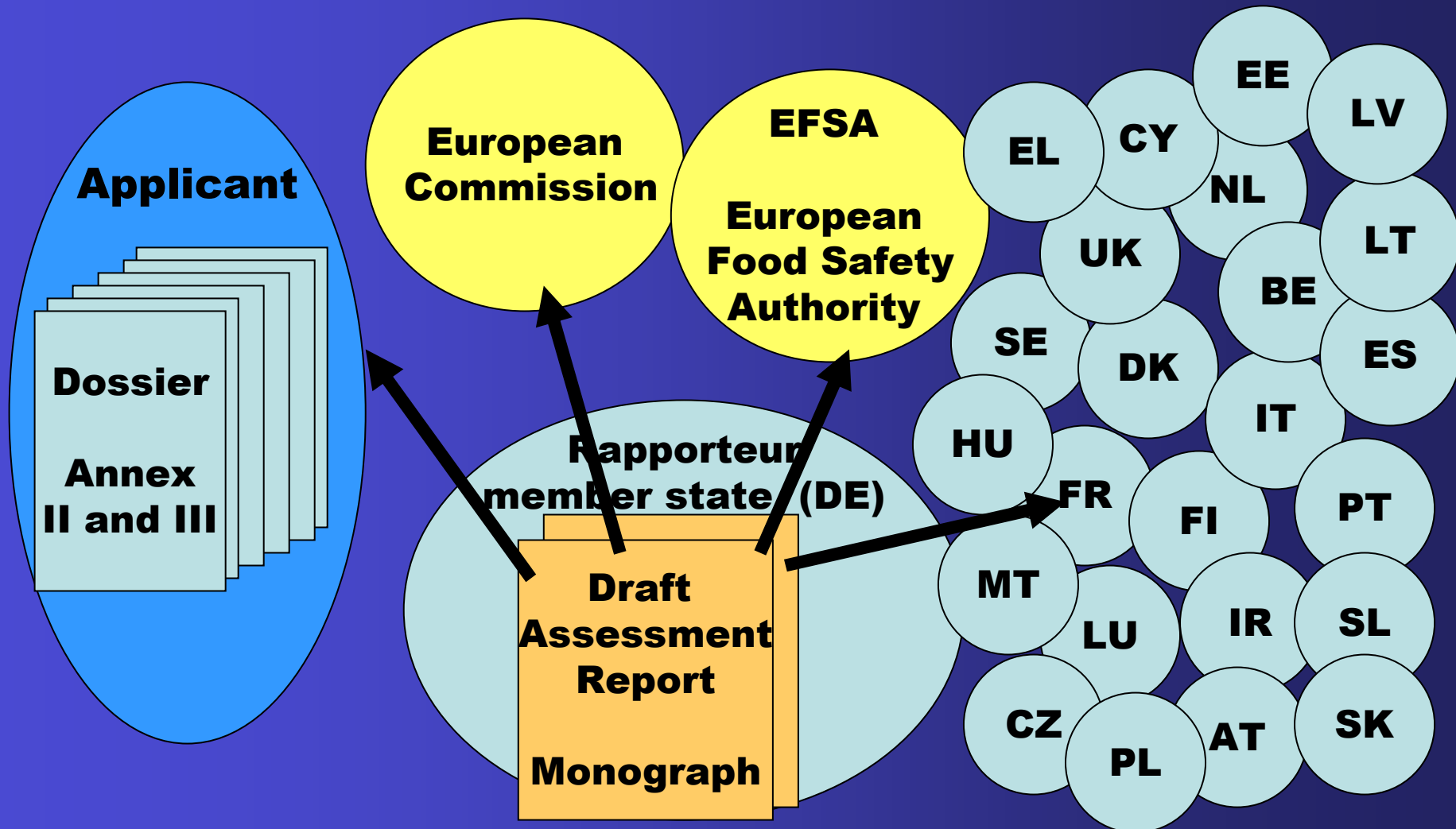
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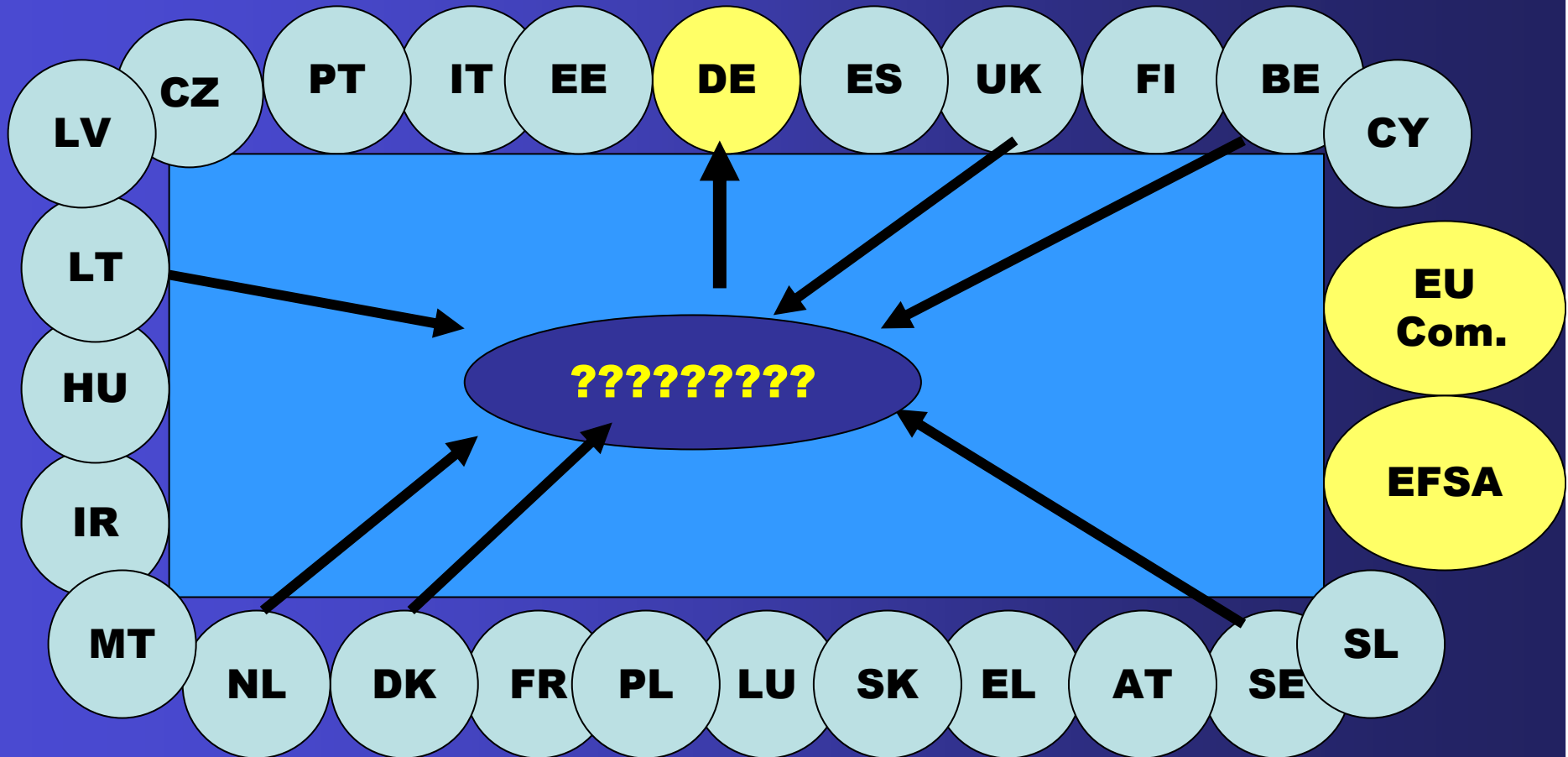
Expectations for the risk assessments of the 4th list micro-organisms

- **The risk assessment process will be much faster than experienced until today**
- **Many waivers will be accepted**
- **Communication between regulators and notifiers will be/has been increased**
- **Communication between EU regulators will be increased**

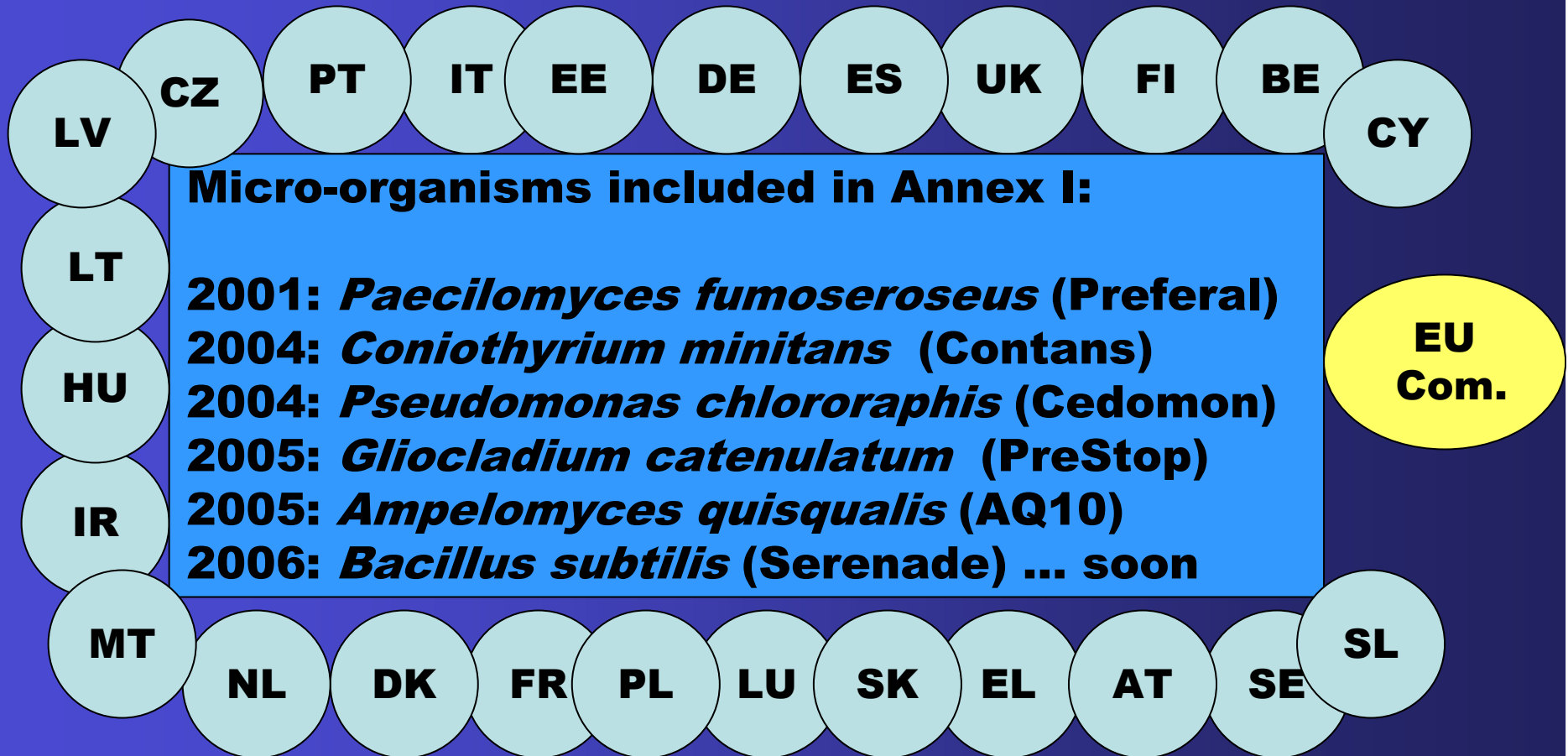
The process of inclusion of the micro-organism in Annex I



The data and the evaluation is being discussed



Finally vote: yes/no to Annex I inclusion



Micro-organisms in process of Annex I inclusion

Fungi

***Paecilomyces lilacinus* (Bioact - nematicide)**

***Pseudozyma flocculosa* (Sporodex - fungicide)**

***Paecilomyces fumosoroseus* (new strain)**

Bacteria

***Agrobacterium radiobacter* (fungicide)**

Virus

***Spodoptera exigua* NPV (Spod-X - insecticide)**

Zucchini Yellow Mosaic Virus (mild strain)

How well does the EU evaluation process work ?

- **The EU evaluation process works too slowly**
- **Many chemical substances**
- **Lack of resources in EU, EFSA and MS – too few people and too low budget for meetings**
- **25 EU member states → many opinions ...**
however, now only few MS comment monographs
- **Diverging evaluation/interpretation of data**
- **Rapporteur + other MS will request further data**
- **Regulators/experts do not always trust the evaluation and expertise in other MS**

How well does the EU evaluation process work ?

Main reason for long evaluation period:

Disagreement between applicants and regulators/experts on need for data/studies and lack of communication between all parties



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EU workshop in Sweden in 1998 (1)

Identification, characterisation, biology

- Culture collection
- Characterised at the strain level
- Antibiotic substances
- Familiarity – open literature incl. in dossier
- Consensus documents on existing knowledge
- List of micro-organisms regarded as safe



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EU workshop in Sweden in 1998 (2)

Production control

- Quality control of production of organism and product
- Contaminants
- Spontaneous changes in characteristics



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EU workshop in Sweden in 1998 (3)

Fate and Behaviour/envIRON. adverse effects

- Experimental data are normally not required when it can be justified that an assessment can be performed with available information
- Post-approval monitoring should be considered for all areas of risk assessment. Particularly for exotic organisms



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EU workshop in Sweden in 1998 (4)

Adverse effects on human health

- Ability to colonise and to cause damage
- Ability to produce toxins and relevant metabolites
- Available information may be sufficient
- The suggested test methods need to be relevant regarding sensitivity, administration route, etc.



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EU workshop in Sweden in 1998 (5)

Adverse effects on human health - 2

- New test guidelines have to be developed within OECD
- Sensitisation – no validated test method
All micro-organisms should be regarded as potential sensitisers.
- Conclusion: Characterisation and identification of the micro-organism is the most important information – further tests should be performed on a case-by-case basis.

Data requirements - organism ⁽¹⁾

Annex IIB of Dir. 91/414

Identity

- **Strain level**
- **Methods to identify and determine content**
- **Impurities**
 - **contaminating micro-organisms**
 - **relevant metabolites**
 - **culture medium**

Biological properties

- **Origin and natural occurrence**
- **Target**
- **Mode of action**
- **Specificity**
- **Dispersal and colonisation ability**
- **Genetic stability**
- **Production of metabolites**

Data requirements - organism ⁽²⁾

Annex IIB of Dir. 91/414

Human health TIER I

- **Medical data**
- **Sensitisation (inhalation and skin)**
- **Acute toxicity, pathogenicity and infectivity (single exposure)**
 - A. Oral**
 - B. Inhalation**
 - C. Intraperitoneal/subcutaneous**
- **Genotoxicity (metabolites)**
- **Short term toxicity and pathogenicity (repeated exposure)**
- **First aid measures**

Human health TIER II

- **In vivo studies in somatic cells**
- **in vivo studies in germ cells**

Data requirements - organism ⁽³⁾

Annex IIB of Dir. 91/414

Residues

- **Persistence and multiplication**
- **Non viable residues**
- **Viable residues**

Fate and behaviour in the environment

- **Persistence and multiplication (soil, water, air)**
- **Mobility**

Effect on non-target organisms

- **Birds**
- **Aquatic organisms (fish, algae)**
- **Bees**
- **Other arthropods**
- **Earthworms**
- **Non-target soil micro-organisms**

Data requirements - Product ⁽¹⁾

Annex IIB of Dir. 91/414

Identity

- **Trade name**
- **Composition**

Physical, chemical, technical properties of the ppp

- **Storage stability - shelf life**
- **Particle size distribution**
- **Etc.**

Data on application

- **Intended use**
- **Mode of action**
- **Application rate**
- **Methods, number and timing of application**
- **Proposed instructions for use**

Data requirements - Product ⁽²⁾

Annex IIB of Dir. 91/414

Further information

- **Re-entry periods**
- **Cleaning of application equipment**
- **Measures in case of an accident**

Efficacy data

Human health

- **Oral toxicity**
- **Inhalation toxicity**
- **Percutaneous toxicity**
- **Skin and eye irritation**
- **Skin sensitisation**

Data requirements - Product ⁽³⁾

Annex IIB of Dir. 91/414

Exposure under the proposed condition of use

Residues

Fate and behaviour in the environment

Effect on non-target organisms

How to overcome the hurdles?

- **Keep current data requirements unchanged but generate an EU guidance document.**
- **Political pressure to reduce fee/no fee**
- **A system with compulsory pre-submission consultation meetings with participation of risk evaluators → agreement on waivers**
- **Resources for regular expert meetings invited by the Commission/EFSA with participation of regulators, experts and applicants**
- **Low risk products like microbials should be given high priority within the EU regulating system and not be “the last point on the agenda ”**



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