



Proposals for improved regulatory procedures for microbial BCAs

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Regulation of microbial BCAs in Europe

Data requirements for the registration of micro-organisms as active substances and of products based on micro-organisms are laid down in the Council Directive 91/414/EEC, amended by the Commission Directive 2001/36/EC (EC 2001). The Uniform Principles for evaluation and authorisation of plant protection products containing micro-organisms are laid down in the Council Directive 2005/25/EC.





Objectives of REBECA action

- To accelerate the regulation process for microbial BCAs in Europe
- To make it more cost-effective without compromising the level of safety”.
- To review the potential risks of microbial BCAs
- To make recommendations how to regulate BCAs which is based on existing risks





REBECA activities

Report based on the outcome of workshops and a REBECA meeting (experts from science, regulatory authorities and industry were involved)

- **Innsbruck, Austria, April 12-13, 2006**
"Current regulation procedures and requirements: Ranking of risks and suggested waivers"
- **Salzau, Germany, September 18-22, 2006**
"Risk assessment strategies" and a comment to the OECD paper on contaminant levels"
- **Alés, France, June 3-7, 2007**
Discussion on two the Issue papers: "Proposal on the risk assessment of metabolites"; "How to evaluate the environmental safety of microbial pest control products"
- **Raisdorf, Germany, September 7-9, 2007**
Discussion on "REBECA Proposal for the risk assessment of metabolites" and "REBECA Proposal to simplify registration"



Identification of risks

Evaluation of potential risks of microbials: priority list for fungal BCAs

REBECA workshop in Innsbruck/Austria (April, 12th -13th 2006)

Impact

Human Risks Toxicity/Genotoxicity/ Allergene/Pathogenicity	Impact of toxins on human health	Sensitisation: users productions consumers	Inhalation: user other workers in field/ glasshouse	Invasive potential on immune depressive patients	Residues: living microbes mycotoxins	<p>high</p>
Metabolites Mycotoxins	Risks of unknown toxins by fungal BCAs	Mycotoxin accumulation in specific environment	Mycotoxin accumulation in product: but quantities are very low	Release of metabolites with non-target effect	Volatiles	
Efficacy active market force	Variation in efficacy (batch-dependent)	Loss of efficacy: no means of changing strains	Products do not work	Failure in control or other effects		<p>low</p>



REBECA activities

Based on the experience with the use of MBCAs and scientific information four proposals were produced and discussed:

- Proposal for facilitated regulation of baculoviruses as active ingredients in plant protection products
- Proposal on the risk assessment of metabolites produced by micro-organisms in plant protection products
- Developing a risk index to comparatively assess environmental risks posed by microbial and conventional pest control agents
- Proposal to simplify registration of microbial BCAs



Proposals for improved regulatory procedures for MBCAs *Baculovirus* – products

Basis for a “new” approach



- OECD Consensus Document
- *Spodoptera exigua* MNPV included in Annex I
- Dossiers submitted for *Cydia pomonella* GV (List 4)
- Dossiers submitted for *Adoxophyes orana* GV and *Helicoverpa armigera* NPV





Proposals for improved regulatory procedures for MBCAs *Baculovirus* – products

**Three proposals were discussed for the
inclusion of *Baculovirus* isolates into Annex I**



- All *Baculoviruses* (including *Dipteran*- and *Hymenopteran*-specific species) – family
- “All *Lepidoptera*-specific *Granuloviruses* and *Nucleopolyhedroviruses* “ – genus
- Individual *Baculoviruses* – species





Comments on data requirements

- **Human infectivity**
- **Genetic stability**
- **Sensitisation**
- **Genotoxicity**
- **Toxicological and exposure data and information on the MBCA**
- **Fate and Behaviour in the Environment**
- **Ecotoxicological Studies on the Microbial Pest Control Agent (Effects on non-target organisms)**
- **Assessment of metabolites in the environment**



Comments on data requirements

Human infectivity

If biological agent is not listed in Directive 2000/54, it is unlikely that it can cause human diseases

- **In that case, no special measures should be required according to the Directive to prevent or reduce the risk of exposure to such an organism**
- **It is questioned whether the classification of MO's into group 1 delivers at least the rationale to waive the clearance investigations in the Tier I assessment**



“Metabolites of concern”

Proposal on the Risk Assessment of Metabolites produced by Micro-organisms in Plant Protection Products

1. September 2007

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* RAFBCA, was an EU-funded project (QLK1-CT-2001–01391) with the aim to establish whether metabolites produced by fungal BCAs entered the food chain and if they posed a risk to human and animal health (see <http://www.rafbca.com>).



General conclusions were drawn by REBECA

- Fungal BCAs investigated produced metabolites in extremely small amounts both *in vitro* and *in vivo* and are, therefore, unlikely to pose a threat to humans and the environment.
- None of the investigated fungal metabolites entered the food chain, even when applied ten times higher than the recommended application rate. Metabolite risks were assessed at all stages of the production and application cycle, i.e. in fermenters, unformulated inoculum, formulated product, on crops and in harvested crops.



General conclusions were drawn by REBECA

- Aspects of the biology of MBCAs should to a larger extent be taken into account when assessing the risks
- Toxins are usually produced under inducible conditions within or in contact with the host or target. Their concentrations are low. Therefore, these toxins are of minor concern
- A risk assessment investigation based on single metabolites is not feasible



Proposal to simplify registration

Information check list for pre-submission

- Identification and taxonomic position of the MBCA
- Natural distribution of the species
- Mode of action and host range
- Toxicity data
- Metabolites produced by the MBCA
- Intended use of the product (target organisms)



Proposal to simplify registration

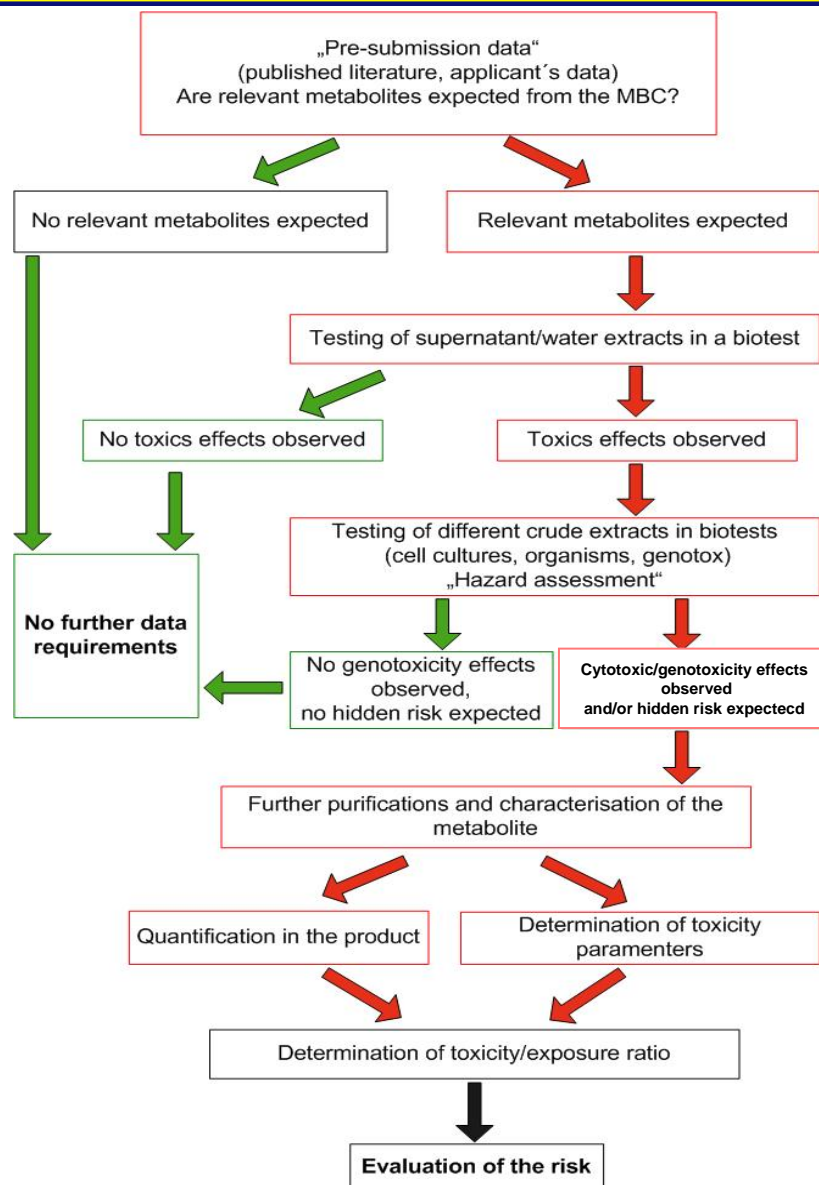
Information check list for pre-submission

- Formulation of the product
- Site and method of application
- Health and medical reports
- Absence from the list provided in Dir. 2000/54 EC concerning workers protection from micro-organisms
- Maximum growth temperature
- List of available antibiotic compounds

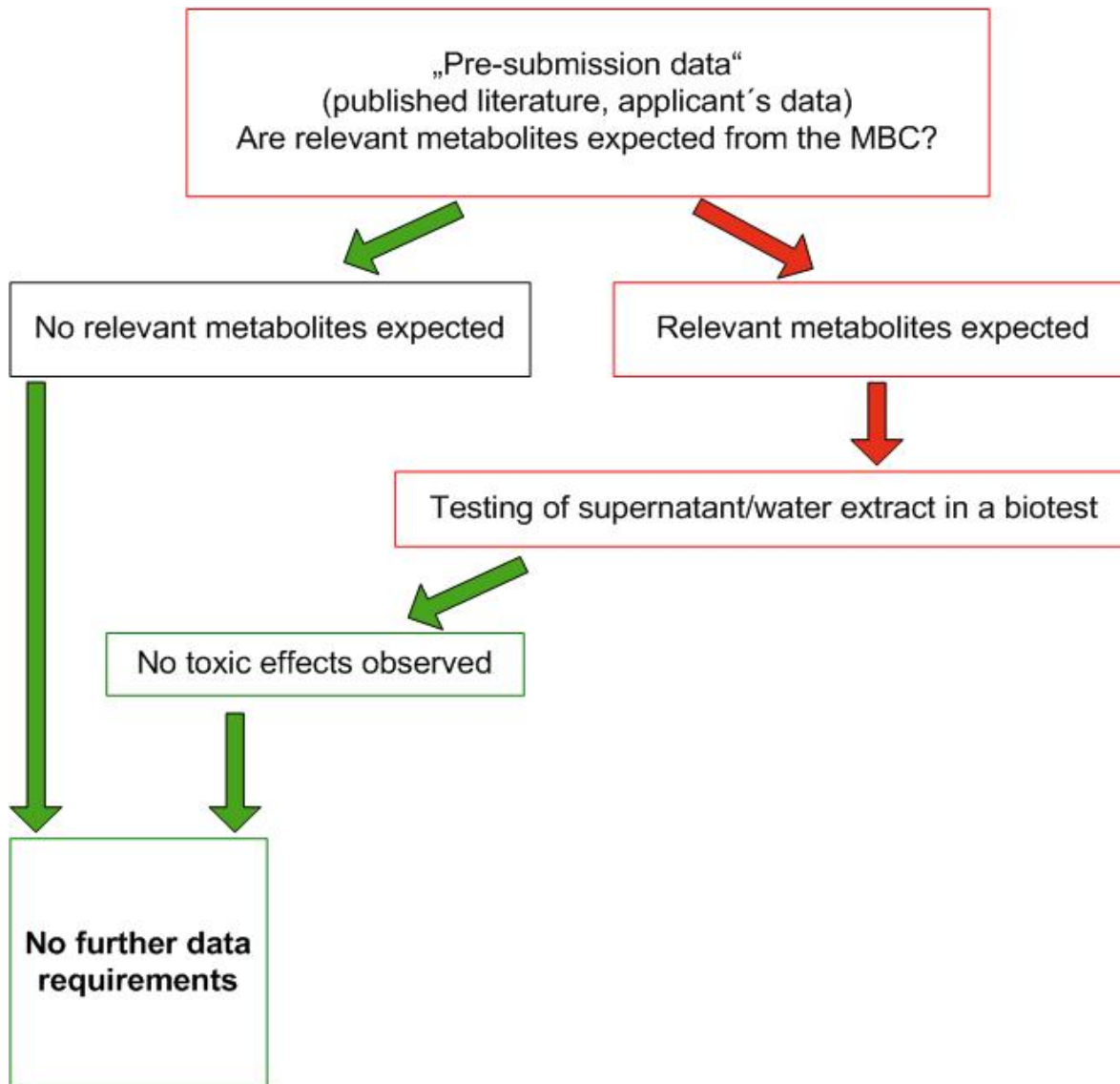


Two important questions

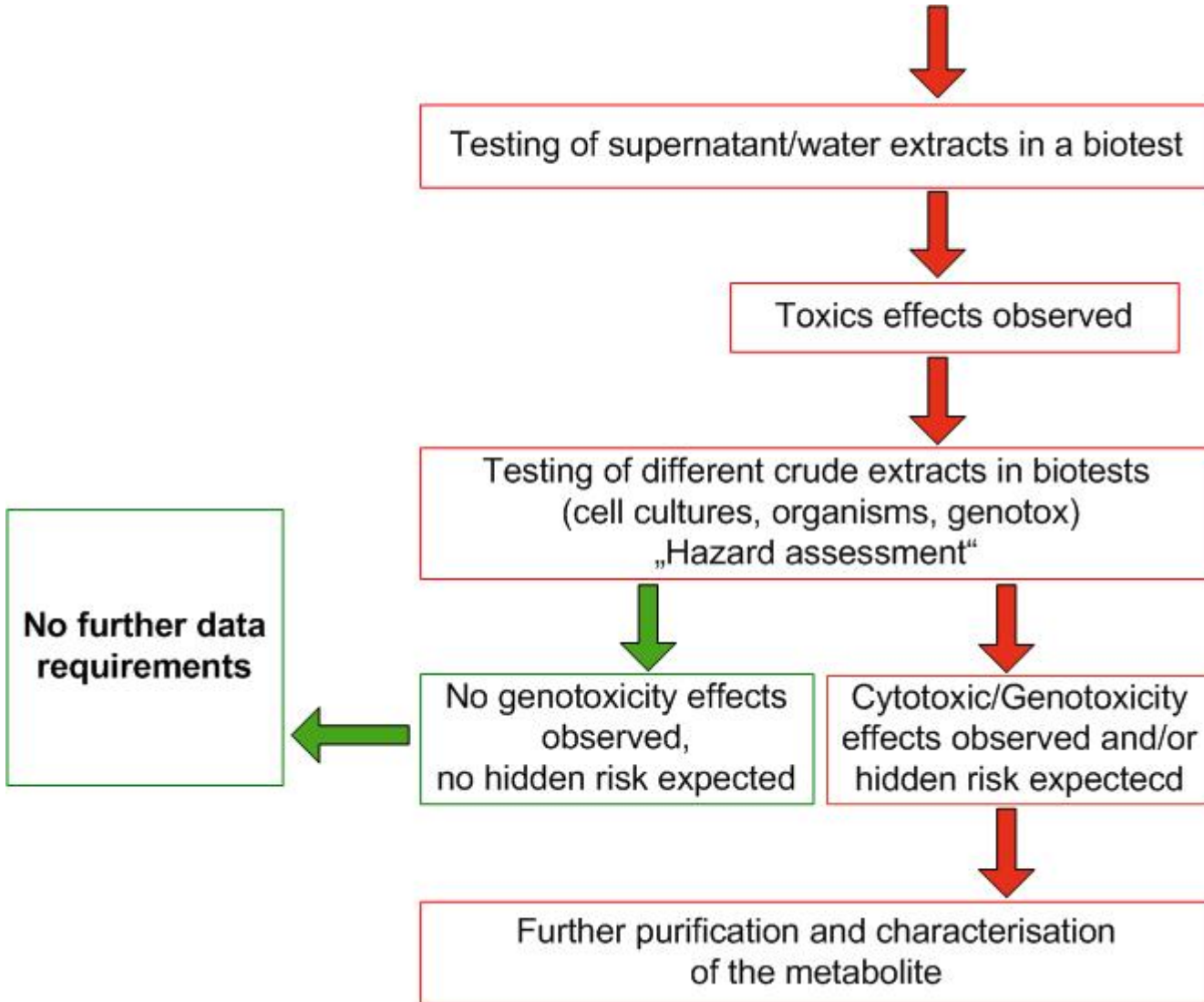
- (1) How should we deal with the regulatory requirements for a microbial BCA that has only recently been described?
- (2) How should we deal with the regulatory requirements for a microbial BCA, for which there is no information on the metabolites it produces?



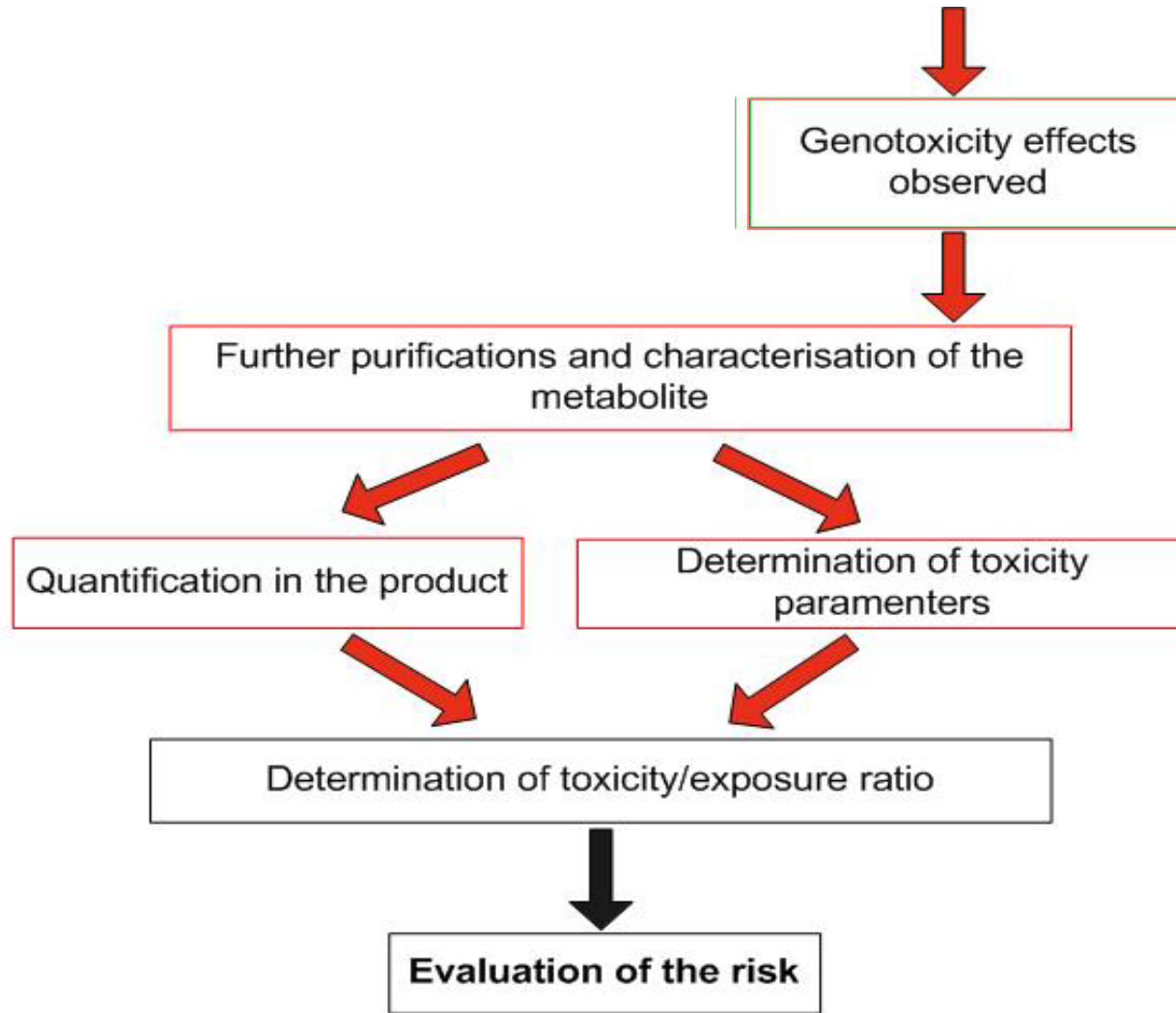
Scheme for assessment of potentially relevant metabolites of microbial BCAs



Scheme for assessment of potentially relevant metabolites of microbial BCAs



Scheme for assessment of potentially relevant metabolites of microbial BCAs



Scheme for assessment of potentially relevant metabolites of microbial BCAs



Risk index to comparatively assess environmental risks

Five basic components are proposed for the calculation of the overall environmental risk score:

- 1) persistence of the substance
- 2) dispersal potential
- 3) range of (non)-target organisms that are affected
- 4) direct and indirect effects on the ecosystem.
- 5) risks regarding vertebrate toxicity.



Risk scores and calculated risk index for selected pest control products

Active Ingredient	Persistence factor	Dispersal factor		Host Range		Direct Effect		Indirect Effects		Vertebrate effects	Risk Index
		Distance	Quantity	Species	Taxonomic level	Likelihood	Magnitude	Likelihood	Magnitude		
<i>Bacillus thuringiensis</i> (spray)	2	2	3	4	4	3	2	2	3	1	280
<i>Coniothyrium/psittacina</i> (soil)	1	1	3	1	1	1	1	2	2	1	24
<i>Metarhizium anisopliae</i> (spray)	1	3	3	4	4	3	2	1	2	1	240
<i>Pantoea. agglomerans</i> (spray)	1	3	2	3	3	2	1	1	1	2	98
<i>Trichoderma harzianum</i> (soil)	2	1	1	3	3	3	2	2	2	1	95
Chlorpyrifos (spray)	3	5	4	5	5	5	5	5	3	2	2610
DDT (spray)	5	5	4	5	5	5	5	5	4	2	4275



Thank you for
your attention !