



Deliverable 28:

Specification of low risk products

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The document is based (i) on the recommendation expressed in a questionnaire sent to participants prior to the Salzau workshop in September 2006, (ii) on recommendations expressed during discussions at the Salzau workshop in September 2006 and (iii) on recommendations expressed at the regulators meeting in September 2006 (iv) the QPS work carried out within an EFSA working group and the final opinion of the Scientific Committee (v) a risk index model proposed by Tobias Längle and Hermann Strasser.

Document Abstract

At present no definition or criteria of low risk plant protection products or active substances exists in the EU regulation. However, it is being introduced in the new proposal for an EU regulation of plant protection products, which is still being negotiated.

During the REBECA project period various stakeholders have given their opinion on which BCAs should be regarded as low risk active substances/products and why. Also the work initiated within EFSA on Qualified Presumption of Safety (QPS) which relates to this subject is discussed within this document. The micro-organisms suggested to be given a QPS status is included in Annex 1 and in Annex 2 a publication by Längle and Strasser introduce a newly developed risk index system, which can be of significance in the definition of "low risk" products. The suitability of the model was demonstrated by calculating the risk scores for 17 selected well-studied biological control agents and chemical products used for similar purposes. The authors conclude that the score of "low risk" products should not exceed 100, whereas a threshold of 500 seems justified for the term "reduced risk".

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Introduction

The main purpose of the REBECA project is to speed up the registration process of BCAs in order to speed up the market introduction of such products. One way of doing this would be to differentiate between low risk and high risk active substances in the EU and national evaluation processes and in this way make a fast track regulatory system for the low risk substances (which, among others, would be expected to be a number of BCAs). In order to do that, it is necessary to establish a definition or criteria of low risk substances that can be used to place the active substances into one of these two categories even prior to a risk assessment process. However, this is quite difficult. This document describes activities carried out within REBECA in order to investigate whether it would be possible to make such a differentiation at an early stage of the evaluation and registration process, with the view of obtaining a faster introduction of new low risk products on the market.

Legal framework

Plant protection products

In the present EU regulation on pesticides (Directive 91/414/EEC) there is no differentiation between low risk and higher risk active substances.

However, the Commission's proposal for a new pesticide Regulation 2006/0136 (COD) which is still being negotiated among EU member states contains separate paragraphs relating to "low-risk substances", "basic substances" and "substances of concern". Article 22 extends the period of approval from the normal 10 years to 15 years for low risk active substances.

Based on the still ongoing negotiations the Commission has published a revised proposal in order to seek agreement between the member states. In the most recent amended proposal of Regulation 2006/0136, which is dated 11 March 2008, the following definition of low risk is included:

Low risk: of a nature considered inherently unlikely to cause an adverse effect on humans, animals or the environment.

Further more a number of criteria are listed in Article 22 for low risk substances. The active substances can not be regarded as low risk if they are classified as one of the following:

- carcinogenic
- mutagenic
- toxic to reproduction
- very toxic
- toxic
- sensitising
- explosive

Further more the substances which are qualified as the following can not be regarded as low risk either:

- persistent (half life of less than 60 days)
- endocrine disrupter
- bioaccumulative and non readily-degradable.

Article 46 sets timelines for the authorization of plant protection products based on low risk substances. The member state shall within 90 days decide whether to approve an application for authorisation of a low-risk plant protection product. This period should only be 60 days in case an authorisation has already been granted for the same low-risk plant protection product by another Member State located in the same zone. However, in case the Member State will need additional information, it shall set a time limit not exceeding 6 months for the applicant to supply it.

These timeframes are shorter than those suggested for active substances that are not regarded as of low risk (article 36). For those the timeframe is 12 months with the possibility of asking for additional information within a period of further 6 months.

Article 23 provides criteria for basic substances and extends the period of their approval to an unlimited time. The basic substances will have to be applied included into a separate list. Article 28 states that plant protection products only containing basic substances (from this list) do not need to go through a national authorization in order to be placed on the market.

The criteria for low risk substances are clearly made with chemical active substances in mind. First of all, there is a general risk of micro-organisms being sensitizers, which would thus right away disqualify them as low risk substances. However, so far no proper guidelines are available that can be used to carry out studies in order to investigate the sensitising properties of micro-organisms. In the data requirements for micro-organisms (Annex IIB to Directive 91/414/EEC) which are listed in Dir. 2001/36/EC, it is mentioned that it is not necessary to present data on sensitisation, due to this lack of guidelines, but in this case the micro-organism is considered to be sensitising.

Secondly, the three terms: persistence, bioaccumulative and non readily-degradable and endocrine disrupters are all terms originating from the classification of chemical active substances. These criteria do not take into account that e.g. micro-organisms are naturally occurring substances.

Biocides

In the Biocide directive 98/8/EC the active substances regarded as being of low risk are included into a specific list: 1A. The criteria for substances to be included into this list are quite similar to the criteria which are now suggested included in the new regulation on plant protection product. However, the biocide criteria does not include: toxic, very toxic, explosive and endocrine disrupters.

Questionnaire on low risk

Prior to the REBECA workshop held in Salzau 18-22 September 2006 a questionnaire was sent to all participants in which they were asked to list active substances (BCAs consisting of micro-organisms, botanicals, semiochemicals or macrobials) which they would regard as being of low risk and to give their reasoning for such proposals for low risk substances. Further more the participants were asked to give a definition and/or criteria for low risk substances.

46 persons replied to the questionnaire (9 regulators, 12 persons representing the industry, 22 from the scientific community and 3 from consultancies).

The participants representing the industry and the scientific community all gave lists of active substances which they regarded as of low risk. In particular the participants gave a long list of macrobials. However, also the semiochemicals, in particular the SCLP were mentioned by representatives from both the industry and regulatory authorities as a category of low risk. It was mentioned by several participants that if SCLP were applied in concentrations similar to the background concentration occurring in areas with high densities of the pest insect, they should definitely be regarded as of low risk. Baculoviruses was another group of active substances that was mentioned by many participants as being of low risk.

A number of botanicals were listed as well. These were products which are also used for human consumption.

Arguments for listing these as low risk were:

Long history of safe use

Micro-organisms that frequently cause natural epizootics in presence of the host pest

Micro-organisms which are ubiquitous in soils around the world

Micro-organisms that do not grow at 37 °C

Narrow host range/very specific

Low persistence

Substances used for human consumption (e.g. rapeseed oil, garlic oil, olive oil)

Substances used as household products (e.g. for cleaning)

During the discussion of the questionnaire at the REBECA workshop in Salzau the general opinion expressed by regulators and the European Commission (DG Sanco) was, that it would not be possible to establish a list of substances of low risk prior to a risk assessment, i.e. a list of substances that would not need a risk assessment. However, all regulators seemed to agree, that there was a need for a definition/criteria of low risk substances for the new EU regulation of pesticides, but, such criteria will be applied only after the risk assessment has been carried out and will rather determine which substances will get an Annex I inclusion of a longer period (15 years) and an easier/faster process for national registration. As mentioned already, the text of the Commission proposal for a new EU regulation of pesticides is still being discussed and negotiated among EU member states.

Regulator's experiences in defining low risk products

At the REBECA stakeholder meeting for regulators which took place in Salzau, Germany on 18 September 2006 (a meeting attended by 27 regulators from Europe, Australia and USA) the participants discussed the possibility of the national authorities to give priority to low risk products during the evaluation and authorisation process.

This issue had been discussed in Sweden, the Netherlands and in the UK. The purpose in all three countries was to increase the number of such products at their market e.g. by reducing the fee requested for low risk products and in the Netherlands and the UK also to provide further guidance to applicants in order to speed up the preparation of dossiers and the subsequent evaluation of those dossier. However, none of the regulatory authorities in the three countries found the term "low risk" very helpful, simply due to the difficulties in defining such a category. In the UK the Pesticide Safety Directorate (PSD) has not used the term *low risk products* in their BioPesticide Scheme but instead the term *alternative products* (however, also without a specific definition). For this product group they have lowered the fees, are arranging pre-submission meetings, they have increased the web-site information of the regulatory process, established a specific contact point in PSD for these product types (a champion) and the applicants can be guided throughout the process of putting together an application.

A somewhat similar project is taking place in the Netherlands, where the project is called GENOEG. It is also aiming at getting further low risk products on the market. In the Netherlands they have used the term *natural pesticides* rather than *low risk products*. Via this project the applicants can get up to 100,000 € co-finance for registration fees and extra studies needed for the risk assessment, and the regulatory authority here also help applicants put together good dossiers and invite applicants for pre-submission meetings.

QPS – Qualified Presumption of Safety

At several REBECA workshops the EFSA initiative on developing a QPS concept (Qualified Presumption of Safety) was discussed. The reason being that it was anticipated, that if the microbial plant protection products were included in the development of this new concept, it would be a way of defining groups of low risk micro-organisms, and a way of obtaining a faster evaluation and market introduction of microbial plant protection products.

The development of a QPS concept was initiated in 2003 by a working group consisting of members of several former (EC) scientific committees. The work was continued within an EFSA working group. The aim was to develop a scheme that would harmonize the risk assessment of micro-organisms throughout the various EFSA panels and a scheme developed as a tool for setting priorities within the risk assessment of micro-organisms used in food/feed. By using this tool risk assessors will for some micro-organisms be able to take a generic approach in the risk assessment instead of a full case-by-case assessment, and in this way make better use of assessment resources by focussing on those organisms that present greatest risk or uncertainties, and which would need a case-by-case risk assessment.

It is proposed, that a safety assessment of a defined taxonomic group should be made based on four pillars (establishing identity, body of knowledge, possible pathogenicity and end use). If the taxonomic group did not raise safety concerns or, if safety concerns existed, but could be defined and excluded the grouping could be granted QPS status. Thereafter, any strain of the micro-organisms given QPS status would be freed for further safety assessments other than satisfying any qualifications specified.

The final opinion of the Scientific Committee (including 4 appendices) was adopted on 19 November 2007. Table 1 contains the 4 groups of micro-organisms included in the concept. The committee explains in this document that the group consisting of filamentous fungi could not be recommended QPS status. Further more they explain that all strains belonging to the *Bacillus cereus sensu lato* group (e.g. *Bacillus thuringiensis*) should not be given a QPS status either, since it is known that the vast majority of strains within this group are toxin producers and thus can not meet the required qualifications.

Table 1. The four groups of micro-organisms which are so far considered in the QPS concept and the number of species proposed for QPS status so far

Group of micro-organism	Number of species proposed for QPS status so far
non-spore forming gram positive bacteria	48 species
<i>Bacillus</i> spp.	13 species
yeasts	11 species
commonly encountered filamentous fungi	None

The Scientific Committee writes as follows in their opinion of 19 November 2007:

“The Scientific Committee is of the opinion that the use of strains from the B. cereus group should be avoided whenever there is a possibility of human exposure whether intended or incidental. The B. cereus group is therefore excluded from consideration for QPS status.

There is an artificial distinction held between B. cereus and B. thuringiensis (used for plant protection) which has little scientific basis. The plasmid encoding the insecticidal enterotoxin, which provides the phenotypic distinction for B. thuringiensis, is readily lost, particularly when grown at 37 °C, leaving an organism indistinguishable from B. cereus. Consequently it is likely that B. thuringiensis has been the causative organism of some instances of food poisoning but identified as B. cereus because clinical investigations would have failed to recognise the distinguishing features characteristic of B. thuringiensis.

However, the Scientific Committee recognises that B. thuringiensis has value to the industry as a means of biological pest control and that its widespread use for this purpose may not lead to significant human exposure.”

Bacteria directly consumed by humans only qualify for QPS status, if they are free of acquired resistance to antibiotics of importance in clinical and veterinary medicine. Furthermore, all bacteria capable of toxin production should be demonstrated to be free of any toxigenic potential.

It is important to stress that QPS does not carry any legal status.

Since neither *B. thuringiensis* nor any of the filamentous fungi are included on the list of species proposed for QPS status, the QPS in its present form does not offer a *generic approach* to the safety assessment of most micro-organisms used as biological control agents. Never the less, the EFSA Scientific Committee considers that it may be possible to devise robust use qualifications which would allow a QPS approach for further groups of micro-organisms relevant for biological control in the future. The system is developed in order to provide a generic assessment system *for use within EFSA* that can be applied to all requests for the safety assessment of micro-organisms deliberately introduced into the food chain or used as producer strains for food/feed additives. This implies, that when industry applies for Annex I inclusion of micro-organisms belonging to microbial taxonomic units, which are now included in the list of organisms for which a QPS status is proposed (e.g. *Bacillus subtilis* and *B. pumilus*) with the intention to market these in plant protection products, the industry can in their dossier argue that the species are given QPS status, and that the risk for consumer health (due to exposure from residues on crops) is likely to be low when these strains are applied as plant protection products. This information can be used as a waiver for residue data for micro-organisms given QPS status. The list of taxonomic units for which QPS status has been proposed can be found in Annex 1.

The applicability of the QPS approach for broad use of micro-organisms as plant protection products needs to be discussed further.

USA: Minimal Risk Pesticides (25b list)

In the USA, there is a list of substances that can be used as pesticides without any registration, however, they still need a residue limit, or exemption, for food or feed uses. These substances are called *Minimal Risk Pesticides*, as described in the US Code of Federal Regulation, 40CFR 152.25(f). The list contains many essential oils¹. All inerts must be on EPA's 4A inert list, all ingredients must be identified on the label, and the label may not contain false or misleading claims. This regulation was developed by an EPA workgroup in 1994 and revised in accordance with public comments for a final Federal Register publication in 1996. The EPA has experienced a problem since it has been difficult identifying exactly which chemical substances are included under the names listed. Currently, CAS numbers are used to describe the substances on the EPA inert substance classification lists.

¹ Currently, the list includes the following substances: castor oil, cedar oil, cinnamon and cinnamon oil, citric acid, citronella and citronella oil, cloves and clove oil, corn gluten meal, corn oil, cottonseed oil, dried blood, eugenol, garlic and garlic oil, geraniol, gernanium oil, lauryl sulfate, lemongrass oil, linseed oil, malic acid, mint and mint oil, peppermint and peppermint oil, 2-phenethyl propionate (2-phenylethyl propionate), potassium sorbate, putrescent whole egg solids, rosemary and rosemary oil, sesame (includes ground sesame, plant) and sesame oil, sodium chloride (common salt), sodium lauryl sulfate, soybean oil, thyme and thyme oil, white pepper and zinc metal strips.

Low risk semiochemicals and botanicals

In REBECA Deliverable 18 (Positive list of low risk candidate botanicals and semiochemicals), gives a discussion on low risk semiochemicals and botanicals and provide lists of such substances which REBECA propose should be given low risk status.

Low risk microbials

Baculoviruses

Baculoviruses in general have low risk for all organisms except their specific hosts. As stated in the "OECD Consensus document No 20 on information used in the assessment of environmental applications involving baculoviruses" from January 2002, «Baculoviruses are naturally occurring pathogens of arthropods. Their host range is exclusively restricted to arthropods. No member of this virus family is infective to plants or vertebrates». Likewise, no sensitisation was observed for baculoviruses so far. The OECD Consensus Document concludes that «No adverse effect on human health has been observed in any of these investigations indicating that the use of baculovirus is safe and does not cause any health hazards.»

The majority of baculoviruses has a very restricted host range, which mainly comprises one or a few species of the same genus, rarely different genera of the same family. Baculoviruses with a broader host range are the exception. Therefore, risks for non-target species can be excluded as well.

Low risk bacterial and fungal products

In REBECA Deliverable 12 (Positive list of low risk candidate microbials), gives a discussion on low risk microbials and provide lists of such substances which REBECA propose should be given low risk status.

This recommendation is based (i) on a case by case evaluation of microbial biocontrol agents, assessed by international experts, recognised by REBECA consortium, (ii) the safety data fact sheet published by the US Environment Protection Agency (EPA) and (iii) publication of the European Council regulations, reporting the opinion of the safe use of Annex I listed micro-organisms.

Annexes

1. List of taxonomic units proposed for QPS status
2. Publication: *Developing a risk indicator to comparatively assess environmental risks posed by microbial and conventional pest control agents.*

Annex I. List of taxonomic units proposed for QPS status

Gram-Positive Non-Sporulating Bacteria ²			Qualifications
Species			Qualifications
<i>Bifidobacterium adolescentis</i>	<i>Bifidobacterium bifidum</i>	<i>Bifidobacterium longum</i>	
<i>Bifidobacterium animalis</i>	<i>Bifidobacterium breve</i>		
<i>Corynebacterium glutamicum</i>			QPS status applies only when the species is used for production purposes.
<i>Lactobacillus acidophilus</i>	<i>Lactobacillus farciminis</i>	<i>Lactobacillus paracasei</i>	
<i>Lactobacillus amylolyticus</i>	<i>Lactobacillus fermentum</i>	<i>Lactobacillus paraplantarum</i>	
<i>Lactobacillus amylovorus</i>	<i>Lactobacillus gallinarum</i>	<i>Lactobacillus pentosus</i>	
<i>Lactobacillus alimentarius</i>	<i>Lactobacillus gasseri</i>	<i>Lactobacillus plantarum</i>	
<i>Lactobacillus aviaries</i>	<i>Lactobacillus helveticus</i>	<i>Lactobacillus pontis</i>	
<i>Lactobacillus brevis</i>	<i>Lactobacillus hilgardii</i>	<i>Lactobacillus reuteri</i>	
<i>Lactobacillus buchneri</i>	<i>Lactobacillus johnsonii</i>	<i>Lactobacillus rhamnosus</i>	
<i>Lactobacillus casei</i>	<i>Lactobacillus kefiranoformis</i>	<i>Lactobacillus sakei</i>	
<i>Lactobacillus crispatus</i>	<i>Lactobacillus kefiranoformis</i>	<i>Lactobacillus salivarius</i>	
<i>Lactobacillus curvatus</i>	<i>Lactobacillus kefiranoformis</i>	<i>Lactobacillus</i>	
<i>Lactobacillus delbrueckii</i>	<i>Lactobacillus mucosae</i>	<i>sanfranciscensis</i>	
	<i>Lactobacillus panis</i>	<i>Lactobacillus zeae</i>	
<i>Lactococcus lactis</i>			
<i>Leuconostoc citreum</i>	<i>Leuconostoc lactis</i>	<i>Leuconostoc mesenteroides</i>	
<i>Pediococcus acidilactici</i>	<i>Pediococcus dextrinicus</i>	<i>Pediococcus pentosaceus</i>	
<i>Propionibacterium freudenreichii</i>			
<i>Streptococcus thermophilus</i>			

Bacillus ⁶			Qualifications
Species			Qualifications
<i>Bacillus amyloliquefaciens</i>	<i>Bacillus lentus</i>	<i>Bacillus pumilus</i>	Absence of emetic food poisoning toxins with surfactant activity.* Absence of enterotoxic activity.*
<i>Bacillus atrophaeus</i>	<i>Bacillus licheniformis</i>	<i>Bacillus subtilis</i>	
<i>Bacillus clausii</i>	<i>Bacillus megaterium</i>	<i>Bacillus vallismortis</i>	
<i>Bacillus coagulans</i>	<i>Bacillus mojavensis</i>	<i>Geobacillus</i>	
<i>Bacillus fusiformis</i>		<i>stearothermophilus</i>	

* When strains of these QPS units are to be used as seed coating agents, testing for toxic activity is not necessary, provided that the risk of transfer to the edible part of the crop at harvest is very low (section 4.3 of Appendix C).

² Absence of acquired antibiotic resistance should be systematically demonstrated unless cells are not present in the final product.

Yeasts			
Species			Qualifications
<i>Debaryomyces hansenii</i>			
<i>Hanseniaspora uvarum</i>			
<i>Kluyveromyces lactis</i>	<i>Kluyveromyces marxianus</i>		
<i>Pichia angusta</i>	<i>Pichia anomala</i>		
<i>Saccharomyces bayanus</i>	<i>Saccharomyces cerevisiae</i>	<i>Saccharomyces pastorianus</i> (synonym of <i>Saccharomyces carlsbergensis</i>)	<i>S. cerevisiae</i> , subtype <i>S. boulardii</i> is contraindicated for patients of fragile health, as well as for patients with a central venous catheter in place. A specific protocol concerning the use of probiotics should be formulated
<i>Schizosaccharomyces pombe</i>			
<i>Xanthophyllomyces dendrorhous</i>			



Annex 2

Developing a risk indicator to comparatively assess environmental risks posed by microbial and conventional pest control agents

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Abstract

Selected biological control agents and conventional pesticides were used to critically review the applicability of a newly developed risk indicator (RI) system. Five basic components are proposed for the calculation of the overall environmental risk score: persistence of the active ingredient, dispersal potential, range of non-target organisms that are affected, and direct and indirect effects on the ecosystem. Several risk measurement systems were reviewed, risk categories in the proposed system were modified from a widely-accepted model (i.e. ERBIC model). Additionally, one new category was implemented to assess the risks to vertebrate non-target species.

Besides a detailed discussion of the new risk indicator model, the suitability of the model was demonstrated by calculating the risk scores for seventeen selected products. It became obvious, that the environmental risk score greatly varied within the assessed chemical products, and also, yet at a much lower level, within the group of biological products. The use pattern greatly influenced the estimated environmental risk posed by any given product. The overall environmental risk score varied between 24 (*Coniothyrium minitans*, soil application) and 4.275 (DDT, foliar spray).

The proposed model can be used to communicate environmental risk and to design lower risk integrated pest management strategies. It is recommended, that the proposed risk indicator system may serve to define low risk (i.e., $RI \leq 100$) and reduced risk (i.e., $500 \geq RI > 100$) pesticides. Yet, it remains debatable whether RI will be useful in determining acceptability of data waivers. Use pattern, application method, persistence, growth temperature range and taxonomic relatedness to known/suspected pathogens should all be considered when justifying data waivers.