Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

09-Apr-2014

English - Or. English

**ENVIRONMENT DIRECTORATE**
**JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY**

**Cancels & replaces the same document of 08 April 2014**

# REPORT OF THE OECD/KEMI/EU WORKSHOP ON MICROBIAL PESTICIDES: ASSESSMENT AND MANAGEMENT OF RISKS - ANNEX 6 (PRESENTATIONS - PART 1/3)

**Series on Pesticides**
**No. 76**

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Unclassified

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This document contains part 1/ 3 of the Annex 6 of the REPORT OF THE OECD/KEMI/EU WORKSHOP ON MICROBIAL PESTICIDES: ASSESSMENT AND MANAGEMENT OF RISKS. Annex 6 includes slides of all presentations made during the seminar.

The main part of the seminar report, as well as Annexes 1-5, is published under the reference ENV/JM/MONO(2014)2.

**PART 1 OF 3**

# COMPILATION OF PRESENTATION SLIDES PRESENTED AT THE OECD/KemI/EU WORKSHOP on Microbial Pesticides: Assessment and Management of Risks

*17-19 June 2013*
*Vår Gård, Saltsjöbaden, Sweden*

**Organised jointly by:**
**OECD (Organisation for Economic Cooperation and Development)**
**KemI (Swedish Chemicals Agency)**
**European Commission**

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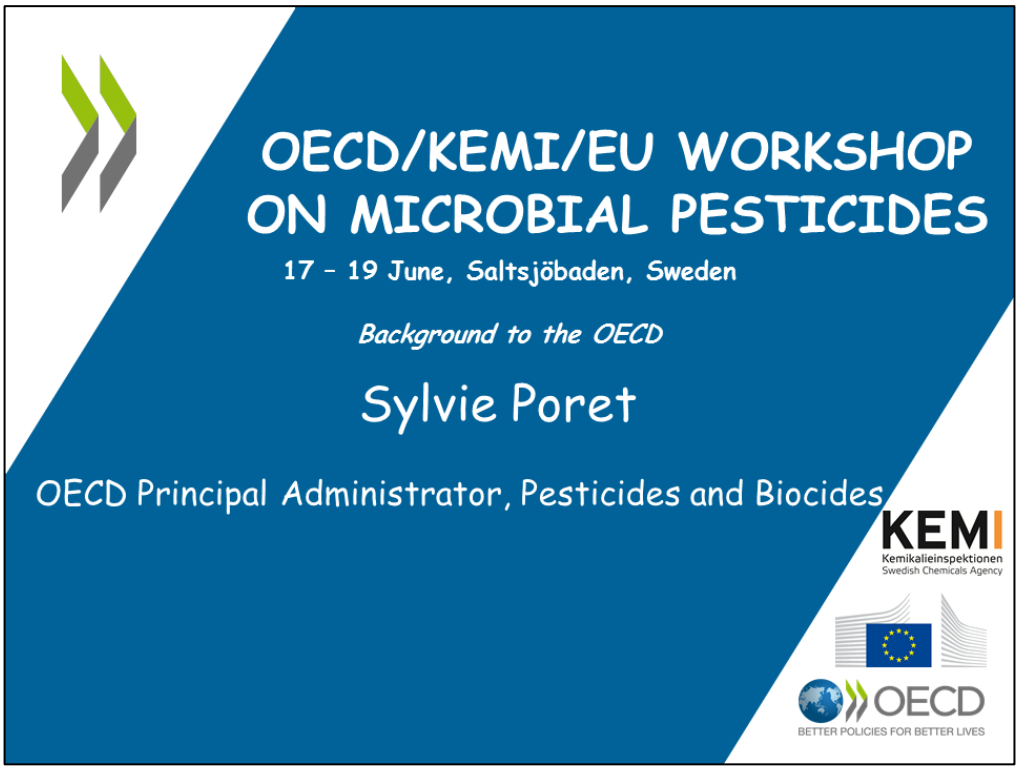
**SETTING THE SCENE**

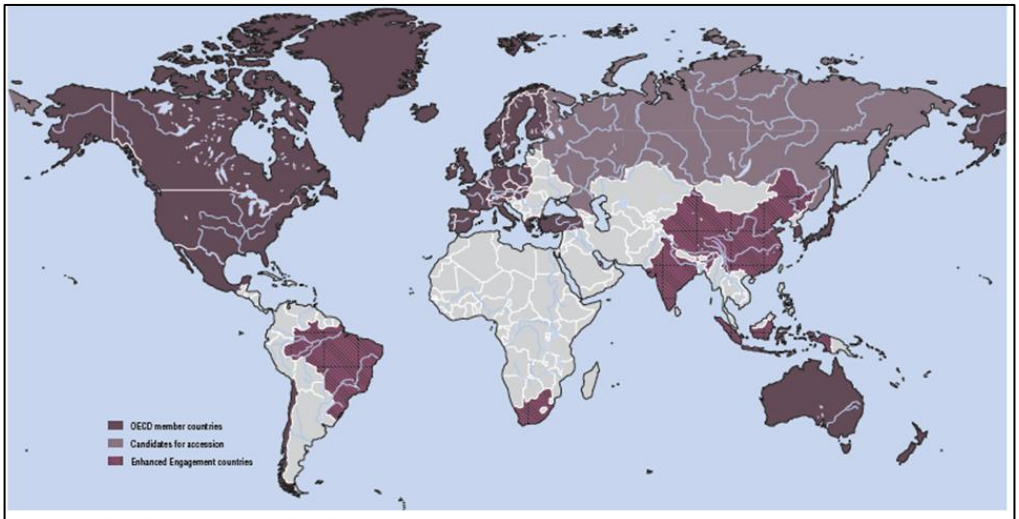
***Background to the OECD***

***By Sylvie Poret***
***Principal Administrator for Pesticides and Biocides, OECD***



# What is the OECD?

- An **intergovernmental organization** (Paris-based), born after World War II to coordinate the Marshall Plan
- A **forum** in which **governments**:
  - work together and with representatives from **business** and **civil society**
  - compare and share **policy experiences** (social, economic, environmental)
  - seek answers to common problems & **identify good practices**
  - **promote decisions** and **recommendations**
- Key words at OECD:
  **dialogue, consensus, peer review & pressure**




## A global outreach: 34 member countries

Relationships with > 70 non-member countries, in particular:

- ✓ One candidate country: Federation of Russia
- ✓ Five « key partner » countries: Brazil, China, India, Indonesia & South-Africa

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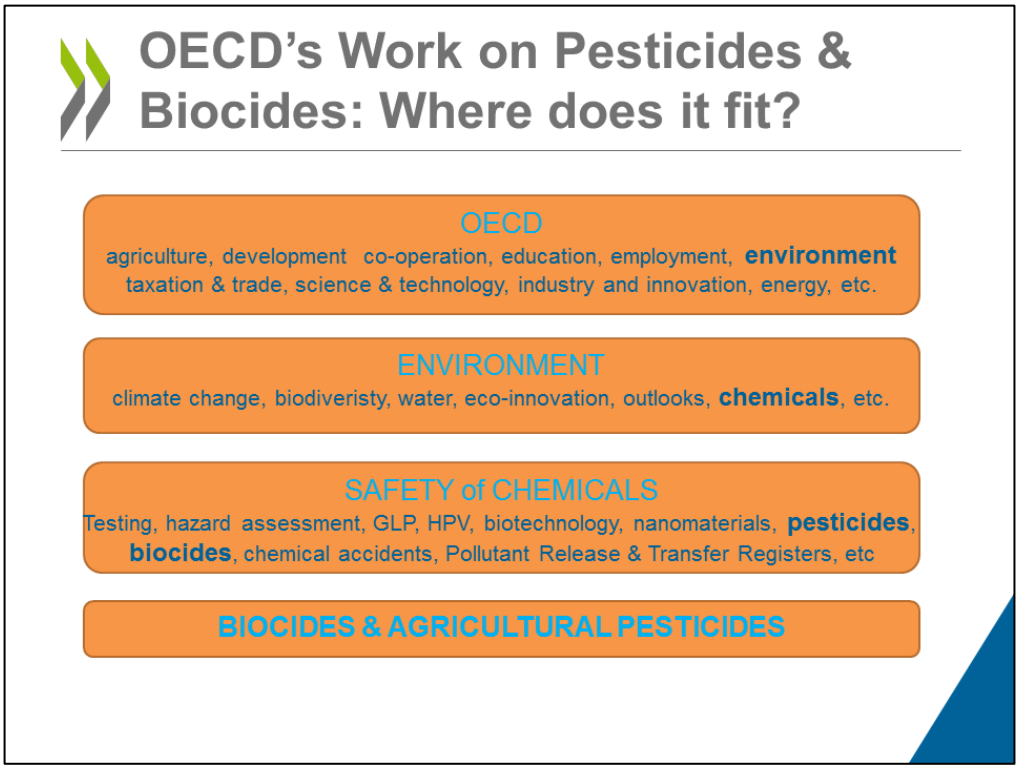
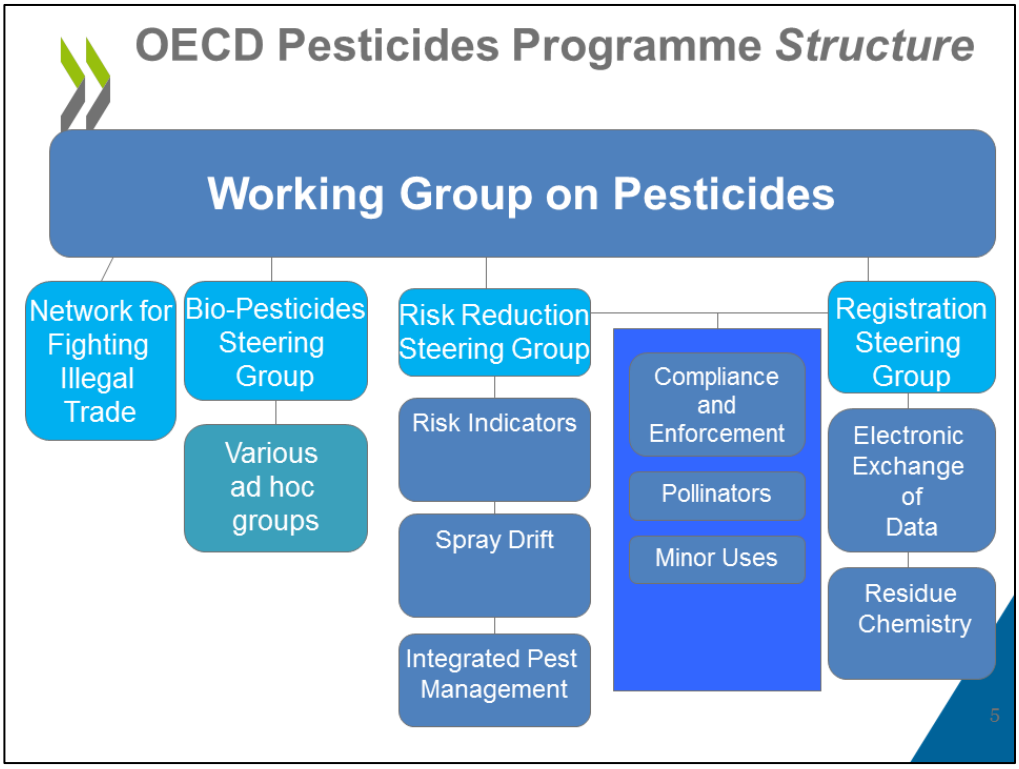

OECD's Work on Pesticides & Biocides: Where does it fit?
OECD
agriculture, development co-operation, education, employment, environment taxation & trade, science & technology, industry and innovation, energy, etc.
ENVIRONMENT
climate change, biodiveristy, water, eco-innovation, outlooks, chemicals, etc.
SAFETY of CHEMICALS
Testing, hazard assessment, GLP, HPV, biotechnology, nanomaterials, pesticides, biocides, chemical accidents, Pollutant Release & Transfer Registers, etc
BIOCIDES & AGRICULTURAL PESTICIDES


OECD Pesticides Programme Structure
Working Group on Pesticides
Network for Fighting Illegal Trade
Bio-Pesticides Steering Group
Various ad hoc groups
Risk Reduction Steering Group
Risk Indicators
Spray Drift
Integrated Pest Management
Compliance and Enforcement
Pollinators
Minor Uses
Registration Steering Group
Electronic Exchange of Data
Residue Chemistry
5

# Back to Saltsjöbaden

- Pesticides Programme:
  - created in 1992 as a follow-up to a meeting on pesticides organised by KEMI in Saltsjöbaden
  - Included biocides at that time
- Task Force on Biocides
  - created as an independent body in 2002

# Why OECD Programmes on Pesticides & Biocides?

## Goals

- Reduce risks for human health and the environment
- Minimise duplication of effort between countries and reduce barriers to trade
- Improve the efficiency of assessment and control

→ ***Benefits for all stakeholders: governments, industry, public***

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## OECD's Pesticides and Biocides Programmes Aim to:

1. Harmonise test methods
2. Facilitate the sharing of data and reviews across governments
3. Share information on new and effective approaches for assessing and managing risk
4. Pesticides: provide guidance on residues and residue chemistry
5. Biocides: provide support to help countries perform exposure assessments (via Emission Scenario Documents)
6. Develop risk reduction best practices and recommendations

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## For more information

www.oecd.org/env/biocides
www.oecd.org/env/pesticides

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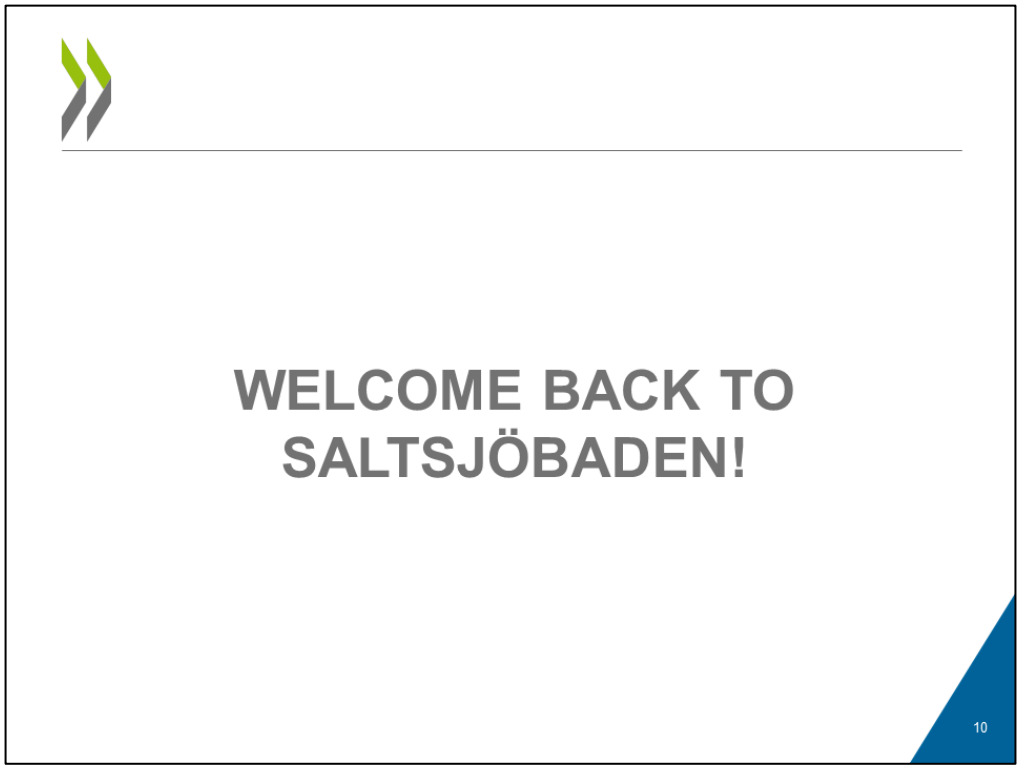
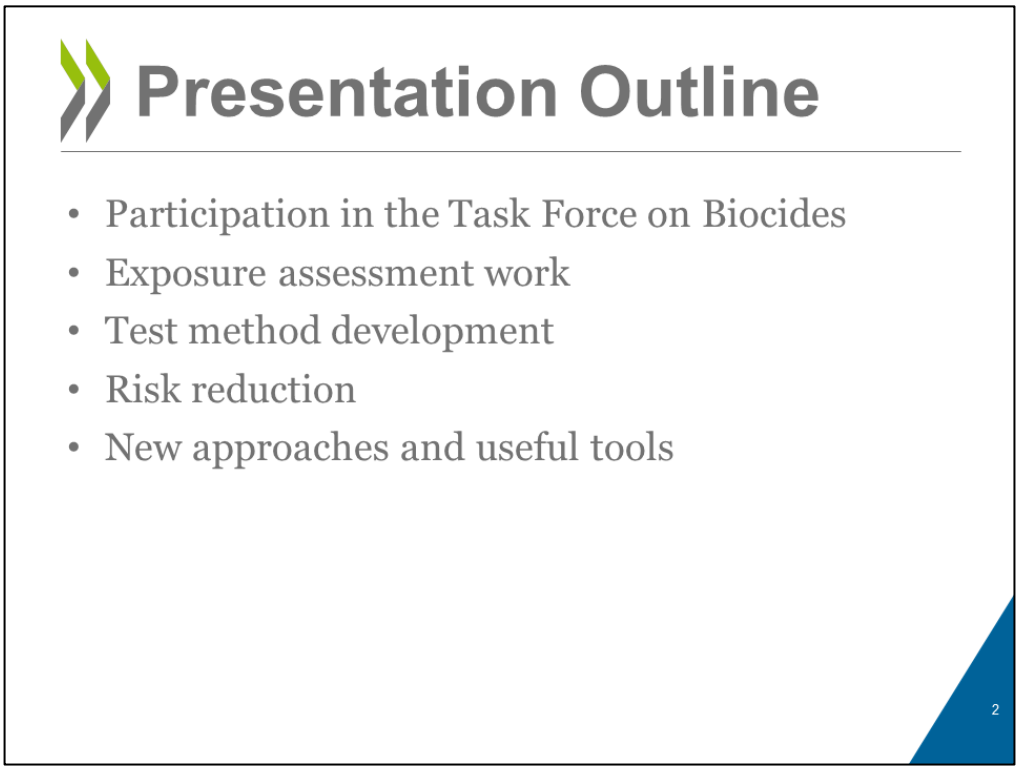

WELCOME BACK TO
SALTSJÖBADEN!
10

***The OECD Task Force on Biocides***

***By Edmund Plattner***
***Chair of the OECD Task Force on Biocides***

## Who is involved in OECD work on Biocides?

**Task Force on Biocides (TFB)**

- OECD Countries and European Commission
- Industry associations: CEFIC, ACC

**OECD Secretariat**

**TFB meets around every 8 months**

**Next meeting 19 - 20 June**

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## Exposure Assessment: Emission Scenario Documents

### Published work:

- ESD for Wood Preservatives (2003)
- ESD for Antifoulants (2005)
- ESD on Insecticides for Stables and Manure Storage Systems (2006)
- ESD on Insecticides for Household and Professional Use (2008)

### Ongoing work:

- Revision of the ESD on wood preservatives
- New ESD on Insecticides for Vector Control

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## Harmonise Test Methods

***OECD Test Guidelines***

**to test all chemicals, including biocides**

1. Physical chemical properties
2. Effects on wildlife (ecotoxicity)
3. Degradation, accumulation and leaching (environmental fate)
4. Effects on human health (toxicity)
5. ***Efficacy (for biocides only)***

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## Harmonise Test Methods
### Efficacy Testing

- Work initiated 2004/2005
- A survey of OECD member countries found:
  - few commonalities of methods or claims for hard surface products;
  - treated articles are generally not regulated
- Work on:

– Test methods for biocides used on hard surfaces;

– TG for biocides used to treat articles/materials;

– Guidance for pool and spa disinfectants

– Guidance for insecticides

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## Risk Reduction for Biocides

- **Objectives:**
  - Promote risk reduction policies
  - Identify effective risk reduction policies
- **First step:** survey of member country existing or planned policies

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## New approaches

- Diversity of biocidal products and uses pose:
  - Scientific challenges
  - Regulatory challenges
- Roles for OECD:
  - Monitoring Emerging Scientific and Policy Areas
  - Sharing information
  - Developing new approaches and tools

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## Micro-organisms

- Up to now the TFB focused its work on chemical biocides
- The TFB welcomes the opportunity to deal with micro-organisms with the current workshop
- Biocidal experts were active in preparing the workshop with their agricultural pesticide colleagues

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## For more information

www.oecd.org/env/biocides

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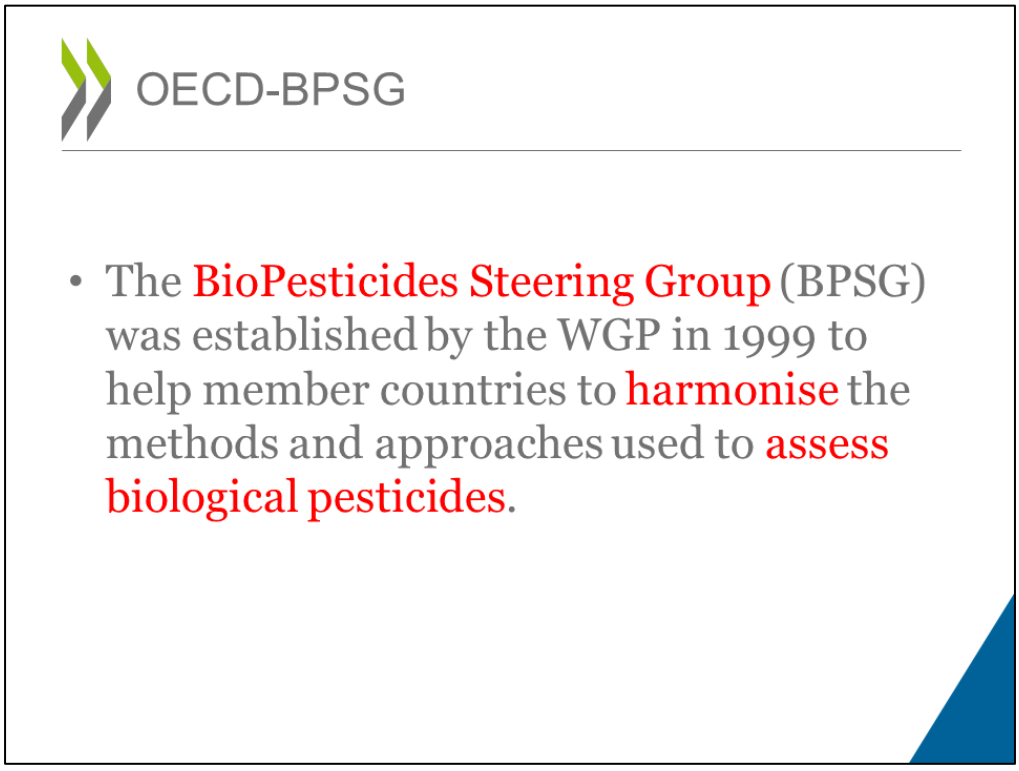
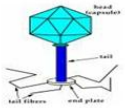
***The work OECD-BioPesticides Steering Group (BPSG)***

***By Jeroen Meeussen***
***BPSG and Workshop Chair***

## OECD-BPSG

### Biological Pesticides:



- Macro-organisms
- Microbial biopesticides
- Semiochemicals
- Plant extracts/Botanicals

## OECD-BPSG

- The first tasks of the BPSG consisted of:

  (i) reviewing regulatory data requirements for three categories of biopesticides; and
  (ii) developing formats for dossiers and monographs for microbials, and pheromones and other semio-chemicals.

## OECD-Publications (I)

- Registration requirements for microbial pesticides (Series on Pesticides, No. 18, 2003);
- OECD Dossier and Monograph Guidance for Microbials, 2003 rev. August 2006;
- Working Document on the Evaluation of Microbials for Pest Control (Series on Pesticides No. 43, 2008).

## OECD-Publications (II)

- Issue Paper on Microbial Contaminant Limits for Microbial Pest Control Products (Series on Pesticides No. 65, 2011);
- Guidance to the Environmental Safety Evaluation of Microbial Biocontrol Agents (Series on Pesticides No. 67, 2012).

## OECD-Seminars

- Report of Seminar on "Identity and Characterisation of micro-organisms", OECD Series on Pesticides No. 53, 2010);
- Report of Seminar on "The fate in the environment of microbial control agents and their effect on non-target organisms", OECD Series on Pesticides No. 64, 2011);
- Report on Seminar on "*Trichoderma* spp. for the use in Plant Protection Products: similarities and differences" (in preparation).

## WORKSHOP

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency


OECD

## Why a workshop?

- Micro-organisms for use as pesticides are regulated in a similar way as chemical pesticides;
- However the biological properties of living micro-organisms differ from the properties of chemical pesticides;
- Therefore it is desirable to reconsider the regulatory requirements for microbial pesticides.

## Previous workshops

- Microbiological Plant Protection Products – Workshop on the Scientific Basis for Risk Assessment; 26-28 October 1998, Stockholm, Sweden;
- Workshop on the Regulation of Biopesticides: Registration and Communication Issues; 15-17 April 2008, EPA, Arlington, USA.

## Aim of the workshop

This workshop is part of the on-going work on biopesticides in the framework of the OECD Biopesticides Steering Group (BPSG) and of the work of its Task Force on Biocides (TFB) and aims:

- to advance issues around both agricultural and non-agricultural microbial pesticides and their assessment from a scientific, technical and regulatory perspective;
- to find a feasible approach for sustainable risk assessment of micro-organisms.

## Outcomes of the workshop

- The report of the workshop, its conclusions and recommendations, including the presentations will be published as an OECD report.
- The workshop should increase mutual understanding and provide suggestions for improvement/more efficiency/cooperation.
- OECD-BPSG and TFB will be organised back-to-back with the workshop.

## Issues to be discussed

- Identity, characterisation, biological properties
- Equivalence
- Metabolites
- Growth temperature
- Contaminants
- Application techniques – exposure scenarios
- Effects on bees/pollinators
- .....

## Objectives

- Overview about current achievements;
- Discuss problems;
- Identify technical and scientific solutions;
- Suggest harmonised solutions to facilitate approval process;
- Conclusions and recommendations for OECD, governments and stakeholders.

## Workshop structure

- The workshop will be structured in plenary and break-out group sessions.
- It will last 2.5 days starting on Monday 17 June in the morning and finishing on Wednesday 19 June by mid-day.
- Around 75 participants from Member countries, COM, EFSA, research/academia and biopesticides industry (IBMA, BIAC)

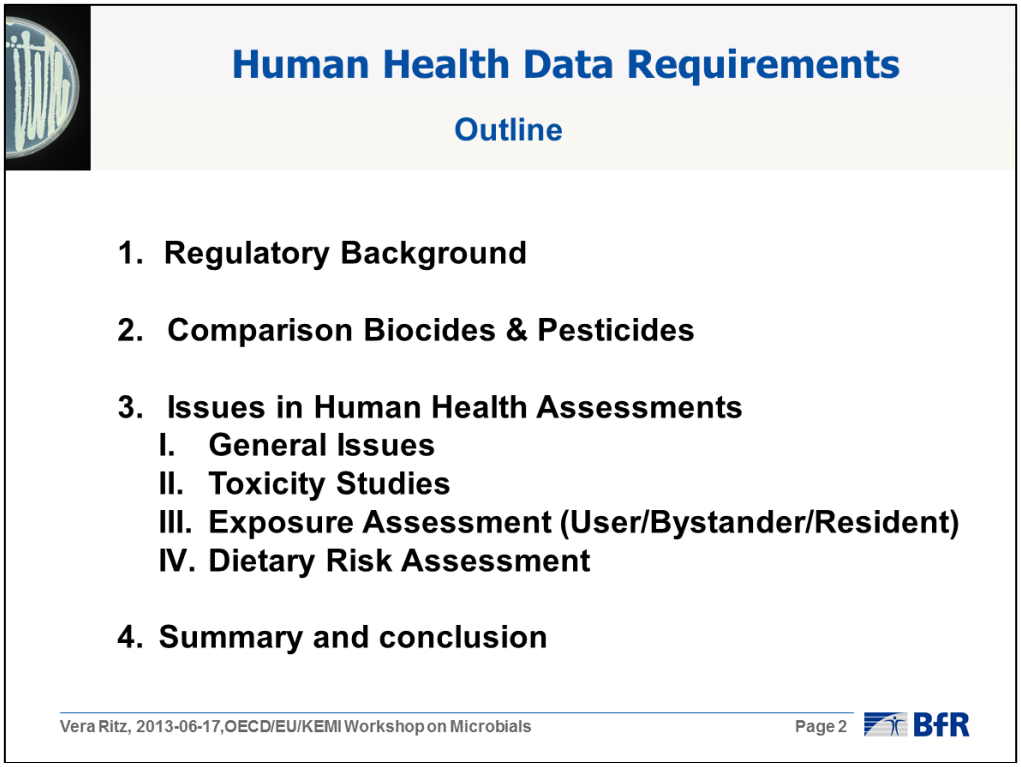
## Välkommen till Vår Gård

I wish you an interesting and useful workshop!

OECD KEMI Kemikalieinspektionen Swedish Chemicals Agency

***Overview on the existing EU regulatory system (biocides and pesticides): Human Health Data Requirements***

***By Vera Ritz, Federal Institute for Risk Assessment, Germany***

# Human Health Data Requirements

## Regulatory Background in the EU

- **Data Requirements for Biocides**
  - in Directive 98/8/EC, Annex IVA and IVB until 31 August 2013
  - in Regulation (EU) No. 528/2012, Annex II, Title 2 (active substances) and Annex III, Title 2 (products) from 1 September 2013

DIRECTIVE 98/8/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 16 February 1998
concerning the placing of biocidal products on the market
ANNEX IVA
DA
FUNC
ANNEX IVB
DATA SET FOR BIOCIDAL PRODUCTS
FUNGI, MICRO-ORGANI

REGULATION (EU) No 528/2012 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 22 May 2012
concerning the making available on the market and use of biocidal products
TITLE 2
MICRO-ORGANISMS
Core data set and additional data set for active substances
TITLE 2
MICRO-ORGANISMS
Core data set and additional data set



# Human Health Data Requirements

## Regulatory Background in the EU

COMMISSION REGULATION (EU) No 544/2011
implementi
COMMISSION REGULATION (EU) No 545/2011
of 10 June 2011
implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for plant protection products

- **Data Requirements for Pesticides**
  - in Commission Regulations (EU) No. 544/2011 (active substances) and No. 545/2011 (products) until 31 December 2013
  - in Commission Regulations (EU) No. 283/2013 (active substances) and No. 283/2013 (products) from 1 January 2014

implementing Regulation (EC) 1107/2009

COMMISSION REGULATION (EU) No 283/2013
setting out
1107/2009
COMMISSION REGULATION (EU) No 284/2013
of 1 March 2013
setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market

## Human Health Data Requirements

### Core data set (Biocides)/Tier I (Pesticides)

- **Basic information**
  - Medical data
  - Medical surveillance on manufacturing plant personnel
  - Sensitisation, allergenicity observation
  - Direct observations, e.g. clinical cases
  - Proposed treatment: first aid measures, medical treatment

- **Basic studies**
  - Sensitisation
  - Acute oral toxicity, pathogenicity, infectiveness
  - In vitro genotoxicity
  - Cell culture study



## Human Health Data Requirements

**Additional data set (Biocides), Tier I (Pesticides)**
**Basic studies**

- Acute inhalative toxicity, pathogenicity, infectiveness
- Intraperitoneal/subcutaneous single dose
- Information on short-term toxicity and pathogenicity
- Health effects after repeated inhalatory exposure

**Additional data set (biocides)/Tier II (PPP)**

- Specific toxicity, pathogenicity and infectiveness studies
- Genotoxicity: in vivo studies in somatic cells
- Genotoxicity: in vivo studies in germ cells
- Residues in or on treated articles, food or feedingstuffs
  - Persistence and likelihood of multiplication
  - Non-viable residues
  - Viable residues

# Human Health Data Requirements

## Regulatory Background in the EU

### Supplementary Guidance Documents

- **Biocides**
  - Technical Notes for Guidance on data requirements for micro-organisms including viruses and fungi (12 December 2005)
  -  Biocides Implementation Project (BIP) 6.8: (Lead: NL + SE)

GUIDANCE

Draft Scientific guidance package for Active Micro-organisms and BiocidalProducts

REGULATION (EU) No 528/2012 Biocidal Products



# Human Health Data Requirements

## Comparison Biocides & Pesticides

| | Biocides | Pesticides |
|---|---|---|
| **Approved Active Substances in the EU[1]** | 1 | 54 |
| **Products in DE[2]** | 27 reg., 1 auth. (3 AS) | 13 auth. (10 AS) |

[1] Biocides: http://ec.europa.eu/environment/biocides/annexi_and_ia.htm
Pesticides:http://ec.europa.eu/sanco_pesticides/public/index.cfm?event=activesubstance.selection
[2] Biocides: https://www.biozid-meldeverordnung.de/offen/
Pesticides: https://portal.bvl.bund.de/psm/jsp/

## Human Health Data Requirements

### Comparison Biocides & Pesticides

- Much longer experience in the evaluation of pesticidal MOs
- More SMEs in the biocides field with less regulatory experience
- Different European and national/zonal evaluation procedures
- Different exposure situations, e.g. regarding food and feed residues, indoor use, consumer products...



## Human Health Data Requirements

### General Issues

- No internationally harmonised specific guidelines for toxicity/pathogenicity testing of microbials
- Only available testing guidelines: EPA OPPTS 885 series
- Suitability of OECD guidelines for the testing of chemicals, section 4, needs to be assessed case-by-case
- Most regulatory agencies have a strong background in chemical risk assessment and less experience with microbiological assessments

## Human Health Data Requirements

### Toxicity Studies: Acute Toxicity

- Inclusion of pathogenicity testing mandatory
- Limit doses to be tested (exposure-driven)?



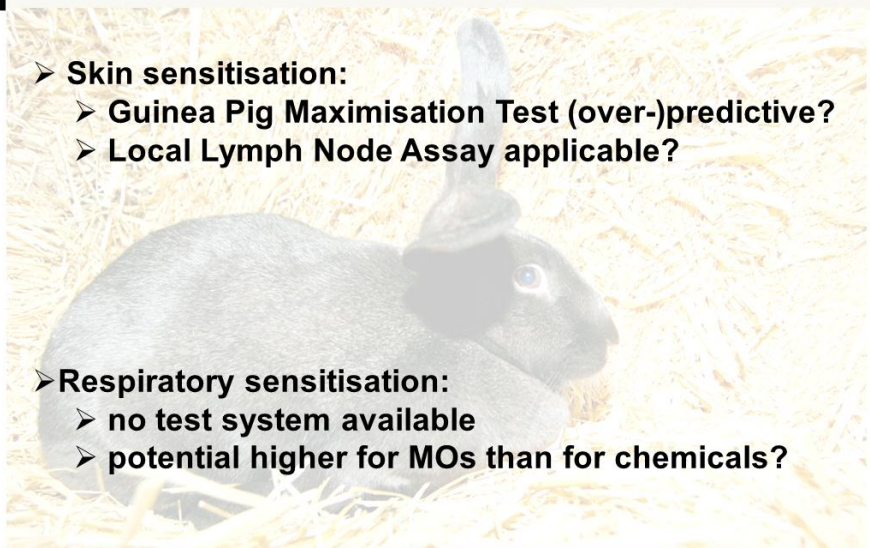
- Assessment criteria for persistent colonisation
- Intratracheal instillation: unspecific effects?



## Human Health Data Requirements

### Toxicity Studies: Sensitisation

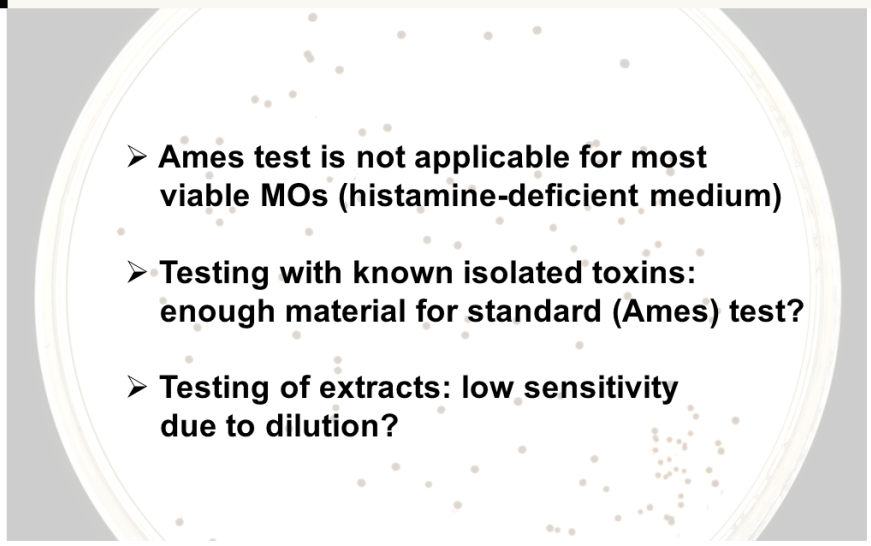
- Skin sensitisation:
  - Guinea Pig Maximisation Test (over-)predictive?
  - Local Lymph Node Assay applicable?



- Respiratory sensitisation:
  - no test system available
  - potential higher for MOs than for chemicals?

## Human Health Data Requirements

### Toxicity Studies: Genotoxicity Testing

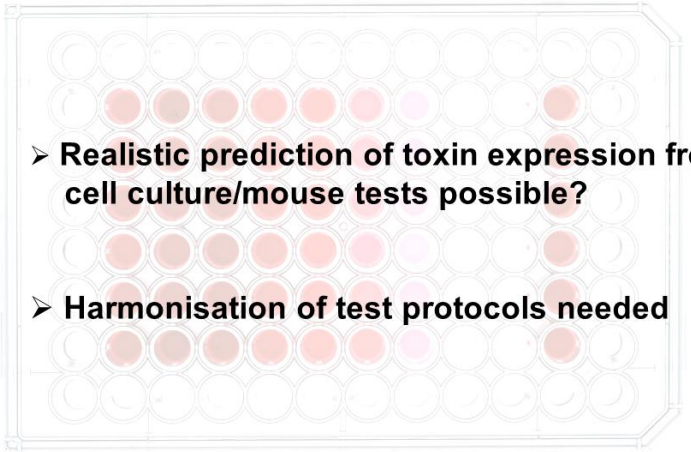


- Ames test is not applicable for most viable MOs (histamine-deficient medium)
- Testing with known isolated toxins: enough material for standard (Ames) test?
- Testing of extracts: low sensitivity due to dilution?



## Human Health Data Requirements

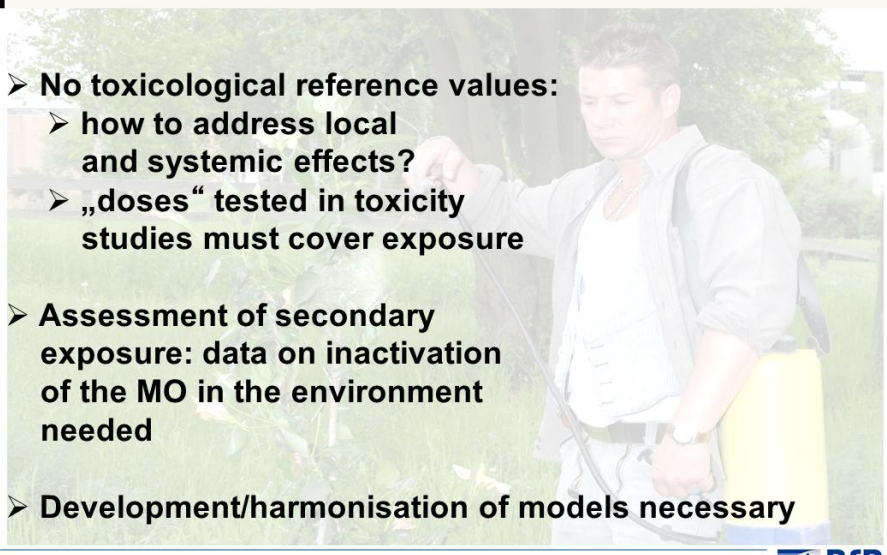
### Toxicity Studies: Toxins



- Realistic prediction of toxin expression from cell culture/mouse tests possible?
- Harmonisation of test protocols needed

## Human Health Data Requirements

### Exposure Assessment

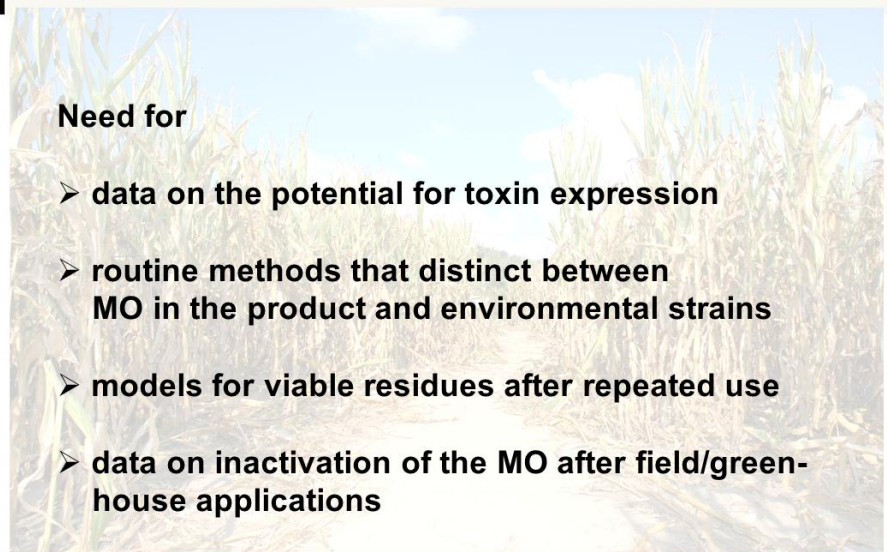


- No toxicological reference values:
  - how to address local and systemic effects?
  - „doses“ tested in toxicity studies must cover exposure
- Assessment of secondary exposure: data on inactivation of the MO in the environment needed
- Development/harmonisation of models necessary



## Human Health Data Requirements

### Dietary Exposure Assessment and Analytical Methods



Need for

- data on the potential for toxin expression
- routine methods that distinct between MO in the product and environmental strains
- models for viable residues after repeated use
- data on inactivation of the MO after field/green-house applications

## Human Health Data Requirements
### Summary & Conclusion

**Main Issues Proposed for BOG Discussions**

- **Toxicity & Analytics:**
  - appropriate & harmonised methods missing for acute toxicity, sensitisation, genotoxicity
  - assessment criteria to be harmonised, e.g. trigger for repeated dose studies, effects in intratracheal studies

- **Exposure Assessment (Incl. Residues):**
  - appropriate & harmonised models missing
  - data on inactivation needed
  - data on the potential for toxin expression

- **Legal Requirements & Guidance**
  - consistent data requirements and guidance for biocides and pesticides



FEDERAL INSTITUTE FOR RISK ASSESSMENT

BfR
Risiken erkennen – Gesundheit schützen

***Overview on the existing EU regulatory system (biocides and pesticides) with focus on differences and similarities between environmental data requirements for microorganisms***

***By Christine Vergnet***
***DPR & ANSES, France***

anses
alimentation, environnement, travail

## Overview on the existing EU regulatory system (biocides and pesticides) with focus on differences and similarities between environmental data requirements for micro-organisms.

*Christine VERGNET*
*DPR – Regulated Products Department*
*ANSES – French Agency for Food, Environmental and Occupational health & Safety*

## Micro-organisms (active substance) in biocides and pesticides in Europe

| | BIOCIDES | PESTICIDES |
|---|---|---|
| Before implementation: | ? | ? |
| From implementation of directives / regulations: | Not supported: ?<br>5 strains<br>Bacteria (all *Bacillus* sp) | Not supported: 3<br>List 4 : 18 (>18 strains)<br>New: 26 (26 strains)<br>Bacteria, Fungi, Virus |
| Biocide and pesticide | *Bacillus thuringiensis israelensis* AM65/52<br>*Bacillus thuringiensis kurstati* ABTS 351 | |
| Under assessment | 4 | 12 (new) + finalisation of the post-inclusion assessments of list 4 |
| Inclusion | 1 | 14 (new) + 18 (list 4) |

2 anses

## Uses in Europe

| | BIOCIDES | PESTICIDES |
|---|---|---|
| Category | Insecticide : 4 TP18<br>Bactericide : 1 TP03 | Fungicide: 17<br>Insecticide: 10<br>Nematicide: 2<br>Bactericide: 1<br>No category: 2 |
| Mode of application | Localised treatment (breeding building: ditches, water retention area, sewage treatment plants...)<br>Foliar treatments (spray – from ground or by aeronef) | Soil treatments (drip irrigation, drench, spray, incorporation)<br>Foliar treatments (spray – from ground or by aeronef)<br>Localised treatment (granules in palm, seed, wound painting, tree injection)<br>Dissemination by pollinator ? |
| Issues | Characterisation of generic exposure scenarios<br>Adjustment of data requirements to the exposure scenarios | |



## Data requirements

| | BIOCIDES | PESTICIDES |
|---|---|---|
| References | Reg.(EU) N° 528/2012 Annex II Title 2 (Active substance) and Annex III Title 2 (Product)<br>+ Draft scientific guidance | Reg.(EU) N° 544/2011 Part B (Active substance)<br>Reg.(EU) N° 545/2011 Part B (Product) |
| | Great similarities at the moment | |
| Issues | Literature data: confidence to the species identification, rare information to the strain level<br>Regulatory studies: test item versus current batch<br>Extrapolation Active substance versus Product (co-formulants not assessed) | |

## Uniform principles

| | BIOCIDES | PESTICIDES |
|---|---|---|
| Reference | Similar to pesticides | Commission Regulation (EU) N° 546/2011 Part II |
| Evaluation | Fate and behaviour in the environment (soil, water, air)<br>Effects on non-target species (toxicity, infectivity, pathogenicity) | |
| Decision | ENVIRONMENT<br>No adverse effects to the environment (*exposed compartments*)<br>No interference with analytical systems (*control of quality of drinking water*)<br>No unacceptable contamination of ground and surface waters<br>No unacceptable effects due to transfer of genetic material<br>Sufficient information on persistence/competitiveness<br>No unacceptable accumulation<br><br>NON-TARGET SPECIES<br>No pathogenicity of the micro-organism<br>No risk due to the toxicity of the product<br>Special attention to beneficial organisms used in biological control and organisms playing an important role in integrated control | |



## Exemples of issues for the environment

| **Issues** | Assessment of potential interference with analytical systems (*control of quality of drinking water of* drinking water)<br>Assessment of potential transfer of genetic material to other organisms |
|---|---|
| | Required for all bacteria (Bacillus, Pseudomonas, Streptomyces) |
| Aim | These methods require pathogenic bacteria to be identified and confirmed as absent. The microorganism should not interfere with these methods.<br>The microorganism should not be a source of uncontrolled dissemination of genes. |
| Further need | Guidance to trigger this assessment<br>Guidance to conduct this assessment<br>Introduce a specific chapter in the dossier and the DAR/CAR |

## Exemples of issues for the environment

| **Issues** | Assessment of persistence / competitiveness, accumulation, and contamination of groundwater |
|---|---|
| | Increasing requirement for bacteria and fungi (persistence/competitiveness)<br>General agreement for low concern at the "background level"<br>Lack of strain specific data (lack of strain specific analytical method – lack of critical concern) |
| Aim | The microorganism should not definitively "disturb" beneficial "natural" communities<br>The microorganism should not raise unacceptable accumulation<br>The microorganism should not raise unacceptable contamination of groundwater |
| Questions | How to solve contradiction with efficiency need?<br>How to get better insight into fate and behaviour of microbial control agents?<br>How to characterise "background level"? (natural/intended exposure)<br>How could a criterion for persistence in the environment be outlined?<br>How to assess mobility for microorganisms and the risk of contamination in groundwater? |



## Exemples of issues for the environment

| **Issues** | Assessment of the risk to biological methods of sewage treatment |
|---|---|
| | Required for all pesticide uses in glasshouses/indoor (bacteria and fungi)<br>Lack of strain specific data (lack of strain specific analytical method – lack of critical concern) |
| Aim | The microorganism should not "disturb" the biological methods for sewage treatments |
| Questions | Is it realistic that microbial pesticides/biocides could reach a sewage treatment plant in high enough concentrations such that activated sludge would be affected?<br>Which uses trigger an assessment? |

## Exemples of issues for the environment

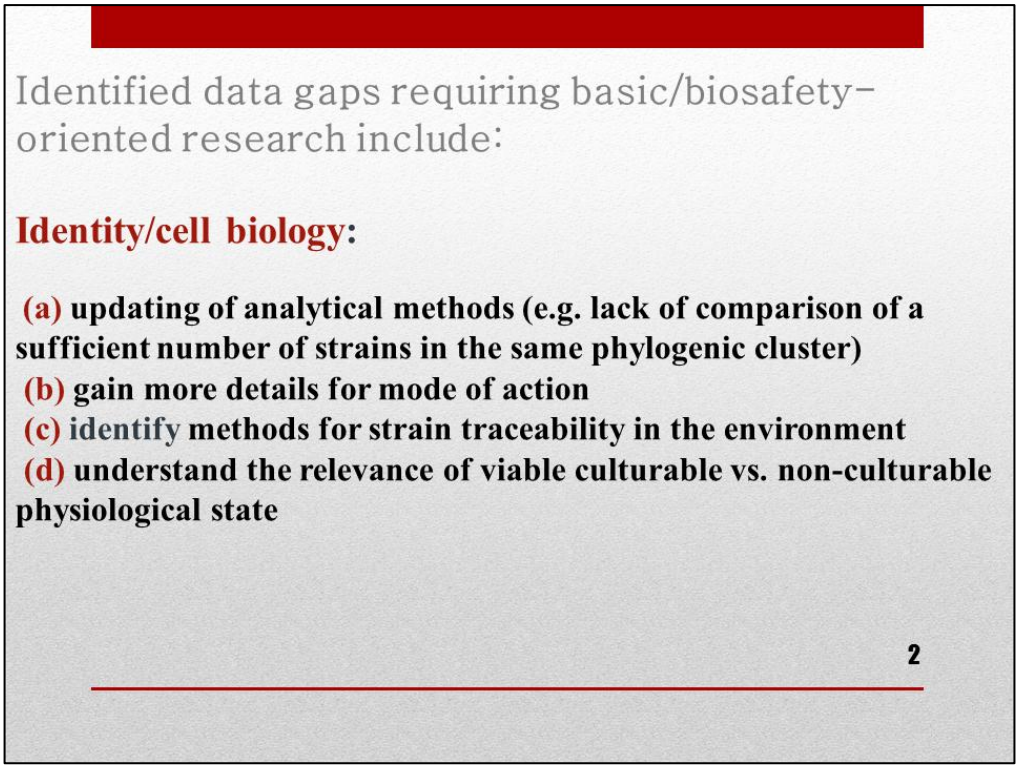
| | |
|---|---|
| **Issues** | Production of secondary metabolites cannot be excluded and therefore the risk assessment cannot be finalised for the environment including the assessment of potential groundwater contamination |
| | Required for all uses outdoor (bacteria and fungi)<br>Extensive characterisation of secondary metabolites that may occur in different compartements/conditions almost impossible |
| Aim (PRAPeR M2) | Relevant toxins should be assessed (toxins present in the product which play a significant role in the mode of action) |
| Questions | How to assess the relevance or not relevance of a secondary metabolites (danger/exposure)?<br>How to set a trigger between relevant toxins and other secondary metabolites? |



## Thank you for your attention

***Critical Issues about Microbials used as Biocides and Plant Protection Products***

***By Marco Nuti, University of Pisa, Italy***

## Toxicology:

(a) Production of toxin(s) and secondary metabolites
(b) Specific toxicity data on each strain vs. specific toxicity data on one strain extrapolated to other strains
(c) Harmonized approach to estimate the levels of exposure for operators/workers/bystanders in order to identify a margin of safety between effects in toxicological studies and estimated exposure
(d) Genotoxicity testing for microbes
(e) Sensitization by inhalation

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## Exposure:

(a) Development of a methodology for a (quantitative) exposure assessment for operator, bystander, worker and resident

(b) Monitoring programs

(c) Sensitive populations

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## Environmental fate:

(a) data on *in vivo* (environment) growth rate;
(b) a model has been developed by RMS (Italy) for the risk assessment of *Bti* strain AM 65-52 as a BIOCIDE for $S_W$; however, to take into account drift during soil applications, a new software has to be prepared considering also sediment adsorption. $DT_{50,s}$ and $DT_{50,sw,}$ values have to be shared by EFSA and COM;
(c) competitiveness of the microbial vs. other soil m.o.

## General :

- develop methodology for cumulative risk assessment

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## Identification (examples)

| ACTIVE INGREDIENT | IDENTIFICATION AT STRAIN LEVEL | comment |
|---|---|---|
| *Bac. thuringiensis* | genomotyping | +++/L/NV |
| *Bac. amyl.* ssp. *plantarum* | ribotyping + RAPD-PCR | ++/L/NV |
| *Lecanicillium muscarium* | sequencing ITS and 3 mitoch. genes | ++/L/NV |
| *Trichoderma atroviride* and *T. polysporum* | sequencing of ITS1, 5.8 rDNA, ITS2 regions | ++/L/NV |
| *Paecilomyces lilacinus* | morpho-physiol, PCR + allozymes electr. | +/L/NV |
| *Pythium oligandrum* | microscopic | -/E/NV |
| *Paecilom. fumosoroseus* | microscopic | -/E/NV |
| *M. anisopliae* | RFLP of rDNA and MtDNA + sequencing of IGS, group-I introns and rDNA | -/L/NV |

**+ = sufficient; ++ = good; +++ = very good; - = insufficient; RAPD = random amplified polymorphic DNA ; RFLP = restriction fragment lenght polymorphism; Mt = mithocondrial; r = ribosomal; ITS = internal transcribed spacers; IGS = intergenic spacers ; PCR = polymerase chain reaction ; E=easy; L=laborious; NV= not validated**

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## identifiability is ok, but ... traceability ?

- **Identifiability : is ok at strain level for inclusion in Annex I, once the actual methods will be validated; it is an advantage for Companies (strain protection)**
- **It is enough for toxicology/exposure studies**
- **It is NOT enough for field studies (exposure, efficacy, environmental fate, ecotoxicology)**
- **We need traceability of the microbial a.i. also to gain the scientific reliability of field data, and for liability aspects**
- **Traceability of microorganisms in the environment can be achieved nowadays by using molecular markers, including "overcrowded" environments such as rhizosphere** (e.g. Felici et al.: Colony PCR with strain-specific SCAR primers. FEMS *Microbiol. Ecol.* 65, 281-298, 2008) **or polymicrobial organic substrates** (Echeverria et al.: Microbially-enhanced composting of wet olive husks. Bioresource Technology 104, 509-517, 2012)

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## Genotoxicity testing (see also the S.O. in EFSA Journal 2011, 9:2379)

Bélin Poletto Mezzomo et al (2012)
http://dx.doi.org/10.1016/j.fct.2012.10.032, Food and Chemical Toxicology
Available online 9 November 2012

Effects of oral administration of *Bacillus thuringiensis* as spore–crystal strains Cry1Aa, Cry1Ab, Cry1Ac or Cry2Aa on hematologic and genotoxic endpoints of Swiss albino mice

Highlights

► Toxins from *Bacillus thuringiensis* are widely used as biopesticides as well as cloned in genetically engineered plants. ► In vivo haematotoxicity and genotoxicity of different Bt–toxins were evaluated in mice. ► Bt–toxins did not show genotoxicity to mice, however induced haematological changes.

**Spore-crystal administrations provoked selective haematotoxicity for the 3 exposure times, particularly for erythroid lineage. A significant reduction in bone marrow cell proliferation demonstrated cytotoxic but not genotoxic effects. These effects persisted for all exposure times, becoming more evident at 7 days. Similar results were observed for binary combinations at 24 h.**

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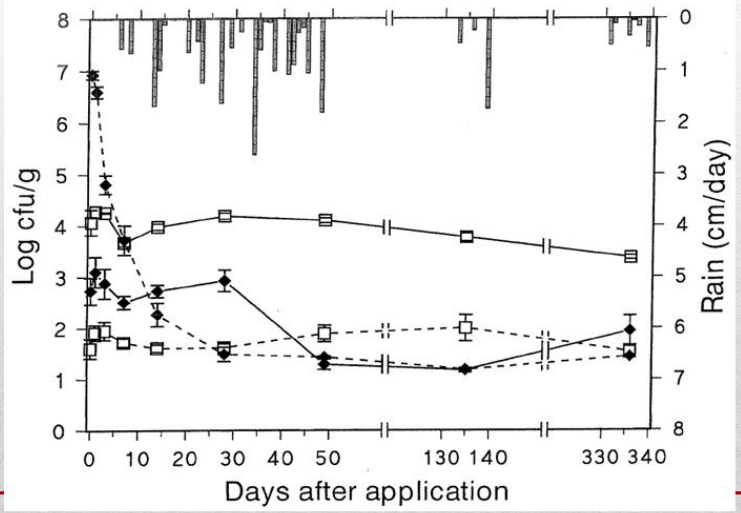
# environmental fate

Fig. 1. Numbers of *B. thuringiensis* DMU67R detected (without heat treatment) on cabbage leaves (◆) and in topsoil (□) in squares with addition of *P. brassicae* larvae and treated with DMU67R either on soil (solid lines) or on leaves (broken lines). Error bars represent SEM ($n = 3$). Hanging columns show daily rainfall.

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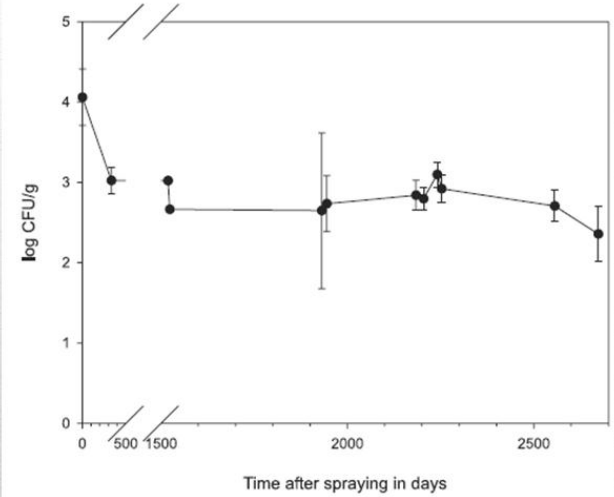
(N.B.Hendriksen)

**Fig. 1.** Numbers of *Bacillus thuringiensis* DMU67R detected in bulk soil samples from the treated area sprayed with *B. thuringiensis* DMU67R in 1993. The results shown are from 1993 to 2000. Error bars represent SEM.

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(N.B. Hendriksen)

## A new approach for assessing fate and persistence: assumptions and methods

### Assumptions

- YES degradation
- NO adsorption (step-1 worst case scenario)
- Application to soil
- YES drift to surface water at the distance of 3 m, different % according to the crop
- Various numbers of applications
- Various intervals between applications
- Results obtained at time zero and following the last application at the highest suggested rate

### Methods

- The population densities have been calculated at time zero and following the last application at the highest suggested rate
- The calculation have been done by using the software PEC-TWA_NEW_1_3_1 (developed by Dr. S. Cervelli stefano.cervelli@ise.cnr.it)

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## environmental fate

*Bacillus thuringiensis aizawai*

**Agree 50 WP strain GC-91**

| Applications | CFU $g^{-1}$ | CFU $L^{-1}$ |
|---|---|---|
| 1 | $5.01 \times 10^4$ | $1.09 \times 10^6$ |
| 4 | $1.38 \times 10^5$ | $3.76 \times 10^6$ |

**XenTari WG strain ABTS-1857**

| Applications | CFU $g^{-1}$ | CFU $L^{-1}$ |
|---|---|---|
| 1 | $3.23 \times 10^4$ | $4.96 \times 10^4$ |
| 6 | $1.05 \times 10^5$ | $2.27 \times 10^5$ |

*Bacillus thuringiensis israeliensis*

**VectoBac WP strain AM65-92**

| Applications | CFU $g^{-1}$ | CFU $L^{-1}$ |
|---|---|---|
| 1 | $8.25 \times 10^5$ | $3.09 \times 10^6$ |
| 3 | $1.89 \times 10^6$ | $8.60 \times 10^6$ |

*Bacillus thuringiensis tenebrionis*

**Novodor SC strain NB-176**

| Applications | CFU $g^{-1}$ | CFU $L^{-1}$ |
|---|---|---|
| 1 | $6.07 \times 10^3$ | $1.50 \times 10^5$ |
| 3 | $1.41 \times 10^4$ | $4.15 \times 10^5$ |

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**Expected environmental density (EED) following repeated applications**

## Sensitization

**SCIENTIFIC / TECHNICAL REPORT (EFSA 2011)**
**Bibliographic review on the potential of microorganisms, microbial products and enzymes to induce respiratory sensitization**
**Cyril Martel[a], Gunnar D. Nielsen[b], Adriano Mari[c], Tine Rask Licht[a], Lars K. Poulsen[a].**

a - Technical University of Denmark, National Food Institute; Mørkhøj Bygade 19, DK-2860 Søborg, Denmark
b - National Research Center for the Working Environment, Lersø Parkallé 105, DK-2100, Copenhagen Ø, Denmark.
c - Center for Clinical and Experimental Allergology, Via dei Monti di Creta 104 I-00167 Rome, Italy

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**Although *in-silico* models can be useful to predict cross-reactivity between allergens, they do not take into account phenomena like the context of presentation of the antigen to the immune system.**

**There is no reliable, predictive *in-vitro* or *in-vivo* model of allergenicity.**
**Cases of occupational allergy to both fungi and bacteria have been documented, but allergic reactions to microorganisms purposedly introduced in the workers environment seem to concern only a limited number of fungi.**

**Enzymes were more a matter of concern, with 17 out of 71 enzymes investigated in this report being linked to respiratory allergies.**
**Because these risks are well known, enzyme exposures are strictly controlled both by regulatory authorities and companies.**

**The patterns of prevalence of allergic reactions to enzyme indicate that they are more common at the level of enzyme manufacturers and large-scale users than in the general population.**

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## Identified issues requiring re-evaluation/guideline update include:

- **Toxicology: (a)** specific test for sensitivity by inhalation; **(b)** specific toxicity data on each strain vs. specific toxicity data on one strain extrapolated to other strains
- **Workers/bystanders exposure: (a)** how the general risk of contact with a high amount of micro-organisms for immuno-compromised persons can be denoted; **(b)** define the necessity of quantitative exposure assessment for environment (and bystanders?); **(c)** need for a harmonized approach to estimate the levels of exposure for operators/workers/bystanders in order to identify a margin of safety between effects in toxicological studies and estimated exposure
- **Ecotoxicology: (a)** define the appropriateness of non-target species and what are appropriate test methods for NTOs; **(b)** define pathogenicity and infectivity for non-vertebrate organisms

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- **Environmental fate:** need for new metrics for microorganisms, e.g. EED (expected environmental density) instead of PEC used for chemicals, etc.

- **General: (a)** guidance on which situations the read across of the results of studies conducted on different sub strains is acceptable; **(b)** 'Low risk' active substances; **(c)** data protection; **(d)** how the areas of growth/persistence following application in relation to background levels should/can be addressed **(e)** specific areas of use (rice pads)

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## Several EU Countries proposed to:

- **Set the specification of the microbial contaminant levels as standard requirement according to the OECD document: OECD Issue Paper on Microbial Contaminant Limits for Microbial Pest Control Products [ENV/JM/WRPR(2011)28]**
- **Develop methodology for an exposure assessment for operator, bystander, worker and resident**
- **Provide guidance on which situations the read across of the results of studies conducted on different sub strains is acceptable.**
- **Decide on how the general risk for immuno-compromised persons of contact with a high amount of micro-organisms can be denoted.**
- **Specify the standard requirements for environmental hazard identification according to the available US-EPA OPPTS Harmonized/885 Microbial Pesticide Test Guidelines/Series**
- **Set more specific criteria for human and environmental Risk Assessment when required for toxin**

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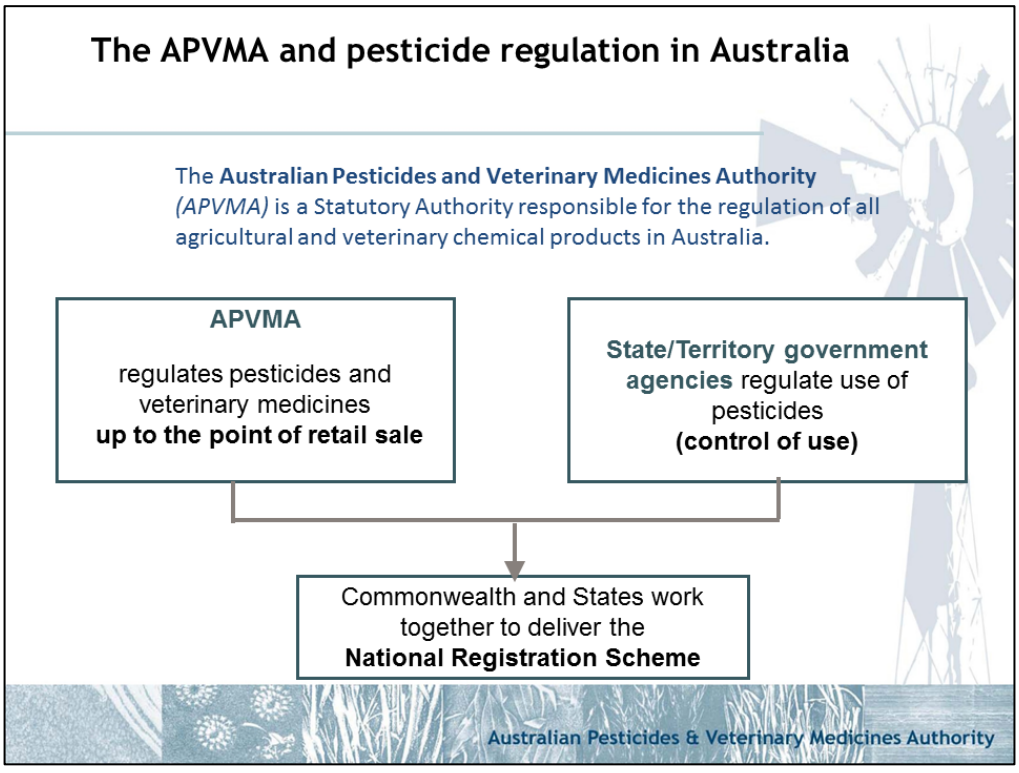
Thanks for your attention !

*An overview of Australia's regulatory system for biological pest control products*

*By Jay Kottege*
*Principal Evaluator Pesticides, Australian Pesticides and Veterinary Medicines Authority*

## What does the APVMA do?

- Registers new pesticides and veterinary products
- Approves variations to existing pesticides and veterinary products
  - Extension of use (new crops; new pests)
  - Changes to withholding periods *etc.,*
- Issues permits
  - Minor use
  - Research
  - Emergency
- Review of registered pesticides
  - Adverse Experience Reporting
- Compliance (registered products and permits)



## Scope of Agricultural chemicals regulated

Defined in legislation and wide in scope

- insecticides
- herbicides
- fungicides
- rodenticides
- swimming pool chemicals, sanitizers and disinfectants
- Biologicals and
- GMOs (when they express insecticidal proteins)

## Agricultural and Veterinary Chemicals legislation

Under the *Agricultural and Veterinary Chemicals Code (1994),* the APVMA has to be satisfied that agricultural chemical products registered for use in Australia are properly formulated and suitably labelled and, when used according to label instructions are:

- safe to the public, the user, consumers and the environment;
- efficacious (that is, the product is effective as it claims it shall be on the label); and
- not unduly prejudicial to Australia's trade.



## Risk assessment components and assessors of risk

- Chemistry and Manufacture (APVMA)
- Toxicology (Department of Health)
- Occupational Health & Safety (Department of Health)
- Residues in food (APVMA)
- Trade (APVMA)
- Environment (Department of the Environment)
- Efficacy and Crop Safety (External expert reviewers)

**APVMA coordinates the assessment process**

## Definition and groups of 'Biological' product…

- According to the APVMA Biological Guideline:

  "A biological agricultural chemical product is one where the active constituent comprises or is derived from a living organism (plant, animal, microorganism, etc), with or without modification."

Four groups of Biological products are listed:

- Group 1— biological chemicals (e.g. pheromones, hormones, growth regulators, enzymes and vitamins)
- Group 2 — extracts (e.g. plant extracts, oils)
- Group 3 — microbial agents (e.g. bacteria, fungi, viruses, protozoa)
- Group 4 — other living organisms (e.g. microscopic insects, plants and animals plus some organisms that have been genetically-modified)



## Recent experience with biological agricultural products…

### Example 1 - Active constituent(s)

- Cotton bollworm (*Helicoverpa sp.)* attractant product based on several plant volatile substances:
- APVMA is required by law to approve the active constituent
  - what constituted the active constituent in this product?
- The active substances were initially a blend of five components. Four of these components were listed in GRAS (Generally Recognized as Safe) list.
- The Initial active constituent blend also included (Z)-3-hexenyl salicylate.
  - little was known of its natural occurrence in plants and it was not in GRAS list.
- Applicant was asked to either provide more information or reformulate. This resulted in a subsequent six component blend, with all components on RGAS list, thus enabling registration to proceed.

## Example 2- Level of efficacy

A certain baculovirus-based product

- data indicated only a 40% level of efficacy
- consultation with the States revealed that the use of this product would still provide a useful tool for the particular cropping system.
- Accordingly, a relatively low level of efficacy was accepted (with suitable label language deployed to alert and communicate this to users.)



## Example 3 – Meeting data requirements is a challenge

A bio-herbicide based on several soil-borne fungi:

- Somewhat unconventional category of biological product
- While the proponents may know the role that these fungi play in nature, they find it hard to establish proof of safety within the current regulatory framework
  - This applies to public safety and environmental safety alike
- Challenges of establishing efficacy: death of target weed (a large perennial plant of significant biomass) takes 12 to 24 months.
  - Not easy to rapidly produce efficacy data to fill any data gaps
- The same challenge applies to proving target specificity, eliciting a cautionary response from assessors of public health and environmental risk.

## Key points…

- Microbial pesticides include a wide array of products
- Justifying relatively low levels of efficacy
- Proving/establishing efficacy and safety for some products (e.g bio-herbicides)
- Acquiring and maintaining regulatory expertise is challenging for most small organisations
- Need for greater collaboration, sharing of expertise/experience internationally

***The actual regulatory frame for the use of microorganisms for pest control***

***By Jose Herrera***
***Federal Commission for the Protection from Sanitary Risk, Ministry of Health, Mexico***

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# Overview of Mexico's Regulatory Frame for the Use of Microorganisms for Pest Control

M. Sc. Jose Herrera

Federal Commission for the Protection from Sanitary Risk (COFEPRIS)

Ministery of Health

Saltsjöbaden, Sweden
Jun 17th, 2013.

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## General Health Act (Article 376)

- Pesticides and plant nutrients requires sanitary registration.
- Registration is a shared process between the agricultural **(SAGARPA)**, environmental **(SEMARNAT)** and health **(SALUD)** Mexican authorities.
- Therefore it is a joint evaluation and only with the approval of the agricultural and environmental authorities, the Ministry of Health (SALUD) would grant the registration.
- The registration will be valid for 5 years, and may be renewed for equal periods, if the person concerned so requests.

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# Basic documents

**"Regulation for *Registration, Export and Import Permits and Certificates for Export of Pesticides, Fertilizers and Toxic and Hazardous Substances*"**

- Published on the Official Journal of the Federation on December 28th, 2004
- Specificis Regulation that establishes the general registration procedure and the specific requirements by pesticide type.

http://www.salud.gob.mx/unidades/cofepris/bv/mj/REGLAMENTOS/12/REGLAMENTORegAutImpoExpoCertPlagui.doc

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# PESTICIDE CLASIFICATION

- I. CHEMICAL TECHNICAL
- II. END-USE CHEMICAL PRODUCT FOR AGRICULTURAL AND FORESTRY USE
- III. END-USE CHEMICAL PRODUCT OF USE HOUSEHOLD, URBAN, INDUSTRIAL AND GARDENING
- IV. END-USE CHEMICAL PRODCUTO FOR LIVESTOCK USE
- V. BIOCHEMICAL
- VI. MICROBIAL
- VII. BOTANICAL
- VIII. MICROBIAL BASIS OF GENETICALLY MODIFIED ORGANISMS
- IX. MISCELLANEOUS

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## Biological Pesticide (Biopesticide) classification

On the Mexican pesticide regulation (General Health Act and specific Regulation), the biopesticides category is not defined, and the pesticides are grouped on:

| | |
|---|---|
| Chemical | Microbial |
| Botanical | Biochemical |

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## Pesticides Classification for Registry on Mexican Regulation

- **Chemical**
  - Technical
  - End-use products
    - Agricultural use
    - Domestic use
    - Forest use
    - Industrial use
    - Gardening use
    - Livestock use
    - Urban use
- **Biochemical** (Pheromones and alelochemicals)
- **Microbial**
  - Bacterium
  - Fungi
  - Virus
  - Nematodes
  - Protozoa
- **Botanical**
- **Miscellaneous** (e.g. soaps)

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## Microbial pesticide (Procedure 06-006)

Product formulated with microorganisms such as bacteria, viruses, fungi or yeast, nematodes or protozoa, used for purposes of pest control.

## Botanical pesticide (Procedure 06-007)

Substances extracted directly from plants and are conditioned to be exploited for pest control.

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## Biochemical pesticide (Procedure 06-005)

Substance that occurs naturally and is used to pest control by nontoxic mechanisms, including insect sex pheromones that interfere with intercourse, these pheromones can be synthesized and placed in traps.

## Miscellaneous Pesticide (Procedure 06-009)

One who lacks pesticides physicochemical and toxicological properties, but has features that allow pest control.

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## General Comparison of Requierements for Chemical and Biological Pesticides

| Requierements | Chemicals /formulated |
|---|---|
| Identity and composition | 4 |
| Analytical Method | 2 |
| Physicochemical properties | 18 |
| Physical characteristics | 9 |
| Toxicology | 17 |
| Ecotoxicology | 9 |
| Stability Study | 1 |
| Label | 1 |
| Technical Opinion biological effectiveness for SAGARPA | 1 |
| Total | Aprox. 62 |

| Requierements | Microbial |
|---|---|
| Identity and composition | 7 |
| Physicochemical properties | 4 |
| Analytical Method | 3 |
| Physical characteristics related to the use | 8 |
| Biological properties of the agent | 7 |
| Toxicology | 5 |
| Ecotoxicológicos | 4 |
| Technical opinion biological efectiveness for SAGARPA | 1 |
| Stability study | 1 |
| Label | 1 |
| Total | 41 |

| Requierements | Microbial GMO |
|---|---|
| Identity and composition | 10 |
| Formulation-related characteristics | 9 |
| Biological properties of organism | 5 |
| Toxicology | 2 |
| Ecotoxicology | 2 |
| Technical opinion biological efectiveness for SAGARPA | 1 |
| Label | 1 |
| Total | 30 |

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| Requierements | Botanical |
|---|---|
| Identity and composition | 5 |
| Analytical Method | 0 |
| Physicochemical properties | 5 |
| Physical characteristics related to the use | 8 |
| Toxicology | 2 |
| Ecotoxicology | 0 |
| Technical Opinion biological effectiveness for SAGARPA | 1 |
| Estability study | 1 |
| Label | 1 |
| Total | 23 |

| Requierements | Biochemical |
|---|---|
| Identity and composition | 5 |
| Analytical Method | 1 |
| Physicochemical properties | 7 |
| Physical characteristics | 2 |
| Toxicology | 2 |
| Common name, genus and species of pest control | 1 |
| Label | 1 |
| Ecotoxicology | 0 |
| Technical Opinion biological effectiveness for SAGARPA | 1 |
| Total | 21 |

| Requierements | Miscellaneous |
|---|---|
| Identity and composition | 5 |
| Analytical Method | 0 |
| Physicochemical properties | 5 |
| Physical characteristics related to the use | 5 |
| Toxicology | 2 |
| Ecotoxicology | 0 |
| Technical Opinion biological effectiveness for SAGARPA | 1 |
| Stability Study | 1 |
| Label | 1 |
| Total | 20 |

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## Microbial Specific Requierements

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**Identity and Composition:**

1. Common name
2. Scientific name
3. Procurement process
4. Min & Max content
5. Inerts
6. Purity (toxic non intentionally added; allergens and impurities produced by the microorganism or the incubation process, etc.)
7. Type formulation

**Physical-Chemical Properties:**

1. Physical State
2. Color
3. Odor
4. pH

**Analytical Methods**

1. For biological agent assessment
2. For biological agent identification
3. For purity determination

**Physical properties related to formulation use :**

1. Moisture content (dust & granules)
2. Wettability (wettable powders)
3. Persistent of foam
4. Suspensibility (wettable powders)
5. Wet sieve test
6. Dry sieve test
7. Emulsion stability

**Biological properties of the agent:**

1. Background and biological properties of the biological agent
2. Attacked species and specificity
3. Genetic stability
4. Controlled pests
5. Interaction of biological agent with culture patogens and vertebrae
6. Presence of organisms in nature
7. Meteorological distribution mechanisms

**Toxicology**

1. Acute toxicity: Oral (LD50) & Dermal (LD50)
2. Skin and eye irritation
3. Human pathogenicity studies
4. Patological alterations in skin and eyes after one application
5. Hipersensibility

**Ecotoxicology**

1. Terrestrial Flora & Fauna effects
2. Acute LC50 on fish
3. Acute LC50 on acuatic plant oranimal that is fish food
4. Impact on beneficial, pollinating insects

**Technical Opinion biological effectiveness for SAGARPA**

**Stability Study**

**Label**

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## GMO Microbial Specific Requierements

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**Identity and Composition:**

1. Scientific & common name, synonymous, species or strains
2. Donor organism information
3. Genetic material inserted
4. Vector used
5. Receptor
6. Technic used
7. By-product information
8. Min & Max content
9. Inerts
10. Type formulation

**Formulation related characteristics:**

1. Moisture content (dust & granules)
2. Wettability (wettable powders)
3. Persistent of foam
4. Suspensibility (wettable powders)
5. Wet sieve test
6. Dry sieve test
7. Emulsion stability
8. Physical/chemical compatibility
9. Stability Study

**Biological properties of the agent:**

1. Background and biological properties of the biological agent
2. Interaction of biological agent with culture patogens and invertebrae
3. Naturally occurring and geographic distribution
4. Biological properties and host specificity
5. Genetic stability of parent organisms and factors affecting it

**Toxicology**

1. Skin and eye irritation
2. Hipersensibility

**Ecotoxicology**

1. Percentage of gene transfer
2. Relative competitiveness for donor rtrains in soil, water and air

**Technical Opinion biological effectiveness for SAGARPA**

**Label**

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## Accepted data

- For physicochemical and toxicological studies, COFEPRIS considers valid studies made under international guidelines (OECD, EPA, etc.) and under Good Laboratory Practices statement.

- In the case that an specific requirement does not apply to a particular product presentation, then the specific Regulation considers to waive this requirement with the respective technical justification (article 5).

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## Before submitting the application…

- Sanitary license for pesticide manufacture, formulation, mixing or packaging. (Procedure 05-022-B)
  - Floor blueprint
  - Worker training program
  - MSDS
  - Worker health surveillance program
  - Special security systems (sprinklers, smoke detectors, leakage detection alarm)
  - Technical information about production lines (raw materials, residues, process description, flow diagram, etc.)
  - Fee (Right Federal Law 2011, art. 195-K-8, $15,944.93 MXP)

- Biological efectiveness opinion (SAGARPA)

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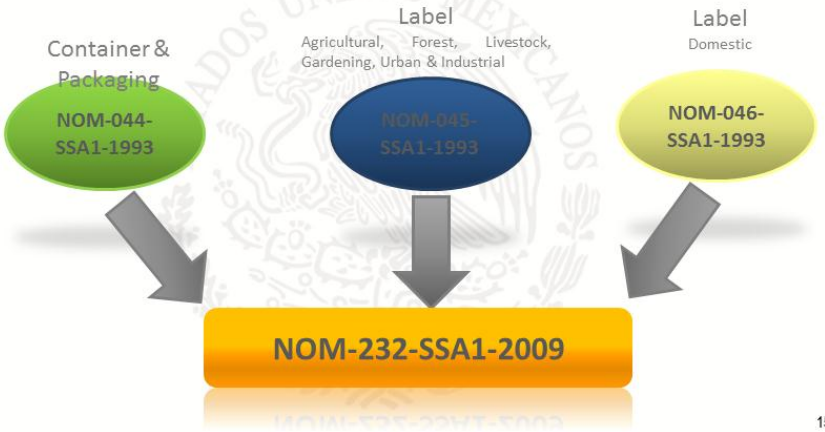
Comisión Federal para la Protección contra Riesgos Sanitarios

# Product label…

## Official Mexican Standard NOM-232-SSA1-2009

**Specify the requirements of container, packaging and label for technical and end-use produts for agricultural, forest, livestock, gardening, urban, industrial and domestic use**

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## Toxicological Classification

- Based on acute effects chapter of GHS.
- Products are classified on five categories based in the oral dermic and inhalatory acute toxicity effects.
- Product classification is based on the acute oral, dermic LD50 or inhalatory LC50 most dangerous for active ingrediente or on the Calculate Acute Toxicity of the most dangerous route for the end-use products.

| | | Category | | | | |
|---|---|---|---|---|---|---|
| Exposure route | | 1 | 2 | 3 | 4 | 5 |
| Oral (mg/Kg) | | 5 | 50 | 300 | 2000 | 5000 |
| Dermic (mg/Kg) | | 50 | 200 | 1000 | 2000 | |
| Inhalatory | Gas (ppm) | 100 | 500 | 2500 | 2000 | |
| | Vapour (mg/L) | 0.5 | 2 | 10 | 20 | |
| | Dust and fogs (mg/L) | 0.05 | 0.5 | 1 | 5 | |

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## Official Mexican Standard NOM-232-SSA1-2009

### Warning Symbols and Phrases

| | | Category 1 | Category 2 | Category 3 | Category 4 | Category 5 |
|---|---|---|---|---|---|---|
| Symbol | |  |  |  |  | |
| Warning Phrase | Oral | Mortal en caso de ingestión (Mortal if ingested) | Mortal en caso de ingestión (Mortal if ingested) | Tóxico en caso de ingestión (Toxic if ingested) | Nocivo en caso de ingestión (Harmful if ingested) | Puede ser nocivo en caso de ingestión (May be harmful if ingested) |
| | Dermic | Mortal por el contacto con la piel (Mortal by skin contact) | Mortal por el contacto con la piel (Mortal by skin contact) | Tóxico por el contacto con la piel (Toxic by skin contact) | Nocivo por el contacto con la piel (Harmful by skin contact) | Puede ser nocivo por el contacto con la piel (May be harmful by skin contact) |
| | Inhalatory | Mortal si se inhala (Mortal by inhalation) | Mortal si se inhala (Mortal by inhalation) | Tóxico si se inhala (Toxic by inhalation) | Nocivo si se inhala (Harmful by inhalation) | Puede ser nocivo si se inhala (May be harmful by inhalation) |
| Warning Word | | **Peligro (Danger)** | **Peligro (Danger)** | **Peligro (Danger)** | **Precaución (Caution)** | **Precaución (Caution)** |
| Color | | Red 199-C | Red 199-C | Yellow 101-C | blue 293-C | Green 347-C |

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## Official Mexican Standard NOM-232-SSA1-2009

### Pictograms on Precautions for Use

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# Official Mexican Standard NOM-232-SSA1-2009

## Example

| | | |
|---|---|---|
| "Alto lea esta etiqueta" | **"USO (por ejemplo pecuario)"** | Instrucciones de uso |
| Equipo de protección | LOGO FORMULADOR — LOGO PRODUCTO | "Calibre su equipo" |
| Primeros auxilios | Nombre común<br>Insecticida, etc.<br>Composición% | dosis, plagas |
| Sugerencias al médico | Propelente<br>Ingrediente Activo<br>Registro RSCO-AABB-CCDD-1122<br>Contenido Neto | Método de aplicación |
| Medio Ambiente | Pictograma<br>Frase de Peligro<br>Leyendas Salud | Incompatibilidad |
| | Lote<br>Nombre<br>Dirección<br>Hecho en… | |
| Pictograma | **Palabra de Advertencia** | Pictograma |

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# Current registries and feed

| | | Fee | |
|---|---|---|---|
| | | Mexican pesos | Estimate in U.S. Dollars (1USD=12.8MXP) |
| Chemical Toxicological Category | 1 | 59,661.83 | 4,661.08 |
| | 2 | 49,718.18 | 3,884.23 |
| | 3 | 34,943.21 | 2,729.94 |
| | 4 | 25,190.55 | 1,968.01 |
| | 5 (Microbial, Botanical, Biochemical) | 16,259.81 | 1,270.30 |
| Plant Nutrients | | 5,164.57 | 403.48 |
| Amendments | Propietary name | 50% of the fee | |
| | Others | 75% of the fee | |

| Current registries | | |
|---|---|---|
| Microbial | Bacteria | 77 |
| | Fungi | 13 |
| | Virus | 2 |
| | Nematods | 19 |
| Botanical | 21 | |
| Biochemical | 39 | |

| | |
|---|---|
| Total registries | around 5000 |

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# To submit…

"Agreement by which the procedures, services and formats registered in the Federal Register of Procedures and Services are released and used by the Ministry of Health, through the COFEPRIS"

- Procedures guide that contains the official formats and the specific procedures that correspond to each pesticide type.
- Published on the Official Journal of the Federation on May 10th, 2012

http://www.cofepris.gob.mx/nom/acuerdos/salud2a28ene11.pdf
http://www.cofemer.gob.mx/BuscadorTramites/BuscadorGeneralHomoclave.asp

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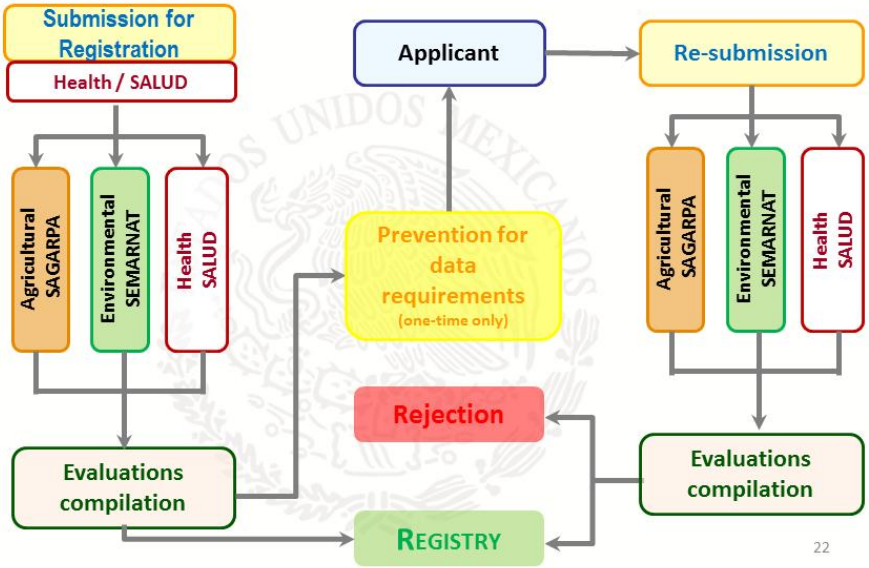
# Registration process

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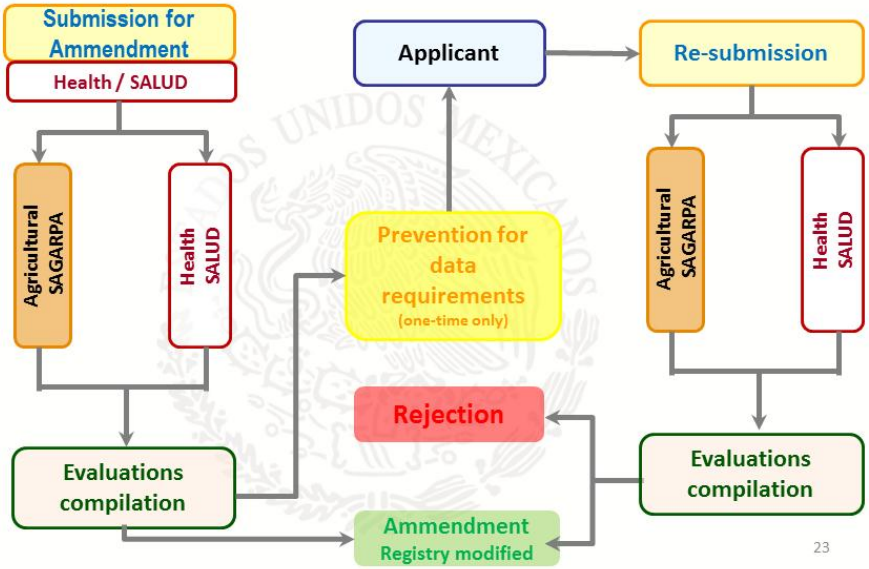
## Registration's ammendment (i.e. add culture use)

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## REDUCED-RISK PESTICIDES PROJECT

**Reduce-Risk Pesticide:**

**Substances, microorganisms, plant extracts and oils that are used for the control of pests and has a minimum risk to human health due to its low toxicity**

- Miscellaneous
- Botanicals
- Biochemicals
- Microbials

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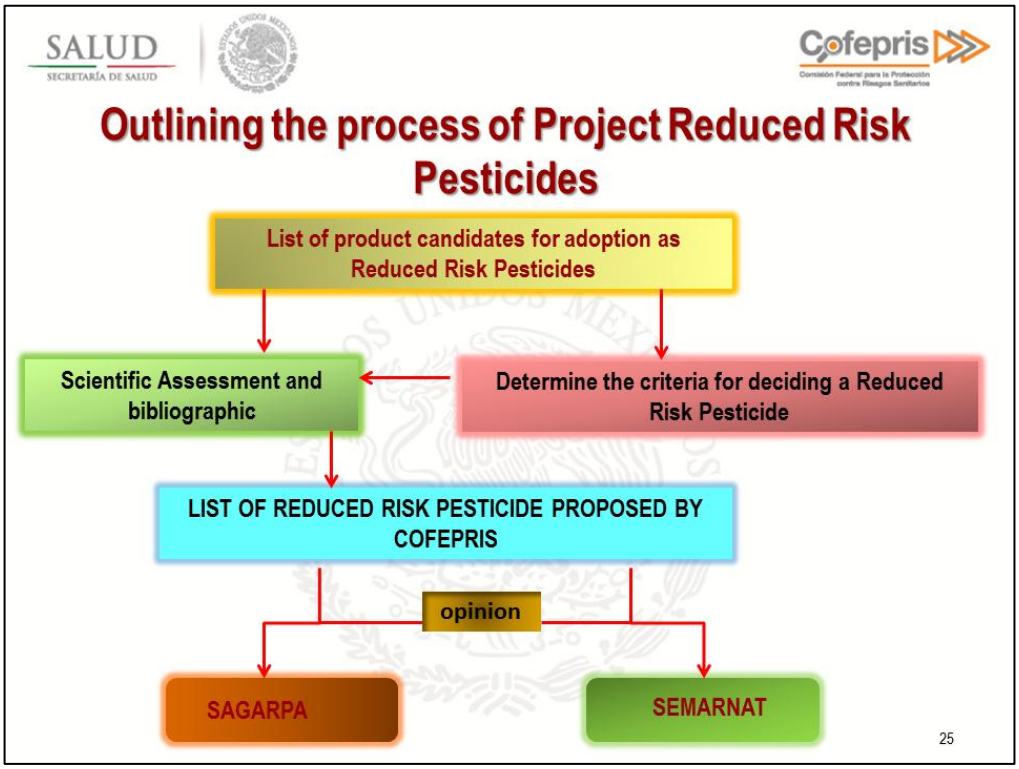
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Cofepris
Outlining the process of Project Reduced Risk Pesticides
List of product candidates for adoption as Reduced Risk Pesticides
Scientific Assessment and bibliographic
Determine the criteria for deciding a Reduced Risk Pesticide
LIST OF REDUCED RISK PESTICIDE PROPOSED BY COFEPRIS
opinion
SAGARPA
SEMARNAT
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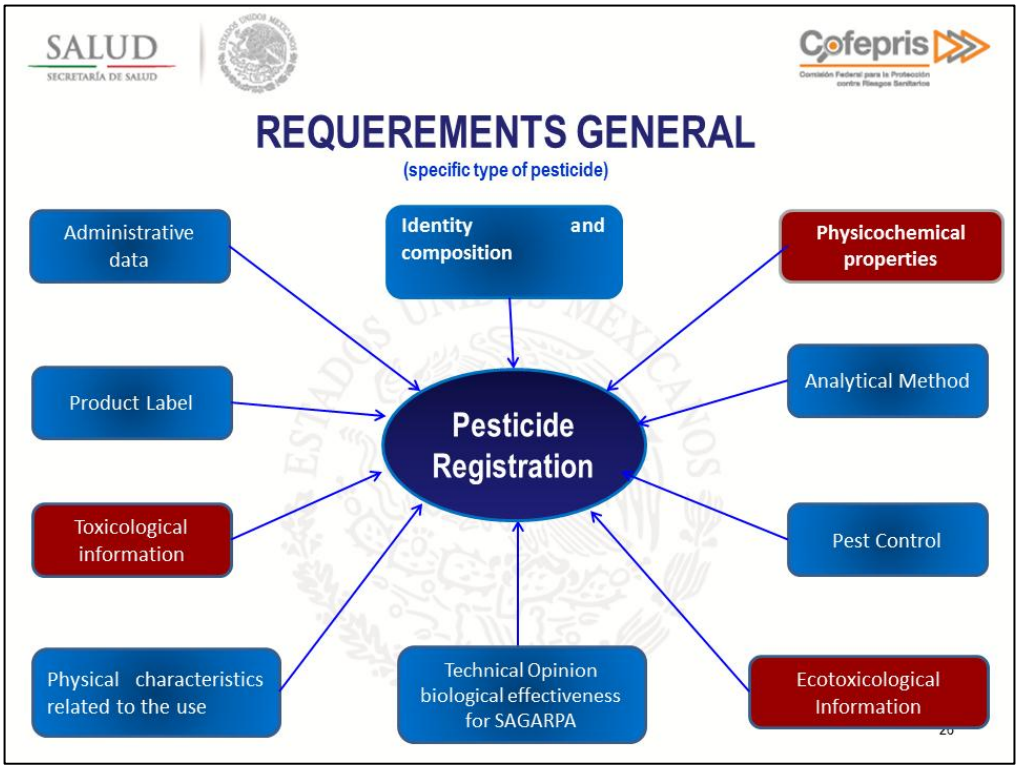
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REQUEREMENTS GENERAL
(specific type of pesticide)
Administrative data
Identity and composition
Physicochemical properties
Product Label
Analytical Method
Pesticide Registration
Toxicological information
Pest Control
Physical characteristics related to the use
Technical Opinion biological effectiveness for SAGARPA
Ecotoxicological Information
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## SOME CRITERIA FOR DETERMINING TO A REDUCED RISK MICROBIAL PESTICIDE (RR)

1) The products should contain as active ingredients only microorganisms substances listed in the list of pesticides for RR. The active ingredient of the product must take action to control pests.

2) The microorganisms in this list could be bacteria, fungi, virus, nematods or protozoa.

3) The microrganisms and the end-use products contain them, toxicity and ecotoxicity must have equal or greater toxicological category 5, according to current and applicable regulation (Regulation NOM-232-SSA1-2009 ).

4) The products should contain as active ingredients only this microorganisms, so it must not contain naturally occurring or added (intentionally or unintentionally) other pesticide residues, heavy metals, pathogens, toxins or other substance that could be considered toxic to humans, animals, crops or the environment.

**At the moment, the list for RR pesticides includes 45 active ingredients, which only 2 are microbials:**
***Aspergillus flavus*** **strains AF36 and NRRL2188.**

# THANK YOU


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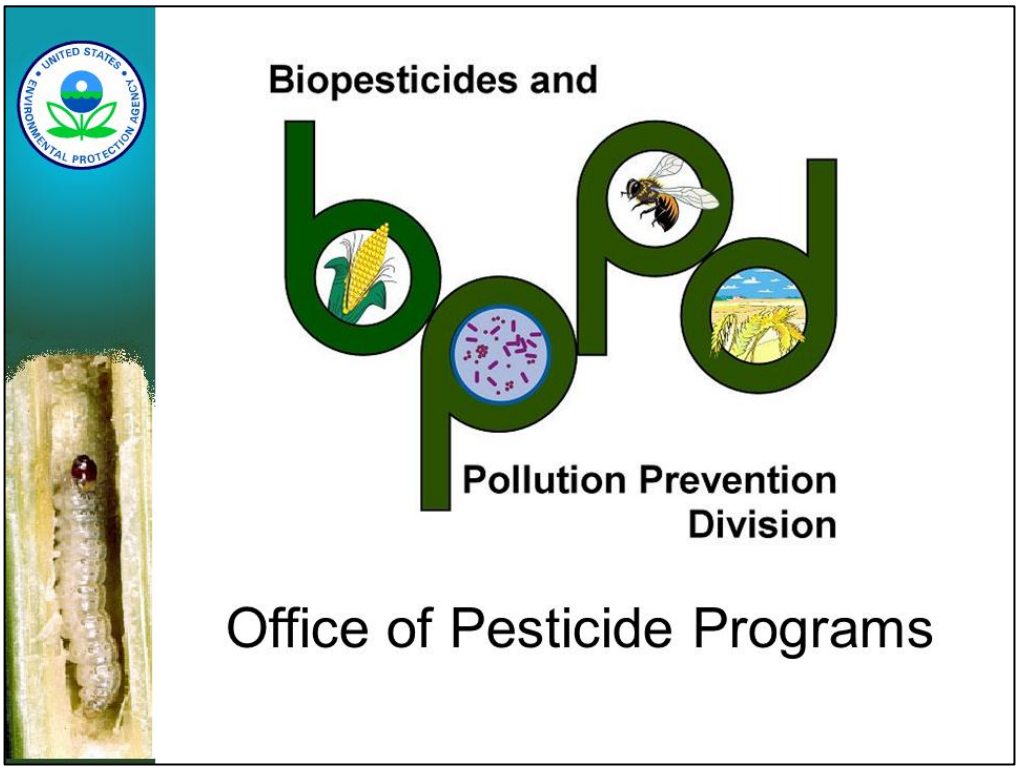
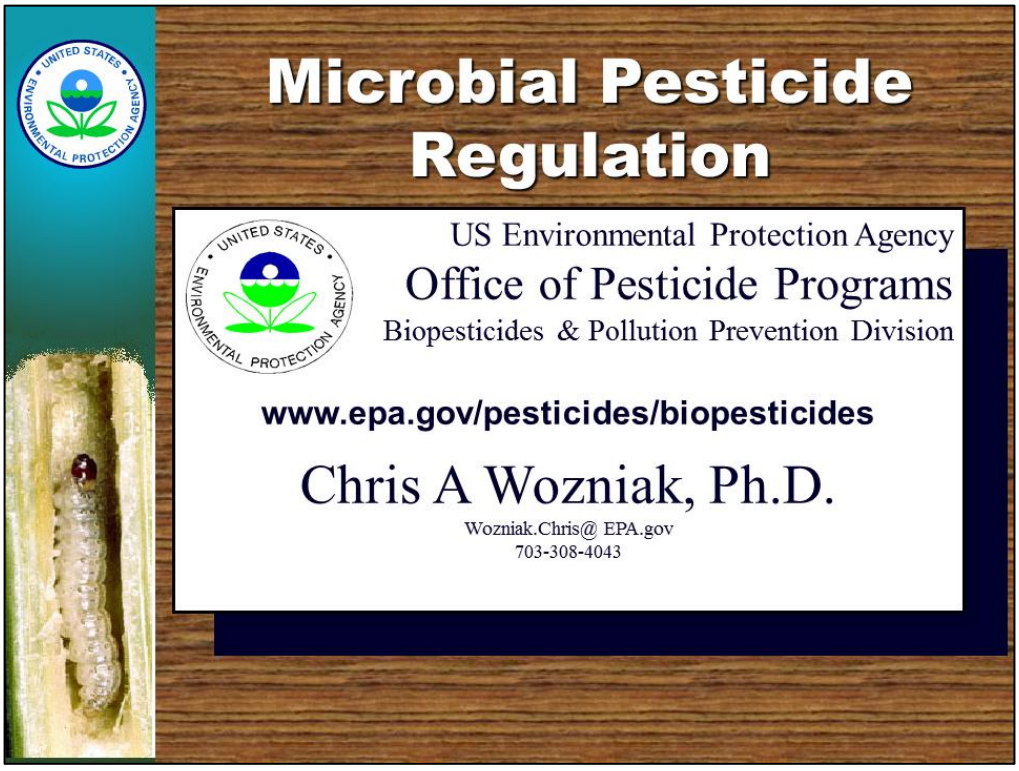
***Regulation of Microbial Pesticides in the United States***

***By Chris A. Wozniak***
***U.S. Environmental Protection Agency***



# Microbial Pesticide Regulation

- Microbial Pesticide:
  - Microbial agent intended for preventing, destroying, repelling, or mitigating any pest, or intended for use as a plant regulator, defoliant, or desiccant.
- Starts at 40 CFR 158.2100.
  - Live or Dead microbes.
    - Eukaryote.
    - Prokaryote.
    - Parasitically replicating microscopic element.
      - Other BioControl Agents, e.g. beneficial insects and nematodes, have been exempted from regulation as pesticides.
        - » Unless microbial symbiont is changed (paratransgenesis).
  - Registration / Experimental Use Permit requirements.
    - No EUP needed if <10 acres land, <1 acre water, and crop destruct.
    - Biotech derived pesticides need a notification for an environmental release.
    - EUP purpose is to develop data for a registration.

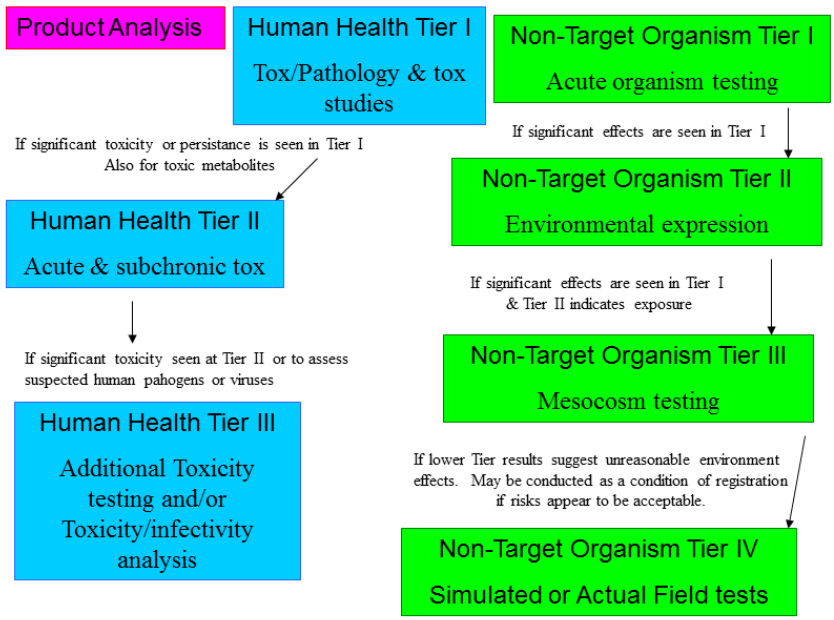
# Microbial Biopesticides

- Bacteriophage
- Viruses (baculoviruses)
- Bacteria
- Fungi
- Algae
- Protozoa
- Not entomopathogenic nematodes*, mites or other biocontrol organisms
- We do regulate paratransgenic insect symbionts such as *Wolbachia* in mosquitoes
  - * if symbiont is engineered, then it is regulated

# Microbial Pesticide Regulation

- Data Requirements and Guidelines – Tier I.
  - Product Characterization: 40 CFR 158.2120
    - Biological and Chemical properties
    - Manufacturing process
    - Label and Confidential Statement of Formula
  - Health Effects: 40 CFR 158.2140
    - Toxicity / pathogenicity testing – oral, pulmonary
      - Clearance from organs and tissues
    - Toxicity testing – oral, inhalation, dermal
    - Irritation testing - dermal, eye
  - Nontarget Effects: 40 CFR 158.2150
    - Avian, wild mammal, fish, aquatic invertebrates, plants, beneficial insects, honeybees.
  - Food Tolerance Exemption Petition.

# Microbial Pesticide Regulation

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# Toxicity/Pathogenicity Testing

- Health Effects:
  - Maximum hazard dose testing:
    - $10^8$ units via oral & pulmonary routes.
    - $10^7$ units if injected:
      - i.v. bacteria, viruses.
      - i.p. fungi, protozoa.
  - 3 animals/sex at each interim & final sacrifice.
  - Continue until a pattern of clearance is seen.
- Nontarget Organisms:
  - Avian oral: [MPCA] in TGAI x 5 mL/kg BW x weight of test bird (kg).
  - Avian inhalation: [MPCA] in TGAI x 0.2 mL/kg BW x weight of test bird (kg).
  - Fish / Invertebrates: At least$10^6$ units/mL in water 'or' 1,000x the theoretical maximum concentration in 6" water (whichever is greater and attainable).
  - Plants: Maximum label use rate.
  - Insects: Increments to 100x the $LD_{50}$ or $LC_{50}$ 'or' 10-100x maximum label use rate.
  - Honeybees: Could be whole hive, larval etc.

# Toxicity/Pathogenicity Testing

- Clinical observation / examination of animals.
  - Morbidity and mortality
- Body weight gain
- Necropsy – compared with controls.
  - Gross pathology
  - Organ weights
  - Histological exam if apparent lesions
- Enumeration of microbial active ingredient.
  - To determine infectivity
  - To show pattern of clearance
  - Kidney, brain, liver, lung, stomach, intestines, cecum, spleen, blood, etc.

# Microbial Pesticide Registration

- Genetically modified microbes:
  - Same as for natural isolates, except:
  - **OCSPP Guideline No. 885.1100:** "If the MPCA in question has been altered genetically ….. the methods used to alter the microbe genetically should be provided. In the case of genetically altered products, the identity of the inserted or deleted genetic material (source, nature, size, base sequence data and/or restriction endonuclease map), information on the gene control region, descriptions of the phenotypic traits to be gained or lost, and information as to the genetic stability (reversion tendency or rate of exchange/transfer with other organisms) of the genetically altered chromosomal region or extrachromosomal entity are to be discussed.
  - Experimental Uses: 40 CFR 172.45
    - **Biotech Notification process provides for small scale testing** when an EUP or registration is not needed for field tests.
    - EPA works jointly with USDA-APHIS on Notifications

# Summary: Regulatory Process

- FIFRA as amended by FQPA:
  - Will unreasonable adverse effects (to man or the environment) result from uses as labeled?
- FFDCA:
  - Is an exemption from the requirement of a food tolerance supportable?
  - Is a numerical tolerance, with generation of residue data, necessary or warranted?
- ESA - Is there a 'may affect' endangered species finding?
- Label and CSF:
  - Should have matching data.
  - Contain risk mitigation information (PPE, REI, etc.).
- **Data waivers:**
  - Data and/or literature that closely address study endpoints.

# Risk Assessment

- Hazard:
  - Toxicity, Pathogenicity
- Exposure:
  - Label: Scale of use, use patterns, application rates.
  - Persistence, degradation, mobility.
    - Water (i.e. irrigation, drinking and recreational use)
    - Soil
    - Plant materials
  - Population dynamics, residues
    - Difficult analysis for microbials that multiply in the environment .
    - Microbial toxins and metabolites may need analysis.
- Risk:
  - Non-target organisms, humans including susceptible populations, domestic animals, endangered species

# Microbial Pesticides

## Regulatory Challenges

- Killed microbes
  - Case-by-case to assure truly killed
  - May require conventional analysis of the toxins
- Microbial mixtures
  - Need to identify each active as a separate a.i., but may test the consortium for guideline studies
- Animal and plant pathogens
  - Host range and strain variation critical
- Biotech products
  - DNA / RNA and metabolites may not fit the microbial definition (but they are biopesticides)
  - Our guidelines are designed for microbes

# Microbial Pesticides

## Process of Registration

- Pre-registration meeting.
- Follows relevant Pesticide Registration (PR) notices and 40 CFR.
- Data matrix – relevant studies addressed.
- Copies of cited literature are submitted.
- Contact / Agent is responsive if details need to be addressed during review.

# Microbial Pesticides

## Data Needs

- Taxonomic distinction
- Appropriate Non-target tests:
  - Aquatic invertebrates – *Daphnia* Aquatic tox
  - Honeybee – larval or whole hive / length
  - Killed microbial agents with dsRNA – dosing

# Microbial Biocides

- USEPA Registrations:
  - Product containing the active ingredient Listeria specific bacteriophages (EPA Reg No. 74234-1) for use in non-food areas of food processing plants as a supplemental treatment (floors/drains). Product registered 6/18/08.
  - Experimental Use Product containing the active ingredient E. coli 0157:H7 specific bacteriophages (EPA EUP No.74234-EUP-2)for use on food contact surfaces in food process plants. A temporary tolerance was established. EUP issued 4/5/11.
- Data required were consistent with data requirements for microbial pesticides (158V). In addition, EPA evaluated antimicrobial efficacy data for a sanitization claim.
- Process used was the process for antimicrobial registrations (i.e., time for review and cost)

# *Bacillus pumilus* GHA 180

- Fungicide for soil / potting mix treatment in greenhouse / enclosed nurseries
- Limited use site – did not trigger non-target and env fate data requirements
- Waiver rationale for acute oral and pulmonary toxicity/pathogenicity based on IV tox/path and oral, dermal and inhalation acute toxicity study results
- GHA 180 cleared rat organs / tissues

## *Bacillus pumilus*

- Reported plant pathogen of mangoes, potatoes, apricot, apple, cabbage, cauliflower, cucumber, garlic, okra, olive, peach, pepper, squash, sugarbeet
- PGPR / ISR of cucumber, pine, tobacco
- Reduction of *Cercospora* leaf spot in beet, late blight in tomato, CMV and *Peronospora* in tobacco, *Erwinia* in cucumber, *Fusarium* on peas, ……

## *Bacillus pumilus* – **QST 2808, GB 34, BU F-33**

- QST2808 – nurseries, landscapes, greenhouse, rights of way
  - Sudden Oak Death Syndrome, others
  - "targeted for use in small-grain cereals, tree fruit, vegetables and vines."
- GB34 – soybean seed treatment fungicide
  - *Fusarium*, *Rhizoctonia*
- BU F-33 - seed treatment as ISR
  - Prohibited use on rice, potato, sweet potato, bean, cabbage, garlic, and pear

## Summary

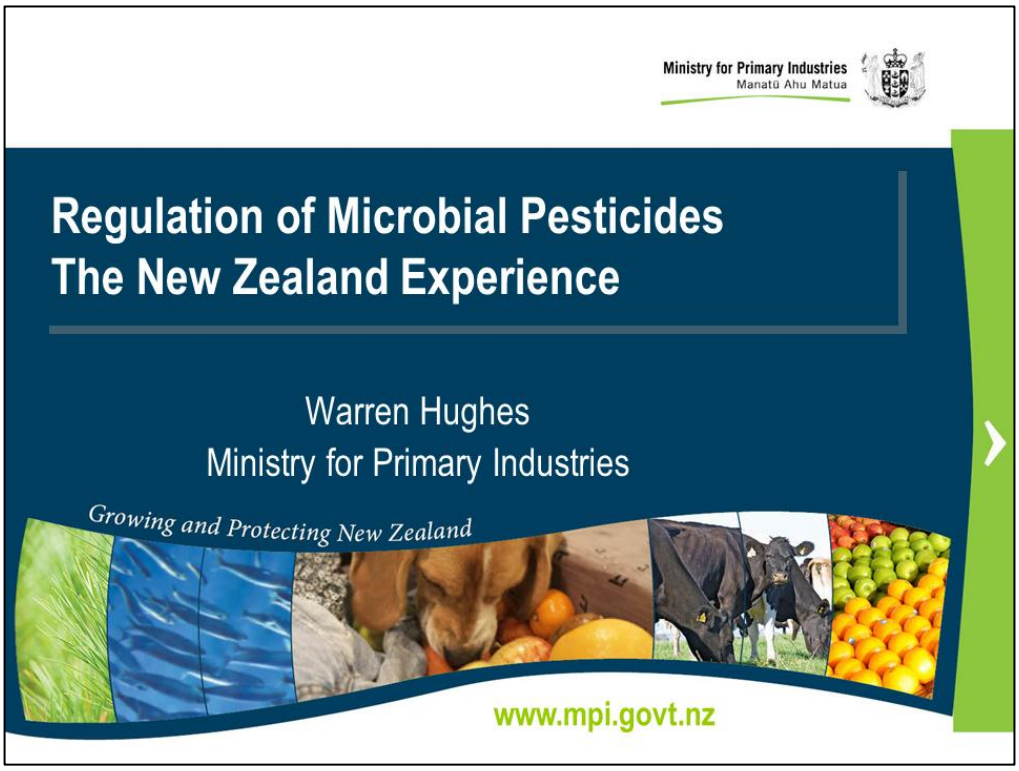
- Modification of some non-target organism guidelines may be in order
- Strain variation needs quantification / characterization with exposure scenarios considered in risk mitigation
- Novel mechanisms of biopesticide action will require consideration of guidelines and data requirements

## Useful Websites

- http://www.epa.gov/pesticides/biopesticides/regtools/oecd-der-template.html - Microbial OECD DER Templates
- http://www.epa.gov/oppbppd1/biopesticides/index.htm - Biopesticide regulation
- http://www.epa.gov/oppfead1/international/naftatwg/index.html - NAFTA Technical Working Group-Joint Reviews

***Regulation of Microbial Pesticides – The New Zealand Experience***

***By Warren Hughes***
***Ministry for Primary Industries, New Zealand***




## Overview

- Regulatory Oversight
- ACVM Act
- HSNO Act
- Regulatory Requirements
- Food Clearance
- NZ Issues

## Regulatory Oversight

- Two main pieces of legislation:
  - **Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997**
  - **Hazardous Substances and New Organisms Act 1996**
- Ministry for Primary Industries (MPI) administers ACVM Act 1997
- New Zealand Environmental Protection Authority (NZEPA) administers HSNO Act 1996

## Regulatory Oversight

- ACVM Act:
  - Register Trade Name Products
  - Manages risks to trade, animal welfare, agricultural security and public health
- HSNO Act:
  - Approves hazardous substances and new organisms
  - Manages health and safety and environment

## ACVM Act

- Manage risks to:
  - Public health
  - Trade in primary produce
  - Agricultural security
  - Animal Welfare
- Avoid non-compliant residues in food
- Ensure sufficient consumer information

**Always in relation to agricultural compounds**

## ACVM Act

- ACVM Act has direct interfaces with the **Food** Act*, the **Animal** Products Act*, the Animal **Welfare** Act*, the Biosecurity Act*, the **Medicines** Act and the Hazardous Substances and New Organisms (**HSNO**) Act

* Legislation administered by MPI

## ACVM Act 1997 - Definition

- **Definition of Agricultural Compound**
  - Substance, mixture, biological compound used to manage animals or plants applied directly, or to the surrounding purposes
  - For a listed purpose

## ACVM Act 1997 – Risk Thresholds & Criteria

- Public Health
  - Relates to health of people and community
  - Does not cover areas managed by other legislation
- Trade in Primary Produce
  - Domestic and Export
  - Loss of market access or non compliance residues

## ACVM Act 1997 – Risk Thresholds & Criteria

- Agricultural Security
  - Relates to Biosecurity Act
  - Management of undesirable pests
- Animal Welfare
  - Relates to Animal Welfare Act
  - Prevent unnecessary and unreasonable pain or distress

## ACVM Act 1997 - Dependencies

- Environmental Protection Authority **(EPA)** approval **is required** prior to registration of TNPs which contain hazardous substances or new organisms
- **Ministry of Health approval** is required for registration of TNPs which are prescription medicines
- MPI **set standards** for the registration of agricultural chemicals and are active in international forums (Codex, OECD).

## ACVM Act 1997 – Exempt from Registration

- Agricultural Compounds and Veterinary Medicines (Exemptions and Prohibited Substances) Regulations
  - Exempt groups of product from registration
  - Considered low risk
  - Generic requirements – fit for purpose, labeling and advertising, and manufacturing and importing

## HSNO Act 1996

- Purpose
  "To protect the environment and the health & safety of people & communities by preventing or managing the adverse effects of hazardous substances"

- Full lifecycle approach
  Setting controls on how substances are classified, contained, labeled, stored, used, transported or disposed of

## HSNO Act 1996 - Scope

Includes:

- Explosives
- Dangerous goods
- Toxic substances
- Pesticides
- Veterinary medicines
- Gases under pressure
- Household chemicals
- Cosmetics

Does not include:

- Manufactured articles (except explosives)
- Radioactive substances
- Infectious substances
- Human medicines
- Food ready to eat

## HSNO Act 1996 – Application and Approval Types

- Each formulation requires a separate approval for plant protection products
- Other Substances (industrial products and some veterinary medicines) may be covered by generic approvals – Group Standards
- Biocides that are not used in a dispersive manner on plants may be covered by group standards, so microbial biocides could fall under some group standard approvals
- Reassessments of existing approvals and amendments to group standards are processed in a similar process to the initial applications.

## ACVM Act 1997 - Requirements for Registration

### Information Requirements

- General information
- Chemistry and manufacture
- Residues
- Efficacy and Plant safety
- Labelling

See

http://www.foodsafety.govt.nz/industry/acvm/publications/information-requirements/index.htm

## ACVM Act 1997 - Registration Process

### Efficacy

- Good Agricultural Practice
  - Minimum to do the job
- Trials
  - Number trials not specified
  - Level Control = commercially acceptable level
  - Number of replications
  - Compare to standard and untreated control
  - Should reflect use pattern on label
  - Also measure yield and safety to crop

## ACVM Act 1997 - Registration Process

### Residue

- Reflects Use Pattern
- Trials
  - Number trials varies
  - Number of replications
  - Spraying, sampling etc based on OECD and CCPR documents
  - Analysis – GLP not mandatory

## ACVM Act 1997 - Registration Process

### Withholding Period

- Needs to fit with use pattern

- Main considerations
  - Grower practices
  - Time of application(s)
  - Days preferred over growth stage

## ACVM Act 1997 - Registration Process

**Labelling**

- Only **relevant** label content is approved
  - Directions for Use
  - Withholding Periods
  - Registrant Details

- Legal statements vs discretionary or advisory statements
- Registration Statement
- Statement about conditions of registration

*

## HSNO Act 1996 - Approval Process: Microbial Pesticides

**Toxicology**

- Data package cut down version for chemical-based pesticides
- Generally based on the USEPA requirements

**Environmental Fate**

- Data required for substance used in a widely dispersive manner, with a case by case assessment

**Ecotoxicology**

Aquatic ecotoxicity essential as an absolute minimum, with a case by case assessment

## HSNO Act 1996 - Approval Process

**Labelling**

- Based on GHS (revision 1) with NZ specific variations

## Food Clearance – Maximum Residue Limits

- **Legislation**
  - Maximum Residue Limits (MRLs) set under the Food Act 1981 as a Standard
- Key Features
  - Table of MRLs
  - Where no MRL exists, default of 0.1mg/kg
  - For imported food, Codex MRLs apply in addition to the NZ MRL Standard
  - Exemptions from MRLs

## Food Clearance – Maximum Residue Limits

- **Criteria**
  - Required when:
    - New active ingredient on any food commodity
    - New food commodity for existing active ingredient
    - Significant change in use (eg rate, timing) or Withholding Period for existing AI/food commodity

## Food Clearance - Hazardous Substances and New Organisms Act

- Sets End Points
  - Acceptable Daily Exposure (ADE)
    - Potential Daily Exposure (PDE) for Food
    - A percentage of the ADE
  - Environmental Exposure

## Food Clearance - Dietary Exposure Assessment

- Chronic Exposure :
  - Exposure over the life time of the residue in a commodity
- Acute Exposure:
  - Short term exposure
  - Consumption of 'hot' commodity

## Food Clearance – Maximum Residue Limits

- **Microbial Pesticides**
  - Covered by an exemption in the Standard

| | |
|---|---|
| *Microbial Pesticide Organisms (consisting of either; whole organism, organism organelles, organism spores or occlusion bodies and genetically modified serotypes and strains)* | Except where otherwise stated in this standard<br>Where an organism is registered under the Agricultural Compounds and Veterinary Medicines Act 1997 and intended for use as a plant compound, and;<br>Where organism leaves no quantifiable residue of toxins or metabolites exceeding that of expected background levels, and;<br>Where organism has been determined to be non-pathogenic or non-toxic to humans. |

## Food Clearance – Maximum Residue Limits

- Applicant has to satisfy MPI that the microbial pesticide complies with the Exemption
- No guidelines to assist Applicants – Case by Case
- Where exemption not appropriate need to set a MRL
  → an alternative option may be to amend the Microbial Pesticide Exemption

## NZ Issues

- Standard guidelines for chemical based pesticides
  – Applicability to microbial pesticides
- Applicants not making good cases to support extrapolation
  – Eg Genus v Species and strain
- Regulators should work more closely together

## NZ Issues

- Chemistry and Manufacturing
  - Identification of the micro-organism
    - Validation
    - International accepted method
    - Consistent nomenclature
  - Stability Data
    - Test Methods
    - Significant degradation – efficacy of formulation

## NZ Issues

- Toxicology
  - Identification of the micro-organism
  - Extrapolation rules
    - Between Strains
    - Same Strain but different source
  - Use of the organism with or without its culture medium is sufficient to address such toxicological concerns
  - Separate consideration of biotoxins should be undertaken in some cases

## NZ Issues

- Efficacy
  - Level of control
  - Claim eg aid in control