

# Biopesticide Program

## **Introduction and Purpose-Overview of the EPA Biopesticide Submission and Review Process**

Michael Braverman, Ph. D

Manager, Biopesticide and Organic Support Program



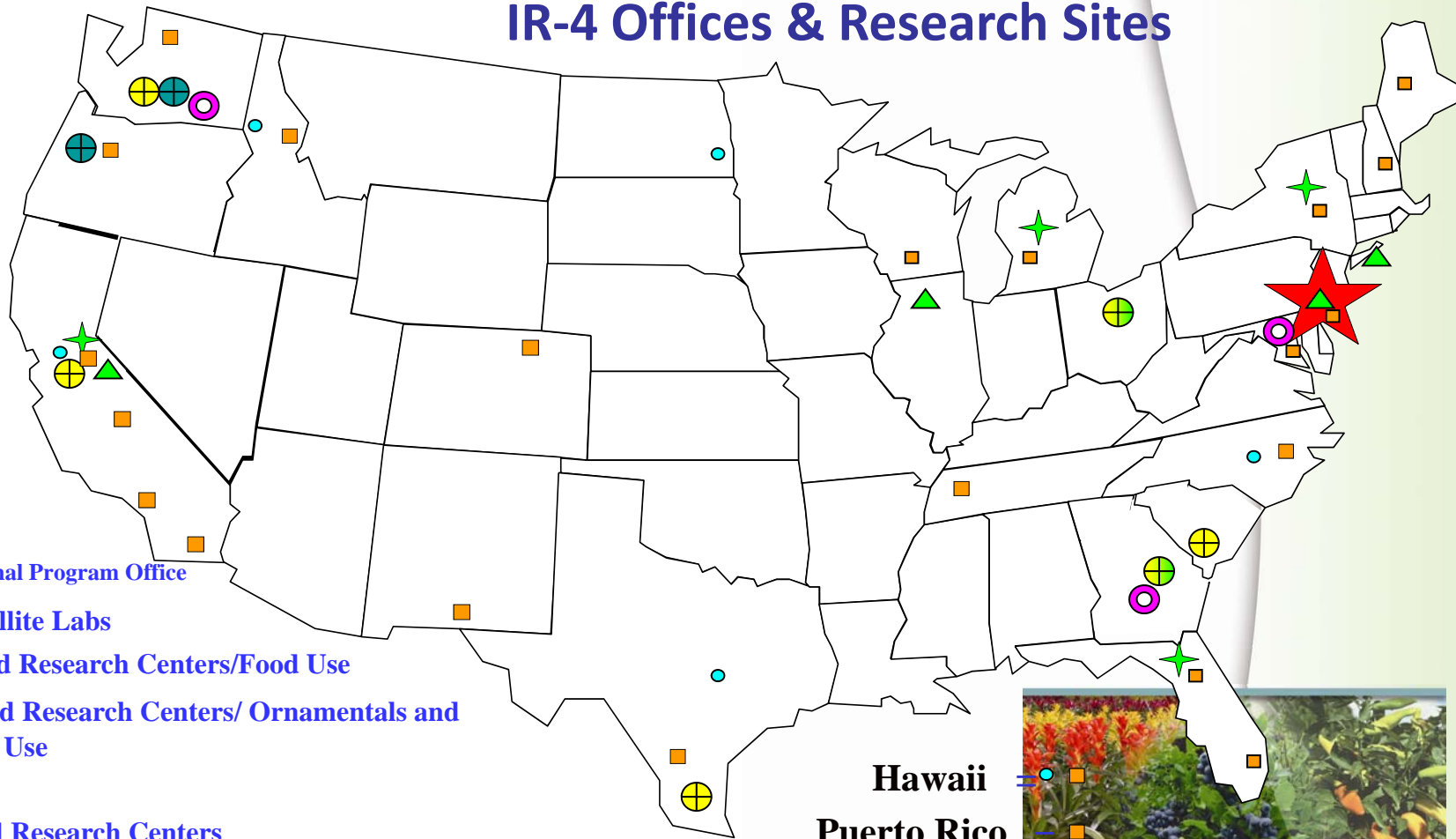
# INTRODUCTION

- **WHO?- What's the IR-4 Project**
- **WHAT?- Agenda**
- **WHERE?- Here!**
- **WHY?**
- **WHEN?- Now!**
- **HOW?**



# IR-4 – Interregional Research Project #4

## IR-4 Offices & Research Sites



-  **IR-4 HQ**
-  **IR-4 Regional Program Office**
-  **State Satellite Labs**
-  **State Field Research Centers/Food Use**
-  **State Field Research Centers/ Ornamentals and Non-food Use**
-  **ARS Labs**
-  **ARS Field Research Centers**
-  **ARS Field Research Centers**
-  **ARS Field Research Centers**

**Hawaii** =    
**Puerto Rico** =  



## GRAM

- **Grant program- University based efficacy trials**
- **Regulatory Assistance**

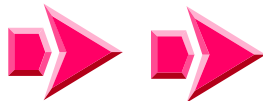


**USDA**

**IR 4**

**State Land Grant  
Universities**

**IR-4 is the only Publicly funded  
program that conducts research and  
submits petitions (Prepare dossiers)  
to Environmental Protection Agency  
(EPA) for tolerances/clearances**





## Regulatory assistance

Review Requests- **Public sector**

**New** Active Ingredients

Scientist, Small Business

Pre-registration meeting

Formatting documents

Government Forms

Label Modification

Communication, Negotiation

Toxicology review



# AF36/ Management of Aflatoxin

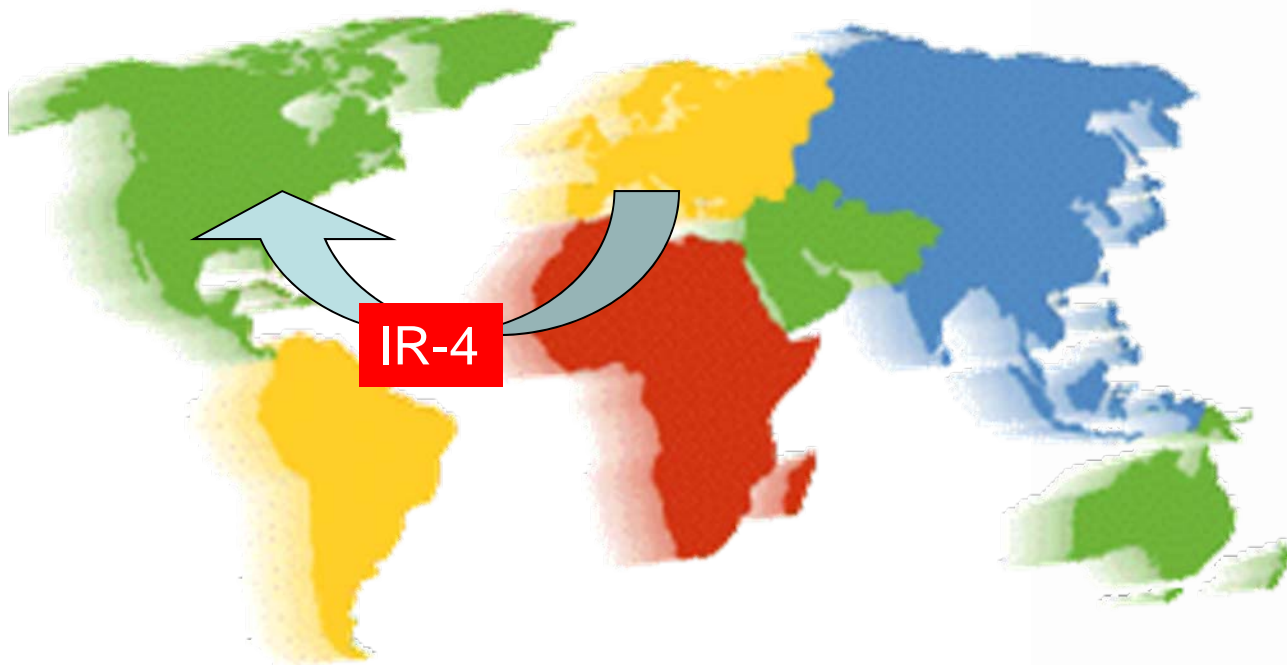
## Cotton- Pistachio- Corn



## US growers want new effective tools

- **IR-4 has submitted 30% of all new active ingredients to EPA over the last 2 years and had some involvement in about 74% of all new active ingredients.**

Germany  
Canada  
Italy  
Israel  
Colombia  
Netherlands  
Costa Rica



## WHAT?

- **What are Biopesticides?**
- **What will we be discussing?**



## What are Biopesticides (biological pesticides)?

- Certain types of pesticides derived from such natural materials, e.g., animals, plants, bacteria, viruses, protozoans, and certain materials.
- 3 biopesticide classes:
  - "Microbials
  - "Plant-incorporated protectants
  - "Biochemicals



## US EPA- Biopesticides

- **First country to recognize this category.**
- **Data requirements first codified in 1984.**
- **To bring ‘safer’ products to the market faster**
- **Tiered Data Requirements.**
  - “to ensure, to the greatest extent possible, that only the minimum data sufficient to make scientifically sound regulatory decisions will be required”



## US EPA- Biopesticides

- Biopesticides and Pollution Prevention Division-BPPD created as Pilot Project in 1994
- Became permanent Division of OPP in 1995



# Other countries that have established **biochemical** guidelines

- **Canada – 2007**
- **EU - very limited**
  - **Only for plant extracts**
    - Only those known to be food stuffs
    - Only under water extraction
  - **Pheromones – Accepting OECD guidance ?**



# Other countries that have established **biochemical** guidelines

- **Australia – 1993, reissued 2005**
  - “biologicals”:  
**Semiochemicals, PGRs & vitamins, Plant extracts**
  - **Limited host range; readily degradable**
- **Brazil – 2002; appears to accept whatever EPA has accepted as a biochemical**
  - **Tiered; revised in 2005**
- **Mexico**
  - **Botanicals, Pheromones, PGRs**



# Other countries that have officially established **microbial** guidelines

- **Canada**
- **Australia – 1993, revised 2005**
- **Brazil- First in 2002; Revised in March 2006**
- **Mexico - 2001**
- **EU – 2004**
- **OECD - 2004**
- **Central America – Still Draft**
- **India**
  - **All tiered, following the same basic principles**
  - **All will consider waiver rational**



## Exemptions from Regulation

- **40CFR152.20 - All Biocontrol Organisms (predatory insects, parasites, entomopathogenic nematodes) except**
  - **Microbial pesticides & Plant Incorporated Protectants**
    - Nematode symbiont policy: exempt unless bacteria grown separately and/or genetically engineered
- **152.10 - Products to attract pests for survey or detection and Physical Barrier Products**
- **152.25 - Specific exemptions**
  - **Pheromones used in pheromone traps**
  - **“Foods” used to attract pests**
  - **“Natural cedar” chips, panels, etc**
  - **“Minimal Risk Pesticides” aka “25b list”**
    - Many essential oils
    - Inerts must be on 4A inert list
    - All ingredients must be identified on label
    - No false and misleading claims on label
- **152.500 - Devices**



## Other Differences: EU & US

- **Antimicrobials (disinfectants) and other non-agricultural uses, e.g. mosquito control**
  - US/Canada: pesticides, EU: “biocides”
- **Growth regulators**
  - US: pesticides, Canada & EU: fertilizers
- **Naturally-occurring chemicals**
  - US: Biochemical Pesticides
  - EU currently only recognize “Semiochemicals”



## REBECA Project

[www.rebeca-de.net](http://www.rebeca-de.net)

- **The EU has formed a group to provide advice on improving their regulatory system for biopesticides**
- **Workshops completed**
  - **Balancing Regulation & Costs**
  - **Environmental Risk Assessment**
  - **Microbial Pesticides**
  - **Botanicals & Semiochemicals**
  - **Macrobials**



## Numbers of Biopesticides- USA

- >200 registered biopesticide active ingredients
- >700 products
- 250 products actively managed
- Bt =70-80% of the market



# Why?

- **Why am I here?**
- **Why are you here?**



## Why am I here?

- **Obama**



## Why am I here?

- **The Kenya Girl Guides Association-Girl Scouts**



## Why am I here?



## Why am I here?

- **Global Minor Use Summit-Lucy**
- **Peter and Ranajit**
- **USDA/FAS- Jason**



## Why are you here?-Why do you regulate?

- **Regulation-Balancing the responsibility**
- **How much regulation is the correct amount of regulation?**
- **Why do you regulate?**

Protect human **health**

Protect **environment**

Protect **farmers-safe**



## Why are you here?-Why do you regulate? Minor Crops

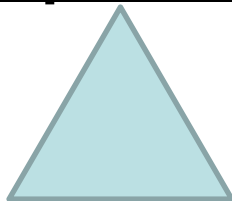
- **How many biopesticide registrations have been completed with minor crops in the last few years? Are growers still using old chemistry?**



Why are you here?-Why do you regulate?

**Human health – environment- growers**

**Old Chemistry- Biopesticides-Unregistered**



**Too much or too little regulation- Biopesticides developed by smaller companies don't get registered growers continue to use old chemistry. Human health, environment and farmers are not protected.**



## How- What are the Goals of the Workshop?

- **What are current regulations?**
- **How have regulations been applied to AF36?**
- **How can we utilize the experience of registration of AF36 to facilitate the registration of the African strains (IITA) of Atoxigenic *Aspergillus flavus*.**
- **Public health**
- **Cooperation-Region: What is the path forward for African strains?**



Environmental Protection Agency-EPA

# EPA Registration Overview and Risk Assessment





# EPA Staff- Thank You

Janet Andersen  
Driss Benmhend  
Teresa Downs  
Linda Hollis  
John Jamula  
Russ Jones  
John Kough  
Sharlene Matten  
Mike Mendelsohn  
Sheryl Reilly  
William Schneider  
Roy Sjoblad  
Zigfridas Vaituzis  
Chris Wozniak



## Registration Procedures

- Presubmission Activities (e.g., meetings)
- Application Package (e.g., Forms, Format, Studies, Label(s))
- Data Requirements
- Regulatory Coordination of the Package
- Science Review of Data [Risk Assessment]
- Regulatory Review Procedures [Risk Management]



## Presubmission Meeting

- Discuss active ingredient and product(s)
  - Classification
  - Use patterns
  - Potential data requirements
  - Relevant policies
  - Relevant rules/petitions
- Timeframe



## Regulatory Review

- Package must pass Front-end review before submission sent to Biopesticides and Pollution Prevention Division (**BPPD**) for review
- Submission logged into BPPD
- Directed to Microbial Pesticides Branch or Biochemical Pesticides Branch
- Submission assigned by to Regulatory Action Leader (RAL)- Primary contact
- RAL coordinates all regulatory activities



## Regulatory Review

- No obvious deficiencies or deficiencies have been addressed then RAL publishes:
- FR notice announcing receipt of new active ingredient (also EUP)
- FR notice of filing for tolerance petition Public comment period (typically 30 days)
- Public docket established



## Preliminary Science Review – Start Risk Assessment

- RAL works with Branch Chief/Team Leader to select appropriate science reviewers
- RAL sends appropriate disciplinary reviews to science reviewers
- Preliminary science screen of submission is done (typically done within 1-3 months)



## Preliminary Science Review – Risk Assessment

- Science reviewer(s) communicate deficiencies to RAL
- RAL communicates “deficiency letter” to registrant (75 days to address issues related to submission package (PR Notice 75-4), additional data needs.



## Full Science Review – Risk Assessment

- Science reviewers perform primary (and secondary data evaluation after preliminary screen completed [Write Data Evaluation Records, Risk Assessment Documents] [Some work done by contractors])
- RAL corresponds with the registrant on additional data needs, questions, concerns etc. during the course of science review
- Timeline for science review for new active ingredient – 6 to 12 months (add several months for any additional submissions)



## More Regulatory Review, cont'd

- Labels (check PR Notices)
- CSF
- Inerts
- Public Interest Finding (if a conditional registration)



## More Regulatory Review cont'd

- Biopesticide Registration Action Document (BRAD)
- Scientific and regulatory review of new active ingredient (and products) [Integrated risk assessment and risk management]
- Plain English Fact (PEF) Sheet
- Prepare Final Rule for tolerance establishment or exemption (if food use for new active ingredient or 1st food use)



## Regulatory (Risk) Management Review Steps

- Risk management, mitigation, and policy decisions made by Science Reviewers, RAL, Team Leader, Branch Chief, Division Director, Office of General Counsel (OGC), Office Director/Deputy Office Director, Assistant Administrator
- BRAD review by science reviewers, BPPD management, OGC



## Regulatory (Risk) Management Review Steps cont'd

- Decision Memorandum, BRAD, labels, Fact Sheet are routed through BPPD management, OGC, Director for concurrence and sign-off
- Director signs-off BRAD and Final Rule
- Notice of Registration for DD's signature



## Regulatory (Risk) Management Review Steps cont'd

- Final Tolerance Rule published in the Federal Register (FR)
- Notice of Registration of new active ingredient published in the FR
- If Experimental Use Permit (EUP), notice of issuance published in the FR
- Timeframe for RAL activities post-science review completion 2-3 months
- Total Timeframe: ave. 18 months



## Additional Post-Registration Review Process

- RAL mails/faxes Registration Notice and stamped label to registrants [For EUP: EPA Regions]
- RAL has administrative duties to close-out the submission record(s)



## Tolerance Petition

- Is new active ingredient for food or feed use?
- Is new use of old active ingredient for 1<sup>st</sup> food/feed use?
- If yes, a tolerance petition (exemption from the requirement of a tolerance) must be submitted
- Registrant must pay tolerance fee (or have waiver granted) prior to review by BPPD- IR-4 Exempt from all fees



## Data Requirements – Public Interest Finding

- Required for new active ingredient having a conditional registration in the absence of certain required data.
- Agency must determine that use of the new chemical during the period of the conditional registration will be in the public interest.
- **Section 18-** For emergency use by farmers
- **EUP- Experimental Use Permit-** Large scale research



# EPA Risk Assessment of Biopesticides



## Why do you regulate?

**Human health – environment- growers**

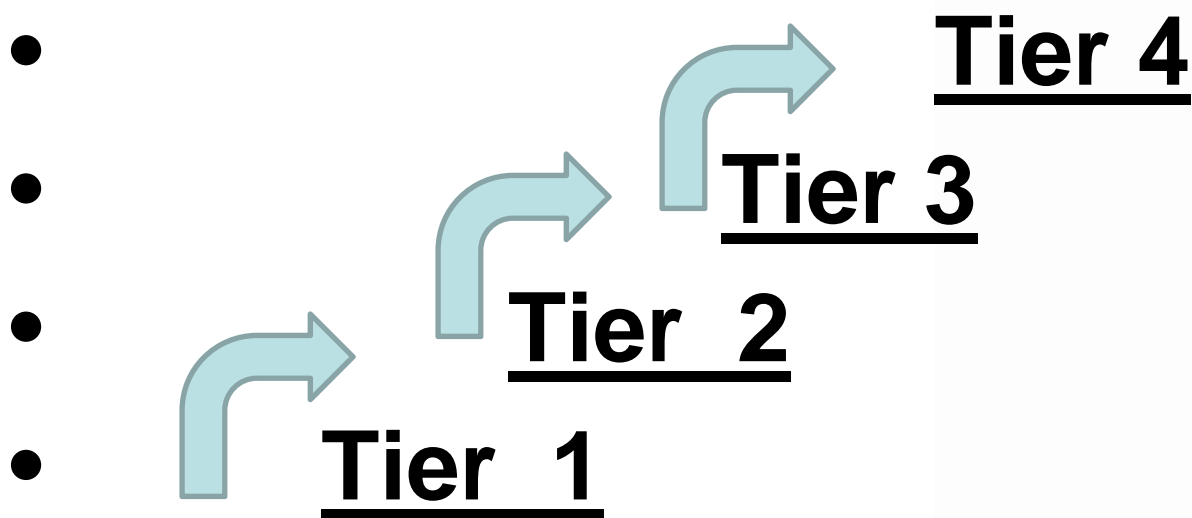
**Old Chemistry- Biopesticides-Unregistered**

**Too much or too little regulation- Biopesticides developed by smaller companies don't get registered growers continue to use old chemistry. Human health, environment and farmers are not protected .**



## Tier Testing

- **Toxicology testing is primarily at the Acute-Tier 1 Level and there are additional levels **if needed.** Have they been needed?**



# Microbial Pesticide data survey 1997 – 2004 Studies that were actually required

	Bacteria (8)	Fungi (9)	Granulosis Virus (1)
Product analysis	78%	67%	75%
Residue Chemistry	3%	1% (1 study)	0%
Toxicology Tier I	51%	51%	27%
Toxicology Tier II	0%	0%	0%
Non-target Organisms Tier I	20%	24%	0%
Environmental Fate, Subchronic & Field studies Tiers II, III & IV	0	0%	0%

# Biochemical data survey 1997 – 2004

## Studies that were actually required

	PGR & IGR (6)	SCLP (5)	Other Pheromones (4)	Repellents (8)	Other Biochemicals (26)
Product analysis	61%	88%	80%	74%	63%
Residue Chemistry	26%	12%*	12%*	12%*	12%*
Human Health Tier I	65%	0%	27%	34%	28%
Human Health Tier II	27%	0%	0.3% (1 study)	17% Creams	0%
Human Health Tier III	0%	0%	0%	0%	0%
Non-target Organisms Tier I	17%	0%	0%	9%	15%
Environmental Fate Tier II	0%	0%	0%	0%	0%
Field studies Tier III	0%	0%	0%	0%	0%

## What is risk?

EPA Risk = Hazard X Exposure

EU Risk = Hazard X Exposure



## Exposure from use versus routine exposure

Exposure from used as a pesticide- aerial liquid application(plane) versus a solid inside a child proof container.

Routine exposure- Oral-Active ingredient found in food, Dermal- skin cream, Inhalation-normally found in air, Bees- ingredients found in nectar, Avian-used in chicken feed.

Waivers- Waivers are scientifically valid information that are used to satisfy a data requirement.

Dose makes the poison(Exposure from use)- Routine dose(Routine exposure) probably means its not a poison.



## US EPA- Biopesticides

- **First country to recognize this category.**
- **Data requirements first codified in 1984.**
- **To bring ‘safer’ products to the market faster**
- **Tiered Data Requirements.**
  - “to ensure, to the greatest extent possible, that only the **minimum** data sufficient to make **scientifically sound** regulatory decisions will be required”



- The Tier I screening maximum hazard dose (MHD) approach to environmental risk assessment is based upon some factor (10X - 100X) times the maximum amount of active ingredient expected to be available to terrestrial and aquatic non-target organisms in the environment (the Estimated Environmental Concentration – EEC)



- **For Tier I screening purposes the maximum label application rate is used as the EEC.**
- **Tier I tests serve to identify potential hazards and are conducted in the laboratory on representative species at high dose levels which increase the statistical power to test the hypotheses.**



## Maximum Hazard Dosage Levels

- In Tier I, test organisms should be exposed to a maximum hazard/maximum challenge concentration of the organism



## Maximum Hazard Dosage Levels

- For avian toxicity testing, dose is a function of some safety factor that is based in part on the route of administration and the organism concentration in the AI



## Maximum Hazard Dosage Levels

- Oral = 5.0 mL/kg bw × Weight of bird (kg)
- Pulmonary = 0.2 mL/kg bw × Weight of bird (kg)
- Intravenous = 0.5 mL/kg bw × Weight of bird (kg)
- Intraperitoneal = 2.0 mL/kg bw × Weight of bird (kg)



## Maximum Hazard Dosage Levels

- For aquatic fish, invertebrates, plants:
  - $10^6$  viable units of organism/mL of water; or
  - 1000X expected environmental concentration, immediately following a direct application at the maximum label rate to a 6-inch (15-cm) layer of water, whichever is greater or achievable (depending on water quality)



## Maximum Hazard Dosage Levels

- For terrestrial insects, invertebrates, microorganisms:
  - $10^6$  active units of the organism per gram of soil; or
  - 1000 times the expected environmental concentration of the organism, immediately following a direct application at the maximum label rate to a 15-cm layer of soil, whichever is greater or achievable



## Maximum Hazard Dosage Levels

- For topical exposure tests, exposure to a concentration that is equivalent to 100X the maximum application rate



## Maximum Hazard Dosage Levels

- For artificial dietary exposures, dose should be equivalent to the maximum concentration found in the target; or feed diet of maximally infected target
- In cases where it is difficult to determine the maximum concentration in the target, feed a diet treated with an application of the organism equivalent to 100X the maximum label rate



- **Failing the Tier I (10X – 100X Estimated Environmental Concentration-EEC) screening does not necessarily indicate the presence of an unacceptable risk in the field but it triggers the need for additional testing.**
- **50% mortality effect at the MHD is taken to indicate minimal risk.**



- **Greater than 50% mortality does not necessarily indicate the existence of unacceptable risk in the field, but it does trigger the need to collect additional dose-response information and a refinement of the exposure estimation (Tier II testing) before deciding if the risk is acceptable or unacceptable.**



- **The number of doses and test organisms evaluated must be sufficient to determine an LD<sub>50</sub> value and, when necessary;**
  - **the LD<sub>50</sub> (infectious dose), Lowest Observed Adverse Effect Concentration (LOAEC)**
  - **No Observed Adverse Effect Level (NOAEL)**
  - **or reproductive and behavioral effects such as feeding inhibition, weight loss, etc.**



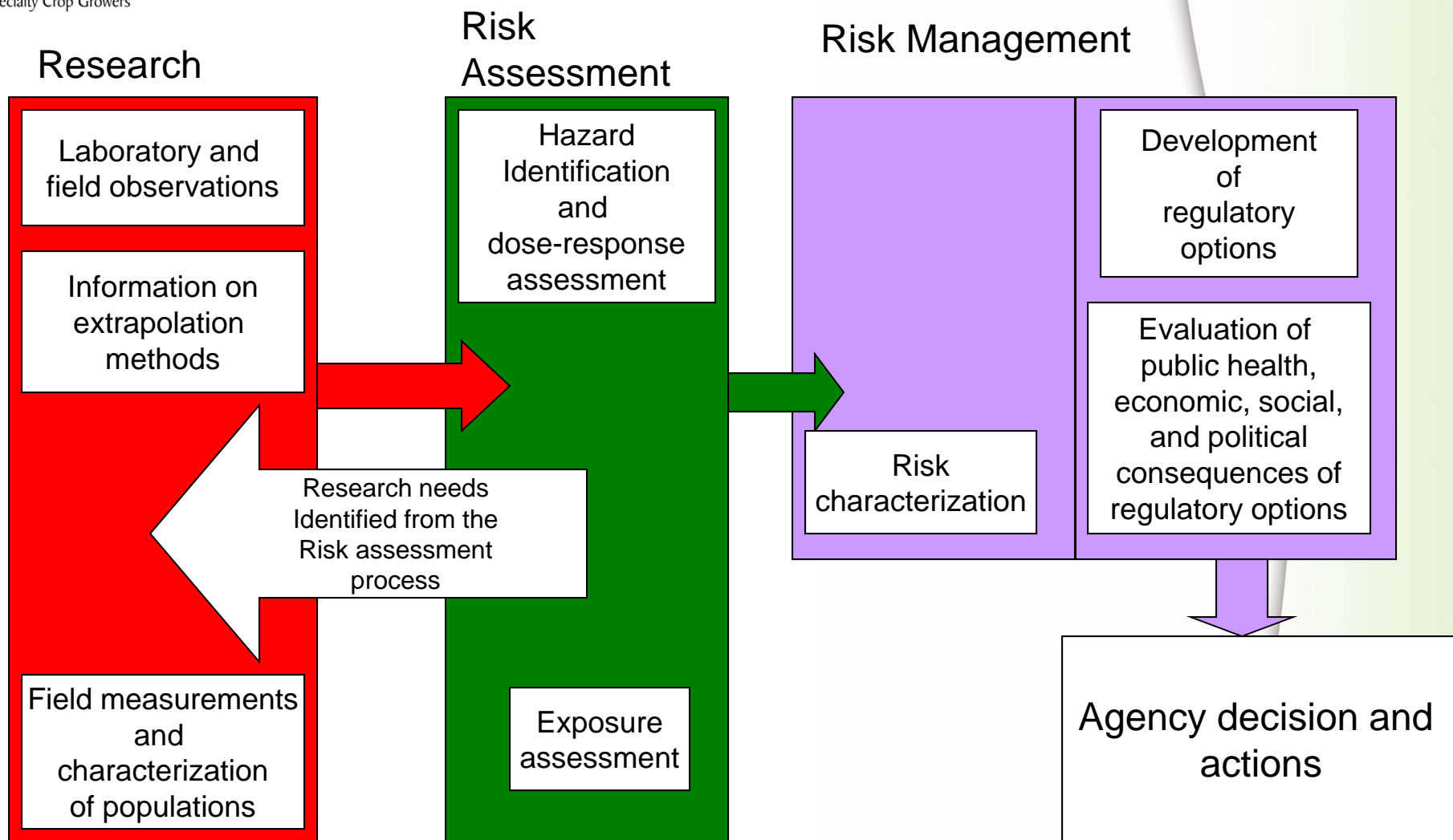
- **Risk assessment is made by comparing the LOAEC to the EEC.**
- **When the EEC is lower than the LOAEC, a no risk determination is made.**



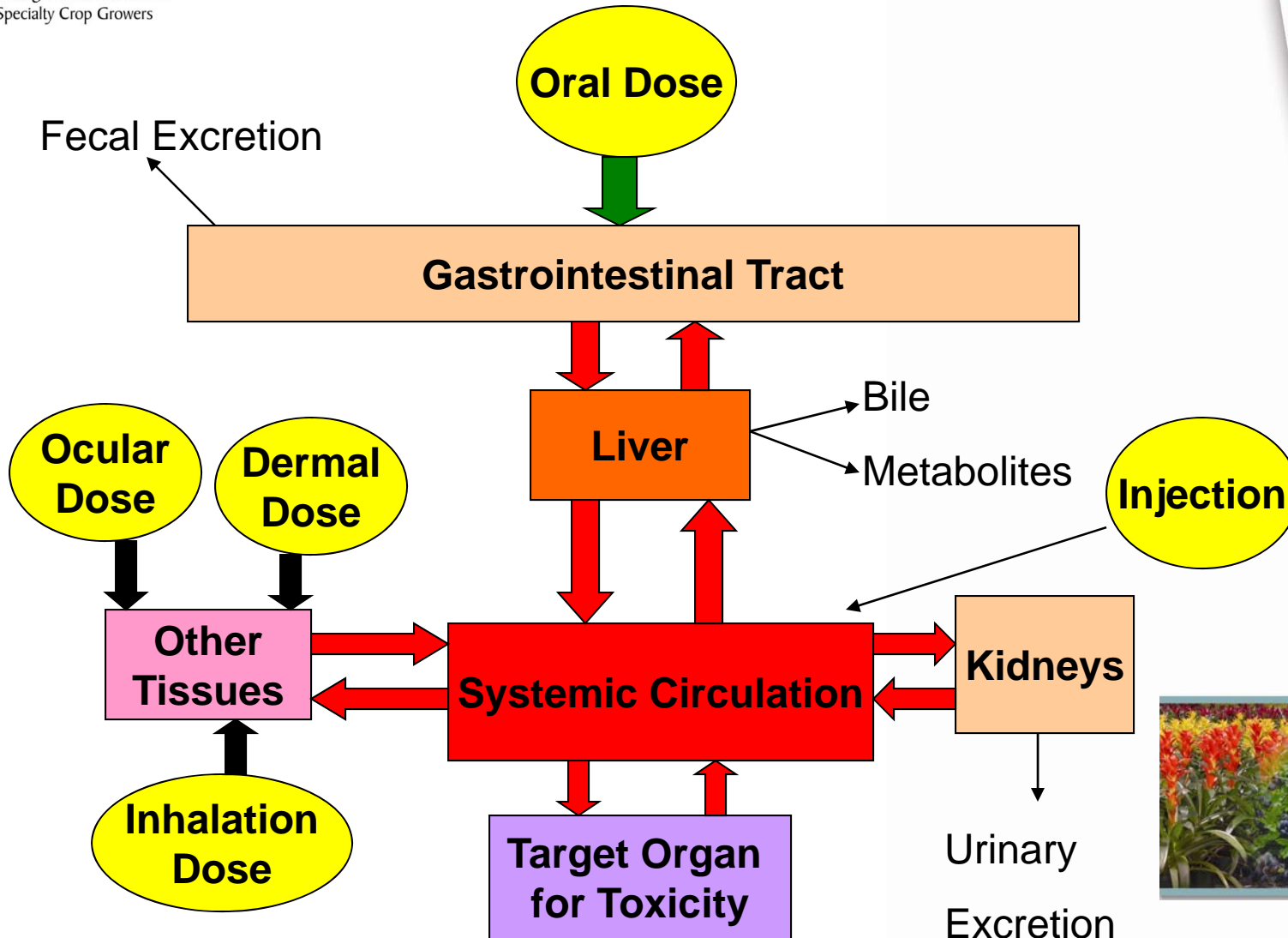
- **In the event that there are adverse effects at a dose equivalent to the EEC, labeling language indicating a hazard to the sensitive non-target species is required, or higher Tier simulated or actual field testing may be performed to determine if the adverse effect observed in the laboratory is also present in the field.**



## Elements of Risk Assessment and Risk Management



## Routes of Administration and Exposure



## General Categories of Animal Observations in Acute, Subchronic, and Chronic Toxicity Studies

### Body weight and food consumption



### Observation and handling

To evaluate:

Skin and fur

Eyes and mucous membranes

Respiratory system

Circulatory system

Autonomic and central nervous  
systems

Motor activity

Behavior

### Clinical laboratory tests

Blood biochemistry

Hematology

Urinalysis



### Necropsy and histopathology

Terminal body weight

Organ weights

Gross pathology

Histopathology



## Weight of Evidence Analysis

### Animal Evidence

#### Increase Evidence-Better study

Number of independent studies with consistent results

Same endpoint across species and among compounds with similar chemical structures.

#### Multiple observations

- Species
- Sites
- Sexes

#### Severity and progression of lesions

- Early in life/tumors
- Dose response relationships
- Lesion progression
- Uncommon tumor

Route of administration like human exposure

#### Decrease evidence- Less confident

Single study  
Inconsistent results

Single site, species, and sex

Benign tumors only

High background incidence of tumors

Route of administration unlike human exposure

## Weight of Evidence Analysis

### Total Evidence

#### Increase Weight

Evidence of human causality

Evidence of animal effects relevant to humans

Comparable metabolism and toxicokinetics between species

Mode of action comparable across species

#### Decrease Weight

Data not available or do not show causality

Data not available or not relevant

Conflicting data

Metabolism and toxicokinetics not comparable

Mode of action not comparable across species

## Identifying a NOAEL

### NOAEL

The highest dose level that does not produce a significant increase in an adverse effect above the background level as defined by an untreated (control) group in a study.

### SIGNIFICANCE

BIOLOGICAL and STATISTICAL criteria should be used together to define significance of a toxicity endpoint.

### INTERPRETATION DEPENDS ON UNDERSTANDING:

The difference between biological and statistical significance

The nature and value of different types of data

Causality

### FACTORS TO CONSIDER

- The necessity of working with small sample sizes
- Data may have to be censored (i.e. some animals must be eliminated from consideration because they died before observation of an endpoint can be made).
- Doses, routes of administration, duration of treatment, and nature of the observations made.
- There may not be time to repeat an experiment to determine if the results can be reproduced.



## Establishing a Reference Dose (RfD)

A Reference Dose (RfD) or a Reference Concentration (RfC) is determined from a NOAEL or NOAEL and uncertainty factors (UF) or modifying factors (MF)

$$\text{RfD} = \text{NOAEL} / \text{UF} \times \text{MF}$$

### UNCERTAINTY FACTORS

- |      |  |
|------|--|
| 10   | Intraspecies variation   |
| 10   | Interspecies extrapolation (animal to human)                               |
| 10   | Sensitivity of infants and children  |
| 3-10 | Extrapolation from a short-duration study to a chronic exposure situation. |

Study limitations (e.g. a LOEL is determined at the lowest dose tested, too few animals for adequate evaluation, etc.).

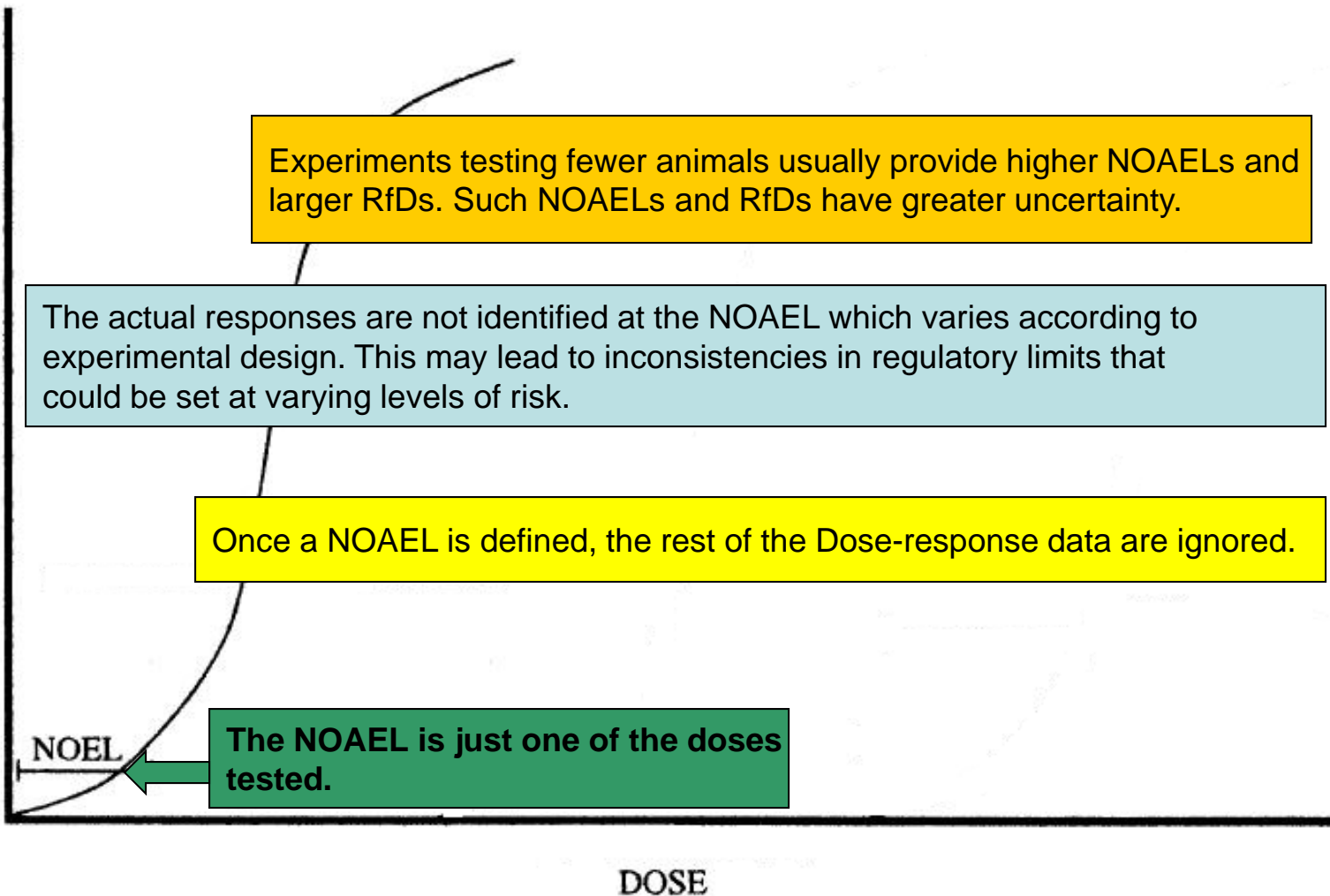
### MODIFYING FACTORS

Modifying factors can be used to adjust the uncertainty factors if data on mechanisms of action, pharmacokinetics and relevance of the animal responses to human risk are available, and they can justify the modifications.



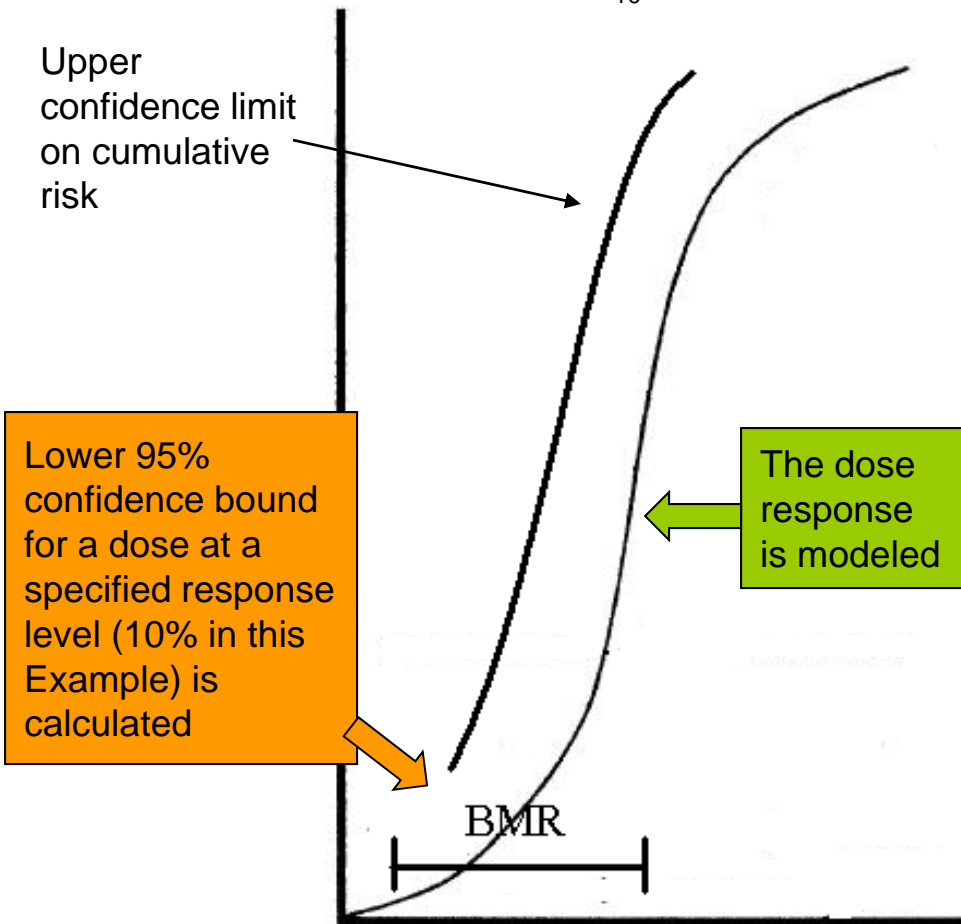
## Criticisms of the Use of the NOAEL Approach in Risk Management

CUMULATIVE RESPONSE (%)



## The Benchmark Dose: An Alternative to the NOAEL in Defining a Reference Dose

$$RfD = BMD_{10} / UF \times MF$$



UFs and MFs are the same or less than those for determining the RfD from a NOAEL. They can be lower because of increased confidence in the response and the use of a lower bound of the dose which recognizes experimental variability.

The BMD method accounts for the full dose-response curve instead of focusing on the NOAEL alone.

The BMD method includes an estimate of the variability (confidence limits).

Responses within the experimental range rather than extrapolation beyond that range are used.

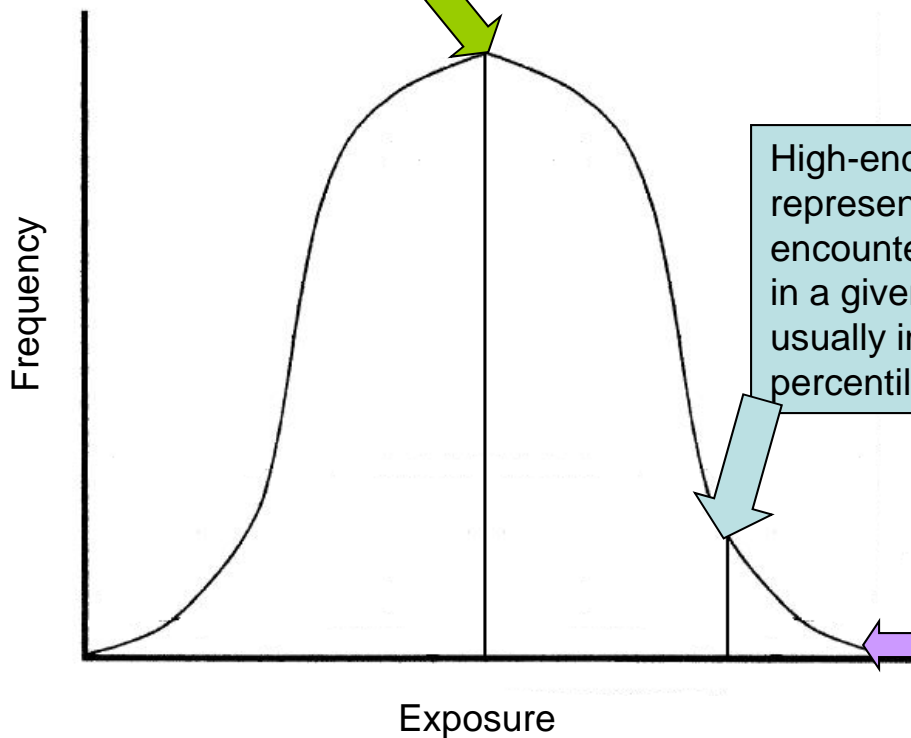
A consistent response level across studies can be used.

DOSE

# Quantitative Methods for Estimating Exposure

A central estimate of exposure for an individual in the population is the lifetime average daily dose of LADD

$$\text{LADD} = \frac{\text{concentration of toxicant in exposure media} \times \text{contact rate} \times \text{contact function} \times \text{exposure duration}}{(\text{body weight}) (\text{lifetime})}$$



High-end exposure estimates represent “plausible” exposures encountered by most individuals in a given population. They are usually in the upper ninetieth percentile of the exposure.

The LADD exposure estimate is appropriate for long-term endpoints, but determining a daily exposure value may be more appropriate for other end-points (e.g. developmental toxicity).

The theoretical upper bound estimate of exposure is a hypothetical maximum exposure estimate that exceeds that any other individual in the population is likely to experience.

## Toxicity Studies Providing Endpoints for Nondietary Risk Assessment

Acute Endpoints (1 day)

Short Term Endpoints (1 to 7 days)

Intermediate Term Endpoints (7 days to a few months)

Long Term Endpoints (a few months to a lifetime)

Dermal LD<sub>50</sub> Irritation

21- & 90-day dermal

0-27% Biochem  
0% Microbial

21- & 90-day dermal

Dermal Absorption Study in the Rat  
OR  
Compare Oral & Dermal Studies to Estimate Dermal Absorption

Oral Study  
(usually developmental or subchronic feeding study)

Dermal Study  
(usually the 21-day dermal toxicity study)

For the comparison of two studies to determine dermal absorption, they must have the following attributes in common:

They must be conducted in the same species.

A NOEL from one study should be compared with a NOEL from the other (i.e., NOEL is not equal to a LOEL).

The endpoint defining the LOEL in each study must be the same as that in the other.

## Items to Include in a Risk Characterization

- **Primary conclusions about hazard, dose-response, and exposure including equally plausible alternatives**
- **Nature of key supporting information and analytical methods**
- **Risk estimates and their attendant uncertainties, including key assumptions when data are uncertain or missing**



## Items to Include in a Risk Characterization

- **Statement of the extent of extrapolation of risk estimates from observed data to exposure levels of interest (i.e. margins of exposure) and its implication for certainty or uncertainty in qualifying risk**
- **Significant strengths and limitations of the data and analyses, including any major peer reviewer's issues**



## Items to Include in a Risk Characterization

- **Appropriate comparison with similar risk analyses or common risks with which people may be familiar**
- **Comparison with assessment of the same problem by another organization**



## Waiver Requests

- EPA waives data requirements on a case-by-case basis, depending on use-pattern and nature of the organism
- Requests for data waivers must be submitted in writing and based on sound scientific reasoning



## Waiver Requests

- **Waiver requests must:**
  - Explain why the data requirement should be waived
  - Describe any unsuccessful attempts to generate the required data
  - Furnish any other information that may support the request
  - Suggest alternative means of obtaining data to address the underlying concern of the requirement



## Published Literature

- All requirements must be supported by relevant data and/or referenced scientific literature; legible copies of the papers must be submitted
- If assumptions on human health and safety rely heavily on published scientific literature, the relationship of active ingredient to the proposed active ingredient for registration must be well described



## Published Literature

- Bridging data to support claims of safety may be acceptable in some cases
- Information on the effects of inerts/formulants must also be addressed (e.g., MSDSs)



## Exposure Assessment

- Depends on use-pattern and worker/bystander exposure potential used to develop product label precautionary statements, guidance (e.g., protective equipment) and decontamination procedures
- Additional data only required if existing information inadequate to address potential safety concerns related to pathogenicity, hypersensitivity, dermal irritation



## Food and Feed Residue Studies

- A Tolerance/Maximum Residue Limit will not be set for an organism if:
  - Characterization data indicate the lack of potential for known mammalian toxin(s)
  - Acute oral infectivity/toxicity testing reveals no significant human health concern



## Food and Feed Residue Studies

- If a mammalian toxin is present, the product will be subject to the same data requirements as a chemical pesticide to establish a tolerance/MRL



## Approach to Testing

- Data requirements aimed at assessing impact of organisms on nontarget organisms and fate/expression in the environment are divided into 4 tiers, with progression dependent on lower tier results
- Data requirements outlined in EPA OPPTS 885 Series Guidelines



## Approach to Testing

- Tier I reflects a maximum hazard approach to testing on non-target organisms
  - Negative results from such tests provide high degree of confidence that no unreasonable/unacceptable adverse effects will likely occur from actual use of organisms



## Approach to Testing

- Tier I:
  - Avian oral
  - Avian pulmonary/inhalation/injection
  - Wild mammals
  - Freshwater fish
  - Estuarine/marine fish
  - Terrestrial and aquatic arthropods (bees)
  - Nonarthropod invertebrates
  - Nontarget microorganisms
  - Terrestrial and aquatic nontarget plants



## Approach to Testing

- If adverse effects observed at maximum doses, then sequentially lower doses should be tested at Tier I to determine an LD50, LC50 or ID50; triggers Tier II testing



## Data Waivers

- Agencies may waive data requirements in response to written requests where:
  - Not possible to generate data
  - Or data not useful in risk evaluation
- Waiver request must address underlying concern behind the requirement with information other than actual test data



## Data Waivers

- Ecological exposure data showing organism cannot survive/persist in the environment can be used to support waiver requests from some Tier I requirements, depending on proposed use pattern
- Encourage early discussion with Agencies on preparation of waiver requests



## Selection of Nontarget Test Species

- Specific selection organisms should be considered to identify groups of NTOs that may be needed to assess the pathogenic/toxicological hazard(s) of the organism:
  - Closely related endangered species to target pest species and other known/suspected hosts



## Selection of Nontarget Test Species

- Known/suspected of being able to be infected by the organism
- Susceptible to pathogens closely related taxonomically to the organism



## Selection of Nontarget Test Species

- Likelihood of exposure to the organism based on use pattern and method of application
- Obviously expected to be exposed to high concentrations of the organism, e.g., species likely to prey upon or scavenge the diseased target host



## Test Substance

- Organism can be applied in any one of a combination of naturally existing forms
  - Use most infectious form whenever infectivity is the primary hazard of concern
  - Use a form of the organism in which the toxin is produced/present when toxicity (e.g. a microbial toxin) is the hazard of concern



## Test Substance

- Testing AI applies in all tests except simulated and actual field studies where use of formulated product applies



## Age of Test Organisms

- Recommend use of immature birds, mammals and fish
  - Immature animals potentially more susceptible to infection and possibly to effects of any toxin(s) produced by organism



## Age of Test Organisms

- Insects, invertebrates, and plants
  - Test species should be treated either at the time (lifestage) of most likely exposure in the field or at the time of most likely susceptibility to organism



## Maximum Hazard Dosage Levels

- In Tier I, test organisms should be exposed to a maximum hazard/maximum challenge concentration of the organism



## Maximum Hazard Dosage Levels

- For avian toxicity testing, dose is a function of some safety factor that is based in part on the route of administration and the organism concentration in the AI



## Maximum Hazard Dosage Levels

- Oral = 5.0 mL/kg bw × Weight of bird (kg)
- Pulmonary = 0.2 mL/kg bw × Weight of bird (kg)
- Intravenous = 0.5 mL/kg bw × Weight of bird (kg)
- Intraperitoneal = 2.0 mL/kg bw × Weight of bird (kg)



## Maximum Hazard Dosage Levels

- For aquatic fish, invertebrates, plants:
  - $10^6$  viable units of organism/mL of water; or
  - 1000X expected environmental concentration, immediately following a direct application at the maximum label rate to a 6-inch (15-cm) layer of water, whichever is greater or achievable (depending on water quality)



## Maximum Hazard Dosage Levels

- For artificial dietary exposures, dose should be equivalent to the maximum concentration found in the target; or feed diet of maximally infected target



## Maximum Hazard Dosage Levels

- For terrestrial insects, invertebrates, microorganisms:
  - $10^6$  active units of the organism per gram of soil; or
  - 1000 times the expected environmental concentration of the organism, immediately following a direct application at the maximum label rate to a 15-cm layer of soil, whichever is greater or achievable



## Maximum Hazard Dosage Levels

- For topical exposure tests, exposure to a concentration that is equivalent to 100X the maximum application rate



## Maximum Hazard Dosage Levels

- For artificial dietary exposures, dose should be equivalent to the maximum concentration found in the target; or feed diet of maximally infected target
- In cases where it is difficult to determine the maximum concentration in the target, feed a diet treated with an application of the organism equivalent to 100X the maximum label rate



## Components of the Risk Assessment (I)

- Chemistry of the active ingredient
  - Mode of action
  - Potential mutagen/carcinogen
  - Persistence
  - Environmental fate
- Product Formulation
  - Liquid
  - Granular
  - Powder/dust



## Components of the Risk Assessment (II)

- Application Method/Rate/Timing
  - Foliar, soil, fog
  - Amount per application per unit area
  - Applications per growing season/calendar year
- Use Site(s)
  - Terrestrial, aquatic
  - Agricultural, natural area, urban/homeowner
  - Target pest(s)



## Components of Risk Assessment (III)

- Requirement for Other Data/Information on a Case-by-Case Basis
- Chemistry/Toxicity of Other (Inert) Ingredients in product Formulation



## The Risk Assessment (I)

- Risk Assessment Components Used To:
  - Assess exposure to non-targets and fate in environment
  - Assess adverse effects/toxicity to nontargets



## The Risk Assessment (II)

### Biochemical Pesticide Data Requirements

- 40 CFR 158.690 (d) Non-Target Organism, Fate, and Expression
- Tiers I, II, and III



## The Risk Assessment (III)

- Tier I (Acute Effects on Non-Targets) Study Guidelines
  - Avian Acute Oral
  - Avian Dietary
  - Freshwater Fish LC50
  - Freshwater Invertebrate LC50
  - Non-Target Plant Studies
  - Non-Target Insect Studies



## The Risk Assessment (IV)

- Tier I (Acute Effects on Non-Targets) Study Guidelines
  - Subdivision M Series 154-6 to 154-11
  - OPPTS Series 850



## The Risk Assessment (V)

### Guideline Studies vs. Waiver Requests

- Guideline Studies – Unambiguous
- Waiver Requests
  - Accompanied by quantitative data
  - Scientifically credible rationale
  - **No data needed if rationale demonstrates a lack of exposure to non-target(s)**



## The Risk Assessment (VI)

- If One or More Tier I Studies Demonstrate Severe Adverse Effects/Toxicity, Higher Tier Studies Will Be Triggered



## The Risk Assessment (VII)

Listed but has never been required

- Tier II Studies – Environmental Fate
  - Volatility
  - Leaching
  - Adsorption/desorption
  - Octanol/Water Partition Coefficient.
  - UV absorption
  - Hydrolysis
  - Aerobic soil/aquatic metabolism
  - Soil/aquatic photolysis



## The Risk Assessment (VIII)

Listed but has never been required

- Tier III Studies – Long-term and/or More Detailed Non-Target Studies
  - Terrestrial wildlife Testing
  - Aquatic Animal Testing
  - Non-Target Plant Studies
  - Non-Target Insect Studies



## The Risk Assessment (IX)

- 40 CFR 158.690(d) Non-Target Organism, Fate, and Expression Data Requirements



## Toxicity Categories- Relationship to LD<sub>50</sub> levels

### **ACUTE ORAL - LD<sub>50</sub> levels**

**Category I Up to and including 50 mg/kg**

**Category II > 50 thru 500 mg/kg**

**Category III > 500 thru 5000 mg/kg**

**Category IV > 5000 mg/kg**



## Toxicity Categories

### **ACUTE DERMAL**

**Category I Up to and including 200 mg/kg**

**Category II > 200 thru 2000 mg/kg**

**Category III > 2000 thru 5000 mg/kg**

**Category IV > 5000 mg/kg**



## Toxicity Categories

### **ACUTE INHALATION**

**Category I Up to and including 0.05 mg/liter**

**Category II > 0.05 thru 0.5 mg/liter**

**Category III > 0.5 thru 2 mg/liter**

**Category IV > 2 mg/liter**



## Toxicity Categories

### Primary Eye Irritation

**Category I Corrosive (irreversible destruction of ocular tissue) or corneal involvement or irritation persisting for more than 21 days**

**Category II Corneal involvement or other eye irritation clearing in 8-21 days**

**Category III Corneal involvement or other eye irritation clearing in 7 days or less**

**Category IV Minimal effects clearing in less than 24 hours**



## Risk Mitigation- Label

### **SIGNAL WORD**

- **Toxicity Category I DANGER**
- **Toxicity Category II WARNING**
- **Toxicity Category III CAUTION**
- **Toxicity Category IV None Required**
- **Based on single most toxic category**
- **Precautionary statements**



## Risk Management

### Risk Assessment Completed

- Product Label
  - Environmental Precautionary Statements
  - Use Restrictions (rate, timing, location)

OR

- Recommend Denial of Registration

