

## The Role of Residue Chemistry in Pesticide Risk Assessment



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## WHAT IS DIETARY RISK?

The potential for unsafe health effects to occur as a direct result of consuming pesticides residues from raw and processed agricultural commodities

- Risk Assessment and Tolerance (MRL) setting and processes are health-driven processes
- Regulators must make a specific determination that MRLs that would be established for a pesticide on foods are "safe"

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## WHERE ARE CHEMICAL RESIDUES FOUND?

- ◆ Raw Agricultural Commodities
- ◆ Processed Commodities
- ◆ Animal Commodities (meat, milk, eggs)
- ◆ Drinking Water

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## WHEN IS A DIETARY ASSESSMENT REQUIRED?

- ◆ Almost any regulatory action
  - New food uses (must fit in safe dose)
  - New uses on animal feed commodities
  - Changes in use patterns or regions which could result in increased anticipated residues
  - Tolerance reassessment activities (FIFRA 88 and FQPA)

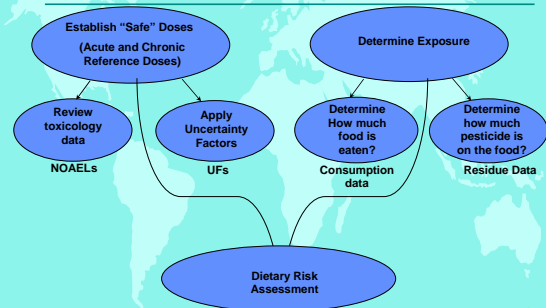
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## ELEMENTS OF DIETARY RISK ASSESSMENTS

- ◆ RISK is a function of HAZARD and EXPOSURE
- ◆ HAZARD: Determined by toxicological data and uncertainty factor or factors
- ◆ EXPOSURE = CONSUMPTION X RESIDUE
  - Consumption Data
  - Residue Data

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## Dietary Risk Assessment Tolerance (MRL) Setting





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## Dietary Exposure

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# RESIDUE X CONSUMPTION

(mg of chemical / kg of food) X (kg of food/day)




## ELEMENTS OF DIETARY RISK ASSESSMENTS

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**Dietary Risk =  $\frac{\text{Amount of Chemical Ingested}}{\text{Amount Considered Safe (RfD)}} \times 100$**

Amount Considered Safe



**REFERENCE DOSE:**  
(Amount considered safe)  
Based upon Toxicological data and uncertainty factor(s)  
**(HAZARD)**

Amount of Chemical Ingested




Based on estimated amounts of chemical in foods (residue data) and how much food is eaten per body wt. (consumption data)  
**(EXPOSURE)**

## HOW DO WE DEFINE "SAFE"?

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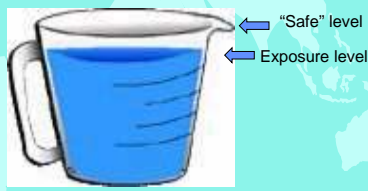
- ◆ When we can demonstrate that a "reasonable certainty of no harm" is associated with exposure to pesticide
- ◆ For the general population as well as subpopulations of people, especially infants and children
- ◆ With consideration of all possible sources of exposure (for example, food residues + water residues)




## HOW DO WE DEFINE "SAFE"?

### (the "Risk Cup" Concept)

**Exposure is lower than "safe" level**








## WHAT IS THE "SAFE" LEVEL?

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- ◆ Need to review the toxicology database to establish "safe" levels or **Reference Doses**
- ◆ Establish a "safe" level for a single or 24- hour exposure (**acute**)
- ◆ Establish a "safe" level for long-term, several months to a lifetime, exposure (**chronic**)







## ESTABLISHING THE ACUTE "SAFE" LEVEL

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- ◆ **Step 1**
  - Review the toxicology database to **identify adverse effects** that could result from an acute (single or 24-hour) or chronic (long term) exposure to a pesticide.
    - toxicology database comprised of carefully controlled, well-designed, well-documented studies conducted under GLP by trained scientists and technicians
    - studies are used by Regulators throughout the world



## WHAT KINDS OF ADVERSE EFFECTS?

- ◆ Clinical signs of toxicity
- ◆ Neurotoxicity
  - behavioral or motor activity effects
  - tremors
  - histopathological effects (tissue lesions)
- ◆ Effects on embryos, fetuses or pups if the possibility that they occurred after a single dose can't be excluded
  - permanent alterations (malformations, variations)
  - deaths
  - body weight effects

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## ESTABLISHING THE ACUTE "SAFE" LEVEL

### ◆ Step 2

- Determine the lowest **NOAEL** for the most sensitive adverse effect
  - NOAEL = No Observed Adverse Effect Level
  - at what dose level is no adverse effect observed?
  - conclusions regarding adverse effects and NOAELs are usually stated in toxicology study reports

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## ESTABLISHING THE ACUTE "SAFE" LEVEL

### ◆ Step 3

- Apply appropriate **uncertainty factors** (UF) to the NOAEL
  - uncertainty factors take into account uncertainties in the database or in our knowledge and ensure adequate safety for humans

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## UNCERTAINTY FACTORS

### ◆ Basic UF = 100

- 10x to account for variability between individuals
- 10x to account for uncertainty between species (how well do animal data predict human response)

### ◆ Regulators may apply additional UFs of 3x to 10x depending on the database for product

- 3x when no NOAEL is established and instead must use a LOAEL
- 10x when database is incomplete

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## HOW ARE UFs APPLIED?

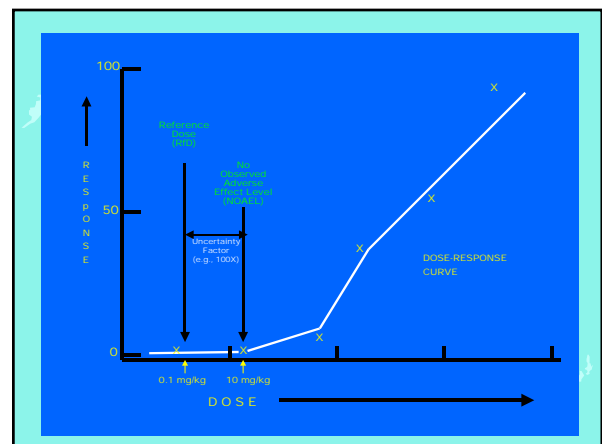
$$\frac{\text{NOAEL}}{\text{UF}_1 \times \text{UF}_2 \times \text{UF}_n} = \text{RfD}$$

RfD = Reference Dose

RfD = "safe" level

$$\frac{50 \text{ mg/kg/day}}{10 \times 10} = 0.5 \text{ mg/kg/day} = \text{RfD}$$

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## ELEMENTS OF DIETARY ASSESSMENTS

- ✓ **Reference Doses (acute and chronic from toxicological studies and uncertainty factors)**
- ◆ **Consumption Data (how much food is eaten)**
- ◆ **Residue Data (how much chemical is on the foods eaten)**

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## CONSUMPTION DATA: USDA SURVEY

USDA National Food Surveys: Continuing Food Survey of Intake of Individuals (CSFII)

1989-92

1994-1996

1996-1996 plus supplemental 1998 children's survey

- ◆ US Survey
- ◆ Phone Survey
- ◆ 3-day Consumption Period
- ◆ Based on Participant Recall
- ◆ All Seasons, All Regions
- ◆ 23 Subpopulations



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## RESIDUE DATA

- ◆ Published Tolerances (US CFR) "Worst Case" in that residues are at the highest allowable level
- ◆ Field Trial Residues - More realistic, but still at max. use rate & min. PHI
- ◆ Monitoring Data (FDA/PDP) - More realistic than FT residues, but still "farm gate"
- ◆ Market Basket Surveys - Most realistic- reflect actual consumer practices
- ◆ Processing Studies - Includes cooking studies

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## Two Types of Exposure

- ◆ **Chronic: long-term**
  - Assumed to be over a lifetime
  - Calculated from **AVERAGE** residues
- ◆ **Acute: short-term**
  - Typically over the course of a data
  - Calculated from **worst-case** residues

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## CHRONIC DIETARY RISK

$$\%cRfD = \frac{\text{Total amount of chemical ingested from all food sources}}{\text{Chronic Safe Dose}} \text{ (RISK)}$$

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## TIERED CHRONIC

- ◆ **TIER I** - Tolerance residues, 100% crop treated (Least Refined)
- ◆ **TIER II** - Tolerances, % crop treated
- ◆ **TIER III** - Anticipated residues (avg. field trial residues or 1/2 LOQ), Processing data, Monitoring data
- ◆ **TIER IV** - Market Basket Surveys (Most Refined)

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## CHRONIC ASSESSMENT WORST CASE (TIER I)

- ◆ Total from all foods consumed
- ◆ Deterministic - Uses Published Tolerances (Maximum Residue Limits)
- ◆ Goal is to evaluate the high-end residues

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## CHRONIC ASSESSMENT REFINEMENTS: objective is to obtain a risk assessment that more closely approximates actual exposure

- ◆ Worst case and refined assessments use the same consumption data
- ◆ Uses “Anticipated Residues” (Field Trial Average Residues)
  - Monitoring data (PDP or MB) may also be used
- ◆ Processing factors (washing, cooking, etc.)
- ◆ Percent crop treated (base acres treated at least once divided by total acres grown)

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## ACUTE ASSESSMENTS

- ◆ Acute: Short-term, typically over the course of a day
  - Deterministic Acute  
Since approximately 1986 in US
  - Probabilistic acute  
Since approximately 1989 in US

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## ACUTE ASSESSMENTS: Types

- ◆ Deterministic (Tier I and II)
  - Point estimates
  - Relatively simple
  - Uses summary data
- ◆ Distributional (Tier III and IV)
  - Input and output distributions
  - Relatively complex
  - May require many resources

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## ACUTE DIETARY RISK

$$\%aRfD \text{ (RISK)} = \frac{\text{Total amount of chemical ingested from all food sources}}{\text{Acute Reference Dose}}$$

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## TIER I ACUTE: Deterministic

- ◆ **EPA TIER I ASSESSMENT**- Tolerance Residues, 100% Crop Treated
  - Entire distribution of consumption
  - Utilizes a single residue point estimate for each food included in the analysis
  - Tolerances or highest field trial residue
  - No probabilistic sampling
  - Output is a dietary exposure distribution

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## TIER II ACUTE: Deterministic

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### EPA TIER II ASSESSMENT

Utilizes a single residue point estimate for each food included in the analysis

- Tolerances or highest field trial residues for single-serving commodities
- Mean field trial residues (or 95<sup>th</sup> percentile residue from monitoring) for blends

- ◆ Uses the entire consumption distribution
- ◆ Assumes 100% of crop treated
- ◆ All foods

## TIER III/IV ACUTE: Probabilistic

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- ◆ **TIER III** - Monte Carlo (probabilistic) for raw agricultural commodities (RACs) and animal diet contribution
- ◆ **TIER IV** - Monte Carlo and Market Basket Survey Data

## DEEM™: Dietary Exposure Evaluation Model

- Software by Exponent, Inc. used to calculate acute and chronic dietary risk (EPA and Syngenta)
- Includes all raw agricultural food forms
- Includes USDA “receipts” to determine ingredients of prepared food items
- Includes CSFII consumption surveys within the software
- Inputs are residue values, processing factors and percent of crop treated information

## DEEM™: Dietary Exposure Evaluation Model: Input

Food Code	Crop	Food Name	NFF	Default Residue (ppm)	Adjust Factor #1	Adjust Factor #2	RDL Pptr #1	Comment (documentation)
98	0	Acacia	0	1	1	1		
316	0	Alcohol-distilled	1	1	1	1		
248	0	Alfalfa sprouts	1	1	1	1		
138	198	Alfalfa	1	1	1	1		
40	14	Almonds	6	1	1	1		
376	0	Aloe vera juice	1	1	1	1		
498	4A	Amaranth	1	1	1	1		
115	198	Anise	2	1	1	1		
52	11	Apples	11	1	0.02			
53	11	Apples-dried	4	8	0.02			
54	11	Apples-juice/cider	7	75	0.02			
377	11	Apples-juice-concentrate	4	2.25	0.02			
410	12	Apricot juice	5	1	1	1		
59	12	Apricots	5	1	1	1		
60	12	Apricots-dried	3	6	1	1		
191	0	Artichokes-globe	1	1	1	1		
203	1CD	Artichokes-jerusalem	1	1	1	1		
491	0	Avocado	1	1	1	1		
260	0	Asparagus	4	1	1	1		
70	0	Avocados	1	1	1	1		
497	9B	Balsam pear	0	1	44			
264	0	Bamboo shoots	3	1	1	1		
72	0	Bananas	7	1	1	1		
73	0	Bananas-dried	4	3.9	1	1		

Max RDL Pointers:  << Quick RDL pointer find    The following food counts are only valid when T  
 << Quick food name find    Total foods:  Total w/o ff:

## DEEM™: Dietary Exposure Evaluation Model: Chronic Output

Syngenta Crop Protection, Inc. Ver. 7.76  
 DEEM Chronic analysis for CHLOROTHALONIL (1994-96 data)  
 Residue File name: Y:\PRODUCT FILES\CHLOROTHALONIL\DATA FROM PRIOR ASSESSMENTS\Dear adjustment factor #2 used  
 Analysis Date 07-17-2002/17:40:15 Residue File dated: 07-16-2002/14:43:20/23  
 Reference dose (RfD, Chronic) = .02 mg/kg bw/day  
 COMMENT 1: Tier 3-4 based on POP/tolerance data and current tox endpoint

Population Subgroup	Total Exposure	
	mg/kg body wt/day	Percent of RfD
J.S. Population (total)	0.000843	4.2%
J.S. Population (spring season)	0.000842	4.2%
J.S. Population (summer season)	0.000835	4.2%
J.S. Population (autumn season)	0.000870	4.3%
J.S. Population (winter season)	0.000822	4.1%
Northeast region	0.000853	4.3%
Midwest region	0.000873	4.4%
Southern region	0.000758	3.8%
Western region	0.000937	4.7%
Hispanics	0.001028	5.1%
Non-hispanic whites	0.000824	4.1%

## DEEM Software Chronic Output

- ◆ Exposure values for each sub-population are calculated by multiplying the mean consumption value for each commodity in mg/kg-bw/day by the residue value (tolerance or average field trial value).

$$\text{CHRONIC EXPOSURE} = \text{AVE. CONSUMPTION} \times \text{AVE. RESIDUE}$$

- ◆ For example, the calculated chronic exposure value for the US population in the example is:  

$$\text{exposure} = 0.000843 \text{ mg/kg/day}$$
- ◆ This value is compared with the Chronic Reference Dose value:  

$$\text{cRfD} = 0.020 \text{ mg/kg/day}$$

## DEEM Software Chronic Output

Chronic Risk is expressed as “ % cRfD ”.

$$\text{Chronic Risk} = \% \text{ cRfD} = \frac{\text{Calculated DEEM Exposure}}{\text{Chronic Reference Dose}} \times 100$$

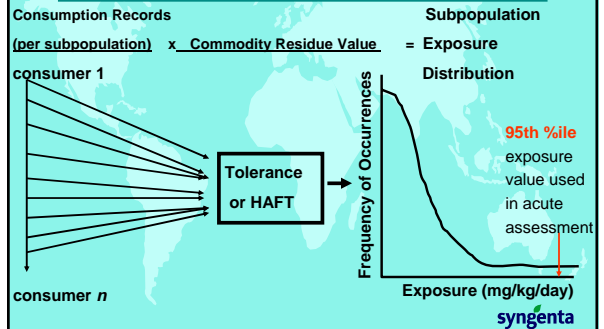
$$\text{US Population, \% cRfD} = \frac{0.000843 \text{ mg/kg-bw/day} \times 100}{0.020 \text{ mg/kg-bw/day}} = 4.2\%$$

Therefore, if %cRfD is < 100%, the chronic dietary risk is considered **acceptable**.

If %cRfD is > 100%, the chronic dietary risk is considered **unacceptable**.

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## DEEM™ Acute Deterministic Calculations



## DEEM Software Deterministic Acute Output

◆ Exposure values for each sub-population are calculated by multiplying commodity consumption data for each in mg/kg-bw/day by the residue value (tolerance or highest average field trial value).

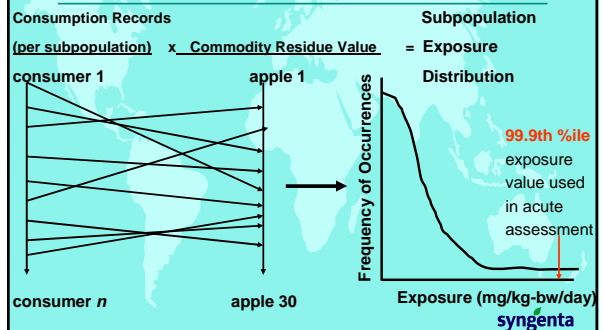
$$\text{ACUTE EXPOSURE} = \text{CONSUMPTION} \times \text{HIGHEST RESIDUE}$$

Acute Deterministic Risk is expressed as “ % aRfD ” at the 95th %ile.

$$\text{Acute Risk} = \% \text{ aRfD} = \frac{\text{DEEM Acute Exposure (95\%ile)}}{\text{Acute Reference Dose}} \times 100$$

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## DEEM™ Acute Probabilistic Calculations



## Health-driven Risk Assessment & Tolerance (MRL) Setting

- ◆ Risk Assessment Processes & Tolerance (MRL) setting and are health-driven processes
  - Regulators must make a specific determination that MRLs that would be established for a pesticide on foods are “safe”

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## Putting Residue Data in Context: Risk Assessment and Tolerance Setting

- ◆ **Data Generation**
  - Exposure (Behavior, Residue)
  - Hazard (Toxicology endpoint and Uncertainty Factors)
- ◆ **Risk Assessment**
  - Integrating Hazard and Exposure
- ◆ **“Regulatory Thresholds”**
  - Maximum Residue Levels (MRLs) or Tolerances
  - Based on “efficacy” and not “toxicology”
- ◆ **Pesticide Labeled Use Pattern (GAP)**

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## Definition of MRL/Tolerance

- The maximum concentration of a pesticide legally permitted in food or animal foodstuff
  - expressed as mg of residue in a kg of crop
- Based on labeled directions for use
- Set for each pesticide in each individual commodity or commodity group
- Used as trading standard *not* health standard

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## Residue of Concern

- ◆ Identified in toxicology studies
- ◆ May be expressed as
  - Parent Compound
  - Major Metabolite
  - Parent and Metabolite(s)

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## Residue Data

### Types of studies

- Rotational crop studies
  - Determines potential residues on crops from fields treated the previous season with a chemical
- Processing studies
  - Determines residues in processed fractions (oils, juices, etc.)
- Livestock feeding studies
  - Determines residues in animal food commodities (meat, milk and eggs)
- Magnitude of residue studies
  - Determines residues in crops under "worst-case" label conditions

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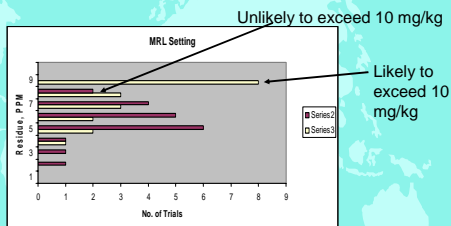
## Past Tolerance Setting (US & Canada)

- ◆ There was no specific formula for establishing the tolerance in the USA prior to August, 2005 as there was in Europe
- ◆ Tolerances were set using a "round-up" method by:
  - Examining the Magnitude of the Residue data and determining the maximum residue from these trials
  - Proposing a number above this level that was
    - A whole number (e.g., 8 mg/kg, but not 7.5 mg/kg)
    - Unlikely to be exceeded (if all of your data is at 7-8 mg/kg, you may want to go to 10 mg/kg).
    - The level is "safe" based on your dietary risk assessment.
    - If no residues were found, the tolerance was set at the method Limit of Quantification.
- ◆ No statistical analysis of the entire dataset

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## "Round-up" Method Challenges

How much higher should the MRL be than the highest field trial residue?



"Round-up" procedures produced different results using the same or similar data sets.

Sample size, professional judgment and experience, and reviewer bias may all effect the determination of the MRL.

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## Current Method for MRL Setting (PMRA & EPA)

- ◆ The NAFTA MRL Harmonization Workgroup was formed to address this issue
- ◆ A EPA/PMRA Standard Operating Procedure (SOP) and calculation spreadsheet developed to
  - Reduce reviewer bias
  - Enhance the reproducibility of MRL determination
  - Adhere to agreed upon methods, assumptions and assumption checking techniques.
- ◆ Procedure incorporates the use of various methods and approaches when certain statistical and other criteria are met.
  - methodology available at: [http://www.pmra-aria.gc.ca/english/pdf/nafta/docs/nafta\\_mrls-e.pdf](http://www.pmra-aria.gc.ca/english/pdf/nafta/docs/nafta_mrls-e.pdf)

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## NAFTA MRL Calculation Procedure



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## MRL Setting Concepts

- ◆ The purpose of a MRL is to serve as an enforcement tool
  - Exceedance of a MRL is not indicative of a potential health risk
  - MRL's meet the regulatory standards (trade) of the regulatory agency
- ◆ MRL setting is based on the residue data
  - Dependent on "use pattern" necessary for efficacy to control a pest, disease, weed
  - Use of field trial data provides sufficient confidence that a legally applied pesticide will not result in residues that exceed the MRL

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## In Closing

- ◆ Residue Chemistry Data has a tremendous impact on pesticide risk assessment results.
- ◆ Since Risk Assessment results can drastically impact the outcome of pesticide registrations, it is important Residue Chemistry Data is reliable and of the highest quality possible.
- ◆ As we enter into global harmonization of MRLs, the quality of residue chemistry data will play an even larger role in global trade issues and human health risk assessment worldwide.

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THE END

THANKS!!

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