

US Registration and Tolerance (MRL) Setting Procedures:

including section on use of Field Trials in
tolerance/MRL setting



*Minor Use Summit,
December 2007
Rome, Italy*

Jeff Herndon
Health Effects Division
Office of Pesticide Programs

Introduction: Types of Actions

- Focus discussion on registering a new conventional chemical, other actions fewer resources:
 - Me-too productions
 - Amendments
 - adding a new use, adding new claims, clarifying use directions, changing precautionary language, adding new sources, adding alternate formulations
 - Inerts
 - Emergency Exemptions (Section 18)
 - Special Local Needs, State Registrations (Sec. 24c)
 - Experimental Use Permits

Five Steps in Registering a New Chemical

1. Front End Processing:

Mail Room Sort, PRN 86-5 Screen, Product Manager Screen, Science Screen



2. Science Reviews

Health Effects Evaluation, Eco. & Enviro. Effects Evaluation, Lab Validations



3. Risk Assessment and Peer Review

Establish Endpoints of Concern, Establish RfD (ADI) and Safety Factors, Assessment of Hazards and Risk



4. Risk Management and Regulatory Decision

Risk Assessors Review of Risk Mitigation Measures, Risk Management Coordination with Registrants and Risk Assessors Management Decision



5. Federal Register Publication

Risk Manager Develops Document, Program Wide Concurrence, Management Signature, Public Dissemination

Step 1: Front-End Processing

- Package mailed or sent electronically to OPP
- Reviewed for completeness
 - If incomplete, work with submitter to obtain
- Forwarded to the regulatory division for further processing

Step 2: Science Reviews

- Animal toxicity data to identify toxicological endpoints for humans
 - Short-term (acute), intermediate-term (subchronic), long-term exposure (chronic)
 - Oral, dermal, and/or inhalation routes of exposure

Science Reviews: Typical Data (cont.)

■ Environmental fate data

- Lab and field data to characterize persistence, mobility and bioaccumulation

■ Water resources data

- Modeling and monitoring data to estimate potential exposure
- Refine estimate of exposure to humans, i.e. actual drinking water values

Science Reviews: Typical Data (cont.)

- Ecological to estimate risk to terrestrial and aquatic organisms
 - Acute and chronic tests to determine toxicity
 - Terrestrial and aquatic field studies to determine toxic effects in the field (on plants)
- Exposure information or data
 - Oral, Dermal, Inhalation studies (generic data may suffice)

Science Reviews: Typical Data (cont.)

- Depending on results from first tier studies, additional more specific studies may be required
 - Data packages sent back to regulatory manager, if additional data critical to making a decision
- Review packages and recommendations are forwarded to appropriate risk assessor

Science Reviews, Data analysis

- Study review process based on Standard procedures and internal EPA policies and guidance.
- Good Laboratory Practice required for all data.

Step 3: Risk Assessment (RA) and Peer Review

- Types of Risk Assessment
 - Varies depending on use pattern and type of compound
- Risk Assessment Process
- Assessing Environmental Risks
 - Animals, Non-target plants, Endangered Species – a major focus now
 - Modeling Water and Spray Drift Exposure

RA and Peer Review (cont.)

- Assessing Human Health Risks
 - Identifying Hazards
 - Occupational and Residential Risk Process
 - Assessing aggregate Risks
- Peer Review Process
 - Human Health Peer Reviews
 - Environmental Peer Reviews
 - Scientific Advisory Panel (SAP)
- Risk Characterization
 - Integrated throughout process

RA and Peer Review: Types of Risk Assessments

- Before OPP can make a “no unreasonable adverse effects” determination, it must assess the human risks to a variety of sources, including:
 - Dietary (food and water)
 - Acute, chronic, cancer (if appropriate)
 - Residential (oral, dermal, and inhalation)
 - Short-term, intermediate-term, chronic, carcinogenic
 - Occupational (dermal and inhalation)
 - Short-term, intermediate-term, chronic, carcinogenic

RA and Peer Review: Types of Risk Assessments (cont.)

- Aggregate (combined food +water+ residential)
 - Acute, short-term, intermediate-term, chronic, cancer
- Ecological (terrestrial and aquatic)
 - Acute and chronic exposure
 - Intentionally conservative to account for wide ranges in variability
 - Endangered species

RA and Peer Review: Risk Assessment Process

- All risk assessments are composed of three elements:
 - Hazard Assessment
 - Exposure Assessment (dietary, residential, and occupational for humans; water, soil, food items for wildlife)
 - Risk Characterization (an integration of hazard and exposure)

RA and Peer Review: Risk Assessment Process

- Risk = Hazard X Exposure
- Hazard identified by selecting appropriate endpoints based on toxicity studies
- Exposure determined by data or combination of modeling and data
 - Water models
 - Food and/or Water Monitoring Data
 - Spray drift modeling and data
 - Dietary models
 - Occupational methodology

RA and Peer Review: Peer Review Process

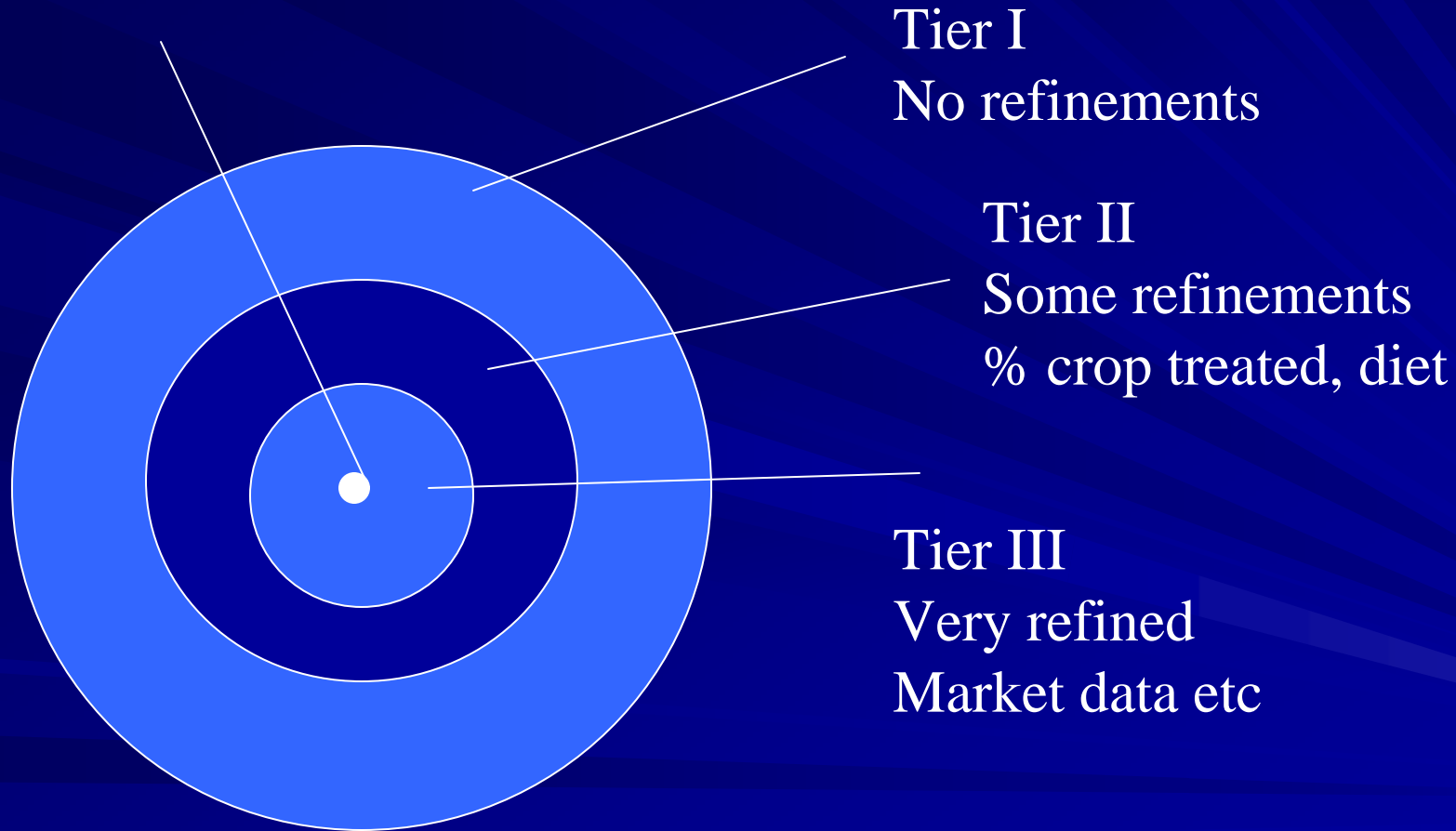
- Peer review panels comprised of senior scientists with specialized expertise in topic being assessed
 - Ensure consistency on decisions and methodology
 - Identify gaps in data or information on compounds
 - Conduct QA/AC of Agency reviews of studies
 - Prepare and update guidance documents and ensure consistent methodology for assessing risks.

RA and Peer Review: Risk Characterization

- Final step of risk assessment process
- Clearly communicates the strengths and limitations of the risk assessment
 - Allow decision – makers to put assessment into context with the other information critical to evaluating options for rules, regulations and negotiated agreements (e.g., economics, social values, public perception, policies, etc.)

Risk Refinement

Actual risk



Step 4: Risk Management and Regulatory Decision

- Evaluating Risks
- Evaluating Benefits
- Managing Risks
- Decision-making Process
 - Requiring additional data
 - Risk/Benefit analysis
 - State and Federal Programs

Risk Management and Regulatory Decision: Evaluating Risks

- Risk manager weighs results of risk assessment against predetermined levels of concern
 - Every risk category (e.g., occupational, ecological, aggregate) has a predetermined level of concern that, if triggered, will cause the agency to further analyze that risk or use

Risk Management and Regulatory Decision: Evaluating Risks

- Further analysis may involve:
 - Specifying exactly when the level of concern is triggered (only rarely, for certain uses or population subgroups, or frequently)
 - Determining whether additional refinements of risk assessment are possible
 - Determining whether additional data could reduce the risk estimate

Risk Management and Regulatory Decision: Evaluating Benefits

- Economic Assessment based upon crop losses, projected use and product performance.
- Use of alternatives for pesticides of concern
- Public Interest Finding for Conditional Registrations.

Risk Management and Regulatory Decision: Managing Risks

- If risk estimates are as refined as possible, then manager seeks risk mitigation measures, which may include:
 - Reduced application rates
 - Spray drift measures
 - Additional protective clothing or reentry restrictions
 - Additional label restrictions, etc.

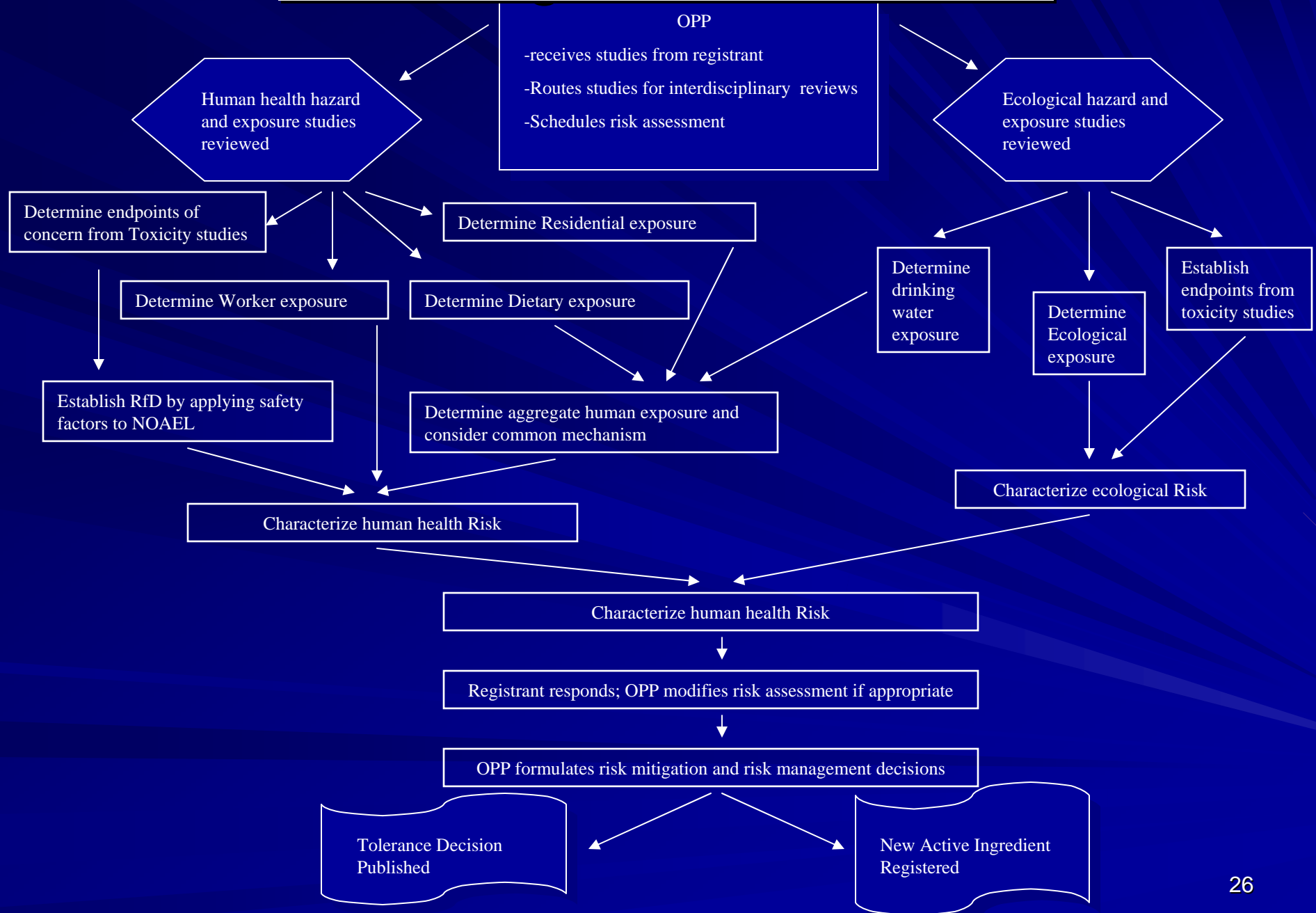
Risk Management and Regulatory Decision: Decision-making Process

- If, through refinement and mitigation, risks no longer are of concern, then registration will likely be granted
- If not, then additional factors may be considered:
 - Benefits for environmental or worker risks
 - Benefits can not be used for dietary risks
 - Replacing a higher risk pesticide
 - Effects on other State or Federal Programs

Step 5: Federal Register Publication

- Once a decision has been made, and approved by management, it will be announced to the public through a Federal Register Notice

OPP Registration Process



Use of Field Trial Data in Tolerance/MRL Setting

Definition of Tolerance/MRL

- What are tolerances? Tolerances are defined as:
 - Maximum legal concentrations in food or feed
 - Regulatory tools to ensure label compliance
 - Found at 40 CFR 180

Definition of Tolerance/MRL (cont'd)

- Based on the highest residue from field trials reflecting the most conservative use pattern (s)
- Intended to prevent/ascertain misuse
 - **If exceeded, the food or feed commodity is considered adulterated and may be seized**
- To protect those legally using the pesticide
- Regulatory tools, i.e., not intended primarily for risk assessment

Registered Use vs. Tolerance

- Pesticide uses are registered under FIFRA
- Tolerances are established under FFDCA
- FQPA more closely links the two by requiring a Safety Finding, aggregate, etc.
- Tolerances are established by EPA/OPP but enforced by FDA and USDA
- Pesticides in drinking water are regulated under the three above and the CWA

Registered Use vs. Tolerance (cont'd)

- **FIFRA** = Federal Insecticide, Fungicide, and Rodenticide Act
- **FFDCA** = Federal Food, Drug, and Cosmetic Act
- **FQPA** = Food Quality Protection Act
- **CWA** = Clean Water Act

Residue Field Trials

- For lower-tier dietary exposure and to set tolerances
- Must reflect legal/proposed uses leading to the highest residues
 - Maximum application rate/use combination
 - Maximum number of applications
 - Shortest preharvest interval (PHI)
- OPPTS Guideline 860.1500

Residue Field Trials (cont'd)

- Field trials must reflect varying use conditions
 - Geographically representative
 - Formulations
 - Application methods

Residue Field Trials (cont'd)

- Number of trials reflect significance of use
 - Total acreage of production
 - Relative human consumption or use as a feed
 - Eg., 20 for wheat, 12 for peach, 1 for shallot
- Location of trials reflect relative production
 - Eg., all 5 for almond in Region 10 (CA)
 - Eg., of 20 for wheat, 5 or 6 in each of three regions and 1 in each of four additional regions
 - Fewer trials/geographic restriction possible

Residue Field Trials (cont'd)

- EPA's 13 U.S. regions were established based on geography, climate, rainfall, etc.
- Location of trials reflect relative production
 - Eg., all 5 for almond in Region 10 (CA)
 - Eg., of 20 for wheat, 5 or 6 in each of three regions and 1 in each of four additional regions
 - Fewer trials/geographic restriction possible

Residue Field Trials (cont'd)

■ Crop Grouping

- Related crops grouped together eg., Pome Fruits or Leafy Vegetables
- Allows use on minor crops by testing only the representative crops eg., only apple and pear are tested for Pome Fruit Group tolerance
- Reduced number of trials are required (25% fewer) for representative commodities as part of a crop group

Residue Field Trials (cont'd)

- Representative formulations are tested
 - Each distinctly different formulation class
 - Rate of absorption, degradation, and persistence often altered by inerts
 - May translate from one class to another if similar, eg., WP to FIC or WDG if inerts similar
 - Sometimes, side-by-side comparison trials conducted to determine worst-case class

Residue Field Trials (cont'd)

- Application methods must be representative in terms of:
 - Type: broadcast, in-furrow, chemigation, etc.
 - Timing: at-plant, dormant, petal-fall, foliar, etc.
 - Equipment: ground, aerial, ULV, etc.
 - Spray volumes and spray additives to appear on the label must be included in the field trials

Residue Field Trials (cont'd)

■ Sampling strategy

- At normal harvest time, samples of each raw agricultural commodity (RAC) are collected
- Composite samples to mimic FDA sampling (enforcement)
- The last pesticide treatment must reflect the shortest PHI proposed/established

Tolerance Setting

■ Conventional method

- Based on the highest residues from field trials reflecting the most conservative use pattern(s)
- Highly dependent in professional judgement of individual scientist

■ New Statistical Method

- Provides a defined method that should result in similar/consistent decisions on tolerance setting
- NAFTA endorsed in 2005
- JMPR recognized and is using the procedure

THANK YOU !