

SUBMISSION REVIEW PROCESS AND HEALTH EFFECTS ASSESSMENT

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Submission Components

- ▶ Administrative Part
 - ◆ Covering letter, application forms, fees forms, Product Specification Form
- ▶ Label
 - ◆ Guarantees, contents, names; Uses; Directions; Warnings; Health information; Environmental information; Commerce class



Submission Components (cont'd)

Studies:

▶ Chemistry

- ◆ Product identity, product composition
- ◆ Physical/chemical properties, manufacturing methods, microcontaminants, analytical methodology

▶ Efficacy/Value

- ◆ Effectiveness, economics, sustainability



Submission Components (cont'd)

- ▶ Environmental
 - ◆ Environmental chemistry and fate – soil, water
 - ◆ Environmental toxicology – plants, aquatic and terrestrial organisms
- ▶ Health Effects
 - ◆ Toxicology
 - ◆ Exposure – Occupational, bystander
 - ◆ Exposure – Food residues/drinking water



Submission Categories

Approach:

- ◆ Submissions sorted to one of 6 categories
- ◆ Descending order of complexity, data and review resources required
- ▶ *A* New technical active ingredient or major new use
- ▶ *B* Amendments or changes to registered use
- ▶ *C* Minor changes or no change to registered use
- ▶ *D* Variable types e.g.
 - User requested minor use label expansion
 - Renewals
- ▶ *E* Research Permits
- ▶ *G* Miscellaneous



Submission Process

Activities:

- ◆ Verification
- ◆ Screening
- ◆ Preliminary Review
- ◆ Evaluation
- ◆ Integration of Reviews
- ◆ Proposed Regulatory Decision Document (PRDD)
- ◆ Final Decision Incorporating Consultation



Health Effects Assessment

Objective:

- ▶ Integration of Toxicology with exposure
- ▶ As warranted, incorporates aggregate and cumulative exposure



Toxicological Evaluation

Objective:

- ▶ Identify inherent hazard
 - ◆ Range of toxicity studies, many species
 - ◆ Acute effects, chronic effects
- ▶ Identify potential for effects on human health
- ▶ Determine the dose that causes no adverse effects in animals (NOAEL)
- ▶ Identify dose considered acceptable for human daily intake (ADI) 100-1000x lower than NOAEL



Toxicology Data Reviewed

- ▶ TOXICOKINETICS – absorption, distribution, metabolism, excretion
- ▶ ACUTE TOXICITY – oral, dermal, inhalation, sensitization, eye/skin irritation
- ▶ REPEAT DOSE, SHORT-TERM – 2-4 weeks, 3-6 months, 1-year
- ▶ REPEAT DOSE, CHRONIC/ONCOGENICITY – 2-years
- ▶ REPRODUCTIVE TOXICITY – reproductive and endocrine



Toxicology Data Reviewed

- ▶ DEVELOPMENTAL TOXICITY – birth defects
- ▶ GENOTOXICITY – interaction with DNA
- ▶ NEUROTOXICITY – effects on nervous system
- ▶ SPECIAL STUDIES – mechanistic, target organs, companion animal studies



Risk Assessment Toxicology Effects

- ▶ Identify adverse effects (hazard) local and systemic, target organs
- ▶ Assess relevance to humans
- ▶ Identify most relevant endpoints and the lowest NOAEL for that effect
- ▶ Assess formulant toxicity via studies on the formulation

Risk Assessment

Toxicology Effects (cont'd)

Foods:

- ▶ Determine Acceptable Daily Intake (ADI)

NOAEL (mg/kg bw/d;2 year study) = ADI

Uncertainty Factor (100-1000x)



Risk Assessment

Toxicology Effects (cont'd)

Occupational/Bystander Exposure:

- ▶ Determine Acceptable Margin of Exposure (MOE)

NOAEL (mg/kg bw/day) = MOE (must be 100-100x)
Exposure during normal use



Dietary Exposure Data Reviewed

- ▶ Product chemistry; ability of analytical methods to detect chemical in foods
- ▶ Use pattern and food crops to be treated
- ▶ Metabolism – animals, plants, soil (EAD), rat (toxicology) – identify residues of concern
- ▶ Residue trials – data for crops and/or animal products at maximum label rates – worst case scenario



Dietary Exposure Data Reviewed (cont'd)

- ▶ Processed food residues
- ▶ Storage stability
- ▶ Livestock feeding studies – meat, milk, eggs
- ▶ Crop rotation data



Risk Assessment

Food Residue Exposure

- ▶ Maximum Residue Levels (MRLs); all crops and food animals
 - ◆ Include processing considerations
- ▶ Using residues
 - ◆ + dietary intake of products
 - ◆ + estimated residues in drinking water
- ▶ Calculate Potential Daily Intake (PDI) for various subpopulations including infants, toddlers, children, adolescents and adults



Risk Assessment

Food Residue Exposure

- ▶ Compare PDI to ADI established from toxicology review
- ▶ PDI must be less than ADI



Occupational/bystander Exposure Studies Reviewed

- ▶ Mixer/Loader/Applicator
 - ◆ Studies of M/L/A
 - Passive dosimetry (dermal, inhalation)
 - Biological monitoring
 - Modelling – Pesticide Handlers Exposure Database (PHED)
 - ◆ Dermal Absorption Studies - animals



Occupational/bystander Exposure Studies Reviewed (cont'd)

- ▶ Post Application (re-entry)
 - ◆ Studies of workers, bystanders
 - Passive dosimetry (dermal, inhalation)
 - Biological monitoring
 - ◆ Dislodgeable Residues – foliar, soil, surfaces
 - ◆ Ambient air samples
 - ◆ Child specific activities and characteristics incorporated



Risk Assessment Occupational/bystander Exposure

Objective:

- ◆ Determine systemic dose during use
 - Amount breathed in
 - Amount deposited on skin and absorbed
- ◆ NOAEL (mg/kg bw/day from animal studies) = MOE
Exposure
- ◆ * MOE must be 100-1000x



Typical Scenarios for Exposure Assessment

► Occupational

◆ Mixer/Loader/Applicator

- Agricultural (ground, aerial)
- Greenhouses
- Industrial
- Pest Control Operators



Typical Scenarios for Exposure Assessment (cont'd)

- ▶ Residential
 - ◆ Home/garden –homeowner
- ▶ Post application
 - ◆ Worker settings i.e, tree pruners
 - ◆ Residential – homeowners, children, pets (aggregated with dietary)



Risk Management Occupational/bystander Exposure

- ▶ Risk Management Trigger:
 - ◆ Margin of exposure less than determined necessary from toxicology review



Risk Management Occupational/bystander Exposure (cont'd)

- ▶ Administrative Controls
 - ◆ Re-entry intervals
 - ◆ Application rate; limit number of applications
 - ◆ Training
 - ◆ Classification – restricted, commercial, domestic
 - ◆ Monitoring
 - ◆ Label Improvement



Risk Management Occupational/bystander Exposure (cont'd)

- ▶ Engineering Controls
 - ◆ Personal protective equipment
 - ◆ Closed systems
 - ◆ Ventilation
 - ◆ Packaging
 - ◆ Reformulation