Registration Review Docket

Hexythiazox

PPDC Registration Review Workgroup Meeting

March 8, 2007

PPDC Registration Review Workgroup Meeting
Hexythiazox
Thursday, March 8, 2007
Potomac Yard South, 1st Floor Conference Center

I. Background—Molly Clayton, CRM

II. Human Health Scoping —Christine Olinger

III. Ecological Risk Assessment Problem Formulation- Jean Holmes

IV. Preliminary Work Plan- Molly Clayton

V. Questions/Comments

EPA United States Environmental Protection Agency

Hexythiazox Background

- Hexythiazox is an ovacide (kills mite eggs)
- Pests controlled include tetranychid mites
- Technical registrant: Gowan
- First registered in 1989; thus, no Reregistration Elgibility Decision (RED) was prepared
- There are no currently registered residential uses
- Pending actions include:
  - Pending new use on turf, both commercial and residential (commercial applicators only)
  - Pending new residential uses (commercial applicators only) on caneberries, pome fruit, stone fruit, and nut trees (these uses are currently registered in commercial plantings only)
  - Petition to establish regional tolerances and Section 3 registration for use on field corn

Hexythiazox Background

Use Information:

- Less than 12,500 lbs. used per year
- Crops with the highest average percent crop treated are hops (60%), strawberries (25%), and dates (10%)
- Hexythiazox is formulated as a wettable powder, emulsifiable concentrate, and dry flowable
- There are seven section 3 active registrations, and one section 18 (emergency exemption) approved for hexythiazox use on field corn in Texas for mite treatments, which expires on12/31/2007

Human Health Problem Formulation Process

- What Risk Assessments are Available?
  - Dietary: Food and Water
  - Residential
  - Occupational
- Is There New Information To Be Considered?
  - Incident Reports
  - Literature Search
  - New Data Submissions to the Agency

Human Health Problem Formulation
Where do we start for Hexythiazox?

- Three most recent RAs conducted in 2001, 2002 and 2005.
  - Last comprehensive RA conducted in July of 2005 to support new uses on pome fruit, citrus and grapes.
- There are currently pending actions for field corn and residential uses, which were NOT included in this review.

Human Health Problem Formulation
What's new With Hexythiazox? (1)

- New data from registrants – no new tox data – new orange processing study that was submitted as conditions of registration
- Changes in use patterns – bridging crop field trial studies for apples and pears were submitted to allow the use of a new formulation

Human Health Problem Formulation
What's New With Hexythiazox? (2)

- Literature reports – no new information relevant to toxicity
- Pesticide incidents – none of concern
- Changes in policy – New Cancer Guidelines

Toxicology

- The toxicity database is complete.
- FQPA Safety reduced to 1x
  - no indications of susceptibility or sensitivity
  - no residual concerns for pre- or postnatal toxicity to infants and children.
- Carcinogenicity studies in rats and mice show effects including ↓body weight gains and ↑liver weights.
- CARC classified hexythiazox as a “possible human carcinogen” in 1988 and established a unit risk of 2.2 x 10^{-2} based on the increased incidence of liver tumors in female mice.

Residue Chemistry

- The residue chemistry database is complete, pending the review of the orange processing study submitted November 2006.
- The Agency anticipates no additional human health risk assessment for existing uses will be required after this data is reviewed, since conservative assumptions were made and default processing factors were incorporated into the previous risk assessment to account for the lack of data.

Dietary

- Acute dietary exposure estimates (females 13-49 years old) represented <1% of the aPAD.
- The somewhat refined chronic dietary assessment resulted in exposure estimates that utilized 1% of the cPAD for the most highly exposed population subgroup- children 1-2 years old.
- The resulting cancer dietary exposure yields a cancer risk estimate of 2×10^{-6}, and is below the Agency's level of concern.

Aggregate

No existing residential uses of hexythiazox, therefore the hexythiazox aggregate incorporates food and water only.

Occupational

- Occupational database is complete.
- All relevant occupational scenarios are assessed for all uses.
- All MOEs for dermal and inhalation exposure are well below the Agency's level of concern.
- Cancer risk estimates for handlers (with gloves as specified on the label), applicators, and post application workers ranged from 9×10^{-6} to 5×10^{-8}.

Conclusion

- Dietary, occupational and aggregate assessments are available for all current uses.
- No dietary or aggregate risks of concern.
- HED may reevaluate cancer classification in association with new uses
- Currently there are no data needs.
- The Agency anticipates no additional human health risk assessments will be needed for the existing uses of hexythiazox.

Hexythiazox Ecological Risk Assessment Problem Formulation

Michael Barrett, Nicholas Federoff, Allen Vaughan, Jean Holmes, and Mah Shamim participated in the ecological risk assessment problem formulation for the hexythiazox registration review.

Problem Formulation Considerations

- **Mode of Action**
  - Hexythiazox is a miticide inhibiting growth and development
  - The mechanism of action in nontarget organism is unknown
  - No pesticide structural analog
- **Use area**
  - Uses are relatively minor; treated acreage probably less than 30,000 acres for all crops
  - Largest uses (ranked by lbs ai applied per year): Strawberries > Hops > Apples, Peaches, Pears, Citrus, Grapes
  - New uses requested on field corn and turf, were not included in this review

Problem Formulation Considerations

- **Several degradates may contribute to toxicity**
  - Six degradates of environmental concern were identified (consistent with HED determination for human health)
  - No specific fate or eco-toxicity studies for the degradates

- **What is known for eco, fate and uncertainties**
  - A number of effects data gaps exist for the parent
  - However, no outstanding fate data needs identified for the parent
  - No fate or eco data needed for the degradates – total residue approach to risk assessment

What We Know: FATE

- Solubility in water is low (0.5 ppm)
- Immobile in soil, strong adsorption (Koc 2k to 14k ml/g) - Not likely to leach
- Stable to hydrolysis; aqueous photolysis $t_{1/2}$ = 17 days (24 days for total residue); soil photolysis $t_{1/2}$ = 116 days
- Moderately persistent in terrestrial systems; parent aerobic half-lives 8 to 25 days; slower anaerobic degradation ($t_{1/2}$ = 4 months).
- Six degradates are structurally similar to parent. The total residues of concern aerobic soil half-life is 2-3 months
- BCF 1000-1600 (peak) – 96% depuration 14 days after end of exposure period
- Aquatic habitats exposed through soil erosion and spray drift, limited amounts dissolved in water

What We Know: ECO

Terrestrial Risk

- Practically non-toxic to birds, mammals and bees
- No LOC exceedance for: acute risk to birds, mammals, terrestrial invertebrates (bees), nor chronic risk to mammals
- Incident Reports
  - No incidents found in EFED database

What We Know: ECO

- Aquatic Risk
  - Highly toxic to freshwater species (but no LOC exceedance)
  - No LOC exceedance calculated for: acute risk to freshwater fish, freshwater invertebrates, and chronic risk to freshwater invertebrates
- Aquatic risk minimized by low application rates, partitioning to sediments

Uncertainties (based on lack of data)

- Chronic risk to birds
  - Have no avian repro studies
- Acute and chronic risk to aquatic organisms
  - Have no freshwater fish chronic study
  - Have no acute or chronic estuarine/marine fish studies
  - Have no acute or chronic estuarine/marine invertebrate studies
- Risk to plants
  - Have no aquatic or terrestrial plant studies

Other Uncertainties

- Since there are no specific fate or eco data for 6 degradates of environmental significance, EECs were estimated using the total residue method (uses conservative assumptions and accounts for degadates).
- Agency has no Ecotox runs at present

Conclusions of Hexythiazox Planning Dialogue

Taxa	Data Gaps	Propose to Request Study
Avian Reproduction Study (71-4)	YES	NO
Estuarine/Marine Fish LC50 Study (72-3a)	YES	NO
Estuarine/Marine Mollusk LC50 Study (72-3b)	YES	NO
Estuarine/Marine Shrimp LC50 Study (72-3c)	YES	YES
Freshwater Fish Early Life Stage (72-4a)	YES	NO
Estuarine/Marine Invertebrate Full Life-Cycle Study (72-4b)	YES	YES
Freshwater Fish Full Life-Cycle Study (72-5)	YES	NO
Estuarine/Marine Fish Full Life-Cycle Study (72-5)	YES	NO
Aquatic Vascular Plant Study (122-2)	YES	NO
Aquatic Non-Vascular Plant Study (122-3)	YES	NO
Terrestrial Plants, Vegetative Vigor and Seedling Emergence (122-1a and 122-1b)	YES	NO
Battery of Fate and Effects Studies for Hexythiazox **Degradates**	YES	NO

Lines of Evidence Considered for Proposing Ecotoxicity Data

- Geographic use area
- Toxicity data
- Magnitude of potential exposure
- Variation in species sensitivity
- Incident data
- Labeling

Lines of Evidence Considered for Proposing Ecotoxicity Data

Line of Evidence	Organism Exposed		
	Birds	Aquatics	Plants
Geographic use area		X	
Toxicity data	X	X	
Exposure magnitude	X	X	
Variation in species sensitivity		X	
Incident data			X
Labeling info.			X

Data NOT Proposed to be Requested [Based on Current Application Rate and Number of Applications]

Battery of Fate and Effects Studies for Degradates

- EECs were estimated using the total residue method
- Total residue method was used because of the structural similarities of the degradates to the parent
- Degradates were included in the eco assessment using a total residue exposure approach and no LOCs were exceeded

Data Proposed to be Requested (Rationale)

Estuarine/Marine Invertebrate Acute and Life-cycle Studies (72-3c and 72-4b)

- Use areas may be in proximity to estuarine/marine habitats
- Currently no data available on any estuarine/marine species
- Hexythiazox is highly toxic to freshwater aquatic invertebrates (daphnid EC 50 = 0.74 ppm; chronic NOAEC = 6.1ppb)
- RQs derived from the daphnid chronic study results are close to the chronic level of concern.
- Will need values from Mysid acute study to determine test concentrations for a Mysid chronic study

Data NOT Proposed to be Requested [Based on Current Application Rate and Number of Applications]

Avian Reproduction Study (71-4)

- EPA will use other lines of evidence
- All avian and mammalian acute data show no effects even at high dose levels
- No indications of reproductive effects in other vertebrate repro. study (rat 2-generation repro. Study)
- Because of low use rate, max. residues on food/feed items very low (45 ppm)
- Hexythiazox would need to be at least 117 times more toxic on a chronic basis relative to its acute toxicity to result in LOC exceedances (this is unlikely).

Data NOT Proposed to be Requested [Based on Current Application Rate and Number of Applications]

Estuarine / Marine Fish LC_{50} and Full Life-cycle Studies (72-3a and 72-5)

- EPA will use other lines of evidence
- In spite of high acute toxicity to freshwater fish, because of low use rate, acute RQ is very low (< 0.01)
- Hexythiazox would need to be at least 160 times more toxic on a chronic basis relative to its acute toxicity to result in LOC exceedances
- No indication of reproductive effects in other vertebrate repro. study (rat 2-generation)

Data NOT Proposed to be Requested [Based on Current Application Rate and Number of Applications]

Estuarine / Marine Mollusk LC_{50} study (72-3b)

- EPA will use other lines of evidence
- Hexythiazox is highly toxic to freshwater invertebrates (EC50 = 0.74 ppm, daphnid), however,
- The requested Mysid shrimp study will be utilized in the assessment of risks to mollusks.
- There is no evidence to suggest that a Mollusk-specific mechanism of action (effect on calcium uptake) is present, and it is seldom that the mollusk is a more sensitive species than the Mysid shrimp

Data NOT Proposed to be Requested [Based on Current Application Rate and Number of Applications]

Fish Early Life Stage and Full Life-Cycle studies (72-4 and 72-5)

- EPA will use other lines of evidence
- Hexythiazox would need to be more than 160 times more toxic on a chronic basis relative to its acute toxicity to result in LOC exceedances.
- No indication of adverse reproductive effects in other vertebrate reproduction studies (rat 2-generational reproduction study).

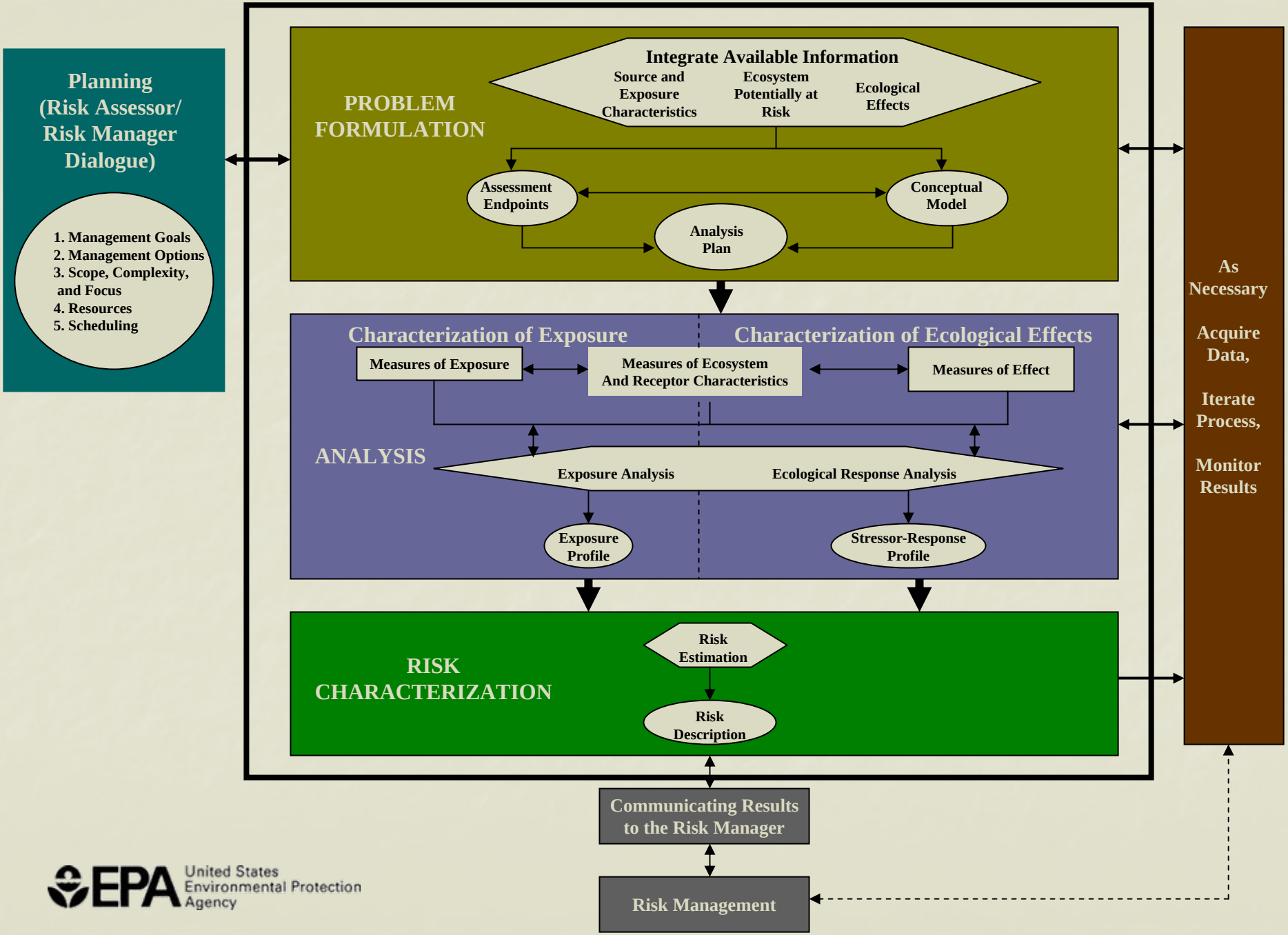
Data NOT Proposed to be Requested [Based on Current Application Rate and Number of Applications]

Aquatic Vascular and Non-Vascular Plant Studies (122-2 and 123-2)

Tier I Terrestrial Plant Studies (122-1a and 122-1b)

- EPA will use other lines of evidence
- Hexythiazox products are registered for use on numerous crop species/taxa, including both monocots and dicots, with no label restrictions based on specific plant susceptibility
- There are no reported incidents in the incident database

FRAMEWORK FOR ECOLOGICAL RISK ASSESSMENT



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Preliminary Work Plan

Anticipated Ecological Risk Assessment and Data Needs:

The Agency anticipates conducting a comprehensive ecological risk assessment, including an endangered species assessment for all uses, and that the following additional ecological data will be needed for registration review.

- Estuarine/Marine Invertebrate, Acute (72-3c)
- Estuarine/Marine Invertebrate Life-cycle (72-4b)

Preliminary Work Plan, Cont.

Anticipated Human Health Risk Assessment and Data Needs:

The Agency believes that previously completed dietary assessments are adequate and that there is no dietary risk that exceeds the Agency's level of concern (LOC); thus, no additional data are needed.

Next Steps

Phase 1: Opening the docket
Close Public Comment Period

Phase 2: Case Development
Develop Final Work Plan (FWP)
Open Public Comment Period for Preliminary Risk Assessments

Close Public Comment Period

Phase 3: Registration Review Decision
Open Public Comment Period for Proposed Reg. Review Decision
Close Public Comment Period
Final Decision and Begin Post-Decision Follow-up

Estimated Timeline for the Completion of the Hexythiazox Registration Review

Activities	Estimated Month/Year
Phase 1: Opening the docket	
Open Public Comment Period for Hexythiazox Docket	February 2007
Close Public Comment Period	May 2007
Phase 2: Case Development	
Develop Final Work Plan (FWP)	July 2007
Issue DCI	March 2008
Data Submission	March 2010
Open Public Comment Period for Preliminary Risk Assessments	July 2011
Close Public Comment Period	September 2011
Phase 3: Registration Review Decision	
Open Public Comment Period for Proposed Reg. Review Decision	December 2011
Close Public Comment Period	February 2012
Final Decision and Begin Post-Decision Follow-up	June 2012
Total (years)	5.5

Questions and Comments