EPA Science Assessment of AEATF II Solid Pour Scenario and Protocol

Note: this document may contain some elements that are not fully accessible to users with disabilities. If you need assistance accessing any information in this document, please contact ORD_Webmaster@epa.gov.

Tim Leighton
Kelly Sherman
USEPA
Office of Pesticide Programs

Jonathan Cohen, PhD
ICF International

April 8, 2014

Organization of Presentations

- Background and Science Assessment
  - Tim Leighton (USEPA)
  - Jonathan Cohen, PhD (ICF International)
- Ethics Assessment
  - Kelly Sherman (USEPA)

Note: Joint Regulatory Committee (JRC) comprised of CDPR and HC/PMRA participated in initial protocol design reviews.

Overview: Solid Pour Scenario/Protocol

- Regulatory Context
- Scenario Definition
- Study Objectives
- Surrogate Material for Testing
- Study Design
- Measurements
- Compliance with Scientific Standards
- Recommendations/Conclusions

Regulatory Context

- This is a proposal for research involving scripted exposure, and thus intentional exposure of human subjects, with the intent to submit the resulting data to EPA under FIFRA
- The following regulatory requirements apply:
  - 40 CFR §26.1125 requires prior submission of the protocol and supporting documentation
  - 40 CFR §26.1601 requires review of the protocol by EPA and the HSRB

New Exposure Studies are Needed

- A new generation of exposure monitoring is needed
  - To address the limitations of PHED/CMA data
  - To maximize the utility of generic data
  - To standardize study design and methods
- FIFRA SAP (Jan 2007) concurred in
  - Need for new studies
  - Soundness of the “generic principle”
  - General methods and study designs

Use Categories	Mop	Wipe	Aerosol	Pour Liquid	Pour Solid	Spray	Immerse/Dip	Pump Liquid	Place Solid	Fog	Pressure Treat	Metalwork Fluid	Brush/Roller	Airless Spray
Ag. Premises & Equipt	X	X	X	X		X	X	X		X				
Food Handling P&E	X	X	X	X		X	X	X		X				
Comm. & Indus. P&E	X	X	X	X		X	X	X		X				
Residential & Public Access	X	X	X	X		X	X			X				
Medical P&E	X	X	X	X		X	X	X		X				
Drinking Water Systems								X						
Indus. Process Water Sys					X			X						
Material Preservatives				X	X	X	X	X	X			X	X	X
Antifoulant Coatings													X	X
Wood Preservatives						X	X				X		X	X
Swimming Pools				X	X			X	X					
Aquatic Areas				X	X			X	X					

Solid Pour Scenario Definition

- Manual pouring of solid formulations to represent an antimicrobial chemical into receiving containers
  - **Includes** manual pouring of solid products
    - Powders
    - Granules
  - **Excludes** applying the product

Objectives

- To develop more accurate information on exposures to antimicrobials to support exposure assessments for solid formulations that are manually poured
- To satisfy a requirement for new data imposed by EPA's Reregistration Eligibility Decision (RED) documents
- To support Registration Review as well as pending and future registrations for various antimicrobial solid products and uses

Quick View of Study Design

Use Pattern Scenarios				
Grouping of AaiH	Occupational Granules	Occupational Powders	Consumers Granules	Consumers Powders
Group 1	5 to 25 lbs (n=6)	5 to 25 lbs (n=6)	1 to 12 lbs (n=6)	1 to 12 lbs (n=6)
Group 2	25 to 50 lbs (n=6)	25 to 50 lbs (n=6)	12 to 30 lbs (n=6)	12 to 30 lbs (n=6)
Group 3	50 to 100 lbs (n=6)	50 to 100 lbs (n=6)	30 to 50 lbs (n=6)	30 to 50 lbs (n=6)

Criteria for a Surrogate Solid Product

- Stable
- Appropriate low vapor pressure
- Robust and sensitive analytical method
- Exposure at the high end of the range for both powder and granule product types
  - Small to large source containers
  - Various receiving container sizes and configurations
  - Use of (or not) scoop
  - Appropriate amount poured

Selected Surrogate Test Material

- Cyanuric Acid (CYA) proposed
  - Pool chemical used as a stabilizer
  - Not an EPA registered antimicrobial
  - CAS Number 108-80-5
  - 100 percent active ingredient
  - Can be formulated as both granule and powder
  - Can be used without chemical resistant gloves

Toxicity of Test Material

- The rat developmental oral NOAEL for monosodium isocyanurate is used to represent CYA
  - NOAEL is 200 mg/kg/day based increased hydrocephaly in offspring at the next highest dose tested (LOAEL = 500 mg/kg/day)
  - No route-specific, repeat dose toxicity testing, for dermal or inhalation routes available
- Acute dermal and inhalation testing in rabbits and rats (respectively) indicate minimal acute toxicity

Subject's Potential Dose Estimates to Powders

- Exposure (Dose) Estimate Approaches
  - Two approaches to evaluate absorbed dermal dose
    - Unit Exposure & Dermal absorption (1 percent)
    - Max skin flux (Jmax in units of mg/cm^2/hr)
  - Inhalation
    - Inhalation dose

Potential Dose/Risk Estimates (continued)

- Unit exposure (UE) approach
  - Dermal (consumer, powder) = 3.7 mg/lb ai * 50 lb ai * 0.01 DA * (1/70 kg)= 0.0264 mg ai/kg
  - Inhalation (worker, powder) = 0.0434 mg/lb ai * 100 lb ai * (1/70 kg)= 0.062 mg ai/kg
- Margin of Exposure (MOE) = NOAEL/Dose
  - Dermal = 200 mg/kg / 0.0264 mg/kg = 7,600
  - Inhalation = 200 mg/kg / 0.062 mg/kg = 3,200

Potential Exposure/Risk Estimates (continued)

- Maximum skin flux (Jmax in units of $mg/cm^2/hr$)

  = Permeability coefficient, Kp (cm/hr) * Solubility saturation, Csat (g/cm^3)

  = 7.54E-3 cm/hr * 2.7 g/cm^3

  = 2.04E-2 $mg/cm^2/hr$

- Theoretical maximum absorbed dose (mg/kg)

  = Jmax ($mg/cm^2/hr$) * Body SA (cm^2) * (1 hr/24 hr) * (1/70 kg)

  = 2.04E-2 $mg/cm^2/hr$ * 20,450 cm^2 * 0.0417 hrs * (1/70kg)

  = 0.249 mg/kg

- MOE (1hr) = NOAEL (200 mg/kg) / Max Abs Dose (0.249 mg/kg) = 800

Study Design: Single Location

- Concord, Ohio
  - Pouring of a solid product does not vary geographically
  - Indoor portion of the study for the occupational scenarios to be conducted in the Ricerca Biosciences laboratory (warehouse)
  - Outdoor portion of the study for the consumer scenarios is outside at same warehouse (simulated pool)

Variables Affecting Exposure from Solid Pouring

- Amount of material poured
- Source container size
- Height of pouring
- Receiving container type, size, and contents
- Number of pours
- Use or non-use of scoop
- Pre-dissolving product
- Inter variability of subjects

Proposed Scoops

Sample Characteristics

- Occupational Scenarios – Test subjects will be professional applicators who pour solids as part of their job; no restriction to a specific industry or years of experience
- Consumer Scenarios – Test subjects will be from the general public, lived within last 5 yrs in a home with a swimming pool, and experienced using pool chemicals (no restriction on years of experience)
- Same subjects will be tasked to participate in both the granule and powder scenarios
  - 18 different subjects to be used for 2 occupational scenarios
  - 18 different subjects to be used for 2 consumer scenarios

Summary of Study Design

Group Number	Occupational (Gloves) 25, 50, and 90 lb containers			Consumer (No Gloves) 1, 2, 6, and 25 lb containers		
	Method	Scenarios		Method	Scenarios	
		Granules	Powders		Granules	Powders
1	Scoop (n=6)	5 - 25 lbs	5 - 25 lbs	Pour (n=6)	1-12 lbs	1-12 lbs
2	Scoop (n=3) Pour&Scoop (n=3)	25 - 50 lb	25 - 50 lb	Pour (n=3) Pour&Scoop (n=3)	12-30 lbs	12-30 lbs
3	Scoop (n=3) Pour&Scoop (n=3)	50 to 100 lbs	50 - 100 lb	Pour (n=3) Pour&Scoop (n=3)	30-50 lbs	30-50 lbs

ME Stratification by Amount Handled

- Constant concentration of test material; exposure varies with amount handled, subject-specific behaviors, and characteristics of sample design
- Minimum amount poured 5 lbs for occupational and 1 lb for consumer
- Maximum amount poured 100 lbs occupational and 50 lbs for consumer
- Amount (weight) to be poured will be randomly selected
  - The number of source containers to be poured by each ME not assigned yet
  - The sizes of source containers to be poured during each ME will depend on the random selection from the fixed container sizes
- Anticipated exposure duration is 6 to 40 minutes

Random Design Elements

- The following is a list of random design elements incorporated in protocol:
  - Selection of study participants
  - Source containers assigned to ME
  - Assigning consumers to pre-dissolve solid product
  - Order in which MEs pour granule vs powder
  - Study participant assignment by size group

Pouring Procedures

- Each subject will open source containers and then pour into receiving containers
  - Source containers: bags, cans, pails, drums
  - Receiving containers will simulate industrial tanks and pools
  - Pre-dissolving powder formulation (4 of 18 consumer MEs)
- Scoop
  - New EPA recommendation: Where scoops are applicable, scoop until you can't scoop no more, then pour remainder
  - Size of scoop to be determined by researchers; subjects will be offered multiple scoops to choose from

Field Measurements

- Air temperature & relative humidity
- Characteristics of HVAC system
- Amount of material applied
- Observations/Video/Photographs

Measurement of Dermal Residues

- Whole body dosimeters
  - Inner dosimeters
    - Long-johns
    - Provide estimate of dermal exposure
  - Outer dosimeters
    - Normal work clothing consistent with label PPE
    - Provide estimate of protection provided by a single layer of clothing
- Hand wash at end of task
- Face/neck wipe at end of task

Measurement of Inhalation Exposure

- Personal Air Samplers
  - OSHA Versatile Sampler (OVS) tubes
  - IOM Sampler
    - Inhalable particles up to 100 µm
    - Respirable particles ≤4 µm
  - Flow rate 2 L/min

Analytical Phase

- Matrices – WBD dosimeters, hand washes, face/neck wipes, and air samples
- Method validation
- QA/QC plan
  - Field recovery analysis
  - Storage stability studies
  - Break-through analysis

Fold Relative Accuracy

Parameter	Fold Relative Accuracy
Arithmetic Mean	2.6
95th Percentile	2.8

Compliance with Scientific Standards

- This protocol has addressed the technical aspects of applicable exposure monitoring guidelines
  - EPA Series 875 Group A - Applicator Monitoring Test Guidelines
  - OECD Applicator Guidelines
  - Good Laboratory Practices (GLPs) (40 CFR Part 160)
- Previous comments by EPA and JRC have all been satisfactorily addressed
- EPA has provided several new recommendations

Recommendations

- Describe the orientation of the airflow in relationship of the “pouring” and the test subject for both indoors and outdoors (e.g., is powder being blown in direction of or away from the subject?).
- The test subjects representing the consumer population should also wear the same respiratory protection as the occupational test subjects (prudent).
- Make final individual ME assignments of scoop sizes, AaiH, and containers.
- Empty source containers (where applicable) with scoop and then pour out the remainder.
- Add a wind speed stop criteria for conducting study outdoors.

Recommendations (continued)

- Need to account for hand wash removal efficiency in the final study (e.g., default correction factors, literature, hand wash removal efficiency study, etc.)
- Default correction factors, if no other information, and if hands and neck/face are:
  - ≤20% of total dermal, then no correction;
  - 20 to 60% of total dermal, then 50% correction;
  - ≥60% of total dermal, then removal efficiency study

Summary Conclusion

- This protocol is likely to yield scientifically reliable information, satisfying the following criteria:
  - It would produce important information to fill an identified regulatory need;
  - This need cannot be addressed except by research with human subjects;
  - It has a clear scientific objective; and
  - The study design should produce data adequate to achieve the objective.

EPA Ethics Assessment of AEATF II Solid Pour Scenario and Protocol

Kelly Sherman
Human Research Ethics Reviewer
Office of Pesticide Programs

Value to Society

- Many consumers and workers pour solid antimicrobial products, so reliable data on potential dermal and inhalation exposure are needed to support EPA exposure assessments
- Existing data have limitations
- Knowledge likely to be gained will be usable in exposure assessments for
  - Both professional users and consumers
  - Wide variety of antimicrobial products and use patterns

Subject Selection

- Subjects will be recruited through newspaper advertisements
- Callers will be informed about the study using an IRB-approved script
- Callers will be screened for eligibility, and then scheduled for informed consent meetings
- Inclusion/Exclusion Criteria are complete and appropriate except that “skin conditions of the face/neck” should be added

Subject Selection 2

- No potential subjects are from a vulnerable population
- Subjects will be recruited through newspaper advertisements, not through employers
- Recruitment materials and interactions with potential subjects will be conducted in English or Spanish, depending on subject preference

Consent Process

- Principal investigator (or bilingual researcher) meets individually with interested candidate
  - Provides information about study design in candidate's preferred language
  - Applies eligibility criteria
  - Reviews Informed Consent Document
  - Provides label and MSDS
  - Answers questions
- Principal Investigator confirms understanding and solicits consent to participate

Risks and Risk Minimization

Four categories of risk; protocol provides appropriate measures to minimize each

1. Irritant response to test material or to the soapy mixture used to wash the hands and face/neck
2. Heat-related illness
3. Embarrassment while changing
4. Unwanted disclosure of pregnancy test results

Benefits

- No direct benefits to subjects
- Sponsors will benefit from improved exposure and risk assessments
- Likely societal benefit is higher quality exposure and risk assessments for antimicrobial products

Risk-Benefit Balance

- Risks have been effectively minimized
- Residual risks to subjects will be low
- Risks to subjects are reasonable in light of potential societal benefits

Respect for Participants

- Participant privacy will be maintained
- Proposed payments to subjects are reasonable
- Participants will be free to withdraw at any time, for any reason

Independent Ethics Review

- Schulman Associates IRB was the reviewing institutional review board
- Schulman Associates reviewed and approved the protocol and supporting documents in English and Spanish

Applicable Ethical Standards

- This is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws
- The primary ethical standards applicable to this research are 40 CFR 26, subparts K and L

Revisions Requested by EPA Before Research Proceeds

- Add “skin conditions of the face/neck” to the exclusion criteria
- Revise section 9D of the protocol to specify that eye irritation or respiratory irritation experienced by two or more subjects (in addition to adverse skin reaction) will trigger the Study Director to contact all subjects to determine if further medical management is needed

Revisions Requested by EPA Before Research Proceeds—2

- Revise residential monitoring consent form to explain that subjects will need to wear a particulate dust mask
- Add “skin reaction and respiratory irritation” to the research-related injuries section of the consent form

Revisions Requested by EPA Before Research Proceeds—3

- Revise the newspaper advertisement for the Occupational Scenario to specify the requirement for job experience pouring solid antimicrobials

Revisions Requested by EPA in Future Protocols

- Incorporate the HSRB's forthcoming guidance about how to provide personal exposure results to subjects

Compliance with Ethical Standards

- All requirements of §26.1111, §26.1116, and §26.1117 are met
- All requirements of §26.1125 are met
- Requirements of §26.1203 are met
- If EPA's and HSRB's requested corrections are made, research conducted according to this scenario and protocol will likely meet the applicable requirements of 40 CFR part 26, subparts K and L

Charge Questions

If the proposed AEATF II solid pour study proposal is revised as suggested in EPA's review and if the research is performed as described:

1) Is the research likely to generate scientifically reliable data, useful for assessing the exposure of individuals who manually pour solid antimicrobial products?

2) Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?