EPA Science Assessment of AEATF II Liquid Pour Scenario and Protocol

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Organization of Presentations

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  - Tim Leighton
- Ethics Assessment
  - Kelly Sherman

Overview: Liquid Pour Scenario/Protocol

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

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					

Liquid Pour Scenario Definition

- Manual pouring of a liquid formulation containing an antimicrobial chemical into receiving containers
  - **Includes** manual pouring of a liquid product
  - **Excludes** applying the antimicrobial

Objectives

- To develop more accurate information on exposures to antimicrobials to support exposure assessments for liquid 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 liquid products and uses

Quick View of Study Design

Scenario	Group	MEs	Number of Source Containers to be Poured	Total Volume Potentially Poured	Receiving Container
Conventional (DDAC)	1 (Small)	6	Each ME to pour 10 small containers	Up to 5 gallons	2 sizes
	2 (Medium)	6	Each ME to pour 10 medium containers	Up to 14 gallons	3 sizes
	3 (Large)	6	Each ME to pour 4 large containers	20 gallons	1 size
Reduced Splash (ADBAC)	1 (Small)	6	Each ME to pour 15 small containers	Up to 7.5 gallons	2 sizes
	2 (Medium)	6	Each ME to pour 15 medium containers	Up to 21 gallons	3 sizes
	3 (Large)	6	Each ME to pour 6 large containers	30 gallons	1 size

Reduced-splash Container

Criteria for a Surrogate Liquid Product

- Stable
- Appropriate low vapor pressure
- Robust and sensitive analytical method
- Exposure at the high end of the range for different liquid product types
  - Small to large source containers
  - Various receiving container sizes and configurations
  - Use of (or not) measuring cup
  - Appropriate volume poured

Variables Affecting Exposure from Liquid Pouring

- Source container design (2 exposure scenarios)
  - Conventional
  - Reduced-splash
- Amount of material poured
- Source container size
- Height of pouring
- Receiving container type, size, and contents
- Volume and number of pours
- Use or non-use of measuring cup
- Inter variability of subjects

Selected Surrogate Test Material

- Two chemicals proposed
  - DDAC for conventional source containers
  - ADBAC for reduced-splash containers
- Maquat WP and Maquat DS 1412
- EPA Reg. Nos. 10324-91 and 10324-25
- Active Ingredients to be used in source containers

0.2%	ADBAC: n-Alkyl dimethyl benzyl ammonium chloride
0.2%	DDAC: Didecyl dimethyl ammonium chloride

Toxicity of Test Materials: ADBAC

- ADBAC dermal NOAEL reported in EPA RED is 20 mg/kg/day (333 ug/cm^2) for dermal irritation
  - No dermal toxicity data available for low concentrations
  - No systemic effects observed, only irritation
- ADBAC inhalation NOAEL reported in EPA RED is 3 mg/kg/day, based on an oral study
- Based on the ADBAC RED, predicted dermal and inhalation risks will not be of concern

Toxicity of Test Materials: DDAC

- DDAC dermal NOAEL reported in EPA RED is 1000 mg/kg/day at 0.13% ai (the highest dose tested)
  - No systemic effects; no irritation observed
  - Proposed concentration of DDAC in the test product is low (0.2% ai)
- DDAC inhalation NOAEL reported in EPA RED is 10 mg/kg/day, based on an oral study
- Based on the DDAC RED, predicted dermal and inhalation risks will not be of concern

Study Design: Single Location

- Concord, Ohio
  - Pouring of a liquid product does not vary geographically
  - Study to be conducted in laboratory
    - 2 rooms with laboratory
    - Room dimension 12 ft x 24 ft (ceiling?)

Sample Characteristics

- Professional janitors and/or maintenance workers—to ensure sufficient volume of product is poured to obtain usable data with exposure >LOD
- Same study subjects will be used for both conventional and reduce-splash container scenarios
  - Within 1 monitoring event (ME) the subject will pour both a series of conventional source containers containing DDAC and a series of reduced-splash containers containing ADBAC
  - Dosimeters analyzed for both DDAC and ADBAC which will make the distinction between the 2 scenarios

Sample Characteristics (continued)

- Characteristics to capture the high end of potential exposure
  - Source container type and size
  - Receiving container type, size, and contents
  - Height of pouring
  - Pouring volume and number of pours
  - Use or non-use of a measuring cup

Summary of Study Design

Scenario	Group	MEs	Source Container Size and Number to be Poured	Total Volume Potentially Poured	Receiving Container
Conventional (DDAC)	1 (Small)	6	Each ME to pour 10 containers randomly selected from 24, 32, and 64 fluid ounce sizes	40 oz to 5 gallons	32 oz spray bottles and 2 gal bucket
	2 (Medium)	6	Each ME to pour 10 containers randomly selected from 96, 128, and 180 fluid ounce sizes	7.5 to 14 gallons	2 and 4 gallon buckets and 10+ gal basin
	3 (Large)	6	Each ME to pour four 5 gallon buckets	20 gallons	10+ gallon basin
Reduced Splash (ADBAC)	1 (Small)	6	Each ME to pour 15 containers randomly selected from 60 and 64 fluid ounce sizes	60 oz to 7.5 gallons	32 oz spray bottles and 2 gal bucket
	2 (Medium)	6	Each ME to pour 15 containers randomly selected from 96, 128, and 180 fluid ounce sizes	11.25 to 21 gallons	2 and 4 gallon buckets and 10+ gal basin
	3 (Large)	6	Each ME to pour six 5 gallon buckets	30 gallons	10+ gallon basin

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 40 fluid ounces
- Maximum amount poured using the 5 gallon buckets is 30 gallons
- Amount (volume) to be poured will be randomly selected
  - 10 source containers to be poured
  - The exact sizes of source containers to be poured will depend on the random selection from the fixed container sizes within each size group
- Anticipated exposure duration is 10 to 60 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
  - Receiving container height
  - Scenario order (conventional vs reduced-splash)
  - Study participant assignment by size group

Pouring Procedures

- Each subject will pour from 10 source containers into empty receiving containers
  - Conventional source containers
  - Reduced-splash source containers
- Measuring cup
  - Single measure cup into spray bottle (Group 1), fill spray bottle with water
  - Two measuring cups into bucket, then pour entire source container into bucket (Groups 1 & 2)

Field Measurements

- Air temperature & relative humidity
- Characteristics of HVAC system
- Measurements of room dimensions
- 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
  - Run at 2 L/min

Analytical Phase

- Collected samples—dosimeters, hand/face washes, and air samplers
- Method validation
- QA/QC plan
  - Samples simultaneously fortified with ADBAC and DDAC
  - Field recovery analysis
  - Storage stability studies
  - Break-through analysis

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

- Additional random elements
  - Randomize the order in which source container will be poured and describe selection process
  - Randomize use of measuring cup (Group 2)
- Allow workers to fill spray bottles as they *normally would do*
- Describe how airflow in room will be measured
- Monitor activities associated with “spills/cleanup”
- Specify allocation of receiving containers in each Group

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
  - The study design should produce data adequate to achieve the objective

EPA Ethics Assessment of AEATF II Liquid Pour Scenario and Protocol

Kelly Sherman
Human Research Ethics Reviewer
Office of Pesticide Programs

Value to Society

- Many consumers and workers pour 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 professional janitorial workers recruited through newspaper advertisements
- Callers will be informed about the study using an IRB-approved script
- Callers will be screened for janitorial experience and other eligibility factors, and then scheduled for informed consent meetings

Subject Selection 2

- Inclusion/Exclusion Criteria are complete and appropriate
- 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 materials or to solvents
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

- Observations will be as unobtrusive as possible
- 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

- Independent Investigational Review Board, Inc. (IIRB) was the reviewing institutional review board
- IIRB 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

- Identify the newspapers in which the recruiting advertisements will be placed
  - Advertisements should be placed in multiple newspapers targeting different demographic groups
- Replace generic references to “second alternate language” with “Spanish”

Revisions Requested by EPA Before Research Proceeds—2

- Add a statement to consent form stating that subjects should contact the study director if, within 24 hours of participation in the study, they experience a reaction or other symptom that they believe is related to the study
- Develop procedures for handling such a call and document them in an SOP

Revisions Requested by EPA in Future Protocols

- Develop and implement a process for improving and verifying the accuracy of the Spanish translations
- 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 liquid 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 liquid antimicrobial products?
2) Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?