EPA Science Assessment of AEATF II Brush/Roller Painting Scenario and Protocol

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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: Brush/Roller Painting 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

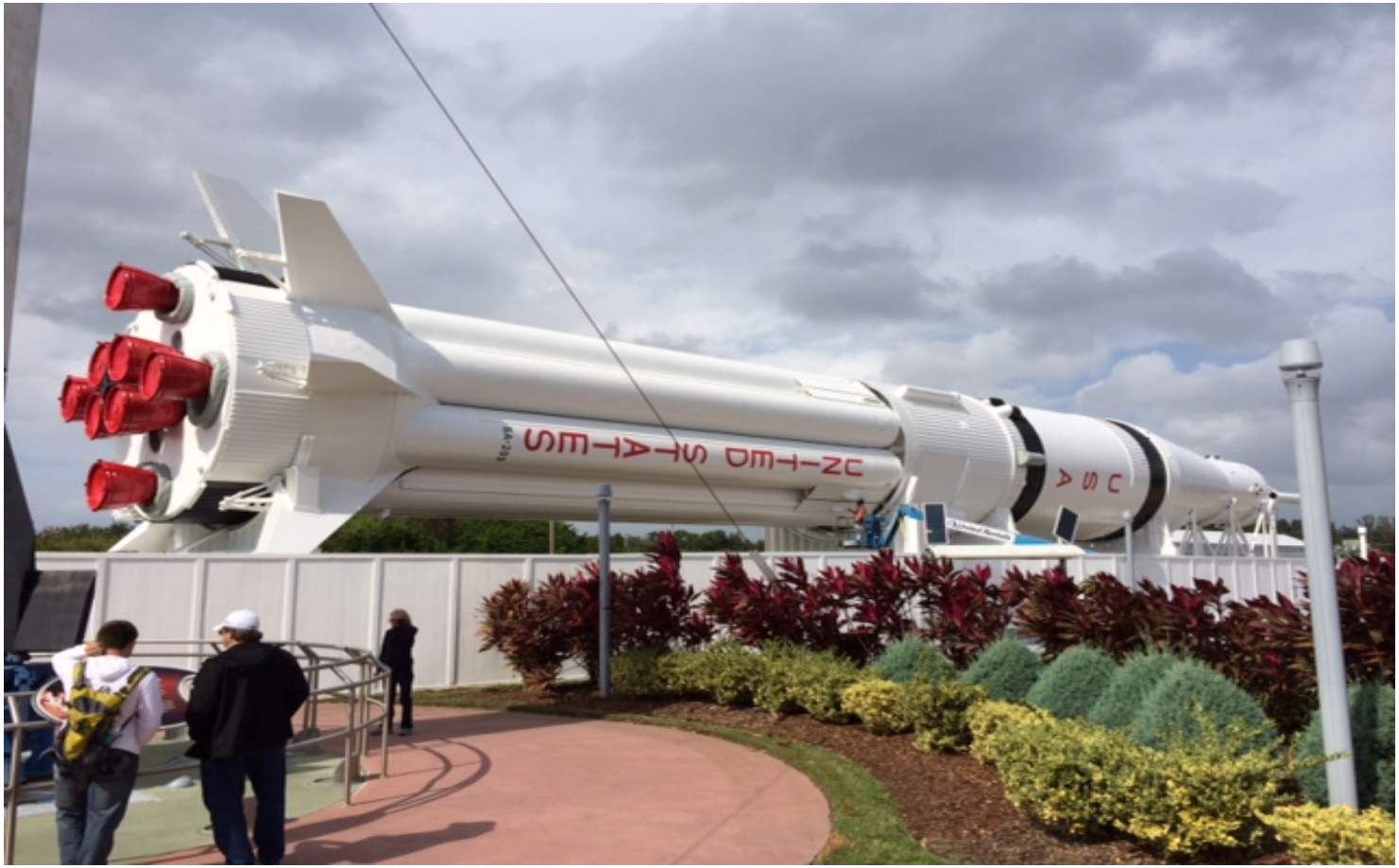
- A new generation of exposure monitoring is needed
  - To address the limitations of PHED/CMA data
  - To maximize the utility of generic data
  - To standardize study design and methods
- FIFRA SAP (Jan 2007) concurred in
  - Need for new studies
  - Soundness of the “generic principle”
  - General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

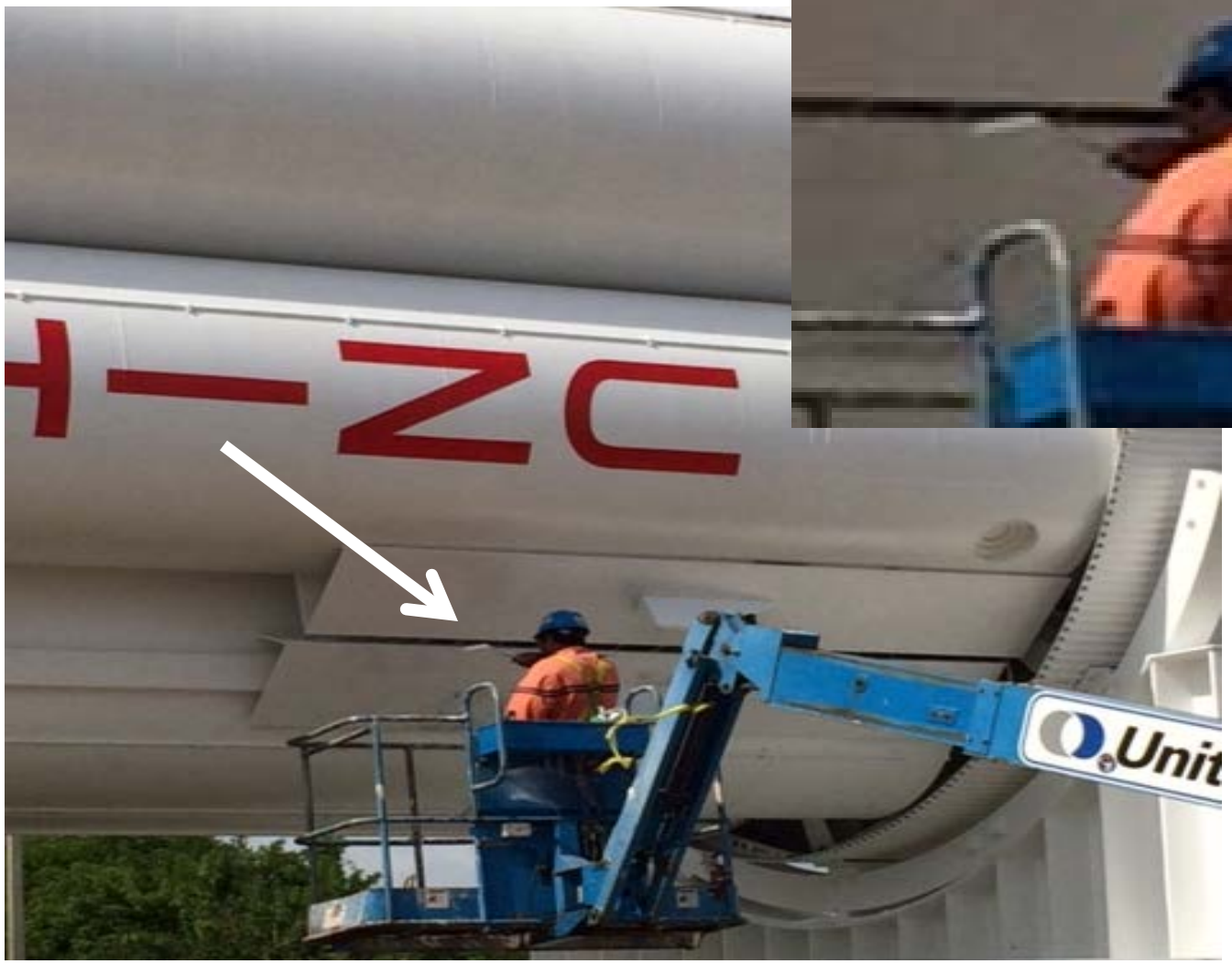
Use Categories	Mop	Wipe	Aerosol	Pour Liquid	Pour Solid	Spray	Immerse/Dip	Pump Liquid	Place Solid	Fog	Pressure Treat	Metalwork Fluid	Brush/Roller	Airless Spray
Ag. Premises & Equipt	X	X	X	X		X	X	X		X				
Food Handling P&E	X	X	X	X		X	X	X		X				
Comm. & Indus. P&E	X	X	X	X		X	X	X		X				
Residential & Public 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					

Brush/Roller Scenario Definition

- Hand-held application of an indoor latex paint containing an antimicrobial chemical
  - **Includes**
    - Painting trim & edges with a brush
    - Painting walls/ceilings with a roller
  - **Excludes**
    - pouring the antimicrobial into the paint
    - painting with an airless sprayer

In Reality, Anything Can Be Painted

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Objectives

- To develop more accurate information on exposures to antimicrobials to support exposure assessments for antimicrobial treated paint
- 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 products (e.g., in-can material preservative)

Criteria for a Surrogate Paint Product

- Stable
- Appropriate low vapor pressure
- Robust and sensitive analytical method
- Active ingredient used in paint
  - In-can material preservative for latex paint
  - Sherwin-Williams latex paint (indoor paint)

Selected Surrogate Test Material

- 1,2-benzisothiazoline-3-one (BIT) proposed
  - Material preservative
  - EPA Registration Number 5385-121
  - CAS Number 2634-33-5
  - 120, 400, and 600 ppm active ingredient in paint
  - Can be used without chemical resistant gloves

Toxicity of Test Material (Dermal)

- The 90-day dermal rat study (MRID 45184601) is used to assess BIT
  - LOAEL is 100 mg/kg/day based on macroscopic and microscopic changes to the stomach mucosa
  - Uncertainties in study based on irritation in the stomach from dermally applied dose
    - Measures were taken to avoid ingestion of test material
    - Selection of LOAEL protective approach
- BIT classified as acute dermal Tox CAT IV (slight irritant) and as a moderate dermal sensitizer

Toxicity of Test Material (Inhalation)

- Inhalation route-specific toxicity not available
- Inhalation toxicity is based on an oral to inhalation route extrapolation from co-critical oral toxicity studies
  - Subchronic dog study with NOAEL of 5 mg/kg/day based on increased incidence of emesis and clinical chemistry alterations at LOAEL of 20 mkd
  - Subchronic rat study with NOAEL of 8 mg/kg/day based on irritation effects in stomach at LOAEL of 25 mg/kg/day

Subject's Potential Dose Estimates to Paint

- Exposure Estimates for the paint brush scenario from PHED
- Unit Exposures (UE)
  - Dermal UE = 180 mg/lb ai for single layer of clothing and no gloves
  - Inhalation UE = 0.28 mg/lb ai

Potential Dose/Risk Estimates (continued)

- Unit exposure (UE) approach
  - Dermal Dose = 180 mg ai/lb ai * 0.0147 lb ai * (1/80 kg)= 0.033 mg ai/kg
  - Inhalation Dose = 0.28 mg ai/lb ai * 0.0147 lb ai * (1/80 kg)= 0.000051 mg ai/kg
- Margin of Exposure (MOE) = LOAEL or NOAEL/Dose
  - Dermal = 100 mg/kg / 0.033 mg/kg = 3,000
  - Inhalation = 5 mg/kg / 0.000051 mg/kg = 97,000

Study Design: Single Location

- Fresno County, CA
- Painting indoor rooms with brush/roller does not vary geographically
- Rooms to be built in warehouse-type of facility, with ceilings and walls constructed of drywall along with trim on door/windows

Variables Affecting Exposure from Painting

- Painting indoors (ceilings, walls, trim)
- Use of both brush and roller (roller on walls and brush for edges/trim; different color paint)
- Amount of active ingredient handled (AaiH)
- Painting duration (slow/fastidious or slow/tired/sloppy?)
- Equipment (brush/roller, roller tray, tape/edger, paint cup, ladder, roller extension, paint rag)
- Clean-up, or not
- Inter variability of subjects

Sample Characteristics

- Test subjects will be from the general public with at least one painting experience in the past 5 years
- Different subjects for each monitoring event (ME)
- Characteristics to capture the high end of exposure
  - Indoors -- rooms will include ceiling (drips/splatters)
  - Consumer test subjects -- less experienced than commercial painters
  - Amount of paint applied -- 2±0.25 gallons
  - No cleanup – cleanup would wash paint from hands

Summary of Study AaiH Design

Group Number	Volume of Paint (gallons)	Concentration of BIT in Paint (ppm)	AaiH (pounds)
Group 1	2 (1.75 to 2.25)	120	0.00261 (0.00228 to 0.00294)
Group 2		400	0.00870 (0.00762 to 0.00979)
Group 3		600	0.0131 (0.0114 to 0.0147)

ME Stratification by Amount Handled

- Constant amount of paint applied (2±0.25 gallons)
- 3 concentrations of test material
  - Group 1 = 120 ppm (n=6)
  - Group 2 = 400 ppm (n=6)
  - Group 3 = 600 ppm (n=6)
- Exposure varies with amount handled, subject-specific behaviors, and characteristics of sample design
- Anticipated exposure duration is 2 to 3 hours (maximum 4 hours anticipated but subject will paint until done)

Random Design Elements

- The following is a list of random design elements incorporated in protocol:
  - Selection of study participants
  - Assigning participants to 3 Groups of different concentrations of BIT

Painting Procedures

- Subjects will be told to paint as they normally would do. Researchers to provide ladder, extension pole, rag, cup
- Specific tasks to be performed by subjects include:
  - Opening paint can lid
  - Painting drywall (walls and ceiling)
  - Painting trim (baseboard and window/door molding)
  - Closing paint can lid
  - No clean-up of paint brush/roller will be performed at end of task (washing equipment would also wash off the paint on hands). Subjects will clean-up routine spills (e.g., drop paint cup).

Field Measurements

- Air temperature & relative humidity
- Characteristics of HVAC system
- Amount of material applied
- Painting duration
- Observations

Measurement of Dermal Residues

- Whole body dosimeters
  - Inner dosimeters
    - Long-johns & painter's cap
    - Provide estimate of dermal exposure
  - Outer dosimeters
    - Normal work clothing
    - Provide estimate of protection provided by a single layer of clothing
- Hand wipe/wash at end of task. Removal efficiency study to be conducted.
- Face/neck wipe at end of task

Measurement of Inhalation Exposure

- Personal Air Samplers
  - OSHA Versatile Sampler (OVS) tubes
  - RespiCon Particle Sampler
    - Inhalable particles < 100 µm
    - Respirable particles <10 µm
  - Flow rate 2 L/min (OVS) and 3 L/min (RespiCon)

Analytical Phase

- Matrices – WBD dosimeters, painter's cap, hand wipes/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	Variance of Log(Exposure)	GSD	Fold Relative Accuracy
Arithmetic Mean	0.285 (PHED Dermal)	1.70	1.30
95th Percentile	0.285 (PHED Dermal)	1.70	1.47

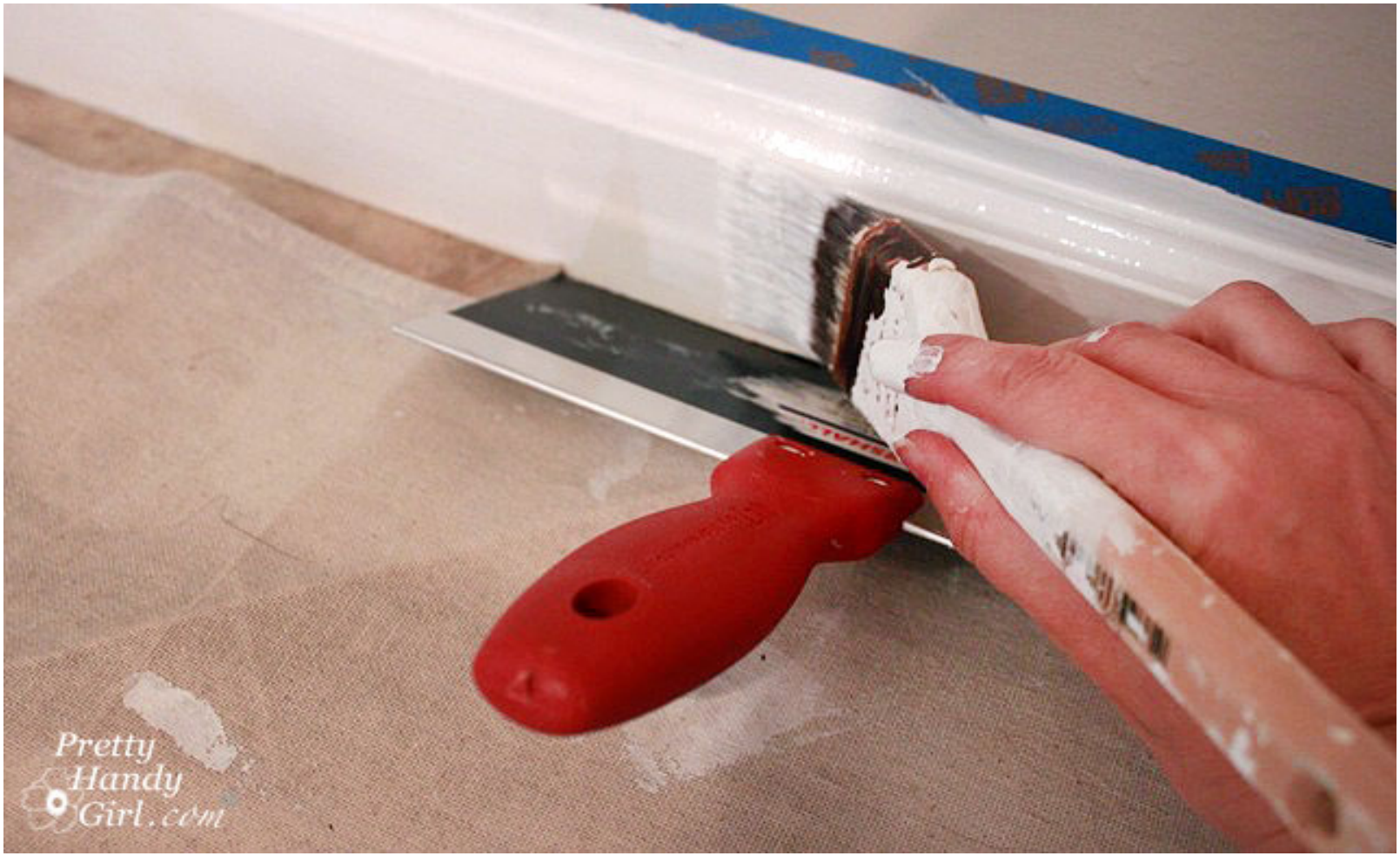
Compliance with Scientific Standards

- 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

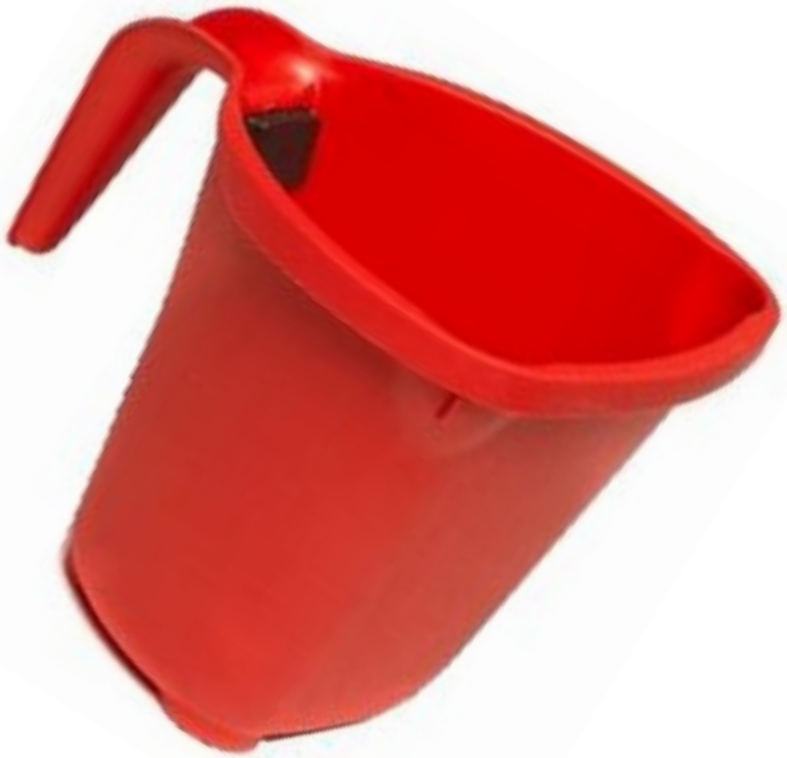
Recommendations

- Describe the orientation of the airflow in relationship to the painting and the test subject.
- Provide the participants with the following (and let the participant decide to use them or not):
  - Paint edger device
  - Paint cup
- Provide the participants with two different colored paints (e.g., white for ceiling and trim, some other color for walls) to foster realistic painting conditions (e.g., need for diligent painting around edges of ceiling/wall and wall/trim)

Paint Edger (Example)



Paint Cup (Example)



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 Brush and Roller Painting Scenario and Protocol

Kelly Sherman
Human Research Ethics Reviewer
Office of Pesticide Programs

Value to Society

- Many consumers and workers apply paint that contains 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” and “allergies or sensitivities to BIT” 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 rubbing alcohol 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 conditionally approved the protocol and supporting documents
  - Full approval will be issued after reviews by CDPR, EPA, and HSRB
  - Spanish translations will be created after approval of English versions

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
- Add “sensitivities” and “BIT or other chemical-based products” to the exclusion criteria
- In the consent form, describe the test product as a pesticide
- Obtain IRB final approval

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 brush and roller painting 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 those who apply latex paint containing an antimicrobial pesticide using a brush or roller?
2) Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?