EPA Science Assessment of AEATF II Hand Wipe/Wash Removal Efficiency (Paint) Protocol

Tim Leighton
Kelly Sherman
USEPA
Office of Pesticide Programs

Jonathan Cohen, PhD
ICF International

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

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Regulatory Context

- This is a proposal for research involving 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

Study Objective

- The primary objective of this study is to determine the removal efficiency of BIT in latex paint, and in isopropyl alcohol (IPA) from human hands
  - Paint portion of the study to be used to correct hand wipe/wash samples in BIT-treated painting studies
  - IPA portion of the study to be used to correct hand wipe/wash samples in non-paint liquid studies in the future and to compare the efficiency results from paint versus IPA solutions

The Need For A Hand Wipe/Wash Removal Efficiency Study to Support the Painting Study

- Removal of dried paint from hands will require a robust hand wash method/procedure
- As noted in Brouwer *et al.* (2000)'s review of the literature:

  "It is recommended to conduct sampling efficiency studies prior to field sampling, under conditions that are quite similar to conditions of exposure regarding exposure process, levels of skin loading, and time of residence of the compound on the skin."

Selected Test Material

- 1,2-benzisothiazoline-3-one (BIT)
  - Material preservative
  - EPA Registration Number 5385-121
  - CAS Number 2634-33-5

Hand Wipe/Wash Procedure

- Hand wipe/wash procedure will mimic the procedure used in brush/roller study, including:
  - Hand scrubbed with gauze sponge
    - Sponge soaked with 50/50 IPA & distilled water
    - Scrub until dried paint is loosened or removed
  - Hand then rinsed with same solution
    - While rinsing subject will rub fingers to palm
    - 250 mL of 50/50 IPA & distilled water rinse
  - Collect sponge & rinse water in steel bowl

Summary of Hand Wipe/Wash Experiment

- 20 test subjects
- 4 Groups, 5 test subjects per Group, 2 hands per subject (n = 10 per Group)
- Volume of treatment solutions:
  - Paint 500 µL per palm
  - IPA 100 µL per palm

Summary of Hand Wipe/Wash Experiment (ctd)

- Concentration of treatment solutions:
  - Paint = 120 and 600 ppm BIT
  - IPA = 0.786 and 3.9 mg BIT/mL IPA
- Palm surface area treated ~50 cm^2
- Two loading rates (~1.6 and 7.8 $\mu g/cm^2$)

Summary Table

Summary of Hand Wash Efficiency Proposal.

Group	No. Test Subjects	Solution (per hand)	Concentration of BIT	AaiH (µg per hand)	Loading (µg/cm^2)[c]
1	5	500 µL Latex Paint	120 ppm	78.2	~1.6
2	5		600 ppm	391	~7.8
3	5	100 µL IPA	0.786 mg BIT/mL IPA	78.5	~1.6
4	5		3.9 mg BIT/mL IPA	390	~7.8

Fortification of Hands with Treatment Solution

- Hand will be pre-washed with Ivory soap and water and then dried
- Two treatment solution experiments:
  - BIT-treated latex paint (500 µL/palm)
  - BIT-treated IPA solution (100 µL/palm)

Fortification of Hands (continued)

- Micropipettes used to fortify palm with treatment solution
- Glass capillary tube will be used to spread treatment solution on palm (2 cm from palm's edges)
- Treatment solution allowed to dry for 45 minutes prior to wipe/wash procedure

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

Subject's Potential Dose Estimates to Paint

Maximum Dose (mg/kg/day) =

0.39 mg/hand x 2 hands x (1/80 kg)=

0.0098 mg/kg/day

Potential Risk Estimates

Margin of Exposure (MOE) = LOAEL/Dose =

100 mg/kg / 0.0098 mg/kg = 10,000

Target MOE 1,000

Analytical Phase

- Matrices – hand wipe/washes
- Method validation
- QA/QC plan
  - Field recovery analysis
  - Storage stability studies

Compliance with Scientific Standards

- This protocol has addressed the following:
  - Test Guidelines – none applicable
  - Good Laboratory Practices (GLPs) (40 CFR Part 160)
- Recommendations in Brouwer et al (2000) used as a guide to review the hand wipe/wash efficiency protocol

Discussion based on Brouwer et al (2000)

- The sample size of 10 palms/group approximates that found in the literature (sample sizes in literature from 3 to 12)
- The proposed hand loading (1.6 and 7.8 µg/cm^2) approximates the anticipated hand exposures in the brush/roller exposure study
  - The average hand loading in the PHED paint brush study was 10.5 µg/cm^2 (range of 4.8 to 19.7 µg/cm^2)
  - PHED paint study hand sampling based on cotton gloves

Discussion (continued)

- Residence time is proposed to be 45 min
  - BIT dermal absorption (rats) is 1.7% over 4 hours
  - Paint study exposure anticipated up to 3 to 4 hours; but not all exposure occurs at time 0
- Method of contamination: palm versus whole hand
- Hand wipe/wash procedure will mimic that used in actual exposure study. Suggest video tape procedure.

Summary Conclusion

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

EPA Ethics Assessment of AEATF II Hand Wash Removal Efficiency Protocol

Kelly Sherman
Human Research Ethics Reviewer
Office of Pesticide Programs

Value to Society

- This study will allow for accurate interpretation of the results of the AEATF's Brush and Roller study and possibly other studies
- 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

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 “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

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

1. Skin reaction to test material or rubbing alcohol used to wash the hands
2. 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 “sensitivities” and “BIT or other chemical-based products” to the exclusion criteria
- In the consent form, describe the test product as a pesticide
- Obtain final IRB 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 hand wash removal efficiency study proposal is revised as suggested in EPA's review and if the research is performed as described:

1) Is this research likely to generate scientifically reliable data, useful for determining the removal efficiency of BIT from the hands due to dermal exposure associated with the use of latex paint and non-paint liquid solutions containing BIT?

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