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**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**  
WASHINGTON D.C., 20460

OFFICE OF  
CHEMICAL SAFETY AND  
POLLUTION PREVENTION

*March 18, 2011*

**MEMORANDUM**

**SUBJECT:** Materials for Review by the Human Studies Review Board for its April 13-14, 2011 Meeting

**TO:** Jim Downing  
Designated Federal Official  
Human Studies Review Board  
Office of Science Advisor (8105R)

**FROM:** William L. Jordan  
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This memorandum describes the materials that the Environmental Protection Agency's (EPA's) Office of Pesticide Programs is providing for review by the Human Studies Review Board (HSRB or Board) at the meeting scheduled for April 13-14, 2011. At this meeting, EPA will ask the Board to address scientific and ethical issues surrounding these three topics, each of which is discussed further below:

1. A report from the Agricultural Handler Exposure Task Force (AHETF) of completed research monitoring the exposure of workers applying pesticide sprays to orchard and trellis crops with open-cab airblast equipment.
2. A report from the Antimicrobial Exposure Assessment Task Force II (AEATF) of completed research monitoring the exposure of professional janitorial workers when wiping indoor surfaces with liquid antimicrobial pesticide.
3. A published report (Gulson et al. 2010) of an intentional exposure human study measuring dermal absorption of zinc oxides contained in sunscreens.

**1. Completed AHETF research on exposure of workers applying pesticide sprays using open-cab airblast equipment.**

In October 2008, the HSRB reviewed three protocols for research to measure the levels of dermal and inhalation exposure received by pesticide applicators who spray pesticides with open cab airblast equipment. Following favorable HSRB reviews and after revisions to address EPA, HSRB, and California Department of Pesticide Regulation (CDPR) comments, this research was conducted in summer 2009. The completed reports and monograph were submitted to EPA in November 2010.

If the data for the Open Cab Airblast Applicator Scenario are accepted by EPA, the resulting data will be added to the Agricultural Handler Exposure Database (AHED<sup>®</sup>). EPA intends to use these data generically to estimate daily dermal and inhalation exposures of workers who treat agricultural crops with conventional pesticides using open-cab airblast equipment. If considered appropriate, data from this scenario addressing exposures from open cab airblast pesticide applications will be combined with data from an appropriate mixing/loading scenario to estimate exposures of workers who both mix/load and apply.

Because this research involved scripted exposure, it meets the regulatory definition of “research involving intentional exposure of a human subject” and thus is covered by subparts K and L of EPA’s amended rule for the protection of human subjects of research. The rule at 40 CFR §26.1303 requires the submitter of reports of completed human research to document its ethical conduct. The rule at 40 CFR §26.1602(a) requires EPA to “review the material submitted under §26.1303 and other available, relevant information, and [to] document its conclusions regarding the scientific and ethical conduct of the research.” The rule at 40 CFR §26.1602(b) further requires EPA to submit the data and EPA’s review to the HSRB if it decides to rely on the data.

EPA has reviewed the AHETF completed study reports, IIRB correspondence reports, and monograph, and has concluded that the research provides scientifically sound, useful information, and was conducted in substantial compliance with the ethics requirements at 40 CFR part 26, subparts A through L.

**Charge Questions:**

- a. Was the research reported in the Agricultural Handler Exposure Task Force (AHETF) completed monograph report and associated field study reports faithful to the design and objectives of the protocol, SOPs, and governing documents?
- b. Has EPA adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating exposure of those who apply pesticides with open cab airblast equipment?
- c. Does available information support a determination that the studies were conducted in substantial compliance with subparts K and L of 40 CFR Part 26?

EPA is providing for HSRB review the following documents concerning the AHETF OCAB completed studies and monograph:

**a. EPA Reviews**

1. EPA Science Review of OCAB Completed Studies
2. EPA Science Review of OCAB Monograph
3. EPA Ethics Review of OCAB Completed Studies

**b. Background Documents**

1. AHE62
  - a. AHE62 Final Cluster Report
  - b. AHE62 IIRB Correspondence Report
  - c. AHE62 Excel Files
2. AHE63
  - a. AHE63 Final Cluster Report
  - b. AHE63 IIRB Correspondence Report
  - c. AHE63 Excel File
3. AHE64
  - a. AHE63 Final Cluster Report
  - b. AHE63 IIRB Correspondence Report
  - c. AHE63 Excel File
4. AHE07 (Pre-rule Study)
  - a. AHE07 Amended Summary Report FINAL
  - b. AHE07 Field Rpt Open-Cab Airblast
  - c. AHE07 Analytical Phase Report
  - d. AHE07 Excel File
5. Monograph
  - a. OCAB Final Monograph Report (MRID 48326701)
  - b. Final MU Selection Plan OCAB 7-21-08
  - c. OCAB Monograph Excel Files
    1. OCAB Data with MEA-QAd FINAL 9-15-10 - to EPA 11-18-10
    2. OCAB-before MEA-QAd - FINAL 9-14-10 & 10-4-10 - to EPA 11-18-10
  - d. OCAB Monograph SAS Files
    1. Eval\_OCAB.sas
    2. Macro\_GetEmpStats.sas
    3. Macro\_NormScores.sas
    4. Macro\_ObjEval\_OCAB.sas
    5. Macro\_TestVCs\_OCAB.sas
    6. MakeSet\_OCAB.sas
    7. OCAB Derm Inh - no Hats - no MEA
    8. OCAB Derm only - wi Hats - no MEA
    9. OCAB Derm only - wi Hats - wi MEA

6. Reference Files
  - a. AHETF SOP Manual for AHE62-AHE63-AHE64 effective February 2009
  - b. AHETF Governing Document Version 2 - August 2010
  - c. EPA Science & Ethics Review Protocol AHE62 (9-23-08)
  - d. EPA Science & Ethics Review Protocol AHE63 (9-23-08)
  - e. EPA Science & Ethics Review Protocol AHE64 (9-23-08)
  - f. HSRB Report of Oct 2008 Meeting - Protocols AHE62, AHE63, AHE64
  - g. IIRB, Inc. Human Research Protection Plan 11-3-10
  - h. IIRB, Inc. Current Membership Roster 11-3-10

**2. Completed AEATF research on exposure of professional janitorial workers when wiping indoor surfaces with an antimicrobial pesticide.**

In April 2008, the HSRB reviewed a protocol for research to measure the dermal and inhalation exposure of professional janitorial workers as they wiped indoor surfaces with a liquid antimicrobial pesticide product. Following favorable HSRB review and after revisions to address EPA, HSRB, and CDPR comments, this research was conducted in summer 2009. The completed report was submitted to EPA in January 2011.

If the data for this scenario are accepted by EPA, the resulting data will be posted to the Biocide Handlers Exposure Database (BHED®). EPA intends to use these data generically to estimate daily dermal and inhalation exposures of those who clean indoor surfaces with antimicrobial pesticides using a trigger-spray bottle and wipes or ready-to-use wipes.

Because this research involved scripted exposure, it meets the regulatory definition of “research involving intentional exposure of a human subject” and thus was covered by subparts K and L of EPA’s amended rule for the protection of human subjects of research. The rule at 40 CFR §26.1303 requires the submitter of reports of completed human research to document its ethical conduct. The rule at 40 CFR §26.1602(a) requires EPA to “review the material submitted under §26.1303 and other available, relevant information, and [to] document its conclusions regarding the scientific and ethical conduct of the research.” The rule at 40 CFR §26.1602(b) further requires EPA to submit the data and EPA’s review to the HSRB if it decides to rely on the data.

EPA has reviewed the AEATF Mop Scenario report and supplements and has concluded that it provides scientifically sound, useful information, and was conducted in substantial compliance with 40 CFR part 26, subparts A through L.

**Charge Questions:**

- a. Was the research reported in the Antimicrobial Exposure Assessment Task Force II (AEATF) completed wipe study report faithful to the design and objectives of the protocol and governing documents of AEATF?

- b. Has EPA adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating exposure of those who clean indoor surfaces with antimicrobial pesticides using a trigger-spray bottle and wipes or ready-to-use wipes?
- c. Does available information support a determination that the study was conducted in substantial compliance with subparts K and L of 40 CFR Part 26?

EPA is providing for HSRB review the following documents concerning the AEATF wipe completed study and monograph:

**a. EPA Reviews**

1. EPA Science Review of AEATF Wipe Completed Study
2. Appendix A – Statistical Review of AEATF Wipe Study Using Trigger Spray and Wipe
3. Appendix B – Statistical Review of AEATF Wipe Study Using Ready-to-Use Wipes
4. EPA Ethics Review of AEATF Wipe Completed Study

**b. Background Documents**

1. Final Report AEATF Wipe Study 070264 - 1-21-2011 signed
2. EPA Science and Ethics Review of Wipe Study Proposal
3. HSRB Report of April 2008 meeting – reviewing Mop and Wipe Study Proposals
4. AEATF II SOPs (7-15-09)
  - a. SOP Table of Contents\_Effective 071509
    - 1A.1 Organizational Structure
    - 1B.1 Personnel Responsibilities
    - 1C.1 Study Director Selection
    - 1D.1 Inspection of AEATF II Facilities Data
    - 1E.0 Communication Directives
    - 1F.0 Adverse Effects Reporting
    - 2A.1 Study Authorization and Approval
    - 2B.1 Study Number Assignment
    - 2C.1 Protocol Design and Preparation
    - 3A.1 SOP Preparation, Approval, Maintenance, and Distribution
    - 3B.1 Use of AEATF II and Contractor SOPs
    - 4A.1 Study Report Preparation
    - 5A.1 QA Personnel Administration.pdf
    - 5B.1 AEATF II QAU Responsibilities
    - 5C.1 QAU Records
    - 5E.1 Protocol and Amendment Review
    - 5F.1 Inspection Audit types and Frequency
    - 5G.1 Study Inspections
    - 5H.1 Data Audits
    - 5I.1 Facility Inspections
    - 5J.1 Report Audits

- 5K.1 Inspection Report Distribution
  - 6A.1 Storage of Raw Data
  - 6B.1 Access to Archived Data
  - 6C.1 Specimen and Retention Sample Storage
  - 7A.1 Test, Control, and Reference Substances Receipt and Shipment
  - 7B.1 Test, Control, and Reference Substances Labeling
  - 7C.1 Disposal of Test, Control, and Reference Substances
  - 7D.1 Test, Control, and Reference Substances Chain of Custody
  - 7E.1 Test and Reference Substance Analysis
  - 8A.2 Whole Body Sampling - Inner, Outer and Socks Dosimeters
  - 8B.3 Hand Wash Samples
  - 8C.2 Dermal Face Neck Wipe Samples
  - 8D.1 Collection of Air Samples using OVS Tubes
  - 8E.1 Fortification of Matrix Samples
  - 8F.1 Sample Identification
  - 8H.0 Pre-Washing Dosimeter Garments
  - 9A.1 Body Surface Areas
  - 9B.3 Field Fortification Adjustment Factors
  - 9C.1 Numerical Formatting and Handling
  - 9D.1 Analytical Method Number Assignment
  - 9E.1 Raw Data Collection
  - 9F.1 Data Corrections
  - 9G.1 Raw Data Handling
  - 9H.1 Preparation of True Copies
  - 9I.1 Analytical Method Development and Validation
  - 9J.1 Storage Stability
  - 10A.1 Rotameter Calibration
  - 10B.1 Packing, Handling and Shipping of Samples
  - 10C.1 Worker and Study Observations
  - 10D.1 Application Equipment Operation Verification
  - 10E.1 Worker Sample Collection Sequence
  - 10F.1 GPI Electronic Digital Flow Meter
  - 10G.1 Personal Air Sampling Pump Calibration
  - 11A.1 Pregnancy Testing and Nursing Status
  - 11B.1 Heat Stress
  - 11C.1 Emergency Procedures
  - 11E.0 Heat Stress Management for Observational Worker Exposures
  - 11F.0 Adverse Events Reporting to IRB
5. IIRB, Inc. Human Research Protection Plan 11-3-10
  6. IIRB, Inc. Current Membership Roster 11-3-10

**3. A published report (Gulson et al. 2010) of an intentional exposure human study measuring dermal absorption of zinc oxides contained in sunscreens.**

EPA is interested in many aspects of nanotechnology, which presents opportunities to create new and better products and improve assessment, management, and prevention of environmental risks. There are, however, unanswered questions about the impacts of nanomaterials on human health and the environment. One of the uncertainties concerns dermal absorption of nanoparticles across intact skin. There is debate in the scientific community as to whether nanoparticles are likely to penetrate the skin barrier upon dermal contact. The results of *in vitro* studies using animal and human skin in the literature indicate that small amounts of different kinds of nanoparticles may penetrate skin in some cases. However, *in vitro* dermal penetration data alone is of limited utility to the Agency in the absence of evidence that the *in vitro* studies are predictive of *in vivo* results. The Gulson et al. (2010) study investigates dermal exposure of human volunteers to ZnO nanoparticles in sunscreen formulations. This study indicates that small amounts of Zn from sunscreens containing nanoscale ZnO particles are absorbed into the bloodstream and eliminated in the urine. It quantifies this amount as approximately 0.001%. This result in humans in the Gulson study *in vivo* is similar to *in vitro* studies with human skin that have been published in the literature. Although the Agency is aware that nanoparticle physicochemical properties, skin treatment conditions, and formulations may differently influence dermal penetration, this corroboration of *in vitro* and *in vivo* dermal penetration results increases the Agency's confidence in the *in vitro* data indicating penetration of small amounts of other kinds of nanoparticles and/or ions from nanoparticles. More importantly, it indicates to the Agency that dermal risk assessments for occupational and residential dermal exposures to nanoparticles should be considered, given evidence of penetration of small amounts of particles and/or ions from nanoparticles both *in vitro* and *in vivo*.

Charge Questions:

- a. Is the Gulson et al. (2010) study scientifically sound, providing reliable data?
- b. If so, is the Gulson et al. (2010) study relevant for qualitative use in support of an assessment of the absorption of metal oxide nanoparticles through the skin?
- c. Is there adequate information to determine that the Gulson et al. (2010) study was conducted in substantial compliance with procedures at least as protective as those in subparts A - L of EPA's regulation at 40 CFR part 26?

EPA is providing for HSRB review the following documents concerning Gulson et al. (2010):

- a. EPA Reviews
  1. EPA Science Review of Gulson et al 2010
  2. EPA Ethics Review of Gulson et al 2010



b. Background Documents

1. Gulson et al 2010 (MRID 48387301)
2. Supplement 1 – Excerpt from Australian National Statement on Ethical Conduct in Human Research 2007