

US EPA ARCHIVE DOCUMENT

DATA REQUIREMENT

Series 875
Occupational and Residential Exposure
Test Guidelines

SUBMISSION TITLE

AHETF Human Research Monitoring Program

--DRAFT--

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SUBMITTED BY

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Statement of No Data Confidentiality Claims

No claims of confidentiality are made for any information contained in this submission on the basis of its falling within the scope of FIFRA 10(d)(1)(A),(B) or (C).

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Administrative Committee Chair
Agricultural Handlers Exposure Task Force

Date

Statement of Compliance with Good Laboratory Practice Standards

Good Laboratory Practice Standards do not apply to this submission. The information contained herein describes the overall testing program and procedures followed by the Agricultural Handlers Exposure Task Force in the occupational monitoring of mixers, loaders, and applicators who handle agricultural pesticides. This submission is provided specifically for review by the United States Environmental Protection Agency and the Human Studies Review Board.

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Introduction

The purpose of this submission is to provide EPA with documentation necessary to evaluate the adequacy of AHETF's overall pesticide handler exposure monitoring program. The package is organized as if it were a study-specific submission comprised of nine chapters; however, for purposes of this submission, only Chapters I, II, III and IX, which contain general information applicable to all studies, are included. Chapters IV through VIII are intended for scenario- or study-specific information and are not pertinent to this submission. A brief description of each chapter follows:

Chapter I contains a reference guide indicating where specific elements from the draft PR-Notice 2006-X (revised) are located within the submission package.

Chapter II contains the Governing Document which describes the overall monitoring program, including technical and ethical considerations. The Governing Document is the primary document in this submission.

Chapter III contains the Standard Operating Procedures (SOPs) developed and used by AHETF. These SOPs cover administrative aspects of the AHETF as well as providing specific technical and ethical requirements for the conduct of field studies. The SOPs will be adhered to unless stated otherwise in a study-specific field protocol.

Chapters IV through VIII are intentionally left blank for purposes of this submission because they are either scenario- or study-specific. When a submission package is prepared for a study-specific protocol, Chapter IV will contain an evaluation of existing scenario-specific data and a justification for additional data; Chapter V will provide a scenario-specific sampling design to collect additional data; Chapter VI will contain study-specific documents, including the study-specific protocol that conforms to the Good Laboratory Practices and other EPA regulations; Chapter VII will contain information regarding the study-specific recruitment and informed consent process, including a copy of the IRB-approved informed consent form; and Chapter VIII will contain study-specific documentation pertaining to ethical oversight, including correspondence between AHETF and an IRB.

Chapter IX contains an important document that was submitted to the January 2007 Scientific Advisory Panel entitled "Comparative Evaluation of Absorbed Dose Estimates Derived from Passive Dosimetry Measurements with Those Derived From Biological Monitoring: Validation Of Exposure Monitoring Methodologies". A revised version of this document has been accepted for publication in *Journal of Exposure Analysis and Environment Epidemiology*.

A nine-chapter submission package such as described here will be prepared for each study-specific protocol and submitted to EPA for review and approval.

**Chapter I. Reference Guide to AHETF Human Research
Monitoring Submission Package**

CHAPTER I

Reference Guide to AHETF Human Research Monitoring Submission Package

This table provides a reference guide indicating where specific elements from the draft PR-Notice 2006-X (revised) are located within the AHETF Human Research Monitoring Program Submission Package. The first column identifies the **Required Elements**. The second column identifies the specific location of the elements in Chapter II (**Governing Document**). The third column identifies the specific location of the elements in Chapter III (**SOPs**). The fourth column (**Other**) identifies the specific location of the elements in Chapters IV through IX.

Required Elements	Governing Doc. (Chapter II)	SOPs (Chapter III)	Other (Chapters IV – IX)
Protocol Identification			
(a) Title			
(b) Date			
(c) Principal Investigator and any sub-investigators			
(d) Participating Laboratories			
(e) Sponsor			
(f) Reviewing IRB	<ul style="list-style-type: none"> GD 13.5 - IRB Review Process 	<ul style="list-style-type: none"> SOP 11.A Ethical Requirements for the Use of Human Subjects 	<ul style="list-style-type: none"> IRB (Chapter VIII)
1. Societal Value of Proposed Research			
(a) What is the stated purpose of the proposed research?	<ul style="list-style-type: none"> GD 1.1 - AHETF & AHED® 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI; 1.3) PHED data evaluation (Chapter IV) Consent Form (Chapter VII)
(b) What research	<ul style="list-style-type: none"> GD - 3.0 – 3.1 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Scenario

Required Elements	Governing Doc. (Chapter II)	SOPs (Chapter III)	Other (Chapters IV – IX)
question does it address? Why is this question important? Would the research fill an important gap in understanding?	Justification for Human Exposure Data		descriptions (Chapter V) <ul style="list-style-type: none"> • Study specific protocol (Chapter VI;2.0) • PHED data evaluation (Chapter IV) • Consent Form (Chapter VII)
(c) How would the study be used by EPA?	<ul style="list-style-type: none"> • GD - 3.1 Regulatory Need for Generic Exposure Data 	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;2.1)
(d) Could the research question be answered with existing data? If so, how? If not, why not?	<ul style="list-style-type: none"> • GD 7.2 - Limitations of PHED • GD 7.3 - Scenario-Specific Data Needs for AHED • GD 8 – Evaluation of Existing Data & Incorporation into AHED® 	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • PHED data evaluation (Chapter IV) • Study specific protocol (Chapter VI;2.2)
(e) Could the question be answered without newly exposing human subjects? If so, how? If not, why not?	<ul style="list-style-type: none"> • GD 3.2 - Alternatives to Additional Human Monitoring 	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • PHED data evaluation (Chapter IV) • Study specific protocol (Chapter VI;2.3)

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Required Elements	Governing Doc. (Chapter II)	SOPs (Chapter III)	Other (Chapters IV – IX)
2. Study Design (a) What is the scientific objective of the study? If there is an explicit hypothesis, what is it?	<ul style="list-style-type: none"> • GD1.3 - General Purpose & Description of AHETF Monitoring Program • GD 9 - Program Design • GD 9.4 - Benchmark Objectives and Required Sample Size 	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Not applicable
(b) Can the study as proposed achieve that objective or test this hypothesis?	<ul style="list-style-type: none"> • GD 4.2 -Likelihood of Realization of Benefits • GD 9 - Program Design • Appendices B and C 	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Not applicable
2.1 Statistical Design			
(a) What is the rationale for the choice of sample size?	<ul style="list-style-type: none"> • GD 9 - Program Design • Appendices B and C 	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;3.0)
(b) What negative and positive controls are proposed? Are proposed controls appropriate for the study design and statistical analysis plan?	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;3.0)
(c) How is the study blinded?	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Not Applicable
(d) What is the plan for allocating individuals to treatment or control groups?	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Not Applicable
(e) Can the data be statistically analyzed?	<ul style="list-style-type: none"> • GD 11.1 - Assessment of Benchmark Adequacy Objectives 	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Not Applicable

Required Elements	Governing Doc. (Chapter II)	SOPs (Chapter III)	Other (Chapters IV – IX)
(f) What is the plan for statistical analysis of the data?	<ul style="list-style-type: none"> GD 11.1 - Assessment of Benchmark Adequacy Objectives 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable
(g) Are proposed statistical methods appropriate to answer the research question?	<ul style="list-style-type: none"> GD 11.1 - Assessment of Benchmark Adequacy Objectives; Appendix C 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable
(h) Does the proposed design have adequate statistical power to definitively answer the research question?	<ul style="list-style-type: none"> GD 11.1 - Assessment of Benchmark Adequacy Objectives Appendix C 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable
2.2 How and to what will human subjects be exposed?			
(a) What is the rationale for the choice of test material and formulation?	<ul style="list-style-type: none"> GD 5.2 - Risk of Exposure to Surrogate Chemicals GD 7.1 - Handler Scenarios Included in the Monitoring Prog. Appendix B (B4.7-Identifying Growers & Contractors) 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;13.4)
(b) What is the rationale for the choice of dose/exposure levels and the staging of dose administration?	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable
(c) What duration of exposure is proposed?	<ul style="list-style-type: none"> GD 9.3 - Monitoring Periods 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;13.8)

Required Elements	Governing Doc. (Chapter II)	SOPs (Chapter III)	Other (Chapters IV – IX)
2.3 Endpoints and Measures			
(a) What endpoints will be measured? Are they appropriate to the question(s) being asked?	<ul style="list-style-type: none"> GD 12 - Exposure Monitoring Techniques 	<ul style="list-style-type: none"> SOP Chapter 8 – Matrix Samples 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;3.0)
(b) What steps are proposed to ensure measurements are accurate and reliable?	<ul style="list-style-type: none"> GD 10.1.3 - GLP Quality Assurance Procedures GD 10.1.4 - Quality Control Procedures 	<ul style="list-style-type: none"> SOP Chapter 5 – Quality Assurance Unit (AHETF only) SOP Chapter 7 – Test, Reference & Control Substances 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;1.13 & 18.0)
(c) What QA methods are proposed?	<ul style="list-style-type: none"> GD 10.1.3 - GLP Quality Assurance Procedures GD 10.1.4 - Quality Control Procedures 	<ul style="list-style-type: none"> SOP Chapter 5 – Quality Assurance Unit (AHETF only) 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;1.13 & 18.0)
(d) How will uncertainty be addressed? Will point estimates be accompanied by measures of uncertainty?	<ul style="list-style-type: none"> GD 11.1 - Assessment of Benchmark Adequacy Objectives Appendix C 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable
3. Subject Selection			
3.1 Representativeness of Sample			
(a) What is the population of concern? How was it identified?	<ul style="list-style-type: none"> GD 9.1 - Target Population GD 9.2 - Purposive Diversity Sampling of MUs Appendix B 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;4.0)

Required Elements	Governing Doc. (Chapter II)	SOPs (Chapter III)	Other (Chapters IV – IX)
(b) From what populations will subjects be recruited?	<ul style="list-style-type: none"> • GD 9.1 - Target Population • GD 9.2 - Purposive Diversity Sampling of MUs • Appendix B 	<ul style="list-style-type: none"> • SOP 11.B – Recruitment of Study Volunteers & Informed Consent 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;4.0)
(c) Are expected participants representative of the population of concern? If not, why not?	<ul style="list-style-type: none"> • GD 9.1 - Target Population • GD 9.2 - Purposive Diversity Sampling of MUs • Appendix B 	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;4.0)
(d) Can the findings from the proposed study be generalized beyond the study sample?	<ul style="list-style-type: none"> • GD 9.1 - Target Population • GD 9.2 - Purposive Diversity Sampling of MUs • GD 9.6 - Scenario Sampling Plans • Appendix B 	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;4.0)
3.2 Equitable Selection of Subjects			
(a) What are the inclusion/exclusion criteria? Are they complete and appropriate?	<ul style="list-style-type: none"> • GD 13.2.3 - Eligibility Criteria 	<ul style="list-style-type: none"> • SOP 11.B – Recruitment of Study Volunteers & Informed Consent • SOP 11.C – Worker Health Status 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;4.0)

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Required Elements	Governing Doc. (Chapter II)	SOPs (Chapter III)	Other (Chapters IV – IX)
(b) What, if any, is the relationship between the investigator and the subjects?	<ul style="list-style-type: none"> GD 13.2.4 - Use of Vulnerable Groups 	<ul style="list-style-type: none"> SOP 11.B – Recruitment of Study Volunteers & Informed Consent 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;4.0) Consent Form (Chapter VII)
(c) If any potential subjects are from a vulnerable population, what is the justification for including them?	<ul style="list-style-type: none"> GD 13.2.4 - Use of Vulnerable Groups 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;4.0)
(d) What process is proposed for recruiting and informing potential subjects?	<ul style="list-style-type: none"> GD 13.2 - Recruitment GD 13.3 - Informed Consent Process 	<ul style="list-style-type: none"> SOP 11.B – Recruitment of Study Volunteers & Informed Consent 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;4.0)
(3) If any subjects are potentially subject to coercion or undue influence, what specific safeguards are proposed to protect their rights and welfare?	<ul style="list-style-type: none"> GD 13.3 - Informed Consent Process 	<ul style="list-style-type: none"> SOP 11.B – Recruitment of Study Volunteers & Informed Consent 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;4.0)
3.3 Remuneration of Subjects			
(a) What remuneration, if any, is proposed for the subjects?	<ul style="list-style-type: none"> GD 13.4 - Subject Remuneration 	<ul style="list-style-type: none"> SOP 11.B – Recruitment of Study Volunteers & Informed Consent 	<ul style="list-style-type: none"> Consent Form (Chapter VII) Study specific protocol (Chapter VI;4.0)
(b) Is proposed remuneration so high as to be an undue inducement?	<ul style="list-style-type: none"> GD 13.4 - Subject Remuneration 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable

Required Elements	Governing Doc. (Chapter II)	SOPs (Chapter III)	Other (Chapters IV – IX)
(c) Is proposed remuneration so low that it will only be attractive to economically disadvantaged subjects?	<ul style="list-style-type: none"> GD 13.4 - Subject Remuneration 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable
(d) How and when would subjects be paid?	<ul style="list-style-type: none"> GD 13.4 - Subject Remuneration 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Consent Form (Chapter VII) Study specific protocol (Chapter VI;4.0)
4 Risks to Subjects			
4.1 Risk characterization			
(a) Have all appropriate prerequisite studies been performed? What do they show about the hazards of the test materials?	<ul style="list-style-type: none"> GD 3.2 - Alternatives to Additional Human Monitoring 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable
(b) What is the nature of the risks to subjects of the proposed research?	<ul style="list-style-type: none"> GD 5 - Risks to Subjects in AHETF Studies 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;5.1)
(c) What is the probability of each risk associated with the research? How was this probability estimated?	<ul style="list-style-type: none"> GD 5 - Risks to Subjects in AHETF Studies 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable
4.2 Risk minimization			
(a) What specific steps are proposed to minimize risks to subjects?	<ul style="list-style-type: none"> GD 5 - Risks to Subjects in AHETF Studies to Subjects GD - 5.7 Likelihood of Serious or Irreversible Effects GD - 13.6 Additional Efforts to Protect Human Subjects 	<ul style="list-style-type: none"> SOP 11.G – Identification and Control of Heat Stress SOP 11.E – Pesticide Safety Precautions 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;5.2)

Required Elements	Governing Doc. (Chapter II)	SOPs (Chapter III)	Other (Chapters IV – IX)
(b) How do proposed dose/exposure levels compare to established NOELs/NOAELs for the test materials?	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Not Applicable 	<ul style="list-style-type: none"> • Not Applicable
(c) What stopping rules are proposed in the protocol?	<ul style="list-style-type: none"> • GD - 5.1.2 Minimizing the Risk of Heat Illness • 13.2.3 - Eligibility Criteria • GD 13.6 - Additional Efforts to Protect Human Subjects 	<ul style="list-style-type: none"> • SOP 11.G – Identification and Control of Heat Stress • SOP 11.E – Pesticide Safety Precautions 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;13.5) • Consent Form (Chapter VII)
(d) How does the protocol provide for medical management of potential illness or injury to subjects?	<ul style="list-style-type: none"> • GD 5 - Study Risks to Subjects in AHETF Studies • GD 13.6 - Additional Efforts to Protect Human Subjects 	<ul style="list-style-type: none"> • SOP 11.G – Identification and Control of Heat Stress • SOP 11.H – Emergency Procedures for Human Subjects 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;7.0) • Consent Form (Chapter VII)
(e) How does the protocol provide for safety monitoring?	<ul style="list-style-type: none"> • GD 5 - Study Risks to Subjects in AHETF Studies • GD 13.6 - Additional Efforts to Protect Human Subjects 	<ul style="list-style-type: none"> • SOP 11.E – Pesticide Safety Precautions • SOP 11.G – Identification and Control of Heat Stress 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;13.5) • Consent Form (Chapter VII)

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Required Elements	Governing Doc. (Chapter II)	SOPs (Chapter III)	Other (Chapters IV – IX)
(f) How does the protocol provide for post-exposure monitoring or follow-up? Is it of long enough duration to discover adverse events which might occur?	<ul style="list-style-type: none"> GD 13.6 - Additional Efforts to Protect Human Subjects 	<ul style="list-style-type: none"> SOP 11.B – Recruitment of Study Volunteers & Informed Consent SOP 11.H – Emergency Procedures for Human Subjects 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;5.3) Consent Form (Chapter VII)
(g) How and by whom will medical care for research-related injuries to subjects be paid for?	<ul style="list-style-type: none"> GD 13.6 - Additional Efforts to Protect Human Subjects 	<ul style="list-style-type: none"> SOP 11.H – Emergency Procedures for Human Subjects 	<ul style="list-style-type: none"> Consent Form (Chapter VII)
5. Benefits			
(a) What benefits of the proposed research, if any, would accrue to individual subjects?	<ul style="list-style-type: none"> GD 4.1.1 - Benefits to Subjects 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;6.0) Consent Form (Chapter VII)
(b) What benefits to society are anticipated from the information likely to be gained through the research?	<ul style="list-style-type: none"> GD 4.1.2 - Benefits to Society 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;6.0) Consent Form (Chapter VII)
(c) How would societal benefits be distributed? Who would benefit from the proposed research?	<ul style="list-style-type: none"> GD 4.1.2 - Benefits to Society 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;6.0) Consent Form (Chapter VII)
(d) What is the likelihood that each identified societal benefits would be realized?	<ul style="list-style-type: none"> GD 4.2 - Likelihood of Realization of Benefits 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable

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Required Elements	Governing Doc. (Chapter II)	SOPs (Chapter III)	Other (Chapters IV – IX)
6. Risk/Benefit Balance (a) How do the risks to subjects weigh against the anticipated benefits of the research, to subjects or to society?	<ul style="list-style-type: none"> GD 6 - Risk versus Benefit Comparison 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;7.0)
7. Independent Ethics Review			
(a) What IRB reviewed the proposed research?	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;8.0) Consent Form (Chapter VII) IRB (Chapter VIII)
(b) Is this IRB independent of the investigators and sponsors of the research?	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> IRB (Chapter VIII)
(c) Is this IRB registered with OHRP?	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> IRB (Chapter VIII)
(d) Is this IRB accredited? If so, by whom?	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> IRB (Chapter VIII)
(e) Does this IRB hold a Federal-Wide Assurance from OHRP?	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> IRB (Chapter VIII)
(d) Are complete records of the IRB review as required by 40 CFR 26.1125 provided?	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> IRB (Chapter VIII)
(e) What standard(s) of ethical conduct would govern the work?	<ul style="list-style-type: none"> GD 13 - Ethical Considerations 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> IRB (Chapter VIII)

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Required Elements	Governing Doc. (Chapter II)	SOPs (Chapter III)	Other (Chapters IV – IX)
8. Informed Consent (a) Will informed consent be obtained from each prospective subject?	<ul style="list-style-type: none"> GD 13.3 - Informed Consent Process 	<ul style="list-style-type: none"> SOP 11.B – Recruitment of Study Volunteers & Informed Consent 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;9.0) Consent Form (Chapter VII)
(b) Will informed consent be appropriately documented, consistent with the requirements of 40 CFR 26.1117?	<ul style="list-style-type: none"> GD 13.3 - Informed Consent Process 	<ul style="list-style-type: none"> SOP 11.B – Recruitment of Study Volunteers & Informed Consent 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;9.0) Consent Form (Chapter VII)
(c) Do the informed consent materials meet the requirements of 40 CFR 26.1116, including adequate characterization of the risks and discomforts to subjects from participation in the research, the potential benefits to the subject or others, and the right to withdraw from the research?	<ul style="list-style-type: none"> GD 13.3 - Informed Consent Process 	<ul style="list-style-type: none"> SOP 11.B – Recruitment of Study Volunteers & Informed Consent 	<ul style="list-style-type: none"> Consent Form (Chapter VII)
(e) What is the literacy rate in English or other languages among the intended research subjects?	<ul style="list-style-type: none"> Unknown 	<ul style="list-style-type: none"> Not Applicable 	<ul style="list-style-type: none"> Not Applicable
(f) What measures are proposed to overcome language differences, if any, between investigators and subjects?	<ul style="list-style-type: none"> GD 13.3 - Informed Consent Process 	<ul style="list-style-type: none"> SOP 11.B – Recruitment of Study Volunteers & Informed Consent 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;9.0) Consent Form (Chapter VII)
(h) What specific procedure will be followed to inform prospective subjects and to seek and obtain their consent?	<ul style="list-style-type: none"> GD 13.3 - Informed Consent Process 	<ul style="list-style-type: none"> SOP 11.B – Recruitment of Study Volunteers & Informed Consent 	<ul style="list-style-type: none"> Study specific protocol (Chapter VI;4.0 & 9.0) Consent Form (Chapter VII)

Required Elements	Governing Doc. (Chapter II)	SOPs (Chapter III)	Other (Chapters IV – IX)
(i) What measures are proposed to ensure fully voluntary participation and to avoid coercion or undue influence?	<ul style="list-style-type: none"> • GD 13.2.4 - Use of Vulnerable Groups • GD 13.3 - Informed Consent Process 	<ul style="list-style-type: none"> • SOP 11.B – Recruitment of Study Volunteers & Informed Consent 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;4.0) • Consent Form (Chapter VII)
9. Respect for Subjects			
(a) How will information about prospective and enrolled subjects be managed to ensure their privacy?	<ul style="list-style-type: none"> • GD 13.2.3 - Eligibility Criteria • GD 13.3 - Informed Consent Process 	<ul style="list-style-type: none"> • SOP 6.D – Access to Confidential Worker Information • SOP 11.D – Pregnancy Testing • SOP 11.B – Recruitment of Study Volunteers & Informed Consent • SOP 11.H – Emergency Procedures for Human Subjects 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;10.1) • Consent Form (Chapter VII)
(b) How will subjects be informed of their freedom to withdraw from the research at any time without penalty?	<ul style="list-style-type: none"> • GD 13.3 - Informed Consent Process 	<ul style="list-style-type: none"> • SOP 11.B – Recruitment of Study Volunteers & Informed Consent 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;10.2) • Consent Form (Chapter VII)
(c) How will subjects who decline to participate or who withdraw from the research be dealt with?	<ul style="list-style-type: none"> • GD 13.3 - Informed Consent Process 	<ul style="list-style-type: none"> • SOP 11.B – Recruitment of Study Volunteers & Informed Consent 	<ul style="list-style-type: none"> • Study specific protocol (Chapter VI;9.0) • Consent Form (Chapter VII)

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**Chapter II. Governing Document for a Multi-Year Pesticide Handler
Worker Exposure Monitoring Program**

Chapter II

Agricultural Handlers Exposure Task Force (AHETF)

Governing Document for a Multi-Year Pesticide Handler Worker Exposure Monitoring Program

Version Number: 0 (Final Draft)

Date: May 21, 2007

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Executive Summary

The Agricultural Handlers Exposure Task Force (AHETF) was formed to develop a generic exposure database for use by the EPA and other regulatory agencies for their assessment of occupational exposures encountered by workers who mix, load and/or apply agricultural chemicals. The new database, AHED[®] (Agricultural Handlers Exposure Database) will serve the necessary role of supplanting data in PHED (Pesticide Handlers Exposure Database) which has been in use since 1992.

The scientific question AHETF will be addressing is:

“What is the distribution of worker exposures to pesticides during distinct occupational pesticide handling scenarios?”

Generating new exposure data involves monitoring potential dermal and inhalation exposure for occupational pesticide handlers performing a variety of mixing/loading and application tasks. Validated passive exposure monitoring dosimetry techniques are utilized in the AHETF field study program. These techniques are preferred as they are non-invasive and provide exposure estimates for individual body parts that can be useful in determining exposure mitigation strategies.

The foundation and justification for the AHETF exposure monitoring program are presented in this “governing document”. Field study protocols, and other detailed documentation, are prepared and submitted separately to support human research protocol submissions.

The degree to which individual workers are potentially exposed while handling pesticides depends primarily on specific activities and conditions. These include:

- Task performed (e.g., mixing/loading or applying, or both);
- Equipment being used (e.g., open or closed loading systems, aerial or ground application equipment, and open or enclosed cab tractors);
- Amount of pesticide handled;
- Use and type of Personal Protection Equipment (PPE) worn; and
- Pesticide product formulation type (e.g., liquid vs. solid)

Since exposure potential is not determined by the particular active ingredient in the agricultural chemical product (with the exception of volatile compounds such as fumigants which AHETF will not address), the use of generic databases are widely accepted by regulatory authorities throughout the world. These generic exposure databases organize exposure measurements in a manner that represents distinct exposure situations, or “scenarios”. AHETF has designed a program to monitor worker exposure for a wide variety of occupational handler scenarios using registered pesticide products and typical worker activities and equipment.

A recent EPA Scientific Advisory Panel has affirmed that the currently available occupational pesticide handler data, primarily in the Pesticide Handlers Exposure Database (PHED), are not adequate to meet contemporary regulatory requirements to properly evaluate agricultural chemical handler exposure potential. AHETF has reviewed thousands of handler exposure measurements in existing studies and identified those that satisfy modern acceptability criteria. Many exposure scenarios need additional data or entirely new data to be useful for regulatory purposes. The AHETF database will contain data for about 30 scenarios that will each be supported by appropriate documentation that describes and justifies the need for additional data. The AHETF scenarios are fundamentally similar to those in PHED that have proven to be practical for regulatory authorities to conduct product-specific exposure assessments using a generic database.

The target population for each AHED[®] scenario is the set of all possible agricultural handlers and the days on which they perform scenario-specific tasks. Each possible handler-day is implicitly associated with a set of conditions that includes, but is not limited to, behavior, chemical, equipment used, location, and environmental conditions. Diversity in work conditions results in a distribution of worker exposure measurements. This distribution (and more often just some characteristic of the distribution) is needed by EPA and other regulatory agencies to conduct quantitative exposure assessments to evaluate the safety of pesticide products. AHETF limits the target population of study participants to include only healthy workers who are 18 years or older, are not pregnant or nursing, speak Spanish or English, and have occupational experience with the particular task being monitored. This monitored population adequately represents the population of agricultural occupational pesticide handlers for the scenarios of concern.

The primary benchmark objective of the database is to describe selected measures of the exposure distribution with a pre-determined level of accuracy for each scenario. Guidance is provided to AHETF from the regulatory authorities on the minimum degree of accuracy needed in particular scenarios for the data to be adequate for regulatory use. For example, a current consensus is that exposure distribution measures (e.g., means and percentiles) generally need to be accurate within approximately 3-fold of the true target population value. Based on this benchmark accuracy requirement and knowledge about the nature of typical monitoring results (i.e., relative variation among workers), AHETF determines an appropriate sample size for each handler scenario. This determination is presented in separate MU sampling plans that will be reviewed by EPA for each scenario.

The AHETF program is descriptive rather than experimental. The focus is on collecting data that adequately describe the expected variation of handler-day exposures throughout the target population of the scenario. Consequently, its purpose is not to determine how well the data can be used to discover causal relationships between study conditions and resulting exposure. However, for most regulatory purposes, exposure is usually expressed normalized by some measure of potential active ingredient contact. This normalizing factor is almost always the amount of active ingredient handled by a worker (AaiH). Therefore, the resulting exposure database can also express individual worker exposure values normalized by AaiH (i.e., μg of exposure/lb. ai handled) or some other measure for each scenario. These normalized exposure values are often used directly by EPA and other regulatory agencies to conduct exposure assessments. Consequently, when the primary benchmark accuracy requirement is expressed in terms of normalized exposure, the AHETF will also, to the extent practical, ensure that there is sufficient diversity in the normalizing factor to permit users of the database to perform a limited examination of the relationship between this factor (e.g., AaiH) and exposure.

The AHETF monitoring program uses a non-random sampling method, known as purposive diversity sampling for selecting handler-days from the target population. This involves purposively selecting a diversity of conditions associated with handler-days in the target population and then recruiting subjects that will perform the scenario task under these selected conditions using an AHETF surrogate chemical. Each individual handler-day selected (i.e., the subject and day of monitoring) is called a “Monitoring Unit” (MU) to emphasize its unique character. Each MU consists of monitoring dermal and inhalation exposure potential for a single worker for a time period that represents a typical workday.

The AHETF purposive sampling process occurs in two stages. First, a sample of appropriate locations and time periods (dates) are selected. From within each such cluster of handler-days, a final sample of monitoring units is then obtained. The statistical design, therefore, requires several clusters of data for each scenario. For 3-fold benchmark accuracy, the typical scenario data set (assuming no existing data and default variation) would consist of 25 total MUs collected from about 5 distinct clusters. Particular attention is also paid to diversifying AaiH (or other normalization factor), location (and date), and individual workers. There will be attempts to recruit workers within each cluster that tend to utilize a variety of equipment and practices within that scenario definition. In most respects, workers will perform their tasks in a normal fashion which typically results in diversity in equipment type, crops, use rates, worker practices, etc.

When completed, scenario data are added to AHED[®]. This database is then used by EPA and other regulatory agencies to characterize agricultural handler exposure potential for the purpose of regulating pesticide use. Key characteristics of AHETF's multi-year pesticide handler exposure monitoring program and the associated AHED[®] database are outlined below:

- Exposure potential for 33 scenarios will be addressed
- Each scenario will contain about 25 MUs in about five clusters
- AHED[®] will contain approximately 825 MUs
- About 100 existing MUs have been identified as useful and put into AHED[®]
- To date, 173 MUs have been generated by AHETF
- The remaining MUs will be collected in clusters of about 5 MUs
- Individual AHETF monitoring studies will generally collect 5 to 15 MUs at one location and involve MUs for 1 to 3 scenarios
- Approximately 50 field studies will need to be conducted over the next several years to complete AHED[®]

Monitoring exposure to professional agricultural handlers who follow their normal practices presents a reasonably low additional risk to participants. The potentially increased risk of heat illness from wearing an inner dosimeter is mitigated by a medical management program which emphasizes measures to prevent heat-related illness and guidelines for stopping participation. The benefit to agricultural workers as a whole and to society in general, in the form of more accurate measurements of potential exposure to pesticides, outweighs the risks to study participants.

1 Introduction

1.1 AHETF and AHED[®]

The Agricultural Handler Exposure Task Force (AHETF) was established in December 2001 to generate exposure data for agricultural pesticide handlers and meet EPA registration requirements. Several AHETF member companies had ongoing data requirements resulting from product-specific data call-in notices, reregistration obligations, or prospective registration obligations. These companies agreed to jointly develop generic data in support of their respective registration obligations since existing data are not adequate.

The scientific question AHETF will be addressing is:

“What is the distribution of worker exposures to pesticides during distinct occupational pesticide handling scenarios?”

The primary AHETF goal is to collect pesticide handler exposure monitoring data and incorporate it into a new generic database that will be used to estimate exposure distributions. The database will be called AHED[®], Agricultural Handlers Exposure Database. AHED[®] will be submitted to EPA and other regulatory agencies and used by those regulators to conduct detailed quantitative exposure assessments and make safety determinations for occupational pesticide uses. The AHETF will exercise the rights associated with submission of data under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) in connection with AHED[®]. AHETF is focused on occupational mixer/loaders and applicators of pesticides on farms, in nurseries, in greenhouses, and in seed treatment facilities. It is not concerned with residential uses, fumigants, or incidental exposures from others using pesticides.

Generic databases were developed over the last twenty years in response to a regulatory need to assess the occupational risks associated with a wide range of pesticide handling situations. The concept was discussed and its development encouraged by a FIFRA Scientific Advisory Panel (SAP) in 1986. In 1992, the Pesticide Handlers Exposure Database (PHED) was first released following a joint effort by pesticide manufacturers, the EPA, and Canadian regulators (Honeycutt, 1986; Lunchick, 1994; Reinert, 1986). Since then, PHED has been used extensively in a generic manner and has successfully supported many occupational risk assessments. Much of the data in PHED are derived from exposure studies that are outdated or scientifically inadequate by current standards (Stasikowski, 2001). In addition, many handler scenarios of interest to EPA are absent or under-represented in PHED. Other regulatory agencies, including Pest Management Regulatory Agency (PMRA) and California Department of Pesticide Regulation (CDPR), have expressed similar dissatisfaction with the limitations of PHED data. In 2007, EPA convened another SAP to discuss the need for new data to replace PHED. The panel agreed with EPA

that “additional data could significantly improve the Agency’s ability to assess worker exposure” (SAP, 2007). A major purpose of the Agricultural Handlers Exposure Database, or AHED[®], is to address PHED deficiencies.

Like PHED, AHED[®] will be populated with exposure data for workers who handle pesticides as part of their normal job, so their participation as subjects in the field studies underlying AHED[®] will not add appreciably to their typical exposure from handling pesticides. All AHETF studies are designed and conducted in accordance with the latest U.S. EPA guidelines for occupational exposure studies.

The development of AHED[®] is funded and directed by the AHETF. An AHETF Joint Regulatory Committee (JRC) has been established to promote active participation by interested regulatory agencies. The JRC is comprised of AHETF representatives and representatives of the U.S. EPA, PMRA, CDPH, and the United States Department of Agriculture (USDA). This committee meets on a regular basis to review program progress and provide technical and regulatory input to the AHETF.

Between AHETF inception (December of 2001) and April of 2006 (effective date of Final Human Testing Rule), AHETF:

- Defined the scope of AHETF
- Developed standard operating procedures and a standardized exposure monitoring protocol
- Reviewed 216 existing studies against acceptance criteria (about 3,000 worker exposure measurements, or monitoring units) for possible incorporation into AHED[®]
- Acquired the right to cite 105 monitoring units (MUs) from existing data (from 6 scenarios)
- Collected 173 MUs (from 11 scenarios)
- Developed and began populating AHED[®]

In 2006, AHETF submitted five study protocols to EPA and the Human Studies Review Board (HSRB) to continue its monitoring program, but the HSRB concluded it did not have sufficient information about the overall monitoring program to evaluate the scientific soundness and ethical acceptability of the protocols (Fisher, 2006). Since that review AHETF has devoted its resources to developing design guidelines that are likely to result in useful data for EPA and other regulatory agencies. It formally documented all of its study design, conduct, and analysis procedures. This included an internal examination of the existing MUs that AHETF acquired and those it collected in the last few years. AHETF intends to submit new pesticide handler exposure monitoring study protocols for review by EPA in 2007 and for conduct by AHETF in 2008.

1.2 Purpose of this Document

This document describes the overall AHETF exposure monitoring program and plans for developing a generic database, AHED[®]. It discusses the need for additional human exposure data, the rationale for determining the use scenarios that will be included in the program, how AHETF will generate new data, how the data will be analyzed statistically, and how the data will be used to support regulatory decisions. However, it is important to point out that each distinct handling scenario that AHETF will address (approximately 30 scenarios, see Section 7.1) will involve an examination of existing data and detailed plans for collecting sufficient new data to meet regulatory needs. This information will be submitted as separate documentation as AHETF studies address the different scenarios. In this sense, each scenario can be considered a distinct research project and this governing document alone will not provide complete information to justify any of those projects.

Further, each field study designed to collect MUs from scenario sampling plans (and there will typically be several studies per scenario) will have a protocol that describes the study-specific information including which tasks are to be conducted (i.e., scenarios included), how many MUs are to be collected, and study-specific details for test substances and exposure monitoring procedures.

This document also discusses important ethical considerations including how AHETF will generally recruit growers (or landowners), recruit workers, obtain informed consent, and minimize risks to study participants. Each field study protocol will address specific procedures that will be followed since different handling scenarios will involve special issues for subjects including study-specific risks and grower/participant recruitment procedures.

This governing document will support each specific study protocol for new AHETF worker exposure studies (in conjunction with the scenario-specific plans and standard operating procedures [SOPs]). Throughout this document, an attempt is made to identify information as specifically describing program-specific approaches (i.e., general information such as the basic sampling method), scenario-specific procedures (such as evaluating the need for additional human data), or study-specific detail (such as the risks associated with the particular task, surrogate chemical, etc.).

This document describes how the AHETF monitoring program will comply with 40 CFR Part 26 regarding intentional human dosing studies. It also addresses concerns raised in the report of the HSRB meeting of June 27-30, 2006 (Fisher, 2006).

1.3 General Purpose and Description of AHETF Monitoring Program

The primary purpose of the AHETF monitoring program is to develop data that will be incorporated into a generic database (Agricultural Handlers Exposure Database, AHED[®]). These data will consist of dermal and inhalation exposure measurements for workers who handle pesticides under a variety of circumstances, using various pesticides and equipment types. AHETF refers to each unique handling situation as a ‘scenario’ and anticipates the database will contain sufficient data to support exposure assessments for many distinct scenarios. In general, a scenario is a combination of similar work task(s), pesticide formulation, equipment, engineering controls, and work practices (i.e., specific procedures used for a particular task). For example, two scenarios of interest are:

- mixing/loading dry flowable pesticides using open pouring techniques
- applying liquid sprays using airblast equipment with open cabs

A specific sampling plan will be designed for each scenario to meet benchmark adequacy objectives established by AHETF. That plan will define the number of clusters to be sampled and the number of MUs to be included for each cluster. A single MU will consist of dermal and inhalation exposure measurements for a single worker for a typical workday. Clusters are MUs collected in a particular location during the same visit by research personnel. Subjects will perform each task as they would during a normal workday. However, scripting of some field studies (i.e., controlling some aspects of the worker activity) may be used to achieve adequate diversity among the MUs. In particular, the amount of active ingredient handled (AaiH) is often used by EPA to normalize exposure during exposure assessments and most scenarios will focus on diversifying AaiH.

As field studies are completed, each will provide additional MUs for one or more scenarios. As each scenario is populated with MUs consistent with the scenario-specific sampling plan (typically requiring multiple field studies), AHED[®] will gradually be completed. When scenarios have been completed, they will be summarized as described in Section 11 of this document, and the study reports and summaries (scenario monographs) will be formally submitted to EPA and other regulatory agencies to support the use of those AHED[®] scenarios. When completed, AHED[®] will be used to support North American regulatory decisions—that is, to estimate exposure for agricultural uses of existing and new pesticide products in the United States and Canada for a wide variety of scenarios. Regulatory users of the AHED[®] database will be able to estimate individual worker exposures for a single workday given only:

- A mixer/loader and/or applicator pesticide handling scenario of interest and
- A value for a commonly-used measure of ‘active ingredient contact potential’, such as the amount of active ingredient (ai) to be handled by the worker

Daily exposures are not expected to be identical for all individuals in a given scenario nor would such exposures be identical for the same individual performing the same work on different days. This is true since many factors influence exposure within a scenario in addition to the amount of ai handled. Therefore, specification of a scenario and an ai contact potential value can only determine a distribution of potential exposures; that is, a statistical description of the probability that a given exposure level is attained for a set of monitoring units within a given scenario. It is this distribution, and more often just some characteristic of the distribution, that is needed for regulatory risk assessments. Examples of commonly used characteristics are the geometric mean, the arithmetic mean, and various upper percentiles.

Consequently, the overall goal of the AHETF monitoring program is to obtain individual exposure data for each scenario sufficient to adequately approximate the distribution of exposures normalized by ai contact potential. When the amount of ai handled (AaiH) is the normalization factor, for example, the predicted distribution of daily exposures can be obtained by simply multiplying this normalized generic exposure distribution by the AaiH for the specific product being evaluated. The desired degree of characterization of a scenario's exposure distribution may depend, in part, upon the relative importance of the scenario in the regulatory process. For example, higher accuracy may not be necessary for scenarios that are less common or that result in very low exposure. In the case of closed loading granules, for example, potential exposure is very low and it may be a better use of resources to more accurately measure the distribution of higher exposure scenarios than pin down exactly how low the exposure potential is for closed loading of granules.

As stated previously, the AHETF monitoring program is designed to answer the scientific question:

“What is the distribution of worker exposures to pesticides during distinct occupational pesticide handling scenarios?”

This information is needed by EPA (and other regulatory agencies) to assess risks to workers who handle pesticides. This safety determination is mandated by FIFRA. AHETF has established two benchmark objectives that will guide scenario sampling plan designs. The primary objective is to adequately approximate the distribution of exposure so that selected measures (i.e., means and upper percentiles) are accurate to a specified degree for each scenario (e.g., 3-fold, but it could vary by scenario). A secondary objective (for most scenarios) is that the data are adequate to distinguish between complete proportionality and complete independence between exposure and the particular normalizing factor used for the primary objective. For most scenarios this will be the amount of active ingredient handled.

It should be emphasized that the secondary objective is not as important as the primary objective and will not apply to all scenarios. For example, some scenarios may not be amenable to varying the AaiH (or other normalizing factors) enough to have sufficient statistical power to meet the objective. In addition, it might be determined (by AHETF and EPA, collectively) that non-normalized exposure may be of greater regulatory interest for a scenario. In this case, the primary objective would be modified to be based on exposure that is non-normalized and no secondary objective would be specified.

The general approach for scenario-specific sampling designs is to select a variety of MUs using different workers and a diverse set of common conditions that reflect current agricultural practices in North America. Due to the complexity of the program and the expense of collecting exposure data, random sampling designs are neither practical nor appropriate. Exposure will usually be monitored at multiple locations and the amount of active ingredient handled (or other measure of contact potential) will be varied to cover the typical range of product handled for each scenario. However, it should be noted that scenario sampling is not designed to statistically test the impact of location or any other condition of exposure, except for possibly the amount of active ingredient handled (or other normalization factor).

2 Plan for Submitting Human Research Protocols

While this governing document presents general guidelines for AHETF to plan and conduct human exposure monitoring studies, this section will describe the plan for submitting to EPA all the necessary information for review and approval of new human studies. As described above, several distinct studies will generally be conducted to fulfill the data needs for a particular scenario and each study will often involve more than one scenario (e.g., some mixer/loader MUs and some applicator MUs). With each new study protocol, AHETF plans to submit a single, continually paginated document (based on the draft PR Notice 2006-X, as modified by EPA) that presents all the necessary information to evaluate the scientific and ethical validity of the study and each scenario involved in the study. This submission will be organized into 9 Chapters as follows:

Chapter I will contain a reference guide indicating where specific scientific elements from the draft PR Notice are located within the submission package.

Chapter II will contain the latest version of the Governing Document which describes the overall monitoring program, including technical and ethical considerations.

Chapter III will contain the Standard Operating Procedures (SOPs) developed and used by AHETF. The SOPs will be adhered to unless stated otherwise in the study-specific field protocol.

Chapter IV will contain an evaluation of existing data and a justification for additional data for each scenario addressed by the study.

Chapter V will contain an MU sampling plan outlining how new exposure data will be collected for each scenario that will be addressed by the study. This includes a characterization of the handling scenario (based on discussions with scientific community experts). It also includes the statistical basis for the number of new clusters and MUs per cluster, and considerations for diversification of important study conditions. As MUs are collected for a scenario, the scenario plan will be evaluated and revised as needed (for example to guide the purposive sampling of MUs for other studies, but not to re-examine the statistical sample size).

Chapter VI will contain study-specific documents, including the study-specific protocol that conforms to the Good Laboratory Practice and human research regulations, the test substance label, and the test substance Material Safety Data Sheet (MSDS). The protocol will specify the study-specific benefits, risks, and procedures to be followed.

Chapter VII will contain information regarding the study-specific recruitment and informed consent process (based on discussions with workplace community members), including a copy of the IRB-approved informed consent form and recruitment material (both generally in English and Spanish).

Chapter VIII will contain study-specific documentation pertaining to ethical oversight of the study, including all correspondence between AHETF and an IRB (and state regulatory agencies, if applicable).

Chapter IX will contain a copy of important referenced materials that are not readily available to the public.

AHETF intends to submit new human study protocols regularly over the next several years as it works toward building the next-generation generic database of pesticide handler exposures. New study protocols will generally be submitted to EPA at least 6 months ahead of intended monitoring times. Due to the seasonality of pesticide applications for many scenarios, most new study protocols will be submitted in the Fall or Winter for studies that will be conducted in the Spring or Summer of the next calendar year.

3 Justification for Human Exposure Data

A necessary condition for both scientific and ethical acceptability of the AHETF program is that the use of humans to generate these data be justified. This requires that human data are necessary for the regulatory risk assessment process and that adequate alternatives to conducting additional human exposure monitoring are not available. This section discusses the program-level need for human exposure data and the value of generic databases to EPA and other regulators. Section 7 discusses the procedures used to examine the need for data on a scenario-specific basis. Each scenario plan will be accompanied by a separate document that confirms the need for additional human exposure data for that scenario.

3.1 Regulatory Need for Generic Exposure Data

FIFRA requires the U.S. Environmental Protection Agency to assure that any pesticide registered in the United States does not have unreasonable adverse effects on workers handling that pesticide. The PCPA requires a similar determination by Health Canada. This safety determination is generally made by means of quantitative risk assessment and risk management procedures. Risk assessments require a detailed evaluation of the toxicity of the pesticide and an estimation or measurement of the exposure potential for workers (and/or amount of pesticide absorbed by the workers as a consequence of its use). Exposure or absorbed dose estimates are used in conjunction with no-effect exposure levels and/or cancer potency factors, Q1* for hazards identified in standardized toxicology studies. During the risk evaluation, the likelihood of the expression of any toxicological effect on the workers and a comparison of the risks and benefits are considered. This basic paradigm (hazard identification, dose-response assessment, exposure assessment, and risk characterization) was summarized by the National Academy of Sciences and has become the standard for risk assessment by regulatory agencies (NAS, 1983; NAS, 2006). More recently, the pesticide handler risk assessment process was fully described in a summary document prepared for a Scientific Advisory Panel review of exposure methodologies (USEPA, 2007). This summary also describes the tiered approach to handler exposure assessments that includes baseline assessments based on generic data (e.g., PHED or AHED[®]) with minimal PPE and no engineering controls and, when needed, followed by assessments using additional PPE and/or engineering controls, followed by product-specific information (including perhaps biomonitoring data).

AHED[®] is intended to provide the North American regulatory agencies with the potential exposure data necessary for them to perform the handler exposure assessment portion of safety determinations. Toxicology data and benefit information are product-specific and must be provided by individual pesticide product registrants.

When estimating exposure to workers who handle pesticides, a major challenge to overcome is that several parameters contribute to the likelihood and level of exposure.

These include factors such as handling liquids versus solids, product packaging type, using open versus closed systems, applying with various equipment types, amount of product handled, use of personal protective equipment (PPE), and whether the worker mixes/loads or applies or does both. The number of combinations of these parameters makes it impractical to generate human exposure data for all situations, so a number of simplifying approaches have been adopted. These include:

- Establishing various ‘scenarios’ that cover common combinations of these parameters and generating data for those scenarios
- Generating data with workers wearing minimum PPE
- Using data for one chemical/product as a surrogate for another (similar) product
- Assembling generic databases (e.g., PHED) for use as surrogate data applicable to many products

Since the early 1980’s it has been the consensus of the scientific community that the amount of residue that contacts a worker’s clothing and skin, and the amount of residue that is available for inhalation, are primarily a function of physical rather than chemical factors. That is, the chemical nature of the active ingredient in a pesticide product has little influence on the extent of exposure compared to physical parameters associated with the use of the product. The physical parameters include formulation type (e.g., liquid or granule product), method of application, and the way in which a person handles the pesticide during mixing, loading and application. Because of this, exposure potential is considered “generic” since it is independent of the specific active ingredient (Hackathorn, 1985; Honeycutt, 1985 and 1986; Reinert, 1985). Generic exposure data may therefore be used in lieu of product-specific data for most safety assessments. One major exception is that exposure to highly volatile compounds, such as fumigants, is not considered generic, and so will not be addressed by AHETF.

The use of generic data enhances the efficiency of regulatory agencies in conducting exposure assessments. Rather than relying on individual studies to evaluate case-by-case uses of each pesticide product, a single, comprehensive database of high quality data applicable to most products can be used. The broad applicability of generic data and the resulting efficiency of their use in regulatory safety assessments led to the widespread acceptance of PHED. PHED components were created by assembling exposure data from studies that had already been conducted and submitted to EPA.

Most of the pesticide exposure data available at that time had been conducted by individual pesticide manufacturers who designed their studies to support the registration of a specific product or a group of similar products. It was very common for these companies to generate a set of exposure data that represented the worst case for exposure potential incorporating design features such as the maximum use rate and minimum engineering controls. If a risk assessment was acceptable for such a situation, then it was argued that an assessment involving lower use rates, additional PPE, and additional engineering controls would also be acceptable. However, this meant it was common for a study to involve 15 or more measurements of essentially the same situation where each person handled the same product, in the same

packaging, in the same amount, using the same equipment, and for the same amount of time. While these studies are useful for product-specific cases, they are less useful for making generic estimates of exposure. Nevertheless, many of these types of studies were assembled to form PHED and, collectively, the database did improve the risk assessment process as regulators could often rely on larger data sets to estimate potential exposure.

As discussed in detail in Section 7, PHED has several technical limitations since the studies included in PHED were not designed to meet the needs of a generic database. In addition, it is now an older database and many agricultural practices have changed. The written summary of a recent SAP meeting (SAP, 2007) concluded:

The Panel agreed with the Agency's concern about the limitations of the existing PHED exposure database. Furthermore, they concluded that additional data could significantly improve the Agency's ability to assess worker exposure. They listed eight limitations within PHED including its inconsistent data quality; a patch-work of methods, some with high uncertainty and data censoring; a high level of "clustering," and an inadequate number of samples and diversity within some scenarios.

Exposure monitoring methods have also changed since most PHED studies were conducted. Basic passive dosimetry methodology has long been accepted as a standard, reproducible procedure that provides accurate and reliable data and does not underestimate exposure. Even though basic passive dosimetry methodology yields a very sound measure of exposure, there have been some improvements. In particular, much of the data in PHED are based on patch dosimetry and exposures were often not measured on all body areas. The recent SAP (2007) also concluded:

The inclusion within PHED of studies where either not all parts of the body were monitored or a substantial number of exposures were undetectable do not allow the results to yield accurate exposure statistics of interest for regulatory assessments.

Nonetheless, PHED provided reasonable estimates of exposure based on the technology of the 1980's. Today, whole-body garment dosimetry is used instead of patches to improve the ability to estimate the distribution of total body exposure.

There is consensus among regulatory agencies that the most efficient means of generating handler exposure data is to pool technical resources and assemble a generic database. This consensus, EPA's recognition of the limitations of PHED, and their intention to use additional data to augment PHED, led to the formation of the AHETF in December, 2001. The task force database, AHED[®], was designed to reflect a logical set of use scenarios with adequate data in each scenario to provide good estimates of exposure potential and its distribution. Individual measurements will involve separate workers and more diversity in equipment and conditions than in

PHED, especially for the amount of product handled. The recent SAP (2007) concluded:

The AHED study design will also include more reliable exposure assessment methods (especially of the hands; see also Charge #2) and newer ("modern") pesticide application equipment and techniques (see also Charge #4).

3.2 Alternatives to Additional Human Monitoring

Regulatory agencies are charged with assuring that registered uses of a pesticide will not cause unreasonable adverse effects to pesticide handlers. As part of such determinations, regulators and risk assessors must be able to estimate with confidence the levels of occupational exposure. Information now available to support these estimates comes primarily from generic data in PHED, but also from pesticide-specific exposure studies and published literature. Modeling or animal data are of limited use in estimating occupational exposure of workers. The best estimates of worker exposure are based on monitoring pesticide handling activities of people who handle pesticides as part of their regular job. This is what the AHETF program involves.

The only alternatives to the conduct of new human monitoring studies appear to be:

- Continued reliance on existing information sources
- Acquisition of additional handler exposure data from other existing product-specific studies that meet established acceptance criteria and that have generic applicability

The recent SAP (SAP, 2007) endorsed the need for new worker exposure data:

This Panel is clearly of the opinion that additional worker exposure data collected on human volunteers under field conditions and label requirements on chemicals that have been approved by the Agency are necessary.

The limitations of PHED are discussed more thoroughly in Section 7.

Under the first stage of the AHETF program, and prior to the conduct of any field studies with human volunteers, the AHETF reviewed existing handler exposure data from various sources (primarily from AHETF members, CDPR, and the open literature) and acquired data that met established acceptance criteria. These activities are described in Section 8 below. Although some useful worker exposure studies were acquired by AHETF, most of the existing data were not sufficient to meet the generic data needs identified in advance by the AHETF and the Joint Regulatory Committee.

A recent SAP (2007) evaluated the AHETF acceptance criteria and concluded:

The Panel viewed the selection criteria proposed by AHETF and AEATF to be reasonable for generating exposure data for using in exposure assessments, with the following caveats. The monitoring duration requirement may be too stringent. Some provision to allow the inclusion of data from settings where only short-term uses are the norm may need to be added.

Given the limitations of PHED and limited useful existing data, no viable alternatives to performing additional human monitoring studies exist for generating an updated exposure database.

It should also be pointed out that pre-requisite studies for AHETF monitoring do not involve human participants. These pre-requisite studies include analytical method validations, field recovery validations, and toxicity studies that support the registrations of the test materials used. Therefore, the exposure measurements (MUs) proposed by this document reflect the entirety of human participation proposed by the AHETF.

4 Study Benefits

A critical principle of ethical human studies research is that the benefits to the subjects and to society must outweigh the risks to the subjects. To approve proposed research with human subjects, an Institutional Review Board must determine that “risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result” (40 CFR §26.1111(a)(2)).

AHETF believes the incremental risks to professional pesticide handlers participating as subjects in this monitoring program are outweighed by the societal benefits expected to be gained from increased knowledge of typical exposure levels in representative agricultural use scenarios. This knowledge will improve the EPA’s ability to assess occupational pesticide exposure and better protect workers.

It is more appropriate to discuss these societal benefits at the scenario level for it is at this level that the validity of the scientific design must be judged; taking into account existing data, the appropriateness of normalization factors (such as AaiH), the scenario-specific sampling design, etc. Furthermore, it is only when the scenario-specific sampling design has been fulfilled—typically only after several discrete field studies are conducted—that the benefits of the research can be realized. The discussion below outlines in general terms how new scenario-specific exposure data will provide a societal benefit, however each field study protocol will detail the benefits applicable to that study and the scenario(s) it supports.

4.1 Description of Potential Benefits

4.1.1 Benefits to Subjects

None of the studies in the AHETF monitoring program will provide direct benefits to the study participants. This means risks to participants must be justified by the societal benefits that are anticipated to come from a successful study (NAS, 2004). Information from this monitoring program will be used to estimate the exposure risk to agricultural workers who mix, load, and apply pesticides. This may lead to safer pesticide handling practices that indirectly benefit the participants and other agricultural pesticide handlers.

4.1.2 Benefits to Society

The AHETF exposure monitoring program will significantly improve the ability of EPA and other regulatory agencies to estimate the risks to professional pesticide handlers from handling agricultural pesticide. This is a benefit to society and these benefits accrue on a scenario-specific basis.

Benefits of human dosing studies have been examined at length by the National Research Council of the National Academy of Sciences (NAS, 2004). These discussions are also applicable to the occupational exposure monitoring that AHETF plans to conduct, including the following:

Any human dosing study, regardless of its risk category, must have a useful purpose and convey some benefit to the participants and/or society. As discussed earlier, the committee concludes that under the risk-benefit balancing required by the principle of beneficence and the Common Rule, personal benefits to participants are insufficient by themselves to justify human dosing studies conducted for EPA regulatory purposes. This means that risks to participants imposed by human dosing studies must be justified by the societal benefits that are anticipated to come from a successful study, if they are to be justified at all.

The NAS concluded that improving the accuracy of the science employed in regulatory decisions “constitutes a societal benefit”, but also indicated several ways that particular studies can generate societal benefits beyond the minimal benefit of increased knowledge, including studies that:

- Result in a more stringent regulatory standards;
- Enable EPA to adopt a public health measure it otherwise could not adopt;
- Support approval of a product that protects public health; and
- Improve the scientific accuracy of risk assessment for a class of chemicals and/or EPA decisions

Knowledge gained from the AHETF monitoring program will be applicable to a variety of pesticides, and will be used to assess risks of new pesticides and new uses of registered pesticides. Knowledge gained from the monitoring program could also be used by EPA to impose stricter safety standards on currently used pesticides, when appropriate (Resnick, 2005). Consequently, agricultural pesticide handlers could be better protected. Some information from AHED[®] will support pesticide products that control disease vectors and protect the public health. These are all examples of situations which provide societal benefit that go beyond the basic benefit of increased knowledge.

The data developed in the AHETF monitoring program will also improve the scientific basis for EPA's occupational risk assessment because worker exposures will be measured under modern, common, and actual conditions. The data collection will reflect current agricultural practices, equipment, and techniques. Monitoring techniques are of high quality and have been standardized for use across the AHETF monitoring program. AHED[®] will become the best available data to support assessments of agricultural pesticide handler exposure.

AHED[®] will not repeat the limitations of PHED. In particular, the AHED[®] database will include only data for individuals with dermal exposure data for all sampled body parts (unlike PHED where many records reflect exposure data for only some body areas). Improved estimates of whole-worker exposure, with a sense of the potential distribution between workers, will now be possible. In addition, to the extent the generic database approach proves successful; it will reduce the need for product-specific worker exposure studies conducted by individual registrants for new products and uses.

Finally, pesticide products do provide certain *direct and indirect* benefits to society. AHED[®] data will support the safe use of pesticides and the more that scientists and regulators know the safer pesticide properties and their uses will become. The removal of safe and effective pesticides due to the lack of appropriate exposure data would impair the ability of farmers to produce food and reduce the ability of health officials to protect the public from dangerous pests like cockroaches, rats, ticks, and mosquitoes that transmit disease. If human exposure monitoring is needed to understand the risks posed by such products and thus support their regulatory approval by EPA, such information would provide an important health benefit (NAS, 2004).

4.1.3 Benefits to AHETF Members

As described in previous sections, pesticide handler exposure data are required by Federal laws. Pesticide registrants (e.g., manufacturers, producers, and marketers) have the obligation to submit such data. Therefore, generating new human exposure data from AHETF studies is a benefit to the members of AHETF as they are all pesticide registrants that need data to meet regulatory requirements.

4.1.4 Benefits to Growers or Landowners

As described in Section 13, AHETF needs to locate growers or landowners who are willing to accept a pesticide product being applied to their crop or land. In the majority of studies, this will be a crop, grown either indoors or outdoors, and a grower will need to give AHETF permission to have their crop treated. However, pesticide treatments may also be made to rights-of-way, pasture land, forests, and other non-crop areas which may be owned by corporations or governmental agencies instead of growers. In many cases, AHETF is also interested in using handlers that handle pesticides for that grower or landowner as part of their job. In almost all cases, these growers or landowners are in operation to make a profit and AHETF experience is that it's very difficult to obtain their cooperation without some compensation.

Growers have considerable expense in cooperating with an AHETF study: time with the study team; lost productivity of their handlers while discussing the study with the study team; lost productivity on the day(s) of monitoring; wear on tractors and sprayers, fuel costs, etc. Therefore, it has become common practice for AHETF to provide the test substance at no cost to the grower or landowner. Providing free product for the acreage treated is viewed as reasonable compensation for the inconvenience associated with the study. To the extent the compensation exceeds the inconvenience product may be a benefit to the grower or the landowner.

4.2 Likelihood of Realization of Benefits

The generation of worker exposure data that can address the data needs of the regulatory community and membership of the AHETF is considered extremely likely. It is also very likely that regulators and risk assessors will use these data extensively. This has been the case for previous FIFRA joint data development task forces of many types, including those developing data for generic exposure assessment (e.g., for reentry and residential worker exposures). Regulatory agencies are strongly committed to using generic exposure databases as an important component of risk assessments. The use of worker exposure data in a generic manner has been generally accepted since 1986 when the concept was discussed and supported by a FIFRA Scientific Advisory Panel. In addition, the successful development and release of PHED in 1992 and its subsequent use by regulators to support many occupational risk assessments strongly suggests that the AHED[®] database will find even greater use.

5 Risks to Subjects in AHETF Studies

For the AHETF monitoring program, risks to subjects occur at the field study level and must be assessed and minimized at that level. This section of the governing document indicates in general terms the qualitative nature of the risks that are expected to be encountered and how they will be reduced in the design and conduct of specific field studies. Risks, and how they will be minimized, will be fully addressed in each field study protocol.

In summary, risk to subjects is classified as “greater than minimal”, primarily since agricultural work is considered a high risk occupation where the likelihood of harm or discomfort is greater than what is encountered in ordinary daily life. People who handle pesticides in their occupational activities are at greater risk than the ordinary public for accidents and physical injuries associated with equipment use or shop activities, and for adverse health effects due to the use of chemicals, which might include pesticides. In addition, AHETF believes the risk of heat-related illness (since workers must wear an extra layer of clothing to trap chemical) may sometimes be increased due to study participation (as compared to the risk associated with the job itself).

5.1 Risk of Heat-Related Illness

The risk of heat-related illness might be increased due to participation in some AHETF studies from the combination of hot and humid climatic conditions, extra clothing (in the form of inner dosimeters worn under normal clothing), and scripting of handling activities. Some of these aspects can be controlled by location and ventilation, yet other aspects are a direct result of the study design and cannot be easily altered without compromising the quality or value of the data collected. In particular, all participants will be asked to wear the inner dosimeters that they normally would not wear, but without compliance with this criterion a full set of dermal exposure measurements cannot be obtained. In addition, some studies will require the use of open cabs or cockpits, so workers will not have the choice of using an enclosed cab or cockpit during the study. As discussed later in this document, scripting in AHETF studies will be minimized and will primarily involve design features that ensure monitoring intervals that represent a typical day’s duration (i.e., not excessively short or long) and coverage of the practical range for amount of product handled within each handling scenario. In some cases, this will increase the length of the work day which might add to the risk of heat-related illness. All of these factors can contribute to the risk of workers overheating and suffering from heat-related illness. Therefore, AHETF has developed an extensive program designed to minimize this risk.

5.1.1 Nature of the Risk of Heat-Related Illness

Heat stress is the build-up in the body of heat generated by the muscles during work and of heat coming from the environment. Heat illness (e.g., heat exhaustion and heat stroke) can result when the body is subjected to more heat than it can accommodate. Weather, workload, clothing/PPE, and worker conditioning can influence the risk of a worker experiencing heat-induced illnesses. In addition to causing serious physiological conditions, early symptoms of heat illness such as dizziness and confusion can lead to an increased risk of occupational accidents beyond that which is already present. Most early and mild heat-related illness conditions are reversible, but it is possible to have irreversible effects, especially if it contributes to an accident or injury. That is why the AHETF program for minimizing heat stress focuses on early identification and intervention.

5.1.2 Minimizing the Risk of Heat-Related Illness

Study participants are asked to wear an extra layer of clothing (whole body inner dosimeter) under their normal work attire which could increase the risk of heat-related illness. Efforts are made to schedule studies during cooler times of the year as much as practical to help minimize this risk. As stated in the informed consent form, heat-related illness is a potential health hazard that may be associated with participating in the study, so AHETF takes steps to prevent such illness. First, the Study Directors must complete a first aid certification course that includes the recognition of heat-related illness. Additionally, the on-site medical professional and study observers are provided with guidance to recognize symptoms of heat stress. Second, researchers always have plenty of water and sports drinks available and workers are encouraged to drink some before and throughout the monitoring period. Most importantly, environmental conditions (temperature and humidity) are regularly monitored and operating procedures are in place to define when a study can start and when monitoring must be stopped. SOP AHETF-11.G addresses identification and control of heat stress in detail and a summary of that procedure is presented below.

In summary, the heat stress management plan includes the following procedures for researchers to prevent illness in study participants:

- Ensure plenty of water and sports drinks are available for the workers.
- During worker orientation immediately before participation in the study, remind the workers of the risk of heat stress, suggest they drink some water before they start work, and let them know how/where they can get water during the monitoring period.
- Urge workers to drink water during the monitoring period and remind them that thirst does not give a good indication of how much water a person needs to drink. There is no need to take hand washes or stop inhalation monitoring during a water break.

- Observe workers during the monitoring period and be aware of the signs and symptoms listed below.
- Require workers to take rest breaks when early signs or symptoms of heat illness are present.
- Monitor the heat index (based on air temperature and relative humidity and derived from a National Weather Service heat index table) throughout all monitoring periods.
- Stop the monitoring when the heat index (adjusted for direct sunlight, if applicable) reaches 130 °F.

During the study, the Study Director is responsible for monitoring ambient temperature (°F) and relative humidity (%) using portable devices (at least every hour when temperature is at or above 70 °F). Based on these measurements, a heat index is determined from the National Weather Service Heat Index chart (reproduced in the SOP). In addition, the heat index is increased by 10 degrees if any study participant is working in the direct sun. If the adjusted heat index is at 130 °F or above, monitoring cannot be started, and any ongoing monitoring will be stopped.

5.1.3 Nature and Likelihood of Residual Risk of Heat-Related Illness

AHETF tries to avoid scheduling studies in locations and at times where very hot and/or humid conditions are likely. However, it is probable that AHETF will be conducting some studies during summer months when climatic conditions will require increased vigilance by AHETF researchers to prevent heat-related illness. It is therefore possible that some monitoring events will need to be cancelled or stopped due to excessive temperature and humidity conditions. Adherence to the procedures developed to identify and control heat stress (SOP AHETF-11.G) will minimize the risks, but early signs of minor heat-related illness could occur on very hot and humid days. This would lead to mandatory rest breaks and other preventive measures. Serious heat-related illness is not likely since researchers and the on-site medical professional will always be nearby to prevent the advancement of heat-related illness.

During 173 MUs collected recently by AHETF, there have been no instances of workers experiencing heat stress or other physical injury that required them to stop to rest or to stop their monitoring altogether.

5.2 Risk of Exposure to Surrogate Chemicals

The surrogate chemical products selected by AHETF have all been through complete regulatory exposure and risk assessment processes and are approved for all uses in AHETF studies (since the products are always used in accordance with the labels). This means that handler exposure levels are not expected to reach a “level of concern” to the EPA. Margins of exposure (MOE), usually based on no observable adverse effect levels (NOAELs), for the labeled uses and rates are considered adequate by the EPA. In addition, whole body dosimeters further mitigate dermal exposure, thus

increasing the confidence that there is no reasonable foreseeable risk to workers handling the products utilized by AHETF. However, the product labels do provide precautionary statements indicating the most likely acute toxicity effects which are usually eye and/or skin irritation. These risks will be identified in the consent form and will be discussed with study participants. These are study-specific requirements.

Since participants are generally allowed to participate on just one day of the study, the impact on their risk of long term toxicity is negligible.

5.2.1 Nature of the Risk of Exposure to Surrogate Chemicals

AHETF monitors exposure to workers who handle commercially available pesticide products. In general, useful surrogate chemicals have multiple uses (e.g., several crops or sites), multiple formulation types, minimal PPE requirements, and reliable and validated analytical methods. To date, AHETF has approved, or is in the process of developing, the following active ingredients as surrogate chemicals for use in its monitoring program:

- Acephate: an organophosphate insecticide
- Carbaryl: a carbamate insecticide
- Chlorothalonil: a substituted benzene fungicide
- Chlorpyrifos: an organophosphate insecticide
- Diazinon: an organophosphate insecticide
- Glyphosate: a glycine analogue herbicide
- Malathion: an organophosphate insecticide
- Mefenoxam (metalaxyl): an anilide fungicide
- Simazine: a triazine herbicide
- 2,4-D: a phenoxy herbicide

A discussion of the likely acute toxicity effects and the status of regulatory exposure assessments for each of these chemicals is presented below, however it should be emphasized that acute effects are formulation-specific, so each field study protocol and consent form will necessarily discuss the particular effects for the test substance used. This will include an MOE calculation for the highest AaiH that is planned for each task (i.e., scenario) included in the study. EPA will verify the MOE calculations.

5.2.1.1 Acute Effects of Proposed Surrogate Chemicals

The AHETF monitoring program is designed to generate exposure data for workers who handle a pesticide in a variety of ways for a period of time representative of a single (scenario-specific) work day. AHETF does not plan to use workers for repeated measurements, so the acute toxicity effects are of primary importance in selection of surrogates for exposure monitoring studies. In addition, AHETF uses only currently registered pesticide products, requires workers to follow all label and Worker Protection Standard (WPS) requirements, and will generally include study participants

who would be using that product in the normal course of their job regardless of their participation in the AHETF monitoring study. Therefore, the one-day exposure will have a negligible effect on each participant's chronic risk.

The use of federally registered products means that the EPA has determined that the use of the product will not cause "unreasonable adverse effects on the environment" (which includes humans). This determination is made for both shorter term toxicity endpoints (including reproductive, neurological, and systemic toxicity) and repeated exposure endpoints. This includes cholinesterase inhibition which is a common endpoint of concern for several AHETF surrogate chemicals.

The table below summarizes the signal word and label precautionary statements (worst case) for formulations of the surrogate chemicals listed above which AHETF intends to use in its monitoring program. These are generally based on the acute toxicity profile of the end-use formulation containing the active ingredient (as prescribed in 40 CFR 156) and provide guidance to AHETF about the relative risks to handlers.

Surrogate Chemical	Signal Word	Label Precautionary Statements
Acephate	CAUTION	Harmful if swallowed. Causes eye irritation.
Carbaryl	WARNING	May be fatal if swallowed. Harmful if absorbed through skin, inhaled, or in eyes.
Chlorothalonil	WARNING	Causes substantial but temporary eye injury. May be fatal if inhaled. Harmful if absorbed through skin. May be a potential skin sensitizer.
Chlorpyrifos	WARNING	May be fatal if swallowed. Harmful if absorbed through skin or inhaled. Causes eye irritation.
Diazinon	CAUTION	Harmful if swallowed, absorbed through skin, or inhaled. Causes moderate eye injury.
Glyphosate	WARNING	Causes substantial but temporary eye injury. Harmful if swallowed, inhaled, or absorbed through skin.
Malathion	CAUTION	Harmful if swallowed, inhaled, or absorbed through skin.
Mefenoxam	WARNING	Causes substantial but temporary eye irritation. Harmful if swallowed or absorbed through skin.
Simazine	CAUTION	Harmful if swallowed, inhaled, or absorbed through skin. Causes moderate eye irritation.
2,4-D	DANGER	Corrosive. Causes substantial eye injury. May be fatal if absorbed through skin. Harmful if swallowed or inhaled.

It should be noted that signal words and precautionary statements do not provide complete information about the relative risks to handlers since PPE and/or engineering controls may be mandated based on other toxicology concerns, such as developmental toxicity. Different formulations of an active ingredient can have different signal words or precautionary statements on their labels. The specific chemical risk of each surrogate chemical formulation used in a study will be addressed in the field study protocol and consent form.

5.2.1.2 Regulatory Risk Assessments of Surrogate Pesticides

All of the surrogate chemicals listed above were originally registered by EPA before November 1984 and are therefore subject to reregistration review, including the considerations dictated by the Food Quality Protection Act (FQPA) of 1996. During the reregistration process, EPA performs complete risk assessments and determines whether any risk mitigation procedures are necessary to ensure safety for that chemical (and perhaps others that operate by a similar mode of toxicity). These assessments include an evaluation on the entire toxicity database including potential chronic effects; developmental and reproductive effects; neurological effects; and other systemic effects. EPA findings are published in Reregistration Eligibility Decisions (REDs) or Interim Reregistration Eligibility Decisions (IREDs) which are sent to all registrants of the particular active ingredient. For handler situations, mitigation could involve reducing application rates, eliminating uses, requiring PPE be worn by workers, or requiring engineering controls for mixing/loading and/or applications. Although registrants generally have some time to evaluate reregistration decisions, respond to EPA, and modify their product labels, AHETF intends to conduct all of its monitoring studies in accordance with published REDs or IREDs. The table below summarizes the pesticide reregistration status for the surrogates listed above. For example, the diazinon IRED required that wettable powder (WP) products be packaged in water-soluble packets to reduce mixer/loader exposure potential, so AHETF will not use diazinon WP products in a monitoring study even though those products may still be in the channels of trade and legal to use.

Surrogate Chemical	Status	Changes which may affect AHETF
Acephate	IRED signed 09/2001	Soluble Powders must be in water soluble packaging (WSP), enclosed cockpits for all aerial applications, eliminate low pressure hand wand applications to trees/shrubs/outdoor flora, no belly grinder application of granules
Carbaryl	IRED signed 06/2003 Revised IRED 10/2004	Added PPE for wettable powders (WP), some aerial applications eliminated
Chlorothalonil	RED signed 09/1998	Current labels meet all requirements
Chlorpyrifos	IRED signed 09/2001	Added PPE for most uses, WP must be in WSP, enclosed cockpits for all aerial applications
Diazinon	IRED signed 05/2004	Eliminate all aerial uses, eliminate most foliar applications to vegetables, WSP or lock-and-load for all products, enclosed cabs only for ground applications
Glyphosate	RED signed 09/1993	Current labels meet all requirements
Malathion	RED signed 07/2006	WP must be in WSP, CR headgear required for all airblast applications, enclosed cockpits required for all aerial applications
Mefenoxam	RED signed 09/1994	Current labels meet all requirements
Simazine	RED signed 04/2006	Eliminate aerial applications
2,4-D	RED signed 06/2005	WP must be in WSP

All of the occupational risk mitigation steps presented in these REDs and IREDs will be followed during AHETF studies.

5.2.2 Minimizing the Risk of Exposure to Surrogate Chemicals

The primary method for preventing chemical toxicity when handling formulations of these surrogate pesticides is to ensure the workers follow the label requirements for clothing and personal protective equipment (PPE).

The Study Director must approve all clothing worn by study participants prior to the start of monitoring to ensure compliance with WPS (SOP AHETF-8.G.). Clothing with large tears, holes, rips, several missing buttons, or other defects that present a significant exposure to the worker's skin or inner dosimeter will not be accepted for use during the study.

During study conduct, researchers assigned to observe participants in AHETF studies will ensure the workers wear all the required PPE while handling product. Non-compliance on the part of the worker will result in discontinuing the monitoring for that worker. For example, the labels for formulated products containing several AHETF surrogate active ingredients include the requirement for all handlers to wear protective eyewear. AHETF will ensure that all study protocols involving any of these active ingredients require workers to wear protective eyewear that meets the requirements of the WPS. Similarly, some product labels require respirators for handlers except when inside enclosed cockpits and AHETF will ensure these requirements are followed during its studies. Researchers are also reminded when particular products may cause allergic skin reactions and that exposure monitoring will be discontinued for any worker that shows signs of such a reaction (including formation of a skin rash and/or itchy skin). Finally, researchers will remind workers just prior to participation about general ways to minimize exposure to chemicals such as washing their hands before eating and removing clothing/PPE that get contaminated by spills.

5.2.3 Nature and Likelihood of the Residual Risk of Exposure to Surrogate Chemicals

Since study participants will be handling approved pesticides for just one day, and AHETF researchers will ensure they wear label-required PPE, it is very unlikely that any serious or irreversible toxic effects will be encountered by study participants. However, acute toxicity effects, primarily reversible skin or eye irritation, may occasionally occur. During 173 MUs that AHETF has already conducted, there was only one report of eye irritation (not confirmed as associated with pesticide handling) that was reported the day after participation in a study. This suggests the probability of even minor effects is very small.

5.3 Risks Associated with “Scripting” of the Field Activities

During the conduct of some studies, AHETF will ask participants to perform their job in certain ways that might not reflect their usual practice; that is, some procedures will be scripted. Scripting is primarily utilized to achieve diversity in certain factors that might have an impact on exposure potential for a particular scenario. In particular, scripting may be needed to ensure that at least three loads are handled or to ensure that certain amounts of active ingredient are handled. Occasionally, workers might also be asked to use equipment they do not use on a regular basis in order to achieve diversity in equipment (however, they must be familiar with that type of equipment).

Scripting may lead to increased AaiH and/or slightly longer work periods which may increase the risks of acute toxicity to the surrogate chemical or heat-related illness. These increases will be discussed in each field study protocol. Use of unfamiliar equipment may increase the risk of accident or injury associated with that equipment.

5.3.1 Nature of the Risk Associated with Scripting Field Activities

Scripting to handle at least three loads per work period often involves making modifications to the mixing/loading and/or application parameters such as using a smaller tank or increasing the application volume per acre (for liquids). Such changes will always be consistent with label directions and common regional practices. These changes will lengthen the work day somewhat, but do not increase the AaiH. Therefore, the added risk will come in the form of increased risk to heat-related illness on hot days.

Scripting to achieve diversity in AaiH may involve increasing or decreasing the amount of product a participant might handle if he weren't participating in the study. In the case of an increase in AaiH, the risks of acute toxicity to the surrogate and the risk of heat-related illness may be increased.

Scripting to achieve diversity in equipment may involve asking participants to use mixing/loading or application equipment they are not familiar with on a regular basis. For example, in an open cab groundboom study in orchards, AHETF asked study participants to utilize adjustable booms to make a banded application of an herbicide under the trees. This type of scripting might increase the risk of accident or injury associated with the equipment.

5.3.2 Minimizing the Risk Associated with Scripting Field Activities

The same general procedures discussed above that are designed to minimize the risks of surrogate chemical risks and the risk of heat-related illness will be followed in all studies, especially for participants who have their work day lengthened or AaiH increased due to scripting of activities.

When equipment unfamiliar to a worker is used, the Study Director will ensure the participant has prior experience with the type of equipment being proposed or will provide an opportunity for the worker to familiarize himself with the equipment before participating in the study. In the example cited above, study participants were familiar with the tractors onto which the adjustable booms were mounted, but did not have experience with that particular type of adjustable boom. Therefore, workers were allowed to use the booms prior to the study in order to familiarize themselves with how to adjust the boom width and how to store the boom during transit.

5.3.3 Nature and Likelihood of Residual Risk Associated with Scripting Field Activities

Scripting will generally increase the risks associated with study participation only slightly. Each field study protocol will describe those situations where scripting is anticipated and the increase in risks associated with that scripting.

5.4 Psychological risks

Participating in AHETF exposure monitoring studies involves activities that are unusual and might lead to psychological concern for subjects. These include:

- Performing an over-the-counter pregnancy test prior to participation (females only)
- Allowing a researcher to assist with removing their long underwear

Every field study protocol and consent form will identify risks associated with taking a pregnancy test and of embarrassment during changing clothes.

5.4.1 Nature of Psychological Risks

5.4.1.1 Risk Associated with Taking a Pregnancy Test

Female workers may be uncomfortable performing a supervised over-the-counter pregnancy test. A female who discovers she is pregnant may be disturbed by that information.

5.4.1.2 Risk of Embarrassment during Changing of Clothes

Subjects may be embarrassed to undress (they wear undergarments of their choice under the long underwear) in the presence of a researcher who will carefully collect the whole body dosimeter for analysis.

5.4.2 Minimizing Psychological Risks

During the consent process, female volunteers are informed they cannot participate if they are pregnant and they will have to take a pregnancy test within 24 hours of participation. The pregnancy test is generally performed after a consent form is signed (since consent is usually taken more than a day ahead of planned monitoring). If a woman is uncomfortable with the thought of taking such a test, the Study Director will urge her not to sign the consent form. However, women who have consented to participate may discover (often on the day of monitoring) that they are pregnant. This could cause significant psychological harm to some women.

Pregnancy tests are self-administered by the subject, but must be supervised by a female researcher. This researcher will explain how to take the test, escort the subject to a bathroom, and wait outside while the subject takes the test. The researcher will also explain that the subject does not have to disclose the results of the test, but that she will be asked to indicate after the test whether she wants to continue with the study. Only if the subject indicates an interest in continuing will the researcher verify the results (i.e., to confirm a negative result, see SOP AHETF-11.D).

The primary mechanism for minimizing the psychological harm of a positive pregnancy test result is to ensure no one but the subject herself is aware of the positive test. However, this risk cannot be eliminated and that point will be emphasized during the consent process.

When subjects complete their assigned handling tasks, they are required to allow researchers to collect OVS tubes, take a final face/neck wipe, take a final hand wash, and remove the whole body dosimeters for analysis. This undressing takes place in a private location and is often the inside of a research truck or trailer that is enclosed by a curtain. Once inside this privacy area, a researcher of the same sex as the subject will remain outside the privacy area and instruct the subject about how to remove the dosimeter. The worker will then pass the dosimeter through the curtain to the researcher who will section it according to the protocol. At this point, the subject will get dressed in the clothes he/she arrived in.

5.4.3 Nature and Likelihood of Residual Psychological Risks

AHETF experience is that handlers rarely exhibit any concerns with the undressing procedure.

None of the women subjects in prior studies have expressed concern about self-administering the pregnancy test. Only a few women have been monitored and none have had a positive test result. The likelihood of a positive test causing psychological harm could be significant. Thus, the risks will be described to potential test subjects for all studies.

5.5 Risks of Exposure to Detergents during Face/Neck and Hand Sampling

For all AHETF studies, a very dilute detergent solution in water is used for face/neck wipes and hand washes. The only variation between MUs is in the duration of exposure since longer work periods or frequent eating breaks can lead to multiple hand washes and/or face/neck wipes. Every field study protocol and consent form will identify this risk of skin or eye irritation.

5.5.1 Nature of the Risk of Exposure to Detergents

During face/neck wipes and hand washes, AHETF uses a very dilute solution of a non-ionic surfactant called sodium dioctyl sulfosuccinate (CAS No. 577-11-7). In its undiluted form, this detergent causes mild to moderate skin and eye irritation in animals, depending on the concentration and duration of exposure. When used by AHETF to remove pesticide residues from workers' faces, necks, and hands a 0.01% v/v dilution in water is used and the duration of skin exposure is about 2 minutes per hand wash and 1 minute per face/neck wipe. Longer work periods or frequent eating breaks can lead to multiple hand washes and/or face/neck wipes and an increase in duration of exposure, but total dermal exposure to detergents is generally less than 10 minutes for an entire monitoring period.

5.5.2 Minimization of the Risk of Exposure to Detergents

The diluted detergent is always prepared for use very shortly before being used in the field, generally within 24 hours of the first monitoring event. Distilled or deionized water is required by SOP and the dilute solution is typically prepared in clean 1 gallon jugs. Eye exposure would only be accidental and researchers are trained to be sure the amount of solution in a face/neck wipe gauze will not cause dripping into workers' eyes. The amount of detergent is limited by SOP to approximately 4 mL (of the 0.01% v/v detergent in water solution). AHETF will have a portable eye rinse system on hand at all studies in case such an accident does occur. Finally, when subjects complete their participation and leave the site in their street clothes, researchers remind them it is always advisable to shower or bathe as soon as possible.

5.5.3 Nature and Likelihood of Residual Risk of Exposure to Detergents

This surfactant use represents a very dilute solution and a very short exposure period. A long history of using this surfactant in pesticide exposure monitoring studies indicates the likelihood of skin or eye irritation is negligible.

5.6 Background Risk of Injury Associated with Agricultural Work

Agriculture (i.e., farm occupations, see Bureau of Labor Statistics) remains one of the country's most dangerous occupations where it perennially ranks in the top ten occupations measured by fatality rate (on-the-job deaths divided by total number of workers) or injury/illness rate. These risks will be present for all AHETF field studies, but the nature of the risks will be scenario- and study-specific. This section describes in general the types of risk that are anticipated during the AHETF monitoring program.

5.6.1 Nature of the Risk of Injury Associated with Agricultural Work

The most common risks for serious injury to farmers are vehicular accidents (especially tractor rollovers, but also accidents while driving machinery on roads) and entanglement with moving parts of farm machinery. Farm workers are also commonly exposed to a variety of chemical products that present increased risks compared to the general public. These include pesticides, fertilizers, solvents, lubricants, fuels, etc.

More than half of the scenarios of interest to AHETF involve some type of application equipment including handheld devices, ground rigs, or aircraft. The risk of injury will probably be greatest for studies involved with these scenarios since they involve intimate contact with large pieces of mechanical equipment. Mixer/loader activities probably involve a lower risk, however these tasks often involve getting close to the application equipment as well. Mixers/loaders are also more prone to lifting injuries since they may be handling containers with several pounds of product inside and sometimes have to move around hoses, pumps, or other equipment as they conduct their work.

Study participants might have an agronomic need to mix/load or apply other pesticides fertilizers or adjuvants in the same equipment as the surrogate pesticide. Thus there might be an added risk of toxicity from these products.

5.6.2 Minimizing the Risk of Injury Associated with Agricultural Work

In general, background risks associated with agricultural work are out of the control of AHETF. However, study plans need to take into account that the risk of injury may be increased by scripting field activities such as using equipment unfamiliar to a subject. The primary consideration when planning and conducting AHETF field studies is to have subjects use clothing, PPE, equipment, and facilities they are familiar with. When these items must be borrowed or provided by AHETF, an attempt will be made to allow potential participants to get some practice working with those items. These situations will be addressed in field study protocols as they arise.

One very important situation might exist that increases these background risks – the potential for early heat illness to cause dizziness or confusion that could lead to an accident or injury. On hot and humid days, researchers will be extra vigilant to prevent heat-related illness and follow established procedures to minimize the risk of heat-related illness.

In addition, care is always taken to keep air sampling pumps and tubes out of the way of workers so they don't interfere with their tasks and increase the likelihood of accidents.

The choice to add tank mix products is determined by the worker (or his supervisor) and generally can not be controlled by AHETF. Study Directors always ask in advance whether the grower thinks tank mix additives will be needed, however it is not uncommon for these decisions to be made on the day of application or shortly before. In particular, weather conditions and pest pressures will often determine what non-surrogate chemicals may be needed. Only registered products and label-compliant uses will be allowed. Whenever possible, Study Directors also check with analytical chemists to confirm analytical interferences between the surrogate and other tank mix components are not likely. Products will not be allowed if the PPE required are contrary to the study objectives, in particular coveralls or chemical-resistant clothing requirements are usually unacceptable for AHETF study designs. If the grower insists such a tank mix product is necessary, and the Study Director determines extra PPE would be contrary to the study design, the study will not be conducted using that grower or any workers who handle that tank mix product.

Individual study protocols and consent forms will address the risk of other tank mix partners in a general sense only, since it is impractical for AHETF to identify all potentially useful products and to define the risks associated with those products in advance.

5.6.3 Nature and Likelihood of Residual Risk of Injury Associated with Agricultural Work

Since AHETF studies involve common agricultural equipment and practices, physical injuries should be considered a possibility. In addition, it is common for growers to tank mix various chemicals to improve the effectiveness of the surrogate chemical or to provide other benefits (e.g., a different pesticide activity or nutrients) and these risks will be described in general. When applicable, field study protocols will also indicate that hot conditions might be expected and that heat stress could increase the likelihood of physical injuries.

5.7 Likelihood of Serious or Irreversible Effects

As discussed above, participation in AHETF exposure monitoring studies might have an impact on the likelihood for acute toxic effects. The most likely routes of exposure are dermal and inhalation, not oral. For some of the surrogates listed above, their labels list possible serious or irreversible effects from eye exposure, inhalation exposure, cholinesterase inhibition, or skin allergies. These types of effects would generally be a result of misuse or accidental spills, not from prescribed label use. Since all pesticides will be handled in accordance with label instructions, misuse should not occur; however, spills are still possible. Accidental exposures of sufficient magnitude for these serious or irreversible effects are unlikely.

In addition, heat stress might cause dizziness or confusion and increase the risk of mechanical accidents that could be serious or irreversible. The heat stress management procedures are designed to minimize this risk, so serious heat-related effects are unlikely.

6 Risk versus Benefit Comparison

In general, the risks to participants in all AHETF studies are outweighed by the benefit to society in the form of high quality exposure data for use in evaluating pesticide safety (as described below). If there is no such need for new exposure data for a particular scenario, no studies will be proposed by AHETF relating to that scenario.

Each field study protocol will discuss the particular benefits, risks, and risk/benefit comparison to ensure the benefits outweigh the risks. This comparison must balance the societal benefit of new scenario-specific exposure data with the study-specific risks to subjects.

There are no direct benefits to subjects, but some future indirect benefits to handlers as a whole are anticipated as new data are used to regulate pesticides. There are also benefits to growers, the EPA, and AHETF members.

AHETF's monitoring program presents a greater than minimal risk to participants. The primary risk comes from their employment as an agricultural worker where accidents and chemicals contribute to injury and illness. The increased risk to heat-related illness caused by the extra layer of clothing is mitigated by a medical management program which emphasizes prevention measures and guidelines for stopping participation when warranted based on environmental conditions.

The benefit to agricultural workers as a whole and to society in general, in the form of more accurate measurements of potential exposure to pesticides, must outweigh the risk to study participants.

7 Description of and Rationale for Scenarios Considered by AHETF

The handling scenarios selected for inclusion in the AHETF program reflect logical classifications of tasks, equipment, and formulations. Many of these scenarios are similar to those in PHED which have proven to be practical for regulatory use (to support product-specific exposure assessments using a generic database). A few others cover use situations that are not included in PHED.

In addition, AHETF evaluates deficiencies in PHED data for each scenario before any monitoring is done for that scenario to be sure adequate data for exposure assessments do not already exist.

7.1 Handler Scenarios Included in the Monitoring Program

This section discusses how scenarios were chosen for inclusion in the AHETF monitoring program.

As discussed above, EPA (and other regulatory agencies) generally utilizes a scenario approach to exposure and risk assessments which is logical and has proven to be practical. The various scenarios reflect logical categories since task, equipment type, formulation type, and engineering controls can greatly impact the potential for handler exposure. These categories are also practical since product labels are formulation-specific and often address only certain types of application equipment. In addition, regulators find scenarios convenient for product-specific exposure assessments and must ensure worker safety for all scenarios in which a product could be used. In practice, regulators can often mitigate exposure by requiring engineering controls for certain mixing/loading or application techniques (i.e., changing the scenarios that are allowed), limiting use rates, eliminating some uses, or a combination of these methods. And all of these mitigation decisions can be supported by scenario-specific exposure data such as those in PHED and AHED[®]. This scenario approach is outlined in the PHED Surrogate Exposure Guide (Keigwin, 1998) and is consistent with Agency-wide guidelines for exposure assessment.

Collecting occupational pesticide handler exposure data by scenario therefore reflects the following parameters that conventional wisdom and experience indicate have a large impact on the potential for handler exposure:

- Task (e.g., mixing/loading or application)
- Application System (e.g., aircraft or ground equipment)
- Product Formulation (e.g., liquid or granule)
- Engineering Controls (e.g., open or closed loading and open or enclosed cabs)

AHETF member companies have also examined their own products and uses so the task force could collectively define the scope of their project in terms of which handler scenarios will be represented by AHED[®]. Since collecting MUs is very costly, generally about \$20,000 each, AHETF does not include scenarios in its scope that EPA rarely considers and that don't represent major use patterns in agriculture. The current scope includes the following 33 scenarios:

7 Mixer / Loader Scenarios:

M/L System	Product Formulation	PHED Scenario Number
Open Pour	Liquid	3
	Dry Flowable	1
	Wettable Powder	4
	Water-Soluble Packets	5
	Granule	2
Closed	Liquid	6
	Granule	No Scenario

17 Applicator Scenarios:

Application System	System Specifics	Formulation (As Applied)	PHED Scenario Number
Aerial	Open Cockpit (rotary-wing only)	Liquid	No Scenario
		Granule	No Scenario
	Enclosed Cockpit (fixed-wing)	Liquid	7
		Granule	8
	Enclosed Cockpit (rotary-wing)	Liquid	9
		Granule	
Airblast	Open Cab	Liquid	11
	Enclosed Cab	Liquid	12
Groundboom	Open Cab	Liquid, no SI ^a	13
		Liquid, SI	
		Granule, no SI	15
		Granule, SI	
	Enclosed Cab	Liquid	14
		Granule	16
Rights-of-Way	Liquid	24	
Hand-Held	Low Pressure	Liquid	18
	High Pressure	Liquid	19

^a Soil Incorporation

5 Mixer / Loader / Applicator scenarios:

Application System	Product Formulation	Mix / Load System	PHED Scenario Number
Belly Grinder	Granule	Open Pour	30
Backpack	Liquid	Open Pour	34
	Granule	Open Pour	No Scenario
Mist Blower	Liquid	Open Pour	No Scenario
Chemigation	Liquid	Open Pour	No Scenario

4 Seed Treatment scenarios:

Seed Treatment Location	Product Formulation	PHED Scenario Number
Commercial	All	No Scenario
On-Farm, Includes Planting Seed	Solid	No Scenario
	Liquid	No Scenario
	Treated Seed	No Scenario

Each of these scenarios can be viewed as a distinct research project for which AHETF will: a) develop a comprehensive MU sampling plan designed to address the primary and secondary objectives, b) conduct one or more studies to collect MUs from different locations, and c) analyze the exposure data from the collected MUs to evaluate whether the objectives were met.

Technical guidelines for how scenario sampling plans will generally be developed and analyzed are provided in Section 9, Appendix B, and Appendix C of this document. For any scenario that requires modifications to the standard statistical design or analysis process, the scenario MU sampling plan will detail the reasons why and provide complete justification for the modifications. Each scenario sampling plan will be referenced by each field study protocol that supports that scenario.

7.2 Limitations of PHED

Since 1992, the EPA has conducted agricultural mixer/loader and applicator exposure and risk assessments relying primarily on the exposure data in PHED. PHED version 1.01 was released in February 1992. It was followed by PHED version 1.1 in February 1995. PHED version 1.1 was described by the Agency as an incremental improvement over the 1.01 version (Pesticides Handlers Exposure Database, User's Guide Version 1.1, Health Canada, U.S. Environmental Protection Agency, American Crop Protection Association, February 1995). The forward to Version 1.1 User's Guide cautions the user that the database still has some limitations and should not be considered a panacea in estimating pesticide handler exposure. Noting the limitations, the guide states that a goal was to release a PHED version 2.0 in 1997. However, no subsequent version of PHED has been released.

By 2000, the U.S. Environmental Protection Agency began evaluating alternatives to PHED. On 16 March 2001, the Agency outlined its intentions regarding PHED (Letter from Margaret Stasikowski, Director, Health Effects Division to Daniel Fay, Valent USA Corporation, 16 March 2001). The letter stated EPA's intention to drastically overhaul PHED version 1.1 because many of the existing exposure studies in the database were outdated or scientifically inadequate by "today's standards". In addition, many exposure scenarios that are being assessed by the Agency are under-represented in PHED version 1.1.

In summary, PHED suffers from a number of limitations regarding its use as a generic exposure database, including:

- Inadequate number of measurements for one or more body areas (that reduces the confidence in exposure estimates for those areas);
- Inadequate quality assurance or quality control data (that sheds doubt on the reliability of all measurements);
- Use of patch dosimeters instead of whole-body dosimeters (that don't accurately reflect entire body exposures and requires extrapolations from a small patch area to the entire body area);
- Lack of entire body dermal estimates for workers (i.e., not all body parts monitored for dermal exposure) (that reduces the confidence in exposure estimates for those areas);
- Many non-quantifiable residues on dosimeters (that can lead to overestimates of actual exposure by assuming one-half the limit of quantification is present on all dosimeters with non-quantifiable residues when it may be even lower – this overestimate can also be magnified when patch dosimeters are used when the assumed residue is extrapolated to an entire body area);
- Lack of diversity for study conditions (e.g., same workers used repeatedly or all workers handling the same amount of product) (that reduces the confidence that measurements are reflective of a variety of common practices); and
- Lack of representativeness of study conditions (e.g., products or procedures that are no longer in common use) (that sheds doubt on exposures for modern agricultural equipment and practices)

The U.S. EPA recently convened a Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) to review the current worker exposure assessment methods, including a summary of the technical plan for AHETF. Advance notice of the meeting was published in the *Federal Register* on October 27, 2006. The review was conducted in an open Panel meeting held in Arlington, Virginia, from January 9 – 12, 2007. Dr. Steven G. Heeringa chaired the meeting. Myrta R. Christian served as the Designated Federal Official. A formal summary of the meeting was provided on April 2, 2007 (SAP, 2007).

Regarding adequacy of handler exposure data in PHED, the SAP (2007) concluded:

The Panel agreed with the Agency's concern about the limitations of the existing PHED exposure database. Furthermore, they concluded that additional data could significantly improve the Agency's ability to assess worker exposure. They listed eight limitations within PHED including its inconsistent data quality; a patch-work of methods, some with high uncertainty and data censoring; a high level of "clustering," and an inadequate number of samples and diversity within some scenarios.

In particular, the SAP (2007) also concluded:

The inclusion within PHED of studies where either not all parts of the body were monitored or a substantial number of exposures were undetectable do not allow the results to yield accurate exposure statistics of interest for regulatory assessments.

Issues regarding the adequacy of the data in PHED can also be illustrated by reviews of Registration Eligibility Decision (RED) documents issued by EPA as part of the recently completed FQPA reregistration process. These documents have characterized the existing PHED data as low confidence for the following important use patterns. Confidence ratings are based on “number of replicates” (quantity) and “QA/QC Grades” (quality). In general, low confidence scenarios have fewer than 15 replicates and/or barely acceptable laboratory fortification recovery data (or worse).

Low Confidence Scenarios in PHED include:

- Mixing/loading of wettable powder in water soluble packaging (Scenario 5);
- Aerial application of a granular formulation (Scenario 8);
- Application by rotary aircraft (Scenario 9);
- Enclosed cab airblast application without gloves (when inside the cab as allowed by the WPS) (Scenario 12);
- Application of granular formulation by broadcast spreader (Scenario 15);
- Low pressure hand spray applications for greenhouses (Scenario 18);
- High pressure hand spray applications for greenhouses (Scenario 19);
- Application by backpack sprayer (Scenario 20); and
- Application to rights-of-way (Scenario 24)

For reference, PHED confidence ratings can be summarized as:

Confidence Rating	Number of Measurements		QA/QC Grading
High	≥ 15 per body part	And	Good laboratory plus good field fortification data (or better) (Grade AB)
Medium	≥ 15 per body part	And	Moderate laboratory fortification data <u>plus</u> either poor field fortification or moderate storage stability data (Grade ABC)
Low	< 15 per body part	Or	Barely acceptable (or unacceptable) laboratory fortification data (Grades D or E = All Grades)

In addition, it should be noted that PHED provides dermal exposure estimates, and confidence ratings, for several distinct clothing situations:

- no clothes (i.e., based on outer dosimeters or clothing);
- single layer of clothing, no gloves;
- single layer of clothing, with gloves; and
- coveralls over single layer of clothing, with gloves (some scenarios)

Therefore, PHED can have low confidence for one clothing/PPE situation and high confidence for another within an exposure scenario. While protection or penetration factors can be used to estimate protected exposure from non-protected exposure results, or vice versa, this creates additional uncertainty for exposure estimates and may not be appropriate for all risk assessments.

7.3 Scenario-Specific Data Needs for AHED[®]

Before AHETF collects additional exposure monitoring MUs for any particular scenario, it will provide a justification that additional data are needed for that scenario. This will primarily involve a detailed analysis of the quality and quantity of exposure data in PHED as well as any data that have already been purchased by (see Section 8) or conducted by AHETF. AHETF will then propose a plan for generating additional MUs sufficient to define the expected distribution of exposure for that scenario (see Section 9 and Appendices B and C for more details). These scenario-specific data evaluations and plans for new MUs will be submitted as separate documentation with each new field study that AHETF proposes to conduct.

These scenario sampling plans will discuss the status of available knowledge; the goals of further research; the most appropriate normalization factor in terms of the primary and secondary objectives (i.e., AaiH, other, or none); and the justification for the number of clusters, number of MUs per cluster, and the factors that will be used to select both clusters and MUs under the purposive diversity sampling approach. They will also discuss the feasibility of implementing the SAP recommendations to go beyond the purposive diversity sampling design. As each field study is completed, the scenario plan should be reviewed, and updated if needed, to reflect what has been learned; for example, to ensure appropriate diversity of conditions within the scenario, especially for the appropriate normalization factor such as AaiH. However, the statistical design will not be modified as MUs are collected since it is only after all planned MUs for a scenario are collected that an evaluation can be made to determine if the data meet the benchmark objectives.

8 Evaluation of Existing Data and Incorporation into AHED[®]

Following the determination that PHED version 1.1, as a whole, did not meet the current needs for the conduct of handler exposure assessments, the AHETF began a process of evaluating existing handler exposure data available to the task force. Each of the studies considered had the potential to provide exposure data and supporting information from monitoring units (MUs) for a proposed AHED[®] scenario. The evaluation process involved the following steps:

- **Development of data acceptability criteria:** The existing data acceptability criteria addressed general study design and exposure monitoring techniques, including the analytical and quality control aspects of the studies. These acceptability criteria are detailed in Appendix A.
- **Primary review:** A process that involved the screening of handler exposure data from PHED version 1.1, publicly available data, and compensable data owned by AHETF members. Approximately 145 studies (about 1,800 MUs) were rejected during this process for not meeting basic design criteria.
- **Secondary review:** A detailed evaluation of data that passed the screening process for acceptability under the acceptance criteria with decision records for each study review. Approximately 71 studies (about 1,200 MUs) were reviewed during this more detailed process.
- **Final review:** A process that involved concurrence by the Joint Regulatory Committee (JRC) on acceptance of the data for use within AHED[®].

A total of 216 existing studies (about 3,000 MUs) were evaluated from which a total of 105 MUs were deemed to be suitable for the AHETF generic database. It should be pointed out that 19 of these studies reflect data from PHED and only one of these studies met the acceptance criteria. AHETF eventually acquired the rights to use these 105 MUs and they were added to AHED[®] under the appropriate scenarios. In most cases, these existing data are not sufficient to satisfy the full MU sampling requirements for the respective scenarios. These scenarios will be supplemented by obtaining new human exposure monitoring data (see Appendix C for more details on sampling designs when there are some existing data).

During the secondary and final review stages, much of the existing data were deemed unsuitable for a generic database (and were not acquired) due to poor QA/QC (generally low or insufficient field fortification results), a preponderance of non-quantifiable residues, or the use of study conditions that do not represent current agricultural practices in North America. However, the technical issue that eliminated the most existing data was the decision to exclude exposure data for workers who wore more than a single layer of clothing. This decision was discussed with the JRC who agreed that a modern generic database would be most useful if it contained exposure data for minimal clothing and PPE situations. Regulators are generally more comfortable estimating exposures to protected areas (e.g., dermal exposure under coveralls plus normal clothing) using exposure measurements from unprotected areas

(e.g., dermal exposure under just one layer of normal clothing) than vice versa. Therefore, AHED[®] has been designed so that clothing/PPE protection factors can be specified by a user in order to estimate protected exposures, but not vice versa.

9 Program Design

This section summarizes the statistical design concepts that will be applied to each AHETF scenario and the statistical basis for determining sample sizes. Appendix B of this document provides complete details of the target population concept and aspects of the purposive sampling methodology that are common across all scenarios. Appendix C provides complete details of the statistical basis and general methodology used by the AHETF to determine the sample size and configuration for each agricultural handler scenario. This information has greatly benefited by both formal and informal input from a recent EPA Scientific Advisory Panel review (SAP, 2007).

9.1 Target Population

As defined in Appendix B, the theoretical target population for each AHETF scenario is the set of all possible agricultural handlers and the days on which they perform scenario-specific tasks. Each possible handler-day is implicitly associated with the use of a particular chemical and with a set of ‘conditions’ that include, but are not limited to worker behaviors, equipment used, location, and numerous environmental factors. Each handler-day is also associated with an exposure. Thus, handler-days randomly selected from this target population would define the distribution of possible single-day exposures for workers. The primary focus of the AHETF monitoring program is to obtain a sample of handler-days (a non-random sample in this case) and their associated chemical exposures. Regulators and others can then use these data to approximate the scenario’s single-day exposure distribution for regulatory purposes.

An important aspect of the scenario target population is that it consists of both handler-days associated with use of one of the AHETF’s surrogate chemicals and handler-days associated with use of other chemicals. Thus, many of the handler-days in the target population will not be directly monitored in the AHETF monitoring program. It is very unlikely that the handler-days using a surrogate chemical will be associated with identical conditions for handler-days using other chemicals in the same scenario. Thus, the subset of surrogate-using handler-days is unrepresentative of the full target population. This disparity complicates the sampling process considerably: In effect, the AHETF monitoring program obtains a sample of the conditions of all handler-days in the scenario target population, but monitors exposure for those conditions only for handler-days associated with use of a particular surrogate chemical. This can be done because of the generic nature of agrochemical handler exposure: under the same conditions, exposure is independent of the particular active ingredient used.

Appendix B describes the target population and discusses the complexity resulting from the choice of an overall design using surrogate chemicals.

9.2 Purposive Diversity Sampling of MUs

Appendix B describes in detail the process of obtaining a purposive sample of conditions from the target population of all handler-days and then locating handler-days associated with those conditions that use an AHETF surrogate chemical. Once selected, these substituted handler-days are referred to as monitoring units (MUs) to emphasize their specialized role in the sampling and measurement process.

The AHETF procedure for defining target MUs is non-random. Appendix B discusses the unique aspects of the program that make purposive sampling necessary and a better choice than multistage probability sampling. The primary focus is on purposive diversity sampling. Purposive diversity sampling (Trochim, 2000) attempts to obtain a sample of handler-days that are diverse with respect to factors important to exposure. AHETF's purposive sampling method does, however, include some aspects of 'representative sampling'. Given the unique aspects of this monitoring program, the AHETF believes this method is adequately representative of the target population.

Diversity is achieved primarily through selecting worker activities and handler characteristics that meet particular, pre-defined conditions. The scenario target population of handler-days provides the conditions that are used to drive the purposive sampling process. Once the conditions that comprise the scenario have been defined, workers are identified and recruited who meet these handler conditions while using a surrogate chemical.

For each scenario, the goal of the non-probability sample is to obtain as much diversity as is practical. Obtaining diversity in three factors is of primary importance. These are (1) the number of geographic locations, (2) the amount of active ingredient handled (or, when applicable, another normalizing factor), and (3) the number of unique workers. In addition to these three primary factors there are many other parameters that can be varied and might have an impact on dermal and/or inhalation exposure for a particular scenario. Such factors might include equipment used, specific worker techniques, and number of product containers used. On a scenario-by-scenario basis, AHETF evaluates the equipment and procedures commonly used, often seeking the advice of experts through a variety of sources. Then, the particular conditions are assigned to the MUs in a particular study based upon (1) diversity of conditions and (2) a focus on more common conditions.

As would be true of any study using non-random sampling, the MU exposure values can only estimate a surrogate distribution of exposures. One cannot equate this surrogate distribution to the actual distribution in the target population using purely statistical sampling theory. However, this surrogate distribution is felt to be adequate for practical regulatory purposes given the 3-fold level of accuracy specified for the

benchmark parameters (see Section 9.4.1). While it might not be estimating the exact target population distribution, it is believed to be capturing the major aspects of it and, given the small sample sizes, is not expected to be substantially different than a same-sized cluster random sample (see Appendix B). Interested regulatory agencies represented by the Joint Regulatory Committee (JRC) are aware of these necessary limitations of the statistical inference. The AHETF feels that this will not be an impediment to the usefulness of AHED[®].

9.3 Monitoring Periods

All MUs will be designed to represent a normal workday for the particular task being monitored. Generally, this will involve monitoring periods of between four and eight hours, since most activities can be performed all day long. For tasks that typically involve shorter time periods, such as cleaning out seed treatment equipment that takes just 1 to 2 hours, workers will generally be monitored for the entire time it takes to perform the task. In some situations, such as handling large amounts of product, workers may need to work and be monitored for more than 8 hours. However, long work-days are not uncommon in commercial agriculture.

Minimum work periods will be specified for each task in each field study protocol. This will be based on the tasks to be monitored in each study and the amounts of active ingredient to be handled. The minimum will usually be 4 hours. This is designed to overcome the criticism of early exposure studies where many of the sampling regimes monitored workers for only a few minutes. Avoiding very short monitoring intervals will ensure that daily exposure estimates are not biased by unusual conditions during that short interval. For tasks where a typical work period is markedly different from about 8 hours, a specific study protocol may indicate a more appropriate minimum monitoring time (i.e., other than 4 hours).

9.4 Benchmark Objectives and Required Sample Size

The AHETF monitoring program is not an experimental study whose purpose is to test hypotheses about the distribution of exposure or about potential determinants of exposure. Its purpose is to collect sufficient data for each handler scenario to meet specified minimum or 'benchmark' adequacy requirements. These data, possibly augmented by additional exposure data from other sources, will then be used for a variety of regulatory purposes by numerous organizations. The design benchmarks are not intended to address all possible ways the exposure data could be used. Rather, they are established to ensure that the data will at least be adequate to meet common regulatory needs. Benchmark adequacy requirements, established based on discussion with the JRC, may differ between scenarios. Appendix C discusses these benchmarks and describes how to determine the sample sizes needed to meet them.

9.4.1 Primary Benchmark Objective

The primary objective for each scenario is that MU-based estimates for selected exposure distribution measures (usually expressed as exposure normalized by pounds of active handled) be accurate to within a specified level at least 95% of the time. This specified level could be scenario-specific. Currently, however, there is a consensus that, for regulatory purposes, 3-fold relative accuracy is a reasonable default for all scenarios. The standard distribution measures considered for the primary benchmark are the geometric mean, the arithmetic mean, and the 95th percentile.

A benchmark based on exposure normalized by amount of active handled is treated as the default because it is currently the most common measure of unit exposure used for regulatory purposes. For some scenarios, however, regulators might prefer to define unit exposure in terms of a different measure of 'active ingredient contact potential'. There could even be scenarios for which users of AHED[®] prefer to use non-normalized exposure. If, for a particular scenario, the JRC and AHETF jointly decide that a different normalization factor (or none at all) is more valuable for regulatory use then it will be used instead to define unit exposure for the primary benchmark objective.

For the primary benchmark, accuracy is determined assuming cluster sampling from a lognormal distribution as a surrogate model for the actual purposive MU sampling. As described in Appendix B, the AHED[®] purposive sampling recognizes larger sampling units referred to as clusters. Clusters are essentially different studies or major geographic locations (e.g., states) within studies.

Note that 3-fold accuracy may not be needed for every scenario. For example, scenarios that involve very low exposure potential will rarely be the limiting factor in a product exposure assessment and regulators may be willing to live with less certainty for the exposure estimates for those scenarios. When this is the case, fewer human participants would need to be monitored for such scenarios and more resources would be available for scenarios with higher exposure potential.

9.4.2 Secondary Benchmark Objective

When exposure normalized by a measure of active ingredient contact potential is of regulatory interest, users might also wish to examine whether exposure appears to be directly proportional to this contact factor. The regulatory usefulness of normalized exposure is greatest when direct proportionality is at least approximately true. Consequently, a secondary objective is that the MU sample provide at least 80% statistical power to distinguish complete proportionality from complete independence between exposure and the normalizing factor used in the primary benchmark. In most cases this factor would be the amount of active handled. Data users would then base such a significance test on a regression of log exposure on log amount of active

ingredient handled. Cluster sampling from a lognormal distribution could be assumed as a model for the actual purposive MU sampling.

As described in Appendix C, however, this benchmark objective is only of value if the practical range in the amount of product handled is at least an order of magnitude or greater. Otherwise a proportional relationship is very difficult to discern given the expected two-order-of-magnitude variation in MU exposures. If the practical range in the normalizing factor is less than 10-fold, then this secondary objective is not considered. In addition, whenever a scenario's primary benchmark is based on non-normalized exposure, then no secondary benchmark will be specified.

It is important to emphasize that the use of this secondary benchmark does not imply that the only two possible relationships between exposure and ai contact potential are complete proportionality and complete independence. Complicated relationships between exposure and many other factors could certainly exist. Although users of AHED[®] are free to examine any such relationships, the data are not expected to be adequate for the development of predictive models of exposure. This secondary objective, when applicable, can only be expected to illuminate the relationship between exposure and the normalizing factor. Such limitations are of minor concern since this benchmark is only of secondary importance to the AHETF monitoring program. As pointed out by the SAP (2007), more complicated relationships are better examined using controlled experimental studies.

9.4.3 Required Number of MUs and Clusters

Methods for determining the number of clusters and MUs per cluster to meet these benchmark objectives under default normalization and variability assumptions and 3-fold accuracy are described in Appendix C. These results indicate that both objectives can be satisfied cost-effectively for most scenarios with 5 clusters (locations/studies) and about 5 MUs per cluster. It is also shown that the same benchmark accuracy can be obtained when cluster sizes are unequal as long as the total number of MUs is 25 and no cluster has more than 5 MUs.

It must be emphasized, however, that a sample size of 5 clusters with 5 MUs/cluster is considered the 'default' or 'standard' configuration. It strictly applies only to scenarios without existing data when the default normalization is used, and when the default variability structure and 3-fold benchmark accuracy are considered reasonable. In other cases, the AHETF will use the simulation techniques described in Appendix C to develop optimal sampling plans for each scenario it addresses. When some MUs already exist, they will be considered. Other, field-related considerations will contribute to these scenario plans by determining appropriate locations for each cluster, whether or not it is practical for cluster sizes to be the same, and targets for allocating an amount of active ingredient handled to each MU in the plan (see Appendix B).

9.5 Monitoring Unique Workers: The Single-Day Exposure and Long-Term Mean Exposure Distributions

By definition, a particular individual handler (i.e., ‘worker’) will appear in the target population of handler-days each day on which he performs scenario-related tasks. Such multiple occurrences of a worker in the target population pose no conceptual difficulty in defining the distribution of single-day exposures. This single-day exposure distribution merely corresponds to the likely exposure for a single handler-day selected randomly from this target population. If it were practical, the results obtained from a simple random sample of handler-days could be used to estimate the single-day exposure distribution. Unless the simple random sample is very large, it would rarely, if ever, contain two or more days for the same worker. Thus, having a sample of only unique-worker handler-days would not be atypical and estimating the single-day exposure distribution would be straightforward. In fact, if exposure shows any positive within-worker correlation, the intentional inclusion of repeated workers in the sample reduces its sampling efficiency. That is, if the sample contains N handler-days but includes, by design, some days with the same workers, then the sample size (for determining the single-day distribution) is effectively less than N . This effective sample size gets smaller as the within-worker correlation increases. If the correlation were perfect (i.e., equal to one), the effective sample size would be the number of unique workers obtained.

The AHETF program was explicitly designed to estimate only the single-day exposure distribution. This is the distribution of primary regulatory interest for the scenarios under consideration. Consequently, the diversity-oriented sampling methodology described in Appendix B purposively selects only unique workers. This focus on unique workers (as well as other aspects of diversity sampling) could, in theory, overestimate the variation in the target population. In practice, however, any such overestimation is expected to be rather small compared with the scenario benchmark requirements (Appendices B and C). Some existing studies purchased by AHETF report multiple MUs with the same worker. The impact, if any, of these or other anomalies in the data will be described in the summary monograph produced for each scenario (Section 11).

There is some regulatory interest in the distribution of long-term mean worker exposure. From a regulatory standpoint, the long-term mean exposure is relevant to risk assessments dealing with cumulative exposure to chemicals. Risk assessors estimate the distribution of long-term exposure by examining the distribution of long-term means multiplied by the number of days exposed (and factoring in other considerations when appropriate such as expected lifetime and years worked).

This distribution of long-term mean exposure is different from, but related to, the distribution of single-day exposures. All the handler-days for a particular worker in the target population could be collected and the resulting exposures averaged. Such an average exposure value exists for each unique handler in the handler-day target

population. In effect, this creates a target population of just unique handlers (not handler-days). Each handler in this new target population has a long-term mean exposure. A distribution of long-term means arises conceptually by imagining selecting a worker randomly from this new target population.

One cannot directly estimate the long-term distribution from a sample having only a single day per worker. Some information regarding the within-worker distribution is necessary. Such information must be obtained by either sampling multiple days per worker or by making assumptions about the degree of within-worker correlation. At the suggestion of the SAP (SAP, 2007), the AHETF considered the feasibility of a monitoring program that could estimate both the single-day and the long-term mean exposure distributions. Sampling designs that can do this are necessarily complex. As shown in Appendix C, a two-random-effect sampling model was necessary to determine sample sizes for the single-day exposure case. The simplest reasonable model for repeated-worker sampling necessary to estimate the long-term distribution has five independent components of variance. These correspond to random effects for:

- Different clusters
- Different visits to the same cluster
- Different workers within a cluster
- Different days of monitoring the same worker in different visits to the cluster
- Different days of monitoring the same worker during the same visit to the cluster

It is critical to note that such a sampling model has two levels of ‘within-worker’ variation:

- Short-term, or ‘repeated-measures’, within-worker variation between days of the same visit to a cluster (usually several days to a week), and
- Long-term, or ‘longitudinal’, within-worker variation corresponding to exposure days separated by much longer periods of time (e.g., months or years apart)

Short-term within-worker variation is expected to be much smaller than long-term variation. A worker’s exposure on two sequential days should have the greatest correlation since many handler-day conditions should be similar. In contrast, exposures separated by a year or more have lower correlation since environmental, behavioral, and other handler-related conditions should have greater differences. It is the longitudinal variation that is most relevant to long-term (or lifetime) mean exposure.

The AHETF has investigated this sampling model and conducted numerous simulations using reasonable values for the random effect variances and assuming the default 3-fold accuracy benchmark for the long-term mean exposure distribution.

These investigations indicate that the smallest acceptable design requires two separate visitations to every cluster. The two visits should be at least a year apart and the same individuals need to be monitored both times. (Since short-term correlation has little impact on the long-term mean distribution, there is no statistical value to monitoring the same individuals multiple times during the same visit to a cluster.) The required number of clusters and number of unique workers per cluster would be approximately the same as the current AHETF single-exposure designs. Thus, the total number of MUs would need to be approximately twice that of the current AHETF design.

Such a repeated monitoring program would be more costly and complex to manage than the current single-visit program. In addition, as pointed out by the SAP, participation is likely to be negatively affected when commitment to a second year of monitoring is required. Such problems would likely more than double the cost of the monitoring program. This would likely mean a reduction in the total number of scenarios that could be addressed.

If the sampling variance structure and sample size requirements were ignored, a small number of repeated MUs could be collected during selected cluster visits. The cost of such ancillary samples would not be as great as the complete design described above, but would still be non-trivial, since the average cost per MU is estimated to be approximately \$20,000.) However, it is not clear that collection of a statistically inadequate set of additional repeated-measure MUs could be justified.

Lastly, it is important to note that methods currently exist for estimating the distribution of long-term means from just the single-day exposure distribution. Under the reasonable assumption that the single-day exposure distribution is approximately lognormal, the long-term mean distribution can be calculated if a value for the long-term within-worker correlation, R_{ww} , is assumed. R_{ww} is always between 0 and 1. When R_{ww} is near one, the long-term mean distribution is the same as the single-day exposure distribution. When $R_{ww}=0$, the long-term mean exposure distribution reduces to a single value, the arithmetic mean of the single-day exposure distribution. When $0 < R_{ww} < 1$, the long-term mean distribution is lognormal with the same arithmetic mean as the single-day exposure distribution and variation that is a known function of R_{ww} .

If the sample sizes are sufficient to estimate the single-day exposure parameters to within 3-fold accuracy, then there is a practical approach for estimating parameters of the long-term mean distribution with similar accuracy. When the value assumed for R_{ww} is close to the true (long-term) within-worker correlation, the estimates of the mean and 95th percentile of the long-term mean distribution should have close to 3-fold accuracy. More importantly, if the assumed R_{ww} is higher than the true R_{ww} , then the mean and 95th percentile might be overestimated, but the underestimation error is always less than 3-fold. From a regulatory perspective, overestimation of exposure is a less serious problem than underestimation. Thus a reasonable, or even conservative, value for R_{ww} can provide information about the long-term mean distribution that is

adequate for regulatory purposes. Estimates of R_{ww} for worker exposure are available in (or can be calculated from) the literature (e.g., Nigg, et al., 1986; Kromhout and Vermeulen, 2001) or PHED (SAP, 2007 and USEPA, 2007). However, such estimates invariably describe only short-term variation and can range anywhere between 0.2 and 0.9 with great uncertainty. In the absence of additional data, this suggests that some value between 0.5 and 0.9 might be a conservative estimate for long-term within-worker correlation.

Although only the single-day exposure distribution is addressed by the AHETF monitoring program, the AHED[®] database will include information that can be used for both short-term and, with conservative assumptions, long-term exposure assessments. Therefore, AHED[®] will be suitable for early tier exposure assessments for short- and long-term assessments, including for cancer and other chronic endpoints of concern.

9.6 Scenario Sampling Plans

The AHETF will develop and document a sampling plan for each scenario. The purpose of each sampling plan is to ensure that the sample size is adequate to meet specific scientific (e.g., benchmark accuracy) objectives and will include a diverse set of common handling conditions.

Construction of a scenario-specific sampling plan first involves several tasks necessary to implement the purposive sampling and to increase the applicability of the purposively selected set of MUs to the target population. Plans are developed by a Field Studies Subcommittee that is made up of agriculturalists from the member companies. These people have considerable experience conducting crop residue, environmental fate, and exposure studies and have a good working knowledge of North American agricultural practices. Planning also involves consultation with agricultural experts (see Appendix B). The steps involved, described briefly, include:

1. Define the handling scenario, both in terms of what it includes and what it does not include (e.g., task, equipment, product formulation, engineering controls, etc.). These definitions are often based on information that is publicly available (e.g., USDA statistics, government reports, or literature references) and by consultation with appropriate experts for each scenario.
2. Identify parameters likely to impact exposure (e.g., worker practices, crops, etc.) and rank their expected impact. This is based on task force expert judgment and discussions with regulators.
3. Identify common variations of these parameters. This will be accomplished by a combination of reviewing public information, discussing with experts in the particular handling scenario, and discussing with local growers or crop consultants.

4. Establish the practical range of amount of active ingredient handled (AaiH) or other normalizing factor. This is often based on reviews of label rates and maximum acres treated per day.
5. Identify a set of diverse locations where the common handling conditions of interest are likely to take place naturally (i.e., selecting study locations). Local site coordinators often help identify suitable locations and for some scenarios crop acreage statistics can be a helpful guide.
6. Identify growers or application contractors within selected locations where suitable conditions are likely to occur naturally and who are willing to cooperate (e.g., by accepting the particular pesticide application of interest and by allowing recruitment of their workers). Local site coordinators often help identify growers.
7. Recruit workers who meet the inclusion/exclusion criteria and who reflect the typical worker population in that location (e.g., in terms of experience and language). This is done by the Study Director after suitable locations and growers are identified.

Appendix B describes each of these steps in detail. Based on the information from these steps, each scenario-specific MU sampling plan will contain the following components:

- Summary of existing MUs and cluster structure (e.g., from PHED or AHETF)
- Proposed number of additional clusters and MUs/cluster, and rationale
- Identification of the most appropriate normalization factor (generally AaiH, but it could be something else or no factor at all)
- Identification of conditions / factors (other than the normalization factor) that may influence the distribution of exposures population and a summary of available information (if any) about the distribution of these conditions across the target population
- Desired location for each cluster
- Target AaiH (or other normalization factor) for each MU
- Guidelines for diversification of other parameters

As each field study is completed and the resulting MUs are posted to AHED[®], all affected scenario-specific sampling plans will be reviewed and revised, if needed. In particular, this review will help ensure appropriate diversity of conditions, especially the appropriate normalization factor such as AaiH.

10 Description and Role of Field Studies under the AHETF Monitoring Program

A field study is the component of the AHETF exposure monitoring program that actually involves sampling MUs. Within the purposive diversity sampling design, each field study typically represents a cluster of MUs from one location for one or more scenarios.

Each field study conducted as part of the AHETF monitoring program will be conducted in compliance with Good Laboratory Practice (GLP) standards issued by EPA (40 CFR 160). As required by GLPs, Standard Operating Procedures (SOPs) have been developed that address many routine elements of AHETF field study operations and these SOPs will be submitted to EPA along with new study protocols and other supporting information. AHETF field studies meet the definition of “study” in the GLPs at 40 CFR §160.3, which reads: “Study means any experiment at one or more test sites, in which a test substance is studied in a test system under laboratory conditions or in the environment to determine or help predict its effects . . . or other characteristics in humans . . . or media.”

Each field study will develop data for MUs in one or more scenarios. For example, a study might be designed primarily to monitor helicopter pilot exposure, but the mixer/loaders who prepare the spray mixture (and whose exposure measurements will go into a different scenario or scenarios) will also be monitored. Each study protocol will summarize and reference this program governing document, AHETF SOPs, a justification for the need for additional data, a detailed sampling plan to collect more data, and study-specific issues such as recruitment, consent, benefits, and risks.

10.1 Relation of Field Studies to Scenarios

AHETF study timing and location is usually dictated by the seasonality of the tasks to be performed, pest pressures, and crop growth stages. This often allows a relatively small window of time each year when a study can be conducted. Finding sites and arranging for studies can be challenging, especially when special efforts are made to monitor workers under actual conditions with minimal scripting. For example, a pilot may spray from hundreds, to sometimes over a thousand, acres during a typical workday. The AHETF must identify sufficient crop acreage to allow a full day of application for each worker (i.e., each exposure measurement or MU) while trying to capture the range of potential acres treated (the typical way to vary AaiH for a particular surrogate product). Since data requirements for most use scenarios cannot practically be accomplished in a single study, most individual AHETF study protocols are part of a multi-study and multi-year plan designed to generate a wide range of data for activities associated with that use scenario. An individual field study typically will not represent a complete stand-alone scenario; but will provide a limited number of MUs, monitored at a specific site (typically a cluster within one or more scenario-specific sampling plans), generally with a single pesticide product. Data from multiple field studies conducted at multiple sites/clusters will typically be combined to complete the sampling design for most use scenarios.

Each worker exposure field study is performed in accordance with EPA guidelines for conducting worker exposure studies (Durham, 1962; Wolf, 1967; WHO, 1975 and 1982, OECD, 1981; NACA, 1985; Chester, 1993; Worgan, 1995) as described in Series 875: Occupational and Residential Exposure Test Guidelines (U.S. EPA, 1986 and 1996). These guidelines are consistent with guidelines used in other countries such as Canada, Australia, and members of the European Union.

Many aspects of individual field study protocols—especially sample collection and analysis methods—will be standardized to ensure consistency and uniformity in the resulting data. Exposure monitoring protocols differ mainly in the specific product used, the amount of active ingredient handled, equipment used, timing of the study, location and activity performed (including the level of scripting). In addition, there will be differences in other aspects of protocols, e.g., recruitment methods and study specific heat stress and medical management plans.

10.1.1 Descriptions of Surrogate, Locations, and Number of Measurements

Since a major component of quality assurance is to perform field fortifications to measure stability of the surrogate chemical (see below), AHETF field study protocols will generally involve a single pesticide product containing one active ingredient. The protocol will generally name the product (since formulation type, container design, and/or product concentration may be important study design factors) and identify the active ingredient. On some occasions, a protocol may identify two or more potential products which could be used, but the raw data collected during the study would always identify exactly what was used. For example, AHETF has a set of validated analytical methods which can quantify two organophosphate insecticides, malathion and diazinon, which have many approved uses in common. Therefore, some protocols may specify the use of malathion or diazinon.

In some cases, the grower may need to add other chemicals to a tank mixture, including other pesticide products, fertilizers, and adjuvants. These decisions are outside of AHETF control and are often not known in advance, so all protocols and consent forms will address this possibility in general terms. AHETF will ensure that only products approved for use by EPA and that don't require added PPE will be utilized.

As described in Appendix B, varying the location of monitoring is an important study design parameter, and some protocols will specify that data be generated in multiple states or provinces. However, since most scenarios consist of multiple studies, perhaps from different sites in different years, there are also situations where a scenario-specific sampling design could call for monitoring at only one site. The location of field studies within a scenario is generally varied to obtain variability in exposure potential that may come from differences in workers, crops, equipment, or environmental conditions as outlined in the scenario sampling plan. For example, studies involving airblast application to grapes would be conducted both in the west

and in the east, so that differences in exposure caused by weather, grape variety, vine management practices, spray equipment size, or other factors would be reflected in the exposure data for those scenarios.

Each field study protocol lists a target number of MUs that will be generated, often separately for mixing/loading versus application activities. The actual number of MUs completed may sometimes be less than the target number due to factors such as availability of workers and equipment, crop acreage available for treatment, worker decisions not to participate or to withdraw, or adverse weather. In these cases, sufficient MUs to fulfill the scenario-specific sampling design must be obtained during a future field study.

10.1.2 Documentation procedures

Exposure monitoring studies conducted by the AHETF are designed to measure exposure to workers as they perform their normal work functions in a particular handling scenario. All aspects of study conduct will be fully documented in compliance with GLP requirements. Most of the information collected in the field during each study is entered by hand by researchers on standard data forms provided by AHETF. Much of this information is also entered into the generic database, AHED[®], for use in data analysis and for examination by database users in conjunction with data from other AHETF studies.

Raw data are collected in a study notebook which will be retained indefinitely in AHETF archives. In addition, a certified copy of the data set is made during report writing and report review in case the original is lost during transit to archives.

These procedures are detailed in Chapter 9 of the AHETF SOP Manual.

10.1.3 Quality Assurance Procedures

A very important requirement of GLPs is rigorous quality assurance to ensure the quality and integrity of the data that will be relied upon for pesticide handler exposure assessments. All aspects of the studies are monitored while they are in progress by appropriate quality assurance units (QAUs) to ensure compliance with GLP regulations and adherence to the protocol and relevant AHETF Standard Operating Procedures. This will typically involve three different QAUs: one from the exposure monitoring contractor that conducts the study in the field, one from the analytical laboratory that determines the level of pesticide residues in field samples, and one contracted directly by the sponsor. For each field study, the following specific activities are conducted by these QAUs:

- Sponsor-contracted QAU inspects all contract research organizations and laboratories prior to use in a study to ensure that those researchers operate in compliance with GLPs

- Sponsor-contracted QAU reviews protocols prior to finalization
- Sponsor-contracted QAU observes study conduct in the field
- Sponsor-contracted and field contractor QAU audits the raw data file from the field and Field Report
- Analytical laboratory QAU audits the raw analytical data and Analytical Report
- Sponsor-contracted QAU reviews and audits the final report which includes the Field Report and Analytical Report as appendices

Each QAU submits an inspection report(s) to the Study Director and AHETF Sponsor Representative and any exceptions to full GLP compliance are summarized in the Final Report associated with each protocol.

Chapter 5 of the AHETF SOP Manual provides details about the responsibilities of and procedures to be followed by the sponsor-contracted QAU. Field contractor and laboratory QAU's follow similar SOPs from their own facility.

10.1.4 Quality Control Procedures

In addition to the formal quality assurance efforts discussed above, there are a number of important analytical and field sampling quality control procedures which are followed in order to assure that exposure measurements are accurate and precise and to define what those exposure measurements represent. These include complete validation of all analytical methods; extensive documentation of exactly what the participant does while handling the pesticide product; field fortification and control samples designed to estimate stability of chemical residues during sampling, transit, and storage; laboratory fortification and control samples designed to establish efficiency of the analytical methods on a day-to-day basis; and detailed guidelines on the use of calibration curves to determine chemical residues found on all sample matrices.

In the field during each study, a chemist prepares exposure matrix positive control samples that are fortified with a known amount of active ingredient. These matrices include whole body dosimeters (WBD, cotton long underwear), hand wash detergent solution, face/neck wipes moistened with detergent solution, and inhalation tubes (referred to as OVS tubes which stands for OSHA Versatile Samplers). OVS tubes are fortified in the laboratory by injecting diluted analytical grade active ingredient onto the sorbent in the tube while all other matrices are typically fortified in the field with a suspension of diluted test substance (from individual vials prepared in the laboratory). Each matrix type is generally fortified at three levels of active ingredient designed to span the range of residues anticipated to be collected from workers. At each level, triplicate samples are fortified. In addition, negative control samples (i.e., blanks) are prepared for each matrix to determine whether background levels of active may be present. In general, field control and fortification samples are collected on at least two days during each study and whenever significantly different weather conditions are

expected. It should also be noted that similar samples were generated as part of the method validation process under conditions that were anticipated in the field to establish, in a preliminary sense, the stability of residues on field sampling media during and after an exposure period.

Fortified WBD and OVS tubes are “weathered” in the field since these sample types involve collection of residues during the monitoring period. For WBD, this involves laying a fortified section of long underwear onto a table in a sunny location and covering that sample with a single layer of outer shirt material. For OVS tubes, this involves drawing air through the tube in the same manner as done for workers. Fortified hand wash and face/neck wipe samples are not weathered since these samples are collected at specific time points during the monitoring period and immediately placed into frozen storage.

Analysis of field fortification samples provides a “recovery” value which will quantify stability of the active ingredient during sample collection (for weathered samples), storage in the field, shipment to the laboratory, and storage in the laboratory freezer. Therefore, field fortification samples serve as a type of positive controls. Field fortification samples are analyzed along with worker exposure samples and it is assumed that the worker samples experience similar stability as the field fortification samples. Therefore, residues found in worker samples are adjusted by appropriate average field fortification results to estimate the residues actually collected in the field. These practices are standard in pesticide exposure monitoring and are discussed in detail in internationally accepted testing guidelines.

Similar quality control procedures are followed in the laboratory, including control and fortification samples which are designed to detect background residues, monitor the performance of the method, and detect matrix or reagent interferences which may be present. These samples serve as a type of positive and negative controls. In addition to the detailed analytical methods for each surrogate and each matrix, all analyses must follow detailed AHETF analytical guidelines which specify procedures related to standard curves, extract handling, documentation, etc.

10.1.5 Reporting Process

A detailed report is generated for each field study—a “final report” in GLP terminology. AHETF calls these “Summary Reports” which include a text and tabular summary; and detailed appendices including a Field Report and an Analytical Report. Summary reports are formally submitted to EPA, California DPR, and PMRA as they are completed. Summary reports submitted to EPA will also be reviewed by the Human Studies Review Board under 40 CFR 26.1602. In general, these documents will report exactly what was done in the field, the results of analyses of residues, and what information will be entered into AHED[®]. However, since individual field studies do not provide all the data necessary for a complete scenario, these Summary Reports of individual field studies will not include an analysis or interpretation of the

exposure data that were generated. Scenario summarization activities are described in Section 11 of this document.

Field study summary reports will document the conduct of exposure monitoring, including:

- Identification of the location of the study, and the environmental conditions during the exposure monitoring period(s)
- Descriptions of the participants in the study
- Description of the test substance and packaging
- A record of the mixing, loading, and/or application, including a description of the workers, equipment, and worker activities
- A summary of worker observations identifying any specific occurrences that may contribute to unusual worker exposure
- Descriptions of the work clothing and personal protective equipment worn by each worker
- A detailed summary of the amount of test substance handled or applied for each worker
- A detailed summary of the length of time each worker was monitored
- A complete description of the field recovery evaluation with a summary of specific handling and weathering of all field samples
- A complete description of collection, handling, storage, and shipping of field samples.
- A complete description of the ethical conduct of the field study, including all elements specified in 40 CFR 26.1303.

Analytical reports of individual field studies will document the handling and analysis of residues in all samples collected in the field, including:

- Results of analysis (e.g., $\mu\text{g}/\text{sample}$)
- A detailed description of the analytical instrumentation and methods
- A detailed description of sample storage conditions and storage intervals
- Example calculations
- A summary of field and laboratory fortification recovery data
- Representative chromatograms of control, treated, fortified samples and calibration standards
- A typical standard curve

Summary reports summarize the field and analytical aspects and include calculations of adjusted residues found in all collected samples (i.e., adjusted for field fortification recovery); total dermal exposure for each worker; and the air concentration of active ingredient associated with each worker's monitoring period.

Study reporting requirements are described in SOPs AHETF-4.A and AHETF-9.I.

11 Scenario Summary (Monographs)

As part of the documentation supporting AHED[®], AHETF will generate scenario monographs for the benefit of regulators and other potential database users. Each monograph will include a description of the scenario as well as an assessment of the data adequacy within that scenario. Based on this analysis, AHETF may include in the monograph additional recommendations concerning the use of the MU results. Scenario monographs will be formally submitted to the regulatory agencies when AHETF determines the data collection for a particular scenario is complete and suitable for use in exposure assessments.

AHETF will not perform any statistical analyses of the scenario data for the purposes of exposure characterization or risk assessment. Such analyses are the responsibility of regulators and other potential users of the generic database. However, as part of the generic database development and documentation activities, AHETF will evaluate how well the collected data for each scenario satisfy the benchmark adequacy objectives. In addition, the AHETF will quantify the impact of ignoring clusters and treating the data as a simple random sample.

11.1 Assessment of Benchmark Adequacy Objectives

Section 9.4 describes AHETF's primary and secondary benchmark objectives for data adequacy. The primary benchmark requires that the relative accuracy of selected parameter estimates of the normalized (or possibly non-normalized) exposure distribution be within specified limits. A secondary benchmark requires that the data be adequate to distinguish a proportional from an independent relationship between exposure and the normalizing factor, usually amount of air handled (AaiH). Appendix C discusses both benchmark objectives in detail.

Both benchmarks are necessarily based on pre-study assumptions about the true nature of the variation and the ability to obtain the target number of clusters and MUs/cluster. In addition, achievement of the secondary objective depends on the ability to obtain the targeted within-cluster and between-cluster diversity in the normalizing factor. It would be unlikely for all of these assumptions to be exactly satisfied for every scenario. Although slight deviations will have little or no impact, large deviations from the assumptions might result in data that deviate too far from the benchmark

objectives. Consequently, it is also of value to assess the benchmark requirements using the data actually obtained.

Both benchmarks were specified in terms of the true variation structure and a calculated probability that certain characteristics would be observed in the data (See Appendix C). For the primary objective, the characteristics are estimates such as the arithmetic mean and 95th percentile of normalized dermal exposure. For the secondary objective the characteristic of interest is the rejection of a hypothesis. Once the data are available, however, such probability statements are less relevant than confidence statements calculated from the actual data. Consequently, evaluation of the benchmark objectives will be based solely on confidence intervals.

11.1.1 Relative Accuracy of the Normalized Exposure Distribution

As defined in Appendix C, the primary benchmark objective specifies that selected lognormal-based estimates of the (usually) normalized dermal exposure distribution be accurate to within K-fold, at least 95% of the time. The benchmark estimates are the geometric mean, arithmetic mean, and the 95th percentile. Of these estimates, the 95th percentile and the arithmetic mean will always have the worst relative accuracies.

To assess this benchmark objective, a 95 percent bound on relative accuracy will be calculated from the confidence interval for each of the three parameters given above. For a particular parameter, θ , let T denote its estimate calculated from the fit of a cluster sampling (mixed) model to the normalized exposure data. Further, let θ_a and θ_b denote the upper and lower limits, respectively, of a 95% confidence interval for θ . In most cases, the confidence interval, (θ_a, θ_b) , will be a parametric bootstrap percentile interval obtained by resampling from a lognormal cluster sampling model. (For the geometric mean only, a Satterthwaite t-based confidence interval can be calculated directly from the mixed model.) The 95 percent upper confidence bound on realized fold relative accuracy is then calculated as:

$$UCL_{95}(fRA) = \text{Max} (T / \theta_a, \theta_b / T)$$

The values of $UCL_{95}(fRA)$ will then be compared with the pre-specified relative accuracy benchmark objective, K . In Appendix C this primary benchmark was expressed in terms of the 95th percentile of fold relative accuracy, fRA_{95} . However, fRA_{95} is only relevant when discussing future results. In contrast, $UCL_{95}(fRA)$ relates to the realized relative accuracy and is the post-data analogue of fRA_{95} .

This primary benchmark objective strictly applies to only dermal exposure. However, for consistency, the 95 percent confidence bounds on the three parameters will also be computed for inhalation exposure.

11.1.2 Adequacy of the Data for Distinguishing a Proportional from an Independent Relationship between Exposure and the Normalizing Factor

This secondary benchmark objective (Section 9.4.2) applies only to handler scenarios for which the practical range in the normalizing factor (NF), usually amount of active ingredient handled (A_{aiH}) exceeds an order of magnitude. In such cases it is reasonable to consider the linear regression of log dermal exposure on log NF. Such a regression would use a mixed model in order to incorporate random cluster effects. In the regression model the true slope, β , would be equal to one if dermal exposure were directly proportional to the normalizing factor. If exposure were independent of NF, then $\beta=0$.

For applicable scenarios, this benchmark objective requires that the number of clusters and the allocation of NF levels to MUs be adequate to ensure that such a regression analysis has at least 80% power to reject the hypothesis that $\beta=0$ when β is actually equal to one. By symmetry, the mixed model linear regression would also have the same power to reject the hypothesis that $\beta=1$ when $\beta=0$.

As described in Appendix C, the number of clusters, number of MUs/cluster, and the NF configurations that satisfy this power objective will be determined and used to establish sampling targets for each scenario. This pre-data power analysis also requires an assumed true variance structure (i.e., the residual geometric standard deviation and a within-cluster correlation). After the MUs have been sampled, the actual MU and NF configurations are available. The true residual variance structure is still unknown, although estimates of this structure would now be obtained from the exposure data using a mixed model regression analysis. In principle, this 'updated' information could be used to re-calculate the power to distinguish proportionality ($\beta=1$) from independence ($\beta=0$). However, such post-hoc power analyses can be somewhat non-intuitive, especially if the data suggest that both hypothesized values of β are false. When the data are available, confidence intervals obtained for the parameters of interest (e.g., β) are considered more relevant than an updated power analysis (Hoenig and Heisey, 2001).

Consequently, for each scenario, a mixed model regression of log dermal exposure on log NF will be performed and a confidence interval obtained for β . As shown in Appendix C, the secondary benchmark power requirement is equivalent to stating that the mean width of a 95% confidence interval for β is approximately 1.4. (The expected width is 1.6 in the case of one-sided hypothesis tests.) Therefore, the width of the 95% confidence interval for slope will be used to gauge the adequacy of the data with respect to the second benchmark. For example, if the width of the confidence interval obtained from regression on the actual data is 1.4 or less, then the data would be judged adequate with respect to the secondary benchmark.

Note that the adequacy of the data depends only on the width of the confidence interval, not on the particular values of the endpoints of the interval or on the observed slope, b . Although the full results of the regression analysis will be summarized in the scenario monograph for completeness, they are not relevant to the question of benchmark adequacy. It is also possible for both $\beta=0$ and $\beta=1$ to be within the 95% confidence interval for the true slope. Such a result is still consistent with benchmark adequacy since a confidence interval whose width is 1.4 could potentially contain both 0 and 1. However, when $\beta=0$ then a value of 1 is expected to be outside such an interval. Similarly, when $\beta=1$ a 95% confidence interval of 1.4 is unlikely to include zero.

As was the case for the primary objective, the secondary objective only applies to dermal exposure. However, for uniformity, the same regression analysis and assessment of the confidence interval will be conducted for inhalation exposure.

11.1.3 Interim Analysis of Benchmark Adequacy

No formal analyses of data adequacy will be conducted until the planned number of clusters and monitoring units have been obtained. In general, the sample sizes for a partial scenario would be too small and variation estimates too imprecise to be of any benefit in improving the design 'mid-stream'. Equally important, any such repeated or sequential uses of the data would be inconsistent with the fixed-sample-size methods used to determine the number of clusters and MUs. If the adequacy analyses described above indicate that the target benchmark objectives for a particular scenario are not met, then the AHETF, in consultation with the JRC, could decide to conduct new studies in order to obtain additional clusters. Since a non-random purposive selection approach is used, augmenting the scenario data with new clusters later is straightforward.

11.2 The Impact of Ignoring Clusters

As described in Appendix B, the AHETF monitoring design involves selecting MUs in clusters. A cluster is a set of MUs obtained in a single study at a particular geographic location over a limited period of time (e.g. several days). Clusters are not a property of the target population, but merely necessary artifacts of the sampling process. It is expected, and existing data confirm, that exposures for MUs in the same cluster are correlated to some degree. In general, estimates of distributional parameters and regression analyses should accommodate this correlation. If a user ignores clusters (i.e., assumes the data are a simple random sample), then some parameter estimates may be biased and the confidence intervals may be too small. On the other hand, for the MUs of a particular scenario, such biases may be small and of little practical importance. When this is the case, analyses of the data can be simplified considerably. As an aid to regulators and other potential AHED[®] users, the impact of ignoring clusters will be examined.

Estimates and confidence intervals for the three parameters of the normalized exposure distribution listed above will be calculated assuming no cluster effect (i.e. assuming simple random sampling). These estimates will be compared to those obtained under the cluster-sampling model. The differences obtained by ignoring clusters will be summarized.

Similarly, a simple linear regression analysis (i.e., without a cluster effect) of log exposure on log normalizing factor will be performed. The estimated slope and confidence interval will be compared with those obtained with the mixed model regression described above. Again, the impact of ignoring a possible cluster effect will be summarized.

11.3 Other Information to be Included in the Scenario Monographs

In addition to an evaluation of data structure and adequacy described above, the monograph reports will also summarize various aspects of the study design. These include:

- A graphical summary of how all MUs in a scenario are structured into clusters and how each cluster is further structured into workers, days, and locations
- Representative use information for AHETF member products to define crops, rates, sites, etc. (used for scenario sampling plans)
- Information about the diversity of equipment and procedures currently in use in North America for this scenario
- Characterization of the important features of any existing data acquired by AHETF for this scenario
- Summary of the design targets developed and used for this scenario

12 Exposure Monitoring Techniques

The AHETF monitoring program is designed to develop exposure data using passive dosimetry rather than biomonitoring techniques. The passive dosimetry methods provide a reliable measure of individual worker exposure and are amenable to determining exposure to a variety of body areas. In addition, AHETF desires to utilize the same methods for all MUs so exposure levels from one handling scenario can be compared to those from all others. In particular, AHETF has selected the following standard dosimetry techniques:

- Whole body dosimeters (cotton long underwear)
- Hand washes (detergent in water)
- Face/neck wipes (gauze pad soaked with detergent in water)
- Head patches (both inside and outside of chemical-resistant headgear; used only when headgear is required by the surrogate product label)
- Socks (as a dosimeter to measure foot exposure in some scenarios)
- OVS tubes with filter and sorbent

Each field study protocol will specify exactly what dosimeter types will be used and how they will be handled in the field and in the laboratory.

12.1 Validation of Passive Dosimetry

Because it is difficult to isolate and validate particular components of dermal dosimetry methods, the best validation is a comparison of the sum of passive dosimetry methods against the biomonitored dose. The data examined in a recent review of both proprietary and published studies demonstrated an excellent correlation between passive dosimetry and biomonitoring (Ross et al., 2007). Passive dosimetry as a measure of dosage appears to be consistent with biomonitoring with no bias, i.e., no tendency to over- or underestimate exposure. This evaluation demonstrated that the total absorbed dose (or daily dosage) estimated using passive dosimetry for important handler and reentry scenarios is generally similar to the measurements for those same scenarios made using human urinary biomonitoring methods. Further, this is strongly supported by statistical analysis of individual worker passive dosimetry to biomonitoring ratio and variance within and between studies. The passive dosimetry techniques currently employed yield a reproducible, standard methodology that accurately and reliably quantifies exposure and does not underestimate daily absorbed dose. The dermal exposure monitoring techniques used in the studies in this comparison were whole body dosimeters or patches; hand washes; and face/neck wipes or head patches.

In 2007, EPA convened a Scientific Advisory Panel to discuss validity of passive dosimetry techniques to collect worker exposure data. The Panel concluded that:

Although a bias may exist, no bias between dermal exposure monitoring and biological monitoring could be detected in large part because of the statistical uncertainty inherent in the exposure data. (SAP, 2007).

12.2 Description of Techniques

Whole Body Dosimeters (WBD)

WBDs (i.e., cotton long underwear) are preferable to patches since they overcome the need to extrapolate residues on a small patch to entire body part areas. They are also easy to cut into sections to determine residues on various body parts. This provides information that can be used to estimate exposure for workers wearing various PPE items, such as aprons. For most studies, AHETF will section the dosimeters into six parts for separate analysis: upper arms, lower arms, front torso, rear torso, upper legs, and lower legs. For some studies (generally when very low exposures are anticipated), AHETF will section dosimeters into two sections: upper body and lower body. Each GLP study protocol will specify how the dosimeters will be sectioned (in the field) for analysis.

AHETF triple-washes the cotton long underwear before use to prevent analytical interference due to chemicals remaining from the manufacturing process (SOP AHETF-8.J). The use of these WBDs is described in detail in SOP AHETF-8.A.

During data analysis, residues from all sections will be summed. Any dosimeter section with residues below an analytical limit (limit of quantitation or limit of detection) is normally assumed to contain half of that limit when summing residues.

Hand Washes

AHETF has selected a standard hand washing technique using a dilute detergent solution. This technique is more efficient than wiping of the hands, and is preferable to cotton glove dosimeters, which overestimate hand exposure by absorbing and trapping more chemical than skin would.

Hand washing involves first having the worker rub his hands together while a researcher slowly pours 400 mL of solution over his hands. The wash solution is collected in a bowl placed under the worker's hands. Researchers are trained to take about 30 seconds to pour the liquid. The worker is then asked to immerse and rub his hands in the wash water in the bowl for about 30 seconds. Finally, 100 mL of fresh detergent solution is poured over the worker's hands to rinse them and the rinse water is collected in the same bowl. The combined wash/rinse water is transferred to a sample container and analyzed to determine total residues.

Since this washing procedure is dependent on cooperation from the subjects, the technique is practiced before monitoring until researchers are comfortable the worker is appropriately rubbing his hands and is not likely to interfere with the collection process. This also creates some consistency in how vigorously workers rub their hands which could impact removal efficiency.

Whenever a worker would normally wash his hands a researcher will collect a hand wash sample instead. This will be done before any eating break and any other time the worker says he would like to wash his hands, so each MU could include several hand wash samples.

The use of hand washes is described in detail in SOP AHETF-8.B.

During data analysis, residues in all washes will be summed for each MU. Any wash sample with residues below an analytical limit (limit of quantitation or limit of detection) is normally assumed to contain half of that limit when summing residues.

Face and Neck Wipes

AHETF has selected a standard face/neck wiping technique involving two successive wipes with gauze pads soaked with a dilute detergent solution (same solution as hand washes). The entire face, front of the neck, and back of the neck are wiped two separate times and the two gauze pads are combined for analysis. This technique is preferred to using hat patches since no extrapolation of residues to the entire face/neck area is needed.

Whenever a worker would normally wash his face a researcher will collect a face/neck wipe sample instead. This will be done before any food break and any other time the worker says he would like to wash his hands. Another sample will be collected at the end of the monitoring interval. These multiple face/neck wipe samples will be combined for analysis, so each MU will have just one face/neck residue value.

The use of face/neck wipes is described in detail in SOP AHETF-8.C.

During data analysis, residues found on the face/neck are extrapolated to the entire head area to account for the possibility that non-face and non-neck head areas may be exposed to similar amounts of pesticide residue. This is done on a body area basis and is considered conservative since hair and hats generally prevent deposition and absorption through those parts of the head (yet the extrapolation assumes the same deposition rate as occurred for the face/neck). Any wipe sample with residues below an analytical limit (limit of quantitation or limit of detection) is normally assumed to contain half of that limit.

Head Patches

For a few scenarios, AHETF will employ a combination of inner and outer head patches to estimate exposure to non-face and non-neck head areas. This will usually be limited to studies that involve overhead exposure where EPA regulations often require chemical-resistant headgear. It will also be utilized any time a chosen surrogate requires chemical-resistant headgear for the task being studied. This will be specified in the field study protocol.

An example is the open cab airblast applicator scenario. In that case, AHETF utilized both inner patches (under the hat) and outer patches (on top of the hat) that were arranged so one is not right on top of the other. Residues found on these patches were extrapolated to the entire non-face/non-neck head area as measures of inner and outer potential exposure. Any patch sample with residues below an analytical limit (limit of quantitation or limit of detection) is normally assumed to contain half of that limit. This allows estimation of head exposure to workers who do or do not wear chemical-resistant headgear. The latter requires summing extrapolated exposure from the inner patch with that from the outer patch.

AHETF uses whole-body dosimeter pieces for head patches and triple-washes them before use to prevent analytical interference due to chemicals remaining from the manufacturing process (SOP AHETF-8.J). The use of hat patches is described in detail in SOP AHETF-8.H.

Socks

For a few scenarios, AHETF will employ sock dosimeters (new cotton socks provided by researchers) to estimate exposure to the feet. Exposure to this body area is generally insignificant for pesticide handlers since shoes and socks (required by the WPS) provide considerable protection. However, scenarios that involve handheld application equipment and workers who walk while they spray (such as backpack applications) might include this dosimetry technique. This determination will be made by AHETF in conjunction with EPA and other regulators and will be specified in the field study protocol. Cotton socks are worn under normal footwear (i.e., shoes/boots and socks) and are collected at the end of the day for analysis, similar to the WBDs. Any sock sample with residues below an analytical limit (limit of quantitation or limit of detection) is normally assumed to contain half of that limit.

AHETF triple-washes socks before use to prevent analytical interference due to chemicals remaining from the manufacturing process (SOP AHETF-8.J). The use of sock dosimeters is described in detail in SOP AHETF-8.I.

Total Dermal Exposure

During data analysis, exposure levels determined from WBDs, hand washes, head (may be based on face/neck wipes and/or hat patches), and socks are summed to provide a measure of total potential dermal exposure. This value is generally used by EPA and other regulators in exposure assessments for individual pesticide products. Dermal exposure can be normalized, for example, by the amount of active ingredient handled.

Air Sampling Tubes with Filter and Sorbent

AHETF has selected a standard inhalation dosimetry technique that has been used extensively and that involves a personal air sampling pump and a collection device (OVS tube) attached to the collar of the worker facing downward. Air is typically drawn through the device at 2 L/min. The collection device is a glass tube containing a sampling train consisting of a filter followed by two sections of sorbent. The tube is mounted in a plastic protective sleeve which is clipped to the collar of the worker. The filter and sorbent type are selected for each surrogate chemical to maximize sorbent retention and analytical removal efficiency, and validation studies are performed to ensure that residues trapped early in the monitoring period will not be stripped away by the constant airflow through the device during an entire day of

monitoring. In the laboratory, the filter and both sorbent sections are extracted together to yield a total residue value (i.e., for particulates and vapors combined).

The use of OVS tubes is described in detail in SOP AHETF-8.D.

During data analysis, total potential inhalation residues collected for the entire monitoring period are reported along with a calculation of the average air concentration (by taking into account the measured airflow rate and the time of monitoring). This probably overestimates exposure, and is therefore conservative, since even large particles that would not be respirable might be trapped on the filter and assumed as potential exposure. Any OVS tube with residues below an analytical limit (limit of quantitation or limit of detection) is normally assumed to contain half of that limit when summing residues. During exposure assessments, potential inhalation exposure to the worker is calculated by taking into account the breathing rate for the level of work activity being performed. The result can be expressed in total mass for the monitoring period (e.g., μg) or normalized by amount of active ingredient handled (e.g., $\mu\text{g}/\text{lb ai}$).

12.3 Nature of Testing Guidelines

Regulatory agencies frequently collaborate to make exposure monitoring guidelines harmonized. A good example is the Series 875 guidelines of US EPA that were designed with multi-national input starting with a meeting in The Hague in 1992 and punctuated with meetings in Ottawa, Toronto, and Washington, DC that culminated with the issuance of OECD and EPA guidelines that are very similar (OECD, 1997; EPA, 1996). All of the dosimetry techniques utilized by AHETF are consistent with these most recent guidelines.

13 Ethical Considerations

All AHETF field studies will be designed and conducted in compliance with the requirements of 40 CFR Part 26, subparts K and L, and will be documented in compliance with the requirements of 40 CFR Part 26, subpart M.

13.1 Community and AHETF Studies

The word “community” means different things to different people. AHETF was guided by two definitions. In public health research, O’Campo and Caughy (2006) note that:

The literature distinguishes between *neighborhood*, which usually refers to a geographically bounded area, and *community*, which often identifies a group of individuals with a common interest.....

A more expansive discussion was found in Green and Mercer (2001):

The issue of whose participation needs to be solicited and incorporated in participatory research hinges on who is to be most directly affected by the research results.....the assumption tends to be that participatory research necessarily engages the lay community. Typically, “community” is understood as a local geopolitical entity, as in the term “community-based participatory research.” If, however, the notion of community includes other groupings of people sharing common characteristics or interests, or if the purpose under consideration is something other than community development, there emerge both the need and opportunity for undertaking participatory research with groups other than community residents. We therefore urge a broader application of participatory research, one in which the participatory research is seen as systematic inquiry, with the collaboration of those affected by the issue being studied...

For the AHETF monitoring program, the scientific community shares a common interest in the objective of the study. The workplace participant community shares a common interest in recruiting methods, risks, and informed consent.

13.1.1 Scientific Community

AHETF has solicited participation of the scientific community and of parties with a direct interest in the database project and in its effort to design a generic exposure database and enhance the credibility of the database regarding its use in regulatory risk assessments. The overall scientific community is a diverse group of entities, including:

- Pesticide registrants;
- AHETF;
- US Environmental Protection Agency (EPA);
- California Department of Pesticide Regulation (CDPR);
- Pest Management Regulatory Agency (PMRA);
- US Department of Agriculture (USDA);
- Scientific Advisory Panels (SAP);
- Human Studies Review Board (HSRB);
- Institutional Review Boards (IRB);
- Principal Investigators (i.e., the 2 AHETF Study Directors); and
- Field investigators (from contract field research organizations, such as Local Site Coordinators)

The entities listed above form a natural community. AHETF member companies are pesticide registrants and all pesticide registrants are eligible for membership. AHETF members and consultants work collaboratively and in cooperation with EPA, DPR, PMRA and USDA, as we all share the common interest of an improved database with which to estimate exposures and evaluate risks. The common goal is that the database be fully deployed for regulatory and product stewardship uses. In another area, the USDA helped in recruiting aerial applicators and loaders by getting AHETF involved with its Boll Weevil Eradication Program. There also exists a community advisory board—the Joint Regulatory Committee (JRC). The JRC consists of science and policy representatives from EPA, CDP, PMRA and USDA. Formal meetings with AHETF are scheduled quarterly or as needed to provide a record and structure for the AHETF program, as well as to resolve technical and policy issues. The SAP and HSRB may also be considered community advisory boards inasmuch as they generally represent academia and have an interest in the study design, methods, and ethics. The IRB is an independent organization, but nonetheless influences the conduct of AHETF studies through oversight. The two study directors are also part of the scientific community in that they are fully involved in study design, methods, and ethics as consultants to the Task Force. They are also the link to implementing the sampling in the field, with the help of local field investigators. In its operation to date, and its planned continued operation, these entities clearly comprise a community and a community-based participatory research program under the above definitions. The scientific community will continue to operate as AHETF considers each handling scenario in its scope to develop justifications for new data, MU sampling plans, and new study protocols.

13.1.2 Workplace Community

The scientific aspects of study design, methods, and objectives of the study (k-fold accuracy, proportionality or lack thereof) are not known to be issues of interest collectively or individually to the workplace community. Nor are these entities expected to use the data derived by the studies, or take any action based on the findings.

Beyond the scientific community, the community of interest for the AHETF handler exposure monitoring program is cadres of workers in distinct areas of North America that mix, load and apply pesticides. These handlers of interest include both employers and their employees as defined in the WPS. Involvement of the workplace community is specific to the individual study sites and will be solicited for each field study protocol.

Members of the workplace community might include the following:

- Farm owners and family
- Farm operators
- Farm employees
- Contractors (e.g., in agricultural research)
- Commercial applicators (owner or employee)

These entities form a natural workplace community in that they are pesticide handlers from a local area that have common interests in pesticide handling procedures and safety practices. They also define the categories of workers that are part of the target population for AHED[®] and AHETF uses these five categories when documenting the nature of each test subject. For the 173 MUs AHETF has collected to date, about one-third of the subjects were farm owners or operators, about one-third were farm employees, and about one-third were contractors or commercial applicators.

Since the members of this community are the subjects of the AHETF research effort (i.e., a database used to assess worker exposure) and are taking the risks associated with generating the data, they will be included in the non-scientific design aspects of the research program. This includes getting input on study-specific recruitment procedures and materials; consent forms and processes; language issues; and the appropriateness of remuneration amounts. These discussions will take place in the local area that AHETF Study Directors plan to visit for monitoring workers (i.e., near study locations) in advance of preparing field study protocols and supporting materials. The plan is to sponsor informational meetings with community members during the planning process and to invite a variety of community representatives to attend. Therefore, input from the community will be included in materials sent to the IRB or EPA or HSRB.

Depending on the nature of the particular study being planned, such as the scenario(s) involved, AHETF might invite the following who can provide input on worker-related issues:

- County Agricultural Extensions Agents (may be applicable to all studies)
- Local growers or land owners (may be applicable to all studies)
- Farm owners/operators and their employees (may be applicable to all studies)
- Commercial application companies (for scenarios that might involve commercial applications such as aerial application)
- Professional crop consultants
- Crop associations (for scenarios that are limited to a few crops or crop types)
- Farm labor organizations or advocates (for scenarios likely to involve employees)

13.2 Recruitment

Recruitment occurs in two phases. In the first phase AHETF identifies growers (or land owners or farm operators) who might use the surrogate chemical under conditions consistent with the scenario-specific sampling design for the desired MUs. In some cases, commercial application services are also recruited that can provide equipment and workers (e.g., for aerial applications). In the second phase, workers are recruited that have experience with the desired handling activities and that are associated with the growers, land owners, or commercial applicators that have agreed to cooperate.

13.2.1 Recruiting Growers, Landowners, or Commercial Applicators

When searching for cooperating growers, landowners, or commercial applicators, AHETF needs to locate certain combinations of conditions including appropriate equipment types, sufficient crop acres, and the number of workers required. AHETF begins by contacting local resources for assistance. These may be agricultural researchers, County Agricultural Extension agents, farm equipment dealers, farm supply dealers, and others in the local community where the study will be conducted. In some cases, AHETF may also rely on commercial pesticide application companies that may be necessary for some scenarios (e.g., aerial applicators).

In the process of locating potential study sites, AHETF typically contracts with one or more “local site coordinators” to identify appropriate growers or commercial applicators, to explain the need to conduct research with volunteer workers who are willing to be monitored while they perform their regular activities of handling agricultural pesticides in a defined scenario. These growers or commercial application companies are not asked if their employees might be willing to participate. Nor are they urged to ask their employees if they might be willing to participate. Cooperating employers are asked only for their permission for study staff to contact their employees at a future time concerning possible participation in the research.

The final step in this phase is for the Study Director to contact the growers and solicit their cooperation in the research study. The AHETF research program and the need for a suitable site are explained. The growers are advised of the research program benefits to agriculture. The growers must agree to the lost productivity of his workers and the disruption of the daily routine by the field study team. Additionally, he must assent to all of the ethical terms regarding lack of coercion, voluntariness, retaliation, and full pay for the handler employees. Only when these conditions have been met can handlers be approached to participate in the research study.

Once suitable cooperators have been identified, the specific location of the field research site and other variables can be incorporated into a site-specific study protocol, and an appropriate recruitment plan can be developed, taking into account site-specific study needs. These may include the need for Spanish interpreters, the nature and size of the potential subject pool, input from the local community where the research will be conducted, and other factors. The study-specific recruitment plan will be incorporated into the protocol.

13.2.2 Recruiting Subjects

A study-specific recruitment plan will be developed for each field study protocol. No recruitment of subjects will be initiated until the protocol and all supporting materials have been approved by the IRB and reviewed by EPA and the HSRB. If the study is to be conducted in California these documents will require prior approval by the Director of the California Department of Pesticide Regulation.

In a typical field study, recruitment of subjects would begin by obtaining permission from all cooperating employers to contact employees who may be interested in participating in the research, and a statement from each employer that the employer will not encourage or discourage employees from participating in the research, and that workers' decision to participate, not participate, or withdraw will not affect their employment or their pay. The form for this statement is included in SOP AHETF 11.B. It should be emphasized that some growers themselves may also be asked to participate in the study, for example farm owners who handle pesticides themselves. This diversity is considered very important by AHETF since there are many farmers who handle pesticides themselves.

The next step typically would be to distribute to the identified handlers (e.g., employees) a flyer summarizing the nature of the study and the eligibility criteria, and inviting interested candidates to contact the Study Director directly to find out more about the study. The flyer would be reviewed and approved by the IRB before use, and included in the package of materials supporting the proposed protocol when it was submitted for EPA and HSRB review. This "self-identify" approach reduces the potential for coercion and undue influence exerted on the workers by his peers and employers to participate (or not participate) in the study. It also enhances the opportunity for the potential subjects to make a completely voluntary decision about participation.

Interested candidates would typically be invited to a meeting without supervisors being present where general information about the research would be provided (according to a script approved by the IRB), including video presentations of how the dosimetry and air samplers would be worn and illustrating face/neck wipe and hand-rinse procedures.

Candidates expressing further interest in the study would then be invited to a private discussion with the Study Director or other responsible research staff, at which the eligibility criteria would be reviewed, the informed consent document would be presented and discussed, and all the candidate's questions would be addressed. The candidate's consent to participate in the research would be sought and documented during this meeting, or arrangements would be made to allow the candidate more time for consideration. The recruitment process is described in more detail in SOP AHETF-11.B.

13.2.3 Eligibility Criteria

The Study Director is responsible for ensuring the following eligibility criteria are met by all participants.

Willingness to Participate

All monitored workers must be freely willing to participate in a study of this type and to sign the approved informed consent form.

Occupation

All monitored workers must be professional agricultural pesticide handlers—that is, their regular job must include handling agricultural pesticides. They may be farm owners, farm operators, farm employees, contractors, commercial applicators, etc.

Training

All monitored workers must have received basic pesticide handling training in accordance with the Worker Protection Standard (WPS) or equivalent Canadian regulations, or must be exempt from such regulations. Each participant must confirm that they have received the required training or that they are exempt from the requirement.

Experience

All monitored workers must have recent experience (i.e., within the last year) performing the particular task they would be performing in the research. No minimum level or amount of experience is required, but researchers will document how much experience (e.g., in months or years) each participant has for the particular task being monitored.

Age

All monitored workers must be at least 18 years old, and able to verify their age with a government-issued photo identification.

Health Status

All monitored workers must consider themselves to be in good general health, with no medical conditions that could impact their ability to participate in the study will be selected. This precludes selection of workers who are chronically ill or terminally ill. See SOP AHEF-11.C for more details.

Product Label Conformance

All monitored workers must agree to perform pesticide handling tasks in conformance with label and WPS requirements. In particular, monitored workers must agree to wear all PPE required by the label. Researchers will remind participants to use required PPE should they be observed not wearing it. Any workers who fail to follow label requirements during the study will be removed from the study.

Normal Use of Extra Clothing or PPE

A worker who normally chooses to wear more protective clothing or PPE than is required by the label may be allowed to wear the additional items, or may be excluded from the study, depending on the goals of the specific field study design. No one included in an AHETF study will be required or permitted to wear less protective clothing or PPE than he or she normally wears when performing the activities monitored in the research scenario.

Pregnant or Nursing

Female workers who are pregnant or nursing are ineligible to participate as subjects in any AHETF study. Nursing will be self-identified. The pregnancy status of all potential female subjects will be ascertained using a supervised over-the-counter urine pregnancy test within 24 hours before the initiation of monitoring. See SOP AHETF-11.D.

Don't Speak or Read English or Spanish

Candidates who do not read or understand English or Spanish are ineligible to participate as subjects in any AHETF study. See also SOP AHETF-11.B.

Employed by a member of AHETF

Employees of any member of AHETF, or of any organization or investigator under contract to AHETF, are ineligible to participate as subjects in any AHETF study.

13.2.4 Use of Vulnerable Groups

AHETF excludes as participants people who are ill (self-identified), cognitively impaired (deemed by Study Director), pregnant (based on over-the-counter pregnancy test), nursing (self-identified), minors (based on government-issued photo identification), employees of the Principal Investigator (for AHETF studies, the Study Director), sub-investigators, or AHETF member companies. However, AHETF often identifies the following potentially vulnerable groups which may be necessary to reflect the target population:

- Employees of the Local Site Coordinator (i.e., research site);
- Employees of a grower or commercial applicator;
- Limited or non-readers;
- Poor people;
- Workers without [health] insurance; and
- Illegal immigrants

Employees of the Local Site Coordinator

As described above, local site coordinators are generally used to locate suitable sites and growers or commercial application contractors – their facilities are identified as research sites in applications to the IRB. Local site coordinators will not be allowed to participate in AHETF studies since they are directly involved in the research. However, AHETF will occasionally allow an employee of the site coordinator to be a participant in a study. In this case, the worker must meet all of the criteria listed above, including the requirement that he/she be experienced in the particular task being monitored. AHETF will only use such research staff if they also have training and experience handling pesticides in a commercial environment, for example as the owner or operator of a separate commercial farm or in a previous job. This group (i.e., employees of research site in IRB terms) may be vulnerable to coercion since the local site coordinator receives the benefit of payment for his services.

AHETF recognizes the need for extra care to avoid the potential for coercion and undue influence from the local site coordinator that may benefit from participating in an AHETF study. However, AHETF occasionally needs to use these employees in order to get an adequate number of workers at a particular site. Therefore, when considering such employees, the cooperating local site coordinator will be required to sign a statement that he/she will neither encourage nor discourage their employees to participate, and that the decisions of their employees to participate, not participate, or withdraw will have no impact on their employment or work opportunities. A copy of this statement will be provided to all affected candidates in the informed consent interview. (See also SOP AHETF-11.B). These study participants will be classified as “contractors” in data records.

Employees of a grower or commercial applicator

Employees of growers or commercial application contractors are allowed to volunteer as study participants. This group may be vulnerable to coercion from the grower who may get the benefit of free pesticide for his crop(s) or the applicator who gets a contract for application services. These study participants will be classified as a “farm employee” or “commercial applicator” in data records, and will provide many of the monitoring units for most scenarios.

The desire to collect exposure data for professional workers who use their own (or their employer's) equipment necessitates that AHETF work with their employers (for example, the grower who plans to use the pesticide) since sending workers to another grower would generally involve a change in equipment used. For example, AHETF would not want to contract with one aerial application company and have their aircraft operated by employees of a different application company. This is not only for safety reasons, but because the generic database is designed to include workers using equipment they are familiar with. AHETF therefore intends to sample MUs from the employees of cooperating growers and commercial applicators, but will take care to prevent coercion of or exertion of undue influence on these workers by their employers.

AHETF recognizes the need for extra care to avoid the potential for coercion and undue influence from growers or custom applicator operators who might benefit from cooperating with an AHETF study. However, these types of handlers constitute a significant portion of the target population and exclusion of these individuals would unjustifiably diminish the value of the data collected by the entire program. Therefore, all cooperating employers of potential subjects will be required to sign a statement that they will neither encourage nor discourage their employees to participate, and that the decisions of their employees to participate, not participate, or withdraw will have no impact on their employment or work opportunities. A copy of this statement will be provided to all affected candidates in the informed consent interview. (See also SOP AHETF-11.B).

Regarding the benefit to growers, in the form of pesticide product provided by the sponsor, AHETF believes the magnitude of this benefit is not likely to result in coercion of employees to volunteer to participate in an AHETF study. As described below, this benefit is appropriate compensation for grower inconveniences, but generally accounts for just less than 1 to 3% of production costs for the acreage that is treated.

The AHETF generally provides the surrogate pesticide that is used to conduct field monitoring studies to the grower or landowner. Growers need to apply the compound specified in the study protocol and the AHETF needs control over the chemical before and during application as required in the Good Laboratory Practice Standard regulations. The chemical also compensates growers for the inconvenience, potential loss of productivity, and potential risk that the product may not perform as adequately as alternative products.

The free chemical is not a major inducement to cooperate because it is a small percentage of the overall cost of producing a crop. The table below lists the cost of five surrogate compounds used in previous AHETF studies along with production costs for four representative crops. The production costs are based on data from universities in the states specified in the table for each crop. The chemical costs were provided by Loveland Products, Inc. The application rates are the maximum labeled rates for each of the compounds and crops.

Crop Type and Surrogate ai	Formulation Type	Production Costs (\$/A)	Chem Cost (\$/lb ai)	Appl Rate (lb ai/A)	Chem Cost (\$/A)	Chem Cost (% of Production Costs)
Corn in IA¹						
Carbaryl	4 lb/gal liquid	\$500	\$8.28	2.00	\$16.56	3.31
Chlorothalonil	6 lb/gal liquid	\$500	\$3.97	1.50	\$5.96	1.19
Diazinon	50% solid	\$500	\$10.54	0.75	\$7.91	1.58
Malathion	5 lb/gal liquid	\$500	\$4.92	1.25	\$6.15	1.23
Simazine	4 lb/gal liquid	\$500	\$3.66	2.00	\$7.32	1.46
Grapes in CA²						
Carbaryl	4 lb/gal liquid	\$1,700	\$8.28	2.00	\$16.56	0.97
Chlorothalonil	6 lb/gal liquid	\$1,700	\$3.97	NA		
Diazinon	50% solid	\$1,700	\$10.54	1.00	\$10.54	0.62
Malathion	5 lb/gal liquid	\$1,700	\$4.92	NA		
Simazine	4 lb/gal liquid	\$1,700	\$3.66	2.00	\$7.32	0.43
Tomatoes in FL³						
Carbaryl	4 lb/gal liquid	\$13,500	\$8.28	2.00	\$16.56	0.12
Chlorothalonil	6 lb/gal liquid	\$13,500	\$3.97	1.50	\$5.96	0.04
Diazinon	50% solid	\$13,500	\$10.54	0.75	\$7.91	0.06
Malathion	5 lb/gal liquid	\$13,500	\$4.92	1.56	\$7.68	0.06
Simazine	4 lb/gal liquid	\$13,500	\$3.66	NA		
Apples in WA⁴						
Carbaryl	4 lb/gal liquid	\$10,000	\$8.28	3.00	\$24.84	0.25
Chlorothalonil	6 lb/gal liquid	\$10,000	\$3.97	NA		
Diazinon	50% solid	\$10,000	\$10.54	0.50	\$5.27	0.05
Malathion	5 lb/gal liquid	\$10,000	\$4.92	NA		
Simazine	4 lb/gal liquid	\$10,000	\$3.66	2.00	\$7.32	0.07
Average						0.76%

Footnotes:

¹ Iowa State University – University Extension. “Estimated Costs of Crop Production in Iowa – 2007”, Updated February 2007. Available from: www.extension.iastate.edu/agdm. Accessed May 16, 2007

- ² University of California Cooperative Extension. "Sample Costs to Establish a Vineyard and Produce Wine Grapes", 2001. Available from: <http://coststudies.ucdavis.edu/>. Accessed May 15, 2007.
- ³ University of Florida, "Tomatoes: Estimated production costs in the Dade County area, 2004-2005", Updated February 2005. Available from: www.agbuscenter.ifas.ufl.edu/cost/cop03-04/DadeTomato.doc. Accessed May 16, 2007.
- ⁴ Washington State University. "Tree Fruit Horticulture Page - Apples in Washington State", Updated August 2002. Available from: <http://www.ncw.wsu.edu/treefruit/aplcrop>. Accessed May 16, 2007.

NA indicates the compound is not registered for use on that crop.

The value of the surrogate chemical is usually less than 1% of the total production cost with an overall average for the examples in the table of 0.76%. The exception is large acreage agronomic row crops (e.g., corn), but the value of the chemical is still low (approximately 1.2 to 3.3%) compared to production costs.

It should also be emphasized that the chemical is only provided for a single application, is only enough to compensate for the actual amount needed for the study, usually does not cover the cost of the actual application itself, and does not cover the total chemical costs to the grower since they usually apply multiple pesticides each year.

This is not an unreasonable benefit for growers and is not large enough to cause coercion or undue influence on an employee to participate in a study.

Limited or non-readers

AHETF does not intentionally recruit subjects with limited literacy, but pesticide handlers occasionally fall into this category and are therefore included in the target population. AHETF has procedures in place to include an impartial witness (i.e., unassociated with the conduct of the research) in the consent process for any candidates who are unable to read the informed consent document. These procedures are discussed in the following section (and in SOP AHETF-11.B).

Poor people and uninsured workers

Another potentially vulnerable group that might be part of the target population is poor/uninsured workers. AHETF does not intentionally recruit these individuals and will not inquire as to the economic or health insurance status of potential study participants. Therefore, this category will not be identified to the IRB as one that is intended to be recruited. As discussed below, the remuneration being offered (generally for just one day of participation) is believed to be not high enough to induce otherwise reluctant workers to participate, so the economic status of participants in these studies is not a concern. In addition, AHETF will cover all costs of injury or illness that workers experience because of participating in the study (that are not covered by the worker's or employer's insurance).

Illegal workers

Another potentially vulnerable group that might be part of the target population is illegal workers. For example, illegal workers may feel obligated to participate (e.g., in order to protect their job) or be reluctant to accept medical treatment. Federal laws give employers the responsibility for ensuring their workers are legal and AHETF does not employ workers. AHETF will therefore assume workers are legal and will not ask about their status. In addition, should researchers become aware of an illegal worker they will not share that information. Workers who might be illegal will be protected from coercion primarily via the mechanism described below where the Study Director will discuss the voluntary nature of study participation with the worker's supervisor/employer. In addition, the consent form indicates workers may refuse medical treatment unless they appear to be suffering acute toxicity from the pesticide product or from heat stress, or if they are unable to make a rational decision. The ability of a subject to make a rational decision will be assessed by the Study Director (in cooperation with the on-site medical professional). For example, a subject who can't answer simple questions like, "What day is it?" will be considered unable to make a rational decision. In addition, any unconscious subject will be considered unable to make a decision.

13.3 Informed Consent Process

When sites have been selected and potential participants have been identified, the Study Director is responsible for obtaining informed consent from all study participants. Initially, the Study Director has a discussion with the supervisor of each potential participant to ensure the supervisor understands that workers should not feel any coercion to participate in the study. The supervisor must confirm there will be no adverse impact on a worker who does volunteer, who does not volunteer, or who withdraws from the study for any reason. This extra care to prevent coercion from employers, especially from growers and commercial applicators, will be documented on a form which the supervisor, grower, or commercial applicator must sign. Then, each volunteer is provided with the supervisor's signed form, the IRB-approved consent form, and a full explanation of the study, its requirements, and any potential risks. This occurs during a confidential and private discussion with the Study Director.

Volunteers are advised of their right to withdraw from the study at any time and for any reason without jeopardizing their job position with their employer. Volunteers are also informed during the confidential consenting process that they will receive an \$80 payment for beginning study participation, even if they withdraw for any reason or the sponsor stops the monitoring for any reason. They will also be informed that their supervisor has certified there will be alternate work available if they don't participate or sufficient work on monitoring days so they will not be denied a full day's pay.

AHETF consent forms are unique to individual studies, but all consent forms will contain the elements required by 40 CFR 26.1116. This includes discussions of the following aspects of the research: purpose, voluntary nature, benefits, risks, alternatives, withdrawal, compensation, confidentiality, where to direct questions, etc.

During the discussions between potential participants and the Study Director, ample time is provided for questions and the Study Director will provide any additional information or clarification that is requested. These discussions typically take place at the worker's location, in a private setting. Consent is generally obtained within one to three days of actual study conduct, but sometimes earlier. If the worker agrees to participate he/she is asked to sign and date the informed consent form and the Study Director provides a copy of the signed form to the worker. Within 24 hours prior to monitoring, any women who agreed to participate will be asked to take a urine pregnancy test (over-the-counter variety) and will be allowed to participate only if the test is negative. This test will be supervised by a female researcher. To protect the privacy of the worker, the test results are not revealed to the employer or co-workers. If the worker chooses to proceed with the study then a female researcher will confirm the test is negative and record this in the study raw data. No positive test results will be documented and the worker will be allowed to withdraw from the study without stating a reason. See SOP AHETF-11.D for details of the pregnancy testing procedures.

For workers whose preferred reading language is Spanish, AHETF obtains an IRB-approved translation of the consent form and ensures that an interpreter is present during the informed consent process and during study conduct. In all cases, the Study Director will conduct discussions in English, but the participant will sign the version of the consent form in his preferred reading language. The interpreter might be an employee at the study site (e.g. employee of a grower or a commercial applicator) or might be someone located during discussions with the local agricultural community on a study-specific basis. If an interpreter is used, the Study Director will ensure the interpreter knows enough about the research design and the content of the consent form to provide an accurate translation. If necessary, this will involve tutorial discussions from the Study Director. To test the understanding by the interpreter, the Study Director will ask him/her to explain some portions of the Spanish consent form to the Study Director, in English. Interpreters will translate the Study Director's (English) discussion into Spanish during the consent process. They will also be utilized during the study should any issues arise which can't be resolved directly with the worker.

In situations where a potential participant cannot read English or Spanish, but can understand the spoken language, an impartial witness will observe the consent meeting. The witness must not be affiliated with the research or investigators. If the volunteer understands English, the Study Director will read the (English) consent form to the volunteer. If the volunteer understands Spanish, an interpreter will be present to read the (Spanish) consent form to the volunteer. The role of the witness is to observe

the consent interview and evaluate whether the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject and that the subject freely consented to participate in the research study. The witness must sign the consent form confirming these conclusions; otherwise the volunteer cannot sign the consent form. When both an interpreter and witness are needed, they may be the same person as long as he/she is impartial. If all questions have been adequately answered and there are no remaining concerns, the witness and the volunteer, as well as the Study Director, will sign the consent form.

In all situations, the Study Director will not sign the ICF unless he/she believes the candidate fully understands the information presented and has made a fully voluntary choice to participate. This will be ascertained by providing repeated opportunities to ask questions and by asking questions of the potential volunteers that would require a response that indicates understanding of key issues. For example:

- Q: When can you withdraw from the study?
A: whenever I want.
- Q: What has your supervisor said about you volunteering?
A: I am free to make that decision on my own and it won't impact my employment.
- Q: What will you wear so we can measure inhalation exposure?
A: an air pump on my belt.
- Q: What type of personal protective equipment must you wear for this study?
A: gloves (the answer will depend on the specific product being used in the study – gloves are an example answer for a product requiring gloves)
- Q: Can you name two risks of participating in the study?
A: risk of accident or injury; risk of chemical effects, risk of overheating, etc.

During the consent process, volunteers will be asked if they would like for their personal results from the study mailed to them. This is entirely optional, but will require they provide their name and address. That personal information will be kept confidential (see Section 13.6).

This process for obtaining informed consent is documented in an AHETF Standard Operating Procedure (AHETF-11.B).

13.4 Subject Remuneration

In almost all cases, AHETF will be monitoring the exposure to pesticides for workers who are performing their usual activities. Monitored workers would be handling pesticides even if they weren't participating in the study. Workers who participate in AHETF exposure monitoring studies are "on the job" and will receive their normal pay and all other compensation they are due, including compensation for any overtime worked according to local laws. This compensation is the responsibility of the worker's employer and not AHETF.

In addition to their normal pay, AHETF will provide payments totaling \$100 (U.S. dollars if in the United States or Canadian dollars if in Canada) to each worker who participates in the study. Twenty dollars (\$20) will be given when a volunteer attends a private consent discussion with the Study Director, whether or not the candidate decides to sign the consent form. Eighty dollars (\$80) will be given when a volunteer begins participation in the study (i.e., donning dosimeters and beginning of handling activities). These payments are in appreciation for the extra effort and inconvenience associated with the consent process and participating in the study. This includes wearing the inner dosimeter (long underwear, requires undressing in a private area); allowing researchers to wash their hands and wipe their faces; allowing researchers to remove the inner dosimeters at the end of the monitoring period; and wearing a personal air sampling pump and tube throughout the workday.

AHETF has selected standard amounts for all AHETF studies and participants since the inconveniences involved are essentially the same for participants in all studies. In addition, AHETF chooses not to offer an hourly rate since it prefers that workers perform their typical tasks and wants to avoid any incentive for workers to choose a particular task since they could "earn more money". The consent process takes about 1 hour. Dressing and undressing workers takes about 20 to 30 minutes total throughout the work day. This includes collecting hand washes, face/neck wipes, and inhalation devices. Collecting interim hand washes and face/neck wipes (e.g., before a lunch break) takes about 5 minutes. Workers may also need to wait about 10 to 15 minutes to be dressed and/or undressed when there is more than one worker ready to start or stop monitoring at the same time. In total then, up to an hour might be necessary to deal with putting on dosimeters and collecting dermal and inhalation exposure samples. In addition, participants may experience embarrassment or thermal discomfort due to the whole-body dosimeter.

While any standard amount of remuneration could represent a very different proportion of various workers' typical daily pay, fairness suggests that each worker should receive the same amount of remuneration since the amount of inconvenience is essentially the same.

AHETF selected the amount of \$100 (total payment) at the outset of the task force project and still believes this is an appropriate amount. AHETF believes it is not practical to ascertain individual worker salaries and regional differences in order to determine an amount of remuneration that might be based on a percentage of daily pay. AHETF believes that \$100 is not sufficiently high as to create undue influence to participate in the study, especially since workers are generally limited to one day of study participation. However, the IRB that reviews individual study protocols might change this value and AHETF will typically consult with local agricultural community members (e.g., County Agricultural Extension agents) to solicit opinions about whether \$100 is appropriate remuneration for the inconvenience involved.

The \$20 payment will be provided in cash at the end of the consent meeting. The \$80 payment will be provided in cash at the end of the monitoring period (whether ended by design, due to participant withdrawal, or by the researchers).

Generally, a worker will be allowed to participate in a specific field study only one time. This study design principal provides data for separate exposure measurements that reflect different workers in order to capture variability between workers. However, the same worker could participate more than once in a study (or in two studies) as long as the worker performs a different task. For example, one person could be monitored for exposure as a mixer/loader on one day and as an applicator on another day (assuming the worker meets all eligibility criteria for both activities). In this case, that person would receive an \$80 payment for participation on each of those two days (in addition to the \$20 for attending the consent meeting).

In addition to the remuneration identified above, AHETF will inform all potential volunteers that they will not be deprived of a full day's wages should they decide not to participate, or choose to withdraw from the study, or if the study is stopped short for any reason. First, their employer or supervisor must certify in advance that alternate work will be available for each volunteer should they decide not to participate, or if they withdraw at any time, or if the monitoring period ends before the typical work day is over. Second, if the worker is unable to complete the work day (e.g., due to an injury or heat stress), AHETF will reimburse the employer for the rest of that day's wages.

13.5 IRB Review Process

AHETF expects to use the Western Institutional Review Board (WIRB) in Olympia, Washington (www.wirb.com) to review each of its study protocols for ethical compliance. For studies conducted in Canada, WIRB uses a special panel that includes Canadian members and complies with U.S. and Canadian regulations. Initial review submissions from AHETF to WIRB typically include the following:

- Initial Review Submission Form (WIRB form)
- Field Study Protocol
- Research Subject Information and Consent Form - English

- Hospitalization Procedures
- Resumes for researchers
- Recruitment materials

The WIRB Initial Review Submission Form identifies AHETF as the sponsor and the Study Director as the Principal Investigator. It also identifies study site(s) (generally local site coordinator research facilities) and provides details about subject recruitment, consent, and payment. Hospitalization procedures are also provided which identify the nearest emergency medical facility to the study site(s). WIRB also maintains files containing the Study Director's curricula vitae and documentation of human subjects training which support the submission.

Protocols and supporting information for studies to be conducted in California are also submitted to the California Department of Pesticide Regulation (CDPR) for their review and approval. Any changes requested by CDPR are incorporated into the study protocol and/or consent forms must then be reviewed and approved by WIRB. Only upon receipt of WIRB-approved protocol and consent forms will DPR grant final approval for the study conducted in California.

Finally, after IRB approval, protocols will be submitted to EPA (and to the HSRB by EPA) and any changes to the study protocol or consent form must again be reviewed and approved by the IRB.

13.6 Additional Efforts to Protect Human Subjects

Additional steps that AHETF takes to ensure the safety and maintain confidentiality of study participants are summarized below.

Minimizing health risks before monitoring

Copies of the material safety data sheet (MSDS) and product label are made available to members of the study team and study participants. During the consent process, the Study Director will provide these documents for review by potential volunteers and will discuss the information contained in them. (For non-English speakers, an interpreter will translate these discussions for the volunteer, but Spanish labels and MSDSs will not be provided.) Particular attention will be paid to the possible acute toxic effects associated with the pesticide product in the study. Workers will also be reminded of standard practices that should be followed to reduce their exposure to pesticides. For example, provisions of the Worker Protection Standard (WPS) will be cited such as the requirement to wear long pants and long-sleeved shirts and to remove clothing that get drenched with chemical from an accidental spill. See SOP AHETF-11.E for more details.

Study subjects are never asked to wear less clothing or PPE than they would ordinarily wear, even if the items are not required by the product label. In cases where a worker

normally wears clothing or PPE not required by the label, the AHETF either allows them to wear the extra clothing (or equipment) or they are excluded from the study, depending on the specific goals of the study. For example, while workers are always allowed to wear a hat of their choice even when headgear are not required by the label, chemical-resistant jackets and hoods would not be allowed unless a particular scenario was designed to include such PPE (as was the case for some MUs in the open cab airblast studies already collected by AHETF). The AHETF may also provide some PPE items required by the product label (e.g., chemical-resistant gloves) to ensure they meet WPS requirements.

Prior to study conduct, the Study Director will assess the availability of medical assistance in the locality of the study and identify appropriate emergency medical facilities that may be utilized.

Just prior to participating in an AHETF exposure monitoring study, the worker's normal clothing will be inspected by researchers and the Study Director must approve of that clothing (see SOP AHETF-8.G). To comply with the WPS the outer layer of clothing must be in good condition and be free of large holes or tears or missing buttons which could lead to increased skin exposure. If necessary, the Study Director will provide a new shirt or pants for the worker to wear during the study.

Observing subjects during studies for adverse effects

During all AHETF studies, the Study Director and the field investigators share the responsibility for awareness of physical injuries, heat illness, toxic responses, and other adverse effects in study participants. All such researchers are required to complete training on the ethical treatment of human subjects.

As a precaution, a medical professional (emergency medical technician [EMT], paramedic, physician's assistant [PA], licensed practical nurse [LPN], or registered nurse [RN]) will be on-site during the conduct of all AHETF studies while workers are being monitored. The medical professional will be provided the product label, its MSDS, and AHETF SOPS related to pesticide safety and heat stress. The medical professional shall become familiar with these documents and conduct periodic observations of workers during monitoring and will alert the Study Director to possible signs of illness (heat-related or chemical) or injury. This person will also provide appropriate medical care when necessary and help determine when additional medical attention is needed.

During each study, every participant will always have a researcher assigned to observe and document his/her handling practices and this "observer" will have the primary responsibility for detecting adverse effects. Typically this observer is close enough to the worker to have a conversation. Observers are trained to recognize heat stress and are informed of the most likely acute effects of overexposure to the pesticide being

used in the study. In addition, the on-site medical professional will check on the workers frequently and help identify early signs of adverse effects.

During study conduct, researchers will also ensure compliance with safety requirements on the product label and with the WPS. For example, workers will be reminded to use the label-specified PPE and to follow use directions on the label. Each worker will be observed by a researcher during the entire monitoring period and the Study Director will be present on all days of monitoring. Any study participant who will not follow the label requirements for wearing PPE will be removed from the study. All researchers who interact with the workers must have completed at least one internet-based course in the protection of human research subjects—either the Basic Collaborative IRB Training Initiative Course (CITI) or the Human Participant Protections Education For Research Teams course (NIH). See SOP AHETF-1.B.

Handling adverse events

Study Directors know in advance where to take workers who might be overheated or who have other medical concerns. If any participant is injured or experiences illness from being in a study, medical treatment will be available at a nearby health care facility. If necessary, AHETF will arrange transportation to receive medical attention. AHETF will cover the costs of reasonable and appropriate medical attention that are not covered by the participant's own insurance or insurance provided by the participant's employer. Treatment records will not become part of the research records for any study, however Study Directors will document that each incident is followed to resolution.

Should an adverse effect occur during an AHETF study, emergency procedures will be implemented. These procedures typically include halting work, removing the worker from the offending environment, and calling 911 (or other local emergency phone number) for medical assistance if needed (see SOP AHETF-11.H). In addition, AHETF has adverse effects reporting policies in place to notify the IRB (SOP AHETF-11.F) and EPA of potential new findings (e.g., as required by FIFRA Section 6(a)(2)).

Protecting subject confidentiality

AHETF researchers take several steps to protect the confidentiality of study participant identification. The consent form includes the name and signature of the study participant and is held confidential, separate from other study data. After making a copy of the form for the participant the Study Director will assign a unique worker identification code (generally a letter) to each participant and write that code on the consent form. This is the only place where the participant's name and code appear together. All other raw data records and all reports will reference only the unique worker identification code. In addition, study participants have the opportunity to request their personal results from the study by filling out a form that includes their

name and address. The Study Director will then place the consent forms and result request forms in a sealed envelope to protect the confidentiality of the participant names and addresses. The envelope will be marked as confidential and kept separate from the other study raw data. Only the Study Director will have access to this information until placed into permanent archives where it will remain in a sealed envelope and access will be further restricted (see SOP AHETF-6.D).

Photographs and video recordings that include study participants may be used to document how the study was conducted and may be retained in the raw data. The subject's name will never be associated with these images and no images will be included in reports of study results. However, EPA and other regulatory agencies may audit the raw data from this study, so absolute confidentiality of study participant images cannot be guaranteed.

Post-study follow-up

At the end of each day of monitoring, the Study Director will remind participants they should bathe or shower as soon as practical and that they have received a copy of the signed consent form that has phone numbers for reporting any health changes the worker thinks may be related to participation in the study. Any post-study inquiries will be forwarded to the Study Director who will deal with the situation as appropriate and notify AHETF management. When necessary, the Study Director will report such incidents to the IRB. AHETF will not initiate contact with participants after study conduct to ask about their health status.

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15 Glossary of Terms

AHETF = Agricultural Handlers Exposure Task Force, L.L.C.

A consortium of 19 companies that formed a FIFRA joint data development task force to design and develop a database of exposure measurements for agricultural workers during mixing, loading, and/or application of pesticides. The exposure data will cover all important types of mixing/loading systems, application equipment, and formulations. The results will satisfy FIFRA data requirements and be used by USEPA (and other regulatory agencies) to assess exposure potential and conduct risk assessments for most pesticide products marketed by AHETF members. AHETF was formed in December, 2001.

Benchmark Objective

This is a specific experimental goal that is used to establish the number and configuration of sampling units. In the AHETF program sufficient data for each handler scenario will be collected to meet one or more specified minimum or benchmark adequacy requirements. The design benchmarks are not intended to address all possible ways the exposure data could be used. Rather, they are established to ensure that the data will at least be adequate to meet common regulatory needs.

Biomonitoring

Measurement of a pesticide or its metabolite(s) in the body of a pesticide handler and the conversion to an equivalent absorbed dose based on knowledge of metabolism and pharmacokinetics. This generally includes measurement of chemical in blood or urine, but does not include measurement of biological effects such as cholinesterase levels. The result is an estimate of total exposure from the dermal, inhalation, and oral routes combined.

Cluster

A set of related handler-days from the same scenario considered a higher-level sampling unit for the purposes of statistical design and analysis. For reasons of efficiency and cost, MUs are selected in stages. First a sample of clusters is selected. Then, following the collection of additional information about the cluster, a purposive sample of individual MUs within the cluster is obtained. Practically, a cluster can be viewed as all possible MUs available at particular location and time period. 'Location' is used here in a broad sense and involves all monitoring sites processed by the same research team during the single visitation period (usually several days to a week in length). Exposures between MUs from the same cluster tend to be more similar than those between MUs from different clusters.

Distribution of Exposure

A statistical description of the probability that any given exposure level is attained. For most practical purposes an exposure distribution can be characterized by standard parameters such as the arithmetic mean, geometric mean, and percentiles. Estimates of these distributional parameters are usually obtained from exposures measured on a sample of monitoring units within a given scenario

Engineering Controls

Equipment or equipment modifications that eliminate or reduce exposure to a chemical, such as enclosed cabs, ventilation, or closed transfer systems.

Exposure Monitoring

Using passive dosimetry techniques to measure dermal and inhalation exposure to professional, occupational pesticide handlers as they perform their typical activities. Researchers will use a variety of pesticide residue collection devices (cloth dosimeters, hand washes, face/neck wipes, and sorbent tubes) and determine the quantity of active ingredient on each device by chemical residue analysis.

Field Study

A convenient grouping of MUs that will be sampled during one 'study' in accordance with GLPs (including just one protocol and one final report). Generally the field portion of a study will be conducted over a short period of time (1 to 2 weeks), with one surrogate chemical, and may include MUs from one or several handler scenarios.

GLP = Good Laboratory Practice Standards

Federal regulations (40 CFR 160) which prescribe good laboratory practices for conducting studies that support pesticide registrations. The standards address the scientific integrity of study conduct and data collection, including specific requirements for study management, equipment calibration, facilities maintenance, record keeping, reporting, and quality assurance. All AHETF studies are conducted in accordance with these standards, both in the field and in the analytical laboratory.

Handler-Day

Refers to a specific handler and workday during which a scenario-specific handling task is performed. Each AHETF MU represents a particular handler-day in the target population for the scenario.

Handling

Generally refers to mixing, loading, transferring, or applying pesticides. However, handling also includes the following common tasks: handling opened containers; disposing of pesticides or pesticide containers; and cleaning, adjusting, handling, or repairing the parts of mixing, loading, or application equipment that may contain pesticide residues.

HSRB = Human Studies Review Board

A board established by EPA under the authority of 40 CFR §26.1603 for the purpose of advising the Agency on scientific and ethical aspects of proposed and completed research involving intentional exposure of human subjects. Research involving intentional exposure of human subjects is defined at 40 CFR §26.1102(i).

JRC = Joint Regulatory Committee

A committee comprised of representatives of the U.S. EPA, the Canadian Pest Management Regulatory Agency (PMRA), the California Department of Pesticide Regulation (CDPR), and the U.S. Department of Agriculture (USDA). This committee meets on a regular basis with AHETF to clarify regulatory data requirements, provide technical and regulatory input on study design, and review progress.

Local Site Coordinator

An agricultural research contractor utilized by AHETF to provide local support with tasks such as receiving and storing test substances, field fortification samples, and exposure samples. These items require storage in restricted-access facilities that are monitored for temperature and include ambient, refrigerated, and frozen conditions. Local Site Coordinators also help identify growers and equipment in a location where AHETF is considering conducting a field study.

Monitoring Program (or Sampling Program)

The monitoring program consists of all the MUs from approximately 60 GLP studies which will be conducted by AHETF to monitor exposure to agricultural pesticide handlers and which will be used to develop a generic database to support pesticide registrations. The planned sampling program will cover many handling situations, or scenarios.

Monitoring Unit (or MU)

All exposure monitoring activities pertaining to a single worker for a time period that represents a typical workday, including the exposure measurements for the worker involved. (An MU was formerly called a 'replicate'.) A number of monitoring units will be sampled for each scenario to adequately define the distribution of exposure for that scenario. MUs corresponding to different scenarios may be sampled as part of a single GLP study.

Normalized Exposure, Normalizing Factor

Normalized (or unit) exposure refers to daily worker exposure expressed relative to (i.e., divided by) a useful measure of potential active ingredient contact. This contact measure is called the normalizing factor. The most common normalizing factor is the amount of active ingredient handled during the workday. The use of normalized exposure may have regulatory value and does not necessarily assume that daily exposure is, on the average, proportional to the normalizing factor.

Passive Dosimetry

Techniques for measuring pesticide exposure to humans that do not involve invasive collection techniques such as collecting urine or blood. In particular, AHETF studies involve whole-body garments that serve to collect potential dermal residues, hand washes to collect hand residues, face/neck wipes to collect residues on the face and neck areas, and sorbent tubes which collect air in the breathing zone of a worker. Occasionally, cloth dosimeters will be used to measure exposure to the feet or to the head area with and without headgear.

PPE = Personal Protective Equipment

Devices and apparel that are worn to protect the body from contact with pesticides or pesticide residues, including but not limited to coveralls, chemical-resistant suits, chemical-resistant gloves, chemical-resistant footwear, respiratory protection devices, chemical-resistant aprons, chemical-resistant headgear, and protective eyewear (40 CFR 170.240).

Purposive Diversity Sampling

The particular type of non-random MU sampling used in the AHETF monitoring program for each scenario. Sampling is purposive because certain important MU conditions are selectively sampled. Diversity (or heterogeneity) sampling means that the purposive sampling is targeted to achieve a diversity of major factors that are likely to influence exposure including: amount of ai handled, workers, and location. Judgment sampling is a common synonym for purposive sampling.

Scenario

A specific pesticide handling situation that will be represented by data with defined common properties; generally a combination of a work task(s), pesticide formulation, equipment, engineering controls, and work practices. For example, a scenario of interest is ‘mixing/loading dry flowable pesticides using open pouring equipment and techniques’.

Scripting, Scripted Study

Scripting is the partial control of the conditions associated with a particular MU. Workers are sometimes asked by AHETF to conduct their work activities under a set of scripted conditions very similar, but maybe not identical, to those they experience in their normal work activities. Scripted studies must be approved for scientific and ethical validity by EPA and HSRB.

Surrogate Chemical

A pesticide active ingredient found in a test material and collected by passive dosimetry matrices during sampling of an MU. AHETF develops validated analytical methods for each surrogate chemical and each exposure matrix so residues collected can be determined. AHETF chooses surrogates which have relatively low volatility and are commercially available in suitable formulations and packaging. Since exposure to handlers is a generic function, exposure measurements from these chemicals are suitable for estimating exposure to other pesticide active ingredients.

Surrogate Distribution

As a result of purposive sampling, the MU exposure values can only be used to establish a surrogate distribution of exposures. That is, for some analyses, users of the data might need to assume that the distribution of the non-randomly generated data is at least similar to some type of random sample from the target population. In the determination of sample size and the statistical summary analysis of MU data, uncertainties for distributional parameter estimates will be based on surrogate cluster random sampling models.

Target Population (or Universe)

The target population for a scenario is the set of all possible agricultural handlers and the days on which they perform scenario-specific tasks. Each possible handler-day is implicitly associated with a set of conditions that include, but are not limited to behavior, chemical, equipment used, location, and environmental conditions. Each handler-day is also associated with a daily exposure for the particular pesticide handler. The single-day exposure distribution is conceptually defined as the result of randomly selecting handler-days from this target population.

WPS = Worker Protection Standard

A Federal regulation (40 CFR Part 170) which contains a standard designed to reduce the risks of illness or injury resulting from workers' and handlers' occupational exposures to pesticides used in the production of agricultural plants on farms, nurseries, greenhouses, and forests, and also from the accidental exposure of workers and other persons to such pesticides. It requires workplace practices for employers and workers that are designed to reduce or eliminate exposure to pesticides, and it establishes procedures for responding to exposure-related emergencies.

Appendix A. AHETF Acceptance Criteria for Existing Studies

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Appendix A

AHETF Acceptance Criteria for Existing Studies

General Study Design Criteria

1. All monitored activities and equipment must be well-described and representative of typical agricultural mixing/loading and application practices.
2. It must be clear that the individuals monitored are normally employed in the mixing/loading and/or application of agricultural products.
3. Appropriate supporting information such as the formulation type, mixing and application method, application rate, duration of the work cycle, amount of AI handled/replicate, etc. must be available.
4. The use of personal protective equipment (PPE) is acceptable.
5. The study location and environmental/weather conditions during the monitoring period must be available.
6. All aspects of the study must have been conducted as per GLP regulators or be free of any significant GLP deviations or shortcomings if not conducted under GLP.

Exposure Monitoring Criteria

Field Aspects

1. Field recoveries must have been collected on a site-specific basis for time periods and environmental conditions representative of those during collection of field activity exposure samples.
2. Field fortification data must include at least triplicate samples at 2 rates and duplicate samples of controls.
3. Dermal exposure monitoring techniques must be specified and must include one of the following approaches.
 - a. whole-body dosimeters inside of clothing plus hand (gloves cannot substitute for hand exposure) and head/face exposure determinations,
 - b. a minimum of 10 patch dosimeters attached inside normal work clothing to the chest, back, both upper arms, both lower arms, both upper legs, both lower legs, plus hand (gloves cannot substitute for hand exposure) and head/face exposure determinations,
 - c. combination of patches and clothing that are representative of the whole body, including hand and head/face exposure determinations.

4. Inhalation exposure – Inhalation data are not required. If data were collected, inhalation exposure must have been measured by sampling the person's breathing zone.
5. Exposure monitoring duration – The monitoring period should be at least half of a normal work period duration or half the default acreage.
6. If the exposure monitoring duration does not meet the requirement of item number 5, then the number of non-detects/less than LOQ values should account for less than 20% of the actual dermal exposure.
7. If the exposure monitoring duration and number of non-detects/less than LOQ values do not meet the criteria in items 5 and 6, then the LOQ must be no more than 1.0 ng/cm² for dermal exposure and no more than 100 ppb for hand exposure.

Analytical Aspects - QA/QC

1. Analytical methods must have been validated for each analyte and substrate by the performing laboratory including establishment of the method's working concentration range to cover values anticipated in the field studies, determination of detector response over a reasonable standard concentration range, and determination of the accuracy and precision of the method within the analytical environment
2. The study must include both field fortification samples and concurrent laboratory spikes.
3. The average recoveries of lab spikes must be between 70-120 percent and the precision value (coefficient of variation) must be less than or equal to 20 percent.
4. Recovery of field fortification samples must be 50-120% with a C.V. ≤25%.
5. Exposure samples must have been analyzed in such a manner that the stability of each analyte in each substrate was assessed for the entire time period from collection to analysis.

Primary Review Process (216 Studies Reviewed)

1. The primary review is conducted by the study submitter (or a designated representative) and provided to AHETF along with a complete copy of the study report at the time the study is submitted to the task force for consideration.
2. The review by the submitter will include all applicable studies, including those that are presently in PHED.
3. The raw data for a study must be available, if requested, in order to be considered for purchase.

4. A list of potential studies must be submitted to the AHETF by March 1 and all primary review forms and reports must be submitted by June 1, 2002.
5. The purpose of the primary review will be to eliminate the submission of studies that clearly do not meet the selection criteria, and to serve as a check on the availability and submission of supporting information.
6. An Excel spreadsheet will be provided to the submitter for use in summarizing the study details and data.
7. A confidentiality agreement will be provided to the submitter to protect the confidential nature of their data.

Secondary Review Process (74 Studies Reviewed)

8. The secondary review will be conducted by a qualified AHETF contractor hired and trained for this purpose.
9. The purpose of the secondary review will be to verify the accuracy of the primary review and, where necessary, provide a more detailed discussion summarizing each specific area of the criteria, including whether each criterion was met and possible deficiencies in the study data.

Final Review Process (6 Studies Acquired)

10. The final review and decision on whether a study is accepted for purchase will be made by the Joint Regulatory/Task Force Technical Committee consisting of representatives from the AHETF, USEPA, PMRA, CDPR, and USDA.
11. The secondary review by the contractor and the regulatory reviews of contributed studies will be made available to the Joint Regulatory/Task Force Technical Committee and will serve as the basis for the final review. The secondary review will be evaluated and a determination made as to whether the study or any of the data could be used in the AHETF database.
12. Studies or portions of studies selected after final review will then be considered for purchase by the AHETF for inclusion in the task force database.
13. Reports for studies that are rejected will be returned to the submitter. Reports of studies that are purchased by AHETF will be placed in the AHETF archives.

Appendix B. Sampling Methods Used in the AHETF Monitoring Program

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Appendix B

Sampling Methods Used in the AHETF Monitoring Program

This appendix describes the AHETF program concept of target population and aspects of the purposive sampling methodology that are common across all scenarios. This expanded version of the sampling methods document has greatly benefited by both formal and informal input from a recent EPA Scientific Advisory Panel review (SAP, 2007).

B1. The Scenario Target Population

The theoretical target population for each scenario in the AHETF program is the set of all possible agricultural handlers and the days on which they perform scenario-specific tasks (Figure 1). Each possible handler-day is implicitly associated with a set of conditions that include, but are not limited to behavior, chemical, equipment used, location, and environmental conditions. Each handler-day is also associated with an exposure (e.g. dermal) for the particular worker (pesticide handler). Handler-days randomly selected from this target population would, therefore, result in a single-day exposure distribution like that illustrated in Figure 2. The primary focus of the AHETF monitoring program is to obtain a sample of handler-days from the scenario target population that could then be used by regulators and others to characterize this single-day exposure distribution for regulatory purposes.

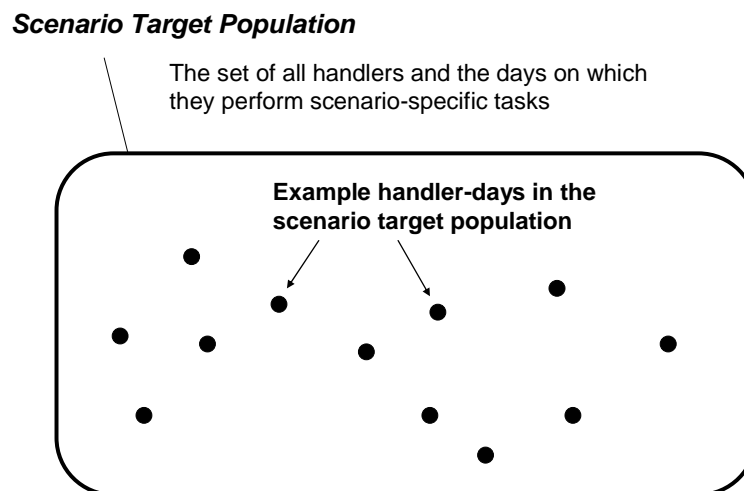


Figure 1. Ideal target population for an AHETF scenario.

For practical and ethical reasons, some handler-days that are part of the theoretical scenario target population must be excluded from the actual target population. The restrictions that apply to all scenarios are shown in Figure 3. Additional restrictions that apply to the target population of a specific scenario may also exist (see Sections B3.1 and B4.2). If so, these would be documented in the scenario-specific sampling plan (Section

B4.1). The AHETF does not believe that such restricted target populations differ substantially from the ideal target population with respect to the distribution of exposures.



Figure 2. The likelihood of exposure for a handler and day (i.e., handler-day) randomly selected from the target population.

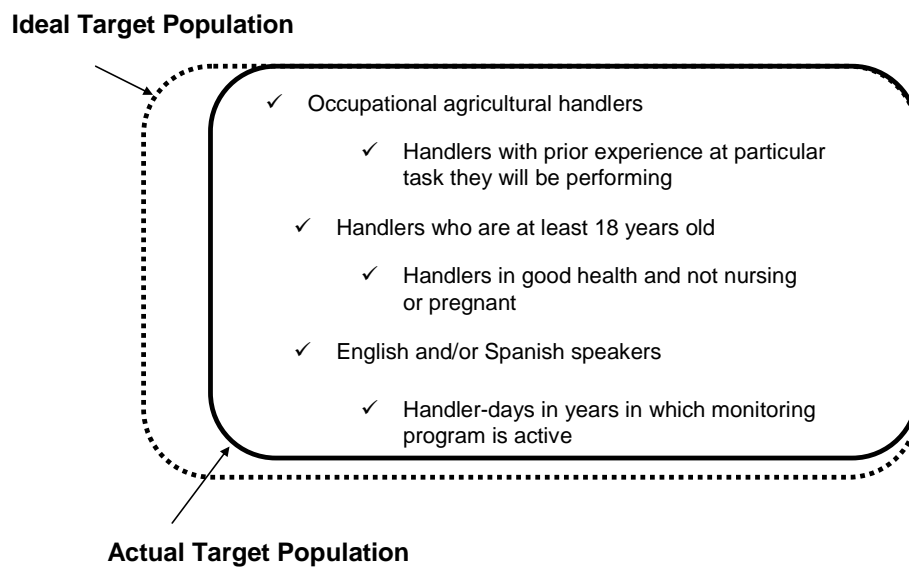


Figure 3. Restrictions to the Ideal Target Population.

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B2. Sampling from the Target Population

If a list itemizing all the handler-days in the target population were available, or could be constructed, then this list would comprise an excellent sampling frame for the target population (Figure 4). In principle, a sample of handler-days could then be randomly selected. If the worker exposures for all selected units could be obtained, the desired exposure distribution could be estimated in a straightforward manner. Even if a complete list of handler-days were available, however, a simple random sample from this frame would be impractical due to the size of the universe. It would require monitoring randomly chosen workers over widely dispersed U.S. locations on randomly chosen days. It would be extremely costly to send several researchers to a new location to collect exposure data for every selected MU. Some form of sampling in logistically convenient clusters of handler-days would be more preferable.

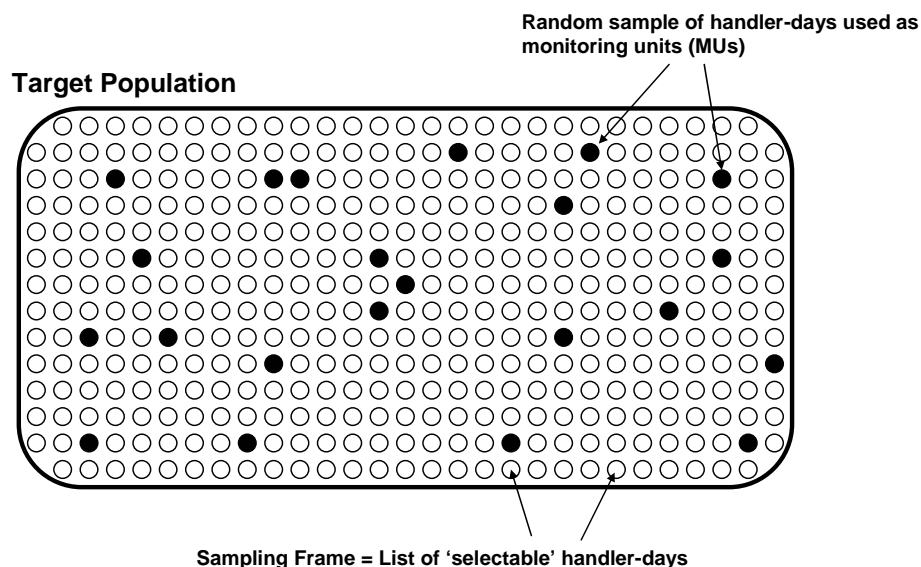


Figure 4. A List of all Handler-days in the Target Population would Comprise an Ideal Sampling Frame for Randomly Selecting Monitoring Units.

Although no such list of handler-days exists, it would still be possible to obtain a valid probability sample from the target population. Complex survey methods are available (e.g., Levy and Lemeshow, 1999) that permit random sampling of larger units that can be easily listed (e.g., counties). Then, a list of smaller units is constructed within each selected unit. From such lists a second-stage sample of smaller units can be selected. This multistage process of randomly selecting smaller and smaller units would continue until a final sample of handler-days is obtained. This complex process can usually be made more efficient by incorporating some form of stratified sampling with the multistage sampling. As might be

expected, this process of obtaining the final sample of handler-days is quite costly and time-consuming.

B2.1. Random versus Purposive Sampling

There are three unique aspects of the AHETF monitoring program that make such probability sampling designs less appropriate than purposive (or judgment) sampling. These involve (1) the level of data adequacy required, (2) the use of surrogate chemicals, and (3) the voluntary nature of study participation.

As discussed in Appendix C, the 3-fold benchmark accuracy requirements for regulatory use of the data result in recommended sample sizes on the order of 25 monitoring units (MUs), obtained in five cluster of five MUs each. Such sample sizes are considerably smaller than the 1,000 or more typical of most sample surveys. However, the cost and effort needed to obtain a multistage probability sample of 25 MUs is not $1/40^{\text{th}}$ that required for a sample of 1,000 units. It is much greater. Thus, there would be a substantial overhead cost (and effort) for a relatively small sample.

Equally important, a small probability sample is usually no better than is a same-sized non-random sample based on judgment (see Kalton, 1983, for example). A same-sized purposive non-random sample will not appear to be any less ‘representative’ of the target population—and it is much less expensive to obtain. This advantage of purposive samples vanishes for large sample sizes. A random survey sample of 1,000 individuals, for example, would be quite superior to a judgment-based sample of 1,000. It is also important to note the impact of cluster sampling used in the AHETF program (Section B3.2.1). During the SAP hearings (SAP, 2007), Dr. Steven Herringa noted that a rule of thumb in survey sampling (attributed to Dr. Leslie Kish) was that judgment sampling was preferable to probability sampling unless the number of clusters exceeds 10-20.

The use of surrogate chemicals adds another level of complexity (Figure 5) that makes probability sampling problematic. If a random sample of handler-days were selected from the target population, it would result in some handler-days that use the AHETF surrogate chemicals (A) and many that do not (B). Thus, many of the selected handler-days could not be monitored. If only the surrogate-using handler days were sampled, then the exposure results would be unrepresentative of the target population. It is very unlikely that the handler-days associated with a surrogate chemical will have the same conditions in the same proportions as handler-days with other chemicals.

The genericness principle holds that, under the same conditions, exposure is independent of the particular active ingredient (ai) used. However, this does not mean that the conditions under which one chemical is used is the same for all chemicals. We expect them to differ. This disparity complicates the sampling process considerably: In effect, the AHETF program is attempting to obtain a sample of the conditions of all handler-days in the target population but evaluate exposure for those conditions with surrogate-using handler-

days. Thus, the AHETF program cannot be purely observational since some handler-day conditions must be scripted to ensure that the target population diversity is represented by the surrogate-using subset. It is possible, for example, to monitor exposure under conditions that are less typical for a particular surrogate chemical, but quite common for a non-surrogate chemical. As a result of the need to recruit surrogate-using handler-days to meet target population conditions, purposive selection of both handlers and conditions is necessary.

Lastly, since pesticide exposure monitoring studies for most scenarios in the AHETF program are not purely observational, only volunteers can be used. By definition, volunteers comprise a self-selected subset of the target population and is not a random sample from the target population. Thus, only non-random methods are feasible with voluntary human research.

For these reasons, the AHETF program has adopted a purposive sampling approach to select MUs from the target population.

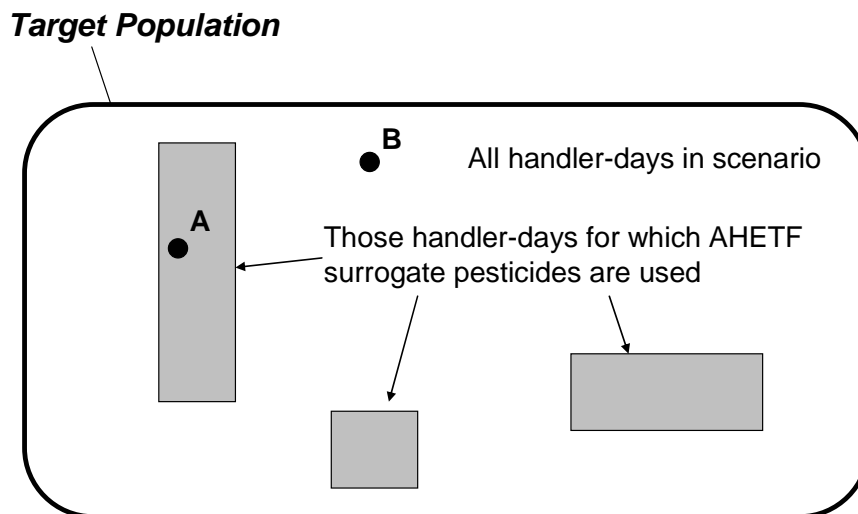


Figure 5. The target population contains some handler-days using surrogate chemicals (e.g. A) and others that do not (e.g., B).

B2.2. Purposive Representative Sampling and Purpose Diversity Sampling

Purposive representative sampling (Trochim, 2000) attempts to obtain a small sample that is a miniature of the target population with respect to important characteristics. In this case, 'important' means 'with respect to an assumed influence on exposure'. This is not an easy task. As emphasized by the SAP (SAP, 2007), it requires that the important characteristics of the target population and their frequency of occurrence be known. Thus, if one wishes a sample to be representative of crop, say, then the proportion of handler-days associated with each crop in the scenario target population must be known. The addition of each 'important' factor exponentially increases the complexity since it requires knowledge of

the likelihood of factors occurring jointly. Even if such detailed information were available, allocating a small number of samples to a very large number of possible conditions, each with its own relative frequency, can be quite difficult. This is complicated even further by the surrogate chemical and voluntary participation issues noted above.

In contrast, purposive diversity sampling (Trochim, 2000) merely attempts to obtain a sample of handler-days that are diverse with respect to important factors. It is a much simpler task to pick a set of MUs with different conditions than it is to try to reproduce target population frequencies in a small sample. Also, when sample sizes are small and extensive information about the distribution of exposure-related factors in the target population is unavailable, diversity sampling counters any tendency to select samples merely for convenience. Diversity sampling also lends itself to accumulating additional MUs over time. New planned MUs need only target conditions that have not been previously covered. The disadvantage of diversity sampling is that its goal is to capture the extent of conditions in the target population, not to obtain a target population in miniature. Therefore, a large purposive diversity sample will tend to have greater variation than would a large purposive representative sample. However, with the smaller sample sizes considered in this program, both purposive diversity sampling and purposive representative sampling are likely to describe the true distribution of single-day exposures equally well.

B3. Components of the AHETF Purposive Sampling Approach

The AHETF sampling methodology focuses primarily on purposive diversity sampling. Although sufficient information and expert opinion will be available about the occurrence of important scenario characteristics (see Section B5), it falls far short of what is needed for true representative sampling, especially given the limited number of monitoring units that will be used. The AHETF feels that, on balance, this is the most practical sampling method for meeting all the needs of the program. Nevertheless, AHETF's purposive sampling method does include some 'representative sampling' elements: The diversification process avoids handler conditions that are rare. In addition, where there is sufficient information regarding the distribution of important exposure factors in the target population, some balancing may be attempted to bring the sample in closer alignment with this distribution.

Diversity is achieved primarily through selecting worker activities and handling characteristics that meet particular, pre-defined conditions. The scenario target population of handler-days provides the conditions that are used to drive the purposive sampling process. Therefore, a precise delineation of the scenario definition is important. Sometimes, conditions that would technically be part of the scenario are intentionally excluded. In such cases, the scenario is redefined or restricted. This might be viewed as redefining the target population or, if probability sampling were used, defining the sampling frame. In any event, the scenario definition would need to explicitly contain such restrictions.

Once the conditions that comprise the scenario have been defined, workers are located that can meet these handler conditions while using a surrogate chemical. For example, airblast equipment is typically used to spray orchard and trellis crops, so AHETF designs for

airblast applicator scenarios include the desire for both crop types. Therefore, AHETF will search out, and recruit for monitoring, workers who plan to treat these two types of crops with a surrogate chemical. This purposive diversity sampling does not introduce artificial conditions, but instead includes normal variations in what is typical within a particular scenario. Major worker activities are not scripted to obtain this diversity in conditions.

As discussed in Section B3.2 below, there are three major factors that will formally drive the diversity sampling within each scenario: (1) the geographic location, (2) the particular measure of potential ai contact used to normalize exposure (e.g., amount of ai handled), and (3) the individual used. Heterogeneity in these three factors is an integral part of the scenario sampling design. Within each location, AHETF non-probability sampling also attempts to achieve a diversity of other conditions that are felt to affect exposure such as crop conditions, equipment, and procedures used.

B3.1. Scenario Definition

Most scenarios in the monitoring program have been adopted by AHETF because they have already proven to be logical and practical for use by EPA. Nevertheless, due to the complexity of pesticide handling conditions, there could be some ambiguity as to which particular conditions are included in a handler scenario. Thus, it is very important to precisely define each scenario prior to study design. In essence, this is nothing more than clearly defining the scenario target population. AHETF will attempt to define a priori what handling conditions will and will not be included in each scenario sampling plan.

For various reasons, a set of handler conditions, although technically part of the scenario, may be excluded from the sampling process. This may occur, for example, if the conditions excluded are extremely rare or even obsolete. When this is necessary, the scenario will be explicitly redefined to make it clear that such conditions were excluded. This provides users of the AHED[®] database a clear and accurate definition of the handler-conditions the data actually represent.

Such restrictions could also occasionally occur if AHETF, in an effort to reduce the total number of MUs in the AHETF monitoring program, focuses its testing within a scenario away from certain conditions believed to result in slightly lower exposure. For example:

- Mixer/loader MUs will always involve preparation of multiple loads since this avoids preparing just a single load that could result in lower exposure than multiple loads (even when handling an equal amount of pesticide). In particular, AHETF has set a minimum of 3 loads as a requirement for mixer/loader MUs. Thus, the target populations for all AHETF mixer/loader scenarios do not include hander-days that utilize 1 or 2 loads.
- Instead of separately monitoring exposure to workers that apply granules to soil using open cabs or enclosed cabs, AHETF might choose to monitor only the open

cab applications since this can be argued to be a worse case (since enclosed cabs generally result in lower exposure). Here, the granule application scenario has been redefined to exclude the closed cab conditions.

- Airblast applications are performed for both dormant and foliar conditions. AHETF believes that foliar applications are more likely to result in slightly higher worker exposures since passing between rows of crop that are more dense slows dissipation of airborne product, causes product to reach greater heights, and thus increases the likelihood that spray will reflect off the crop and contact the worker. Therefore, AHETF is generating all of its airblast applicator exposure data for foliar applications. Handler-days for dormant applications are excluded from the scenario target population.

Such restrictions to these scenarios do not limit the regulatory usefulness of the sample for representing the full (unrestricted) scenario. Without data for enclosed cab granule applications, for example, regulators will simply use the (higher) exposure data from open cab applications (restricted scenario) to represent all granule applications (unrestricted scenario). While this might over-estimate the exposure to granules during enclosed cab ground applications, it avoids the need for an additional data set for granule applications and saves valuable resources. From a regulatory perspective, overestimation of the exposure distribution is of less concern, especially given that it reduces the total number of human subjects involved in the monitoring program. And as long as workers commonly handle pesticides in the manner prescribed, electing to monitor exposure for these situations only does not trigger ethical concerns about exposing subjects to higher than necessary levels.

In other situations AHETF plans to avoid sampling a scenario altogether when data from another, higher exposure, scenario could be used by regulators as a surrogate for exposure assessments. This will save significant resources by avoiding an entire scenario of MUs, but may result in over-estimating exposures for the “lower exposure” situation by using data from the “higher exposure” scenario in an exposure assessment. This approach will not be used frequently, but will be considered when practical and in situations with limited AHETF resources.

B3.2. The Three Primary Factors Controlled in AHED Diversity Sampling

For each scenario, the goal of the non-probability sample is to obtain as much diversity as is practical. Although many potential factors are considered, obtaining diversity in three factors is of primary importance. These three are the number of geographic locations, the exposure normalizing factor, and the number of unique workers. These conditions are considered the most important based on reviews of existing pesticide handler exposure data (e.g., in PHED) and this was presented to the Scientific Advisory Panel (SAP, 2007).

B3.2.1. Geographic-Temporal Clusters

MUs are not selected independently from the target population. For reasons of efficiency and cost, the sample is selected in stages. First a sample of clusters is selected. Then, following the collection of additional information about the cluster, a purposive sample of individual MUs within the cluster is obtained. Practically, a cluster can be defined as a particular location and time period. 'Location' is used here in a broad sense and involves all monitoring sites processed by the same research team during the single visitation period (usually several days to a week in length). In a sampling sense, each location-period may be envisioned as a cluster of related handler-days. This is the origin of the term 'cluster'.

Because all the MUs in the same cluster are geographically (and temporally) related, diversity in location will be the largest component of total diversity in the sample. It is a common observation in many pesticide worker exposure studies, including many studies conducted by AHETF, that geographic location has a large impact on measured exposure. Varying the location of studies sometimes reflects known or suspected regional differences in a particular agricultural parameter. More often, however, changing geographic locations merely varies exposure potential that comes from unknown differences in workers, equipment, or environmental conditions. For example, it is typical for all MUs in the same cluster to use the same surrogate chemical. Thus, 'location' is merely a surrogate for a cluster of known and unknown factors that affect exposure. Clusters can be temporal as well as spatial. Exposure monitoring studies conducted at the same general location, but years apart, also differ in many ways and could result in different exposure measures.

To capture this important source of variation, AHETF purposively allocates the clusters for each scenario over several distinct geographic locations. The desired number of clusters and number of monitoring units per cluster are established for each scenario based on benchmark adequacy needs and cost-effectiveness (See Appendix C). Studies are then designed to ensure that the complete MU sample includes the desired number of clusters. In some cases, a single study protocol will specify that data be generated in multiple states or provinces. However, since most scenarios consist of multiple studies, perhaps from different sites in different years, there are many situations where a field study reflects just a single cluster per scenario. (See Section B4.9)

B3.2.2. Exposure Normalizing Factor (NF)

For purposes of sample size determination, a primary benchmark objective for each scenario requires that certain characteristics of the normalized exposure distribution have specified accuracy (see Appendix C). Normalized exposure is simply the daily exposure divided by a measure of potential active ingredient contact that has regulatory value for a scenario. In most cases the normalization factor (NF) used is the amount of ai handled (AaiH). It is conceivable, albeit unlikely, that a normalizing factor would not be of interest for a particular handling scenario. (This might be the case, for example, if potential ai contact was felt to be identical for all handler-days or there were no regulatory desire to relate

exposure to potential ai contact.) The AHETF sampling program will attempt to diversify the normalizing factor as much as possible. If the primary benchmark is specified in terms of unnormalized exposure, then AaiH will be diversified by default

In the target population for any scenario, there may be a large range in the levels of the factor used to normalize exposure. In different portions of this range, there could also be differences among many other factors that influence exposure. For example, the equipment and handling activities could be quite different for handling small amounts of active ingredient than for handling larger amounts (e.g., in size or type of application equipment into which the pesticide is mixed/loaded). To capture these sources of variation it is important that a substantial portion of the practical AaiH range be sampled. The same is true when a normalizing factor other than AaiH is used.

In addition, for many scenarios, a secondary objective is to ensure there are adequate data to allow AHED[®] users to determine if, on the average, exposure appears proportional to the normalizing factor (See Appendix C). This will also require obtaining a sufficient number and type of MUs over the practical range of the normalizing factor so that if exposure is truly unrelated to NF, a test of consistency with a proportional relationship will be rejected. As noted by the SAP (SAP, 2007) and discussed in Appendix C, power is greatest when there is a large range in the NF within each cluster. Consequently, meeting this secondary objective could result in the sacrifice of some representativeness if atypical conditions are introduced merely to increase this range within clusters. The AHETF is aware of this issue and only selects NF levels that are characteristic of the handler population in a particular location.

AHETF first estimates the practical range of the NF for each scenario based on information such as current product use rates and assumptions for the amount of crop that can be treated in a day. For example, with AaiH the upper limit of the practical range (ULPR) might include aerial applications of high use rate products. The lower limit of the practical range (LLPR) reflects handling of very low use rate products. In general, however, the LLPR does not extend below 5 lb. ai since AHETF wants to ensure that quantifiable residues are found for most worker exposure samples and wants to monitor workers for a period of time that is representative of a full workday.

For practical reasons, the exact mechanism for diversifying this practical NF range will vary. Since each MU involves monitoring an actual commercial work activity, fine control over the NF is not always possible. The AHETF does, however, follow the same general guidelines for all scenarios:

- (1) Establish several strata of the normalizing factor such that each stratum represents an equal interval on a log scale and, collectively, the strata cover the entire practical range. Generally, the number of strata will be the same as the typical number of MUs in a cluster. This is usually 4 or 5. For example, when the normalizing factor is AaiH and the practical range is LLPR = 5 lbs. and ULPR = 2,000 lbs., five strata would be:

- 5 to 17 pounds
 - 17 to 55 pounds
 - 55 to 182 pounds
 - 182 to 603 pounds
 - 603 to 2,000 pounds
- (2) Attempt to collect MUs within the entire scenario so the levels of the normalizing factor (e.g., AaiH) are evenly allocated to all strata.
 - (3) Within each cluster attempt to get one, but not more than one, MU from each stratum.
 - (4) Attempt to vary the exact levels within each stratum to avoid several MUs (in different clusters) with exactly the same level of the normalizing factor.

B3.2.3. Subjects Monitored

Within each scenario every attempt is made to ensure that every monitoring unit involves a different worker (i.e., different person). Diversification of workers is a key element of the AHETF sampling methodology. Because positive within-worker correlation of exposure is expected, the use of only unique workers in the diversity sample should tend to capture more of the variation that exists in the target population. Given the smaller sample sizes used, any overestimation of variability is acceptable since it would provide some degree of conservatism to the estimates of means and upper percentiles. However, in the AHETF program, overestimation of variability by using different workers is expected to be slight. This can be illustrated with a small artificial target population of $N=32$ handler-days. This target population consists of only 8 workers and 4 days per worker and has the exposure values shown in Figure 6. The within-worker correlation of exposure in this artificial target population is quite large ($R_{ww}=0.9$) and the total variance is 84.6. What would be the variance if one only considered unique workers? Figure 6 shows that one possible set of days using the 8 unique workers has a variance of 68.1, slightly smaller than the population variance. But there are a total of $4^8 = 64,536$ possible sets of days containing only the 8 unique workers. Some of these have a smaller variance than the population variance and some have a larger variance. The average of these between-worker variances is 83.7. For all practical purposes, this is identical to the population variance.

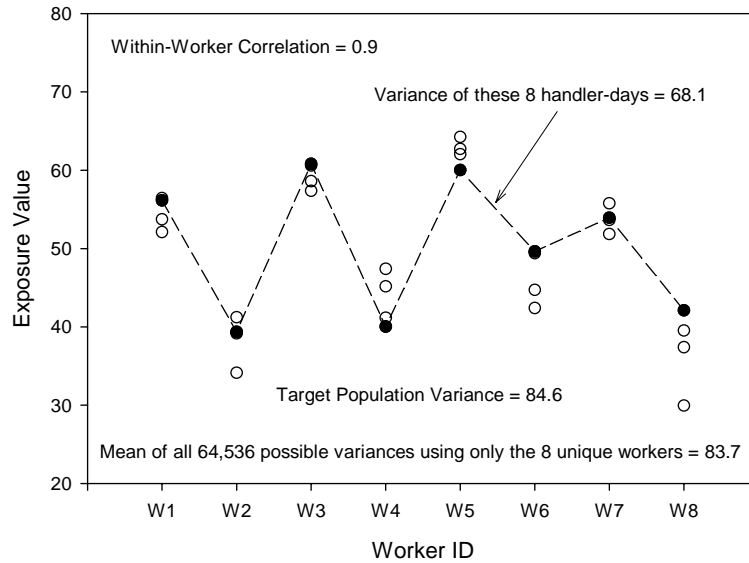


Figure 6. An illustration of how the variation between unique workers compares with the total variation in an artificial N=32 handler-day target population having a within-worker correlation of 0.9.

Similar results can be seen in same-sized target populations with a moderate within-worker correlation of $R_{ww}=0.5$ (Figure 7) and a smaller correlation of $R_{ww}=0.2$ (Figure 8). In both cases, the expected between-worker variation in the target population is little different from the total variation in the target population. Certainly, the scenario target populations will have considerably more than 32 handler-days. Nevertheless, the general features are expected to be similar to those illustrated by these artificial examples.

Since it is the intent of the AHETF monitoring program to focus on variation between workers, the use of the same worker is strongly discouraged. In an extreme emergency, such as a subject withdrawing from the study at the last minute and there are no unused volunteers available, a worker can be used for a second MU. In this case, however, as many other conditions as possible should be varied to reduce the correlation due to the repeated use of the same individual. For example, the MU for the same person might use a different AaiH, different equipment, and occur on a different day. Regardless, multiple MUs with the same subject should be a very rare occurrence for AHETF-conducted studies.

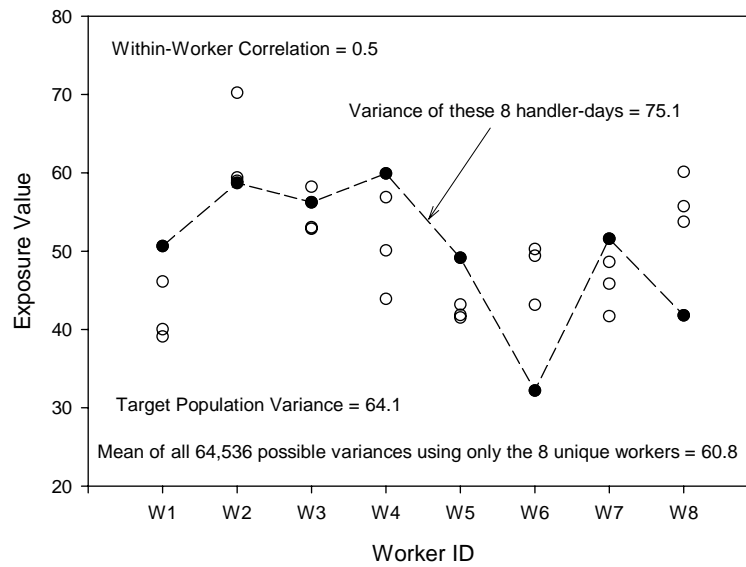


Figure 7. A comparison of between-worker variation and total variation in an artificial N=32 handler-day target population with a within-worker correlation of 0.5 .

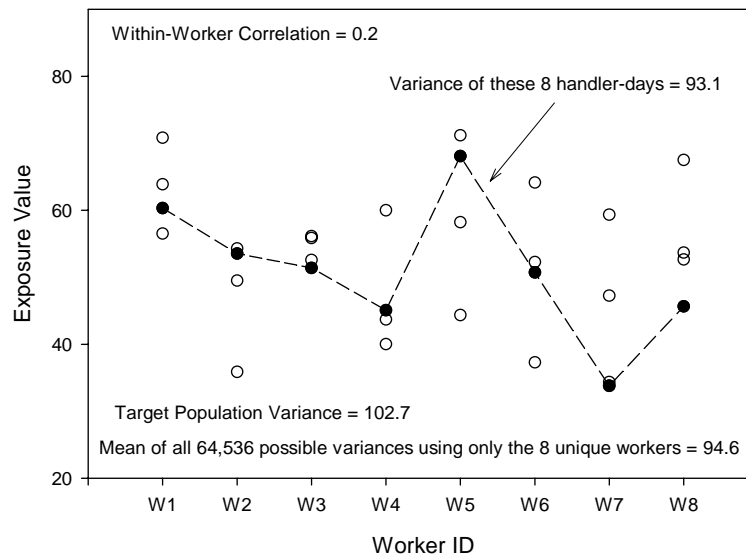


Figure 8. A comparison of between-worker variation and total variation in an artificial N=32 handler-day target population with a small within-worker correlation of 0.2 .

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B3.3. Additional Factors

In addition to the three primary factors discussed in sections B3.2.1 through B3.2.3, there are many other parameters that can be varied and might have an impact on dermal and/or inhalation exposure for a particular scenario. These include factors such as equipment used, specific worker techniques, and number of product containers used. There are no strict rules established to diversify these factors within clusters or scenarios. However, AHETF has established a few basic guidelines to be used for each field study that help determine the variety of conditions among the monitoring units.

On a scenario-by-scenario basis, AHETF evaluates the equipment and procedures commonly used, often seeking the advice of experts through a variety of sources (see Section B5 below). Then, the particular conditions are assigned to the MUs in a particular study based upon two considerations:

- Diversity of conditions
- Focus on more common conditions

B3.3.1. Diversity of Conditions

During study design, AHETF attempts to identify typical situations for pesticide handling for each scenario and to identify specific parameters that differ and to evaluate which parameters may have an impact on worker exposure. These factors are varied as much as practical within each study.

Example: Open-pour mixing/loading of dry flowables

In these 5 studies, all of the workers open-poured a dry flowable product, but the 25 total monitoring units (MUs) included:

- 24 different subjects from 4 different states
- two different products with separate active ingredients
- some subjects who measured partial containers and some who didn't
- some subjects who used pre-mix (i.e., slurry) tanks and some who didn't
- one subject who used an eductor system
- some subjects loading groundboom equipment and some loading aircraft
- subjects mixing/loading from 3 to 24 loads
- load sizes that varied from 20 to 1500 gallons
- subjects handling from 5 to 2,052 pounds of active ingredient

B3.3.2. Focus on Common Conditions

When planning the scenario MUs, conditions should be focused towards including commonly occurring conditions as opposed to those that are believed to be rare. This makes the non-probability sample slightly more representative. Note, however, that bias towards common conditions (or, equivalently, bias away from rare conditions) should not mean selecting MU conditions that are simply ‘more convenient’.

Example: Open cab groundboom applicator

When designing the testing program for open cab groundboom applicator exposures, AHETF purposely included some subjects who applied a spray to bare ground along with immediate incorporation into the soil (such as with a disc or tiller pulled behind the spray boom) since this practice is common and could potentially lead to a slightly different exposure potential than application to a growing crop. However, the more common situation is application to growing crops, so most of the MUs in this scenario involved application to various crops.

B3.4. Surrogate Random Sampling Model

As a result of purposive sampling, the MU exposure values can only be used to establish a surrogate distribution of exposures. That is, for some analyses, users of the data might need to assume that the distribution is at least similar to a random sample (of some form) from the target population. This is true for all studies unable to generate a true probability sample. In the determination of sample size and the statistical summary analysis of MU data for scenario monograph reports, uncertainties for distributional parameter estimates will be based on surrogate cluster random sampling models. This surrogate distribution is felt to be adequate for practical regulatory purposes given the 3-fold level of accuracy specified for the benchmark parameters. While it might not be estimating the exact target population distribution, it is believed to be capturing the major aspects of it and, given the small sample sizes, is not expected to be substantially different than a same-sized cluster random sample.

B4. Practical Implementation of Purposive Sampling for a Scenario

The elements of the AHETF sampling methodology are described in Section B3 above. The practical implementation of this methodology for each scenario is quite involved and all scenarios are not amenable to exactly the same approach. This section describes the practical process of purposive sampling in general and includes illustrations of how this may work in practice. However, it should be emphasized that each scenario-specific sampling plan (submitted as a separate document along with each study that addresses that scenario) will

include more specifics about how particular handler-day conditions were selected from the target population.

B4.1. The Scenario-specific Sampling Plan

The AHETF will develop and document a sampling plan for each scenario within its scope. The purpose of each sampling plan is to ensure that the sample size is adequate to meet specific scientific (e.g., benchmark accuracy) goals and will include a diverse set of common handling conditions.

Construction of a scenario-specific sampling plan first involves several tasks necessary to implement the purposive sampling and increase the generalizability of the purposively selected set of MUs to the target population. These tasks often involve consultation with agricultural experts (see Section B5). The steps involved are:

1. Define the handling scenario, both in terms of what it includes and what it does not include (e.g., task, equipment, product formulation, engineering controls, etc.)
2. Identify parameters likely to impact exposure (e.g., worker practices, crops, etc.) and prioritize by expected impact. The formalization of this process was a recommendation by the SAP (SAP, 2007).
3. Identify the common variations of these parameters over the scenario.
4. Establish the practical range of amount of active ingredient handled (AaiH) or other normalizing factor if appropriate
5. Identify a set of diverse locations where the common handling conditions of interest are likely to take place naturally (i.e., selecting study locations)
6. Identify growers within selected locations where suitable conditions are likely to occur naturally and who are willing to cooperate (e.g., by accepting the particular pesticide application of interest and by allowing recruitment of their workers)
7. Recruit workers who meet the inclusion/exclusion criteria and who reflect the typical worker population in that location (e.g., in terms of experience and language)

Based on the information obtained, each scenario-specific MU sampling plan will be constructed and will contain the following components:

- Summary of existing MUs and cluster structure (e.g., from PHED or AHETF)
- Proposed number of additional clusters and MUs/cluster
- Desired location for each cluster
- Target levels of the normalizing factor (e.g., AaiH) for each MU
- Guidelines for diversification of other parameters

B4.2. Defining the Scenario

As discussed in Section B3.1 above, it is very important to precisely define each scenario in the early stages of planning. Thus, the AHETF will attempt to define, *a priori*, what handling conditions will and will not be included in each scenario sampling plan.

The resulting scenario will certainly include some handling conditions that are more common than others. This information is irrelevant to the definition of scenario, but may sometimes be taken into account during the purposive selection of MUs.

Example: The mixing and loading of liquid products using enclosed systems

Before embarking on an MU sampling program, AHETF must determine (among other things) whether any or all types of liquids are appropriate, what types of closed systems should be included, what packaging types and sizes should be included, and whether the liquid products must be diluted with carrier or not. Based on some preliminary planning, AHETF might propose the following:

- Any liquid is appropriate for inclusion (solution, emulsifiable concentrate, suspension concentrates, flowable, etc.).
- Closed systems can conveniently be put into 3 general categories: suction/extraction, direct drop/gravity feed, and container breach; and that only the first two will be considered part of the scenario (and included in the sampling plan) since container breach systems are no longer in common use.
- A variety of packaging types (jugs, small drums, large drums, and plastic totes) and sizes (from 1 gallon jugs to ≥ 250 gallon totes) will be included, but packaging types are generally associated with system types
- Most closed system mixing/loading of liquids involves dilution with carrier, however it is common for large volume products/systems to be “ready-to-use”. Therefore both diluted and undiluted conditions are included in the definition.

In most situations, these evaluations will be made based on information that is publicly available (e.g., USDA statistics, government reports, or literature references) and by consultation with appropriate experts for each scenario (see Section B5). However, these decisions may also be based in part on discussions with EPA and other regulators so that the scenario definition, and hence the data collected according to the definition, will be useful for regulatory purposes.

It is important to distinguish between conditions that are explicitly excluded from the definition of a scenario and those conditions that are just not selected for monitoring. This distinction is straightforward for probability sampling. In that case, if there is zero chance that a handler-day condition can be selected, then it is simply not part of the scenario (and sampling frame). Otherwise it is. With non-random sampling, however, it makes no sense to talk about 'chance of being selected'. For purposive sampling, we define a scenario as those conditions that would have been considered valid for selection before the purposive selection is made. It is this set of conditions (e.g. handler-days) that the purposive sample is intended to represent in a valid way. In the example above, it is reasonable that the container breach systems not be considered part of the 'realized' scenario. In contrast, in a finite number of purposive samples, a particular type of emulsifiable concentrate may have been excluded. It was not excluded because it was considered in any way atypical. Rather, there was just no way to include every possible formulation type in a limited size sample. While there is some ambiguity, it is probably reasonable to consider the excluded formulation type as part of the scenario. This would be valid if the unselected formulation is considered to be 'just as well represented' by the purposive sample as would be one of the formulations actually selected. There is clearly some subjectivity in this classification. Unfortunately, this is a common (but often ignored) problem when random sampling cannot be used.

B4.3. Identifying Parameters Likely to Impact Exposure

One group of parameters that clearly affect exposure are those involved with defining the scenario (see Section B4.2). These include:

- Task (e.g., mixing/loading or application)
- Application System (e.g., aircraft versus ground equipment)
- Product Formulation (e.g., liquid or granule)
- Engineering Controls (e.g., open or closed loading and open or enclosed cabs)

As discussed in Section B3.2 above, a second group includes the three standard parameters that will be diversified within almost all scenarios:

- Location
- Workers
- Level of the normalizing factor (usually AaiH)

These standard parameters will usually be formally diversified within the scenario plans as discussed in Sections B4.5, B4.6, and B4.8.

In addition, each specific scenario will be evaluated to determine whether other conditions might be important to diversify because they particularly impact the potential for exposure. In many cases, this finest level of diversification will be done less formally and will often occur naturally when other parameters, most notably AaiH, are diversified.

Examples of other parameters that might impact exposure for various scenarios, and that will be diversified to some degree within scenario plans are:

- Application equipment size (e.g., boom length, tank size, etc.)
- Crop, crop size, or growth stage
- Number of loads
- Spray volume

B4.4. Identifying Commonly-occurring Handler Conditions for Important Parameters

For the parameters identified as possibly having a major affect on exposure, AHETF will try to determine what common variations exist, within each scenario. This will be accomplished by a combination of reviewing public information, discussing with experts in the particular handling scenario, and discussing with local growers or crop consultants. Depending on the scenario involved, experts could include university contacts, crop and applicator associations, crop consultants, equipment manufacturers, independent research organizations, and field experts employed by AHETF members.

As discussed previously, the objective is not to collect MUs that are representative of all the conditions that are found in the target populations by mimicking their frequency. The extremely large number of possible conditions makes such a ‘target population in miniature’ impossible to obtain by either purposive or randomly sampling. Rather, the goal is to collect MUs that involve a diverse set of common situations for important parameters that might impact the potential for handler exposure

Example: Spray volume

At the finest level of diversification, consider spray volume with respect to airblast applications in trellis crops in New York. After determining that New York grows the most grapes in the eastern U.S. and so would be a good place to locate a study, AHETF contacted local crop consultants who help growers make pesticide application decisions to get advice on the common range in volume of spray solution applied per acre by airblast to grapes. Based on the information that the vast majority of applications are between 50 and 100 gallons per acre, AHETF plans to try to diversify this parameter across that range. Logically, when we specify a larger AaiH, the grower will tend to use a smaller spray volume in order to spray sufficient acreage within a single workday. However, spray volume will probably be a lower priority item in terms of expected impact on exposure, so diversification will be less formal and a specific study protocol will likely specify only a target GPA or a desired range in GPA. As with many specifics for pesticide applications, the grower will likely make the final decision based on his particular needs or desires.

B4.5. Establishing the Practical Range of the Normalizing Factor

As discussed in Section B3.2.2 and in Appendix C, AEHTF will take special care to vary the normalizing factor (NF) over a wide range in order that AHED[®] users will be able to examine the relationship between this factor and exposure. To do this, AHETF first establishes a practical range of the NF for each scenario. For the default normalizing factor, amount of ai handled (AaiH), the low end of the range is generally set at 5 pounds of active since handling amounts below this level may result in residue levels that are not quantifiable. Non-quantifiable exposures are not very useful for a generic database since the true exposure is somewhere below the analytical limit and some assumption is needed in order to make a reasonable estimate of predicted exposure. The upper end of the AaiH range is generally based on high end product use rates and maximum acres treated per day for various crops and application techniques. However, AHETF sometimes sets the practical range at a somewhat lower value than the calculated maximum in order to prevent workers from handling excessive amounts of product that might take significantly longer than 8 hours. Pesticide use rates are generally found by surveying member products and there are a number of publicly available resources for estimating acres treated, including Policy 9.1 (EPA, 2001) that EPA uses. Similar methods are used when the normalizing factor is something other than AaiH.

Example: Dry flowable, open pour, mixer/loader

When designing studies for this scenario AHETF established a practical range of ai handled as 5 to 2,000 pounds of active ingredient. The upper limit was based on a high end use rate of 2 lb ai/acre, the assumption that up to 1,200 acres of crop could be treated by air but reduced somewhat since open pouring small containers would probably not be the technique of choice for the very highest use level (i.e., bulk packaging of liquids would be more common).

AHETF then formally diversifies the AaiH both within clusters (i.e., studies) and within the scenario using the approach described in Section B3.2.2 above.

B4.6. Selecting Study Locations

As discussed in Section B3.2.1 above, MUs are selected in ‘clusters’ of handler-days. Each cluster is associated with a particular broadly defined location and time period and is the first-stage unit of sampling. Because the AHETF purposive sample begins with location, it can make the biggest difference to total diversity in the sample. Thus, the geographic location will be diversified within all MU sampling plans.

In addition, AHETF attempts to identify locations where the particular handling situation of interest will commonly occur. For some application scenarios, specific crops are

desirable and locations can be selected to reflect areas of the country where that crop(s) is predominantly grown.

Example: Airblast applications.

Airblast applications are commonly made to orchards and to trellis crops, but not to field crops. The USDA National Agricultural Statistics Services (NASS) database can be used to determine that the largest trellis crop by acreage is grapes and that most grapes are grown in California. This is a strong indication that AHETF should plan some airblast application MUs on grapes in California. In this way, AHETF can sometimes choose suitable locations and crops so the data set will reflect the target population.

For other scenarios such as mixing/loading of water soluble packets, it is less important to focus on particular geographic regions since this task is performed in virtually all areas of the country. In situations like this, AHETF often collects mixing/loading MUs in conjunction with applicator studies and limits the number of MUs/study so the planned set will have a sufficient number of clusters and MUs to meet benchmark accuracy goals (see Appendix C).

And one final consideration for selecting locations is that AHETF prefers to use local researchers who can help with some of the GLP requirements for field studies, in particular by providing storage facilities that are monitored for temperature and have access restrictions (ambient for test substances, refrigerated for field fortification solutions, and frozen for exposure dosimeter samples). These researchers also tend to have many contacts with local growers to assist with identification of suitable growers and they are also familiar with common growing practices for local crops. And not coincidentally, these researchers (which AHETF calls Local Site Coordinators) are typically located in important growing regions in North America.

B4.7. Identifying Growers and Contractors

After defining a sampling plan for a scenario and selecting locations (and sometimes also a target crop or other sites such as a greenhouse) for studies, AHETF usually often needs to find growers (e.g., farm owners or operators) who commonly perform the types of pesticide handling tasks for the particular scenario being planned. This usually means finding suitable acreage or a specific crop or crop type (or other application site); suitable equipment and engineering controls that are consistent with the scenario definition; several workers who are experienced with those particular equipment and practices; and the anticipated need for application of a pesticide product that meets AHETF needs. The choice of surrogate chemical is limited by the set of active ingredients that have been deemed suitable by AHETF (see Sec. 4.2 of Governing Document) and involves discussions between the grower and the Study Director to find a chemical that meets both of their needs. If this is not possible, other

growers will need to be identified. The choice of the particular product to be used can be influenced by the scenario being tested (e.g., mixing/loading scenarios necessitate a particular formulation type) or the need for diversity of conditions within a scenario (e.g., container sizes), however growers may choose between equivalent or similar products (e.g., manufacturer or strength), if available. When growers are participants (e.g., farm owners), they have some influence on the active ingredient and/or product. However, other participants (e.g., farm employees and contract applicators) do not choose the product or active ingredient that they will be asked to handle.

For some scenarios, such as aerial applicators, it may be just as important to identify suitable commercial applicators (e.g., pilots) since growers rarely apply pesticides by air themselves. In these cases, the grower provides suitable acreage and the need for the pesticide while the application and/or labor contractor provides the pesticide handlers themselves and equipment they typically use.

As mentioned above, Local Site Coordinators are often utilized to assist with initial screening of locations (e.g., towns, regions, or states); growers; and application or labor contractors. This screening process generally begins with personal contacts between the Coordinator and growers or contractors in the local area to explore the chances that the desired combination of crops, acres, equipment, workers, and surrogate use might be available. This can be quite a challenge, especially with respect to surrogate use and the usual desire for several different workers with experience conducting the particular task(s) of interest to volunteer and participate. For this reason, and because AHETF seeks diversity in conditions, AHETF frequently works with a variety of growers in a particular location/study and collection of MUs takes place over a several day period. This often involves moving from one city to another within the area ('location') and in this way AHETF can obtain exposure data from large growers and small growers at the same location.

Example: Dry flowable mixing/loading.

The sampling plan for this scenario (conducted in 2005) involved five different mixer/loader workers (MUs) handling approximately 5 to 2,000 pounds of active ingredient at each of five sites. One study was located and conducted in the Pacific Northwest and this study involved sampling MUs in four cities of two states over a six-day period. The following diversity in growers and contractors was utilized:

- One small, independent grower with about 30 acres of orchard to be treated by ground (grower provided all workers, equipment, and acreage)
- Three moderate-size growers who each treated 100 to 250 of grass grown for seed with ground equipment (grower provided all workers, equipment, and acreage)
- One block of forestry (100 acres, owned/operated by local government) that was treated by helicopter (commercial mixer/loader and applicator workers using their own equipment)

- One very large (i.e., corporate) grower (provided acreage) who treated a total of 1,825 acres of potatoes using two fixed-wing aircraft (commercial mixer/loader and applicator workers using their own equipment).

B4.8. Identifying Workers

It is a challenge to set up each study to include the kinds of diversity described above, especially when scenarios must also vary the AaiH. It would be impractical for AHETF to simply identify all the pesticide handlers within a location and randomly select enough of them to meet our sampling needs. Instead, AHETF is looking for a handful of distinct combinations of handler-conditions that reflect a diverse set of commonly-occurring conditions for several important factors. If a sample of five MUs is required at a location then it is necessary to search for:

- Five workers
- Experienced in the particular task of interest
- Using specified equipment and engineering controls
- In one general location
- At one particular time
- With sufficient crop or site acreage
- Where a grower is planning to use our surrogate pesticide
- And to have each worker handle a different amount of product

In practice, locating the growers and/or contractors that can meet these complex set of conditions is the most difficult aspect of purposive sampling. After this task has been accomplished, the pool of workers is not very large. This is primarily because AHETF believes it is usually not appropriate to bring workers in from other areas to perform pesticide-handling tasks because this would require workers to deal with farms, equipment, and facilities that they are not familiar with. AHETF believes this becomes a safety issue and will unduly increase the risk of injury for study participants. Therefore, AHETF generally needs to find purposively diverse sets of conditions that exist naturally. And it must be emphasized again that AHETF is not just sampling workers, it is sampling a complex set of conditions that includes a separate worker for each MU.

Based on the MUs that AHETF has collected in the last several years, it is uncommon to have more than twice as many potential volunteers as MUs in the plan. When there are excess qualified volunteers for a study on the day of monitoring, the Study Director will select workers for MUs randomly (e.g., by lottery).

B4.9. The Role of Field Studies in MU Sampling

The entire non-probability sample of MU conditions applies to a worker exposure scenario. However, for practical reasons, sets of MUs are collected in one or more field

studies. The purpose of each field study is to conduct a subset of the scenario's monitoring trials, generally in a particular region of the country over a short period of time (e.g., one week). Efficiency requires that some scenarios are jointly addressed by the same field study. For example, it is usually more efficient to conduct mixer/loader trials and applicator trials at the same time. As a result, the general guidelines for diversity sampling described in Section B3.2 apply to the scenario and, to some extent, to the field study as well. These guidelines need to be somewhat flexible since many MU decisions have to be made or revised in the field (e.g., based on grower needs or weather conditions).

B5. Sources of Expert Information

In order to assess which factors are most relevant for diversity sampling, the AHETF will solicit information from a variety of experts. The exact sources of expert information will generally be scenario-specific, but may also be study-specific and is used to guide scenario plans (e.g., diversity of conditions) and/or study-specific procedures (e.g., recruitment and remuneration). Following are some examples of the types of experts that might be consulted during the planning process.

For most scenarios, general information that will characterize the handling scenario (e.g., common sites, equipment, workers, and practices) will be obtained from the following sources:

- AHETF member company experts
- USDA County Agricultural Extension Agents
- Professional crop consultants
- Academic and governmental research organizations

For many scenarios or studies, planning will be based on a particular crop or a crop group. Examples are airblast applications that are unique to orchards and vineyards. In these cases, grower associations, governmental agencies, and applicator associations may be contacted.

For other scenarios, the equipment or worker practices rather than crops may determine what expert advice is needed. For example, ground boom sprayers, chemigation applications, hand-held sprayers, or enclosed mixing/loading systems. In these cases, farm equipment manufacturers, pesticide dealers, and commercial applicators may be contacted.

For worker issues (e.g., handling procedures, diversity, recruitment, etc.), farm labor contractors, labor advocacy groups, or pesticide safety training organizations, and farm workers may be contacted.

The information collected will be used to guide the purposive diversity sampling plans and will be summarized in the written plans prepared by AHETF for each scenario.

B6. References

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Appendix C. Procedures for Determining the Required Number of Clusters and Monitoring Units per Cluster to Achieve Benchmark Adequacy

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Appendix C

Procedures for Determining the Required Number of Clusters and Monitoring Units per Cluster to Achieve Benchmark Adequacy

This appendix describes the statistical basis and methodology used by the AHETF to determine the sample size and configuration for agricultural handler scenarios. This expanded version of the sample size methodology document has greatly benefited by both formal and informal input from a recent EPA Scientific Advisory Panel review (SAP, 2007).

C1. Benchmark Objectives of the AHETF Monitoring Program

The AHETF monitoring program is not an experimental study whose purpose is to test hypotheses about the distribution of exposure or about potential determinants of exposure. Rather, its purpose is to collect sufficient data for each handler scenario to meet specific minimum or ‘benchmark’ adequacy requirements. These data, possibly augmented by additional exposure data from other sources, will then be used for a variety of regulatory purposes by numerous organizations. The design benchmarks are not intended to address all possible ways the exposure data could be used. Rather, they are established to ensure that the data will at least be adequate to meet common regulatory needs.

The primary benchmark data objective for each scenario in the AHETF program will be of the form:

The number (and configuration) of sampled monitoring units (MUs) should be adequate so that selected measures of the normalized dermal exposure distribution (e.g., means, percentiles) are accurate to within K-fold.

Throughout this appendix, normalized exposure refers to exposure divided by the amount of active ingredient handled by the worker (or AaiH). A benchmark based on AaiH is treated as the default for the primary benchmark because it is currently the most common measure of unit exposure used for regulatory purposes. For some scenarios, however, regulators might prefer to define unit exposure in terms of a different measure of ‘active ingredient contact potential’. There could even be scenarios for which users of AHED[®] prefer to use unnormalized exposure. If, for a particular scenario, the JRC and AHETF jointly decide that a different normalization factor (or none at all) is more valuable for regulatory use then it will be used instead to define unit exposure for the primary benchmark objective.

The desired relative accuracy, K, can be scenario dependent. For example, less accuracy (i.e., a larger value of K) might be tolerated for scenarios that are expected to have lower exposures. Such considerations are often necessary to better allocate limited resources and avoid unnecessary human exposure monitoring. Currently, however, there is a general consensus that, for regulatory purposes, 3-fold relative accuracy (i.e., K=3) is a reasonable default for all scenarios.

Using K-fold accuracy for exposure normalized by amount of ai handled (or a different normalizing factor) as a benchmark does not necessarily imply that other ways of expressing exposure will result in less accuracy. Because many potential normalizing factors (e.g., time worked, loads handled) are usually correlated with the amount of ai handled, similar accuracies are likely in those cases as well. However, for design purposes, the AHETF monitoring program only uses the distribution of exposure normalized by a single measure of contact potential. For simplicity, unless noted otherwise, AaiH will be assumed to be the normalizing factor throughout this appendix.

A secondary benchmark objective is considered for scenarios for which normalized exposure is relevant and when the practical range of this factor is sufficiently large. In such cases it is also desired that:

The number (and configuration) of monitoring units (MUs) should be adequate so that it is possible to statistically distinguish between complete proportionality and complete independence of dermal exposure and the normalizing factor (e.g., amount of ai handled).

If, for a particular scenario, the JRC and AHETF jointly decide that unnormalized exposure has greater regulatory value, then no secondary benchmark will be considered.

It is not the objective of the AHETF monitoring program to guarantee that the data will be able to discern more complicated relationships between exposure and amount of ai handled. Nor is it the intent to guarantee that future analyses of the data will be able to choose between several potential normalizing factors or combinations of factors. The SAP (SAP, 2007) correctly noted that this secondary objective in the AHETF program merely ensures that the data would be adequate to illuminate the relationship between AaiH and exposure. They suggested that a controlled experimental study, beyond the scope of the AHETF program, might be a better way to address this issue more extensively.

It must be emphasized that the use of amount of ai handled as the default measure of ai contact potential in these benchmark objectives is both reasonable and based on considerable historical precedent. This does not mean, however, that a proportional relationship between dermal exposure and amount of ai handled is assumed to be always the case. In fact, the AHETF monitoring data (assembled in a database called AHED[®]) will always include measured exposures (generally μg of ai for the entire monitoring period) and the values of many potential normalizing factors, including amount of ai handled. Users of the data are always free to consider any (or no) normalization.

C2. Assumptions and Surrogate Sampling Model for MU Exposures

The AHETF monitoring program uses purposive diversity sampling, a type of non-random sampling, to select a sample of monitoring units. This reflects very complex logistical limitations and the unique nature of the AHETF program (see Appendix B). For the purposes of determining the number of monitoring units needed, however, a surrogate

cluster-sampling model is used. This surrogate sampling model has the following characteristics:

- Observed exposures can be viewed as arising (at least approximately) from a random sample of clusters and then from a random sample of monitoring units within each cluster. These clusters are merely artifacts of the sampling process and are usually associated with separate studies in geographically separated locations (e.g., different states or crop-growing regions). Clusters could also be viewed as studies separated by sizeable time periods (e.g., different years).
- The sampling distribution of normalized exposures within and between clusters is, at least approximately, lognormal.

Thus, for determining sample sizes, normalized exposures, Q , are assumed to follow the nested variance component model

$$(1) \quad \text{Log} (E_{ij} / H_{ij}) = \text{Log} Q_{ij} = \text{Log} GM_Q + C_i + W_{ij}$$

where

E_{ij} = the exposure obtained for MU j in cluster i

H_{ij} = the amount of a_i handled by worker for MU j in cluster i

Q_{ij} = the exposure for MU j in cluster i normalized by amount of a_i handled

GM_Q = the population geometric mean for normalized exposure

C_i = a random effect of cluster i

W_{ij} = a random effect of MU j within cluster i

As stated in the previous section, the default assumption is that H_{ij} is the amount of a_i handled. However, it could represent any normalizing factor. In addition, (1) applies to unnormalized exposure when $H_{ij} = 1$. The random effects C_i and W_{ij} are normally distributed with means 0 and variances V_c and V_w , respectively.

The population variance of $\log Q$ is then equal to $V = V_c + V_w$ and the square root of V is the true population standard deviation, SD . The quantity $GSD_Q = \text{antilog} (SD)$ is the true population geometric standard deviation of normalized exposure. The 'intra-cluster' correlation (i.e., the intraclass correlation due to clusters) is defined as

$$(2) \quad ICC = V_c / V = 1 - V_w / V$$

The ICC is irrelevant to the population distribution of normalized exposure, per se. However, this intra-cluster correlation is a necessary part of the sampling model because the MUs are obtained in clusters (see Appendix B). Under this sampling model, the only quantities needed to determine relative accuracy of population parameter estimates are reasonable values for GSD_Q and ICC.

C3. Estimates of GSD_Q and ICC from Existing Data

Estimates of the GSD_Q and ICC were obtained from existing AHETF monitoring data. Although these data are incomplete, they are sufficient to provide reasonable values for normalized exposure variation and the intra-cluster correlation. The scenarios and clusters for which data were available (as of April, 2007) are listed in Table 1.

For each scenario in Table 1, both GSD_Q and ICC were estimated by fitting the variance-component sampling model (1) to the available data. The estimates obtained for total dermal exposure are given in Table 2. For completeness, the estimates obtained for inhalation exposure are shown in Table 3. Two scenarios, closed granular ML and hopper box seed treatment MLAP contain only a single cluster and therefore the ICC cannot be estimated. For these scenarios the GSD_Q is only an estimate of the within-cluster variation. The confidence intervals for GSD_Q and ICC are parametric bootstrap percentile intervals based on N=1000 bootstrap replications. Also shown in both tables are various summary measures of these estimates over all scenarios.

For normalized dermal exposure (Table 2) the GSD_Q estimates range from about 2 to 5 with a typical value slightly less than 4. The ICC estimates range from 0 to 0.66. As the confidence intervals indicate, however, uncertainties in the individual ICC estimates are very large. This is not unusual when the number of clusters is small. The mean ICC is slightly less than 0.3. Table 2 also gives the estimates of GSD_Q and ICC obtained from the fit of a mixed model using all the scenario data together. In this case, the geometric mean was allowed to differ for each scenario but common values of GSD_Q and ICC were required. These common values of GSD_Q and ICC were 3.8 and 0.26, respectively.

Normalized inhalation exposures (Table 3) appear slightly more variable than dermal exposures. The GSD_Q estimates range from about 2 to 6 with a typical value being slightly greater than 4. The ICC estimates range from 0 to 0.71 with a mean around 0.36. For the combined model, the common GSD_Q and ICC estimates are 4.2 and 0.37, respectively.

From this analysis it appears that a GSD_Q of 4 and an ICC of 0.3 are reasonable values of variability and within-cluster correlation to use for planning purposes. Although the benchmark objectives apply only to dermal exposure, these two values should be satisfactory for inhalation exposure as well. The normalized inhalation exposure, at least on the average, appears to be only slightly more variable than dermal exposure.

Table 1. Scenarios and Clusters with Available Monitoring Unit (MU) Exposure Results

Scenario	Clusters	Monitoring Dates	# MUs
Closed Granular ML	AH516-M, 5 towns in NE	Apr-May 1998	15
Airblast Application	AHE07-A, GA	Oct 2003	5
	AHE07-A, ID	Oct 2003	6
	AHE07-A, FL	Dec 2003	4
Granular Backpack MLA	AH207-MLA, Spain	May 1998	16
	AH208-MLA, Martinique	Aug 1998	11
Dry Flowable ML	AHE17 + AHE19, IL	Apr 2005	10
	AHE18, OR/WA	May 2005	5
	AHE20, GA	Jul 2005	5
	AHE21, FL	May-Jun 2005	5
Aerial Application	AH501-A-1, CA, CV	Oct 1991	8
	AHE18-A, WA, CV	May 2005	2
	AHE13-A, TX, ULV	Oct 2004	16
Open-Pour ML Liquids	AH204-M, France	Mar 1997	16
	AH501-M-2, MS	Sep 1991	8
	AHE30, OR	Oct 2005	2
	AHE31, CA	Nov 2005	3
	AHE32, FL/GA	Dec 2005	6
Closed Liquid ML (bulk/minibulk)	AHE13-M, TX, ULV	Oct 2004	15
	AH501-M-1, CA, CV	Oct 1991	7
Hopper-box Seed Trt MLAP	AHE10, AR/TX	Apr-May 2004	16
Open Cab Groundboom App	AHE18, OR/WA	May 2005	2
	AHE20, GA	Jul 2005	1
	AHE21, FL	May 2005	2
	AHE30, OR	Oct 2005	5
	AHE31, CA	Nov 2005	5
	AHE32, FL/GA	Dec 2005	6

Table 2. Dermal Exposure Variability Estimates for Each Scenario

Scenario	GSD	95% CI	ICC	95% CI
Aerial Application	4.2	2.1 – 12.0	0.62	0 – 0.89
Airblast Application				
With Headgear	3.2	2.1 – 4.9	0.00	0 – 0.49
No Headgear	2.9	2.0 – 4.3	0.00	0 – 0.47
Closed Granular ML	2.1 ¹	1.6 – 2.8	–	–
Closed Liquid ML	4.2	2.7 – 7.8	0.11	0 – 0.59
Dry Flowable ML	2.5	1.8 – 3.8	0.41	0 – 0.75
Granular Backpack MLA	4.2	2.0 – 16.3	0.66	0 – 0.92
Hopper-box Seed Trt MLAP	3.3 ¹	2.2 – 5.0	–	–
Open Cab Groundboom App	3.9	2.4 – 6.3	0.24	0 – 0.65
Open-Pour ML Liquids	5.0	3.5 – 7.8	0.00	0 – 0.30
Mean ²	3.8		0.29	
Median ²	4.0		0.24	
Geometric Mean ²	3.3		–	
Combined Model ³	3.8		0.26	

¹Only a single cluster: ICC cannot be calculated and GSD estimates only within-cluster variation

²Closed granular ML excluded from calculation of mean, median, and geometric mean GSD; only airblast with headgear values are used

³Estimates from a mixed linear model allowing different scenario geometric means but assuming a common GSD and ICC

C4. Relative Accuracy and Fold Relative Accuracy

As stated above, the primary objective of the AHETF monitoring program is to achieve adequate relative accuracy of selected parameters of the normalized exposure distribution. Given the sampling model (1), this benchmark target can be stated more precisely as:

Estimates of the geometric mean, arithmetic mean, and 95th percentile of an underlying lognormal distribution should be within K-fold of the true values at least 95% of the time.

If θ denotes the distributional parameter of interest and T is the estimate of that parameter obtained from monitoring data, then the relative accuracy of T is defined simply as:

(3)
$$RA(T|\theta) = T/\theta$$

Table 3. Inhalation Exposure Variability Estimates for Each Scenario

Scenario	GSD	95% CI	ICC	95% CI
Aerial Application	4.4	2.1 – 12.8	0.71	0 – 0.91
Airblast Application	2.6	1.9 – 3.8	0.00	0 – 0.45
Closed Granular ML	4.5 ¹	2.6 – 7.6	–	–
Closed Liquid ML	6.0	2.4 – 28.8	0.62	0 – 0.92
Dry Flowable ML	4.6	2.9 – 7.4	0.16	0 – 0.55
Granular Backpack MLA	1.8	1.5 – 2.4	0.23	0 – 0.67
Hopper-box Seed Trt MLAP	3.8 ¹	2.4 – 6.2	–	–
Open Cab Groundboom App	5.9	3.1 – 13.3	0.43	0 – 0.78
Open-Pour ML	4.3	2.8 – 7.2	0.38	0 – 0.71
Mean ²	4.1		0.36	
Median ²	4.3		0.38	
Geometric Mean ²	4.2		–	
Combined Model ³	4.2		0.37	

¹Only a single cluster: ICC cannot be calculated and GSD estimates only within-cluster variation

²Closed granular ML excluded from calculation of mean, median, and geometric mean GSD

³Estimates from a mixed linear model allowing different scenario geometric means but assuming a common GSD and ICC

Satisfying the benchmark objective above requires that there be at least a 95% chance that T/θ is between 1/K and K. More formally this is stated as:

$$(4) \quad \text{Prob} \{ 1/K \leq RA(T|\theta) \leq K \} \geq 0.95$$

It is more convenient, however, to consider relative accuracy expressed as a ‘fold relative difference’. This is because statements such as “T is within K-fold of θ” are more intuitive than the formulation given in (4). The ‘fold relative accuracy’, *fRA*, is defined as:

$$(5) \quad fRA(T|\theta) = \text{Max} \{ RA(T|\theta), 1/RA(T|\theta) \} = \text{Max} (T/\theta, \theta/T)$$

Then, statement (4) is equivalent to

$$(6) \quad \text{Prob} \{ fRA(T|\theta) \leq K \} \geq 0.95$$

and simply says that the estimate, T, will be within K-fold of the true parameter, θ, at least 95% of the time. The 95th percentile of *fRA*, *fRA*₉₅, is the specific fold-accuracy value that satisfies (6). Consequently, the benchmark adequacy goal reduces to requiring that:

$$(7) \quad fRA_{95} \leq K$$

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If we denote the 2.5th and 97.5th percentiles of the sampling distribution of T by $T_{2.5}$ and $T_{97.5}$, respectively, then the 95th percentile of fold relative accuracy can also be calculated from

$$(8) \quad fRA_{95} = \text{Max} (T_{97.5} / \theta, \theta / T_{2.5})$$

C5. Parameter Estimates

As defined above, relative accuracy applies to the particular quantity T that is used to estimate the distributional parameter θ . Thus, it is important to consider which types of estimates of the geometric mean, arithmetic mean, and 95th percentile are used to evaluate fRA_{95} . The relative accuracies could differ depending on the particular estimates used.

There are often multiple choices for the parameter estimates. The estimators can be broadly grouped into either empirical or parametric. Empirical estimates are the commonly-used statistics available in spreadsheet programs. They do not (explicitly) assume any distribution. However, they can sometimes require simple random sampling for greatest efficiency. Parametric estimates incorporate the fact that the surrogate distribution is lognormal and could also account for cluster sampling being used.

The most straightforward statistic is the geometric mean (GM_Q). In the balanced case, the simple empirical estimate of GM_Q can be calculated by averaging the log-transformed normalized exposures and then taking the antilog of this value. In this case, the empirical and parametric estimates of GM_Q are identical. If the number of MUs per cluster varies, however, one could consider geometric means with different degrees of weighting by cluster size. The arithmetic mean can also be calculated empirically by summing up the normalized exposures and dividing by the total number of MUs. Again, when the cluster sizes differ, other types of weighted empirical arithmetic means exist. In the unbalanced case, neither the weighted nor the unweighted estimates of GM_Q or AM_Q are universally best. Consequently, for this investigation, the simple (and most common) versions of the empirical geometric and arithmetic means seem preferable. Empirical percentiles could, theoretically be calculated in the conventional manner. However, when there is cluster sampling and the number of MUs are not large, empirical estimates of the extreme upper (or lower) percentiles are not especially efficient. The parametric percentiles (see below) are usually preferred in this case.

Parametric estimates are those closely aligned with the sampling model used. In this case one uses the fit to the variance component model described in (1) above to get estimates for the geometric mean (GM_Q) and the total geometric standard deviation (GSD_Q). To estimate the arithmetic mean (AM_Q) and 95th percentile (Q_{95}) one could then use the lognormal relationships:

$$(9) \quad AM_Q = GM_Q \times \text{Exp} \left\{ \frac{1}{2} (\log_e GSD_Q)^2 \right\}$$

$$Q_{95} = GM_Q \times \text{Exp} \{ Z_{95} \log_e GSD_Q \}$$

where Z_{95} is the 95th percentile of the standard normal distribution. For simplicity, these will be labeled the 'parametric cluster sampling estimates'.

It can be argued that few if any users of the AHETF monitoring data will choose to (or be able to) fit variance component models to the data. They will probably ignore the sampling model and use more conventional estimates. In this case empirical estimates of GM_Q and AM_Q defined above would probably be used.

Potential data users might also be less inclined to use empirical percentiles, especially with smaller sample sizes. The lognormal percentile estimate of Q_{95} in (9) above would then still be used but perhaps with the mixed model GSD_Q estimate replaced with the more conventional GSD_Q (i.e., the back-transformed simple standard deviation of log exposures.) For convenience, estimates that assume lognormality but not cluster sampling will be labeled 'simple random sampling parametric percentiles'.

Any or all of the above estimators could be evaluated. However, for the purposes of determining sample sizes, focus will be on the following estimators:

- GM_Q – simple empirical estimate
- AM_Q – simple empirical estimate
- Q_{95} – parametric cluster sampling estimate

C6. Calculation of fRA_{95} given the Number of Clusters (N_c) and a Fixed Number of MUs per Cluster (N_m)

Calculation of the 95th percentile of fold relative accuracy is complex and is usually best accomplished using Monte Carlo simulation methods. When the number of MUs per cluster, N_m , is the same for all clusters, the geometric mean, fRA_{95} can be calculated directly from the GSD_Q and ICC as:

$$(10) \quad fRA_{95} = \exp \left\{ 1.96 \ln GSD_Q \sqrt{\frac{ICC}{N_c} + \frac{1-ICC}{N}} \right\}$$

where N is the total number of MUs (i.e., $N=N_c \times N_m$). For parameters other than the geometric mean, a straightforward simulation approach can be used to determine fRA_{95} . This procedure is:

1. Simulate a set of normalized exposure data for N_c clusters and N_m monitoring units per cluster using the sampling model defined in (1) above.
2. From each set of simulated data, calculate T , the estimate of θ
3. Repeat steps 1 and 2 above M times to get M values of the estimate T

4. From these M T -values calculate $T_{2.5}$ and $T_{97.5}$, the 2.5th and 97.5th percentiles of T , respectively.
5. Calculate the 95th percentile of fold relative accuracy, fRA_{95} , using formula (8) above.

The number of simulations, M , should be some large number such as 1,000 or 10,000.

C7. Determination of Feasible Values of N_c and N_m

The methods in the previous section can be used to find those combinations of N_c and N_m that will achieve the default 3-fold level of accuracy (or any other desired accuracy goal). For different combinations of N_c and N_m , the simulation method above was implemented in SAS with $M=10,000$ to obtain fRA_{95} values for the arithmetic mean and 95th percentile estimators. The 95% bound for geometric mean relative accuracy was calculated directly from equation (10). The values used for the true GSD_Q and true ICC were 4 and 0.3, respectively.

Table 4 illustrates how N_c and N_m affect the upper bound of fold relative accuracy. For any configuration, the geometric mean will always be the most accurate since it is in the center of the lognormal distribution. The 95th percentile and, usually, the arithmetic mean estimates tend to be the least accurate for any sample size. Lower percentiles (e.g., 75th, 90th) would have smaller accuracy bounds than would the 95th percentile. The value of fRA_{95} for percentiles exceeding the 95th will be greater.

Increasing either N_c or N_m will improve the accuracy of all estimators, but adding clusters is more effective than increasing the number of MUs per cluster. With just 4 clusters it takes 10 MUs per cluster ($N=40$) to achieve about the same level of accuracy as with $N_c=5$ and $N_m=5$.

The number of clusters needed to achieve an fRA_{95} of approximately 3 was determined for N_m values ranging between 1 to 10. These nearly-equivalent 3-fold accuracy configurations are listed Table 5. Any of these combinations of N_c and N_m would be feasible from a benchmark accuracy standpoint.

Table 4. 95% Relative Accuracy Bounds for Lognormal Distribution Parameter Estimates When GSD = 4 and ICC = 0.3.

# Clusters, N _c	# MUs per Cluster, N _m	Total # MUs, N	95% Relative Accuracy Bound, <i>fRA</i> ₉₅		
			Geometric Mean ¹	Arithmetic Mean ²	95 th Percentile ²
3	5	15	2.8	3.9	4.5
4	5	20	2.5	3.3	3.6
5	5	25	2.2	2.9	3.1
6	5	30	2.1	2.7	2.8
7	5	35	2.0	2.5	2.6
4	5	20	2.5	3.3	3.6
4	6	24	2.4	3.1	3.4
4	8	32	2.3	3.0	3.1
4	10	40	2.3	2.9	3.1
4	4	16	2.6	3.5	3.8
5	4	20	2.3	3.1	3.3
6	4	24	2.1	2.8	2.9

¹Exact calculation

²Based on 10,000 simulations

Table 5. Configurations Yielding Nearly Equivalent 95% Relative Accuracy Bounds of 3-Fold or less when GSD = 4 and ICC = 0.3.

# Clusters, N _c	# MUs per Cluster, N _m	Total # MUs, N	95% Relative Accuracy Bound, <i>fRA</i> ₉₅		
			Geometric Mean ¹	Arithmetic Mean ²	95 th Percentile ²
15	1	15	2.0	2.8	3.0
9	2	18	2.1	2.8	2.9
7	3	21	2.1	2.8	3.0
6	4	24	2.1	2.8	2.9
5	5	25	2.2	2.9	3.1
5	6	30	2.2	2.8	3.0
5	7	35	2.2	2.7	2.9
4	8	32	2.3	3.0	3.1
4	9	36	2.3	3.0	3.1
4	10	40	2.3	2.9	3.1

¹Exact calculation

²Based on 10,000 simulations

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C8. Optimal Configuration of N_c and N_m based on Relative Costs

As Table 5 illustrates, there can be many configurations of N_c and N_m that will give acceptable benchmark adequacy. However, some of these feasible configurations are more costly than others. As suggested by the SAP (SAP, 2007), the choice between equivalent configurations is best made on the basis of cost-effectiveness. A commonly-used model approximating the total cost of cluster sampling, C_T is:

$$(11) \quad C_T = C_F \times N_c + C_{MU} \times N$$

C_{MU} is the variable cost per MU and C_F is the fixed cost per cluster. The ratio of C_F to C_{MU} determines which configurations are the most cost-effective. If C_{MU} in (11) above is set equal to one, then $C_F/C_{MU} = C_F$ and C_T can be thought of as the total relative cost as a multiple of the 'per MU' cost. The 10 nearly equivalent configurations in Table 5 are reproduced in Table 6 along with their relative total costs for different values of the fixed-to-variable cost ratio. When the cost-ratio is equal to zero, there are no fixed costs associated with a cluster and total cost is just a multiple of the number of MUs. In this case the $N_c=15$ and $N_m=1$ configuration will be optimal since it achieves the desired accuracy with the smallest N . As the ratio C_F/C_{MU} increases, the penalty for each new cluster increases and the total costs are smaller when there is more than one MU per cluster. For $C_F/C_{MU}=1$, $N_m=2$ is optimal. When C_F/C_{MU} is in the 5-10 range a configuration of $N_c=5$ and $N_m=5$ is more cost-effective. With a cluster cost 25 times that of the per MU cost, the optimal configuration is $N_c=4$ and $N_m=8$.

The AHETF has examined the cost structure of previous studies and concluded that most scenarios should have fixed-to-variable cost ratios between 6.5 and 8. Values of C_F/C_{MU} as low as 4 and as high as 9 are possible, but are expected to be rare. Table 7 lists these same 10 configurations with the total relative costs based on these AHETF cost ratios. Over this entire range, it appears that a configuration of $N_c=5$ and $N_m=5$ is the most reasonable choice.

C9. Sensitivity of fRA_{95} to the GSD and ICC

It is important to consider how sensitive $(N_c, N_m) = (5, 5)$ configuration is to the assumed values of GSD_Q and ICC. Table 8 gives the results of simulations varying ICC from 0.1 to 0.5 while GSD_Q is kept at 4. As would be expected, increasing ICC reduces the fRA_{95} slightly and decreasing the within-cluster correlation improves it. These changes are modest, however.

Table 6. Relative Costs per Scenario for Configurations Yielding Nearly Equivalent 3-Fold Relative Accuracy when GSD = 4 and ICC = 0.3.

N _c	N _m	N	95% Relative Accuracy Bound, fRA_{95} ¹		Total Cost ² when the Fixed to Variable Cost Ratio is:					
			Arithmetic Mean	95 th Percentile	0	1	2	5	10	25
15	1	15	2.8	3.0	15	30	45	90	165	390
9	2	18	2.8	2.9	18	27	36	63	108	243
7	3	21	2.8	3.0	21	28	35	56	91	196
6	4	24	2.8	2.9	24	30	36	54	84	174
5	5	25	2.9	3.1	25	30	35	50	75	150
5	6	30	2.8	3.0	30	35	40	55	80	155
5	7	35	2.7	2.9	35	40	45	60	85	160
4	8	32	3.0	3.1	32	36	40	52	72	132
4	9	36	3.0	3.1	36	40	44	56	76	136
4	10	40	2.9	3.1	40	44	48	60	80	140

¹ Based on 10,000 simulations

² Total relative cost assuming the variable cost per MU, C_{MU}, is equal to 1

Table 9 shows the effect of changes in GSD_Q on fRA_{95} . As was the case with ICC, increasing GSD_Q when ICC is fixed at 0.3 makes fRA_{95} worse and decreasing GSD_Q improves (i.e., decreases) fRA_{95} . Overall, however, the effects of changes in the GSD of ±1 on the 95th percentile of fold relative accuracy do not appear substantial.

Table 10 shows more extreme situations in which both GSD_Q and ICC are perturbed together. As would be expected the worst case is seen when both GSD_Q and ICC increase. The bound on fold relative accuracy for the arithmetic mean and 95th percentile can be nearly 5-fold when GSD_Q=5 and ICC=0.5. On the other hand, when these two variation parameters vary in opposite directions, little change in fRA_{95} will occur. Of course, if both parameters decrease, great improvements in relative accuracy can occur.

Table 11 demonstrates configurations of (N_c, N_m) that would be necessary to achieve 3-fold relative accuracy for the worst-case situation shown in Table 10. It appears that with 5 MUs/cluster, approximately 10 clusters (50 MUs) would be necessary. With 3 MUs/cluster it would take about 12 clusters (36 MUs) to achieve the same degree of accuracy. The relative costs for the configurations in Table 11 are generally double those for the feasible configurations in Table 7.

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Table 7. Expected Relative Costs per Scenario for Nearly Equivalent ‘3-Fold Accuracy’ Configurations using the AHETF-Estimated Cost Ratio Range

N _c	N _m	N	95% Relative Accuracy Bound, fRA_{95} ¹		Total Cost ² when the Cluster to MU Cost Ratio is:			
			Arithmetic Mean	95 th Percentile	4	6.5	8	9
15	1	15	2.8	3.0	75	112.5	135	150
9	2	18	2.8	2.9	54	76.5	90	99
7	3	21	2.8	3.0	49	66.5	77	84
6	4	24	2.8	2.9	48	63	72	78
5	5	25	2.9	3.1	45	57.5	65	70
5	6	30	2.8	3.0	50	62.5	70	75
5	7	35	2.7	2.9	55	67.5	75	80
4	8	32	3.0	3.1	48	58	64	68
4	9	36	3.0	3.1	52	62	68	72
4	10	40	2.9	3.1	56	66	72	76

¹ Based on 10,000 simulations

² Total relative cost assuming the variable cost per MU, C_{MU}, is equal to 1

Table 8. 95% Relative Accuracy Bounds for Lognormal Distribution Parameter Estimates Obtained by Varying ICC when GSD = 4, N_c = 5 and N_m = 5.

Geometric Standard Deviation, GSD	Intracluster Correlation, ICC	95% Relative Accuracy Bound, fRA_{95}		
		Geometric Mean ¹	Arithmetic Mean ²	95 th Percentile ²
4	0.5	2.6	3.5	3.8
4	0.4	2.4	3.2	3.4
4	0.3	2.2	2.9	3.1
4	0.2	2.1	2.6	2.7
4	0.1	1.9	2.4	2.5

¹ Exact calculation

² Based on 10,000 simulations

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Table 9. 95% Relative Accuracy Bounds for Lognormal Distribution Parameter Estimates Obtained by Varying GSD when ICC=0.3, $N_c = 5$ and $N_m = 5$.

Geometric Standard Deviation	Intracluster Correlation	95% Relative Accuracy Bound, fRA_{95}		
		Geometric Mean ¹	Arithmetic Mean ²	95 th Percentile ²
5	0.3	2.5	3.7	3.7
4.5	0.3	2.4	3.3	3.4
4	0.3	2.2	2.9	3.1
3.5	0.3	2.1	2.5	2.8
3	0.3	1.9	2.2	2.4

¹Exact calculation

²Based on 10,000 simulations

Table 10. 95% Relative Accuracy Bounds for Lognormal Distribution Parameter Estimates Obtained by Varying Both GSD and ICC when $N_c = 5$ and $N_m = 5$.

Geometric Standard Deviation	Intracluster Correlation	95% Relative Accuracy Bound, fRA_{95}		
		Geometric Mean ¹	Arithmetic Mean ²	95 th Percentile ²
5	0.5	3.0	4.7	4.7
5	0.1	2.1	3.0	2.9
4	0.3	2.2	2.9	3.1
3	0.5	2.1	2.5	2.9
3	0.1	1.7	1.9	2.0

¹Exact calculation

²Based on 10,000 simulations

On balance, a configuration consisting of 5 clusters with 5 MUs/cluster seems to be a reasonable compromise given the existing variation seen in the current exposure data. Obviously, fewer resources would be necessary when it is felt that the GSD and ICC for normalized exposure can be less than the assumed values of 4 and 0.3, respectively. Smaller sample sizes could also be used when $K > 3$ is considered acceptable. For tighter accuracy requirements, additional samples would be needed. The methods described above can be used, as needed, to determine the sample sizes for other combinations of GSD, ICC, and K.

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Table 11. Expected Range of Relative Costs per Scenario for Nearly Equivalent ‘3-Fold Accuracy’ Configurations when GSD = 5 and ICC = 0.5.

N _c	N _m	N	95% Relative Accuracy Bound, <i>fRA</i> ₉₅			Total Cost ³ when the Cluster to MU Cost Ratio is:			
			Geometric Mean ¹	Arithmetic Mean ²	95 th Percentile ²	4	6.5	8	9
21	1	21	2.0	3.1	3.0	105	157.5	189	210
22	1	22	2.0	3.0	2.8	110	165	198	220
13	2	26	2.1	3.1	3.1	78	110.5	130	143
14	2	28	2.1	3.1	2.9	84	119	140	154
15	2	30	2.0	3.0	2.9	90	127.5	150	165
11	3	33	2.2	3.1	3.0	77	104.5	121	132
12	3	36	2.1	3.1	2.9	84	114	132	144
13	3	39	2.0	2.9	2.8	91	123.5	143	156
10	4	40	2.2	3.1	3.1	80	105	120	130
11	4	44	2.1	3.0	2.9	88	115.5	132	143
10	5	50	2.2	3.1	2.9	90	115	130	140
11	5	55	2.1	2.9	2.8	99	126.5	143	154
10	6	60	2.1	3.0	2.9	100	125	140	150

¹Exact calculation

²Based on 10,000 simulations

³Total relative cost assuming the variable cost per MU, C_v, is equal to 1

C10. The Impact of Unequal Numbers of MUs per Cluster

In the preceding evaluation of sample sizes, it was assumed that each cluster would have exactly N_m monitoring units. As the SAP (SAP, 2007) correctly noted, equal cluster sizes are not always possible, or even desirable, in practice. Therefore, the effect of unequal cluster size on relative accuracy should be considered.

When the number of MUs per cluster varies from cluster to cluster, the variation of the distributional estimates is larger than it would be with equal cluster sizes. For example, if m_i denotes the number of MUs in cluster i then the formula for *fRA*₉₅ for the sample geometric mean given in (10) generalizes to:

$$(12) \quad fRA_{95} = \exp \left\{ 1.96 \ln GSD_{\rho} \sqrt{\frac{ICC \sum m_i^2}{N^2} + \frac{1 - ICC}{N}} \right\}$$

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With the same number of clusters, N_c , and total number of MUs, N , formula (12) will always give a larger value of fRA_{95} whenever $ICC > 0$ and m_i are not all equal. When all $m_i = N_m$, then (12) reduces to (10). This is true for other parameter estimates as well. Table 12 illustrates this negative effect on relative accuracy of unequal cluster size with $N=25$ MUs distributed over $N_c=5$ clusters. These results were obtained using equation (12) for the geometric mean and an unequal-cluster-size version of the simulation approach described in Section C6 above for the arithmetic mean and 95th percentile. When the variation in cluster size is moderate, Table 12 shows that the loss in accuracy is barely discernable within simulation error. Only when the cluster sizes vary more widely (e.g. from 1 to 9 in this example) are losses evident.

Table 12. Loss in Accuracy with Variation in the Number of MUs per Cluster when GSD = 4 and ICC = 0.3.

# Clusters, N_c	# MUs per Cluster	Total # MUs, N	95% Relative Accuracy Bound, fRA_{95}		
			Geometric Mean ¹	Arithmetic Mean ²	95 th Percentile ²
5	5 5 5 5 5	25	2.2	2.9	3.1
5	4 5 5 5 6	25	2.2	2.9	3.0
5	3 4 5 6 7	25	2.3	3.0	3.1
5	1 3 5 7 9	25	2.4	3.2	3.6
5	1 1 5 9 9	25	2.6	3.2	3.7

¹Exact calculation

²Based on 10,000 simulations

However, for sample size determination purposes, there is a simple, practical solution to the potential loss of efficiency with unequal cluster size. Suppose that an acceptable configuration of N_c clusters with exactly N_m MUs in each cluster has been found such that $fRA_{95} = K$. Then, although the actual number of MUs per cluster in an actual design is allowed to vary, we enforce the following restrictions:

- The total number of MUs is no less than $N = N_c \times N_m$
- The number of MUs per cluster is never greater than N_m

Under these conditions, it appears that the resulting fRA_{95} will never exceed K . For the geometric mean, this result follows directly from formula (12). Numerous simulations indicate that this ‘accuracy conservation’ effect also holds for the arithmetic mean and percentiles as well. The accuracy conservation (or AC) effect is illustrated for several configurations in Table 13. All four configurations have $N=25$ total MUs and no cluster has more than 5 MUs. All configurations have fRA_{95} values less than or equal to that obtained with 5 clusters of 5 MUs each. The reason for the AC effect is straightforward: Variation in the cluster sizes reduces accuracy. But because of the two restrictions above, reducing the

number of MUs below 5 makes it necessary to collect additional clusters. The effect of additional clusters more than compensates for the variation in cluster size. This result holds for all levels of intra-cluster correlation. If ICC=0 then all configurations would yield the same fRA_{95} as with equal cluster sizes. As the ICC increases, the benefit of having more clusters is greater and fRA_{95} is much better with more, but unequal-sized, clusters.

The accuracy conservation effect means that a configuration of equal-sized clusters can be assumed in order to establish the total number of MUs and the maximum number of MUs per cluster (i.e., to develop a scenario-specific sampling plan as described in Appendix B). Then, whenever a full set of MUs cannot be obtained for a particular cluster, additional clusters can be used until the total N is achieved. This permits some flexibility in design and/or study conduct at the cluster level.

Table 13. Illustrating the Accuracy Conservation Effect for Unequal Numbers of MUs per Cluster when GSD = 4 and ICC = 0.3.

# Clusters, N_c	# MUs per Cluster	Total # MUs, N	95% Relative Accuracy Bound, fRA_{95}		
			Geometric Mean ¹	Arithmetic Mean ²	95 th Percentile ²
5	5 5 5 5 5	25	2.2	2.9	3.1
6	5 5 5 5 4 1	25	2.2	2.9	3.0
7	5 5 3 3 3 3 3	25	2.1	2.7	2.8
12	4 3 3 3 2 2 2 2 1 1 1 1	25	1.9	2.5	2.6

¹Exact calculation

²Based on 10,000 simulations

C11. Sampling Model for Investigating the Secondary Benchmark Objective

A more precise characterization of the secondary goal first requires that the sampling model (1) be recast in a more general form assuming that log exposure is linearly related to log amount of ai handled:

$$(13) \quad \text{Log } E_{ij} = \alpha + \beta \text{ Log } H_{ij} + C_i + W_{ij}$$

(Note that this model does not state that each individual handler’s exposure is linearly related to amount of ai handled, only that this relationship holds ‘on average’.) The random effects C and W have the same meaning as in (1). If the primary benchmark is based on a normalizing factor other than $A_{ai}H$ then H_{ij} in (13) represents the value of that factor. Of course if non-normalized exposure was used in the primary benchmark then this secondary benchmark would not be relevant.

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When exposure is proportional to amount of ai handled, then $\beta=1$, $\alpha = \text{Log GM}_Q$ and equation (13) reduces to (1). That is,

$$(14) \quad \text{Log } E_{ij} - \text{Log } H_{ij} = \text{Log } Q_{ij} = \text{Log } \text{GM}_Q + C_i + W_{ij}$$

When $\beta=0$, exposure is unrelated to amount of ai handled and (13) simplifies to:

$$(15) \quad \text{Log } E_{ij} = \text{Log}_e \text{GM}_E + C_i + W_{ij}$$

Thus, the difference between a proportional relationship and independence can be reduced simply to whether $\beta=1$ or $\beta=0$, respectively. In this context, then, the secondary goal can be stated more precisely as:

The data should be adequate so that, if the sampling model (13) is approximately true, the null hypothesis $H_0: \beta=0$ will be rejected (in favor of $H_A: \beta>0$) at least 80% of the time when $\beta=1$. Because of symmetry, this is equivalent to saying that the null hypothesis $H_0: \beta=1$ will be rejected (in favor of $H_A: \beta<1$) at least 80% of the time when $\beta=0$.

This secondary benchmark is expressed in terms of a desired power to reject a particular one-sided hypothesis about the regression slope. (A two-sided hypothesis test, probably more familiar to AHED[®] users, would have lower power.) It is important to note that a complementary relationship exists between this pre-data power statement and the expected width of the confidence interval for β . If the hypothesis test for non-zero slope is one-sided with a 5% significance level, then it can be shown that, to a reasonable approximation, the expected difference between the upper and lower limits of the 95% confidence interval for β is:

$$(16) \quad EWCI = \frac{2Z_{0.975}}{Z_{0.95} + Z_{0.8}} = \frac{2 \cdot (1.96)}{(1.64) + (0.84)} = 1.6$$

The quantity Z_p in (16) denotes the P^{th} percentile of the standard normal distribution. If the hypothesis test is two-sided, then 80% power corresponds to an expected confidence interval width of, approximately,

$$(17) \quad EWCI = \frac{2Z_{0.975}}{Z_{0.975} + Z_{0.8}} = \frac{2 \cdot (1.96)}{(1.96) + (0.84)} = 1.4$$

Thus, the secondary benchmark can be expressed as either a target power or as an expected width of the confidence interval. From a pre-data standpoint, the power formulation is more common. However, the observed width of the confidence interval provides a simpler and more intuitive mechanism for post-data assessment of data adequacy than would a corresponding 'post-hoc' power analysis.

In addition to the GSD, ICC, N_c and N_m , the power to discriminate proportionality from independence now also depends on the specific values of a_i handled, H_{ij} . This a_i -configuration has several aspects that need to be considered. Namely:

- the range in the amount of a_i handled and
- the degree of confounding of the amount of a_i handled with clusters

In general, the wider the range in a_i amount the higher the power. Power is also increased when there is a large range in a_i amount within clusters. When clusters have non-overlapping ranges of a_i handled, then cluster effects become confounded with the effects of a_i and power is reduced.

For any given scenario, the relative range in the amount of a_i handled, R_H , is defined to be the ratio of the maximum to the minimum amounts. Obviously, there are an infinite variety of H_{ij} levels that can be specified for any given R_H . For the purposes of investigating power under sampling model (13), however, it is sufficient to consider just two standardized configurations of amount of a_i handled. For both of these configurations it is assumed each of the $N=N_c \times N_m$ MUs have unique amounts of a_i handled and that these levels are equally spaced on a logarithmic scale. That is, if H_{\min} and H_{\max} are the minimum and maximum amounts of a_i handled in the scenario, then $R_H = H_{\max} / H_{\min}$ and the N different a_i levels are:

$$(18) \quad H_{\min}, H_{\min} \times \Delta, H_{\min} \times \Delta^2, H_{\min} \times \Delta^3, \dots, H_{\min} \times \Delta^{N-1} = H_{\max}$$

where

$$(19) \quad \Delta = (R_H)^{1/(N-1)}$$

The difference between these two configurations is how the N a_i amounts are allocated among the N_c clusters. If $H_1, H_2, H_3, \dots, H_N$ denote the ordered values of amount of a_i handled, then the two configurations are defined as follows:

Configuration A (minimum within-cluster variation)

In this configuration the smallest N_m a_i amounts are assumed to be in cluster 1, the next smallest N_m a_i amounts are in cluster 2, and so forth. For example, if $N_c=3$ and $N_m=4$ then configuration A would be:

$$\begin{aligned} \text{Cluster 1} &= (H_1, H_2, H_3, H_4) \\ \text{Cluster 2} &= (H_5, H_6, H_7, H_8) \\ \text{Cluster 3} &= (H_9, H_{10}, H_{11}, H_{12}) \end{aligned}$$

Configuration B (maximum within-cluster variation)

In this configuration, cluster 1 is allocated ai level 1, N_c+1 , $2N_c+1$, etc. Cluster 2 then gets ai level 2, N_c+2 , $2N_c+2$, etc. Again, if $N_c=3$ and $N_m=4$ then configuration B would be:

Cluster 1 = (H₁, H₄, H₇, H₁₀)

Cluster 2 = (H₂, H₅, H₈, H₁₁)

Cluster 3 = (H₃, H₆, H₉, H₁₂)

C12. Calculating the Power to Distinguish Proportionality and Independence

The simulation method for determining the power for rejecting the null hypothesis $H_0: \beta=0$ when $\beta=1$ is as follows:

1. For each of the two configurations of amount of ai handled, simulate a set of exposure data for N_c clusters and N_m monitoring units per cluster using the sampling model defined by (13) above with $\beta=1$.
2. For each set of simulated data, perform a mixed-model regression analysis using model (13) above. Determine if the slope is significantly greater than zero at the 5% level. Also calculate the confidence interval for the slope and determine its width (WCI). Do this for both configurations A and B.
3. Repeat steps 1 and 2 above M times and tally the proportion of times that a significant result is obtained. This proportion is the estimated power to reject $\beta=0$ when $\beta=1$ is true. The average of the M WCI values is the expected width of the confidence interval, EWCI.

C13. Ability of Specific Designs to Distinguish Proportionality from Independence

It is again assumed that the residual GSD (i.e., GSD_Q) is equal to 4 and the ICC=0.3. The simulation method above was implemented in SAS using $M=1,000$. Strictly speaking, the highest power would result when the alternative hypothesis for the test of $\beta = 0$ is one-sided (i.e., $H_a: \beta > 0$). However, users of the data might tend to use a 2-sided hypothesis (i.e., $H_a: \beta \neq 0$) instead. Consequently, power was calculated for both 1-sided and 2-sided tests.

Table 14 lists the powers obtained for different values of R_H when $N_c=5$ and $N_m=5$. When the range of ai handled is only 5-fold there is insufficient power to discriminate between proportionality and independence. The (1-sided test) power for configuration B is considerably better (0.63) but still does not reach 0.8, a conventionally accepted minimum power. As the range of amount of ai handled increases, the power obtained for both configurations increases as well. It is clear, however, that configuration A always has the lower power. Configuration B has a 1-sided test power of 0.82 when R_H is only 8. But the range in ai handled must be nearly 50-fold before acceptable 1-sided-test power is obtained

with configuration A. To obtain adequate 2-sided-test power with configuration A, the range in ai handled needs to be at least 100-fold. This disparity in power between situations A and B is quite reasonable: when clusters have non-overlapping ranges of ai handled, the cluster differences will tend to mask the relationship between amount of ai handled and exposure.

Table 14. Estimated Power¹ for Discriminating a Proportional from an Independence Relationship between Exposure and Amount of AI Handled for Different R_H when N_c=5 and N_m=5.

Relative Range in Amount of AI Handled, R _H	Configuration of AI Levels					
	A: Minimum within-cluster differences			B: Maximum within-cluster differences		
	Power (1-sided test) ²	Power (2-sided test) ³	Mean width of 95% CI ⁴	Power (1-sided test) ²	Power (2-sided test) ³	Mean width of 95% CI ⁴
5	0.26	0.16	4.4	0.63	0.51	2.0
8	0.37	0.23	3.4	0.82	0.72	1.5
10	0.41	0.27	3.1	0.89	0.80	1.4
50	0.76	0.59	1.8	>0.99	>0.99	0.82
100	0.87	0.72	1.5	>0.99	>0.99	0.70
200	0.94	0.83	1.3	>0.99	>0.99	0.61

¹ Based on 1,000 simulations

² 1-sided test of H₀: β=0 vs H_A: β>0 at the 5% significance level when true β = 1.

³ 2-sided test of H₀: β=0 vs H_A: β≠ 0 at the 5% significance level when true β = 1.

⁴ Average width of 95% confidence interval for β

Table 15 gives the results of additional simulations varying N_c and N_m while assuming an order of magnitude range in the amount of ai handled (i.e., R_H=10). These results show that the masking effect of clusters reflected in configuration A could be overcome by increasing the number of clusters. As N_c increases from 5 to 12 the (1-sided test) power for configuration A increases from 0.42 to 0.8. The power for configuration B increases with N_c as well, but it was already quite large. Thus, with R_H=10, it would take 60 monitoring units in 12 clusters to achieve 80% 1-sided test power for both configurations. It would require 16-17 clusters (80-85 total MUs) to get 80% power for 2-sided tests.

US EPA ARCHIVE DOCUMENT

Table 15. Estimated Power¹ for Discriminating a Proportional from and Independence Relationship between Exposure and Amount of AI Handled For Various Combinations of Number of Clusters (N_c) and Number of MUs per Cluster (N_m) when R_H=10.

N _c	N _m	N	Configuration of AI Levels					
			A: Minimum within-cluster differences			B: Maximum within-cluster differences		
			Power (1-sided test) ²	Power (2-sided test) ³	Mean width of 95% CI ⁴	Power (1-sided test) ²	Power (2-sided test) ³	Mean width of 95% CI ⁴
5	5	25	0.41	0.27	3.1	0.89	0.80	1.4
12	5	60	0.80	0.67	1.7	>0.99	0.99	0.90
16	5	80	0.89	0.79	1.4	>0.99	>0.99	0.78
17	5	85	0.91	0.83	1.4	>0.99	>0.99	0.75
5	60	300	0.80	0.68	1.7	>0.99	>0.99	0.40
5	94	470	0.88	0.79	1.4	>0.99	>0.99	0.32
5	95	475	0.89	0.81	1.4	>0.99	>0.99	0.31
16	3	48	0.80	0.69	1.6	0.98	0.97	1.0
19	3	57	0.87	0.78	1.4	0.99	0.98	0.94
20	3	60	0.90	0.82	1.4	0.99	0.99	0.92
18	2	36	0.79	0.70	1.6	0.95	0.90	1.2
19	2	38	0.84	0.74	1.5	0.94	0.90	1.2
22	2	44	0.88	0.79	1.4	0.98	0.95	1.1
23	2	46	0.89	0.81	1.4	0.98	0.95	1.1

¹ Based on 1,000 simulations

² 1-sided test of H₀: β=0 vs H_A: β>0 at the 5% significance level when true β = 1.

³ 2-sided test of H₀: β=0 vs H_A: β≠ 0 at the 5% significance level when true β = 1.

⁴ Average width of 95% confidence interval for β

The simulation results in Table 15 also show that the power can be improved by increasing the number of MUs per cluster (N_m) in lieu of the number of clusters (N_c). However, this approach to improving power is very inefficient. With 5 clusters, it takes N_m=60 monitoring units per cluster to achieve 80% 1-sided test power for configuration A. (An N_m of at least 94 is needed for 2-sided test power.) Obviously, devoting a total of N=5×60=300 monitoring units to a single scenario is quite impractical. This is especially true when only N=60 MUs in 12 clusters would achieve the same power.

US EPA ARCHIVE DOCUMENT

The efficiency of N_c over N_m raises the possibility of reducing the total N by using more clusters with fewer MUs per cluster. Table 15 shows that when $R_H=10$, adequate (1-sided test) power can be obtained for configuration A with $N=36$ monitoring units if there are 18 clusters and 2 MUs/cluster. Note, however, that when the size of the cluster (N_m) decreases, the power for configuration B also decreases, albeit only slightly.

These examples illustrate that acceptable power to discriminate between proportionality and independence can be attained with $N_c=5$ and $N_m=5$ if R_H is nearly two orders of magnitude. This range could be as small as one order of magnitude if the ai-configuration is closer to B than to A. Increasing the number of clusters would improve power, but little advantage is realized by increasing the number of MUs/cluster.

In practice, exact control over the amount of ai handled (or another normalizing factor) is difficult. Consequently, the spacing of amount of ai handled will only be approximately logarithmic and configurations will be intermediate between A and B. However, as described in Appendix B, scenario and study plans will strive toward configuration B.

C14. Summary

Nested lognormal variance component assumptions were used in a surrogate-sampling model to determine the sample sizes necessary to achieve a 3-fold relative accuracy of distributional parameter estimates. Reasonable values for the geometric standard deviation (GSD_Q) and the within-cluster correlation (ICC) of exposure normalized by the amount of ai handled were obtained from an analysis of existing data. This analysis suggests that values of $GSD_Q=4$ and $ICC=0.3$ are reasonable defaults for both dermal and inhalation exposure. Simulation analyses indicate that $N_c=5$ clusters with $N_m=5$ monitoring units per cluster will achieve the desired benchmark goal and is more cost-effective than other feasible configurations. As long as a cluster size of 5 is not exceeded, the same total number of MUs ($N=25$) will also achieve this same level of relative accuracy even if the number of MUs per cluster varies.

An analogous regression model, along with two assumed configurations for amounts of ai handled, was used to investigate the power for distinguishing between proportionality and independence between exposure and amount of ai handled. An analysis using $GSD_Q=4$ and $ICC=0.3$ indicates that adequate power is possible with 5 clusters and 5 MUs/cluster if (1) the range in amount of ai handled is nearly two orders of magnitude in general or (2) one order of magnitude if there is strong overlap between the ai levels in different clusters.

It must be emphasized that the recommended sample size of 5 clusters with 5 MUs/cluster is considered a 'default' or 'standard' configuration only. It strictly applies only to scenarios without existing data and when the default variability structure (i.e. $GSD=4$, $ICC=0.3$) and benchmark accuracy ($K=3$) is considered reasonable. In other cases, the AHETF will use the simulation techniques described above to develop optimal sampling plans for each scenario it addresses. This will sometimes involve considering some MUs that

already exist (generally that AHETF has acquired or conducted themselves). Other, field-related considerations will contribute to these scenario plans by determining appropriate locations for each cluster, whether or not it is practical for cluster sizes to be the same, and targets for allocating an amount of active handled to each MU in the plan (see Appendix B).

C15. References

Scientific Advisory Panel (SAP) Meeting 2007. Memorandum from M. Christian to A. Lindsay, Acting Director, EPA Office of Pesticide Programs, "Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held January 9 - 12, 2007 on the Review of Worker Exposure Assessment Methods", April 2, 2007.

Chapter III. Standard Operating Procedures (SOPs)

CHAPTER III

STANDARD OPERATING PROCEDURES (SOPs)

PREAMBLE FOR CHAPTER III

The purpose of Chapter III is to provide reviewers with a comprehensive list of Standard Operating Procedures (SOPs) for the Agricultural Handlers Exposure Task Force (AHETF). SOPs are required under Good Laboratory Practice (GLP) regulations in 40 CFR Part 160. The SOPs provide an overriding framework that set forth procedures that AHETF uses to ensure the consistency, quality and integrity of the data generated in its monitoring studies. More detailed information on study conduct is provided in specific GLP study protocols. Protocols take precedence over the SOP if there are potential conflicts.

Several existing SOPs have been modified and several new SOPs (e.g., all SOPs in Chapter 11) have been written to address issues relating to the new 40 CFR, §26 guidelines. Therefore, an unusually high number of SOPs are currently in draft form. These draft SOPs will be finalized after review by EPA and the Human Studies Review Board.

The AHETF SOPs are broadly divided into two groups: Chapters 1 through 6 primarily address administrative issues, and Chapters 7 through 11 primarily address technical study conduct issues. A list of all SOPs is attached, followed by copies of all AHETF SOPs.

Agricultural Handlers Exposure Task Force

STANDARD OPERATING PROCEDURES

CHAPTER 1: ADMINISTRATION (AHETF Only)

AHETF-1.A.0.	ORGANIZATIONAL STRUCTURE
AHETF-1.B.1.	PERSONNEL RESPONSIBILITIES
AHETF-1.C.1.	STUDY DIRECTOR SELECTION
AHETF-1.D.0.	INSPECTIONS OF THE AHETF FACILITIES/DATA
AHETF-1.E.0.	COMMUNICATION DIRECTIVES
AHETF-1.F.0.	POTENTIAL REFERRABLE FINDINGS
AHETF-1.G.0.	EXTERNAL DISTRIBUTION OF AHETF DOCUMENTS

CHAPTER 2: PROTOCOLS (AHETF Only)

AHETF-2.A.0.	STUDY AUTHORIZATION AND APPROVAL
AHETF-2.B.0.	STUDY NUMBER ASSIGNMENT
AHETF-2.C.2.	PROTOCOL DESIGN AND PREPARATION

CHAPTER 3: STANDARD OPERATING PROCEDURES (AHETF Only)

AHETF-3.A.0.	SOP PREPARATION, APPROVAL, MAINTENANCE AND DISTRIBUTION
AHETF-3.B.1.	USE OF AHETF AND CONTRACTOR SOPS

CHAPTER 4: STUDY REPORTS (AHETF Only)

AHETF-4.A.3.	STUDY REPORT PREPARATION
AHETF-4.B.0.	FINAL REPORT ISSUE

CHAPTER 5: QUALITY ASSURANCE UNIT (AHETF Only)

AHETF-5.A.0.	QA PERSONNEL ADMINISTRATION
AHETF-5.B.1.	QAU RESPONSIBILITIES FOR AHETF STUDIES
AHETF-5.C.1.	QAU RECORDS
AHETF-5.D.1.	QA MASTER SCHEDULE
AHETF-5.E.0.	PROTOCOL AND AMENDMENT REVIEW
AHETF-5.F.1.	INSPECTION/AUDIT TYPES AND FREQUENCY
AHETF-5.G.1.	STUDY INSPECTIONS
AHETF-5.H.0.	DATA AUDITS
AHETF-5.I.0.	FACILITY INSPECTIONS
AHETF-5.J.0.	REPORT AUDITS
AHETF-5.K.1.	INSPECTION REPORT DISTRIBUTION

CHAPTER 6: ARCHIVES (AHETF Only)

AHETF-6.A.0.	STORAGE OF RAW DATA
AHETF-6.B.1.	ACCESS TO ARCHIVED DATA
AHETF-6.C.0.	SPECIMEN AND WET SAMPLE STORAGE
AHETF-6.D.0.	ACCESS TO CONFIDENTIAL WORKER INFO

CHAPTER 7: TEST, REFERENCE AND CONTROL SUBSTANCES

AHETF-7.A.0.	TEST, REFERENCE AND CONTROL SUBSTANCE RECEIPT AND SHIPMENT
AHETF-7.B.0.	TEST SUBSTANCE LABELING
AHETF-7.C.1.	DISPOSAL OF TEST SUBSTANCES
AHETF-7.D.0.	TEST SUBSTANCE CHAIN OF CUSTODY
AHETF-7.E.1.	TEST SUBSTANCE ANALYSES

CHAPTER 8: MATRIX SAMPLES

AHETF-8.A.3	WHOLE BODY SAMPLING - INNER DOSIMETERS
AHETF-8.B.4.	HAND WASH SAMPLES
AHETF-8.C.3.	DERMAL FACE/NECK WIPE SAMPLES
AHETF-8.D.2.	COLLECTION OF AIR SAMPLES USING OVS TUBES
AHETF-8.E.4.	FORTIFICATION OF MATRIX SAMPLES
AHETF-8.F.4.	SAMPLE IDENTIFICATION
AHETF-8.G.2.	WORKER CLOTHING ACCEPTABILITY CRITERIA
AHETF-8.H.2.	HEAD PATCH SAMPLES
AHETF-8.I.3.	FOOT SAMPLING - SOCKS
AHETF-8.J.1.	LAUNDERING OF DOSIMETER MATERIALS

CHAPTER 9: DOCUMENTATION

AHETF-9.A.0.	DEFINITION OF LOD AND LOQ
AHETF-9.B.0.	FORMATTING FOR TABULAR PRESENTATION
AHETF-9.C.4.	NUMERICAL FORMATTING AND HANDLING
AHETF-9.D.0.	ANALYTICAL METHOD NUMBER ASSIGNMENT
AHETF-9.E.0.	RAW DATA COLLECTION
AHETF-9.F.0.	DATA CORRECTIONS
AHETF-9.G.0.	RAW DATA HANDLING
AHETF-9.H.0.	PREPARATION OF TRUE COPIES
AHETF-9.I.0.	PHASE REPORT TEMPLATE

CHAPTER 10: FIELD STUDY PROCEDURES

AHETF-10.A.0.	ROTAMETER CALIBRATION
AHETF-10.B.1.	PACKING, HANDLING, AND SHIPPING OF SAMPLES
AHETF-10.C.3.	WORKER AND STUDY OBSERVATIONS
AHETF-10.D.0.	APPLICATION EQUIPMENT OPERATION VERIFICATION
AHETF-10.E.2.	WORKER SAMPLE COLLECTION SEQUENCE

AHETF-10.F.1. GPI ELECTRONIC DIGITAL METER
AHETF-10.G.1. PERSONAL AIR SAMPLING PUMP CALIBRATION

CHAPTER 11: HUMAN SUBJECT MANAGEMENT

AHETF-11.A.0. ETHICAL REQUIREMENTS FOR THE USE OF HUMAN SUBJECTS
AHETF-11.B.0. RECRUITMENT OF STUDY VOLUNTEERS AND INFORMED CONSENT
AHETF-11.C.0. WORKER HEALTH STATUS
AHETF-11.D.0. PREGNANCY TESTING
AHETF-11.E.0. PESTICIDE SAFETY PRECAUTIONS
AHETF-11.F.0. ADVERSE EVENTS REPORTING FOR IRBS
AHETF-11.G.0. IDENTIFICATION AND CONTROL OF HEAT STRESS
AHETF-11.H.0. EMERGENCY PROCEDURES FOR HUMAN SUBJECTS

Total Available SOPs: 68

SOPs listed in **BOLDFACE** are draft versions.
SOP Chapters 1-6 are designated “AHETF Administrative SOPs” for internal use only. They are not distributed to outside parties and may not be included in contractor SOP manuals.

Organizational Structure
Chapter 1: Administration
AHETF-1.A.0.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>Michael Sandert</u>	DATE <u>01-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) provides a description of the Agricultural Handlers Exposure Task Force (AHETF) and background information, including committee structure.

2.0 INTRODUCTION

- 2.1 The AHETF is a Limited Liability Corporation (LLC) of agrochemical companies involved in the generation of data for mixer/loader and applicator (M/L/A) exposures associated with pesticide use for/during agricultural practices. Information is being collected to satisfy US Environmental Protection Agency (EPA), Pest Management Regulatory Agency (PMRA), and California Department of Pesticide Regulation (CDPR) regulatory requirements.

3.0 ORGANIZATION

- 3.1 The AHETF consists of several manufacturers and formulators of agricultural pesticides. Representatives from member companies are available to participate in the planning, execution, and evaluation of the field exposure studies.

SOP AHETF-1.A.0.

- 3.2 The AHETF is composed of Administrative and Technical Committees, plus several Subcommittees.
- 3.3 The Technical Committee serves as the Testing Facility for the studies performed. It is the portion of the Task Force that is subject to Good Laboratory Practice (GLP) regulations. The Technical committee is subdivided into several subcommittees, that will be established as needed.
- 3.4 Representatives from member companies participate in various committees and subcommittees, each with a chosen chair.
- 3.5 The AHETF itself will be the sponsor for all studies and other projects performed. Individual companies that comprise the Task Force are considered sponsor representatives, with designated individuals participating on Task Force committees. Should a company disassociate itself from the AHETF prior to completion of all work, that company will no longer be considered a sponsor representative.
- 3.6 A Technical Committee Manager for the AHETF will be designated. Responsibilities include approval of AHETF SOPs, as needed, contractor oversight, protocol approval, and signing final reports as the official sponsor representative. Please refer to SOP AHETF-1.B.
- 3.7 Representatives of the AHETF may provide technical assistance on AHETF studies and other projects, as necessary. Such individuals will not serve in an official capacity in making decisions regarding the conduct of the study.
- 3.8 A third-party quality assurance unit will oversee the operations of the studies and provide the necessary Good Laboratory Practice (GLP) oversight and support, which will include facility inspections, GLP training, study inspections, data audits, and report reviews. Please refer to SOP AHETF-5.C.
- 3.9 Contract laboratories will be used for the conduct of field work (e.g., application, sample collection) and analytical work (e.g., sample analysis) as needed for each study.

Personnel Responsibilities
Chapter 1: Administration
 AHETF-1.B.1.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: February 1, 2003	Previous Version Number: 1.B.0

US EPA ARCHIVE DOCUMENT

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) defines the roles and responsibilities of personnel participating in studies conducted for the Agricultural Handlers Exposure Task Force (AHETF). This may include contracted personnel who directly oversee the conduct of a study, or phase of a study.
- 1.2 This SOP was revised to modify section 6.0 to define Principal Field Investigator and Principal Analytical Investigator, and to add section 7.0 to describe the required ethics training for AHETF personnel.

2.0 RESPONSIBILITIES

- 2.1 The Task Force member companies and contracted companies will provide the appropriate personnel to manage, conduct, and monitor all regulated studies and other projects.
- 2.2 The AHETF is both the study Sponsor and testing facility. Independent companies that are members of the Task Force are sponsor representatives. They will assure compliance with the following requirements. Please refer to SOP AHETF-1.A.

3.0 TESTING FACILITY (AHETF) MANAGEMENT

- 3.1 The testing facility management for the AHETF consists of member company representatives serving on various committees and subcommittees, with various levels of responsibility and in various capacities.
- 3.2 There will be chosen representatives who will be the primary management contacts for the AHETF. These positions will be the Technical Committee Chair, the Technical Committee Vice-Chair, the Task Force Manager, and the Subcommittee Chairs.
- 3.3 As required by the EPA GLPs, § 160.31, the testing facility management shall:
 - a. designate the Study Director.
 - b. Replace the Study Director promptly, when necessary during the conduct of the study.
 - c. Assure that there is an independent QAU.
 - d. Assure that the test, control, and reference substance(s) or mixture(s) have been appropriately tested for identity, strength, purity, stability, and uniformity, as applicable.
 - e. Assure that personnel, resources, facilities, equipment, materials, and methodologies are available as scheduled.
 - f. Assure personnel clearly understand the functions they are to perform via the study protocol, SOPs, and memoranda.
 - g. Assure that corrective actions are taken, as necessary, for all GLP regulation deviations reported by the QAU, and documented.

4.0 AHETF TASK FORCE MANAGER

- 4.1 A designated individual will serve as the Task Force Manager for the AHETF. This person may be consulted regarding study conduct by the participants listed above, and may serve as an arbiter to settle issues involving AHETF studies.
- 4.2 The Task Force Manager, as well as the Study Director, has the authority to terminate an AHETF study that no longer has interest to the AHETF, or has been compromised (scientifically or through regulatory misconduct) by the contractor(s).
- 4.3 One individual will be assigned by AHETF management as the Task Force Manager, who will authorize study protocols, approve SOPs, oversee the contracting of third-party companies for studies and other projects, and provide overall study coordination until study completion and archiving. The Task Force Manager is a representative of AHETF management.

5.0 STUDY DIRECTOR

- 5.1 Good Laboratory Practice Standards require that a single person assume responsibility for the conduct of a study. Responsibilities, as defined in the GLPs, §160.33, apply to the scope of the AHETF Study Director's involvement in assigned studies. The Study Director shall assure that:
 - a. The protocol, including any change, is approved - in writing by the Study Director and sponsor's representative - and followed.
 - b. All experimental data are recorded and verified.
 - c. Unforeseen circumstances that may affect the integrity of the study are noted as they occur, and corrective action is taken and documented.
 - d. Test systems are as specified in the protocol.
 - e. All applicable good laboratory practice regulations are followed.

SOP AHETF-1.B.1.

- f. All raw data, documentation, protocols, specimens and final reports are transferred to the archives during or at the close of the study.
 - g. Specific responsibilities are assigned to AHETF personnel, contracted Principal Investigators, or other designees, as necessary.
 - h. The progress of the field and analytical portions of AHETF studies, including the preparation of each final report, are monitored and the AHETF Management is informed of progress ^{and}/_{or} problems.
- 5.2 The AHETF Study Director will be contracted to oversee the field and analytical phases of each AHETF study. Please refer to SOP AHETF-1.C.

6.0 PRINCIPAL INVESTIGATORS

- 6.1 For each field and laboratory study, contractor facility management may assign a person to fulfill the role of principal investigator (PFI: Principal Field Investigator; PAI: Principal Analytical Investigator), as necessary. The PFI's and PAI's responsibility involves direct communication with the AHETF Study Director. The PFI/PAI may have direct and immediate responsibility over an AHETF study in the absence of the Study Director or designated AHETF member.
- 6.2 In situations where several contractors are participating on an AHETF study, each contractor will designate its own PFI/PAI who will coordinate with the Study Director.

7.0 ETHICS TRAINING FOR RESEARCHERS

- 7.1 Researchers that participate in the study and interact with study participants must undergo ethics training.

SOP AHETF-1.B.1.

- 7.2 The training shall include successful completion of the course from the National Institutes of Health (NIH; Human Participant Protections Education for Research Teams) and/or the Basic Collaborative IRB Training Initiative Course (CITI; The Protection of Human Research Subjects). There are links to both of these on-line training courses at www.wirb.com (start with link at bottom of home page called Training Requirements).
- 7.3 Copies of the certificates of completion for the ethics courses will be included in the raw data and in the respective personnel files.

Study Director Selection
Chapter 1: Administration
 AHETF-1.C.1.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: February 1, 2003	Previous Version Number: 1.C.0

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes the procedure to follow for selecting a Study Director for the Agricultural Handlers Exposure Task Force (AHETF) exposure studies.
- 1.2 The SOP was revised to include specific ethics training requirements for AHETF Study Directors in section 3.3.

2.0 SELECTION PROCEDURE

- 2.1 The AHETF management will choose a third-party consultant or company representative to serve as the Study Director for each regulated study. The person chosen will have appropriate qualifications and experience with the particular type of study he/she will be responsible for.
- 2.2 Should the chosen person be unable to fulfill the responsibilities assigned, the AHETF management will choose an appropriate replacement.

US EPA ARCHIVE DOCUMENT

SOP AHETF-1.C.1.

3.0 DOCUMENTATION

- 3.1 A single Study Director will be identified in each Sponsor-approved protocol. Any change in the Study Director will be noted in a written protocol amendment.
- 3.2 Each Study Director shall maintain training records that shall be available for review.
- 3.3 Each assigned Study Director will be responsible for the items listed in SOP AHETF-1.B, 40 CFR Part 26, and 40 CFR Part 160, §160.33.

Inspection of AHETF Facilities/Data**Chapter 1: Administration**

AHETF-1.D.0.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>Melvin Shaudert</u>	DATE <u>01-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) establishes guidelines for the Agricultural Handlers Exposure Task Force (AHETF) to follow when an outside agency (e.g., US EPA) or a member company conducts an inspection or review of a study, Archives, ^{and}/or the AHETF data and reports.

2.0 INTRODUCTION

- 2.1 Good Laboratory Practice Standards require the Agricultural Handlers Exposure Task Force to permit authorized representatives of federal agencies to inspect the testing facility at reasonable times and in a reasonable manner. The Agricultural Handlers Exposure Task Force is considered the testing facility. This includes all contracted facilities and laboratories that perform study functions (*i.e.*, field operations, sample analysis, data storage) for the AHETF.

3.0 NOTIFICATION OF PENDING INSPECTION

- 3.1 Upon notification of an impending inspection, contacted personnel will inform the AHETF Management.
- 3.2 AHETF management will notify appropriate personnel of the pending inspection. This includes the Study Director, the Quality Assurance Unit (QAU), and appropriate AHETF members and contractors.

4.0 PREPARATION FOR INSPECTION

- 4.1 Upon arrival of an outside inspector(s), the management designated AHETF representative will greet the inspector(s). A representative of the AHETF QAU should be present for all inspections. Appropriate personnel (*e.g.*, AHETF management, contract facility management, *etc.*) will be notified of the inspector's arrival.
- 4.2 An inspector(s) may not enter the AHETF designated facilities without an escort. The designated escort must remain with the inspector(s) at all times (within reason) during the inspection. The escort may be a representative of the AHETF or of the contract facility.
- 4.3 The inspector(s) will be taken to a neutral room (or office with limited access) or designated staging area (field sites) and asked to:
 - a. State the purpose of the visit
 - b. Show his/her credentials, as appropriate
 - c. Present a written note of inspection, as appropriate
- 4.4 An outline of the inspection should be discussed with AHETF representatives and the QAU in order to facilitate the process and control the length of the inspection.
- 4.5 The inspector(s) should be informed of this AHETF inspection policy.

5.0 DURING EPA INSPECTIONS

- 5.1 All AHETF personnel and contractors should cooperate with the inspector(s) and answer any questions asked. However, if a representative or contractor employee is asked a question which he/she is not qualified to answer, he/she **must not** attempt to answer but refer the inspector(s) to qualified AHETF personnel, such as the Study Director, Management/Sponsor Representative, QAU, *etc.*
- 5.2 Only specified studies will be audited; therefore, information related to other studies should not be offered.
- 5.3 EPA inspectors do not have authorization to review the following information:
 - a. Quality Assurance Unit documents that report inspection/audit findings and actions recommended and taken.
 - b. Personnel records other than those for training and qualifications.
 - c. Financial records.
- 5.4 The inspector(s) shall not be offered or given anything of value, no matter how small, for his/her personal use.

Communication Directives
Chapter 1: Administration
AHETF-I.E.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>Michael Staudat</u>	DATE <u>01-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) establishes the pathways to relay information between contacted facilities and technical advisors to the Agricultural Handlers Exposure Task Force (AHETF) management and Study Directors for all AHETF studies.
- 1.2 This SOP also addresses official communication between the AHETF and regulatory agencies and industry professionals.

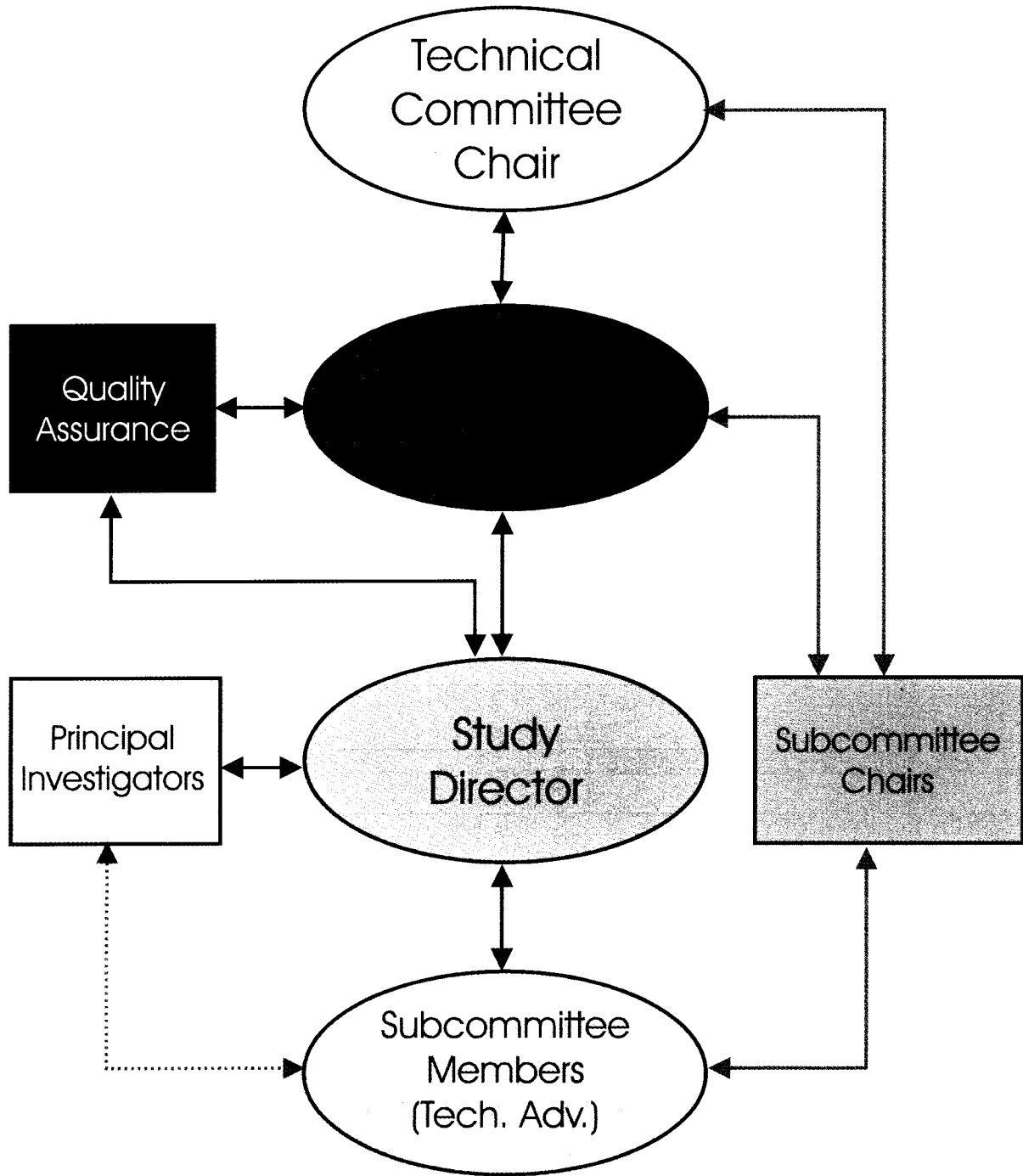
2.0 COMMUNICATION PROCESS

- 2.1 It is imperative that the Study Director and Task Force Manager (TFM) be kept informed of study progress, delays, and compliance issues. All decisions regarding the conduct of the study must be made and documented by the Study Director and Task Force Manager, who is the designated official Sponsor Representative.
- 2.2 Any changes regarding the design, conduct, or cost of an AHETF study must be discussed and approved by the Technical Committee Chair after consultation with the appropriate Subcommittee chairs, Task Force Manager, and/or Study Director.
- 2.3 The Study Director will provide regular updates on the progress of AHETF studies to the Task Force Manager. In turn, the TFM will inform the Study Director of situations that may be a concern to the Task Force.

SOP AHETF-1.E.0.

- 2.4 The Study Director will relay decisions made by AHETF management to individual contractors and subcommittee personnel. The TFM will provide this information when the Study Director is unavailable.
- 2.5 The Subcommittee Chairs will relay information to the Task Force Manager.
- 2.6 The principal investigators or contract facility management will relay information to the Study Director and/or TFM.
- 2.7 Study Monitors (field and analytical) will provide technical information to the Study Director.
- 2.8 Communication between subcommittee personnel (technical advisors) and laboratory/facility personnel may occur, but information must be relayed to the Study Director.
- 2.9 The following flowchart graphically illustrates the communication pathways of the AHETF.

AHETF Communication Pathways



Potential Referable Findings
Chapter 1: Administration
 AHETF-1.F.0.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: N/a	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) defines the policy for reporting to EPA potential adverse findings related to an AHETF study as required by FIFRA Section 6(a)(2).

2.0 DEFINITIONS

- 2.1 Study Director – The consultant who is appointed by the AHETF as the Study Director of a field exposure study as defined in the GLP regulations. The Study Director is responsible for the conduct of the study, reviewing the data as they become available and writing the final report.
- 2.2 Field Monitor – The AHETF member representative who is assigned to assist the Study Director and provide oversight to a specific field exposure study.
- 2.3 Adverse Effects Screening Subcommittee – The Subcommittee that will be the first point of contact when a potential adverse effect is identified. This Subcommittee will decide if the potential adverse effect should be referred to the Potential Referable Findings Review Subcommittee.

US EPA ARCHIVE DOCUMENT

SOP AHETF-1.F.0.

- 2.4 Potential Referable Findings Review Subcommittee – The Subcommittee that will decide if a potential adverse effect should be reported to EPA and, if so, will direct the preparation of the submission. The Subcommittee consists of:
- a. Members of the Adverse Effects Screening Subcommittee
 - b. Administrative Committee chair
 - c. Technical Committee chair
 - d. Field Studies Subcommittee chair
 - e. Registrant representative of the relevant test material (in the case of multiple registrants of a test material or a product-specific task force, a representative from each)
 - f. Task Force counsel
- 2.5 New findings – This is any potentially adverse data that are generated by AHETF and are not presently covered in PHED or in previously submitted studies.

3.0 BACKGROUND INFORMATION

- 3.1 EPA rules under FIFRA Section 6(a)(2) concerning the reporting of potential adverse findings was revised on September 19, 1997 as referenced in 62 FR 49370; 63 Fed. Reg. 33580 (June 19, 1998). These rules describe EPA's interpretation of the requirements for pesticide registrants to submit information to EPA concerning adverse effects to the environment, wildlife and human health from their products. The rule applies to registrants, including any employee, agent or other person acting for the registrant.
- 3.2 There is no requirement for AHETF to submit a 6(a)(2) report since the Task Force is not a registrant. However, the AHETF may make a 6(a)(2) submission on behalf of all Task Force members when the finding involves AHETF studies and results.
- 3.3 If AHETF discovers a potential adverse finding during the course of field testing or data analysis that falls within the definition of FIFRA 6(a)(2), or an analogous State law, AHETF will report the finding in accordance with EPA and State requirements, as applicable. For exposure monitoring studies, if the results show a higher level of risk or exposure than would be expected from prior reports, data, etc., then a potential adverse finding may exist.

SOP AHETF-1.F.0.

- 3.4 There are three reporting times (15 days, 30 days, and 3 months). The more common is 30 days after an incident occurs in the field, 30 days after the final report is signed, or 30 days after the results are known which applies when there is a potential serious finding.
- 3.5 It may be necessary, depending on circumstances, either for the registrant of the test material or a representative from multiple registrants to report a potential referable finding directly, rather than AHETF reporting on their behalf.
- 3.6 Any AHETF member has the right to submit their own 6(a)(2) letter if they wish, without regard to whether it agrees with the determination of AHETF.
- 3.7 Regarding the use of surrogate compounds, the AHETF, on the advice of the Potential Referable Finding Review Committee is at liberty, without liability, to report findings under FIFRA 6(a)(2). Prior to reporting, the AHETF shall raise issues and discuss them with registrant(s) of the surrogate compound.
- 4.0 PROCEDURES FOR IDENTIFYING AND REPORTING POTENTIAL REFERABLE FINDINGS**
- 4.1 Purchase of Existing Data
- If data have been previously submitted to EPA (and state agencies where applicable), they are not considered “new” and are not Referable Findings.
 - If a Potential Referable Finding issue is identified during data review, the technical subcommittee should bring it to the attention of the registrant(s) of the study test material for resolution.
 - It will be the responsibility of the registrant(s) to report Potential Referable Findings.
- 4.2 Incidents that Occur During the Conduct of a Study (active ingredient-specific findings)

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- a. It will be the responsibility of the Study Director, Field Monitor, field contractor, and any other individuals involved with the field exposure study to identify and promptly report any potential adverse effects during the conduct of the study to the Adverse Effects Screening Subcommittee and the registrant(s) of the surrogate active ingredient.
- 4.3 Data Generated Under Sponsorship of the AHETF that Affects the Surrogate Compound (active ingredient-specific findings)
- a. It is the responsibility of the Study Director, or any other Task Force personnel who are reviewing the study data, to keep the registrant(s) of the surrogate compound informed of the results.
 - b. If there is a potential adverse effect that might affect the registration of the surrogate compound only, it will be the responsibility of the registrant(s) to file a Potential Referable Finding report with the EPA and applicable states.
- 4.4 Data Generated Under Sponsorship of the AHETF that Could Potentially Affect All Member Products (non-active ingredient-specific finding)
- a. Data that could potentially affect all member products would include circumstances where the exposure data exceed what would be derived from a specific scenario in the Pesticide Handlers Exposure Database (PHED), other previously submitted data, or that are defined as “new findings”.
 - b. It is the responsibility of the Study Director, or any other Task Force personnel who are reviewing the study data, to identify and report any potential adverse effects to the Adverse Effects Screening Subcommittee.
 - c. The Adverse Effects Screening Subcommittee will be the first point of contact to evaluate whether a potential adverse effect may be referable. If so, then the matter will be referred to the Potential Referable Finding Review Subcommittee.
 - d. The Potential Referable Finding Review Subcommittee will determine whether a potential adverse effect will be reported to the EPA and any applicable states and, if so, will direct the preparation of the Potential Referable Findings submission.

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- e. The AHETF Administrative and Technical Committee representatives will be informed in writing of the Potential Referable Finding and the recommendation of the Potential Referable Finding Review Subcommittee. The Task Force representatives will have an opportunity to ask questions and express their opinions during a subsequent conference call or meeting.

External Distribution of AHETF Documents

Chapter 1: Administration
AHETF-1.G.0.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: N/a	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

1.1 This Standard Operating Procedure (SOP) defines the policy for reporting the results from an exposure study conducted by the Agricultural Handlers Exposure Task Force (AHETF) to non Task Force members, government agencies, or other interested parties.

2.0 BACKGROUND

2.1 The Agricultural Handlers Exposure Task Force Limited Liability Company (AHETF) ¶ 15.4 states that:

“All Task Force studies shall be regarded as confidential proprietary data. No Member shall submit or permit the submission of Task Force studies to any individual or governmental authority without first confirming that the individual or authority will recognize the proprietary character of Task Force studies”.

2.2 Notwithstanding this AHETF LLC prohibition, however, AHETF studies filed with the U.S. Environmental Protection Agency are available for disclosure under § 10(g) of the Federal Insecticide, Fungicide, and Rodenticide Act to anyone who is not an employee or agent of a foreign or multinational pesticide producer. Furthermore, the AHETF has interest in making its data available for use by public and other researchers and educators so long as such use does not place the studies into the public domain or otherwise enable their uncompensated use by third parties to support pesticide registrations.

SOP AHETF-1.G.0.

- 2.3 To this end, the AHETF has prepared this draft Policy and Procedures for Distribution of AHETF Information for consideration by the Administrative Committee. In essence, the Policy authorizes disclosure of AHETF data to specific categories of requestors subject to confidentiality agreements.

3.0 AHETF DATA CATEGORIES

- 3.1 Generic study documents (protocols, report templates, technical Standard Operating Procedures, etc.)
- 3.2 Outreach materials (published papers, articles to trade magazines, etc.)
- 3.3 Individual submitted reports
- 3.4 Individual internal reports
- 3.5 White Papers
- 3.6 AHED™ software without data
- 3.7 AHED™ with data

4.0 REQUESTORS

- 4.1 Government Regulatory Agencies
 - a. U. S. Environmental Protection Agency
 - b. Canada's Pest Management Regulatory Agency
 - c. California Department of Pesticide Regulation
 - d. U. S. Department of Agriculture
- 4.2 State Agencies, Other than CDPR
 - a. State regulatory agencies
 - b. State departments of agriculture
 - c. Universities

SOP AHETF-1.G.0.

4.3 Other Groups

- a. Independent organizations involved in research and/or education
- b. Member companies including affiliates and consultants
- c. Anyone not fitting into the other categories

5.0 POLICY ON PROVIDING INFORMATION

5.1 The following chart outlines the AHETF policy for data/information release:

	State Agencies and Independent Groups	Member, Affiliates and Consultants
Outreach	Upon Request	
Generic	If no objections from Admin Committee	Upon Signed Agreement with Member Company
Submitted Reports	Upon Approval of the Administrative Committee and Signed Agreement	
Internal Reports		
White Papers		
AHED™ w/o Data		
AHED™ with Data		
Other Materials		

6.0 APPROVAL AND SUPPLY OF INFORMATION

6.1 All requests for reports and outreach materials will be directed to the Task Force Manager for processing in accordance with these procedures.

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SOP AHETF-1.G.0.

- 6.2 Outreach materials will be provided upon request without further approval.
 - 6.3 Requests for all other materials must be in writing with an explanation about how the information will be used.
 - 6.4 The Manager will forward these requests to the Administrative Committee representatives for review.
 - 6.5 Requests for generic documents (protocols, SOPs and report templates) will be provided if no Administrative representatives files an objection. If anyone files an objection, the request will be referred to the entire Administrative Committee for resolution.
 - 6.6 Requests for reports that have been submitted to the regulatory agencies and/or AHED™ must be approved by the Administrative Committee and conform to the terms of the Joint Data Development Limited Liability Corporation Agreement.
 - 6.7 Confidentiality Agreements (such as the model agreement attached thereto, “Confidentiality Agreement”) must then be signed by the recipient.
 - 6.8 The Manager will maintain copies of all written requests and a record of all materials provided.
 - 6.9 Copies of Confidentiality Agreements will be sent to CropLife America.
- 7.0 OTHER REQUIREMENTS**
- 7.1 Academic people will be asked to submit manuscripts to the AHETF for review as a courtesy before publication.
 - 7.2 Non-academic people will be required to submit manuscripts for review and approval before publication.
 - 7.3 Publications should acknowledge the AHETF as the source of the data.
 - 7.4 Any request that will evaluate the adequacy of the data for regulatory purposes will not be approved.

SOP AHETF-1.G.0.

- 7.5 Confidentiality Agreements can be modified as needed to address specific requests or limitations imposed by the Administrative Committee.

8.0 CONFIDENTIALITY AGREEMENT

- 8.1 The attached Confidentiality Agreement prevents use of data to support registration and giving the reports/data files to someone else, but allows the reports/data to be cited, used in preparation of education materials, and in research.

Attachment A: Confidentiality Agreement Sample

CONFIDENTIALITY AGREEMENT

THIS CONFIDENTIALITY AGREEMENT is made and entered into as of this ____ day of _____, 2006, by and between the undersigned individual (the "Recipient") and The Agricultural Handlers Exposure Task Force, a Delaware Limited Liability Company (the "AHETF" or "Task Force").

WITNESSETH:

WHEREAS, the Task Force owns studies and data, including but not limited to field exposure studies, analytical studies, database software, surveys, reports, white papers and other information related to such studies, and exposure data furnished to the Task Force by a Task Force Member (the "Member" or collectively "the Members") or third party, and such studies and data are the confidential and proprietary property of the Task Force and its Members;

WHEREAS, the Task Force has a policy and procedure for the distribution of its confidential and proprietary studies and data to interested third parties, upon their request and at no charge, solely for the limited purposes described herein;

WHEREAS, the Task Force wishes to ensure and preserve the confidential and proprietary character of studies and data released to third parties under its policy and procedure; and

WHEREAS, the Recipient agrees to abide by the confidentiality requirements set forth in this AGREEMENT in consideration of his or her use of the Task Force's confidential and proprietary studies and data;

NOW, THEREFORE, in consideration of the foregoing, the parties agree as follows:

1. **Confidential Information.** For purposes of this AGREEMENT, the term "Confidential Information" shall include any and all confidential and proprietary Task Force studies and data, including but not limited to field exposure studies, analytical studies, database software, surveys, reports, white papers and other information related to such studies and data furnished to the Task Force by a Member or third party. "Confidential Information" shall not include (1) information that was, or is, in the public domain at the time of its disclosure by the Task Force to the Recipient; (2) information that becomes part of the public domain after its disclosure by the Task Force to the Recipient through no act or omission on the part of the Recipient; and (3) information that the Recipient receives from a third party who is not under any obligation of secrecy to the Task Force. A list of information provided by Task Force to recipient is attached as Exhibit 1.

SOP AHETF-1.G.0.

2. **Restrictions on Use of Confidential Information.** The Recipient acknowledges and agrees that Confidential Information is proprietary to the Task Force and its Members. The Recipient agrees to use Confidential Information solely and exclusively for the purposes of research and education, including to cite or excerpt the Confidential Information in his or her professional writing and scholarly work. The Recipient agrees not to publish, use or appropriate Confidential Information for any other purpose or reason, without the prior written consent of the Chairman of the Administrative Committee of the Task Force (the "Chairman").
3. **Return of Confidential Information.** Upon the request of the Task Force, the Recipient shall promptly return all Confidential Information (including any copies, extracts, summaries or facsimiles thereof) to the Task Force upon request.
4. **Disclosure.** The Recipient agrees to hold Confidential Information in strict confidence and not to disclose it to any person for any purpose or reason, without the prior written consent of the Chairman.
5. **Right to Injunction.** As a violation by the Recipient of the provisions of this AGREEMENT could cause irreparable injury to the Task Force and its Members, and there is no adequate remedy at law for such violation, the Task Force and its Members shall have the right, in addition to any other remedies available to them at law or in equity, to seek to enjoin the Recipient in a court of equity from violating this AGREEMENT.
6. **Term.** The provisions of this AGREEMENT shall survive for a period of fifteen years from the date of submission of the last Task Force study and data to the United States Environmental Protection Agency.
7. **Governing Law.** This AGREEMENT shall be governed by and interpreted and enforced in accordance with the laws of the State of Delaware.
8. **Waiver.** The waiver by any person of a breach of any provision of this AGREEMENT by the Recipient shall not operate as waiver of any other breach of any provision of this AGREEMENT by the Recipient.
9. **Successors and Assigns.** This AGREEMENT shall inure to the benefit of, and be binding upon, the Recipient, the Task Force, and its Members and their respective successors, heirs, personal representatives, and permitted assigns.
10. **Assignment.** The obligations of the Recipient under this AGREEMENT shall not be assigned.
11. **Severability.** If any term, condition or provision of this AGREEMENT, or the application thereof to any party or circumstance shall, at any time to any extent be invalid or unenforceable, the remainder of this AGREEMENT, or the application of such term, condition or provision to parties or circumstances other than those as to which it is held invalid or unenforceable, shall not be affected thereby, and each term, condition and provision of this AGREEMENT shall be valid and enforceable to fullest extent permitted by law.

SOP AHETF-1.G.0.

IN WITNESS WHEREOF, the parties have executed this AGREEMENT as of the date written above.

RECIPIENT:

Signature

Print Name

Address

Affiliation

THE AGRICULTURAL HANDLERS EXPOSURE TASK FORCE

By: _____
Richard H. Collier, Ph.D.,
Chairman of the Administrative Committee

US EPA ARCHIVE DOCUMENT

Study Authorization and Approval

Chapter 2: PROTOCOLS

AHETF-2.A.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>Mickey Staudert</u>	DATE <u>01-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) outlines how an Agricultural Handlers Exposure Task Force (AHETF) study is authorized and approved. Studies conducted internally or by contract test facilities are addressed in this SOP.

2.0 AUTHORIZATION

- 2.1 The need for a study is dictated by international, federal ^{and/or} state registration or re-registration requirements for information on the potential worker exposure to pesticides, in conjunction with AHETF assessment of the importance and representativeness of the work task, and any existing data. All AHETF studies performed must be authorized by AHETF management.
- 2.2 The designated Study Director will be notified (either verbally or in writing) by the AHETF management of a proposed study. The Study Director or designee will be responsible for the preparation of the study protocol, to be submitted to the AHETF for review.

3.0 STUDY NUMBER ASSIGNMENT

- 3.1 Once an AHETF study has been proposed, a unique study number is assigned by the AHETF Task Force Manager.

4.0 STUDY APPROVAL AND ACCEPTANCE

- 4.1 Each AHETF study will have a protocol approved by the Study Director and Sponsor Management (*i.e.*, Task Force Manager or Technical Committee Chair) in the form of a dated signature.
- 4.2 Each protocol will be acknowledged, in writing, by the AHETF Study Monitors (field and analytical). This acknowledgement may be completed after the protocol has been approved by the Study Director

Study Number Assignment

Chapter 2: PROTOCOLS

AHETF-2.B.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>Michelle Soudant</u>	DATE <u>01-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes how an Agricultural Handlers Exposure Task Force (AHETF) study number is assigned. The Task Force Manager is responsible for tracking and assigning AHETF study numbers.

2.0 RESPONSIBILITY

- 2.1 The assignment of AHETF study numbers will be the function of the AHETF Task Force Manager. This will ensure continuity and enable the AHETF to keep accurate records of the individual studies conducted.

3.0 PROCEDURE

- 3.1 A unique AHETF study number for each study will be assigned and documented. It will consist of a prefix code and a unique, sequential number pair.
- 3.2 The prefix code for AHETF studies is: **AHE**
- 3.3 The sequential identification numbers will begin with "01" and increase by one with each new AHETF study.

SOP AHETF-2.B.0.

- 3.4 The study ID numbers will be assigned as follows:
- a. The Study Monitor, Study Director, or designee will contact the Task Force Manager for assignment of the next number in the study series.
 - b. The Task Force Manager will document the study number assigned and provide the number to the Study Monitor, Study Director or designee.
 - c. A list of study numbers will be maintained by the Task Force Manager or designee to prevent confusion or duplication of study numbers.
- 3.5 Study numbers will be a five (5) character alphanumeric code. The following are examples of typical study numbers:

AHE01	first AHETF study
AHE02	second AHETF study
AHE03	third AHETF study
AHE10	tenth AHETF study

Protocol Design and Preparation

**Chapter 2: PROTOCOLS
AHETF-2.C.2.**

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: January 1, 2006	Previous Version Number: 2.C.1.

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes the content requirements, standard format, responsible personnel, review, and distribution of Agricultural Handlers Exposure Task Force (AHETF) study protocols, which are the written instructions to perform specific experiments investigating exposure to pesticides.
- 1.2 This SOP is for internal administrative use by the AHETF. It is not to be distributed to contractors, unless specific authorization is provided by the AHETF management.
- 1.3 This SOP was revised to incorporate additional protocol elements regarding the use of human subjects in exposure research.

2.0 DEFINITIONS

- 2.1 The EPA GLPs define a study as “any experiment at one or more sites, in which a test substance is studied in a test system under laboratory conditions or in the environment to determine or help predict its effects, metabolism, product performance, environmental and chemical fate, persistence and residue, or other characteristics in humans, other living organisms, or media.” (40 CFR Part 160, August 17, 1989, § 160.3).
- 2.2 A protocol is a written study plan that indicates the objectives and all methods for the conduct of a study.

3.0 PROTOCOL REQUIREMENTS

- 3.1 AHETF protocols must contain (but not be limited to) the following information for GLP compliance and ethics requirements for human testing. Certain GLP and ethics requirements that are not applicable to most studies conducted by/for the AHETF have been taken into account and either modified or omitted, based upon the importance and impact of those requirements.
- a. Descriptive title and objective of the study.
 - b. Identification of the test substance and control or reference substances by name, chemical abstract service (CAS) number or code number.
 - c. Name and address of sponsor (AHETF).
 - d. Name and address of contracted testing laboratories (including field contractors).
 - e. Proposed experimental start and termination dates.
 - f. Justification for selection of test system.
 - g. Procedure for test system identification.
 - h. Description of the experimental design including the methods for the control of bias.
 - i. Each level of the test, control, or reference substance to be administered, expressed in appropriate units.
 - j. The method and frequency of administration of the test, control or reference substance, (*e.g.*, backpack/ knapsack sprayer, granular application, *etc.*), and the reason for its choice.
 - k. The type and frequency of tests, analyses, and measurements to be made.
 - l. The records to be maintained.

SOP AHETF-2.C.2.

- m. Dated signatures of the Study Director and AHETF Sponsor Representative (Task Force Manager, and/or Technical Committee Chair).
 - o. Proposed statistical methods.
 - p. Ethics requirements for human testing as required by 40 CFR, part 26, including but not limited to: recruitment procedures, health and safety issues, remuneration, and inclusion/exclusion criteria.
- 3.2 The Study Director or designee is responsible for preparing protocols for studies under his/her direction according to a standard format to be provided by the AHETF.
- 3.3 All AHETF study protocols will be signed and dated by the Study Director, and Technical Committee Chair or Task Force Manager to initiate the study and indicate Sponsor approval of the protocol. Approval signatures must be obtained from the Study Director before any data collection for that study. The protocol should be acknowledged, either electronically or in writing, by the AHETF Field Monitor and AHETF Analytical Monitor, as appropriate. Monitors do not need to sign the protocol, amendments, or deviations.

4.0 REVIEW PROCESS

- 4.1 Draft protocols will be forwarded to the appropriate AHETF representatives (as noted in section 6.0 and at the Study Director's discretion) and to the AHETF contracted Quality Assurance Unit for review before finalization.
- 4.2 The Study Director will be notified of errors found or requested changes noted during the review process. Appropriate corrections or changes will be returned to the Study Director. The revised copy will be approved (*i.e.*, signed and dated) and distributed to the designated personnel.
- 4.3 The Study Director will submit the final draft protocol, as well as any amendments issued, to a pre-selected Institutional Review Board (IRB) for review prior to finalization and distribution.

SOP AHETF-2.C.2.

5.0 PROTOCOL FORMAT

- 5.1 Details of the protocol must address all of the applicable items in section 3.1. of this SOP. Requests for copies of AHETF protocols may be directed to the Study Director or the AHETF Task Force Manager. Changes to the protocols will be issued according to section 8.0.
- 5.2 A standard design, developed by the Task Force, will be followed when preparing study protocols.
- 5.3 All protocol files must be written in specified word processing program, to be provided to the Task Force upon request. The software that has been selected is the Microsoft® Word® for Windows® (version XP or previous) document processing program. Macintosh® formatted data are not acceptable.
- 5.4 All signed pages will be optically scanned separately and stored in PDF® format. These signed pages need to be inserted into the final phase report file.
- 5.5 Electronic submissions to the EPA must be in Adobe® Acrobat® PDF format version 5.0. Later versions of Acrobat® may be used; however, the output must be in the 5.0 format.

6.0 DISTRIBUTION OF STUDY PROTOCOLS

- 6.1 The original AHETF study protocol, and any amendments, will be submitted to the sponsor-contracted QAU for review. Before study completion, the original protocol, amendments and deviations, if applicable, will be forwarded to the AHETF Archives. The following is the distribution list for protocols and amendments, as appropriate:
 - a. Study Director (maintain original)
 - b. AHETF Study Monitor, (field or analytical, as appropriate)
 - c. AHETF Task Force Manager
 - d. AHETF Technical Committee Chair
 - e. AHETF contracted Quality Assurance Unit (copy during study)

SOP AHETF-2.C.2.

- f. AHETF Subcommittee Chairs (as applicable)
- g. Principal Investigator(s)
- h. AHETF Study Archive File (original to archives upon completion)
- i. Other appropriate government or regulatory agencies as required.

7.0 Protocol Amendments

- 7.1 A change of Study Director or any planned change or revision to an AHETF protocol is issued as a protocol amendment. The reason for the change(s) or revision(s) and the effective date(s) of each revision is documented in the amendment.
- 7.2 The contract principal investigator or facility management will notify the AHETF Study Director of any procedures or items in an AHETF protocol that may need to be revised, added, or deleted. The Study Director will prepare and distribute the amendment(s).
- 7.3 The Study Director will prepare the amendment(s), and will allow the AHETF Study Monitor(s), Task Force Manager and sponsor-contracted QAU to review it before finalization, if possible. Amendments will be sent to the reviewing IRB as well (see section 4.3.)
- 7.4 All protocol amendments will be approved by the AHETF Study Director and Task Force Manager, by a dated signature. The appropriate AHETF Study Monitor will acknowledge the amendment as described in section 3.3. Distributions of the original amendment and copies will be followed as outlined in section 6.1 of this SOP.
- 7.5 Protocol amendments are sequentially numbered according to the date of issue. The first amendment issued for a study is AHETF Protocol Amendment No. 1. The second protocol amendment issued is AHETF Protocol Amendment No. 2, and so on.

SOP AHETF-2.C.2.

8.0 PROTOCOL DEVIATIONS

- 8.1 Whenever a deviation from the protocol occurs, the Study Director must be notified of the deviation. The AHETF Study Director is responsible for the documentation of any protocol deviation noted for their study.
- 8.2 The Study Director is required to document the nature of the deviation, date(s) of occurrence, reason for the deviation, effect on the study, and any corrective actions (if any) on an appropriate form or in the raw data. The deviation must be written in a timely manner and acknowledged with the dated signature of the Study Director.
- 8.3 The Study Director shall notify the appropriate AHETF Study Monitor and QAU of all deviations as soon as practicable.
- 8.4 All protocol deviations will be approved by the AHETF Study Director and Task Force Manager, by a dated signature. The appropriate AHETF Study Monitor will acknowledge any deviation as described in 3.3. Distributions of the original deviations and copies will be followed as outlined in section 6.1 of this SOP.

SOP Preparation, Approval, Maintenance, and Distribution
Chapter 3: Standard Operating Procedures
AHETF-3.A.O.

Effective Date : February 1, 2003

APPROVAL <u><i>David Johnson</i></u>	DATE <u>01-22-03</u>
APPROVAL <u><i>Mickey Staudert</i></u>	DATE <u>01-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) provides guidelines for the preparation, revision, distribution and maintenance of the Agricultural Handlers Exposure Task Force (AHETF) Standard Operating Procedures and SOP Manuals.

2.0 INTRODUCTION

- 2.1 A Standard Operating Procedure is the written instruction for performing a common, repetitive procedure. An SOP provides instruction for a procedure that is repeated without significant variations in the normal course of several studies.
- 2.2 Procedures specific to one study should not be formatted as an SOP, but should be documented in the study record or protocol as a study specific procedure.
- 2.3 The contents of all SOPs will be adequate to insure the continuity and direction of operations. All SOPs will provide sufficient detail to accurately describe procedures and methods. The SOP will be written to provide references for experienced personnel, and as a training tool for new personnel.

SOP AHETF-3.A.0.

3.0 FORMAT

- 3.1 The SOP manual contains several chapters based on a topic (*e.g.*, study reports, protocols, *etc.*). Each chapter is divided into individual SOPs and sections (specific items within an SOP).
- a. Chapters are designated by a number and title (example: Chapter 3: Standard Operating Procedures).
 - b. SOPs within a chapter are designated by a letter and title (example: SOP 3.A.: SOP Preparation, Approval, Maintenance and Distribution).
 - c. Sections within an SOP are enumerated using a decimal format (*e.g.*, 3.1). If necessary, lowercase letters can be used to emphasize additional points under subsections.
- 3.2 SOPs will be identified by the chapter number and section letter, preceded by the prefix "AHETF-", which will identify the SOP as property of the Agricultural Handlers Exposure Task Force. The revision number will be the third digit in the SOP number. Original issue SOPs will have a revision number of "0". As an example, Chapter four, third SOP ("C"), second revision would be written as: "AHETF-4.C.2."
- 3.3 SOPs are written in an outline format. The SOP will always start with a purpose and scope that explains the intent and contents of the SOP. The remainder of the SOP should be presented in a concise, logical manner with each section titled.
- 3.4 SOPs will address how documentation will be recorded (when appropriate).
- 3.5 Any attachments ^{and/or} exhibits to SOPs will be clearly labeled and referenced in the text of the SOP. These attachments are considered part of the SOP and will have page numbers that will be included in the total number of pages.
- 3.6 Attachments or exhibits are numbered sequentially in a section by chapter number, SOP designation letter, and an attachment number. For example, the first attachment referenced in Chapter 3, SOP B, becomes Attachment 3-B-1; the fourth attachment, Attachment 3-B-4, *etc.*

SOP AHETF-3.A.0.

- 3.7 SOPs are to be added sequentially to the appropriate chapter, assigning the next available alphabetical letter.

4.0 PREPARATION GUIDELINES

- 4.1 When possible, the SOP should be limited to one procedure. If there are two or more ways of doing the task, it is recommended that there be a separate SOP for each. An SOP may be referenced in AHETF protocols. The Study Director may use the SOP to define the procedures that are to be followed in the study. If the SOP has more than one procedure included, the protocol must explain which one is to be used.
- 4.2 Any procedure that is common and repetitive should have an SOP. Complex procedures that comprise several steps (*i.e.*, application, calibration, cleaning, sampling) should be separated into individual SOPs for each distinct procedure.
- 4.3 Ideally, an SOP should be able to stand alone, and the procedure may be completed by following the SOP instructions.
- 4.4 Procedures that are unique to one particular study should be prepared as study specific procedures, noted in the study file.
- 4.5 An SOP will be written so that experienced personnel can perform the procedure, but in a clear manner so that inexperienced personnel could understand the operation. This will result in the most effective SOPs, for use as a training tool and as a reference.
- 4.6 An SOP may be initiated by any AHETF member or contractor. An individual may write an SOP or notify the QAU of the need for an SOP. The QAU may elect to write the SOP or designate a person with technical knowledge appropriate for that procedure.
- 4.7 All SOPs will be forwarded to the QAU for formatting, using the established format described in this SOP.
- 4.8 A draft SOP will be submitted to appropriate AHETF management for scientific review. The QAU will be responsible for regulatory compliance requirements. Following the initial review, the SOP will be circulated to the appropriate personnel for their remarks (please refer to section 5.0).

SOP AHETF-3.A.0.

- 4.9 The author of the SOP, in consultation with AHETF management and the QAU, will make any changes/corrections before final AHETF management review and approval.

5.0 APPROVAL

- 5.1 Each SOP will be signed by two (2) members of the AHETF, which include the Task Force Manager, Technical Committee Chair, appropriate Subcommittee Chairs, or the QAU. One signature will be from the AHETF management and the second will be from a person with technical background for a particular procedure.
- 5.2 The Task Force Manager is the primary AHETF management contact and reserves the right to abstain from approving any SOP, if conditions warrant. In such cases the SOP may be deferred to committee for approval.

6.0 REVIEW AND REVISION

- 6.1 The SOPs will be reviewed annually and revised if needed. The same guidelines that were outlined in section 4.0 of this SOP will be followed for Revision, including management approval. Documentation of annual review will be maintained by the QAU.
- 6.2 After the review of the SOP revision, a new SOP Revision number is assigned as discussed in section 3.0.
- 6.3 When revisions are made to an SOP, the outdated original SOP is archived in the AHETF QAU Historical SOP Files as set forth in section 9.0 of this SOP. Existing copies of the SOP are replaced in the SOP manuals. All previous copies of SOPs will be destroyed.
- 6.4 A section describing the reason for the revision will be added to the Purpose and Scope section of the revised SOP.

7.0 RETIREMENT

- 7.1 Should an SOP become obsolete, a notification of retirement will be sent to appropriate AHETF members. If there is an agreement, the SOP will be removed from the active SOPs. The original copy of the SOP will be archived as described in section 9.0.

8.0 DISTRIBUTION OF SOPS AND SOP MANUALS

- 8.1 Complete, approved sets of all Standard Operating Procedures or individual SOPs are available to all AHETF members and contractors, upon request. Specific members of the AHETF and the QAU will be assigned an SOP manual.
- 8.2 AHETF SOPs and SOP Manuals can exist in printed formats or electronic formats. Electronic versions will be distributed in a format to prevent unauthorized changes (e.g., PDF format), and will be available online through a secured website or on a CD-ROM.
- 8.3 Each SOP manual will be assigned a unique number. A list of personnel in possession of an AHETF SOP Manual will be maintained. The QAU will be responsible for providing new and revised SOPs to all personnel assigned a manual.
- 8.4 AHETF personnel in possession of a printed AHETF SOP manual will be responsible for maintenance of that manual. Personnel with CD-ROM manuals will receive updated discs as necessary.
- 8.5 An SOP manual may **not** be transferred to any other person by an AHETF member responsible for a manual. All manuals will be returned to the QAU when the personnel assigned a manual no longer require the SOPs.
- 8.6 Please refer to SOP AHETF-3.B regarding the use of contractor SOPs.

9.0 RETENTION

- 9.1 All original signed copies of the SOPs and all original copies of subsequent revisions will be kept by the QAU in the Standard Operating Procedures Historical File until completion of all AHETF work. At that time, all AHETF SOPs will be transferred to the AHETF archives for permanent storage, for the period of time set forth in the EPA GLPs, §160.195(b).

Use of AHETF and Contractor SOPs
Chapter 3: Standard Operating Procedures
 AHETF-3.B.1.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: February 1, 2003	Previous Version Number: 3.B.0

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) provides guidance for use of contract facility (field and analytical) SOPs in place of Agricultural Handlers Exposure Task Force (AHETF) SOPs.
- 1.2 The SOP has been revised to include Chapter 11 SOPs for Human Subject Testing.

2.0 WHEN TO USE AHETF SOPS

- 2.1 Administrative and quality assurance SOPs that have been developed are for internal AHETF use only. These include Chapters 1, 2, 3, 4, 5, and 6.
- 2.2 Specific technical procedures that are essential to AHETF study conduct have been prepared as SOPs and are to be followed by all contracted study personnel. Such SOPs will be identified in the study protocols. These include Chapters 7, 8, 9, 10, and 11.
- 2.3 Specific procedures for protocol (Ch. 2) and final report (Ch. 4) preparation will also be used by the AHETF Study Directors.
- 2.4 Chapter 11 SOPs are specific for ethical treatment and safety of human subjects volunteering for all AHETF studies. Special attention to these requirements is necessary to comply with Federal Regulations.

3.0 WHEN TO USE CONTRACTOR SOPs

- 3.1 Procedures for equipment maintenance and operation, documentation, field operations, laboratory procedures, personnel records, and archiving are the responsibility of the contract facility (unless otherwise specified in the study protocol).
- 3.2 Should an existing contractor SOP be unacceptable to the AHETF, then the appropriate AHETF SOP will be followed. Contractor SOPs that are updated or corrected may then be followed, after sponsor review and approval. Specific SOPs followed will be appropriately documented in the study file.

Study Report Preparation
Chapter 4: Study Reports
 AHETF-4.A.3.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: January 15 2005	Previous Version Number: 4.A.2.

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes what information is to be contained in an Agricultural Handlers Exposure Task Force (AHETF) study report, and when and how these reports are to be issued by the AHETF or contract test facility.
- 1.2 Submission package organization, according to EPA notice PR 86-5, is discussed.
- 1.3 Formatting requirements (font type and size, margins, *etc.* . . .) are presented for all reports prepared for the AHETF, which include electronic formats.
- 1.4 This Information contained in this SOP was revised to include the ethics requirements as set forth in 40 CFR, Part 26 for human subject testing.

2.0 REQUIRED INFORMATION

- 2.1 A final study report is a complete, comprehensive presentation of experimental methods, analysis and interpretation of results, and conclusions. Interim or phase study reports are limited reports issued during the conduct of a study or at the end of a specific phase of a study (*e.g.*, field phase report) that present only certain portions of the study results. Specifically, per GLP and Ethics

US EPA ARCHIVE DOCUMENT

SOP AHETF-4.A.3.

Testing requirements, all reports must include, but are not limited to the following (note - all sections listed may not apply to interim/phase reports):

- a. Name and address of the facility(s) performing the AHETF study and the dates on which the study was initiated and completed, terminated or discontinued.
- b. Objectives and procedures stated in the approved AHETF protocol, including any changes in the original protocol.
- c. Statistical methods employed in analyzing the data.
- d. The test, control, and reference substances identified by name, chemical abstracts service (CAS) number or code number, strength, purity, and composition or other appropriate characteristics.
- e. Stability and when relevant to the conduct of the experiment, the solubility of the test, control and reference substances under the conditions of administration.
- f. A description of the methods used.
- g. A description of the test system used.
- h. A description of the informed consent process.
- i. A description of the route of administration, application rate and duration.
- j. A description of all circumstances that may have affected the quality or integrity of the data.
- k. A description of any circumstances that may have affected the health of the worker volunteers.
- l. The name of the AHETF Study Director, the names of other scientists or professionals closely involved in the study, and the names of all supervisory (contract test facility) personnel involved in the study.

SOP AHETF-4.A.3.

- m. A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.
 - n. The signed and dated reports of each contract testing facility involved in the study. [when applicable]
 - o. The locations where all specimens, raw data, and the final report are to be stored.
 - p. The dated signatures of the AHETF Study Director and sponsor's representative.
 - q. The statement prepared and signed by the AHETF-contracted Quality Assurance Unit indicating the location within the final report of contractor QA reports or statements, phases inspected by the AHETF-contracted QAU, dates of the inspection, and dates reported to the Study Director/ Management.
- 2.2 A **DRAFT** report will be prepared before the final report. This copy will serve to evaluate the content and accuracy of the report. The draft final report will not be signed by any study personnel. The appropriate contract facility quality assurance unit should review the report before its completion. The draft final report may be audited by the AHETF-contracted Quality Assurance Unit (please refer to SOP AHETF-5.K.). In addition to undergoing a compliance and accuracy review by the QAU, each draft final report will be subjected to a technical review by members of the AHETF.
- 2.3 Final reports are to be issued by the AHETF after the completion of an AHETF study. Final reports will be issued to the EPA by the AHETF and not by any contractors. The specific schedule for the completion of a final report will depend on the length of the study, amount of data generated, and the time necessary to produce and review the report.

3.0 REPORT ORGANIZATION

- 3.1 The final report will meet the requirements of the EPA PR Notice 86-5 and follow the general format of the EPA Data Reporting Guidelines. A general outline of a final report format is as follows:
- a. Study Title page (this is always page no. 1)
 - b. Statement of **(No)** Data Confidentiality Claims
 - c. Good Laboratory Practice Compliance Statement
 - d. QA Statement(s)
 - e. Certification of Authenticity
 - f. Key Study Personnel, including Study Director and management approval signatures
 - g. Table of Contents
 - h. Text
 - i. Tables
 - j. Figures
 - k. Attachments/Appendices (submitter's option) [NOTE: *by definition, an attachment is a general term for all materials added to the report; an appendix is an addition providing additional statistical or explanatory information.*]
 - l. Raw Data (submitter's option)

4.0 REPORT FORMATTING

- 4.1 Due to the possibility that these reports will be scanned onto optical data storage medium, certain precautions are to be taken to ensure clarity and accuracy of transferred data.

SOP AHETF-4.A.3.

- 4.2 Times New Roman, or equivalent font, shall be used for all text, tables, and figures. The standard size will be 12 pt. with no text smaller than 8 pt. Italicized fonts should be avoided and script fonts may not be used. This is the default font requested by the USEPA for electronic submissions.
- 4.3 Boldface should be used for highlighting section titles and key words and phrases in the text. Underlining should be avoided. Shading in tables may be used if no greater than 40% or reversed text (white text on a black background) may be used. Single lines are preferred to double lines.
- 4.4 Line spacing should be 1.0 and not greater than 1.5. Line height should be set to automatic. All documents should be set to automatic kerning.
- 4.5 Margins should be at least 1.25" on the left and no less than 0.75" on the right. Top and bottom margins should be set between 0.75" and 1.00". For field and analytical reports to be appended to the final summary report, the top and bottom margins may be adjusted to accommodate additional pagination.
- 4.6 Each page, except the cover page, must have a header or footer with the AHETF study number and pagination. The header or footer may contain a single line at its bottom edge to set it off from the text. The header or footer text shall be in 10 pt.
- 4.7 Text alignment should be set to either left or full (preferred), and must be consistent throughout the report. Subsections and paragraphs should be indented on the left, with no hanging indentation (even left alignment at each outline level). Tab stops should be no less than 0.25" per level and no greater than 0.50" per level.
- 4.8 Titles and section headings should be larger than the body text. These items should be set to no more than 14 pt. and should be set in boldface. Individual sections shall be identified by a whole number, with subsections being identified by that number and a sequential decimal, then by a lowercase letter.
- 4.9 Tables and figures should be identified by numbers, such as "Table 1." or "Figure 7." Appendices shall be identified by Arabic Letters, such as "Appendix A." All tables, figures and appendices must have a descriptive title.

SOP AHETF-4.A.3.

- 4.10 Photocopies of data may be included in an appendix, as necessary. Copies should be copied at their original size (1:1 if 8.5" x 11.0" or smaller). If oversized pages are to be copied, they should not be reduced greater than 80%. **All information must be legible.** Contrast must be adjusted so that no areas are too dark or light. Any unreadable copies will be rejected, and must be re-photocopied or removed and excluded from the report.

5.0 ELECTRONIC FORMATS

- 5.1 All report and manipulated data must be presented to the AHETF in an electronic format. To maintain consistency from all contractors, each report document must be in Microsoft® Word® for Windows® 98 or compatible format. All spreadsheet data must be in Microsoft® Excel® for Windows® 98 or compatible format. Macintosh® formatted data are not acceptable. Refer to SOP AHETF-9.1.
- 5.2 It is strongly recommended that preparation of report tables and figures use the ability to link spreadsheet information with report tables and figures. This automatic linking between documents will reduce repetitive errors due to many versions or multiple entries of the data in the report.
- 5.3 File size must be considered as well. Text, tables and figures should be separate files. Any computer-generated appendix should be a separate file, also. All spreadsheets will be maintained separately. All related files must be presented together on CD-ROM discs.

6.0 FINAL REPORT MODIFICATIONS

- 6.1 Once the final report of a study is issued and submitted to the EPA, any modification must be issued as an "Amended Final Report" (OPPTS requirement, except those involving format changes only). A page (or pages) is (are) inserted into the reissued final report (placed in front of the QA Statement) that clearly identifies that part of the final report being modified, states the changes that are being made, and gives the justification for the change(s).

SOP AHETF-4.A.3.

- 6.2 The amended report receives a new title page stating “Amended Final Report,” revised table of contents [to include the page(s) with the amended changes], and a revised QA Statement that includes the date(s) the amended changes were reviewed.
- 6.3 Each page of the report that was amended should state “amended page” in a page footer.
- 6.4 The amended report is signed and dated by the AHETF Study Director and all key study personnel involved in the generation or analysis of data modified in the amended report.

Final Report Issue
Chapter 4: Study Reports
AHETF-4.B.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>Michelle Staudert</u>	DATE <u>02/04/03</u>
Last Revision Date: <u>N/A</u>	Previous Version Number: <u>N/A</u>

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes the procedure for issuing an Agricultural Handlers Exposure Task Force (AHETF) final study report to the Environmental Protection Agency (EPA), to AHETF member companies, and to industry groups or academia.

2.0 REPORT PREPARATION

- 2.1 A final report for each protocol-driven study will be prepared by the appropriate personnel (*i.e.*, Study Director). Subcontractors will prepare their individual reports to be appended to the final report.
- 2.2 The report will be reviewed by the AHETF and appropriate management representatives will sign the Compliance, Data No Confidentiality, and Authenticity statements, as necessary.

- 2.3 After all necessary signatures are collected, the Compliance Statement will be signed by the Study Director and then the report will be forwarded to the AHETF Task Force Manager. It is imperative that the raw data have been transferred to the designated archives at or before this stage, to comply with 40 CFR, Part 160, §160.185(a)(13) and §160.190(a).

3.0 EPA SUBMISSION PER PR NOTICE 86-5

- 3.1 The final report will be copied before submission. Three (3) complete, identical copies will be submitted to the EPA. Materials sent via USPS must be sent to the following mailing address:

Document Processing Desk (ETF)
Office of Pesticide Programs (H7504C)
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

- 3.2 Hand-carried or overnight courier submissions must be delivered to:

Document Processing Desk (ETF)
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Crystal Mall, Bldg. #2, Rm. 266A
1921 Jefferson Davis Highway
Arlington, VA 22202

- 3.3 Each copy must be on 82" by 11" white paper, single-sided printing, in black ink with good contrast and resolution. Individual copies must be secure, but easily removable to permit disassembly for microfilming. Check with EPA for special instructions before submitting data in any medium other than paper, such as magnetic media.
- 3.4 The following points will be considered:
1. Do not include frayed or torn edges.
 2. Do not include carbon copies, or copies in other than black ink.
 3. Make sure that photocopies are clear, complete and fully readable.

4. Do not include oversized computer printouts or fold-out pages.
 5. Do not bind any documents with glue or binding tape.
 6. Make sure that all pages of each study, including any attachments or appendices, are present and in correct sequence.
- 3.5 Please refer to SOP AHETF-4.A. for final report preparation, and EPA PR Notice 86-5 complete information on report organization, format, and submission requirements.

4.0 REPORT DISTRIBUTION TO AHETF MEMBER COMPANIES

- 4.1 Current AHETF member companies have access to all final reports and data. Written requests for copies of specific reports and data must be directed to the Task Force Manager.

5.0 REPORT PRESENTATION TO INDUSTRY AND ACADEMIA

- 5.1 Any information to be disseminated by the AHETF to nonmember companies, professional societies, and academic researchers must be approved by the AHETF Administrative Committee, through the Technical Committee Chair.

QA Personnel Administration
Chapter 5: Quality Assurance Unit
AHETF-5.A.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>G. Thomas Hale, Jr.</u>	DATE <u>02-24-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1. This Standard Operating Procedure (SOP) establishes guidelines for Agricultural Handlers Exposure Task Force (AHETF) Quality Assurance Unit (QAU) personnel matters such as training and maintaining employee records.

2.0 QA PERSONNEL TRAINING

- 2.1. All QAU personnel must have adequate training on procedures related to their assigned duties. Training is the responsibility of QAU management and will be properly documented.
- 2.2. Personnel shall maintain a résumé or CV, or a record of training, as appropriate. Documentation of AHETF SOP reviews will also be maintained. Any additional training shall be documented and will be placed in the training records.

3.0 QA PERSONNEL RECORDS

- 3.1. A personnel file is maintained for each AHETF QAU member involved in AHETF QA activities. These files are maintained by the QAU and will be archived at the AHETF Archives upon completion of AHETF activities.

SOP AHETF-5.A.0.

- 3.2. Job descriptions will be maintained in the appropriate files. These documents shall describe the responsibilities of AHETF QAU.
- 3.3. The following records of training and experience will be maintained:
 - a. Résumés or CVs reflecting education, academic or technical degrees, prior employment, and professional experience (signed and dated.)
 - b. A current job description indicating present responsibilities.
 - c. Records of attendance and participation at quality assurance, scientific, or technical meetings or training seminars.
 - d. Records of training for AHETF QAU functions (including SOP review documentation).

4.0 INDIVIDUAL RESPONSIBILITIES

- 4.1. It is the responsibility of each QAU individual to inform QAU management of any necessary changes or additions to the training file.

5.0 RECORD RETENTION

- 5.1. Job descriptions and résumés or CVs will be dated with each revision in order to determine which version was applicable during the performance of a specific function.
- 5.2. The information listed in 3.3 will be retained for the length of time set forth in the EPA GLPs §160.195(b).

6.0 RECORD REVIEW

- 6.1. Each personnel file will be subject to review by the QAU and AHETF management on an annual basis, or as needed.

QAU Responsibilities For AHETF Studies
Chapter 5: Quality Assurance Unit
 AHETF-5.B.1.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: February 1, 2003	Previous Version Number: 5.B.0

US EPA ARCHIVE DOCUMENT

1.0 PURPOSE AND SCOPE

- 1.1. This Standard Operating Procedure (SOP) describes the responsibilities of an independent Quality Assurance Unit (QAU) used by the Agricultural Handlers Exposure Task Force (AHETF) with respect to the requirements of the AHETF studies to be conducted.
- 1.2. Section 1.1 and 2.1 were clarified to state an independent QAU will be used by the AHETF. Section 2.0 was clarified to indicate the specific GLP responsibilities of the QAU. Section 3.0 was added to describe the non-GLP (ethical) responsibilities of the QAU.

2.0 QAU GOOD LABORATORY PRACTICES RESPONSIBILITIES

- 2.1. The independent QAU assures that the following Federal Regulations are adhered to:
 - a. EPA - Pesticide Programs; Good Laboratory Practice Standards 40 CFR part 160 (FR Vol. 54 No. 158: pp. 34067-34074)
- 2.2. The QAU will have direct interaction with the Study Director(s),

SOP AHETF-5.B.1.

contractors, and AHETF management for monitoring the level of GLP compliance (*i.e.*, assuring that the facilities, equipment, personnel, scientific methods, field practices and records are in compliance with the Good Laboratory Practices.)

- 2.3. The GLP responsibilities of the QAU are to:
- a. Maintain a regularly updated copy of the master schedule for all studies conducted by the AHETF.
 - b. Maintain copies of all protocols, amendments and standard operating procedures pertaining to all AHETF studies expected to be performed in compliance with the GLPs in the QAU archive files.
 - c. Periodically inspect selected phases of each type of laboratory or field study conducted by the AHETF and associated raw data, and maintain properly signed and dated records of each inspection.
 - d. Immediately provide the Study Director, AHETF designated study contractors, and AHETF management with a written report of any problems or deficiencies found during inspections.
 - e. Provide written summaries of individual study inspections/audits to the Study Director(s) and appropriate AHETF management representatives.
 - f. Review the study protocols and assure that no changes to approved protocols (amendments or deviations) are made without written acknowledgment.
 - g. Review the interim and final reports (contractor and AHETF) of each study conducted to assure that the report(s) accurately describe the experimental methods, raw data, observations, results, and procedures pertaining to the study.
 - h. Prepare and sign a statement, to be included in the final report, specifying the nature of the inspections, the dates of inspections/audits of the study and the dates that findings were reported to the Study Director and AHETF management.
 - i. Maintain a QA study file, which is the repository of all Quality

SOP AHETF-5.B.1.

- Assurance documents pertaining to ongoing AHETF studies.
- j. Conduct periodic GLP facility inspections of contract facilities.
 - k. Conduct GLP training for all contractor personnel involved with the AHETF studies, as necessary.
 - l. Prepare, revise, and distribute all AHETF SOPs; as well as coordinate use of AHETF member company and contractor SOPs. Assure that the Study Director is aware of SOP deviations.
 - m. Assist in the preparation and review of data forms used on all AHETF studies, as needed.
 - n. Oversee the GLP programs at contract laboratories by assisting the lab QAU with maintenance of facility records, study inspections, data and report audits, and GLP training, as needed.
 - o. Assist with regulatory agency inspections of the AHETF studies and facilities.
 - p. The independent QAU is contracted by the AHETF on an annual basis. QAU management will update the AHETF management on the QA costs incurred on a routine basis.

3.0 QAU PROTECTION OF HUMAN SUBJECTS RESPONSIBILITIES

- 3.1. The QAU Officer(s) shall complete the course from the National Institutes of Health (NIH; Human Participant Protections Education for Research Teams) and/or the Basic Collaborative IRB Training Initiative Course (CITI; The Protection of Human Research Subjects) as described in SOP 1.B.
- 3.2. The QAU shall inspect the forms relating to the ethical treatment of volunteers (40 CFR, §26) (e.g., ensure that every participant has a signed consent form).
- 3.3. The QAU will report directly to AHETF Management any and all findings related to ethical treatment of study volunteers.

QAU Records
Chapter 5: Quality Assurance Unit
 AHETF-5.C.1.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: February 1, 2003	Previous Version Number: 5.C.0

1.0 PURPOSE AND SCOPE

- 1.1. This Standard Operating Procedure (SOP) describes what records are to be maintained by the Quality Assurance Unit (QAU) for studies conducted by the Agricultural Handlers Exposure Task Force (AHETF).
- 1.2. This SOP was modified to clarify that the AHETF QAU is a separate, third-party contractor.

2.0 PROCEDURE

- 2.1. All Quality Assurance records are maintained by a third-party quality assurance contractor/consultant, serving as the AHETF-contracted QAU, with access strictly limited to QAU personnel. For each AHETF field or laboratory study conducted, a separate file is maintained and indexed by AHETF study number.
- 2.2. Each study file will contain the following items:
 - a. Protocol
 - b. Amendments/Deviations
 - c. Protocol/Amendment Acceptance pages (if applicable)

SOP AHETF-5.C.1.

- d. QA Study Inspection/Audit Log
- e. Inspection/Audit reports and Summaries, and responses to findings
 - i. Protocol Reviews
 - ii. Data Audits
 - iii. In-Process or study conduct inspections
 - iv. Final Report Audits

3.0 QAU RECORD RETENTION

- 3.1. The QAU records will be retained in the contracted QAU until completion of all AHETF activities when all records will be transferred to the AHETF archives for retention for the length of time set forth in the EPA GLPs, §160.19.

**Chapter 5: QA Master Schedule
Quality Assurance Unit
AHETF-5.D.1.**

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: February 1, 2003	Previous Version Number: 5.D.1

1.0 PURPOSE AND SCOPE

- 1.1. This Standard Operating Procedure (SOP) describes what information is recorded on the QA master schedule, how it is to be maintained, the authorized personnel, and capabilities of the master schedule system.
- 1.2. This SOP has been revised to clarify the procedures for maintaining an electronic Master Schedule.

2.0 PROCEDURE

- 2.1. The QAU shall prepare and maintain a Master Schedule in an electronic format for all AHETF studies conducted.
- 2.2. The master schedule is indexed by test substance, AHETF study number, and study initiation date. It contains, but is not limited to, the following information:
 - a. Test substance name or code number
 - b. Sponsor
 - c. Study number
 - d. Type (nature) of study

SOP AHETF-5.D.1.

- e. Test system
 - f. Study initiation date
 - g. Current status (Protocol Signed, Field Phase, Analytical Phase [continuation of field sample analysis], Report Phase, Terminated, Completed)
 - h. Study Director
 - i. Contract facility or field cooperator
- 2.3. Studies are to be entered on the Master Schedule at the time of study initiation, or when the approved protocol is received by the QAU.
- 2.4. The Master Schedule is to be updated as needed.
- 2.5. The Master Schedule is a strictly confidential document and is to be treated as such by all personnel.
- 2.6. The output of the Master Schedule may be customized, as required by the AHETF management. Confidential information may be printed at the direct request of the AHETF. Standard output that will be kept as a hard copy, will contain the information noted in section 2.2.
- 2.7. The AHETF Master Schedule will be maintained electronically in a spreadsheet format (e.g., Microsoft Excel[®] or Access[®]). Entry into the system requires the appropriate password. The database will be backed-up on a floppy disk, CD-ROM, or other appropriate storage media. Copies of the printout will be distributed to the AHETF management personnel as needed (e.g., as changes are made).

Protocol and Amendment Review
Chapter 5: Quality Assurance Unit
 AHETF-5.E.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>G. Thomas Haley, Jr.</u>	DATE <u>02-24-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1. This Standard Operating Procedure (SOP) describes how the Agricultural Handlers Exposure Task Force (AHETF) study protocols and amendments will be reviewed and maintained by the AHETF QAU.

2.0 PROCEDURE

- 2.1. When the protocol has been received by the AHETF QAU, it is reviewed for compliance with applicable GLP and AHETF SOP requirements. If possible, the **draft** protocol is to be reviewed. Subsequent protocol amendments will also be reviewed by the QAU for compliance with applicable GLPs and AHETF SOPs.
- 2.2. Any issues or concerns are brought to the attention of the Study Director(s) and AHETF management for consideration. If an agreement cannot be reached between the Study Director and the QAU, AHETF management may be asked to settle the issue.
- 2.3. The protocol review is filed in the QA study file.

SOP AHETF-5.E.0.

- 2.4. All intentional or planned changes to the approved protocol are made in writing as protocol amendments by the Study Director(s). Any unplanned changes in a study protocol without this prior approval are to be reported as deviations to the Study Director and documented in the study data.
- 2.5. The QAU will maintain copies of all protocols and amendments for the duration of the studies. Upon completion, all original protocols and amendments (maintained by the Study Director), will be transferred to the permanent AHETF archives for storage per §160.19.

Inspection/Audit Types and Frequency
Chapter 5: Quality Assurance Unit
 AHETF-5.F.1.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: February 1, 2003	Previous Version Number: 5.F.0

1.0 PURPOSE AND SCOPE

- 1.1. This Standard Operating Procedure (SOP) describes inspection/audit frequency to be followed by the Quality Assurance Unit (QAU) for field and laboratory inspections, data and final report audits, documentation, and reporting of the inspections/audits conducted for the Agricultural Handlers Exposure Task Force (AHETF).
- 1.2. This SOP has been revised to include inspection of the human subjects ethics-related phases of a study.

2.0 IN-PHASE INSPECTION PROCEDURES

- 2.1. The QAU may periodically inspect selected phases of each study, as required. Frequency of inspections will be determined on a study-by-study basis by the GLP Subcommittee and the Task Force Manager. The AHETF-contracted QAU will maintain written (signed/dated) records of each inspection.
- 2.2. Each study will be inspected at least once by the AHETF-contracted QAU or contractor QAU during its conduct. The AHETF-contracted QAU may perform inspections of studies contracted to any test site/laboratory at any time. (Please refer to SOP AHETF-5.G.)

US EPA ARCHIVE DOCUMENT

SOP AHETF-5.F.1.

- 2.3. The inspection phases of a particular study will be determined by the nature of the study. The phases of a GLP study can generally be defined as (but not limited to) the following:
- a. Method Validation
 - b. Test Substance Administration
 - c. Test System Observation
 - d. Informed Consent Forms
 - e. Sampling
 - f. Receipt, Log-in, Identification and Storage of Samples
 - g. Subsampling and Sample Preparation
 - h. Analytical Standard(s) Preparation
 - i. Extraction
 - j. Analysis by Instrumentation

3.0 DATA REVIEWS

- 3.1. Data generated on any AHETF study may be reviewed by the AHETF-contracted QAU at anytime. (Please refer to SOP AHETF-5.H.)
- 3.2. All raw data should be thoroughly reviewed by the contract facility's QAU; however, any data not reviewed to the satisfaction of the AHETF/QAU will be reviewed by the AHETF-contracted QAU prior to inclusion in the final report.

4.0 REPORT AUDITS

- 4.1. The final report, analytical reports ^{and/or} contractor reports will be reviewed at the completion of the AHETF study for compliance with all applicable GLPs, study protocol, and SOPs. (Please refer to SOP AHETF-5.J.)

5.0 REPORTING INSPECTION/AUDIT RESULTS

- 5.1. A record of inspection dates, study number, phases inspected, date reported to the AHETF Study Director and management, and the identity of the person performing the inspection will be reported in the AHETF Summary Report on the QA Statement page. (Please refer to SOP AHETF-5.C.)

SOP AHETF-5.F.1.

- 5.2. Results of individual study inspections will be reported to the contract facility management, and the Study Director, AHETF management, and other designated AHETF personnel. The inspection report will note findings and suggested actions to be taken to address or correct the errors. (Please refer to SOP AHETF-5.K.)
- 5.3. If corrective action is required, the Contract Facility Principal Investigator (P.I.) or the AHETF Study Director (or designate) should respond within fifteen working days. Corrective actions taken by supervisory or contract facility personnel (P.I.) will be acknowledged by the Study Director.
- 5.4. Any significant problems found, which are likely to affect the study integrity, during the course of an inspection are *immediately* brought to the attention of the Study Director and AHETF management, through telephone conversations, faxes, email, or direct discussion at the test site. Such issues will still be written in the inspection report, even if corrective actions were already taken.

Study Inspections
Chapter 5: Quality Assurance Unit
 AHETF-5.G.1.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: February 1, 2003	Previous Version Number: 5.G.0

1.0 PURPOSE AND SCOPE

- 1.1. This Standard Operating Procedure (SOP) describes the procedure the AHETF-contracted QAU will follow when performing an inspection on any portion of an ongoing study conducted for the Agricultural Handlers Exposure Task Force (AHETF) at any designated test site or laboratory facility.
- 1.2. This SOP has been revised to include the inspection of certain aspects of human studies for ethics requirements, as set forth in 40 CFR, Part 26.

2.0 PROCEDURE

- 2.1. The designated QAU personnel will schedule inspections with the appropriate Study Director, AHETF management, and the principal investigator (if required) for each study to be inspected.
- 2.2. The QAU will allow adequate time for travel to the site/facility in order to observe critical operations of the study. (Please refer to SOP AHETF-5.F.)
- 2.3. The QAU will have the appropriate study protocol/amendments, analytical methods, and SOPs available during the inspection for reference.

SOP AHETF-5.G.1.

- 2.4. Notes may be taken during the inspection for reference during the inspection report preparation. Checklists and inspection forms may be used at the QAU's discretion.
- 2.5. During an inspection, the QAU will determine whether the GLP and protocol requirements for that phase have been met and whether the procedure is performed in accordance with applicable AHETF or contract facility SOPs (unless superseded by the AHETF protocol). In addition to these verifications, study aspects are also inspected (as applicable) for, but are not limited to, the following:
 - a. Reagents and solutions labeled per GLP
 - b. Maintenance and calibration logs of all equipment used during the procedure
 - c. Documentation of test substance receipt and distribution
 - d. Verification of study calculations
 - e. Contamination prevention procedures
 - f. Samples labeled per protocol or SOP requirements
 - g. Proper storage of chemicals and samples
 - h. Health and Safety procedures are observed
 - i. Complete documentation of each procedure performed
 - j. Training records of study participants
 - k. Availability of SOPs for study personnel
 - l. Proper completion of Informed Consent Forms
- 2.6. The QAU should also verify that the contract facilities for study conduct are adequate. The following aspects will be considered (as appropriate):
 - a. Are application or testing equipment of appropriate size, design, and construction?

SOP AHETF-5.G.1.

- b. Are the field sites of appropriate size and location?
- c. Does the design of the analytical facilities allow for separation of test systems samples and isolation of individual projects?
- d. Are worker consent forms properly signed and maintained?
- e. Are environmental conditions and instrumentations appropriate for the protocol? Is there documentation?
- f. Are adverse events addressed in a timely manner and properly documented?
- g. What is the source of water (carrier) used? Does the water quality and composition meet protocol requirements, if any?
- h. Are there adequate areas for storage of supplies and equipment? Are these areas separate from the test system location?
- i. Are samples collected per applicable SOPs and the study protocol?
- j. How are test substances received, stored, distributed? Are environmental conditions of storage areas monitored? Are the storage areas secured? Who is responsible? Who has access?
- k. Where are mixtures stored? Are storage conditions monitored?
- l. Do laboratory areas appear to be adequate? Is there ample space for sample preparation and instrumentation?
- m. Are raw data and specimens appropriately archived?
- n. Do contract facility archives meet GLP requirements? (if required)

- 2.7. All findings will be discussed with study personnel upon completion of the inspection. Copies of notes taken during the inspection shall be offered to the field or laboratory personnel.

SOP AHETF-5.G.1.

- 2.8. Any deviations from the GLPs ^{and/or} the study protocol shall be noted and immediately (within reason) be conveyed to the Study Director. Should the deviation be serious enough to warrant the termination of the study, the QAU shall inform all study personnel of the problem and wait for the sponsor and the Study Director to decide upon appropriate action(s).
- 2.9. An inspection report will be generated as described in SOP AHETF-5.K.

Data Audits
Chapter 5: Quality Assurance Unit
AHETF-5.H.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>G. Thomas Kelly</u>	DATE <u>02-24-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1. This Standard Operating Procedure (SOP) describes the procedures to be followed by the Quality Assurance Unit (QAU) when auditing study data generated during Agricultural Handlers Exposure Task Force (AHETF) exposure studies.

2.0 PROCEDURE

- 2.1. Study notebooks/files are reviewed for compliance with the EPA GLPs and the AHETF study protocol; *i.e.*, the data are reviewed for documentation of performance of test requirements as described in the protocol.
- 2.2. Documentation of procedures performed or reference to appropriate AHETF or contractor SOPs is verified.
- 2.3. Study notebooks/files are reviewed for proper data entry and error documentation per GLPs and SOPs.
- 2.4. Documentation of test substance application is reviewed, including application calculations, preparation and administration procedures, and test substance receipt, storage and distribution.
- 2.5. Proper documentation and Study Director acknowledgment of any SOP or AHETF protocol deviations are verified.

SOP AHETF-5.H.0.

- 2.6. Exact copies of original data must have been clearly identified as such, and has been signed/dated at the time of copying by the person verifying the copies.
- 2.7. Data forms are reviewed for completeness; *i.e.*, each assigned space must have a data entry, or be addressed if no entry was made.
- 2.8. Computerized calculations or spreadsheets are checked against raw data numbers and all calculation equations and methods are verified.
- 2.9. Computerized data (summary or transcribed) are checked for proper identification (*e.g.*, study, data type) and calibration (*e.g.*, efficiencies and standards) procedures.
- 2.10. Calibration and equipment logs are randomly checked, as well as test, reference, and control substance receipt and use logs.
- 2.11. Printouts from analytical instruments (GC, HPLC, *etc.*) are checked for proper documentation of run conditions and column information, and proper identification (project number, sample number, treatment level, instrument operator, injection amount), as well as random verification of integration summaries.
- 2.12. Data reviewed may be copied. All errors found or comments made by the QAU may be directly noted on any prepared copies. Any additional notes may be taken for later reference in preparing the inspection report.
- 2.13. All reviewed data copies and notes taken will be maintained in the QAU files.

Chapter 5: Facility Inspections
Quality Assurance Unit
AHETF-5.I.O.

Effective Date : February 1, 2003

APPROVAL <u><i>Davit Johnson</i></u>	DATE <u>01-22-03</u>
APPROVAL <u><i>G. Thomas Gale, Jr.</i></u>	DATE <u>02-24-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1. This Standard Operating Procedure (SOP) describes, in general terms, what the Quality Assurance Unit (QAU) is to inspect during an Agricultural Handlers Exposure Task Force (AHETF) facility inspection.

2.0 PROCEDURE

- 2.1. During a facility site visit an extensive inspection is made to assess the facility's compliance with the EPA Good Laboratory Practice Standards. The inspection includes a review of:
- personnel training records
 - equipment maintenance procedures and records
 - standard operating procedures
 - health and safety equipment
 - test substance receipt, distribution, and storage
 - QA records, as appropriate
 - archives
 - test system sample handling
- 2.2. An appropriate checklist may be used as a guideline during the facility inspection to assure that all aspects of the GLP requirements have been reviewed.

SOP AHETF-5.1.0.

- 2.3. The QAU will schedule the inspection with the facility after obtaining the authorization from the AHETF management to inspect the facility.
- 2.4. Facility inspections should be performed at any laboratory that has not been inspected by a Task Force member company within the last twelve (12) months, or whenever there is a question concerning the facility's integrity.
- 2.5. In order to maintain the highest level of compliance, facility inspections of contracted facilities should be performed at least annually.
- 2.6. The QAU will allow sufficient time to completely inspect the contract facility, including timeliness in arriving and departing the facility. All QAU personnel will conduct the inspection in an open and professional manner.

3.0 REPORTING INSPECTION FINDINGS

- 3.1. Deficiencies and recommended corrective actions are reported, in writing, to AHETF management, Study Director(s), other appropriate AHETF personnel, and the contract facility QAU and management.
- 3.2. The original inspection report will be sent to the facility; copies sent initially to the AHETF management and Study Director(s), if necessary. The original inspection report, with responses and the signature(s) from the facility, will be returned to the QAU, when it will be forwarded to the AHETF management for signature(s).

Report Audits
Chapter 5: Quality Assurance Unit
AHETF-5.J.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>G. Thomas Gale, Jr.</u>	DATE <u>02-24-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1. This Standard Operating Procedure (SOP) describes the procedures that the Quality Assurance Unit (QAU) will follow for auditing draft, summary, progress, field, analytical and final study reports generated for/by the Agricultural Handlers Exposure Task Force (AHETF).

2.0 QUANTITY OF REPORTED DATA TO BE AUDITED

- 2.1. The quantity of data (reported values vs. raw data) reviewed will depend on the type of study and the nature of the data. The greater the number of errors found within the reviewed data, the more extensive the audit may be.
- 2.2. The quantity of reported data reviewed will be at the discretion of the QAU. A minimum of 25% of all data (specific values or information) will be reviewed for each study, with the option to review up to 100% of all reported data, should circumstances warrant. As much data as feasible will be reviewed during each audit.
- 2.3. The data points (tables, appendices) chosen for review will be at the discretion of the QAU. However, the QAU will choose enough data points to be reasonably assured that the data are accurately reported. For example, the QAU may choose to verify every 5th data point in a set of analytical data or may review all of the presented data in a table. (*i.e.*, computer generated data need not be reviewed as thoroughly as hand-recorded data)

SOP AHETF-5.J.0.

- 2.4. If a significant number of data errors are found (e.g.; >5%) the QAU will either review the data completely (i.e., 100% verification) or reject the report, or any portion thereof (table, appendix, text), until corrections have been made by the author(s).

3.0 REPORTS

- 3.1. The QAU is given a copy of each report prepared for each AHETF study conducted and all supporting data, as necessary.
- 3.2. The AHETF protocol should be read prior to report auditing for QAU familiarity with the study purpose and requirements.
- 3.3. Raw data not audited during the conduct of the study should be reviewed for GLP, AHETF protocol and, AHETF ^{and/or} contract test facility SOP compliance. Items to be reviewed include, but are not limited to: transcription of data to spreadsheets and worksheets, and verification of calculations. Additionally, equipment calibrations and test substance logs should be checked. (For example, if samples were weighed on a particular day, the QAU would check to see that the balance was calibrated on that day, and that the calibration weights bracketed the sample weights.)
- 3.4. The report should be read through prior to auditing for QAU familiarity with format and contents.
- 3.5. The report is reviewed to assure that all AHETF protocol requirements have been met and that any differences are specified in the report.
- 3.6. The compliance statement will be reviewed for true and accurate reflection of the study conduct.
- 3.7. The contents (procedures, results, etc.) of the report are verified against the raw data. All descriptions, methods and procedures described in the report must be documented in the raw data. Routine procedures must be referenced in the data to the AHETF ^{and/or} the contract test facility SOPs. Study specific procedures should be documented in the raw data.
- 3.8. Report tables are checked for accuracy of numerical data transcriptions. Computerized calculations and statistics are randomly checked.

SOP AHETF-5.J.0.

- 3.9. Calculations are checked for accuracy. Selected data points on graphs are verified.
- 3.10. The table of contents is verified against headings and titles in the report.
- 3.11. The report is reviewed for compliance with the applicable EPA GLP requirements.
- 3.12. The report format must be checked for consistency with applicable EPA Data Reporting Guidelines and PR Notice 86-5, as necessary.
- 3.13. The report is checked for clarity, readability, spelling, *etc.*

4.0 REPORT AUDIT FINDINGS

- 4.1. The QAU findings may be made directly on the copy of the report. A copy of the audited report with findings indicated will be kept by the QAU.
- 4.2. At the completion of the audit, any findings, questions, or raw data errors as well as recommended actions will be noted.
- 4.3. The audited report and Quality Assurance (QA) Inspection Report will be returned to the Study Director or appointed personnel for corrections and finalization.
- 4.4. Once the Study Director has addressed the QA findings, and the responses have been reviewed by AHETF management, the QA Inspection Report and the audited copy of the report will be returned to the QAU to be maintained in the QAU files as a record of the audit.
- 4.5. Prior to issuing the final report, the QAU may perform a post-audit inspection to assure all corrections have been made and any additions to the report are accurate.

5.0 QUALITY ASSURANCE FINAL REPORT STATEMENT

- 5.1. Upon acceptance of the final report by AHETF management, the QAU will prepare and sign a statement to be included with the final AHETF study report which specifies the inspections conducted, dates of inspections/audits, and the dates findings were reported to AHETF management and the Study Director(s).

Inspection Report Distribution
Chapter 5: Quality Assurance Unit
 AHETF-5.K.1.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: February 1, 2003	Previous Version Number: 5.K.0.

1.0 PURPOSE AND SCOPE

- 1.1. This Standard Operating Procedure (SOP) describes the procedure that the Agricultural Handlers Exposure Task Force (AHETF) Quality Assurance Unit (QAU) will follow when raw data audit, study report audit, facility inspection, and field-site inspection reports are written and distributed to the appropriate AHETF personnel. The routing of inspection reports for signature and review is described.
- 1.2. This SOP has been updated to include ethical treatment criteria for worker volunteers as described in 40 CFR Part 26 and to clarify the distribution as an electronic formatted report.

2.0 INSPECTION REPORTING PROCEDURES

- 2.1. Significant GLP, protocol, or SOP deviations, or ethical treatment violations as determined by the QAU, will be reported to the Study Director, Task Force Manager and designated AHETF management immediately.
- 2.2. Inspection reports of study findings may be reported as a draft report to the contract test facility for general content and accuracy otherwise the report will be issued directly. If a draft is issued and after corrections of any reporting errors, the report will be issued as a final inspection report, indicated by the signature of the QAU personnel. The need for such actions will be determined by the QAU on a case-by-case basis.

SOP AHETF-5.K.1.

- 2.3. The original, electronically signed report will be sent to the Study Director or contractor/P.I. for a formal response. Copies of the report will be issued to the Study Director and Task Force Manager, AHETF management, and other designated AHETF personnel (if necessary). Responses are due within 15 working days.
- 2.4. Upon receipt of the responses, actions taken will be reported to the Study Director and AHETF management. The Study Director will acknowledge receipt of the audit report by replying to the designated QAU via email.
- 2.5. Once all required personnel have acknowledged receipt of the audit report it will be archived by the QAU. Copies of completed inspection reports may be distributed to AHETF personnel as needed.
- 2.6. The following personnel are required to review the inspection findings audit report issued by the contracted AHETF QAU:
 - a. AHETF QAU (required electronic signature)
 - b. Study Director
 - c. Task Force Manager
 - d. AHETF Management (if necessary)
 - e. Contractor (Principal Investigator/Management), if necessary
- 2.7. A summary of study inspection findings may be circulated to the AHETF members. This summary may be prepared by the QAU and circulated through the AHETF members on an as needed basis.
- 2.8. All AHETF QAU Inspection Reports are confidential and will not be distributed to unauthorized personnel. Reports will be available to any Task Force representative upon request.
- 2.9. Final Report audit findings will be issued directly to the Study Director for comment and correction. Final Report audits will also be forwarded to the AHETF management. The QAU will not issue the Final Report QA Statement until discrepancies are addressed by the Study Director and approved by AHETF management.

SOP AHETF-5.K.1.

- 2.10. All inspection reports should be acknowledged by email to the AHETF QAU within fifteen days of receipt. All inspection report files will be maintained by the contracted AHETF QAU.

3.0 FACILITY INSPECTIONS

- 3.1. Facility inspections include any general inspection of a testing facility. Inspection reports will be generated and signed/dated by the QAU. Facility inspection reports will be distributed as described in section 2.0 of this SOP.
- 3.2. Inspection reports should be addressed and signed by the appropriate contractor personnel and returned to the QAU within 25 working days.
- 3.3. Facility inspections may be used by the AHETF management to decide if a facility is capable of conducting a GLP study for the AHETF.

Storage of Raw DataChapter 6: ARCHIVES
AHETF-6.A.O.

Effective Date : February 1, 2003

APPROVAL <u><i>David Johnson</i></u>	DATE <u>01-22-03</u>
APPROVAL <u><i>G. Thomas Hale J</i></u>	DATE <u>02-24-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes how and where raw data are to be stored by the designated Agricultural Handlers Exposure Task Force (AHETF) archive facility.

2.0 AHETF GENERAL ARCHIVING PROCEDURES

- 2.1 All raw data, documentation, protocols, correspondence collected during any AHETF study will be reviewed by the Study Director or authorized personnel and submitted to the designated AHETF archive facility. The Study Director will assure that this material is placed into temporary or permanent archive storage before study completion.
- 2.2 Certified copies of all raw data (refer to SOP AHETF-9.H.) should be sent to the AHETF Study Director or Quality Assurance Unit before the transfer of original data to the designated archives. Once receipt of the copies has been verified, the original data may be sent directly to the archives. Under no circumstances, should the original data and certified copies be shipped simultaneously.

SOP AHETF-6.A.0.

- 2.3 Non-study specific raw data (e.g., facility records) and copies of raw data from completed AHETF studies may be maintained in the contracted field or analytical facilities' archive, or if necessary, by designated AHETF personnel. Original raw data should be sent directly to the permanent AHETF archive facility.
- 2.4 Any temporary archive should be designed for orderly storage and expedient retrieval of all raw data, documentation, protocols, and final reports. Data should be kept in a secured area under ambient environmental conditions. Appropriate contractor SOPs will be followed.
- 2.5 Quality assurance documents will be **maintained separately** by the AHETF Quality Assurance Unit (QAU). QA documents will be transferred to the designated permanent archive facility upon completion of AHETF activities.
- 2.6 Once placed in permanent archival storage, all requests for data must be directed through the Task Force Manager. AHETF technical personnel should **not** directly contact the archiving facility unless otherwise stated. (Please refer to SOP AHETF-6.B.)

3.0 AHETF DATA STORAGE REQUIREMENTS

- 3.1 Conditions of storage are set up to reduce deterioration of the documents and provide for their security according to the EPA GLP requirements during their retention and the nature of the documents.
- 3.2 Any machine generated data that will degrade with time, such as fading of thermal paper, will be photocopied and certified as "copy(s) of the original(s)" before being archived. *These copies are in addition to the complete set of certified copies to be prepared.*
- 3.3 Direct access to the archives for placing or retrieving data is limited to the designated Archivist or alternate.
- 3.4 Raw data, documentation, and other study records are to be retained in the AHETF archives for, at least, the period during which the Agricultural Handlers Exposure Task Force or other registrant holds any research or marketing permit to which the study is pertinent, or;

SOP AHETF-6.A.0.

- 3.5 Original raw data may only be removed from the archive area when copies are needed, personnel wish to review data on-site, or data are being transferred to another location (please refer to SOP AHETF-6.B.).
- 3.6 All electronic and optical storage media will be retained as described above. Electronic and optical media may be defined as raw data, depending upon the type of data contained on electronic media (*e.g.*, video tapes, CD-ROM, original data collected onto a floppy diskette, audio tapes).

4.0 CONTRACTOR TO AHETF ARCHIVES: DATA TRANSFER PROCEDURES

- 4.1 Upon receipt and acceptance of the certified copies of the raw data by the AHETF Study Director or QAU, the contractor will be directed to send the original raw data to the designated archive personnel.
- 4.2 All original data must be sent to the AHETF Archives from the contracted facilities by registered or certified mail, or by overnight courier (*i.e.*, Federal Express, UPS, *etc.* . .) with appropriate transmittal forms or chain of custody forms.
- 4.3 Data packages will be addressed to the attention of the AHETF Archivist.
- 4.4 Data sets, as received at the archives, will be inspected for shipment damage. Any chain of custody forms will be completed and distributed as necessary. Copies or originals of such transmittal forms will be maintained in the archives.
- 4.5 Contents of the data package will be compared against the required chain of custody or contents list, as appropriate.
- 4.6 Appropriate Archive Facility SOPs will be followed for logging-in, handling, and storing archived materials.

Access to Archived Data
Chapter 6: ARCHIVES
 AHETF-6.B.1.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: February 1, 2003	Previous Version Number: 6.B.0

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes the Agricultural Handlers Exposure Task Force (AHETF) policy for member companies to obtain access to AHETF study data and final reports for review after being placed in the designated permanent archive facility.
- 1.2 This SOP was revised to add section 5.0 Confidential Worker Information.

2.0 ACCESS RESTRICTIONS

- 2.1 Only personnel authorized by AHETF management may have access to review the data. Any person(s) requesting access to AHETF study data must contact the proper AHETF management personnel or Task Force Manager for authorization. All requests must be made in writing.
- 2.2 Only the Archivist, or alternate, should have direct physical access to the data. A written record of access should be maintained by the designated archive facility for all AHETF studies.
- 2.3 A list of personnel with clearance to access archived materials should be maintained by the designated archivist, if available.
- 2.4 No original data may be removed and distributed from the AHETF archives without the written approval of the AHETF. Only verified copies shall be provided for off-site data review, unless otherwise stated.

SOP AHETF-6.B.1.

- 2.5 As all AHETF data are strictly confidential, no additional or unauthorized copies of any AHETF data may be made, except as authorized in writing by the AHETF.
- 2.6 Photocopies of the raw data may be retained by the AHETF Quality Assurance Unit, as needed, and will be destroyed at the direction of the AHETF.

3.0 DATA ACCESS PROCEDURES

- 3.1 The applicable standard operating procedures of the archiving facility shall apply to all access, maintenance, and record keeping of the archived materials.

4.0 POST-ARCHIVING DATA TRANSFER

- 4.1 Should it become necessary, AHETF study data, or portions thereof, may be transferred to another designated facility or location for retention at the discretion of the AHETF management. The AHETF will notify the archive facility personnel which data will be transferred.
- 4.2 Data transfer procedures, as described in SOP AHETF-9.G, will apply to all transfers.

5.0 CONFIDENTIAL WORKER INFORMATION

- 5.1 Certain worker information will be collected during the course of any AHETF that will contain confidential worker information. This information will be kept separate from the raw data generated during the AHETF study. Refer to SOP AHETF-6D for specific handling and access requirements to confidential worker information.

Specimen and Wet Sample StorageChapter 6: ARCHIVES
AHETF-6.C.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>M. Thomas Gale, J</u>	DATE <u>02-24-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes how and where specimens and retention samples of test, reference, and control substances, from Agricultural Handlers Exposure Task Force (AHETF) studies are to be stored, and who will have responsibility over all samples. Duration of retention and access are covered in this SOP.

2.0 PROCEDURE

- 2.1 Retain samples of test and reference substances (analytes and active ingredients) will be stored at the appropriate AHETF contract research facility. Specific locations will be specified in the study protocols and documented in the study files.
- 2.2 The samples are to be stored according to AHETF or manufacturer specifications; (*i.e.*, room temperature, refrigerated, or frozen) in secured storage areas.
- 2.3 Storage areas are to be monitored for temperature. The samples may be retained in the archive storage facilities of contract test facilities if necessary, as determined by AHETF management.

SOP AHETF-6.C.0.

- 2.4 Samples are retained as long as the quality of the preparation affords evaluation, as determined by the Study Director(s). Samples will be organized for expedient retrieval and to reduce the possibility of contamination.
- 2.5 Stored samples may be returned to the AHETF (if the specimens have been stored at a contract test facility), discarded, or stored under a renewed contract. No EPA GLP study materials will be discarded without first offering the AHETF the opportunity to obtain all study samples. Transfer or disposal of samples will be documented and maintained in the appropriate AHETF study files.
- 2.6 Specific samples to be retained will be discussed in the individual study protocols.

3.0 SAMPLE TRANSFERS

- 3.1 Should wet samples and specimens need to be transferred from one archiving facility or another, the AHETF management must be notified of the intended transfer; including the reason for transfer, which samples are being moved, and the anticipated date of transfer. The AHETF will choose the second designated facility.
- 3.2 Written approval from the AHETF must be obtained before the release of any samples. The AHETF may elect to have a representative present during any transfer procedures.
- 3.3 Proper documentation must be maintained throughout the transfer process. This includes a detailed Chain of Custody form that must accompany the samples during transit, and will be maintained in the appropriate archives upon completion.

Access to Confidential Worker Information

Chapter 6: ARCHIVES
AHETF-6.D.0.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: None	Previous Version Number: None

1.0 PURPOSE AND SCOPE

1.1 This Standard Operating Procedure (SOP) describes the Agricultural Handlers Exposure Task Force (AHETF) policy to obtain access to AHETF confidential worker information for review after being placed in the designated permanent archive facility.

2.0 CONFIDENTIAL WORKER INFORMATION

2.1 Certain worker information will be collected during the course of any AHETF worker exposure study. Forms and paperwork that contain personal information (such as worker’s name and address) must be kept confidential.

2.2 The Study Director will place any forms containing such information in a sealed envelope, marked as “CONFIDENTIAL WORKER INFORMATION – DO NOT RELEASE – CONTACT AHETF ADMINISTRATIVE CHAIR” along with the AHETF Study No. and will be placed in the study file with the remaining raw data.

2.3 The confidential information shall be permanently archived with the study raw data as required by Good Laboratory Practices (GLP) regulations (40 CFR Part 160)

3.0 ACCESS RESTRICTIONS

- 3.1 Only personnel authorized by the AHETF Administrative Committee Chair may have access to the data. Any person(s) requesting access to confidential worker information must submit the request and the reasons for the request in writing to the AHETF Administrative Committee Chair for authorization.
- 3.2 The designated AHETF Archivist, or alternate, is instructed to remove the Confidential Worker Information envelope from the archived data file when presenting the raw data for review to any AHETF member, company representative, or regulatory agency; unless otherwise directed by the AHETF Administrative Committee chair.
- 3.3 Access can only be authorized when specifically requested by EPA or when required for legal reasons.
- 3.4 Only the Archivist, or alternate, should have direct physical access to the data. A written record of access shall be maintained by the designated archive facility for all AHETF studies.
- 3.5 No confidential worker information may be removed and distributed from the AHETF archives without the written approval of the AHETF Administrative Committee Chair. Only verified copies shall be provided for off-site data review, unless otherwise stated.
- 3.6 Other than restrictions provided in this SOP, these data are subject to the same storage and handling requirements as set forth in SOPs AHETF-6.A and AHETF-6.B.

Test, Reference, and Control Substance Receipt and Shipment
Chapter 7: TEST, REFERENCE, AND CONTROL SUBSTANCES
AHETF-7.A.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>Wiley Staudert</u>	DATE <u>01-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) presents the minimum requirements for the inspection, receipt and shipment of Agricultural Handlers Exposure Task Force (AHETF) test, reference and control substances by contracted performing laboratories.
- 1.2 This SOP is also intended as a guide for assessing the SOPs available at the contracted facilities, and shall be followed only when the contracted facility SOP is unacceptable. The SOP(s) followed will be documented in the study file.

2.0 TEST SUBSTANCE INSPECTION

- 2.1 The appropriate field and analytical facilities should have personnel who are responsible for all test, reference, and control substances used in exposure studies and analytical portions of all AHETF studies.
- 2.2 The appropriate personnel should inspect each test substance shipment received for, at least the following conditions:
 - a. Physical damage to the packaging.

SOP AHETF-7.A.0.

- b. Loss of substance (*i.e.*, half-full or empty containers).
 - c. Possible contamination of the substances (*i.e.*, unusual color, particulates, physical change).
 - d. Proper use of special shipping procedures designed to preserve the Test Substance integrity; *i.e.*, substances shipped frozen should be frozen upon receipt.
- 2.3 Test substance documentation, submitted with the shipment, should be examined and must correspond with the test substances received. If labeling is unclear, inadequate, or nonexistent, the Study Director, the Technical Committee Manager, or designated personnel shall be notified. The shipping facility should be contacted for clarification. The test substance should be returned if it cannot be properly identified.

3.0 LOG-IN, TRANSFER, AND RETURN TEST SUBSTANCES

- 3.1 Test substances should be checked in as they are received. Pertinent information including, but not limited to, receipt date, substance identification, amount received, carrier (if applicable), and shipment origination should be recorded in the contractor's receipt and inventory log, as appropriate.
- 3.2 The test substance information should be entered into the contractor's facility's receipt log or appropriate document, which should include the receipt date, test substance(s) name or ID, lot number, sender/manufacturer, and amount received. The test substances should be stored in the appropriate chemical storage area.
- 3.3 When a test substance is sent to the field test sites the following information, as a minimum, should be recorded by the sender on a shipping log: the date sent, test substance name/ID, lot/batch number, amount shipped and destination. All appropriate shipping receipts will be retained and kept in the appropriate study file.

- 3.4 Should any remaining test substances be returned from the field test site to the AHETF or contractor, an appropriate facility will be designated to receive the unused test substance. The field contractors will be notified of which facility, and the responsible person will receive the incoming substance(s). The amount of material will be estimated [if unable to determine accurately] and indicated as such. These procedures will be followed until all of the test substance(s) is (are) used, stored, or properly disposed of, per the facility's or appropriate SOPs.

4.0 SHIPPING TEST SUBSTANCES

- 4.1 The AHETF representative, Study Director, principal investigator, or other designee will prepare the packages according to Department of Transportation (DOT) regulations, complete a packing list or chain of custody for chemical shipments, include an MSDS (if available), and ship them to the appropriate test sites.
- 4.2 The amount of substance to be shipped, the toxicity of the substance (oral LD₅₀, inhalation, and dermal toxicity), whether it is flammable or corrosive, and the common or chemical family name will be determined before shipment.
- 4.3 Proper packing methods, materials, and outer labeling will be determined and utilized.
- 4.4 When the test substance has been packed and is ready for shipment, the package and required paperwork will be reviewed by a second designated party. If any items are missing or incorrect, the faults will be corrected.
- 4.5 An appropriate shipping company will carry the test substance according to appropriate DOT regulations. No test substance will be sent via U.S. mail. Flammable materials **should not** be sent via air.
- 4.6 The recipient must be notified that the chemical is *en route*.
- 4.7 Appropriate contractor SOPs shall be followed for all chemical shipments made by each facility, unless otherwise noted.

Test, Reference, Labeling

Chapter 7: TEST, REFERENCE, AND CONTROL SUBSTANCES
AHETF-7.B.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>Misty Staudert</u>	DATE <u>01-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) provides guidelines on how test, reference and control substances [referred to as "Test Substance" in this SOP] should be labeled once they are received by the Agricultural Handlers Exposure Task Force (AHETF) or at designated test sites or performing laboratories.
- 1.2 This SOP is also intended as a guide for assessing the SOPs available at the contracted facilities, and will be followed only when the contracted facility SOP is unacceptable. The SOP followed will be documented in the study file.

2.0 LABELING

- 2.1 Every container of test, reference or control substance must have certain information directly attached to the container, even if it has been transferred or repackaged. Every container must be appropriately labeled and be easily identifiable at all times. The following type of labeling is recommended.

SOP AHETF-7.B.0.

- 2.2 **Test Substance Label** - Test substance containers that are used for all AHETF studies will be labeled with the following information, as per 40 CFR, Part 160, §160.105(c) and sponsor requirements:
- a. Test substance name
 - b. CAS number or code number
 - c. batch number
 - d. expiration date (if applicable)
 - e. storage conditions (at least minimum ^{and}/or maximum temp.)
- 2.3 Storage containers are to be assigned to a particular test substance until properly disposed of. All test substance containers will be retained until the final report is complete, unless an exemption has been granted by the EPA.

Disposal of Test, Substances

Chapter 7: TEST, REFERENCE, AND CONTROL SUBSTANCES
 AHETF-7.C.1.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: February 1, 2003	Previous Version Number: 7.C.0

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes how test substances are to be disposed of by the Agricultural Handlers Exposure Task Force (AHETF) or contract facilities, the documentation required at the completion of an AHETF study, and the AHETF policy on container retention.
- 1.2 This SOP has been updated to reflect current contact information for the US EPA as stated in section 3.5.

2.0 PROCEDURE

- 2.1 A reserve sample from each batch of test substance will be retained from each study more than four weeks in duration [EPA GLPs §160.105 (d)]. Storage time is only to be as long as the sample affords evaluation. Samples may only be discarded with written permission from the Study Director.
- 2.2 Samples of test substances that have been archived may be discarded after acceptance of the final report by the AHETF or returned to the AHETF Study Director. Written authorization must be obtained from the AHETF Study Director or designate prior to disposal of any of the test, control, or reference substances.
- 2.3 Disposition of all substances must be recorded on an appropriate inventory log.

SOP AHETF-7.C.1.

- 2.4 If the AHETF study was conducted using a registered or experimental material from an outside source or AHETF company member, the Study Director is responsible for assuring that the remaining test, reference, and control substances are returned to the supplier or manufacturer, if requested, or disposed of. Written authorization must be maintained in the AHETF study file upon the return or disposal of the test, control, or reference substances. Refer to SOP AHETF-7.A. for shipping guidelines or follow the appropriate contract facility SOP(s).
- 2.5 Once sponsor approval has been obtained, all materials will be properly disposed of by the AHETF or contract laboratories/test sites per federal, state and local regulations.

3.0 CONTAINER RETENTION

- 3.1 Label requirements for container handling and disposal after use (e.g., triple rinsing before disposal, or special conditions for disposal) will be considered part of the handling exposure period for each AHETF study. Containers will only be retained by the AHETF or designated facilities after handling activities have been completed.
- 3.2 All original test substance containers used in each AHETF study **will be retained** in compliance with the GLPs, unless an exemption is granted by the EPA. The location of the containers will be documented in the appropriate study file.
- 3.3 If a waiver for container retention is granted, then empty containers will not be retained; however, the following documentation must be maintained in the study data files:
- a. Information of shipments pertaining to each container leaving the storage site (e.g., shipping requests, bills of lading, carrier bills, monthly inventories, etc.)
 - b. Test substance receipt records at each testing facility or field site.
 - c. Complete usage logs of material taken from each container.

SOP AHETF-7.C.1.

- d. A record of the final destination of the container(s), including the place and date of disposal or reclaiming, and any appropriate receipts.
- 3.4 In addition, the AHETF will be responsible for the following documentation:
- a. A statement will be included in the final report indicating the compliance or noncompliance required by 40 CFR 160.12 describing that this exception to Good Laboratory Practices is in accordance with the conditions provided under the exemption.
 - b. An inventory of empty containers before disposal, including sufficient information to uniquely identify containers will be prepared and maintained; the inventory will be periodically updated to indicate the arrival and disposal of empty containers. NOTE: this inventory is considered raw data.
 - c. The identity of the locations of each facility where: test substances are stored; empty containers are stored prior to disposal; records of use, shipment, and disposal of containers are maintained; and the test substances were used in each study.
- 3.5 Individual study protocols will provide information regarding any GLP exemptions. Exemptions may be granted, based upon the design of the proposed studies, the length of time per study, and amount of material to be used.
- 3.6 Should the EPA request an inspection of the AHETF studies, the EPA will be notified - within two (2) weeks of the inspection - of the locations described in 3.3 c. This information will be sent to:

Rick Colbert, Director
Agriculture and Ecosystems Division (2225A)
Office of Compliance - USEPA Headquarters
Ariel Rios Building
1200 Pennsylvania Avenue, N. W.
Washington, DC 20460
202-564-2320
colbert.richard@epa.gov

Chapter 7: Test, Substance Chain of Custody
TEST, REFERENCE, AND CONTROL SUBSTANCES
AHETF-7.D.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>Wally Stauder</u>	DATE <u>01-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes how test substances will be identified and tracked for the Agricultural Handlers Exposure Task Force (AHETF) during scheduled studies.

2.0 PROCEDURE

- 2.1 All test substances will be shipped and handled according to SOP AHETF-7.A.
- 2.2 Each test substance will be identified according to SOP AHETF-7.B.
- 2.3 A chain of custody (COC) form will accompany each shipment of a test substance after receipt from the supplier. Either the appropriate AHETF representative or Study Director will initialize a COC form upon receipt of any compound.
- 2.4 Attachment 7-D-1 is an example of an acceptable chain of custody form.

SOP AHETF-7.D.0.

- 2.5 The form contains information on three phases for each test substance: initial shipment to field site(s), usage information on study, and disposal/return information upon trial completion. Each section must be addressed appropriately, and in a timely manner.
- 2.6 A new form must be used for additional shipments of the test substance(s) for each study, or for the transfer of the test substance(s) to another test site, or for the use on another AHETF study.
- 2.7 Copies of partially completed and fully completed forms should be sent to the Study Monitor upon completion of each stage of the study. The original form will be maintained in the raw data by the Study Director.
- 2.8 The completed form(s) will be placed in the study file for archiving upon completion of the study.

Example Test Substance Chain of Custody Form

Agricultural Handlers Exposure Task Force Chain of Custody			
AHETF Study No.:	Contents:	Priority:	Page:
Ship To:		Ship From:	
Shipper/Carrier:	Airbill No.:	Date Shipped/Initials:	
Comments:			
Shipped:	Description of Materials Sent:	Received:	
Date Received:		Received By/Company:	
Condition Received:			

Test and Reference Substance Analyses
Chapter 7: TEST, REFERENCE, AND CONTROL SUBSTANCES
AHETF-7.E.1.

Effective Date : February 27, 2004

APPROVAL <u><i>David Johnson</i></u>	DATE <u><i>May 24, 2004</i></u>
APPROVAL <u><i>Monty W. Denton</i></u>	DATE <u><i>June 2, 2004</i></u>
Last Revision Date: February 1, 2003	Previous Version Number: 7.E.0.

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes how test substances will be characterized and documented for all Agricultural Handlers Exposure Task Force (AHETF) studies.
- 1.2 This SOP was revised to explain the concept of test substance use in AHETF exposure studies and describe the specific analyses to be determined on AHETF test and references substances.

2.0 TEST SUBSTANCE DEFINITION AND USAGE

- 2.1 The USEPA defines "test substance" {§ 160.3 (7)} as "... a substance or mixture ... added to a test system in a study, which... is the subject of an application for a research or marketing permit, ... or, ... a substance used in a study to assist in characterizing the toxicity, metabolism, or other characteristics..."
- 2.2 In respect to this definition, the AHETF use of a "test substance" does not fall within this scope. The AHETF is utilizing commercially available, registered products to provide an analytical marker in the determination of exposure routes to agricultural workers mixing, loading, ^{and/or} applying agricultural pesticides under typical working conditions.

SOP AHETF-7.E.1.

- 2.3 The term “test substance” is used by the AHETF to describe all registered pesticides that may be used on an AHETF study for the sole purpose of providing detectable residues in the determination of a pesticide exposure profile.

3.0 ANALYTICAL INFORMATION AND DOCUMENTATION

- 3.1 The AHETF will obtain a GLP determination of the percent active ingredient for each lot of formulated test substance. The preferred means of obtaining this information is through a GLP certificate of analysis (COA) from the manufacturer. In the absence of a manufacturer’s GLP COA, the AHETF will determine the percent active ingredient under separate protocol using the manufacturer’s analytical methods, if readily available, or the designated analytical laboratory’s SOP if methods are not available. These analyses can be obtained prior to or concurrently with the field testing.
- 3.2 The AHETF prefers that GLP certified reference standards be used for all analyses. The percent purity will be documented in the analytical study file (A GLP certificate of analysis will be maintained by the manufacturer). If a non-GLP certified reference standard is available, the Study Director must be notified in advance and appropriate actions taken to ensure the integrity of the reference material(s).

Whole Body Sampling – Inner Dosimeters

Chapter 8: MATRIX SAMPLES
AHETF-8.A.3.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: April 30, 2006	Previous Version Number: 8.A.2.

US EPA ARCHIVE DOCUMENT

1.0 PURPOSE AND SCOPE

- 1.1. This Standard Operating Procedure (SOP) provides a description of procedures for collecting pesticide residues from whole body dosimeters worn by workers during the Agricultural Handlers Exposure Task Force (AHETF) exposure studies.
- 1.2. The inner dosimeter will be used as a collection medium and will be analyzed. The inner dosimeter will be worn over the worker's own undergarments and directly underneath the specified work clothing and personal protective equipment (PPE), if appropriate.
- 1.3. This SOP was revised to clarify the privacy allowed the volunteer workers in Sections 3.1 and 4.3.

2.0 MATERIALS REQUIRED

- 2.1. The following materials are required for using and collecting whole body dosimeter samples from each worker/replicate:
 - a. 100% cotton, white, long underwear (inner) — with long sleeves, round neckline and no elastic (pre-washed - see SOP AHETF-8.J.).
 - b. Disposable gloves (*i.e.*, latex)
 - c. Scissors

SOP AHETF-8.A.3.

- d. Cleaning solutions (*i.e.*, methanol, isopropanol, alcohol/water mixture, acetone, *etc.*)
- e. Sealable bags or other suitable bags
- f. Aluminum foil wrap
- g. Disposable paper or plastic mat
- h. Hangers, if appropriate
- i. Cooler with dry ice, or freezer

3.0 USE OF WHOLE BODY DOSIMETER

- 3.1. The worker(s) will be given a new inner dosimeter prior to initiation of each monitoring period. The workers will be allowed to change in a clean “privacy area”. Once the worker is inside the privacy area, a researcher of the same sex as the worker will remain outside of the privacy area and instruct the worker on how to put on the dosimeter. Disposable gloves should be worn by the worker and the research personnel to minimize contamination.
- 3.2. Care should be taken to provide clothing of adequate fit. The inner dosimeter arm and pant cuffs should not extend beyond the work clothing cuffs (wrists and ankles).
- 3.3. Cut the large excess off the pant legs and pull up the inner dosimeter arms so that the inner dosimeter will not come out from underneath the outer dosimeter during the performance of the activity.

4.0 COLLECTION PROCEDURE

- 4.1. Upon completion of the sock sample collection, as described in SOP 8.1 (if sock sample collection is required by the study), the inner dosimeters will be collected. The inner dosimeters must be collected after all other samples have been collected from the worker.
- 4.2. Disposable paper, plastic mat, or aluminum foil will be placed on the chairs and floor of the changing area to reduce cross-contamination. The materials will be changed after the processing of each worker.

SOP AHETF-8.A.3.

- 4.3. After completion of monitored activities and collection of other samples, the worker will return to the privacy area. Once the worker is inside the privacy area, just one researcher of the same sex as the worker will accompany the worker of the privacy area to assist with removing the dosimeter, to minimize cross contamination between the worker's clothing and the inner dosimeter, and to minimize loss of residues.
- 4.4. The research personnel collecting samples will always wear disposable gloves when handling any work clothing, dosimeters, and PPE. Gloves will be changed between handling PPE, work clothing, and inner dosimeter collection. Remove garments in a manner to avoid cross-contamination.
- 4.5. Ensure that the scissors have been decontaminated with solvent prior to use. Scissors must be cleaned between each worker's dosimeter.
- 4.6. Remove and discard any buttons from clothing.
- 4.7. As described in the study protocol, the inner dosimeters will be sampled in one of two methods. If the upper/lower method is used, follow Section 4.8 the six section method is used, then follow Section 4.9.
- 4.8. Cut the dosimeter into two (2) sections:
 - a. Lower Body (all sections below waist*)
 - b. Upper Body (all sections above waist*)

* Cut just below the second button from the bottom to separate the torso from the lower section.

Proceed to section 4.10 of this SOP.
- 4.9. Cut the inner dosimeter into six (6) sections:
 - a. Right & left upper arms (shoulder to elbow)
 - b. Right & left lower arms (elbow to cuff)
 - c. Front torso (above the waist*)
 - d. Rear torso (above the waist*)
 - e. Right & left upper legs (waist to knee)
 - f. Right and left lower legs (knee to cuff)

* Cut just below the second button from the bottom to separate the torso from the lower section. Cut along the seams to separate the front torso from the rear torso. Refer to Attachment A.

SOP AHETF-8.A.3.

Continue on to Section 4.10 of this SOP.

- 4.10. Inner dosimeters may be hung on hangers during the sampling as long as the dosimeters do not contact the floor or other dosimeters.
- 4.11. Place each sample section on a piece of aluminum foil (sufficient size to completely wrap the dosimeter). Do not allow samples to contact any surface before placement onto the foil. Ensure that the edges of the foil wrap are folded together to prevent loss of test material. Place a label on the aluminum foil that identifies the sample and place the sample into a labeled, sealable bag. Seal all bags.
- 4.12. There shall be either two (2) or six (6) inner dosimeter samples per worker, depending upon the protocol specified sampling method.

5.0 SAMPLING INTERVALS

- 5.1. Inner whole body dosimeters will be collected at the end of each monitoring period, unless otherwise instructed by the protocol.

6.0 FIELD STORAGE

- 6.1. Place samples collected during the study in the field in a cooler with dry ice or portable freezer until processed and placed into frozen storage for shipping at the end of the monitoring day (or as soon as practical). If dry ice is not available, the Study Director must be notified before sample collection and other suitable storage conditions must be noted in the raw data.

Attachment A

Diagram of Inner Dosimeter



Hand Wash Samples
Chapter 8: MATRIX SAMPLES
 AHETF-8.B.4.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: January 1, 2006	Previous Version Number: 8.B.3.

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) provides a description of procedures for collecting pesticide residues from worker’s bare hands during the Agricultural Handlers Exposure Task Force (AHETF) exposure studies.
- 1.2 This SOP was revised to clarify that the workers will have their hands washed prior to participating on an AHETF study, as stated in sections 4.1 and 5.1.

2.0 EQUIPMENT REQUIRED

- 2.1 The following materials are required for collecting dermal hand wash samples:
 - a. Metal or glass bowl (**Do not use plastic bowls for performing handwashes**)
 - b. Aerosol[®] OT Solution, 10% w/w. This is a concentrated solution of the anionic surfactant dioctyl sodium sulfosuccinate (also known as AOT) which will be diluted in water and used to wash hands (500 mL for each handwash).
 - c. Distilled or deionized water (in 1 gallon jugs, or other appropriate container)

SOP AHETF-8.B.4.

- d. Graduated cylinder or appropriate measuring device
- e. Glass jars with Teflon[®] lined lids, or equivalent
- f. Reclosable plastic bags (1 gallon size; optional for storage)
- g. Disposable gloves (*i.e.*, latex)
- h. Pipette(s) (*e.g.*, 2, 5, 10 mL, *etc.*)
- i. Cleaning solutions (*i.e.*, alcohol (methanol, isopropanol), alcohol/water mixture, acetone, *etc.*)
- j. Paper towels
- k. Cooler with dry ice or freezer

3.0 HAND WASH SOLUTION PREPARATION

- 3.1 The desired solution concentration is 0.01% v/v Aerosol[®] OT (AOT) in water (500 mL for each handwash). Sufficient quantities should be made for the projected number of handwashes to be collected on a daily basis, or within the allowable shelf life time period.
- 3.2 Pipette an appropriate amount of 10% w/w AOT solution into the water and dilute 1,000-fold to make a bulk 0.01% v/v AOT solution. For example, 3.8 mL of 10% AOT in one gallon of water or 4 mL of 10% OT in 4.0 liters of water. Document the brand of water (if store bought) and where it was purchased. If the water is **not** store bought, document the source. The AOT solution may be made up in plastic water jugs prior to use, for handwashes or field fortifications. Add the appropriate amount of AOT concentrate directly to the water in the jug or bottle, or other suitable container(s).

SOP AHETF-8.B.4.

- 3.3 Store the bulk AOT solution in glass jars, plastic bags, water jugs, or suitable container(s). The shelf life of the 0.01% Aerosol[®] OT solution at room temperature is 48 hours. Reclosable plastic bags may also be used for short-term storage of AOT solution aliquots to facilitate collecting handwash samples in the field.

4.0 WASHING PROCEDURE

- 4.1 Prior to participating in an AHETF exposure monitoring study, each worker will have their hands washed by a researcher according to the procedure outlined in this SOP. This will serve to clean the hands as well as providing some practice for the hand wash procedure that will be used in the study. The researcher will describe and assist with at least one washing procedure. The rinsate will be discarded.
- 4.2 At the end of the monitoring period, upon removal of the worker's personal protective equipment (PPE) and shoes/socks, the worker will be taken to a designated clean "privacy area" for removal of exposed outer clothing. For interim handwashes during the monitoring period, follow steps 4.5 through 4.9.
- 4.3 Disposable paper, plastic mat, or aluminum foil will be placed on the chairs and floor of the changing area to reduce cross-contamination. The materials will be changed after the processing of each worker.
- 4.4 Handwash samples must be collected **after** the outer clothing and PPE have been removed, or after sock dosimeters have been collected, as described in SOP 8.I, if applicable. Hand washes must be completed **before** the face/neck samples are collected.
- 4.5 Don clean disposable gloves, and carefully push up the whole body (inner) dosimeter cuffs from the worker's wrists. Have the worker place both hands over a bowl, and pour approximately 400 mL of 0.01% Aerosol[®] OT solution over the worker's hands for approximately 30 seconds. The worker will scrub their hands while the wash solution is slowly poured over the worker's hands.
- 4.6 The worker shall then immerse their hands in the 400mL of the wash solution in the collection bowl and scrub their hands in the solution for a minimum of 30 seconds.

SOP AHETF-8.B.4.

- 4.7 The worker should lift their hands out of the wash solution, and while holding their hands over the bowl, the remaining approximate 100 mL of Aerosol[®] OT is poured over the worker's hands to rinse. Allow the hands to drain for approximately five seconds.
- 4.8 Carefully pour the entire 500 mL of rinsate into a pre-labeled jar seal and place in cool storage. (A total of 500 mL must be collected for each handwash sample.)
- 4.9 Clean the bowl with solvent between workers. Rinse once with clean water, followed by two rinses with solvent, followed by a final rinse with water. Allow the bowl to air dry or wipe dry with a paper towel before reusing.

5.0 SAMPLING INTERVALS

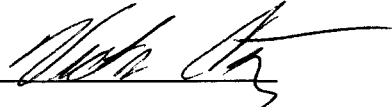
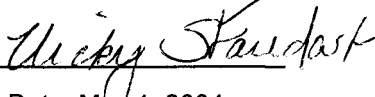
- 5.1 Workers' hands will be washed with the diluted AOT solution with the assistance of a researcher, and prior to the monitoring period. This hand wash sample will be discarded.
- 5.2 Handwash samples should be collected whenever the workers would normally wash their hands; (*i.e.*, before eating, before using the bathroom, *etc.*) unless specified differently in the study protocol. For interim handwashes, carefully unbutton the cuffs of the worker's outer shirt and push up the sleeves before washing hands.
- 5.3 After the monitoring period is completed, one final wash will be collected from each worker.

6.0 FIELD STORAGE

- 6.1 Place samples collected during the study in the field in a cooler with dry ice or portable freezer until processed and placed into frozen storage for shipping at the end of the monitoring day (or as soon as practical). If dry ice or portable freezer is not available, the Study Director must be notified before sample collection and other suitable storage conditions must be noted in the raw data.

Dermal Face/Neck Wipe Samples
Chapter 8: MATRIX SAMPLES
AHETF-8.C.3.

Effective Date : April 30, 2006

APPROVAL 	DATE <u>4/26/06</u>
APPROVAL 	DATE <u>5/11/06</u>
Last Revision Date: May 1, 2004	Previous Version Number: 8.C.2.

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes procedures for collecting pesticide residues from workers' face/neck during the Agricultural Handlers Exposure Task Force (AHETF) worker exposure studies.
- 1.2 This SOP was revised to clarify the number of layers each wipe/pad should have in sections 2.1.a and 3.1.

2.0 EQUIPMENT REQUIRED

- 2.1 The following materials are required for collecting dermal face/neck samples:
 - a. 100% cotton gauze (8 layers, 4" x 4"/10cm x 10cm sponges)
 - b. Anionic detergent solution (Aerosol[®] OT - sodium dioctyl sulfosuccinate).
 - c. Syringe or pipette
 - d. Disposable gloves (*i.e.*, latex)
 - e. Aluminum foil
 - f. Resealable bags or glass jars with Teflon-lined lids

SOP AHETF-8.C.3.

- g. Cooler with dry ice or a freezer

3.0 SAMPLING PROCEDURE

- 3.1 The field personnel collecting samples will wear clean, disposable gloves while collecting these dermal samples. (Note: some packaging may contain two sponges; check to make sure each sponge is 8 layers)
- 3.2 Dispense approximately 4 mL of the detergent solution (0.01% Aerosol® OT) on the gauze sponge with the syringe or pipette (or other appropriate means of moistening the sponge).
- 3.3 Thoroughly wipe the test subject's face/neck (front & back) with the moistened sponge.
- 3.4 Repeat steps 3.2 and 3.3 again, for a total of two dermal wipes per sample. Wrap both sponges in aluminum foil (only if using a sealable bag) and place in the prelabelled bag otherwise place both wipes in a prelabelled jar, close the top, and place in frozen storage.

4.0 SAMPLING INTERVALS

- 4.1 Prior to the exposure replicate, one dermal face/neck wipe sample will be collected from each worker and the wipes discarded.
- 4.2 One dermal face/neck wipe sample will be collected prior to eating.
- 4.3 After the replicate is completed, one dermal face/neck wipe sample will be collected from each worker after the hand wash sample is collected per SOP 8.B. and before removal of whole body dosimeters. The wipes will be combined with the samples collected prior to eating, if applicable. If more than two samples (4 wipes) are in a sample bag or jar; the laboratory must be notified as to the total number in the container.

5.0 FIELD STORAGE

- 5.1 Place samples collected during the study in the field in a cooler with dry ice or portable freezer until processed and placed into frozen storage for shipping at the end of the monitoring day (or as soon as practical). If dry ice is not available, the Study Director must be notified before sample collection and other suitable storage conditions must be noted in the raw data.

Collection of Air Samples Using OVS Tubes

Chapter 8: MATRIX SAMPLES
AHETF-8.D.2.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: March 10, 2003	Previous Version Number: 8.D.1.

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) provides a description of procedures for collecting air samples using OSHA Versatile Sampler (OVS) tubes during the Agricultural Handlers Exposure Task Force (AHETF) exposure studies.
- 1.2 The OVS tube will be positioned in the breathing zone of the worker. The air will be sampled at a flow rate applicable to the characteristics of the OVS tube. A plastic tube holder will be used to position and protect the OVS tubes on the worker.
- 1.3 This SOP was revised to change the term “replicate” to monitoring period or worker.

2.0 MATERIALS REQUIRED

- 2.1 The following materials are required for collecting air samples from each worker:
 - a. OVS Tubes, 13 mm glass tubes [e.g.; mfr. SKC, Inc. with 270 mg & 140 mg absorbent beds separated by polyurethane plug, and glass fiber filter at the inlet], or equivalent
 - b. Plastic OVS tube holder

SOP AHETF-8.D.2.

- c. Tygon[®] or equivalent tubing and clips for securing tubing to the worker (a minimum of two required)
- d. Low volume personal air-sampler pump (battery operated)
- e. Air flow meter (*e.g.*, Kurz Mass Flow Meter, rotameter, bubble flowmeter, or equivalent)
- f. Sealable bags (*e.g.*, Ziploc[®] freezer bags)
- g. Disposable gloves (*i.e.*, latex)
- h. Cooler with dry ice, or freezer

3.0 AIR-SAMPLER PUMP PREPARATION

- 3.1 Place air-sampler pumps on chargers before each use. If the pump is fully charged proceed to 3.2.
- 3.2 Adjust air-sampler pump flow rate before use in each monitoring period. Air sample pump flow rate adjustment will take place on the day prior to or the same day the pumps are to be used.
- 3.3 Adjust air pumps to the targeted airflow rate with the appropriate OVS tube/ sampling train attached.
- 3.4 Follow appropriate contractor SOPs for the individual calibration methods for contractor equipment.
- 3.5 Adjust the airflow rate to appropriate target rate as defined in the study protocol [*e.g.*, 2 liters per min (L/min)] and document the flow rate and pump number in the raw data.
- 3.6 Turn off the air-sampler pump and set aside. Repeat steps 3.3 and 3.5 until all needed sampling pumps (including backups) have been adjusted.

4.0 SAMPLING PREPARATION

- 4.1 Remove the outlet cap from the OVS tube and connect the outlet of the tube (the smaller 6 mm end) to the end of the air tubing that is connected to an adjusted personal air-sampler pump. Be sure the glass fiber filter is attached to the inlet (the larger 13 mm end) and is left open.
- 4.2 Position a belt snugly around the worker's waist, or use that worker's belt (if appropriate) to support the sampling pump. Attach the pump to the belt using the clip on the pump. Position the pump wherever it feels most comfortable to the worker.
- 4.3 Place the OVS tube over the shoulder of the worker (to the front of the torso) in the approximate position for sampling (in the breathing zone of worker).
- 4.4 Use a binder clip to attach the tubing, approximately at its midpoint, to the worker's clothing so that it will not interfere with the normal work operations nor catch on anything. The tubing may be run inside the worker's clothes. If tubing is run inside, ensure that clean, decontaminated tubing is used. **Do not reuse contaminated tubing!**
- 4.5 Remove the inlet cap and start the pump. Check the flow rate with a calibrated rotameter (Please refer to the AHETF or appropriate contract testing facility SOP). Adjust the air-sampler pump flow rate if the measured flow rate deviates greater than $\pm 5\%$ from the target flow rate.
- 4.6 Document the pump number, start time and the flow rate measured with the rotameter in the raw data.
- 4.7 Place the OVS tube in the plastic holder and clip the holder to the workers' collar (in the breathing zone). If the holder does not have an integral clip, use a binder clip, wire or plastic tie to attach to the worker's collar or lapel. Be sure the tubing is not crushed or restricted when attached. The inlet must face downward, in a vertical orientation.
- 4.8 Observe the worker for a few minutes upon starting to work to ensure the sampling apparatus is functioning properly, and is not interfering with the worker. Periodically monitor the pump during the monitoring period to ensure it is functioning properly.

SOP AHETF-8.D.2.

- 4.9 Pumps will run continuously throughout the duration of the monitoring period, including lunch and other breaks.
- 4.10 Should a pump malfunction during the monitoring period, it will be replaced immediately with a new, prior adjusted pump (section 3). Remove the OVS tube from the old pump and attach it to the new, adjusted pump, and repeat steps 4.6 through 4.9. These activities will be documented in the appropriate study file(s) and include (at a minimum) the time the malfunction was discovered, the time reading on the pump (if available), the time the new pump was started and the new measured flow rate.
- 4.11 At the end of the monitoring period, remove the OVS tube from the plastic protective holder, measure the terminal flow rate with the rotameter, turn off the pump, record the stop time and flow rate, and remove the pump, tubing and OVS tube from the worker.

5.0 SAMPLING PROCEDURE

- 5.1 Upon completion of the monitoring period, remove the OVS tube from holder, cap both ends and place into frozen storage (*i.e.*, on dry ice or in a freezer).
- 5.2 Clean disposable gloves will be worn by sampling personnel to minimize any contamination of the OVS tube. Gloves will be changed after handling each tube.

6.0 SAMPLING INTERVALS

- 6.1 OVS tubes will be collected at the end of the monitoring period, unless otherwise instructed by the protocol.

7.0 FIELD STORAGE

- 7.1 Place samples collected during the study in the field in a cooler with dry ice or portable freezer until processed and placed into “permanent” frozen storage for shipping at the end of the monitoring day (or as soon as practical). If dry ice is not available, the Study Director must be notified before sample collection and other suitable storage conditions must be noted in the raw data.

Fortification of Matrix Samples**Chapter 8: MATRIX SAMPLES
AHETF-8.E.4.**

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: April 30, 2006	Previous Version Number: 8.E.3

1.0 PURPOSE AND SCOPE

- 1.1 This SOP describes the methods by which agricultural worker exposure monitoring matrices, (*i.e.*, inner dosimeters, hand washes, face/neck wipes, inner socks, outer head patches, inner head patches, and OVS tubes) are to be spiked. This SOP applies to the use of all worker exposure matrices when used for producing field fortification recovery data for the Agricultural Handlers Exposure Task Force (AHETF).
- 1.2 This SOP was revised to change the term “replicate” to monitoring period or worker.

2.0 EQUIPMENT/REAGENTS REQUIRED

- 2.1 The following examples of equipment and solutions are required for each day that field fortifications are to be conducted:
 - a. Exposure monitoring matrix samples based upon protocol specified monitoring matrices (inner dosimeter material cut according to SOP AHETF-8.A. [upper and lower sections for two section monitoring or upper/lower arms & legs and front/rear torso for six section monitoring], moistened face/neck wipes, OVS tubes, and hand wash solutions, and if required, 50 cm² and 100 cm² head patches [made of inner dosimeter material], and socks).

SOP AHETF-8.E.4.

- b. Appropriate containers for fortified matrix samples (e.g., bags, bottles, jars, etc.)
- c. Appropriate pipettes (e.g. 1.0 mL, non-graduated Pasteur pipettes, etc.)
- d. Appropriate syringe (e.g., 100 µL)
- e. Distilled or deionized water
- f. Anionic detergent solution (0.01% v/v Aerosol® OT 75). Refer to the SOP AHETF-8.B for solution preparation.
- g. Paper towels
- h. Disposable gloves
- i. Aluminum Foil
- j. Rinsing solvent (to be the same as the solvent used to make spiking solutions)

3.0 SPIKING MATERIALS

3.1 Spiking materials may be in the following forms:

- a. Active ingredient (ai) in an organic solvent
- b. Formulated product in water
- c. Formulated product pre-weighed into a container in which a specific amount of water is to be added in the field prior to being spiked onto (into) a matrix material.
- d. Pre-spiked OVS tubes.

SOP AHETF-8.E.4.

4.0 SPIKING TECHNIQUES

- 4.1 There are two (2) basic procedures that may be used for the fortification of worker dermal exposure matrices for the AHETF. They are by pipette and by vial.
- 4.2 When applying a spiking material to the various matrices, it is important to ensure that the solution/suspension gets well mixed prior to spiking and/or distributed as evenly as possible.
- 4.3 The spiking material needs to be distributed mechanically, typically with a pipette or vial, over the largest amount of matrix area as possible.
- 4.4 **Spiking in solvent:** A volume, typically 1 mL, of spiking solution will be drawn up into the pipette and then applied appropriately to the matrix of choice.
- 4.5 **Spiking formulated product in water:** A well-mixed aliquot, typically 1 mL, will be taken from a well-shaken bottle of the formulation suspended in water. The shaking may be done by hand, on a stirring plate, or using a mechanical shaker. Once the suspension looks evenly distributed, an aliquot is taken and applied appropriately to the matrix of choice.
- 4.6 **Spiking using entire solution vials:** Vials containing a known aliquot of a known concentration of spiking material will be sent to the field along with instructions on how to apply the spike to a matrix. The person doing the spiking will take a given spiking vial, unscrew the cap, and apply the contents to the matrix. The contents may be poured directly from the vial or removed via a Pasteur pipette (or equivalent). Use of a pipette may be desired for smaller matrices where more exact placement of material is necessary. The vial and pipette will sometimes be rinsed several times with the solvent (*e.g.*, deionized or distilled water, acetone, acetonitrile, *etc.*) that was used to prepare the solution and applied to the matrix or as directed by the analytical laboratory (see below). The vial shall be retained with the fortified sample. The cap should be discarded and should not be rinsed. Vials should be marked with a label that may be tied to the vial with string or is a self adhesive label, which may be removed easily from the vial and will not interfere with analysis of fortified matrices.

5.0 SPIKING PROCEDURES

5.1 Inner Dosimeters

- a. The dosimeters must be placed on a piece of aluminum foil prior to spiking. After spiking and weathering (if applicable), the sample will be wrapped in the same piece of foil it was placed on for spiking and weathering then inserted into the sample container.
- b. The spiking material will be added to inner dosimeters; ensure the fortification is added to a dosimeter that has been folded to provide at least 6 layers of cloth. This insures that all the material is absorbed by the cloth.
- c. When spiking with solution vials, the person doing the spiking will unscrew the cap and apply the contents to the matrix. The vial will be rinsed several times as directed by the analytical laboratory with the solvent that was used to prepare the solution or suspension. This may be done several times, however; too much solvent will cause the spike to run through the fabric, so judgment is needed. The empty spiking vial will be placed on its aluminum foil with the matrix prior to folding the foil.
- d. When pipetting the solution onto the dosimeter, the tip of the pipette may be used to help distribute the spike (typically 1 mL) in lines evenly over the surface of the dosimeter. At no time can there be a bead of spiking material left on the surface. (The spiking liquid may tend to bead up on the surface. Gently pushing the pipette tip over the bead will help to get the liquid into the matrix.)
- e. For dosimeters exposed to ambient conditions, the inner dosimeters will be folded over after fortification and covered with a single layer of shirt material during exposure. Effort should be made to ensure that the spiking solution has been completely absorbed by the material prior to covering.

SOP AHETF-8.E.4.

5.2 Hand Washes

- a. When spiking from a solution or suspension in the field, the appropriate amount of spiking solution (typically 1 mL) will be added to the hand wash.
- b. When spiking with vials, the cap to the solution vial will be unscrewed from the vial and discarded without rinsing. The contents will be added to a 500 mL Aerosol OT (AOT) sample and the vial then dropped into the sample. The sample will then be swirled or the jar inverted to ensure proper mixing of the spiking material with the sample matrix.

5.3 OVS tubes

- a. The tubes will be spiked at the laboratory with the proper amount of analytical standard. The tubes will always be spiked with an ai solution using a syringe. The spike will be applied by inserting the needle through the glass fiber filter and approximately one quarter of the way into the front sorbent bed.
- b. Depress the syringe plunger slowly to avoid the ai solution from “bleeding out” of the sorbent and adhering to the glass tube. Each tube will be spiked with a minimum of 5 μ L up to, but not exceeding, 100 μ L of solution. The actual amount of spiking solution to use will be determined by the analytical laboratory and documented in the raw data.
- c. Tubes fortified in the laboratory will be sent frozen in plastic bags to the field. The bags will be to be taken out of the freezer and allowed to come to ambient temperature before they are used in the field. Just before they are to be put on the personal air sampling pumps, they should be taken out of the bag and allowed to finish equilibrating with the environment. They then will be placed onto the pumps and air pulled through them for the approximate length of time the workers are in the field.

SOP AHETF-8.E.4.

5.4 Face/Neck Wipes

- a. Pre-wet two face/neck wipes as described for field samples in SOP AHETF-8.C.
- b. When spiking with solution vials, the two gauze pads will first be placed into the sample jar or on clean foil. The contents of the vial will then be transferred onto the gauze pads. The vial will be placed with the sample without being rinsed. The cap will be discarded without rinsing. The sample will be wrapped in foil and placed in a plastic bag, or the jar will be capped and sealed after fortification, as appropriate. In the laboratory, the vial will be rinsed as part of the extraction procedure.
- c. When pipetting the solution onto the wipe, the tip of the pipette may be used to help distribute the spike (typically 1 mL) in lines evenly over the surface of the wipe, if necessary.

5.5 Socks

- a. The socks must be placed on a piece of aluminum foil prior to spiking. After spiking and weathering, the sample will be wrapped in the same piece of foil it was placed on for spiking and weathering then inserted into the sample container.
- b. When adding spiking material to socks, ensure the sock sample consists of 2 socks (1 pair). The actual spiking material will be to be placed on the one sock (2 layers) that is closest to the foil.
- c. When spiking with prepared solutions in vials, the person doing the spiking will unscrew the cap and apply the contents to the matrix. The cap will be discarded without rinsing. The vial will be rinsed several times with the solvent that was used to prepare the solution, as directed by the analytical laboratory. Multiple rinses may be done; however, too much solvent will cause the spike to run through the fabric, so judgment is needed. Place the empty spiking vial in its aluminum foil with the matrix.

SOP AHETF-8.E.4.

- d. When pipetting the solution onto the dosimeter, the tip of the pipette may be used to help distribute the spike (typically 1 mL) in lines evenly over the surface of the dosimeter. At no time can there be a bead of spiking material left on the surface. (The spiking liquid may tend to bead up on the surface. Gently pushing the pipette tip over the bead will help to get the liquid into the matrix.)
- e. For socks exposed to ambient conditions, place two socks together on aluminum foil, pour the spiking solution evenly on the upper sock, then fold the two socks over each other. Outer dosimeter shirt material **should not** be placed over the sock sample.

5.6 Outer Head Patches

- a. For field fortification samples, only, an outer head patch will consist of 6 layers of inner dosimeter material, each layer cut to a 50 cm² area wrapped in aluminum foil. The foil should be placed underneath the pile of patches and used to wrap the weathered spiked patch sample once the weathering period is completed.
- b. The field fortification suspensions will be applied to the topmost layer of patches. The additional layers will be used to ensure that no spiking material leaches out onto the foil that underlies the pile of patches.
- c. Outer head patches **will not be** covered during the weathering period.

5.7 Inner Head Patches

- a. For field fortification samples, only, an inner head patch will consist of 4 layers of inner dosimeter material, each layer cut to a 100 cm² area, wrapped in aluminum foil. The foil should be placed underneath the pile of patches and used to wrap the weathered spiked inner dosimeter patch sample once the weathering period is completed.

SOP AHETF-8.E.4.

- b. The field fortification suspension will be applied to the topmost layer of material. The additional layers will be used to ensure that no spiking material leaches out onto the foil that underlies the pile of patches.
- c. Inner head patches will be covered with chemical resistant headgear similar to the type worn by the workers during the application period, or other suitable material to simulate the headgear, as approved by the Study Director.

6.0 FORTIFICATION SAMPLE IDENTIFICATION AND HANDLING

- 6.1 Refer to SOP AHETF-8.F. for the procedures to uniquely identify fortification samples.
- 6.2 Fortification samples that are exposed under the open sky should have the necessary materials to protect the samples in the event of rain.
- 6.3 Fortification samples are packaged, stored and transported in the same manner as the test samples for a particular matrix. The fortification samples should not be placed into the same shipping/storage container with control samples or with field samples.

Sample Identification
Chapter 8: MATRIX SAMPLES
 AHETF-8.F.4.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: April 30, 2006	Previous Version Number: 8.F.3.

US EPA ARCHIVE DOCUMENT

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes the procedures to uniquely identify field samples collected during Agricultural Handlers Exposure Task Force (AHETF) worker exposure studies.
- 1.2 This SOP was revised to change the term “replicate” to monitoring period or worker.

2.0 NUMBERING PROCEDURE

- 2.1 All samples (exposure and fortification) will be identified by the protocol (AHETF study) number and a unique identification number that describes the type of sample. Individual sample numbers (worker monitoring numbers) may not be reused should a specific worker’s monitoring period be started and then cancelled, even if no samples were collected for analysis. Additional sample number(s) will be added to the sample list to account for the lost worker(s).
- 2.2 The sample identification number will be formatted as an alphanumeric string, separated by hyphens (-) between each code pair:

SN-XX-NN-YY-ZZ

- 2.3 The identities of the code pairs are listed on the following page.

SOP AHETF-8.F.4.

2.4 The following is a list of the codes pairs to be used in the sample identification format SN-XX-NN-YY-ZZ:

SN: The last two digits of the AHETF five character study number.

XX: A code for the type of sample:

- WS - Worker Sample
- FF - Field Fortification Sample

NN: For exposure samples - The two-digit worker sample number. This can be modified to distinguish between applicator and mixer/loader replicates, only when less than 10 monitored workers each, as follows:

- Ax - Worker Sample – Applicator only with sequential sample no.
- Mx - Worker Sample – Mixer only with sequential sample no.

For exposure field fortification samples - A two digit number to denote the study day of fortification (e.g. day 01, 02, 03) depending upon the actual day of the study the samples are fortified on.

YY: A code for the type of the samples

- ID - Inner Dosimeter
- AR - Air Sampling Media
- HW - Hand Washes
- FW - Face/Neck Wipe

ZZ: Unique 2 Character Codes For All Samples

Fortifications (FF samples only)	Dosimeters (FS ID samples only)
Tx* - travel spike	LB - lower body
Lx* - low spike	UB - upper body
Mx* - mid spike	LA - lower arms
Hx* - high spike	UA - upper arms
Cx* - control sample	FT - front torso
	RT - rear torso
	UL - upper legs
	LL - lower legs
	SX - socks
	OH - head patch, outer
	IH - head patch, inner

- A sequential number will be noted for each control and fortified sample to note worker samples.

SOP AHETF-8.F.4.

Air – Handwash - Face/Neck Wipe Samples
(Worker FS, AR, HW & FW samples only)

Sequential number to denote multiple samples (if more than one sample is collected) from the same worker. -01 is the first sample collected, -02 is the second, *etc.* If only one wash or wipe sample is collected, then -01 will be the only sample number used. If more than one must be collected during the monitoring period, use a sequential number for each, with the highest number used for the final sample collected that day.

2.5 The following is a list of example sample ID numbers:

- 01-WS-02-ID-LL: Study AHE01 - worker sample - worker 2 - inner dosimeter - lower legs
- 41-WS-A5-ID-BL: Study AHE41 - worker sample - applicator 5 - inner dosimeter - lower body
- 05-WS-05-HW-01: Study AHE05 - worker sample - worker 5 - first hand wash collected (*i.e.* worker used the bathroom before end of rep.)
- 05-WS-05-HW-02: Study AHE05 - worker sample - worker 5 – second hand wash collected, in this instance at the end of the worker activity
- 05-WS-03-AR-01: Study AHE05 - worker sample - worker 3 - air sample
- 05-WS-09-FW-01: Study AHE05 - worker sample - worker 9 - face/neck wipe
- 06-WS-07-SX-01: Study AHE06 - worker sample - worker 7 - socks
- 07-WS-01-OH-01: Study AHE07 – worker sample - worker. 1 - outer head patch
- 07-FF-01-IH-L1: Study AHE07 - Field Fort. - first study day - inner head patch - first low level
- 11-FF-01-ID-L2: Study AHE11 - Field fort. - first study day - inner dosimeter - second low level
- 22-FF-03-FW-H1 Study AHE22 - Field fort. - third study day - face/neck wipe - first high level [this may be the *second* day of fortifications for AHE22]
- 22-FF-03-FW-H2: Study AHE22 - Field fort. - third study day - face/neck wipe - second high level

Worker Clothing Acceptability CriteriaChapter 8: **MATRIX SAMPLES**
AHETF-8.G.2.

Effective Date : September 1, 2003

APPROVAL <i>David Johnson</i>	DATE <u>08-29-03</u>
APPROVAL <i>Misty Stewart</i>	DATE <u>9-11-03</u>
Last Revision Date: May 25, 2003	Previous Version Number: 8.G.1.

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes the criteria to follow when evaluating individual workers' outer work clothing prior to participation in an Agricultural Handlers Exposure Task Force (AHETF) worker exposure study.
- 1.2 These criteria were selected based upon the criteria presented in the Worker Protection Standards (WPS) 40 CFR 170, and in the spirit of product stewardship.
- 1.3 This SOP was revised to allow the workers the choice to wash their own clothing prior to participation on an AHETF study or have their work clothes laundered by AHETF designated personnel as in section 2.1.5. and to add this section as an explanation.

2.0 ACCEPTANCE/REJECTION CRITERIA

- 2.1 The Study Director will evaluate each worker's outer (work) clothing prior to his or her participation in an AHETF worker exposure study using the following criteria as guidance:
 - 2.1.1 **Condition:** Work clothing should be in relatively good condition. Clothing that does not comply with the spirit of the WPS (e.g. clothing with large tears, holes, rips, several missing buttons, or other defects that present a significant exposure to the worker's skin or inner dosimeter) will not be accepted for use during the study. In such cases, if the Study Director feels appropriate, the AHETF will provide the worker with new outer work clothing.

SOP AHETF-8.G.2.

- 2.1.2 **Coverage:** Only long sleeves and long pants are acceptable. Sleeves and pant legs may not be rolled-up during the exposure phase of the study. Rolled-up sleeves, T-shirts, and shorts will not be accepted for use during the study.
- 2.1.3 **Fit:** The outer clothing must completely cover the inner dosimeter. Clothing that is too short, whether during movement or at rest will not be accepted for use during the study.
- 2.1.4 **Size:** Work clothing must be loose enough to allow for wearing an inner dosimeter under the work clothing, and still completely cover the inner dosimeter. Clothing that is too tight to allow the use of the inner dosimeter garment or does not sufficiently cover the inner dosimeter will not be accepted for use during the study.
- 2.1.5 **Cleanliness:** Workers' clothing should be reasonably clean prior to participation. Clothing should be free from fresh soiling or chemical exposure. Stains and discolorations might be acceptable, if from a previous event. Any clothing that is freshly or grossly soiled, or has any distinct pesticide odors or stains will not be accepted for use during the study.
- 2.2 All articles of a worker's outer clothing must be laundered prior to participation in an AHETF exposure study. Workers will be notified in advance of this criterion and should make arrangements to have their work clothes laundered. If necessary, clothing will be collected by the AHETF prior to the start of the study, laundered with detergent by the AHETF, and returned to the worker at the start of their exposure period.
- 2.3 Should the Study Director deem any article of a worker's clothing unacceptable, that specific article shall be replaced with a clean, new garment provided by the AHETF.
- 2.4 The Study Director will document each article of clothing replaced and the reasons for the rejection of the original workers' clothing in the raw data.
- 2.5 For exposure scenarios where low exposure is expected (e.g., closed-system mixing and loading), only AHETF-provided outer garments will be worn.

Head Patch Samples
Chapter 8: MATRIX SAMPLES
 AHETF-8.H.2.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: April 1, 2003	Previous Version Number: 8.H.1.

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes procedures for collecting pesticide residues from worker's head during the Agricultural Handlers Exposure Task Force (AHETF) worker exposure studies.
- 1.2 This SOP was revised to clarify section 2.1.a, that head patch material will be pre-washed.

2.0 EQUIPMENT REQUIRED

- 2.1 The following materials are required for collecting head patch samples:
 - a. 100% cotton inner dosimeter (1 layer, 100 cm² for inner & 50 cm² for outer, cut from a whole body inner dosimeter, excluding and seams, collars, cuffs, or buttons; pre-washed – see SOP AHETF-8.J.)
 - b. Disposable gloves (*i.e.*, latex)
 - c. Aluminum foil
 - d. Resealable bags or glass jars
 - e. Cooler with dry ice or a freezer

SOP AHETF-8.H.2.

- f. Suitable mechanism for attaching patch to worker's head and outside of hat or chemical-resistant (CR) headgear

3.0 PATCH PLACEMENT

- 3.1 The inner head patch will be placed at the crown of head, and the edges must not extend beyond the coverage provided by the hat or CR headgear. The inner patch will be secured to the worker's head via nonabsorbent cord(s), which will be cut off during collection.
- 3.2 The outer head patch will be placed on the top of the hat or CR headgear in a manner that will not compromise the integrity of the hat and will remain securely attached even if wet. Portions of the patch where it attaches to the headgear/hat will be cut off during collection.

4.0 SAMPLING PROCEDURE

- 4.1 The research personnel collecting samples will wear clean, disposable gloves while collecting these patch samples.
- 4.2 The head patches will be collected after the research personnel have checked the air pump flow rate and collected the OVS tube sample.
- 4.3 Outer head patch(s) attached to the worker's hat or CR headgear will be removed by the research personnel after the worker removes their headgear. Using clean scissors cut the outer head patch along the prescribed lines prior to placing in the sample container. Wrap the patch in aluminum foil and place it in the appropriately labeled container, close the container, and then place in frozen storage. Research personnel must change gloves after handling the outer head patch.
- 4.4 After the worker has removed their hat or CR headgear, the inner head patch from the worker's head will be removed by the research personnel. Research personnel must wear clean gloves to collect the inner head patch. Cut the cord(s) used to secure the patch to the worker's head and discard before placing the inner head patch in a sample container. Wrap the patch in aluminum foil and place it in the appropriately labeled container, close the container, and then place in frozen storage.

SOP AHETF-8.H.2.

5.0 SAMPLING INTERVALS

- 5.1 One inner and outer head patch sample will be collected from each worker at the end of the monitoring period.
- 5.2 Should it become necessary to replace an inner or outer head patch sample during a replicate, the worker will be taken to a clean area, the existing patch will be properly collected as described in Section 3.0, and a replacement patch placed on the worker. All additional patches will be documented in the raw data, and multiple head patches will be combined in one container. The total number of patches in a sample should be noted for the analytical laboratory.

6.0 FIELD STORAGE

- 6.1 Place samples collected during the study in the field in a cooler with dry ice or portable freezer until processed and placed into frozen storage for shipping at the end of the monitoring day (or as soon as practical). If dry ice is not available, the Study Director must be notified before sample collection and other suitable storage conditions must be noted in the raw data.

Foot Sampling – Socks
Chapter 8: MATRIX SAMPLES
 AHETF-8.1.3.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: January 1, 2006	Previous Version Number: 8.1.2.

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) provides a description of procedures for collecting pesticide residues from workers' feet by use of cotton socks worn by workers during the Agricultural Handlers Exposure Task Force (AHETF) exposure studies.
- 1.2 The cotton sock dosimeter will be used as a collection medium and will be analyzed. The socks will be worn under the worker's own socks and shoes.
- 1.3 This SOP was revised to clarify section 2.1.a that socks will be pre-washed.

2.0 MATERIALS REQUIRED

- 2.1 The following materials are required for using and collecting sock dosimeter samples from each worker:
 - a. 100% cotton, lightweight socks, ankle high (pre-washed – see SOP AHETF-8.J.)
 - b. Disposable gloves (*i.e.*, latex)
 - c. Scissors

SOP AHETF-8.I.3.

- d. Cleaning solutions (*i.e.*, methanol, isopropanol, alcohol/water mixture, acetone, *etc.*)
- e. Sealable bags or other suitable containers
- f. Aluminum foil wrap
- g. Disposable paper or plastic mat
- h. Cooler with dry ice, or freezer

3.0 USE OF SOCK DOSIMETER

- 3.1 If specified in the study protocol that sock/foot dosimetry will be worn and collected, the worker will be given a new pair of socks prior to initiation of each monitoring period. These socks will be worn on bare feet under the worker's normal work socks and shoes/boots. The worker and the research personnel, to minimize contamination, should wear disposable gloves whenever handling the dosimeters.

4.0 COLLECTION PROCEDURE

- 4.1 The worker will be taken to a designated clean "privacy area" for removal of exposed clothing.
- 4.2 Disposable paper, plastic mat, or aluminum foil will be placed on the chairs and floor of the changing area to reduce cross-contamination. The materials will be changed after the processing of each worker.
- 4.3 The research personnel collecting samples will always wear disposable gloves when handling any work clothing, dosimeters, and PPE. Gloves will be changed between handling PPE, work clothing, and dosimeter collection. Remove garments in a manner to avoid cross-contamination.
- 4.4 The worker will remove their work shoes/boots before entering the "privacy" area. The worker's socks will remain on the worker, over the sock dosimeters, until he/she removes them.

SOP AHETF-8.I.3.

- 4.5 After removal of the worker's outer clothing (first shirt, then pants, then work socks), and before the hand wash and face/neck wipe samples have been collected, the research personnel will collect the sock dosimeters.
- 4.6 Both left and right socks will be placed on a piece of aluminum foil (sufficient size to completely wrap the socks). Do not allow samples to contact any surface before placement onto the foil. Ensure that the edges of the foil wrap are folded together to prevent loss of test material. Place a label either on the aluminum foil or sample container that identifies the sample and place the sample into a labeled, sealable container. Seal all containers.

5.0 SAMPLING INTERVALS

- 5.1 Sock dosimeters will be collected at the end of each monitoring period, unless otherwise instructed by the protocol.

6.0 FIELD STORAGE

- 6.1 Place samples collected during the study in the field in a cooler with dry ice or portable freezer until processed and placed into frozen storage for shipping at the end of the monitoring day (or as soon as practical). If dry ice is not available, the Study Director must be notified before sample collection and other suitable storage conditions must be noted in the raw data.

Laundering of Dosimeter Materials

**Chapter 8: MATRIX SAMPLES
AHETF-8.J.1.**

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: April 30, 2006	Previous Version Number: 8.J.0

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) provides a description of procedures for laundering whole body inner dosimeter garments, head patch material, and sock dosimeters to be worn by workers or used for field fortifications during the Agricultural Handlers Exposure Task Force (AHETF) exposure studies.
- 1.2 Inner dosimeter garments, head patch material, and sock dosimeters must be washed prior to use in an AHETF worker exposure study.
- 1.3 This SOP was re-titled and revised to include sock and head patch dosimetry.

2.0 MATERIALS REQUIRED

- 2.1 The following materials are required for laundering dosimeter materials:
 - a. 100% cotton, white, long underwear (inner) — See SOP AHETF-8.A for description of material)
 - b. 100%, cotton inner dosimeter material for head patch (1 layer, 100 cm² for inner & 50 cm² for outer) — See SOP AHETF-8.H for description of material
 - c. 100% cotton, lightweight socks, ankle high — See SOP AHETF-8.I for description of material

SOP AHETF-8.J.1.

- d. Low-suds laundry detergent
- e. Washing machine
- f. Automatic clothes dryer or clothesline
- g. Scissors (cutting off buttons and sectioning dosimeters)
- h. Zip-Loc®-style plastic bags (gallon and quart size)

3.0 LAUNDERING OF WHOLE BODY DOSIMETER

- 3.1 For field and laboratory fortification samples only, remove all buttons from the inner dosimeter garments, prior to washing. Dosimeters that will be worn by workers **must not** have the buttons removed.
- 3.2 Place an appropriate number of dosimeters in a washing machine. Follow washing machine operating instructions for proper loading.
- 3.3 Wash the dosimeters, in warm water, **three** separate times (complete washing cycle) using a low suds detergent (e.g. All) with the amount specified by the product and washer size each time. For each wash event, allow the washing machine to go through a complete wash, rinse, and spin cycle.
- 3.4 In addition to the three washings, subject the dosimeters to **two additional** rinse-only cycles (*i.e.*, one full cycle of the washing machine without detergent) to remove all of the detergent.
- 3.5 Dry the dosimeters, using natural air drying or using an automatic clothes dryer.
- 3.6 The dosimeters are now ready for use.
- 3.7 Fold and place each clean dosimeter in Zip-Loc®-style plastic bags for storage and transport to field site or laboratory. Fold and place a single, whole inner dosimeter (up to size XL) in a gallon size bag. For larger sizes, use a suitable plastic bag or container. Socks and head patches should be bagged separately according to size also.
- 3.8 Use a permanent marker to label each bag or container with dosimeter size. (“S” for small, “M” for medium, “L” for large, “XL” for extra large, *etc.*)

SOP AHETF-8.J.1.

- 3.9 For fortification pieces, fold and place two-section dosimetry (*i.e.*, upper and lower halves) in gallon size bags; for six-section dosimetry (*i.e.*, upper/lower arms & legs, front & back torso, *etc.*...) fold and place individual pieces in quart size bags. One cut section per bag.
- 3.10 Use a permanent marker to label each bag/container with the garment size as described in Section 3.9 above and the body part as follows:

FT = front torso

UB = upper body

RT = rear torso

LB = lower body

LA = lower arm

SX = Sock Dosimeter

UA = upper arm

IH = Head patch – inner

LL = lower leg

OH = Head patch - outer

UL = upper leg

4.0 DOCUMENTATION OF WASHING PROCEDURE

- 4.1 A note to the study file shall be prepared for each batch of dosimeters that have been laundered per this SOP. The date of the washing event, person responsible, type of detergent used, and location of washing shall be noted.

5.0 DOSIMETER STORAGE

- 5.1 Store the washed dosimeters in a clean, dry environment until shipped to the field or analytical laboratory.

Definition of LOD and LOO
Chapter 9: DOCUMENTATION
AHETF-9.A.0

Effective Date: June 30, 2006

APPROVAL <u>Thomas Schreier</u>	DATE <u>17 Aug 2006</u>
APPROVAL <u>Mickey Standart</u>	DATE <u>Aug 22, 2006</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes how analytical Limits of Detection (LOD) and Limits of Quantification (LOQ) will be defined for analyses conducted on Agricultural Handlers Exposure Task Force (AHETF) studies.

2.0 DEFINITIONS OF LOD AND LOQ

- 2.1 The Limit of Quantification (LOQ) for all AHETF studies is defined as the lowest level fortified for a matrix in a study. The LOQ for each matrix is defined in the appropriate analytical method. These are for reporting laboratory results to the AHETF.
- 2.2 The Limit of Detection (LOD) for all AHETF studies is 0.3 times the defined LOQ in section 2.1. *For example, if the lowest matrix fortification is 1.0 **pg** for the LOQ, then the LOD will be $1.0 \times 0.3 = 0.300$ **pg**.*
- 2.3 If a sample result is greater than the LOD, but less than the LOQ, the number shall be reported in the analytical data as the value obtained from the instrument, or if the result is less than the LOD, it shall be reported as less than the numerical value of the LOD, such as: "<0.300 μg ". Report values to two (2) digits beyond the LOQ value unless otherwise specified by the AHETF.

Formatting for Tabular PresentationChapter 9: DOCUMENTATION
AHETF-9.B.0

Effective Date : June 30, 2006

APPROVAL <u><i>Micky Standart</i></u>	DATE <u>06/22/06</u>
APPROVAL <u><i>Wade King</i></u>	DATE <u>12/01/06</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes how numerical data generated on an Agricultural Handlers Exposure Task Force (AHETF) study shall be formatted for presentation in the Summary Report tables.

2.0 AHETF SUMMARY REPORTS

- 2.1 All calculations will be made using the reported values from the analytical and field reports.
- 2.2 Dermal dosimeters, Face/Neck Wipes, Hand Washes:
- In the study summary report, round and report all raw or adjusted whole-body dosimeter residues, dermal patch residues, body area exposures extrapolated from patch residues, face/neck wipe residues, and hand-wash residues as follows:
 - Values ≥ 100 , round and report as a whole number
 - Values < 100 , but ≥ 1 , round and report to one decimal place; and
 - Values < 1 , round and report no more than two digits past the LOQ as defined in SOP AHETF-9.A.
 - In specific situations when the data do not conform to these conditions, the Study Director will decide the proper format.

SOP AHETF-9.B.0.

2.3 Air Sampling Media:

- a. In the study summary report, round and report raw or adjusted air sampling media residues as follows:
 - Values ≥ 1 , round and report as one or two decimals, depending on the order of magnitude, at the Study Director's discretion.
 - Values < 1 , round and report no more than two digits past the LOQ as defined in SOP AHETF-9.A.
- b. In specific situations when the data do not conform to these conditions, the Study Director will decide the proper format.
- c. Total airflow is calculated as the average flow rate (expressed as L/min) multiplied by the duration in minutes. Air concentration is calculated as the residue value divided by the total airflow value. Either rounded or un-rounded values may be used for these calculations.

2.4 Adjusting Field Sample Results with FF Recoveries:

- a. Analytical field sample data (as reported in the analytical report) will be adjusted for representative field fortification mean recoveries; *i.e.*, percent recovery for that matrix and residue level (rounded to one decimal place, following standard rounding rules).
- b. Data that are less than the Limit of Quantitation (LOQ) will be given a value equal to $\frac{1}{2}$ LOQ, by default, and no further adjustment will be made for percent recovery.
- c. The value ($\frac{1}{2}$ LOQ value) will be expressed to the same number of decimal places as specified in sections 2.2.a, 2.3.a, and 2.4.a. All non-detects or " $\frac{1}{2}$ LOQ" values will be referenced with a footnote in tabular presentations.

2.5 Means and Standard Deviations:

- a. Means and standard deviations will be calculated from **unrounded** values and expressed to the same number of decimal places as specified in sections 2.2.a, 2.3.a, and 2.4.a.

Numerical Formatting and Handling

Chapter 9: DOCUMENTATION
AHETF-9.C.4

Effective Date : June 30, 2006

APPROVAL <u>Thomas Spruill</u>	DATE <u>27 JULY 2006</u>
APPROVAL <u>Wiley Standard</u>	DATE <u>Aug 10, 2006</u>
Last Revision Date: April 30, 2006	Previous Version Number: 9.C.3.

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes how numerical data generated on an Agricultural Handlers Exposure Task Force (AHETF) study shall be handled during calculation and in contractor reports.
- 1.2 The SOP will set forth specific requirements for rounding and fixed decimal places.
- 1.3 The requirements set forth in this SOP are designed to maintain consistency for reporting purposes, recognizing that numbers with greater precision are sometimes used in the calculations.
- 1.4 Information concerning the definitions of the Limit of Detection (LOD) and Limit of Quantification (LOQ), and the reporting requirements for the AHETF Summary Report were removed. Both were placed in new AHETF Standard Operating Procedures. The information pertinent to contractor reports were renumbered in this SOP.

2.0 ANALYTICAL DATA AND CONTRACTOR REPORTS

- 2.1 All analytical laboratory calculations will be performed using only **un-rounded** numbers (*i.e.*, as generated by the instrumentation), but reported to no more than four decimal places. These include, but are not limited to: means, standard deviations, *etc.* All results must be reported to the AHETF. Calculated values should be presented in the analytical report tables and appendices as described in SOP AHETF-9.B.

SOP AHETF-9.C.4.

- 2.2 All sample and QC results reported in the summary tables and appendices found in the Analytical Report will be reported to the same accuracy and precision as the final results found in the raw data spreadsheets for these samples. Data should be reported to no more than four decimal places, unless otherwise specified by the AHETF (Study Director or Analytical Monitor).
- 2.3 If a sample result is greater than the LOD, but less than the LOQ, the number shall be reported in the analytical data as the value obtained from the instrument, or if the result is less than the LOD, it shall be reported as less than the numerical value of the LOD, such as: "<0.300 µg". Report values to two (2) digits beyond the LOQ value unless otherwise specified by the AHETF.

3.0 FIELD DATA AND CONTRACTOR REPORTS

- 3.1 Raw data will generally be collected to the precision of the equipment or measuring devices. All field calculations with field sample data will be performed using the values provided by the laboratory (*i.e.*, as generated by the instrumentation), and these values will be reported to no more than four decimal places when presented to the AHETF in raw data tables or spreadsheets, unless otherwise specified by the AHETF Study Director. Do not perform calculations on numbers that have been rounded further than those reported by the laboratory. All results must be reported to the AHETF.
- 3.2 Any calculated values should be presented in the field report tables as described in SOP AHETF-9.B.

Analytical Method Number AssignmentChapter 9: DOCUMENTATION
AHETF-9.D.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>Melba J. L. L. L.</u>	DATE <u>1-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes how an Agricultural Handlers Exposure Task Force (AHETF) analytical method number is assigned. The Task Force Manager is responsible for tracking and assigning AHETF method numbers.

2.0 RESPONSIBILITY

- 2.1 The assignment of AHETF analytical method numbers will be the function of the AHETF Task Force Manager. This will ensure continuity and prevent duplication of method numbers, and enable the AHETF to keep accurate records of the individual methods prepared.

3.0 PROCEDURE

- 3.1 A unique AHETF analytical method number for each method will be assigned. It will consist of the form of AHETF-AM-nn, where nn is a two digit, sequential number beginning with 01. Example method numbers are:

AHETF-AM-01
AHETF-AM-02
AHETF-AM-03

SOP AHETF-9.D.0.

- 3.5 The analytical method numbers will be assigned as follows:
- a. The appropriate personnel shall contact the AHETF Task Force Manager for assignment of the next number in the analytical method series.
 - b. The AHETF Task Force Manager shall document the method number assigned and provide the number to the requesting personnel, the Study Director or other appropriate personnel.
- 3.6 Analytical method numbers will be tracked on a form maintained by the AHETF Task Force Manager and will contain the following:
- a. Analytical method number
 - b. Method title
 - c. Method author (laboratory facility)
- 3.7 Revisions to AHETF analytical methods will be denoted by a version number, e.g. Version 1, Version 2, *etc...* The revision date, laboratory, and principal chemist who made any changes should also be noted on the revised method(s).

Raw Data Collection
Chapter 9: DOCUMENTATION
AHETF-9.E.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>Melissa L. L. L.</u>	DATE <u>1-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes the preferred methods for documenting raw data, identifying automated data, and identifying who is responsible for reviewing the raw data generated for/by the Agricultural Handlers Exposure Task Force (AHETF).

2.0 PREFERRED METHODS FOR MANUALLY RECORDED DATA

- 2.1 All persons involved in an AHETF study should record all raw data on standard data forms (designed for recording raw data pertaining to the particular type of study being conducted) or in a (preferably bound) notebook.
- 2.2 All raw data should be collected with the utmost care, accuracy, neatness and legibility. Personnel involved in collection of raw data shall:
- a. Initial and date all entries in data notebooks/files and entries made on data collection forms. Initials and date must be made on the day of entry and by the person making the entry.
 - b. Record all data in indelible ink, preferably black. Do **NOT** use pencil, water soluble ink or erasable ink to record raw data.
 - c. Record units of measure when appropriate.

SOP AHETF-9.E.0.

- d. Record the AHETF study number and contractor number (if applicable) on notebook covers, 3-ring binders and all loose pages or standard data forms.
- e. No data prompts on a form should be left unanswered or blank. If the required information is not applicable, state "N/A" or draw a line through the unused portion. It is not necessary to address blank comment sections or sections to provide additional information.

3.0 PREFERRED METHOD FOR AUTOMATED SYSTEMS DATA

- 3.1 All data generated by automated laboratory instruments and computer systems, including spreadsheets, should indicate (or have added to the print-out) the following information:
 - a. Date
 - b. Sample numbers/Identity
 - c. Cross-reference to the study notebook or data collection form that describes the experiment, if applicable
 - d. Signature or initials of person generating data
 - e. AHETF Study number
 - f. System description (*e.g.*, GC column type, oven temperatures, weather station brand/model, mobile phase, flow rates, HPLC unique instrument number, *etc.*) This system description can be added to the first page of an analytical data set if documentation exists indicating this information pertains to the entire data set.
- 3.2 The first printout from automated systems is considered the original raw data.

4.0 SCIENTIFIC/TECHNICAL REVIEW OF RESULTS

- 4.1 It is the responsibility of the Study Director, or his/her designate, or the contract laboratory management to ensure that all results on data forms, notebooks and automated printouts are accurate. All mistakes should be noted and corrected by the personnel who recorded the data.

- 4.2 The AHETF Quality Assurance Unit (QAU) may review the raw data at any given time.

Data Corrections

Chapter 9: DOCUMENTATION
AHETF-9.F.O.

Effective Date : February 1, 2003

APPROVAL <u>David Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>William Harty</u>	DATE <u>1-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes the procedure for making proper changes ^{and/or} corrections to raw data generated in all Agricultural Handlers Exposure Task Force (AHETF) studies.

2.0 PROCEDURE

- 2.1 Changes to the raw data are made by drawing a single line through the original entry so as to not obscure the entry then adding the correct entry. The change ^{and/or} correction must be initialed and dated by the individual making the change, and an explanation (either written out or coded) must be given for the change. The following codes and their definition can be used:

WL	=	Inadvertently recorded in wrong location
CC	=	Changed for greater clarity
WO	=	Write over. (Personnel inadvertently wrote over the error instead of drawing a line through the error). Cross out the error and re-enter the correct data.
SP	=	Spelling error
CE	=	Calculation error

SOP AHETF-9.F.0.

RE = Recording error

NI = Entry not initialed and dated at time of entry

FC = Form change (*i.e.* incorrect unit contained in column header)

RO = Rounding error

- 2.2 Codes, other than those defined in section 2.1 may be used, if clearly explained (defined) in the notebook or data file.
- 2.3 Error codes should be circled to distinguish the code from the individual's initials, and placed as close to the correction as possible. If this is not possible, the error should be footnoted and explained elsewhere on the page.
- 2.4 Errors that cannot be explained with an appropriate defined code must be explained in detail on the page at the time of correction.
- 2.5 The field and laboratory facilities may follow the examples in this SOP or use their own internal SOPs on data correction.

Raw Data Handling
Chapter 9: DOCUMENTATION
AHETF-9.G.O.

Effective Date : February 1, 2003

APPROVAL <u><i>Daniel Johnson</i></u>	DATE <u>01-22-03</u>
APPROVAL <u><i>William Ditty</i></u>	DATE <u>1-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes the methods to follow when contract facilities forward raw data to the Agricultural Handlers Exposure Task Force (AHETF).

2.0 PROCEDURE FOR THE SHIPPING OF RAW DATA

- 2.1 The contract facility will assemble all original data plus a detailed itemized list of all data/material being sent, and prepare it for shipping via acceptable carrier (e.g., one providing tracking accountability such as Federal Express). An appropriate Chain of Custody Form will accompany the data. (Refer to the attached example).
- 2.2 The facility will produce true copies of the original data, which will be subject to QA review (if necessary).
- 2.3 The true copies will be shipped to the AHETF QAU, Study Director or other designee for report preparation and review. Originals will be shipped directly to the AHETF archives. Copies and originals may not be shipped together or at the same time (i.e., one complete set must be secured by the contractor or AHETF while the other is in transit).
- 2.4 Data should be sent via overnight carrier, or transferred to the Study Director, committee member, or designated personnel for hand delivery.

SOP AHETF-9.G.0.

- 2.5 Upon receipt of the shipment, the data package will be inspected. The condition of the data package will be noted and acknowledgment of receipt will be noted on the Chain of Custody form.
- 2.6 The AHETF Task Force Manager, Study Monitor, or designate will review the copies and the report for scientific accuracy and regulatory compliance. The copies will be maintained as long as the data are required for report preparation or review. Upon completion of the final report, but prior to finalization (Study Director signature), all original raw data will be placed in the AHETF designated archives.

3.0 RETURN POLICY

- 3.1 All original data and contractor report(s) should be sent directly to the designated archives. The contract test facility will be responsible for the condition of the data until it has been received by the AHETF archives.
- 3.2 True copies of the raw data will be maintained by the Study Director or AHETF Quality Assurance Unit (QAU). All original raw data will be maintained in the AHETF archives after study completion. The AHETF will authorize all transfers and distributions of AHETF study data.
- 3.3 No contract laboratory may retain copies of AHETF study data unless authorized in writing by the AHETF. Raw data packages will consist of original AHETF data, and true copies of lab/facility specific data (*i.e.*, temperature records, SOPs, personnel records, maintenance logs, *etc.*).

Attachment

Chain of Custody Form
(example)

Agricultural Handlers Exposure Task Force				Data Chain of Custody	
AHETF Study No. <i>AHE99</i>	Data Type: <i>Analytical raw data</i>	Priority: <i>Overnight</i>	Page: <i>1 of 1</i>		
Ship To: <i>AHETF Archives Archivist Address City, State Zip Code</i>			Ship From: <i>Study Director Facility/Company Address City, State Zip Code</i>		
Shipper/Carrier: <i>FedEx</i>	Airbill No. <i>123-456-7A</i>	Date Shipped/Initials: <i>10/16/02 mm</i>			
Comments: <i>3 boxes packed with raw data</i>					
Shipped:	Description of Materials Sent:	Received:			
✓ ✓ ✓	Box 1: <i>Field notebook Test substance records Application video</i>	✓ ✓ ✓			
✓	Box 2: <i>Analytical data 7-1-97 to 8-19-97</i>	✓			
✓ ✓ ✓	Box 3: <i>Analytical data 8-26-97 to 9-15-97 Final report QA records (in separate envelope)</i>	✓ ✓ ✓			
Date Received: <i>10/18/02</i>	Received By/Company: <i>J.Doe/Archives, Inc.</i>				
Condition Received: <i>Good, sealed boxes. 3 boxes received.</i>					

Preparation of True CopiesChapter 9: DOCUMENTATION
AHETF-9.H.O.

Effective Date : February 1, 2003

APPROVAL <u>Daniel Johnson</u>	DATE <u>01-22-03</u>
APPROVAL <u>William J. O'Leary</u>	DATE <u>1-28-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes the process for making true or exact photocopies of original raw data to be used in place of the original data by the Agricultural Handlers Exposure Task Force (AHETF).
- 1.2 All original study data will be retained by the AHETF and all original facility records will be the responsibility of the individual contractors; however, copies of these data may need to be produced to complete study files, facilitate preparation of the report(s), or be used in auditing the final report(s).

2.0 PROCEDURE

- 2.1 The necessary data will be photocopied by the contractor. All copied pages of raw data will be immediately reviewed by the persons making the copies for clarity and completeness.
- 2.2 Any pages that are poorly copied (*i.e.*, smeared, unclear, too light or dark, missing text, *etc.*) are not acceptable, and must be re-photocopied.

SOP AHETF-9.H.0.

- 2.3 Individual pages will be certified as a true, exact, or certified copy, either with an appropriate rubber stamp or written by the person(s) verifying the copied pages. The person's initials (or a signature) and the date verified must be noted on the copied page(s).
- 2.4 Whole sections of data (e.g., chromatogram sets, entire data notebooks, etc.) must be verified completely, but only the cover page of the set need contain the true copy designation and the person's initials and date. In addition, the cover page must indicate the total number of pages in the set and clearly state that all pages contained in the set are true copies. All pages in such a set must be paginated or otherwise marked to ensure they remain together.
- 2.5 True copies must be handled as raw data (when replacing the original data), and are subject to all AHETF and GLP handling and retention requirements.
- 2.6 True copies may be discarded by the AHETF or contractors only when the original raw data are properly archived and there is no longer a need for such copies. Verification must be obtained from the Study Director, Task Force Manager, AHETF QAU, or designated archive facility(s) before disposal.
- 2.7 Copies of data made for transfer of information within the AHETF need not be authenticated. Only copies of data intended to replace the original raw data must follow the above listed procedures.

Phase Report Template**Chapter 9: DOCUMENTATION**
AHETF-9.1.0.

Effective Date: January 15, 2005

APPROVAL <u><i>Mickey Stanford</i></u>	DATE <u>1-18-05</u>
APPROVAL <u><i>LOUIE JOHNSON</i></u>	DATE <u>01/28/05</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes the process for use and completion of the standardized phase report template designed for the contract facilities conducting field and analytical studies for the Agricultural Handlers Exposure Task Force (AHETF). Contents and required elements for individual reports are detailed in SOP AHETF-4.A.
- 1.2 Due to government requested specifications for electronic submissions of study reports, the original document may be created in any recent version of Microsoft® Word® (i.e., Office 2003, 2002, 97). However, the conversion of the file into Adobe® Portable Document Format (PDF) must be done to Adobe® 5.0. Later versions must have the PDF file saved to the 5.0 format.

2.0 REPORT FORMATTING

- 2.1 The electronic template is preformatted as described in this section. No changes shall be made to the formatting unless otherwise approved by the AHETF. Requests for changes to the formatting should be directed to the appropriate Study Director. This template was modeled after the EPA OPP – Electronic Submission and Review Specifications.

SOP AHETF-9.I.0.

- 2.2 Times New Roman (the default font requested by the USEPA for electronic submissions) or an equivalent font, shall be used for all text, tables, and figures. The standard size will be 12 pt. with no text smaller than 8 pt. Italicized fonts should be avoided and script fonts may not be used. This is the default font requested by the USEPA for electronic submissions.
- 2.3 Boldface should be used for highlighting section titles and key words and phrases in the text. Underlining should be avoided. Shading in tables may be used if no greater than 40% or reversed text (white text on a black background) may be used. Single lines are preferred to double lines.
- 2.4 Line spacing should be 1.0 and not greater than 1.5. Line height should be set to automatic. All documents should be set to automatic kerning.
- 2.5 Margins should be at least 1.25" on the left and no less than 0.75" on the right. Top and bottom margins should be set between 0.75" and 1.00". For field and analytical reports to be appended to the final summary report, the top and bottom margins may be adjusted to accommodate additional pagination.
- 2.6 Each page, except the cover page, must have a header and/or footer with the AHETF study number and pagination. The header and/or footer may contain a single line at its bottom edge to set it off from the text. The header and/or footer text shall be in 10 pt.
- 2.7 Text alignment should be set to either left or full justification (preferred), and must be consistent throughout the report. Subsections and paragraphs should be indented on the left, with no hanging indentation (even left alignment at each outline level). Tab stops should be no less than 0.25" per level and no greater than 0.50" per level.
- 2.8 Titles and section headings should be larger than the body text. These items should be set to no larger than 14 pt. and should be set in boldface. Individual sections shall be identified by a whole number, with subsections being identified by that number and a sequential decimal, then by a lowercase letter.

SOP AHETF-9.1.0.

- 2.9 Tables and figures should be identified by Arabic Numerals, such as "Table 1." or "Figure 7." Appendices shall be identified by capital letters, such as "Appendix A." All tables, figures and appendices must have a descriptive title.
- 2.10 Where superscripts are necessary to designate a footnote, these should be letters and not numbers.
- 2.11 Optically scanned copies of data may be included in an appendix, as necessary. Copies should be copied at their original size (1:1 if 8.5" x 11.0" or smaller). If oversized pages are to be copied, they should not be reduced less than 80% of original size. All information must be legible. Contrast must be adjusted so that no areas are too dark or light. Any unreadable copies will be rejected, and must be re-scanned or removed and excluded from the report.

3.0 ELECTRONIC FORMATS

- 3.1 All report and manipulated data must be presented to the AHETF in an electronic format. To maintain consistency from all contractors, each report document must be in Microsoft® Word® for Windows® 97 or compatible format. All spreadsheet data must be in Microsoft® Excel® for Windows® 97 or compatible format. Macintosh® formatted data are not acceptable. This template was created using EPA's Specifications for Creating PDF® Version of Study Reports.
- 3.2 All signed pages will be optically scanned separately and stored in PDF® format. These signed pages need to be inserted into the final phase report file.
- 3.3 Electronic submissions to the EPA must be in Adobe® Acrobat® PDF format version 5.0. Later versions of Acrobat® may be used; however, the output must be in the 5.0 format. EPA's website (http://www.epa.gov/oppfod01/eds/softset_study.pdf) contains a guidance document entitled, "Software Settings for the Creation of PDF Files for Electronic Submission." This document should be referred to when setting the PDF conversion settings. All documents will be converted versus distilled.

- 3.4 All data should be electronically available. All word processing files, spreadsheets, photographs, and optically scanned figures must be submitted to the AHETF on a CD-ROM, along with the completed PDF® phase report. One original signed hard copy of the phase report will also be submitted.

4.0 COMPLETION OF ELECTRONIC TEMPLATES

- 4.1 It is imperative to complete the electronic template in the prescribed manner in this SOP. Failure to follow the specified techniques will result in an incoherent electronic version of the phase report.
- 4.2 After all reviews have been completed, the report must be converted to Adobe® PDF® then printed. This will serve as the final original document. As different printers produce slightly different formatting, it is important to edit the document layout with an Acrobat® compatible printer as the selected printer.
- 4.3 Cutting and pasting from an old document presents problems both in appearance and in the conversion process. If you need to do this, do not copy a whole section but by paragraph. Use the styles box to keep text in the proper formatting, if necessary.
- 4.4 Refer to your "STYLE" bar to see the applicable formatting. The "STYLES" have been preset to wrap a paragraph to the correct position without placing a hard return then tabbing or spacing over. Do not space to align (this will not convert to PDF format cleanly).
- 4.5 All paragraphs in the templates are defaulted to be full aligned (per SOP). Cutting and pasting from another document may change the default alignment and you will need to follow the steps noted above in §4.3. You will then need to manually change the alignment for pasted sections.
- 4.6 Spacing between paragraphs and sections is also embedded using styles so no extra lines need to be added.

SOP AHETF-9.1.0.

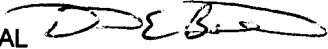

- 4.7 Starting with an existing document and trying to add these new styles, one may get it to look right when printed, but electronically it has too much extraneous formatting and cannot be converted properly. This also increases the document size.
- 4.8 All "<>" are placeholders for information. All print in italics are places needing appropriate text inserted, usually encased by < >. Some examples are given in italics. Delete "<>" marks from completed sections.
- 4.9 Do not alter the template margin settings.
- 4.10 On the field and analytical templates, landscaped pages have a text box that will contain the footer information. The verbiage "AHETF Template <date>" that appears on portrait pages was purposely omitted from landscaped pages on the templates. This verbiage will need to be replaced with appropriate report information on all footer sections for the draft and final reports.
- 4.11 On the field and analytical templates, within Microsoft® Word® change the document properties to reflect the author of the report and a descriptor of the report (i.e., AHE06 - Acephate Method Validation or similar verbiage). This is changed by selecting the file menu, then properties, and choosing the summary tab.
- 4.12 Manually add the final hard page breaks only after all other formatting and changes have been completed, and then convert to PDF format.
- 4.13 It is recommended not to change any format setting in the templates, as it may affect several sections throughout the document. Local formatting may be adjusted manually, as necessary.
- 4.14 Extra figures, spreadsheets, tables, photographs, etc. should be converted into PDF format separately from the text in the template, then combined, in proper order in Adobe® Acrobat® before completion.

5.0 CONVERTING PROCESS

- 5.1 EPA's website contains a guidance document entitled, "Software Settings for the Creation of PDF Files for Electronic Submission." This document should be referred to when setting the PDF conversion settings. Unlike printing direct to Distiller, the use of PDFMaker allows for the creation of tagged PDF files, preservation of bookmarks and links, and conversion of metadata from the original Word document.
- 5.1.1. No passwords shall be used. The encryption level will be set to 128-bit. Permissions will be set to enable content access for the visually impaired and allow content copying and extraction. Changes allowed will be limited to comment authoring, form field fill-in or signing and printing will be fully allowed.
- 5.1.2. "Cross-document links" and "convert internet links" should all be enabled. Set link destination magnification to "inherit zoom." The Comments - Notes, Text Boxes – Article Threads, Page labels, cross-reference & ToC links and footnote & endnote links should all be selected.
- 5.1.3. Convert word headings to bookmarks should be chosen.
- 5.1.4. Set the document open options to "Bookmarks and Page", "Page Number" as "1" and open magnification to "default." Set link appearance type to "thin visible rectangle," highlight to "invert", line style as "solid" and color to "blue".

Rotameter Calibration**Chapter 10: FIELD OPERATIONS**
AHETF-10.A.0.

Effective Date : October 15, 2003

APPROVAL 	DATE <u>09-27-03</u>
APPROVAL 	DATE <u>09-26-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) provides the steps to properly calibrate a rotameter used for measurement of the air flow rate through an OVS air sampling tube used to collect air monitoring samples during Agricultural Handlers Exposure Task Force (AHETF) worker exposure studies.

2.0 EQUIPMENT REQUIRED

- 2.1 The following equipment is needed to calibrate the rotameters:
- Personal low-volume air-sampler pump(s) (e.g., SKC, or equivalent)
 - Tygon[®] tubing or equivalent
 - Appropriate calibration device or primary air flow meter (e.g., BIOS DryCal[®], Kurz Mass flow meter, Buck Calibrator, bubble meter and stopwatch, or equivalent)
 - Field rotameter with an appropriate measurement range

SOP AHETF-10.A.0.

3.0 CALIBRATION PROCEDURE

- 3.1 Place air-sampler pumps on chargers before each use. If the pump is fully charged proceed to 3.2.
- 3.2 Verify calibration of a rotameter once a year or if rotameter operation becomes suspect.
- 3.3 Start by calibrating five individual air-sampler pumps to five individual flow rates using a primary air flow meter (e.g. BIOS DryCal[®], calibrated according to the SOP for the appropriate flowmeter). Select five flow rates that span the scale of the rotameter being calibrated.
- 3.4 Evaluate the rotameter calibration by attaching, one at a time, the five air flow calibrated air-sampler pumps from 3.3 to the rotameter. Hold the rotameter perpendicular to the ground and after the rotameter has been allowed to stabilize, a reading from the middle of the ball can be taken and recorded.
- 3.5 If any reading deviates more than $\pm 5\%$, the rotameter will be discarded and replaced with a new rotameter.

Packing, Handling, and Shipping of SamplesChapter 10: FIELD OPERATIONS
AHETF-10.B.1.

Effective Date : January 1, 2006

APPROVAL <u>Mickey Standard</u>	DATE <u>01/05/06</u>
APPROVAL <u>[Signature]</u>	DATE <u>05/04/06</u>
Last Revision Date: February 1, 2003	Previous Version Number: 10.B.0.

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) provides a description of procedures for handling the Agricultural Handlers Exposure Task Force (AHETF) test system [matrix] samples collected at the field test sites. This SOP also covers storage, packing, and shipping procedures.
- 1.2 This SOP, section 2.4, was revised to clarify the separation of controls and treated samples while in temporary storage and during shipment to the analytical lab. The example form was changed to be presented as a blank form.

2.0 SAMPLE HANDLING AND STORAGE

- 2.1 All samples will be collected as directed by the study protocol or appropriate SOP to prevent degradation and/or contamination.
- 2.2 Place "dry" field samples (e.g., body dosimeters in aluminum foil) in appropriate labeled containers, then "immediately" place in an ice chest with dry ice or in a freezer.
- 2.3 All liquid samples should be placed in appropriate jars with lids. Allow sufficient headspace when freezing these samples to prevent cracking or breaking from expansion.

SOP AHETF-10.B.1.

- 2.4 Untreated control samples and treated field samples (including field fortification samples, field fortification solutions, and worker dosimetry samples) must be maintained separately while in temporary storage locations (e.g., coolers with dry ice) or in shipping containers (e.g., boxes). At a minimum, untreated samples must be physically separated from treated samples by at least two boundary layers (e.g., double bagged, separate boxes/partitions, etc...) while in the same cooler/freezer, but preferably would be stored in completely separate coolers/freezers. Efforts should be taken to keep field fortification samples, field fortification solutions and dosimetry samples separate at all times; however, these samples may be stored and shipped together provided there is adequate separation and protection from potential cross-contamination. The Study Director shall make any decisions regarding the combining of samples in the same device.

3.0 SAMPLE PACKING AND SHIPPING

- 3.1 Samples, when packed for overnight shipping, should be placed on dry ice in insulated containers (boxes or coolers). Be sure to add enough dry ice to keep the samples frozen for at least 36 hours. Samples packed for transport by freezer truck service will be boxed and stored frozen until picked up by freezer truck.
- 3.2 Before shipping, all sample numbers should be checked against a sample list to provide an accurate chain of custody form for the analytical laboratory. A copy of the signed form will remain in the raw data logbook. Chain of custody documents will be included with the shipment to the analytical laboratory. See the attached example.
- 3.3 All samples in bottles or jars should be placed in sealable bags and wrapped with protective wrapping materials (e.g., bubble wrap or newspaper) to minimize breakage. Bottles or jars must be securely packed in each shipping container so that there is minimal or no movement. Additional bubble wrap or paper may be placed in the sample shipping container to provide cushioning.
- 3.4 If samples must be shipped via a commercial overnight freight carrier, they are always shipped on a priority basis. For local studies, samples may be transported on dry ice, in a cooler, from the field to a laboratory freezer.

SOP AHETF-10.B.1.

- 3.5 An effort should be made to ship samples to arrive at the designated facility on a weekday. Do not ship samples over a weekend unless a freezer truck service is being used.

Sample Shipping Form
(example)

Agricultural Handlers Exposure Task Force			
Sample Shipping Chain of Custody			
AHETF Study No.	Sample Type:	Priority:	Page:
Ship To:		Ship From:	
Carrier:	Waybill/Airbill No.	Date Shipped/Initials:	
Approximate Amount of Dry Ice Included:		Conditions of Samples when Packed:	
Comments:			
List of Samples Shipped:	Received:	List of Samples Shipped:	Received:
Date Received:		Received By/Company:	
Condition Received:			
Destination of Samples at Analytical Facility:		Date Placed in Storage/Initials:	
Do not ship samples over a weekend unless on a freezer truck.			

US EPA ARCHIVE DOCUMENT

Worker and Study Observations

Chapter 10: FIELD OPERATIONS
AHETF-10.C.3.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: January 1, 2006	Previous Version Number: 10.C.2.

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes procedures for the necessary observations to be performed during the field phase of the Agricultural Handlers Exposure Task Force (AHETF) exposure studies.
- 1.2 The SOP was revised to include more details on what observers should be looking for in relation to worker health status.

2.0 FIELD NOTEBOOKS

- 2.1 To standardize and facilitate data collection, a field notebook will be provided to the field contractors prior to the exposure-monitoring period. The notebook will provide the necessary forms for study data collection. Instructions for the use of notebook will be located at the front of notebook.
- 2.2 The provided notebook will contain the AHETF study number and contractor project number on each page. If additional pages are inserted into the field notebook, this information must be included on the inserted pages.

US EPA ARCHIVE DOCUMENT

3.0 SITE DETAILS

- 3.1 Record site details on the appropriate forms in the field notebook.

The Principal Field Investigator (PFI) should record the following information, at a minimum:

- a. Prepare a sketch map of the working area giving key details such as compass points, orientation of rows in test plot, mixing/loading area.
- b. Record on the form the study number, site reference, date and initials.
- c. Attach a copy of a map with the nearest town circled and give details from there.
- d. If details of the location change (e.g., move to a different location for application), prepare a new sketch showing the new conditions.

4.0 ENVIRONMENTAL CONSIDERATIONS

- 4.1 Outdoor environmental conditions, including but not limited to, wind speed, wind direction (relative to the test site and direction of application), air temperature and relative humidity will be monitored and recorded locally by means of a weather station at each trial site during worker monitoring, or by reference to data from the nearest NOAA weather station. Measuring equipment for on-site weather stations will be calibrated per the contractor's SOP.
- 4.2 Indoor environmental conditions, including but not limited to, air temperature and relative humidity will be monitored and recorded by means of calibrated measuring devices located within the designated test areas. Measuring equipment for indoor monitoring will be calibrated per the contractor's SOP. The ventilation system will be described in the raw data.
- 4.3 At all test sites, environmental conditions that could pose a potential heat-related illness threat will be diligently monitored as part of the AHETF program to minimize potential heat stress on workers. Refer to SOP AHETF-11.G.

5.0 EQUIPMENT DETAILS AND OPERATION VERIFICATION

- 5.1 Details of application equipment will be recorded in the field notebook. Application equipment operation will be verified, and calculations recorded, as defined in the study protocol and SOP AHETF-10.D.

6.0 WORKER OBSERVATIONS

- 6.1 Each dedicated worker's observer must use the appropriate form in the field notebook to record the times and descriptions of all activities including mixing, loading, and/or application activities; resting, lunch, washing hands, driving vehicles, *etc.*
- 6.2 Describe clothing and personal protective equipment (PPE) worn and crop/site condition. Document all clothing worn, including PPE prior to the start of observations during the work period. Note any clothing defects and bring to the attention of the Study Director, Principal Field Investigator (PFI), or AHETF personnel on-site. Record any instances of removal of protective equipment during the monitoring period.
- 6.3 Be sure that the air sampling pump has been turned on before the worker enters the mixing/loading areas, begins any activities for the day, or uses any application equipment. If the PFI has not turned on the air sampling pump immediately after the worker was dressed, it is the observer's responsibility to turn the pump on and record the start time in the field.
- 6.4 Record start and stop time for all activities. Record the productivity of each worker during the activities (*e.g.*, specifically the amount of product handled, if known). It is recommended that all study personnel synchronize their watches prior to the start of the day's activities.
- 6.5 Record any actions that might explain any unusually high or low exposure values for any of the body parts (*e.g.*, spills, maintenance of equipment, keeps gloves on, *etc.*).
- 6.6 Pay attention to the workers' hands during the exposure monitoring period, this includes time handling the test substance, donning/removing PPE, standing around waiting, or performing non-study related activities. Look for hand contact to contaminated equipment or clothing associated with contact to the head/face, other workers, personnel, *etc.*

SOP AHETF-10.C.3.

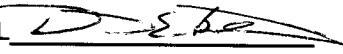
- 6.7 Periodically note the workers' clothing. Look for new rips or tears, perspiration, chemical spills/stains, or anything that appears out of the ordinary. Also check and document the operation of the personal air sampling pump. Document as "Pump Running" not "Pump On".
- 6.8 Report any unusual or unauthorized activities observed (eating without handwash, not wearing PPE during chemical exposure, *etc.*) to the Study Director, PFI, or AHETF QAU.
- 6.9 Record observations pertinent to the worker assigned. For example, when observing a loader, it is not necessary to note the specifics of the application equipment. This information can be cross-referenced later.
- 6.10 Monitor the health status of the worker, especially under conditions of temperature and humidity which may promote a heat-related illness. Refer to SOP AHETF-11.G for specific warning signs and condition criteria. Record any reactions a worker may exhibit and any remedial actions taken.
- 6.11 Keep observations brief and to the point. Don't use worker names; rather use their ID for the study. Don't record long explanations of activities unless absolutely necessary to explain what is occurring. Document what activities are directly related to handling the test substance.
- 6.12 The observations made will be reviewed and placed in the field report at the conclusion of the study. Try to write neatly and clearly while describing the activities observed. Be as succinct as possible. Typically 3-5 pages of notes should be collected during an average work period.
- 6.13 Observe the worker for the entire time period of the exposure monitoring, from when the worker is dressed at the start of the day until he/she enters the staging area for sample collection; this includes during lunch breaks, performing other daily activities, and during interim sample collections. This does not include observing the worker during restroom breaks. If the worker cannot be seen during application, this should be noted, and is to be expected at times. If the observer needs to take a break, get another researcher to monitor the worker during the observer's absence.
- 6.14 Do record the names of non-study compounds observed being handled during the monitoring period. Use generic terms like anti-foam agent, surfactant, insecticide, *etc.* in observation notes and document chemical or trade names, if known, in the specific loading/application procedures.

SOP AHETF-10.C.3.

- 6.15 A pre-study explanation of required observations may be conducted before the conduct of the study commences. The AHETF QAU and/or Study Director will be responsible for providing additional training on this SOP. The AHETF Study Director will determine if research personnel would benefit from such training on a per study basis.

Application Equipment Operation Verification**Chapter 10: FIELD OPERATIONS
AHETF-10.D.0.**

Effective Date : October 15, 2003

APPROVAL 	DATE <u>09-27-03</u>
APPROVAL <u>David Johnson</u>	DATE <u>09-26-03</u>
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) provides the steps for the Study Director, or designee, to follow when assessing the operability of application equipment (groundboom, aerial, airblast, handheld, etc.) prior to being used in Agricultural Handlers Exposure Task Force (AHETF) worker exposure studies.
- 1.2 This SOP will cover various commercial application equipment that may be used on AHETF worker exposure studies. Since the AHETF will measure handler exposure (applicator) under expected working conditions using standard industry practices, no modifications or maintenance will be performed by the AHETF to the equipment. In order to maintain an acceptable level of scientific integrity, the AHETF will perform several steps to assess the operational capabilities of the application equipment.

2.0 EQUIPMENT RECORDS REVIEW

- 2.1 The Study Director will obtain copies of pertinent maintenance and calibration records provided by the equipment owner. These copies will be maintained by the AHETF in the appropriate study file.
- 2.2 The Study Director, or designee, will review the equipment records prior to the application. The records should indicate reasonable maintenance has been conducted by the equipment owner/operator, and that the output of the equipment has been checked within the six months prior to the AHETF study.

3.0 VISUAL EQUIPMENT INSPECTION

- 3.1 The Study Director, or designee, will perform a general visual inspection of the application equipment. Visible signs of damage shall be noted. The overall condition of the equipment will be documented.
- 3.2 The Study Director shall point out any deficiencies or questionable parts of the equipment to the owner/operator. If deemed necessary, the owner/operator shall perform the needed repairs prior to the AHETF application.
- 3.3 All observations and corrective actions (if applicable) will be documented in the study file.

4.0 VERIFICATION OF GENERAL OPERATION

- 4.1 The output of the application equipment will be visually assessed prior to the application. This entails verifying that each nozzle (or other delivery mechanism) is discharging while the equipment is running and at operating pressure. This should be done without the test substance in the tank. Individual output from any nozzle may be collected and measured at the discretion of the Study Director. All observations or measurements made will be documented in the study file.
- 4.2 The overall operation of the equipment shall be verified. Any significant problems that interfere with the application shall be discussed before proceeding with the application. All observations and corrective actions (if necessary) will be documented in the study file.

5.0 APPLICATION EQUIPMENT OUTPUT

- 5.1 If deemed necessary by the Study Director, a complete measurement of each nozzle's output shall be completed, in duplicate, prior to the AHETF application. If the output is dependent upon the equipment's speed, then timed passes will be conducted over a known distance of similar terrain to the treated areas. All results and calculations will be documented in the study file.

Worker Sample Collection Sequence

Chapter 10: FIELD OPERATIONS
AHETF-10.E.2.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: January 1, 2006	Previous Version Number: 10.E.1

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) describes the sequence for the research personnel to follow when collecting worker samples from the field phase of the Agricultural Handlers Exposure Task Force (AHETF) exposure studies.
- 1.2 This SOP was revised to change the term “replicate” to monitoring period or worker.

2.0 COLLECTION SEQUENCE

- 2.1 Upon completion of the monitoring period, the worker shall return to the appropriate staging area. Research personnel collecting dosimetry samples must change their disposable gloves (latex, vinyl, etc..) between each sample collected described as follows.
- 2.2 The research personnel will check the air pump flow rate using equipment and techniques described in SOPs 8.D and 10.A. The air sample will be collected according to SOP 8.D, and the air pump and lines removed from the worker.

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SOP AHETF-10.E.2.

- 2.3 The worker will then remove their own personal protective equipment (PPE), which may include chemical-resistant (CR) gloves, a respirator, glasses, hat or CR headgear. This headgear may contain head patch samples. If inner head patches were utilized during the study, the researcher will remove the inner head patch according to SOP 8.H.
- 2.4 If head patches were utilized in the study, the outer head patch will be collected by research personnel, according to SOP 8.H., after the worker removes their headgear.
- 2.5 The worker will then remove any body PPE (e.g., apron, coveralls, or gloves) and their shoes, then the worker may enter the clean, private area where they will remove their outer work clothes and socks.
- 2.6 If no sock dosimeters were used on the study, skip to section 2.7 and collect a hand wash sample. Otherwise, upon removal of outer garments (shirt, then pants, then outer socks) by the worker, the researcher will remove the sock dosimeters, according to SOP 8.I.
- 2.7 Immediately after the worker has removed his outer clothing and if the socks dosimeters (if used) have been collected, the researcher will collect hand wash samples, according to SOP 8.B.
- 2.8 After collection of hand washes, the researcher will collect face/neck wipe samples, according to SOP 8.C.
- 2.9 After collection of the face/neck wipes, the researcher will remove the inner dosimeter from the worker and process it, according to SOP 8.A.
- 2.10 At this point, all worker samples will have been collected and the worker shall dress in his/her street clothes and may be dismissed.
- 2.11 Any deviations to this procedure must be documented in the raw data and the Study Director informed of the changes and reasons. This sequence only applies to the post-monitoring period sample collection procedure. Interim samples that are collected will be done according to the specific matrix sample SOPs and identified according to SOP 8.F.

GPI Electronic Digital Meter
Chapter 10: FIELD OPERATIONS
AHETF-IO.F.I.

Effective Date : October 20, 2003

APPROVAL <u>William Otterly</u>	DATE <u>3-5-04</u>
APPROVAL <u>William Standart</u>	DATE <u>03-04-04</u>
Last Revision Date: September 1, 2003	Previous Version Number: 10.F.0.

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) provides the steps to properly operate, calibrate and maintain the Great Plains Industries, Inc. (GPI) Electronic Digital Meter for recording application solution amounts during Agricultural Handlers Exposure Task Force (AHETF) worker exposure studies.
- 1.2 This SOP was revised to correct typographic errors.

2.0 EQUIPMENT REQUIRED

- 2.1 The following equipment is needed to calibrate the flow meters:
 - a. GPI Electronic Digital Meter
 - b. "Calibrated" Bucket/Container or equivalent
 - c. Water Source
 - d. GFI Electronic Water Meter Operations Guide and Owner's manual

SOP AHETF-10.F.1.**3.0 CALIBRATION VERIFICATION PROCEDURE**

- 3.1 If necessary, prepare the meter according to the manufacturer's directions by installing two lengths of pipe (20" and 5", minimum) on the inlet and outlet ends, respectively.
- 3.2 Attach the water source to the inlet pipe. Secure the connection and ensure that there are no leaks.
- 3.3 Zero the meter by pressing and holding the DISPLAY button for three seconds. The meter should read zeros on the display.
- 3.4 Turn on the water source and fill the container to the predetermined volume mark. Use a continuous, full stream for the flow. Turn off the water.
- 3.5 Record the reading on the meter. Compare to the predetermined volume and calculate the percent difference.
- 3.6 Repeat steps 3.3 to 3.5 a minimum of three times for each meter until all meters to be used have been calibrated. Each meter should be within 5% of the expected volume.
- 3.7 If the reading on the meter is consistently greater than 5% of expected, then the meter must be electronically calibrated according to the manufacturer's directions. Refer to the Calibration section in the Owner's manual, pp. 10-13. After electronically calibrating the meter, recheck the meter as described above.

4.0 OPERATION

- 4.1 A complete description of operation controls is described in the Owner's Manual, Operations section, pp. 6-10.
- 4.2 Turn the meter on by pressing and releasing the DISPLAY button. The meter will automatically turn on when liquid flows through it. The meter will automatically turn off after approximately four minutes of non-use.
- 4.3 To clear the batch totals display, press and hold the DISPLAY button for three seconds. The cumulative total cannot be cleared, except by removing the batteries.

SOP AHETF-10.F.1.

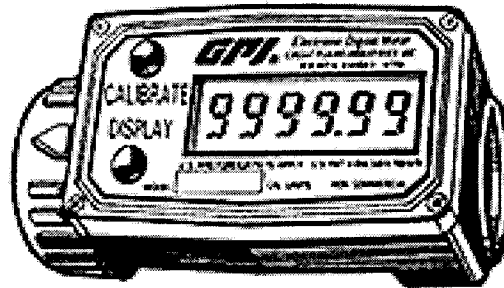
- 4.4 To select a calibration curve, hold the CALIBRATE button while pressing and releasing the DISPLAY button until the desired calibration curve shows on the display. The factory calibration curve should be selected. If a field calibration curve is necessary, then follow the manufacturer's directions for creating a field calibration. See the Owner's Manual, Calibration, pp. 10-13. Document this action in the raw data.
- 4.5 If the display is dim or non-existent, then the batteries are too weak to operate the meter properly.

5.0 MAINTENANCE

- 5.1 A complete description of maintenance procedures is described in the Owner's Manual, Maintenance section, pp. 14-16.
- 5.2 During daily or routine use, these meters are maintenance-free.
- 5.3 The meter should be cleaned after each use to prevent debris from accumulating on the interior, which can degrade accuracy and damage the turbine. Dried material should be cleaned with a penetrating lubricant, such as WD-40[®]. Do not submerge the meter.
- 5.4 If the reading is dim or blank, replace the batteries. Remove the cover by unscrewing the four face screws. Lift-off the faceplate, remove the old batteries, clean the battery terminal, and replace with fresh batteries. Replace the faceplate, and retighten the four screws.
- 5.5 If the meter fails to operate properly, cannot be adequately calibrated, or otherwise does not operate, then the meter should be removed from service, and either returned to the manufacturer for repair, or be replaced. Do not attempt to repair or modify the internal structures.
- 5.6 Record battery changes as "routine" maintenance. Record cleaning procedures and "routine" maintenance. Record non-functioning returned for repair or replacement and "non-routine" maintenance.

SOP AHETF-10.F.1.**6.0 REFERENCES**

- 6.1 For complete and detailed information on the operation, calibration, and maintenance procedures refer to:
- 6.1.1 GPI Electronic Digital Meter Owner's Manual No 920685-8
 - 6.1.2 GPI Operations Guide for Electronic Digital Meter No 920731-2
- 6.2 Great Plains Industries, Inc.
5252 East 36th Street North
Wichita, KS 67220-3205
TEL: 316-686-7361 toll-free: 1-800-835-0113
FAX: 316-686-6746
www.gplains.com/gpi

7.0 REFERENCE DIAGRAMS

Personal Air Sampling Pump Calibration

Chapter 10: FIELD OPERATIONS
AHETF-10.G.1.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: October 15, 2003	Previous Version Number: 10.G.0

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) provides the steps to properly calibrate the personal air sampling pumps used to collect air monitoring samples during Agricultural Handlers Exposure Task Force (AHETF) worker exposure studies.
- 1.2 This SOP has been revised to change the term “replicate” to monitoring period or worker.

2.0 EQUIPMENT REQUIRED

- 2.1 The following equipment is needed to calibrate the sampling pumps:
 - a. Personal low-volume air sampling pump(s) (e.g., SKC, or equivalent)
 - b. Tygon® tubing or equivalent
 - c. Appropriate OSHA Versatile Sampler (OVS) Tubes
 - d. Appropriate calibration device (e.g., Kurz Mass flow meter, Buck Calibrator, bubble meter and stopwatch, or equivalent)

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SOP AHETF-10.G.1.

3.0 CALIBRATION PROCEDURE

- 3.1 Place air sampling pumps on chargers before each use. If the pump is fully charged proceed to 3.2.
- 3.2 Calibrate air sampling pumps before use in each monitoring period. Calibrations will take place on the day prior to or the same day the pumps are to be used.
- 3.3 Calibrate the pumps under actual use conditions, as the air temperature may affect the airflow (e.g., calibrate outside rather than inside for exposure trials). Calibrate pumps with the appropriate OVS tube/ sampling train attached.
- 3.4 Follow appropriate contractor SOPs for the individual calibration methods for contractor equipment.
- 3.5 Adjust the airflow rate to appropriate rate as defined in the study protocol [e.g., 2 liters per min (L/min)] and document the flow rate and pump number in the raw data.
- 3.6 Turn off the air sampling pump and set aside. Repeat steps 3.4 and 3.5 until all needed sampling pumps (including backups) have been calibrated.

4.0 POST EXPOSURE FLOW RATE CHECK

- 4.1 Using the same methods to calibrate the air pump, measure the airflow with a new OVS tube. Document the results in the study file.
- 4.2 Check the post exposure flow rate after the worker's OVS tube has been removed by the field sample collection personnel.

Ethical Requirements for the Use of Human Subjects

Chapter 11: HUMAN SUBJECT MANAGEMENT AHETF-11.A.0.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

1.1 This Standard Operating Procedure (SOP) defines the ethical requirements necessary to obtain approval from various groups for Agricultural Handlers Exposure Task Force (AHETF) protocols that involve monitoring workers in its field studies. The groups that may be involved in granting permission to work with human subjects include an Institutional Review Board (IRB), U.S. EPA, the Human Studies Review Board (HSRB), the Pest Management Regulatory Agency (PMRA) of Canada when the study is planned for Canada, the California Department of Pesticide Regulation (CDPR) when the study is planned for California, and other state agencies.

2.0 RESPONSIBILITIES

2.1 Prior to the start of any worker exposure monitoring study conducted for the AHETF, approvals must be obtained from the appropriate groups. Obtaining these approvals is the responsibility of the Study Director (SD) and the study sponsor, AHETF.

3.0 ETHICS TRAINING FOR RESEARCHERS

- 3.1 The SD, the Principal Field Investigator (PFI), the Task Force Field Study Monitor, the worker observers, and other researchers working on behalf of the AHETF who interact with study participants, will have completed one or more training courses for protection of human subjects. Certificates of completion for the course(s) will be available prior to these individuals participating in the field phase study on behalf of the AHETF. Details on the courses that may be completed are described in SOP AHETF-1.B.

4.0 ADHERENCE TO ETHICAL STANDARDS

- 4.1 All AHETF field studies involving worker exposure monitoring are designed and conducted in accordance with scientific and ethical criteria set forth in the following ethical codes:
- a. U.S. EPA's "Protections for Subjects in Human Research" (Federal Register: February 6, 2006, Volume 71, Number 24) [Rules and Regulations] [Page 6137-6176] From the Federal Register Online via GPO Access [wais.access.gpo.gov] [DOCID:fr06fe06 -7] [Page 6138].
 - b. The Belmont Report, Office of the Secretary, "Ethical Principles and Guidelines for the Protection of Human Subjects of Research", The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979 (<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>).
 - c. Code of Federal Regulation, Title 40, part 26 "Protections for Subjects in Human Research" [which is referenced by the Department of Pesticide Regulation (DPR) pertaining to pesticide exposure studies involving human subjects at 3 CCR 6710].
 - d. Department of Health and Human Services (HHS) regulations at 45 CFR 46, Subpart A, which constitutes the Federal Policy (Common Rule) for the Protection of Human Subjects. (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>)

5.0 INSTITUTIONAL REVIEW BOARD (IRB)

- 5.1 All protocols and informed consent forms must undergo review and approval for ethical compliance by an IRB prior to enrolling any subjects for studies. The Western Institutional Review Board (WIRB; Olympia, Washington; www.wirb.com) is often used by AHETF and is used as an example here to illustrate the review process and required filings.
- 5.2 Initial review submissions from AHETF to WIRB typically will include the following:
- a. Initial Review Submission Form (latest version from WIRB)
 - b. GLP and Human Studies Protocol (unsigned final draft)
 - c. Research Subject Information and Consent Form – English (AHETF will request a Spanish version when appropriate)
 - d. Hospitalization Procedures
 - e. Resumes for principal investigator and any sub investigators, including credentials pertaining to ethics training and knowledge of human research
 - f. Recruitment materials
- 5.3 The WIRB Initial Review Submission Form identifies AHETF as the sponsor and the SD as the Principal Investigator (PI). It should be noted that this designation for the SD is different from the designation used in the AHETF GLP protocols (requirement of 40 CFR, Part 160 for the conduct of EPA GLP studies). It also identifies study site(s) (generally local site coordinator research facilities) and provides details about subject recruitment, consent, and payment. Hospitalization procedures are also provided which identify the nearest emergency medical facility to the study site(s) and indicate that 911 will be used as the primary method for obtaining emergency medical attention. Additional details of procedures for medical emergencies are outlined in SOP AHETF-11.H.

6.0 CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION (CDPR)

- 6.1 All studies involving worker exposure monitoring to be conducted in California must also have protocols reviewed and approved by the CDPR. This involves science and ethical reviews by the Office of Environmental Health Hazard Assessment (OEHHA) and the Worker Health and Safety Branch (WHS) of CDPR. The SD is responsible for obtaining this approval.
- 6.2 Any changes requested by CDPR must be incorporated into the study protocol and/or consent forms which must then be reviewed and approved by the IRB. Only upon receipt of the IRB-approved protocol and consent forms will CDPR grant final approval for the study to be conducted in California.

7.0 PROTECTIONS FOR SUBJECTS IN HUMAN RESEARCH

- 7.1 Protocols for all worker exposure studies will be submitted to EPA in accordance with EPA's final regulation published at 40 CFR Part 26 that establishes requirements for the protection of subjects in human research. The protocol, informed consent form, IRB materials, and other supporting documents, must be submitted to EPA.

Recruiting, Informing and Seeking Consent from Study Volunteers

Chapter 11: HUMAN SUBJECT MANAGEMENT
AHETF-11.B.0.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This Standard Operating Procedure (SOP) defines general procedures for recruiting, informing, and seeking informed consent from workers in field studies being conducted by the Agricultural Handlers Exposure Task Force (AHETF). A more detailed study-specific recruitment plan will be developed for each field study and will be included the study-specific protocol.

2.0 ETHICS TRAINING FOR RESEARCHERS

- 2.1 The Study Directors (SD), Principal Field Investigators (PFI), Task Force Field Study Monitors, Local Site Coordinators (LSC), worker observers, and others working on behalf of the Task Force who interact with study participants, will have completed one or more ethics training courses. Certificates of completion for the course(s) will be available prior to their participation in the field phase of the study on behalf of the AHETF. Details on the courses are defined in SOP AHETF-1.B.

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3.0 PROTOCOL APPROVAL

- 3.1 Workers will not be recruited for participation in any field study until after the following items have been completed:
- a. IRB approval has been obtained for the study protocol, consent forms and documentation required by 40 CFR 26
 - b. Approval of the proposed study by the Director of the California Department of Pesticide Regulation when a study is to be conducted in California
 - c. Review of the proposed study by EPA and the Human Studies Review Board, and
 - d. IRB approval of any changes in the protocol or any supporting document required as a result of the reviews by EPA, the HSRB, and/or CDPR

4.0 RECRUITMENT OF WORKERS

- 4.1 Recruitment of workers typically occurs in two phases. The first phase occurs during the planning stages of the study and involves communications between the SD and prospective cooperators or LSCs. These communications or visits are to determine the suitability of potential sites for the study and to identify potential pools of workers for monitoring. However, no contacts with prospective workers will be made during this time unless the protocol has gained final approval by the appropriate agencies as described above. During the first phase, written assurance will be obtained from the employer that the workers will not suffer any consequence if they decide either to participate or not to participate in the study and that there will be no coercion of the workers (see Attachment 11-B-1).
- 4.2 When all appropriate approvals for the protocol have been obtained the SD may initiate the second phase of recruitment in which contacts are made with prospective workers. The process is as follows:

SOP AHETF-11.B.0.

- a. Growers will have been identified who are willing to cooperate with AHETF in the monitoring study and the SD will have determined the grower site(s) to be acceptable. The grower or other responsible personnel will have given permission for the SD to contact their employees to determine employee interest in study participation
 - b. The SD then initiates contact with the employees typically by distributing an IRB-approved flyer which generally describes what participation in the study entails and providing a contact number for the SD. The SD organizes a private group meeting with only the interested workers present.
- 4.3 The private group meeting with interested workers will consist of the following:
- a. Growers, LSC or other personnel to which employees might report will not attend.
 - b. The SD will explain the nature of the study and the general content of the protocol and Consent Form (according to a script approved by the IRB).
 - c. The SD may also show an IRB-approved video presentation or pictures of how the dosimetry and air samplers are worn and how face/neck wipe and hand-rinse sampling is performed.
 - d. Eligibility criteria will be reviewed and all questions will be answered.
 - e. Informed Consent Forms will be available for review by potential workers.
 - f. Potential workers also will be shown the written assurance obtained from the employer that they will not suffer any consequence if they decide not to participate in the study and that there will be no coercion of, or undue influence on, the workers.
 - g. At the conclusion of the group meeting interested workers may either contact the SD at a later time to express their intent to participate or may go through the individual private consent process at that time (described below in Section 7).

- 4.4 Attachment 11-B-2 provides a flow diagram of the recruiting and consent processes.

5.0 INCLUSION AND EXCLUSION CRITERIA

- 5.1 Potential participants may be farm owners, farm operators, farm employees, contract applicator employees, or commercial applicators, etc. Employees of agricultural research facilities may be used if they meet the inclusion/exclusion criteria for the study.
- 5.2 Inclusion criteria include people who:
- a. Are freely willing to participate.
 - b. Are trained in the task that will be monitored - workers must have received basic pesticide handling training in accordance with the Worker Protection Standard (WPS) or equivalent Canadian regulations, or must be exempt from such regulations. Each participant must confirm that they have received the required training or that they are exempt from the requirement.
 - c. Have recent (i.e., within the last year) experience performing the task that will be monitored in the study.
 - d. Are at least 18 years old (age must be verified with a government-issued photo identification).
 - e. Consider themselves to be in good general health with no medical conditions that could impact their ability to participate in the study (see SOP AHETF-11.C for more details).
 - f. Agree to perform pesticide handling tasks in conformance with label and WPS requirements (e.g., monitored workers must agree to wear all PPE required by the label).
 - g. Are English or Spanish speakers (*see below for further discussion of this topic*).

SOP AHETF-11.B.0.

- 5.3 Exclusion criteria include people who:
- a. Are ill or physically unfit to perform the work tasks (see SOP AHETF-11.C for more details).
 - b. Are cognitively impaired as deemed by the SD.
 - c. Are pregnant or nursing (pregnancy status will be determined no more than 24 hours prior to participation in the study - see SOP AHETF-11.D for more details; nursing status is self-reported).
 - d. Are minors, *i.e.*, under 18 years of age.
 - e. Can't produce a government-issued photo identification to prove their age.
 - f. Normally elect to wear more protective clothing or PPE than is required by the study protocol and/or product label.
 - g. Act as the local site coordinator; or are employees of the: SD, Principal Field Investigator or Task Force member companies.
 - h. Are not fluent in English or Spanish

6.0 LANGUAGE REQUIREMENTS

- 6.1 Study participation will be limited to English or Spanish speakers. All workers can select the Consent Form in the language of their choice for reading during the consent process (if they are readers) and will sign their preferred version of the form. For workers whose preferred reading language is Spanish, AHETF obtains an IRB-approved translation of the Consent Form.
- 6.2 While AHETF does not intentionally recruit workers with limited literacy, pesticide handlers occasionally do fall into this category and are therefore included in the target population. Special precautions are used with such workers (described below). Reading ability will be self-reported by the worker.

SOP AHETF-11.B.0.

- 6.3 When the need for a witness arises, i.e. if a worker has limited reading ability, only an impartial witness, i.e., a person unassociated with the conduct of the research, will be used. The witness will also sign the Consent Form.
- 6.4 Since the SDs contracted by the AHETF are typically monolingual (they are only English speakers) there is a need for an interpreter to communicate with workers who only speak Spanish. The interpreter might be an employee at the study site (e.g., employee of a grower or a commercial applicator), a person of the worker's choosing, or might be someone located during discussions with the local agricultural community on a study-specific basis. If an interpreter is used, the SD will ensure the interpreter knows enough about the research design and the content of the Consent Form to provide an accurate translation. If necessary, this will involve tutorial discussions from the SD. To test the understanding by the interpreter, the SD will ask him/her to explain some portions of the Spanish Consent Form, in English. Interpreters will translate the Study Director's (English) discussion into Spanish during the consent process. They will also be utilized during the study should any issues arise which can't be resolved directly with the worker. Interpreters are not considered to be part of the research team and will not sign the Consent Form.
- 6.5 In instances where the translator is not associated with the conduct of the research and is considered impartial, he/she may also serve as a witness for Spanish speaking workers with limited reading ability. In this instance, the translator who is also serving as the witness would sign the Consent Form as the witness to the consent process.
- 6.6 The following procedures will be followed with each individual wanting to participate in an AHETF study. The SD will go through the entire consent process with the worker (see Section 7.0 below). The following paragraphs describe how workers with varying reading and language skills will be guided through the consent process. Attachment 11-B-3 provides a summary of the procedures described below.
- a. Workers who are fluent in English and have the ability to read English will be provided a copy of the Consent Form in English, will be allowed to read the Consent Form in its entirety and ask questions of the SD or research staff pertaining to their participation in the study. A copy of the signed Consent Form will be provided to the worker.

SOP AHETF-11.B.0.

- b. Workers who speak English, but cannot read English will have the Consent Form read to them and they will be allowed to ask any questions of the SD or research staff pertaining to their participation in the study. An impartial witness will verify that the worker has apparently understood the materials read to and discussed with them. The witness may assess the worker's understanding by their answers to the questions asked of the worker by the SD (see Section 7 below). A copy of the signed Consent Form will be provided to the worker.
- c. Workers who are fluent in Spanish and have the ability to read Spanish will be provided a copy of the Consent Form in Spanish, will be allowed to read the Consent Form in its entirety and ask questions of the SD or research staff pertaining to their participation in the study. Interpreters for Spanish speakers will be provided. A copy of the signed Consent Form will be provided to the worker.
- d. Workers who speak Spanish, but cannot read Spanish will have the Consent Form read to them and they will be allowed to ask any questions to the SD or research staff pertaining to their participation in the study. Interpreters for Spanish speakers will be provided. An impartial witness will verify that the worker has apparently understood the materials read to and discussed with them. The witness may assess the worker's understanding by their answers to the questions asked of the worker by the SD (and relayed by the interpreter; see Section 7 below). A copy of the signed Consent Form will be provided to the worker.

7.0 INFORMED CONSENT PROCESS

- 7.1 Although Consent Forms are unique to individual studies, each Consent Form will contain the elements required by 40 CFR 26.1116.
- 7.2 The SD will be responsible for obtaining informed consent from all study workers prior to their participation in the study.

SOP AHETF-11.B.0.

- 7.3 Informed consent discussions will be conducted by the SD in private with each worker and others that the worker may want to have present. Interpreters and other witnesses may also be present as described above in Section 6.0.
- 7.4 The SD will inform the worker that he/she will receive a \$20 payment even if he/she decides not to participate following the discussion.
- 7.5 During the private meeting the SD will provide each worker with a full explanation of the study, its requirements, any potential risks, its benefits, alternatives to participation, etc. Workers will be advised of their right to withdraw from the study at any time and for any reason without jeopardizing their normal position with their employers or their daily wages. Workers will receive an additional \$80 if they decide to participate (don the dosimeters) but withdraw before the end of the monitoring period. Each worker will be provided a copy of the supervisor's signed form (described above) that states they will not suffer any consequence if they decide not to participate.
- 7.6 The SD will provide information about the risk of the surrogate chemical in the study, including signs and symptoms of acute overexposure. The product label and Material Safety Data Sheet also will be explained. WPS requirements, especially proper use of clothing, personal protection equipment, etc., will be discussed. Refer to SOP AHETF-11.E for details.
- 7.7 The SD will discuss the medical management plan with the prospective participants. Information will be provided about the risk of heat stress, including signs and symptoms, and ways to prevent it. Details on heat stress and its presentation are outlined in SOP AHETF-11.G, while details on emergency medical procedures are outlined in SOP AHETF-11.H.
- 7.8 During the discussions between potential participants and the SD, ample time will be provided for questions and the SD will provide any additional information or clarification that is requested.

SOP AHETF-11.B.0.

- 7.9 The IRB-approved Consent Form will be presented in the preferred language (English or Spanish) of the worker. All sections of the Consent Form will be explained in detail. When the SD is satisfied that the worker understands the requirements and risks of the study, and if the worker still wants to participate, he/she will be asked to sign and date the Consent Form and the SD will provide a copy of the signed form to the worker.
- 7.10 In all situations, the SD will not sign the Consent Form unless he/she believes the candidate fully understands the information presented. This will be ascertained by providing repeated opportunities to ask questions and by asking questions of the potential workers that would require a response that indicates understanding of key issues. The following is an example of some possible questions and possible answers:
- a. Q: When can you withdraw from the study?
A: Whenever I want.
 - b. Q: What has your supervisor said about your volunteering?
A: I'm free to make that decision on my own & it won't affect my employment.
 - c. Q: What will you wear so we can measure the amount of chemical in the air that you breathe?
A: An air pump on my belt.
 - d. Q: What type of personal protective equipment must you wear for this study?
A: Gloves (the answer will depend on the specific product being used in the study – gloves are an example answer for a product requiring gloves)
 - e. Q: Can you name two risks of participating in the study?
A: Physical risk, chemical risk, overheating, etc.
- 7.11 The SD will not sign the Consent Form unless he/she believes they have done everything possible to ensure that the process has been free of any element of coercion or undue influence, and that the worker understands the material in the Consent Form.
- 7.12 If more workers volunteer to participate than required for the study, the SD will randomly select the required number of workers from the available pool.

8.0 FOLLOW-UP PROCEDURES

- 8.1 Each study participant will be provided an opportunity to request a copy of the exposure data resulting from their activities in the study. A summary of their personal study data will be mailed to the address of record for all participants desiring it (the SD or designee will complete the form in Attachment 11-B-4). This form (and all forms that contain the worker's name and address) will be maintained in a confidential file with the study records as outlined in SOPs AHETF-6.B and -6.D.

- 8.2 When the monitoring period is completed, or at the time a participant withdraws from the study, the SD will remind the worker that he/she has received a copy of the signed Consent Form that has phone numbers for reporting any health changes the worker thinks may be related to his/her participation in the study. Worker inquiries of this nature will be forwarded to AHETF management to be resolved on a case-by-case basis.

ATTACHMENT 11-B-1

Employer Cooperation Statement

Employer / Supervisor: _____

Study Director: _____

Date of Discussion: _____

Site of Discussion: _____

Employer / Supervisor Cooperation Statement:

I certify that I'm authorized to make the following statements:

- After discussing the nature of the study with the Study Director, I will allow AHETF to recruit any of my employees with applicable training and experience (as determined by the Study Director) in the tasks involved in the study.
- While I acknowledge that there may be benefits to me:
 - I will neither encourage nor discourage my employees to participate in the study.
 - An employee's decision to participate, not to participate, or to withdraw from participation in the study will have no impact on his/her employment status or pay.
 - Employees who decide not to participate, who withdraw from participation, or who complete participation in less than a typical work shift will be offered alternative work at their usual pay to complete their usual work shift.
 - Employees will receive their normal pay for days they participate in the study.

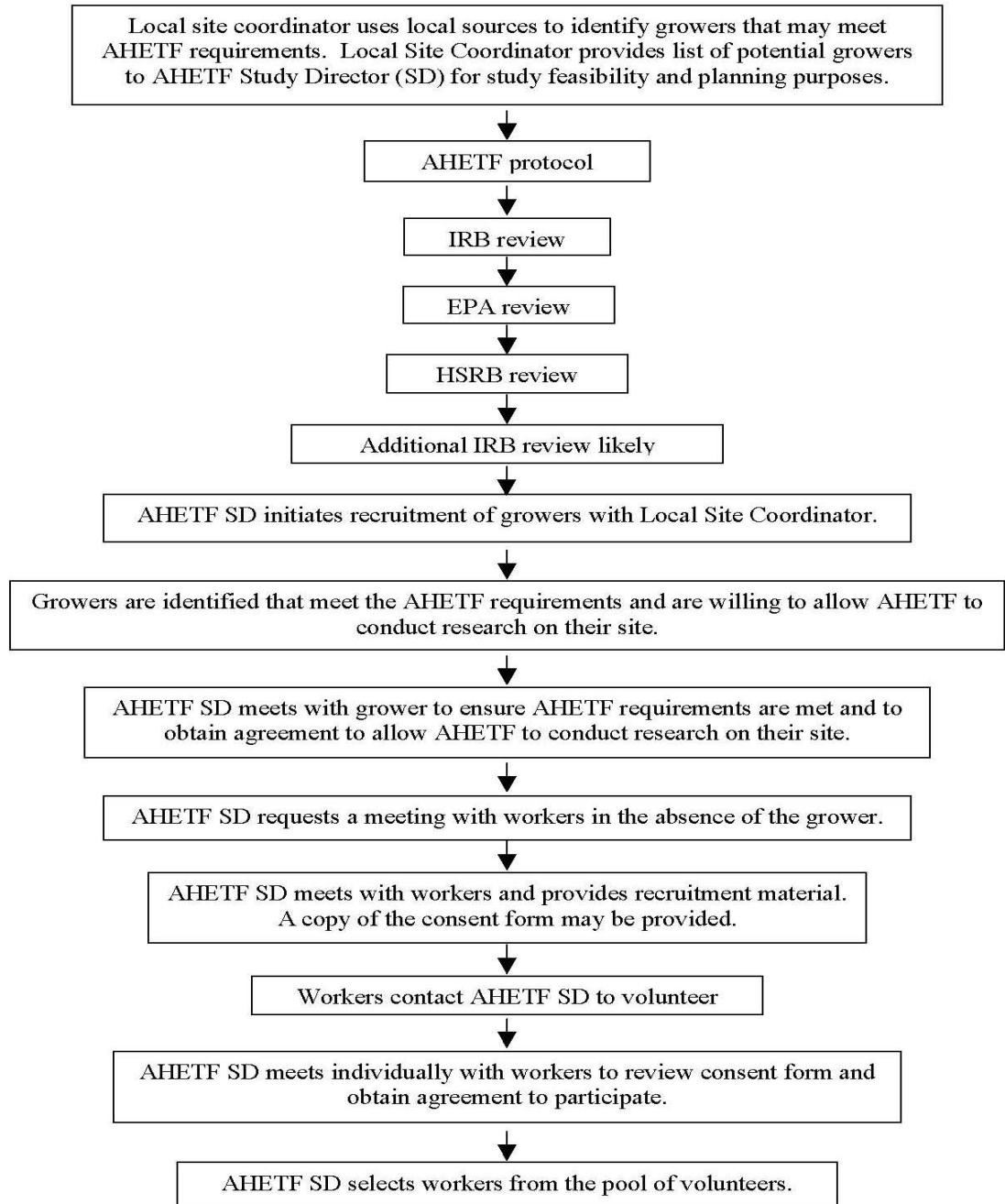
Signature: _____

Date: _____

Title and Affiliation: _____



ATTACHMENT 11-B-2



US EPA ARCHIVE DOCUMENT

ATTACHMENT 11-B-3

Language Procedures

	Worker Speaks English (and maybe Spanish, too)	Worker Speaks Spanish (but not English)
Worker Can Read This Language	SD Discussions in English Consent Form in English No Translator needed No Witness needed	SD Discussions in English Translated into Spanish Consent Form in Spanish Translator needed No Witness needed
Worker Cannot Read This Language	SD Discussion in English SD reads English Consent Form to worker No Translator needed Witness needed (English)	SD Discussion in English Translated into Spanish Translator reads Spanish Consent Form to worker Translator needed Witness needed (bilingual)

US EPA ARCHIVE DOCUMENT

ATTACHMENT 11-B-4

REQUEST FOR PERSONAL STUDY RESULTS - AHETF Study (AHExx)

This worker wishes to receive a copy of his/her personal study results.

Name: _____
Address: _____
City: _____
State: _____
Zip Code: _____

Study Worker
ID: _____

Description of Data Sent: _____

Sent By: _____

Date Sent: _____

Worker Health Status
Chapter 11: HUMAN SUBJECT MANAGEMENT
 AHETF-11.C.0.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

1.1 The following SOP describes the procedure used during the informed consent process to determine the general health status of potential participants and whether they have any medical condition(s) which could impact their ability to participate in an Agricultural Handlers Exposure Task Force (AHETF) worker exposure study.

2.0 INTRODUCTION

2.1 The AHETF requires workers to be in good health and able to perform the work activity for which they will be monitored. The AHETF respects the medical privacy of the worker. As a result, the AHETF will make no effort to obtain worker medical records and will rely on self-reported health status.

3.0 PROCEDURE

3.1 The worker will be asked during the informed consent process if they consider their general health status to be good. Only workers who answer “yes” will be allowed to participate in the study.

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SOP AHETF-11.C.0.

- 3.2 The worker will be asked during the informed consent process if he/she has any medical condition(s) that could impact his/or ability to participate in the study. If needed, the Study Director will discuss with the worker what this question means. Only workers who answer “no” will be allowed to participate in the study.

Disqualification of a worker due to health concerns will not be documented in the raw data and all other data pertaining to this individual will be promptly discarded. However, they will be counted as having been screened for participation, as per IRB guidelines.

Pregnancy Testing
Chapter 11: HUMAN SUBJECT MANAGEMENT
 AHETF-11.D.0.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 This SOP outlines the steps to be taken to assess the reproductive status of a female worker who is being considered for participation in an Agricultural Handlers Exposure Task Force (AHETF) worker exposure study. AHETF policy does not permit pregnant workers to participate in its worker exposure studies. Federal Regulations (40 CFR Part 26, §26.203) prohibit a pregnant or nursing female from participating in these studies.
- 1.2 These procedures are also intended to protect the worker's privacy with respect to her employer and co-workers concerning the outcome of the pregnancy test.

2.0 PROCEDURES

- 2.1 Each female worker will be told during the consent process that any woman who is pregnant or nursing is ineligible to participate in an AHETF worker exposure study. The worker will be informed that no additional remuneration will be provided for taking the pregnancy test (i.e., the \$80 for the inconvenience of participating in the exposure monitoring will not be provided to a woman who has a positive pregnancy test result and who therefore cannot participate in the study).

SOP AHETF-11.D.0.

- 2.2 Within 24 hours prior to study participation, any woman who is being considered for participation will be asked to take a urine pregnancy test (over-the-counter variety).
 - a. The pregnancy test kit will be provided by AHETF.
 - b. The pregnancy test will be supervised by a female researcher who will explain how to take the test.
 - c. The researcher will escort the female worker to the bathroom and wait outside while the worker self-administers the test.
- 2.3 The outcome of the test will initially be known only to the worker.
- 2.4 After the test, the worker will state her desire to continue or withdraw from participation in the study.
 - a. If the worker chooses to withdraw from the study
 - i. She will be allowed to do so without stating a reason.
 - ii. The test results will not be revealed to the employer or co-workers.
 - iii. The test results will not be documented. Consent forms and all other records associated with the worker will be promptly discarded.
 - b. If the worker states the desire to participate
 - i. A female researcher trained in the interpretation of pregnancy tests will confirm that the pregnancy test is negative.
 - ii. The negative pregnancy test results will be recorded in the study raw data.
- 2.5 With the confirmation of a negative test result, the worker will be permitted to continue in the study.

Pesticide Safety Precautions

Chapter 11: HUMAN SUBJECT MANAGEMENT
AHETF-11.E.0.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

1.1 This SOP describes measures intended to promote pesticide hygiene measures, which may result in decreased risk for illness or injury during participation in an Agricultural Handlers Exposure Task Force (AHETF) worker exposure study. These procedures will be followed during the worker informed consent process and exposure monitoring.

2.0 TRANSLATION

2.1 If needed or requested by the worker, a translator will be provided during any discussions described below.

3.0 COMPLIANCE WITH SAFETY REQUIREMENTS

3.1 Material Safety Data Sheets (MSDS) and labels will be summarized and available during the informed consent process and available during the exposure monitoring.

3.2 The Study Director will discuss the pertinent sections of the MSDS and label, but will emphasize sections that relate to possible signs and symptoms of acute over-exposure to the product being used in the study.

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SOP AHETF-11.E.0.

- a. For example, if the product is a cholinesterase inhibitor, specific signs and symptoms are stated. For example, *“Too much exposure to this product may cause nausea, dizziness, confusion, and difficulty breathing.”*
 - b. Workers will be advised that there may be risks from using the product, which are unknown at this time.
- 3.3 Additional information on the product label that will be discussed with the worker includes the use of personal protection equipment (PPE) required during product handling and other user safety recommendations.
- a. Workers will be reminded of standard practices that need to be followed to reduce exposure to pesticides. For example, provisions of the Worker Protection Standard (WPS) will be cited such as the requirement to wear long pants and long-sleeved shirts and labeled specified PPE; and safety recommendations for washing hands before eating, drinking or using the toilet, and to remove clothing that gets drenched with pesticide, for example from an accidental spill.
- 3.4 During the study conduct, researchers will ensure compliance with safety requirements on the product label and with the WPS. For example, workers will be reminded to use the label-specified PPE and to follow use directions on the label.
- a. Each worker will be observed by a researcher during the entire monitoring period.
 - i. Study observers will not advise workers on how to perform their work unless a safety issue is involved. The observer will then immediately notify the Study Director.
- 3.5 The Study Director may stop the worker’s participation in the study if he/she is engaging in unsafe work practices such as not using label-specified PPE. The participant will still receive the \$80 payment for his/her inconvenience and the Study Director will decide whether the exposure monitoring has been compromised and whether the matrices should be collected from the worker.

4.0 ADDITIONAL SAFETY PRECAUTIONS

- 4.1 AHETF will have an on-site contracted medical professional at each study as an added safety precaution (see AHETF-SOP-11.H for further details).
- 4.2 AHETF will have a portable on-site eye-wash station at every study in the event that exogenous substances (e.g., dirt, droplets or splashes, etc.) get in the eye of study participants, study researchers, or other on-site individuals.

Adverse Events Reporting for Institutional Review Boards
Chapter 11: HUMAN SUBJECT MANAGEMENT
AHETF-11.F.0.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: N/A	Previous Version Number: N/A

US EPA ARCHIVE DOCUMENT

1.0 PURPOSE AND SCOPE

1.1 This SOP outlines the steps to be taken to address an unanticipated adverse event resulting from participation in an Agricultural Handlers Exposure Task Force (AHETF) worker exposure study.

2.0 PROCEDURES

2.1 The investigator (the Study Director) must familiarize himself with the references cited in this document.

2.2 Investigators are required to report adverse events that meet both of the following criteria (definition is from the Western Institutional Review Board):

- a. Event is **UNANTICIPATED** (An unanticipated event is any adverse experience where the nature, severity or frequency is not identified in the investigator brochure or described in the protocol. Events which are already cited in the investigator brochure or protocol are not unanticipated and do not have to be reported to WIRB),

AND

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- b. Event is **POSSIBLY RELATED** to the study design, procedures, or drug/device. If the adverse event is clearly not related to the study drug, device, procedures, or washout process, it would not represent a risk to other subjects in the research and, therefore, does not have to be reported to WIRB.
- 2.3 If these criteria are not met then the event does not have to be reported to the IRB.
 - 2.4 The Study Director (SD) must submit the written report of any suspected adverse event that occurs during a study, even if the event is brought to his attention by another researcher. The report should fully describe the event and any pertinent information leading up to it and following it (e.g., observers and/or medical professional comments prior to the occurrence). The report should include all relevant information of any similar events that occurred previously in other AHETF-conducted studies.
 - 2.5 The SD must submit the written report to the IRB within 10 business days of the occurrence of the potential adverse event.
 - 2.6 The report should include all relevant information, including any similar events that occurred previously in other AHETF-conducted studies.

3.0 REFERENCES

- 3.1 Office for Human Research Protections (OHRP), Dept of Health and Human Services: Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. January 15, 2007 (guidance on regulations at 45 CFR part 46).
- 3.2 U.S. Dept of Health and Human Services (DHHS): Guidance for Clinical Investigators, Sponsors, and IRBs – Adverse Event Reporting – Improving Human Subject Protection). April 2007.
- 3.3 Western Institutional Review Board (WIRB): A guide for Researchers. Version 1.5, October 2006. www.wirb.com. Download on May 3, 2007.

Identification and Control of Heat Stress

Chapter 11: HUMAN SUBJECT MANAGEMENT

AHETF-11.G.0.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: N/A	Previous Version Number: N/A

1.0 PURPOSE AND SCOPE

- 1.1 The purpose of this Standard operating Procedure (SOP) is to provide information on the recognition of conditions that contribute to heat-related illness that may occur during the conduct of an Agricultural Handlers Exposure Task Force (AHETF) worker exposure study.
- 1.2 Since workers wear an extra layer of clothing during AHETF exposure studies in addition to any required PPE, the risk of heat-related illness may be increased. This document presents a summary of situations that increase the risk of heat-related illness, procedures for preventing heat-related illness, early signs and symptoms of heat-related illness, and what to do if heat-related illness becomes apparent or suspected. AHETF Study Directors will use this information to brief field investigators and field monitors prior to each exposure study conducted by the Task Force.
- 1.3 This SOP describes the measures to be taken to minimize the risk of heat-related illness to workers during their participation in an Agricultural Handlers Exposure Task Force (AHETF) field study, measures to be taken if a worker is affected by heat-related illness, and how AHETF researchers will monitor environmental conditions (ambient temperature and humidity).

2.0 INTRODUCTION

- 2.1 There is potential for heat stress to agricultural workers under certain conditions of temperature and humidity. For workers who participate in AHETF studies, this potential increases because of an additional layer of clothing (inner dosimeters) he/she is required to wear during the study monitoring period.
- 2.2 The Study Director will identify any employer response plans that address heat-related illness. As an adjunct to existing plans, the Study Director will discuss the AHETF procedures with the on-site employer and workers. The Study Director shall gain agreement to utilize the AHETF procedures during the conduct of the study. This will be documented and included in the raw data.

3.0 RISK FACTORS

- 3.1 Heat stress is the build-up in the body of heat generated by the muscles during work and from the environment. Heat exhaustion and heat stroke result when the body is subjected to more heat than it can accommodate. The following factors can increase the risk of a worker experiencing heat-related illnesses:
 - a. **Weather:** increased temperature, increased humidity, direct sunlight, and low winds all contribute to heat stress. Keep in mind the effects of high temperatures and high humidity are more than additive.
 - b. **Workload:** the body generates more heat during heavy work than during light or moderate work, so activities involving lifting and/or walking contribute more to heat stress than sedentary tasks.
 - c. **Clothing and PPE:** the evaporation of perspiration on the skin helps cool a person so the more clothes a person wears, the slower the perspiration evaporates and the longer it takes to cool down. In addition, coated and non-woven synthetic garments (e.g., rainsuits) effectively block evaporation of perspiration and contribute to heat stress.

- d. **Worker conditioning:** younger workers, well-rested workers, and physically fit workers are less likely to suffer heat illness than other workers. In addition, workers who are not acclimated to working in the heat are at much greater risk of heat illness. Most importantly, workers must remain adequately hydrated, which means liquids such as water or sports drinks should be consumed before and regularly during work.

4.0 PREVENTION PROCEDURES

- 4.1 The Study Director shall make arrangements to provide a medical professional (emergency medical technician [EMT], paramedic, physician's assistant [PA], licensed practical nurse [LPN], or registered nurse [RN] on-site during the conduct of an AHETF study while workers are being monitored. The medical professional shall conduct periodic observations of workers during the study and will advise the Study Director regarding possible signs of heat-related illness.
- 4.2 During all AHETF studies, the Study Director, on-site medical professional, and the field investigators share responsibility for awareness and prevention of heat illness. The following procedures will be followed:
 - a. Post a copy of the poster titled "Controlling Heat Stress Made Simple" at each field site (for example, in the staging or dressing area) so workers and field investigators will remain aware of the issue and can refer to the information on the poster (which is similar to this document). Both the English and Spanish versions will be posted (see Reference 13.5).
 - b. Initiate worker exposure monitoring during the cool part of the day whenever practical
 - c. Ensure plenty of water and sports drinks are available for the workers.
 - d. Assure that shady areas are available during breaks.
 - e. Immediately before monitoring begins, remind the workers of the risk of heat stress, suggest they drink some liquid before they start

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work, and let them know how/where they can get liquid during the monitoring period.

- f. Urge workers to drink liquid during the monitoring period and remind them that thirst does not give a good indication of how much liquid a person needs to drink. There is no need to take hand washes or stop inhalation monitoring during a water break.
- g. Observe workers during the monitoring period and be aware of the signs and symptoms listed in Attachment 11-G-1.
- h. Require workers to take rest breaks when any signs or symptoms outlined below are present (see Attachment 11-G-1).

5.0 SIGNS/SYMPTOMS AND FIRST AID MEASURES

- 5.1 Researchers should be familiar with the signs, symptoms, and treatment of heat-related illnesses outlined in Attachment 11-G-1: Heat Illness Symptoms and Treatment Chart.

6.0 FIELD PERSONNEL RESPONSIBILITIES

- 6.1 During all AHETF studies, the Study Director, field investigators, and on-site contracted medical professional share the responsibility for awareness of heat illness. This section stresses the importance that symptoms be recognized and responded to promptly and appropriately. The on-site medical professional is described in SOP AHETF 11.H.
- 6.2 The Study Director will have received training, such as by the American Red Cross or other recognized training organization, in the recognition of symptoms associated with heat-related illness and in what measures should be taken to relieve symptoms of heat-related illness. Documentation of training will be kept in their personnel file.

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- 6.3 The Study Director or AHETF representative will provide instruction to the field investigators, including study observers and field monitors, regarding the recognition of signs and symptoms of possible heat-related illnesses and actions necessary if heat-related illness occurs. The basis for this instruction is outlined in sections 3.0, 4.0 and 5.0 of this SOP.
- 6.4 During the consent process, the Study Director will provide the worker with information on early signs and symptoms of heat-related illnesses.
- 6.5 Just prior to monitoring, the Study Director will discuss heat-related illness with the participants and the need to immediately report to the individual observer or other researcher any illness or injury.
- 6.6 The Study Director will ensure that a copy of the poster entitled “Controlling Heat Stress Made Simple” is posted at each field study site (such as in the staging or dressing area). It will be visibly placed so workers and field investigators will remain aware of the issue and can easily refer to the information on the poster. Both English and Spanish versions will be posted.
- 7.0 RESPONSIBILITIES FOR CONTROL AND TREATMENT OF HEAT-RELATED ILLNESS**
- 7.1 The Study Director is responsible for taking actions are taken to minimize the risks of heat stress during field monitoring. These include:
- a. monitoring environmental conditions (heat index based on ambient temperature and relative humidity) which may influence the risk of heat-related illness
 - b. when necessary, initiating specific steps intended to prevent or minimize the occurrence of various heat-related illnesses
 - c. when necessary, relieving symptoms of heat- related illnesses
 - d. determining, in consultation with the on-site medical professional, if medical treatment is required.

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- 7.2 Prior to monitoring, the Study Director or Principal Field Investigator will coordinate with local emergency response or medical professionals to provide medical coverage if needed. This should include at least identifying and locating the closest facility, calling or visiting the facility, and determining the best way to get emergency medical assistance. If possible, the staff of the medical facility should be informed when and where the research will be conducted, and that any participants needing medical attention will be brought to that facility.
- 7.3 The Study Director will inform all study observers at the start of the study of the current Heat Index (Apparent Temperature) Category. The observer will be informed if or when the Heat Index Category subsequently changes.
- 7.4 The study observers will look for signs of heat illness and record their findings on their Observation Form. Recordings will be made periodically or when they are informed that a Heat Index Category has changed.
- 7.5 If a study observer believes a worker is showing signs of heat-related illness, he/she reports to the Study Director immediately. The affected worker will be taken to a shady or cool location and checked by the Study Director and on-site contracted medical professional. A decision will then be made as to whether the worker will continue to participate in the study.
- 7.6 The Study Director, in consultation with the on-site contracted medical professional, will decide if and when to stop a worker's participation in the study. As per GLPs, the final authority to terminate a worker's participation in the study rests with the Study Director.
- 7.7 In response to indications that conditions are conducive to high temperatures and high relative humidity, the Study Director may elect not to initiate the study or to terminate the study operations on a particular day.

8.0 HEAT INDEX CATEGORIES

- 8.1 The National Weather Service (NWS) Heat Index Chart will serve as the basis for determination of the Heat Index Categories. The Heat Index Chart (calculated from a combination of ambient temperature and humidity; see next section for determination of the heat index) is divided into color-coded categories, each denoting a range of heat index (HI) temperatures at which heat-related illnesses can possibly or are likely to occur. (Ref. 13.1) See Attachment 11-G-2 for a copy of the Heat Index Chart.
- 8.2 The following table summarizes the HI Categories.

National Weather Service Heat Index (Apparent Temperature)		
CATEGORY	HEAT INDEX TEMPERATURE RANGE, °F	POSSIBLE ILLNESS
Not applicable	Less than 80	None anticipated
Caution	80-89	Fatigue possible with prolonged exposure and/or physical activity
Extreme Caution	90-104	Sunstroke, heat cramps or heat exhaustion possible with prolonged exposure and/or physical activity
Danger	105-129	Sunstroke, heat cramps or heat exhaustion likely , and heatstroke possible with prolonged exposure and/or physical activity
Extreme Danger	130 or higher	Heat/Sunstroke highly likely with continued exposure

9.0 DETERMINATION OF HEAT INDEX

- 9.1 The heat index determination requires readings of local ambient temperature and relative humidity. Appropriate meteorological instrumentation will be used to determine the HI, such as a portable monitoring device, a sling psychrometer or on-site weather station. Measurements will be recorded and included in the raw data.

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- 9.2 Temperature and relative humidity readings will be applied to the Heat Index Chart to determine the HI. Match the measured readings to those on the Heat Index Chart. The Heat Index will be the temperature shown at the intersection of the measured temperature and humidity readings.
- 9.3 The resulting HI will be increased by 10° F [6° C] **if the worker is working in direct sun**. This includes work performed in greenhouses taking direct sunlight. If working in shaded areas such as enclosed cabs, tractors with canopies, or shade houses, or during evening or prevailing cloudy conditions, then the heat index reading needs no adjustment. (Ref. 13.2)
- 9.4 It is not necessary to monitor the heat index if the ambient temperature is below 70° F [21° C]. However, certain combinations of ambient temperatures between 70-79° F [21 - 26° C] and relative humidity readings are equivalent to HI values found in the CAUTION Category if adjusted for working in direct sun. Therefore, once the ambient temperature reaches 70° F [21° C], begin monitoring the Heat Index at least every hour. (Ref. 13.3)

10.0 CRITERIA FOR FIELD MONITORING INITIATION

- 10.1 Worker exposure monitoring will be initiated as scheduled unless extremely hot conditions are present. Specifically, worker exposure monitoring will not begin if the HI is $\geq 130^{\circ}$ F [54° C], or $\geq 120^{\circ}$ F [49° C] when working in direct sun (EXTREME DANGER Category). These are the beginning of the range of temperatures at which heat stroke is highly likely. (Ref. 14.4) The Study Director, at his discretion, may choose not to initiate monitoring, regardless of the HI.
- 10.2 The principal field investigator will exercise the requisite vigilance to heat stress conditions, sections 10.4 through 10.8. The degree of vigilance adjusts to changing environmental conditions (heat index based on temperature and humidity) that may affect worker risk to heat stress. In addition, the on-site medical professional will periodically observe workers when conditions exist for potential heat related illness.

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- 10.3 The symptoms of heat-related illness and measures to relieve symptoms as described in the following sections are based on EPA's "A Guide to Heat Stress in Agriculture", *Table 1 - Heat Illnesses and First Aid Measures*. They are not meant to be all-inclusive, but serve as general guidance for purposes of this SOP. The Study Director will be trained in the recognition of signs and symptoms of heat-related illness, and in determining measures needed to relieve symptoms, and he will exercise appropriate diligence under the specific conditions of a heat-related event. Additionally, the Study Director should consult with the on-site medical professional with regard to suspected cases of heat-related illness.
- 10.4 If the HI is < 80° F [27° C], or < 70° F [21° C] when working in direct sun, no specific vigilance is necessary. Observe for early signs of **possible** heat illness, such as fatigue.
- 10.5 If the HI falls between 80° - 89° F [27 - 32° C], or between 70° - 79° F [21 - 26° C] when working in direct sun (CAUTION Category), increase vigilance by specifically observing for **possible** signs of early heat illness, which can include fatigue, dizziness, irritability or decreased concentration, especially if the worker has been working for a while. Inquire periodically about how they feel. If symptoms arise, rest the worker in the shade for approximately 30 minutes until cool and give water or sports drink.
- a. NOTE: If the worker develops heat rash, rest the worker, give water or sports drink. If the rash persists or bothers the worker, then STOP THE WORKER EXPOSURE MONITORING.
- 10.6 If the HI falls between 90° - 104° F [32 - 40° C], or between 80° - 94° F [27 - 34° C] when working in direct sun (EXTREME CAUTION Category), increase vigilance even further by observing for **possible** signs of: heat cramps, such as muscle spasms, heavy sweating, thirst; heat exhaustion, such as fatigue, headache, dizziness, fainting, heavy sweating increased pulse; heat stroke, such as headache, dizziness, irrationality, coma, rapid breathing. These conditions are possible if the worker has been working for a while. Inquire periodically about how they feel.

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- a. With signs of heat cramps, give access to plenty of water or a sports drink and assure that they are drinking. Have the worker rest in the shade until cool. STOP THE WORKER EXPOSURE MONITORING. Advise the worker to be aware of symptoms of heat exhaustion and heat stroke. Remind the worker of the AHETF policy to provide medical coverage and to seek medical help immediately if symptoms develop.
 - b. If the SD believes that a worker may be suffering heat exhaustion or heat stroke, immediately STOP THE WORKER EXPOSURE MONITORING. The SD should also consult with the on-site medical professional. However, if the worker's condition is considered to be serious and to require additional emergency care, a member of the study team will call 911 (or other local emergency number) and allow emergency medical personnel to respond and treat the study participant as appropriate. Take measures to relieve symptoms until professional medical care arrives.
 - i. Heat exhaustion: treatment includes providing rest in shade, giving plenty of drinking water or sports drink, splashing cold water on worker.
 - ii. Heat stroke: treatment includes moving to shaded area, removing outer clothing and shoes; wrapping in wet sheet or towel and fan to cool worker.
- 10.7 If the HI falls between 105° - 129° F [41 - 54° C], or between 95° - 119° F [35 - 48° C] when working in direct sun (DANGER Category), then the SD, study observers, and on-site medical professional should pay particular attention to **likely** signs of heat cramps and heat exhaustion or **possible** signs of heat stroke with prolonged exposure.
- a. If signs of heat cramps occur, treat as recommended in section 10.7, above.
 - b. If the SD believes that a worker may be suffering from heat exhaustion or heat stroke, immediately STOP THE WORKER EXPOSURE MONITORING.. The SD should also consult with the on-site medical professional. However, if the worker's condition is considered to be serious and to require additional emergency care, a member of the study team will call 911 (or other local

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emergency number) and allow emergency medical personnel to respond and treat the study participant as appropriate. Take measures to relieve the symptoms until professional medical care arrives. See sections 10.8 a. & b. above.

- 10.8 If the HI reaches 130° F [54° C], or 120° F [49° C] when working in direct sun, STOP THE WORKER EXPOSURE MONITORING, as heatstroke is **highly likely** with continuous exposure. This stop point represents the beginning of the EXTREME DANGER category in which there is a high likelihood of heat stroke. However, the risk of possible and likely illnesses associated with the CAUTION, EXTREME CAUTION, and DANGER categories (see table in Section 8.2) will be minimized because of the previously described procedures in place. That is, workers will be constantly observed by investigators and a medical professional for possible signs of illness and steps will be immediately taken to relieve symptoms if they occur. Furthermore, there are specific stop rules in place for these illnesses regardless of the heat index value or category. (REF. 13.4)

11.0 EXPENSES

- 11.1 Expenses associated with the reasonable and appropriate treatment for heat-related illness as a result of participating in this study will be paid for by AHETF unless such expenses are covered by the worker's own insurance or insurance provided by the employer.

12.0 INCIDENT REPORTING

- 12.1 Any incident of heat-related illness will be reported by the Study Director or member of the research team to the Sponsor (AHETF) and the Institutional Review Board. See SOP AHETF 11.F for additional details on reporting such events to the IRB.

13.0 REFERENCES

- 13.1 The Heat Index Chart used as a reference in this SOP is taken from the Washington State Department of Labor and Industries "Application of Standards to Address Heat Related Illnesses in the Outdoor Environment" dated July 13, 2006. It is from the National Weather Service HI Chart, but provides a wider range of ambient temperature and humidity combinations, allowing for greater ease of use in the field.
- 13.2 The National Weather Service suggests a heat index adjustment of an additional 10-15°F [6 - 8° C] for sunny conditions. The AHETF rationale for the adjustment of the heat index for sunny conditions is contained in Attachment 11-G-3.
- 13.3 A Guide to Heat Stress in Agriculture. May, 1993. Document EPA-750-b-92-001 prepared by the United States Environmental Protection Agency and the Occupational Safety and Health Administration. *A Basic Program to Control Heat Stress – Step 4*, recommends hourly measurements of temperature and humidity.
- 13.4 National Weather Service – Apparent Temperature Categories indicates that heat stroke is highly likely at 130° F [54° C] (or 120° F [49° C] adjusted for sunny conditions). This temperature is also used by the University of Florida in its *Heat Stress Policy* as a criterion for discontinuing work.
- 13.5 Controlling Heat Stress Made Simple. September, 1995. GPO Document Number 055-000-00474-9 prepared by the United States Environmental Protection Agency and the Occupational Safety and Health Administration.

ATTACHMENT 11-G-1: HEAT ILLNESS SYMPTOMS AND TREATMENT CHART

Illness	Signs and Symptoms	Treatment
Early Heat Illness	Mild dizziness, fatigue, or irritability; Decreased concentration; Impaired judgment	Loosen or remove clothing, Rest the worker in the shade until cool, and give water to drink
Heat Rash	Tiny, blister-like red spots on skin; prickly sensations (generally caused by plugged sweat glands)	Rest the worker in the shade until cool, give water to drink; if the rash persists and bothers the worker, stop the monitoring.
Heat Cramps	Painful spasms of leg, arm, or abdominal muscles; Heavy sweating and thirst	Loosen clothing, give water or sport beverages, and rest the worker in the shade until cool. Stop monitoring the worker.
Heat Exhaustion	Fatigue, headache, dizziness, muscle weakness, loss of coordination, fainting, collapse. Profuse sweating; pale, moist cool skin; excessive thirst; dry mouth; dark yellow urine. Fast pulse, if conscious. May also have heat cramps, nausea, urge to defecate, rapid breathing, chills, tingling of the hands or feet, confusion, giddiness, slurred speech, irritability.	Remove to cooler, shaded area ASAP and stop monitoring . Rest worker lying down. Give water, as much as the worker will drink. Loosen or remove clothing. Splash cold water on body. Massage legs and arms to increase circulation. If worker has collapsed, get evaluation by physician or nurse specified in the study protocol and Consent Form.
Heat Stroke	Often occurs suddenly and is a life- threatening medical emergency. Headache, dizziness, confusion, irrational behavior, coma. Sweating may slow down or stop. Fast pulse, if conscious. Rapid breathing. May also have convulsions, nausea, incoherent speech, very aggressive behavior.	Immediately call emergency medical services. Move to cooler, shaded area immediately and stop monitoring . Remove outer clothing/shoes. Wrap in wet sheet or towel and fan to cool worker. Get immediate evaluation from physician or nurse specified in the study protocol and Consent Form.

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Attachment 11-G-2: Heat Index Chart

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WRD 11.20

NOAA's National Weather Service Heat Index

Heat Index	General Effect of Heat Index on People in Higher Risk Groups
80 to 89° - Caution	Fatigue possible with prolonged exposure and/or physical activity
90 to 104° - Extreme Caution	Sunstroke, heat cramps and heat exhaustion possible with prolonged exposure and/or physical activity
105 - 129° - Danger	Sunstroke, heat cramps or heat exhaustion likely, and heatstroke possible with prolonged exposure and/or physical activity
130° or higher - Extreme Danger	Heat/Sunstroke highly likely with continued exposure



Attachment 11-G-3: AHETF Rationale for the Heat Index Adjustment for Sunny Conditions

The Heat Index Chart developed by the National Weather Service (NWS) was primarily intended for public use (Ref: "Heat Stress Guidance" from the NWS). Portions of the public include susceptible groups such as children, elderly and infirmed. Underlying assumptions in the development of the heat index values included wearing long trousers and short sleeves, light wind, and shady conditions. To account for full sun conditions, the NWS recommends a heat index adjustment of an additional 10-15° F (6-8° C). That is, if people are in full sun an additional 10-15° F is added to the current Heat Index (HI) value which is calculated based on the current temperature and humidity.

In this SOP, heat index values were adjusted by 10° F (6° C) for full sun conditions. This adjustment is reasonable under the conditions of AHETF worker monitoring studies for the following reasons:

- Workers who participate in these studies perform this work as part of their normal job, including having familiarity with working in hot environments
- Workers who participate in these studies are adults in good health
- Workers who participate in these studies are acclimatized
- No impervious clothing will be worn.
- Mixing/loading and/or applying activities are generally moderate workloads (Reference EPA "A Guide to Heat Stress in Agriculture", *Table 5- Approximate Workload Levels*)
- Heat indices are monitored hourly with appropriate control measures in place
- Study investigators constantly observe workers for signs of heat-related illness and take control measures accordingly
- A medical professional is on-site during the monitoring period to observe for signs of heat-related illness and provide treatment if necessary, including calling for medical emergency assistance

SOP AHETF-11.G.0.

AHETF study participants wear an inner dosimeter under their work clothing, thus increasing their risk of heat-related illness. However, it is believed that this increased risk is offset by the conditions listed above and the implementation of a heat stress management plan as described in this SOP. Furthermore, conditions of worker scenarios being monitored by AHETF should be put in perspective with other occupations involving hot working environments. For example, road construction activities often involve heavy workload levels, radiant heat from hot pavement, etc. It may be reasonable under those conditions to increase the solar load adjustment by more than 10° F. However, for agricultural mixing/loading and application activities included in the AHETF monitoring program, a 10° F adjustment is considered to be adequately protective.

Emergency Procedures for Human Subjects
Chapter 11: HUMAN SUBJECT MANAGEMENT
 AHETF-11.H.0.

Effective Date : June 30, 2007

APPROVAL _____	DATE _____
APPROVAL _____	DATE _____
Last Revision Date: N/A	Previous Version Number: N/A

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1.0 PURPOSE AND SCOPE

- 1.1 This SOP describes the procedure(s) to be followed in the event that a study participant requires emergency medical attention during his/her participation in an Agricultural Handlers Exposure Task Force (AHETF) worker exposure monitoring study.
- 1.2 The user of this SOP should be familiar with the SOP AHETF-11.G, *"Identification and Control of Heat Stress"*.
- 1.3 The Study Director will identify any employer plans to handle on-site emergencies. As an adjunct to existing plans, the Study Director will discuss the AHETF procedures with the on-site employer and workers. The Study Director shall gain agreement to utilize the AHETF procedures during the conduct of the study.

2.0 PROCEDURES

- 2.1 Prior to initiation of exposure monitoring, the Study Director will determine the emergency facility nearest to the study site(s) that may be used in event of a medical emergency during the study.
 - a. Specific information about the facility, including the address, telephone number and directions from the field site will be obtained.

SOP AHETF-11.H.0.

- b. Since monitoring of study participants can occur on a variety of nearby agricultural farms, a participant may be taken to another facility if it is closer or more convenient.

The Study Director shall make arrangements to provide a medical professional (emergency medical technician [EMT], paramedic, physician's assistant [PA], licensed practical nurse [LPN], or registered nurse [RN]) on-site during the conduct of an AHETF study while participants are being monitored. The medical professional will be provided the product label, its MSDS, and AHETF SOPs related to pesticide safety and heat stress. The medical professional shall become familiar with these documents and conduct periodic observations of participants during monitoring and will alert the Study Director to possible signs of illness (heat-related or chemical) or injury.

- 2.2 If a study participant is injured or becomes ill (including heat related illnesses) during the study, the medical professional shall provide appropriate medical care. However, if the injury or condition requires emergency care, a member of the study team will call 911 (or other local emergency number) and allow emergency medical personnel to respond and treat the participant as appropriate.
 - a. If cell phone service is needed to make the 911 call but service is not available, a study team member will drive to the nearest phone or until cell phone service is available.
- 2.3 As deemed appropriate by the emergency medical personnel, the participant may be taken by ambulance to the nearest emergency medical facility.
 - a. The Sponsor will not have a physician on-call at any medical facility, but will rely on local emergency services as described above.
- 2.4 If a participant is taken to a medical emergency facility for examination or care, a member of the research team will accompany the participant to the facility so the Sponsor can stay informed through discussions with the physician or other medical professional that is involved.

3.0 COLLECTION OF DOSIMETRY MATRICES

- 3.1 No exposure samples will be collected from a participant taken to a medical facility.
- 3.2 The participant must withdraw from the study in order to receive medical treatment; he/she will still receive the remuneration (\$80) from AHETF for their participation in the study.

4.0 FOLLOW-UP OF EMERGENCY OR HOSPITALIZATION EVENT

- 4.1 If a participant is taken to a medical facility for treatment related to his/her participation in the study, the Study Director will document whether the participant was treated and released. This includes whether or not the participant refused treatment.

5.0 MEDICAL RECORDS

- 5.1 Medical records will not become part of the research records.

6.0 EXPENSES

- 6.1 Expenses associated with reasonable and appropriate treatment for illness or injury incurred as a result of participating in this study will be paid for by AHETF unless such expenses are covered by the participant's own insurance or insurance provided through his/her employer.

7.0 INCIDENT REPORTING

- 7.1 Any emergency event will be reported by the Study Director to the Sponsor (AHETF), the EPA, and the Institutional Review Board (SOP AHETF-11.F).
- 7.2 If the emergency event is a result of exposure to the pesticide product, additional reporting to EPA may be required in accordance with AHETF's SOP AHETF-1.F Potential Referable Findings.

**Chapter IV. Evaluation of Existing Scenario-Specific Data and
Demonstration of Data Needs**

This section is purposely left blank because the applicable information will be scenario-specific. This submission package only contains information that is applicable to all AHETF scenarios and studies.

Chapter V. Scenario-Specific Sampling Design(s)

This section is purposely left blank because the applicable information will be scenario-specific. This submission package only contains information that is applicable to all AHETF scenarios and studies.

Chapter VI. Study-Specific Documents

This section is purposely left blank because the applicable information will be study-specific. This submission package only contains information that is applicable to all AHETF scenarios and studies.

Chapter VII. Recruitment and Informed Consent Process

This section is purposely left blank because the applicable information will be study-specific. This submission package only contains information that is applicable to all AHETF scenarios and studies.

Chapter VIII. Ethical Oversight (IRB Review, Approval, etc.)

This section is purposely left blank because the applicable information will be study-specific. This submission package only contains information that is applicable to all AHETF scenarios and studies.

Chapter IX. Reference Materials

REPORT TITLE

Comparative Evaluation of Absorbed Dose Estimates Derived From Passive Dosimetry Measurements With Those Derived From Biological Monitoring:

Validation of Exposure Monitoring Methodologies

REPORT DATE

December 8, 2006

SUBMITTED BY

Agricultural Handlers Exposure Task Force
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I. INTRODUCTION

A. Historical Perspective on Passive Dosimetry Methods used to Estimate Farm Worker Exposure and Risk to Pesticides

Passive Dosimetry (PD) methods for measuring and estimating exposure to agricultural workers (i.e. persons handling agricultural chemicals and working in treated crops) have been in use since the 1950s and have evolved through refinement of the techniques (Batchelor and Walker, 1954; Durham and Wolfe, 1962; World Health Organization, 1982; Fenske, 1989). These methods have subsequently been applied to consumers in residential settings. Overall, a large number of studies was conducted in the 1950s through 1970s to characterize exposure. PD, as originally practiced, involved placement of gauze patches on the outside of work clothing in 1 to 6 body regions to characterize the areas of primary exposure. PD also included ambient air monitoring. Over time the method evolved to placement of patches on and under clothing to estimate the amount of pesticide reaching the skin. Thus, the number of locations was increased to 10 to represent all regions of the body (US EPA, 1986). In the 1980s the ‘whole body’ PD method was developed and became the standard method of measuring dermal exposure in agricultural workers exposed to pesticides (World Health Organization, 1982). As a result of considerable research and the long term acceptance of PD as a method for estimating agricultural worker exposure, these monitoring methods have been codified in international and national regulatory guidelines (OECD, 1997; US EPA, 1997).

Dermal PD methods are used in conjunction with inhalation dosimetry methods. These exposure or absorbed dose estimates can then be quantitatively compared to ‘no effect’ exposure levels for hazards identified in toxicology studies. This basic paradigm (hazard identification, dose-response-assessment, exposure assessment, and risk characterization) was summarized by the National Academy of Sciences and has become the standard for risk assessment for regulatory agencies (NAS, 1983; NAS, 2006).

As risk assessment methodology evolved, the concept of a tiered approach to the process applied to agricultural workers was developed (Carmichael, 1995; OECD, 1997). At its simplest, the tiered approach involves using default upper-bound assumptions and generic exposure data (e.g. from the Pesticide Handlers Exposure Database, PHED) for the first and most conservative Tier 1. If further refinement is necessary, Tier 2 utilizes more accurate data for dermal absorption and exposure mitigation factors, e.g. for the use of personal protective equipment, alongside the same generic exposure data. The most refined and therefore most accurate Tier 3 involves obtaining chemical-specific exposure data on the pesticide under consideration from either PD or biological monitoring (biomonitoring) field studies. The tiered approach has been used routinely since the 1990s in North America and elsewhere.

B. Validation of Passive Dosimetry Methods

Validation in the context of human exposure monitoring methods means that a method has been shown to accurately measure a delivered dose in humans. Validation of PD methods by isolating the various components or routes of exposure (e.g., hand wash alone) is very difficult. Such an approach has been successfully adapted to validate inhalation exposure monitoring for gases and vapors in humans (Nomiya and Nomiya, 1974). However, the respiratory system is reasonably localized, while the skin covers the entire body. Isolating and validating the recovery from hands or the face/neck, for instance, are much more challenging. Part of the challenge would be preventing contact of the treated hand or face/neck with any other surface for up to 8 hours to mimic a normal work day to allow for absorption loss but not redistribution to untreated surfaces. Further, in order to ensure the ability to monitor and quantitatively recover all of the applied test substance, the active ingredient would need to be radio-labeled.

Even with radiolabel, it may not be possible to account for bound skin residues that are not bio-available and might take several days to be removed through normal physiologic processes such as loss through sloughing dead skin cells (Thongsinthusak et al., 1999). In conducting human dermal absorption studies, this problem has been resolved by two methods. One is skin stripping (applying adhesive tape to an area and forcefully removing the tape up to 20 times). This method certainly wouldn't be favorably received by humans particularly on the face. The alternative method adapted from dermal absorption methodology is to administer the test compound intravenously and determine the fraction of labeled material excreted in urine. This is an indirect way of determining the relative fraction of dose on skin that would be excreted in urine (Feldmann and Maibach, 1974).

The most practical alternative to isolating parts of the epidermis for validating recovery methods is to utilize field exposure studies in which concurrent or consecutive measurements have been made with PD and biomonitoring in the same cohorts of workers. This method has the advantage of not using radio-labeled material, but rather whatever formulations are in common commercial use. Further, rather than intentionally applying a chemical to human subjects, the exposures described in the following sections have occurred during normal activities associated with pesticide use. In essence, the standard PD method for estimating dermal exposure is modified such that the dosimeters closely represent the normal work clothing and thereby permit the concurrent conduct of the biomonitoring phase. This ensures that a direct comparison can be made between the estimated exposure and the absorbed dose arising from this exposure. These variants of the PD-biomonitoring methods have been described previously by Chester (1993, 1995) and Honeycutt et al. (2000). In this current paper, the results of the two methods will be compared within each study as a means of validating all of the techniques typically used in a PD monitoring study. The approach also offers opportunities to examine the effect of dosimetry matrix pass-through, porosity or bypass, hand wash efficiency and other questions about the validity of the PD methods.

Biomonitoring, as a means of exposure measurement, is rarely required by government regulatory authorities. Historically, biomonitoring was developed in the fields of occupational medicine and industrial hygiene as an alternative to commonly used PD methods. It offers the best means of accurately assessing human exposure to specific chemicals because it determines actual, rather than potential, absorbed dose (Woollen, 1993). In the context of exposure to pesticides, Woollen defined biomonitoring as “Measurement of a pesticide or its metabolites in the body fluids of exposed persons, and conversion to an equivalent absorbed dose of the pesticide based on the knowledge of its human metabolism and pharmacokinetics”. Biomonitoring is recognized as the “gold standard” (Sexton et al., 2004) against which other estimates of exposure can be compared; hence biomonitoring’s value in this description of validating PD methods.

Biomonitoring has been used extensively in industrial settings as a measure of exposure and an adjunct with air sampling in hygiene monitoring and surveillance programs to prevent over-exposure and ensure compliance with limit values such as the ‘Threshold Limit Values’ (TLV) set by the American Conference of Governmental Industrial Hygienists (ACGIH). This organization also sets ‘Biological Exposure Indices’ based primarily on urinary biomarkers (<http://www.acgih.org/Products/beintro.htm>). During the evolution of PD, biomonitoring was sometimes used as a “backup” or insurance method while conducting PD monitoring. In other instances biomonitoring was used as the primary means of measuring the absorbed dose by integrating all contributions from multi-route exposure, i.e., a means for method validation. If it did not produce a perceived or actual improvement in understanding measured exposure, governmental regulators would not request confirmatory biomonitoring studies as they have done, and industry would not perform them because of the great expense and additional time required to develop the supporting pharmacokinetic studies necessary to interpret a biomonitoring study.

An important issue in estimating human exposure is to demonstrate that the principal methodology used to generate the exposure data is valid. “Valid” in this context means that the exposure methodology is sound, defensible and capable of a sufficiently accurate estimate of true occupational or residential exposure for eventual use in human health risk assessment. This validation determines if the combined standardized PD methods in their entirety, when used collectively, give a reasonable estimate of the absorbed dose. In this context validation is not intended for each specific method in isolation, such as patches, whole body dosimeters, hand washes, face/neck wipes, etc., from the other methods used to determine the dermal and inhalation exposure. One means of validating PD is to compare the absorbed dose estimated by this exposure monitoring methodology with that estimated using biological monitoring.

There are several studies available (some published, and some proprietary) that have employed both these approaches. For the express purpose of validation of PD using biomonitoring, it would be ideal if concurrent measurement data could be compared. This is because the uncertainty associated with the assumption that the measured exposure is representative of that from which the biomonitoring absorbed dose is derived is minimized. For example, if PD and biomonitoring were to be measured consecutively in the same workers because of the use of fully interceptive whole body dosimetry, there would be some

degree of uncertainty as to whether the actual exposures of the workers were directly comparable on the two occasions when PD and biomonitoring were conducted. That is to say that more uncertainty exists because it cannot be excluded that the exposures differ for some reason, such as change in behavior, local conditions or variation in application equipment and associated variables such as amount of product used and application rate. If the exposures differ significantly, then the comparison of absorbed dose via the PD and biomonitoring routes is that much more uncertain, because of the potentially different starting points, i.e. dermal and inhalation exposure on the two occasions.

A frequently used approach, which has been adopted in the evaluation of most of the studies, is to simply calculate the estimated total absorbed dose by multiplying the PD dermal and inhalation exposure data by appropriate route-specific absorption factors and then summing the resulting dermal and inhalation doses to obtain a total absorbed dose estimate. This PD-based total absorbed dose estimate can then be compared to the estimate of total absorbed dose given by the biomonitoring data. This approach ignores any ‘bypass’ of the dermal PD method and assumes that all active ingredient is captured and retained by the dermal dosimeters, including the hand wash and face/neck wipe.

Studies involving concurrent measurement with PD and biomonitoring would most likely have employed partial dosimetry, i.e. clothing, to ensure that the biomonitoring is not compromised by use of unrepresentative clothing that workers would not ordinarily wear for the work activities under study. This variant of the whole body method is described in the OECD guidance document for the conduct of studies of occupational exposure to pesticides (OECD, 1997). Typically, outer dosimeters would consist of cotton or cotton/polyester long-sleeved shirt and trousers (normal work clothing) and inner dosimeters of T-shirt and briefs (normal underwear). Face wipes and hand washes would be used to estimate the dermal exposure of the face/neck area and hands, respectively. Inhalation exposure would be measured using a relevant personal air sampling technique in the breathing zone. Several studies of this type are available.

The validation process involves estimating the total absorbed dose arising from all routes of exposure. Using the PD approach, estimated actual dermal exposure (aggregation of estimated penetration of outer dosimeters to underlying skin, handwashes and face/neck wipes) is adjusted for an appropriate dermal absorption factor, preferably from a human study if available, to give the absorbed dose from the dermal route. The inhaled dose is estimated from the calculated airborne concentration and appropriate ventilation rate for the work activity. The total of the two dose routes gives the combined total absorbed dose estimated from the partial dosimetry which could be compared with the total absorbed dose determined through biomonitoring:

$$\text{ADD} = (\text{ODE} \times \text{CPF} \times \text{DA}) + (\text{IDE} \times \text{DA}) + (\text{ADE} \times \text{DA}) \quad [1]$$

$$\text{AID} = (\text{IE} \times \text{IA}) \quad [2]$$

$$\text{TAD} = (\text{ADD} + \text{AID}) \quad [3]$$

Where:

ADD is Absorbed Dermal Dose;

ODE is Outer Dermal Exposure (from outer dosimeter);

CPF is Clothing (or outer dosimeter) Penetration Factor*;

DA is Dermal Absorption factor;

IDE is Inner Dosimeter Exposure

ADE is Actual Dermal Exposure (from hand wash and face/neck wipe);

AID is the absorbed inhalation dose;

IE is Inhalation Exposure;

IA is Inhalation Absorption factor (default 100%);

TAD is Total Absorbed Dose.

* Derived from actual study data on penetration of outer dosimeter to inner dosimeter or based upon penetration data derived from other studies where outer and inner dosimeters have been measured for the same body area.

The purpose of this document is to summarize representative modern exposure monitoring studies for pesticide handlers and reentry exposure and to compare the estimates of dose given by PD and biomonitoring. This document summarizes some recent biomonitoring studies that have been conducted concurrently with PD or consecutively using the same subjects for both methods. The estimated absorbed doses using PD are then compared with those given by biomonitoring to determine if there is agreement and to test the hypothesis that PD does not underestimate the absorbed dose. Relevant statistical techniques are used to facilitate the comparisons.

II. BIOMONITORING AND PASSIVE DOSIMETRY VARIABLES

Pesticide biomonitoring studies typically involve collecting urine from individuals (Woollen, 1993). The urine is analyzed for a compound that is either the parent or a known human metabolite. The kinetics of excretion, preferably in humans, must be known. If this is impracticable, animal kinetics data may be considered; although the greater uncertainty associated with inter-species extrapolation must be recognized (OECD, 1997). Studies in closely related primate data may also carry least uncertainty in extrapolation. The essential information from the study is the fraction of administered dose excreted in the urine as metabolite(s) and/or parent compound. The basic method for calculating an absorbed dose from biomonitoring data is shown in equation [4].

$$AD (\mu\text{g}) = (\sum \mu\text{g metabolite}) \times (\text{MW Parent} / \text{MW metabolite}) / \text{Fraction excreted} \quad [4]$$

Where, AD = Absorbed Dose and MW = molecular weight.

For PD, the absorbed dose is estimated as shown generically in equation [5].

$$AD = (\text{dermal exposure} \times \text{abs. fraction}) + (\text{inhalation exposure} \times \text{abs. fraction}) \quad [5]$$

Selection criteria for an ideal concurrent biomonitoring study for comparison with PD include the following:

- a. Known human or closely related primate dermal absorption value (typically >1% of applied dose unless detection limits are very low), measured in the range of typical exposure;
- b. Known human or closely related primate excretion pharmacokinetics and a metabolite standard;
- c. Urinary excretion half-life less than 24 hours; (not essential but desirable to reduce the number of 24 hour urine collections);
- d. Excretion levels greater than background for the first 24–48 hours;
- e. Adequate number of individuals monitored;
- f. Sequential 24-hour urinary collections;
- g. The urinary metabolite must be a “major” metabolite (ideally ~30% or more of dose); metabolites representing smaller fractions of the parent molecule are acceptable if the fraction excreted is consistent, with minimal variation;
- h. The urine metabolite should be unique to the active ingredient being monitored;
- i. Knowledge of whether exposure was isolated (i.e., no prior exposure and no additional exposure during the collection interval) or “steady state”;
- j. No additional layer(s) of clothing that would not normally be worn under the prevailing conditions and would therefore be unrepresentative. The key difference between standalone PD studies and concurrent PD : biomonitoring studies is the modified inner dosimeter, usually consisting of a t-shirt/brief arrangement rather than a full inner dosimeter, e.g. ‘long johns’ that would interfere with the process of dermal contact and absorption. The important point is that all the dosimeter clothing should be completely representative of the normal clothing worn by the workers. An example would be use of normal outer clothing as dosimetry garments without any inner dosimeter.

Over time, a large number of concurrent or consecutive PD-biomonitoring studies have been conducted. Those that did not conform to the criteria outlined above were eliminated from quantitative comparison in the discussion that follows. For example, 34 studies were considered, but 14 studies were accepted for further quantitative comparison. While the selection criteria eliminated more studies than were accepted for quantitation, the concurrent or consecutive PD-biomonitoring studies summarized in this document represent a wide variety of common exposure scenarios. When the biomonitoring data from these studies are compared with the PD data for the same scenarios, conclusions may be drawn about the representativeness of the central tendency values from PD that have historically formed the basis for regulatory decision making.

For each study summarized, the data for dermal and respiratory exposure monitoring and total absorbed dosage as well as the absorbed dosage estimated from concurrent biomonitoring were recorded in spreadsheets for each subject. In this way statistical comparisons could be conducted on results from individuals and the central tendency in any given study.

III. DERMAL ABSORPTION AND PHARMACOKINETICS: KEY EXPOSURE VARIABLES

Dermal absorption is a key component of any risk assessment involving a pesticide when the magnitude and temporal profile of a systemically absorbed dose is of concern. With most pesticides, exposure occurs primarily via the dermal route with a minor inhalation component (Wolfe, 1976). An accurate measurement of dermal absorption is necessary to estimate dermal absorbed dosage from PD studies for comparison with data from biomonitoring studies. Variables that can affect absorption include exposure time, dose, site of application, formulation, and absorption time. The dermal absorption test species is also a crucial factor. Rat skin, in common with many animal species' skin, is not an ideal model for human dermal absorption. It has been shown to overestimate human dermal absorption by an average of approximately 5-fold (Ross *et al.*, 2001). For the purpose of comparing PD and biomonitoring absorbed doses in this analysis, there was a preference for using human dermal absorption data, if available. Table 1 shows the human *in vivo* dermal absorption of several pesticides for which there were concurrent or consecutive PD and biomonitoring data.

Because dermal absorption is so important for estimating the absorbed dermal dose from dermal PD data, it is worthwhile to discuss the uncertainties involved in measuring or estimating dermal absorption in humans. First, it is critical to recognize that all of the values listed in Table 1 were derived from human studies, so the uncertainty of animal surrogates is not a concern. Second, all of the *in vivo* human values were published in the peer-reviewed literature, which lends some credibility to the values reported. Third, when more than one level was tested in humans, the highest dermal absorption value (typically associated with the lowest application rate on human skin) was reported which was most similar to the dose density observed in the PD studies.

In most cases, human dermal absorption studies were conducted with male volunteers, and the vast majority of biomonitoring studies reported in this document were also conducted with male volunteers. Likewise, most human dermal absorption studies were conducted with a wash off of the applied dose after 8-10 hours, which is consistent with the upper bound of times individuals were exposed on the job during the biomonitoring studies and reducing (or conservatively overestimating) absorption due to differences in residence time of pesticide on the skin. Because the fraction of applied pesticide that is dermally absorbed is generally inversely related to application (dose) rate, it is important to test absorption at loading doses similar to those incurred by workers during pesticide use (Thongsinthusak *et al.*, 1999).

Collection of urine must continue long enough to collect at least 3 urinary excretion half-lives (88%) to justify not correcting for incomplete excretion. For virtually every biomonitoring study discussed here, this guideline was followed. In some cases, the biomarker was excreted via other routes in addition to urine and some correction must be made for this differential e.g., Chlorpyrifos where only 70% is excreted in urine. Finally, the biomarker may represent only a fraction of the parent and some correction must be made for that factor. Listed in Table 1 in the right hand columns are the biomarker (metabolite) name, excretion half-life, and a combined factor that reflects both fraction excreted in urine and fraction of total dose

excreted as the biomarker. Data for three of the compounds in Table 1 regarding pharmacokinetics and metabolism were taken from summaries in the exposure monitoring studies, and these numbers were not verified from the original proprietary studies. In the narrative description of each study, there is an indication of duration of urine collection and any departure or other correction from these practices.

Table 1: *In Vivo* Dermal Absorption of Selected Pesticides in Humans

Pesticide	Human Absorption (%)	Dermal Absorption Assumed in Study (%)	Metabolite	Excretion Half-Life (hr)	Excretion Fraction (%) ^m
Atrazine	5.6 ^a	5.6	chlorotriazines	12 ⁱ	12
Chlorpyrifos	3.0 ^b	1.0-9.6	TCP	27 ⁱ	60-72
Cypermethrin (as surrogate for Cyfluthrin)	1.2 ^c	1.2	4-FPBA	16 ^j	100
Diazinon	3.6 ^d	3.6	G 27550	~10	7.9
Diquat	0.3 ^e	0.3	parent	4 ^k	61
Fluazifop-butyl	8.0 ^f	8.0	Fluazifop	9-37 ⁱ	90
Paraquat	0.3 ^g	0.3	parent	NA ^l	59
2,4-D	5.7 ^h	5.7	parent	13	100

^a Wester and Maibach 1993

^b Nolan *et al.*, 1984; highest value measured

^c Woollen *et al.*, 1992

^d Wester *et al.*, 1993b

^e Feldman and Maibach, 1974

^f Ramsey *et al.*, 1992

^g Wester *et al.*, 1984

^h Ross *et al.*, 2005

ⁱ Following oral dosing

^j Following dermal dosing

^k Following intravenous dosing

^l NA = Not Available

^m Excretion fraction in urine at an interval of 3+ half-lives

IV. CLOTHING PENETRATION: ANOTHER KEY VARIABLE

As dose density to outer dosimeters increases, percent clothing penetration decreases resulting in an inverse relationship between challenge and penetration (Ross *et al.*, 1997). This is consistent with the hypothesis that single-layer clothing percent penetration increases with decreasing outer dosimeter loading or challenge, i.e., a higher proportion of the outer dosimeter values appears on the corresponding inner dosimeters, as the outer values decrease. This is consistent with observations made in mammalian dermal absorption studies where the

fraction of applied dose penetrating the skin appears to increase at decreasing external dose. This phenomenon is associated with the use of the percent term; in pure quantitative terms, there tends to be more penetration with increasing external loading, although not in direct proportion. The same loading/absorption phenomenon applies to skin, so both dermal loading and dosimeter loading influence variability observed between individuals monitored.

Mean clothing penetration was calculated from 2129 paired inner and outer dosimeters and found to be 8 to 12 percent for whole body dosimeters (WBD) and patch dosimetry, respectively from the Pesticide Handlers Exposure Database (Ross et al., 2006a). Thongsinthusak et al., (1993) summarize results from a number of other exposure monitoring studies that support this observation. An average clothing penetration value of 10% was used in two exposure monitoring studies where clothing penetration could not be estimated from study data. This value was considered conservative, because in most studies whole body dosimetry or some variant was used, and in most cases there was substantial concentration on the outer dosimeter. Further supporting the conservatism of this default is the fact that the measured clothing penetration as recorded in Table 2 was consistently less than 10%.

V. BIOMONITORING AND PASSIVE DOSIMETRY STUDY SUMMARIES

Narrative summaries of study design are provided for those studies for which there were quantifiable PD and biomonitoring results for a majority of study participants. The preponderance of quantitative data was derived from 9 studies that are protected by data compensation requirements under FIFRA and are labeled “proprietary”. Another group of 6 studies was published in the peer reviewed literature. Additional study details are provided in Tables 2 and 4.

A. Proprietary Documents on Concurrent Passive Dosimetry and Biomonitoring

Airblast Mixer/Loader (M/L), Applicator, and Cleanup Workers (Honeycutt and Day, 1994)
Fifteen applicators, 15 M/L, and 15 cleanup workers were monitored while handling Chlorpyrifos for airblast application on citrus in California. The M/L open-poured the Lorsban 4E from its container into a pail and/or directly into a nurse tank. Applicators drove open-cab tractors. Cleanup workers washed equipment post-use. Workers made applications from 0.4-9.8 hours per day (Table 2). All workers wore a minimum of an outer coverall over a short-sleeved shirt, long pants, underwear, socks, and boots. The underwear (T-shirt and briefs) were used as inner dosimeters, while coveralls were used as outer dosimeters. Additionally, workers wore helmets, a respirator, goggles, and chemical-resistant gloves. Inhalation exposure was monitored using a personal air pump with a flow rate of 1-2 L/min through a cassette with a pre-filter followed by Chromosorb 102 sorbent. The workers were assumed to breathe at 1.5 m³/hr. Face and neck exposure were estimated based on two 4”x4” patches placed on the helmet. Urine was collected from each worker one day prior to use and for four days after handling Chlorpyrifos. Urine was analyzed for 3,5,6-TCP. Replicates in each work category were examined for pre-study TCP levels greater than post-exposure TCP levels, and those replicates were excluded from further consideration.

Open-Pour Aerial M/L (Knuteson *et al.*, 1999)

Fifteen workers mixed and loaded Lorsban 4E for aerial application. The study was conducted in Texas and Arizona. Each worker opened, pierced the foil seal of, emptied, and rinsed 25–50 jugs containing 2.5 gallons each. After open-pouring the Lorsban 4E into the mix tank and adding water, each worker transferred the contents to planes via hose. Each worker mixed and loaded sufficient Chlorpyrifos to cover approximately 500 acres. Workers wore a coverall over underwear, goggles, a cap, a chemical-resistant apron, boots, and gloves. The underwear (T-shirt and briefs) were used as inner dosimeters, while coveralls were used as outer dosimeters. Inhalation exposure was monitored using a personal air pump with a flow rate of 1-2 L/min through a cassette with a pre-filter followed by Chromosorb 102 sorbent, and workers were assumed to breathe at 1.5 m³/hour. Urine was collected from each worker one day prior to use and for four days after handling Chlorpyrifos. Urine was analyzed for 3,5,6-TCP. The pre-exposure (background) TCP levels were subtracted from the daily post exposure analyses for TCP. Four of 15 replicates were not used in this study due to confounding caused by pre-exposure or post-exposure urinary metabolite concentrations.

Groundboom M/L, Applicator, Reentry Scout Exposure (Shurdut *et al.*, 1993)

Nine applicators were monitored during groundboom application of Chlorpyrifos to low crops using open-cab tractors in Michigan, Arizona and Florida. Each applicator handled 27–330 lb AI. Nine Mixer/Loaders used either Lorsban 50W or 4E. Ten scouts were monitored in Arizona and Florida 24 hours post-application. Mixer/Loaders and applicators wore coveralls over underwear, socks, baseball cap, goggles and chemical-resistant boots. Mixer/Loaders that handled Lorsban 50W also wore half-face respirators equipped with particulate filters and organic vapor cartridges. Scouts wore T-shirt and briefs, closed toe footwear, baseball cap, and coveralls with sleeves cut off above the elbows. Sweat bands served as forearm dosimeters. Concurrent PD consisted of underwear (T-shirt and briefs) used as inner dosimeters, while coveralls were used as outer dosimeters. Inhalation exposure was monitored using a personal air pump with a flow rate of 1-2 L/min through a cassette with a pre-filter followed by Chromosorb 102 sorbent, and workers were assumed to breathe at 1.5 m³/hr. Urine from applicators was taken one day before and for five days after application. Urine was analyzed for 3,5,6-TCP.

Open-Pour Groundboom Granular M/L/A (Murphy *et al.*, 1998)

Sixteen mixer/loader/applicators were monitored while handling Chlorpyrifos for groundboom application during planting seed corn in Michigan and Kentucky. M/L open-poured the Lorsban 15G from its container into a hopper of a seed planter. Applicators drove open- and closed-cab tractors. Workers handled Chlorpyrifos for at least 3.1 hours per day (Table 3). All workers wore a minimum of an outer coverall over a short-sleeved shirt, long pants, underwear, socks, and boots. The underwear (T-shirt and briefs) were used as inner dosimeters, while coveralls were used as outer dosimeters. Additionally, they wore baseball caps. Inhalation exposure was monitored using a personal air pump at a flow rate of 1 L/min through a cassette with a pre-filter followed by Chromosorb 102 sorbent, and workers were assumed to breathe at 1.5 m³/hr. Urine was collected from each worker one day prior to use and for four days after handling Chlorpyrifos. Urine was analyzed for 3,5,6-TCP.

Citrus Pruners and Harvesters (Honeycutt and Day, 1993)

Fifteen reentry workers, 10 pruners, and 5 harvesters were monitored while reentering Chlorpyrifos-treated citrus following airblast application in California. Workers contacted treated foliage for at least 6.2 hours per day (Table 2). All workers wore a minimum of an outer coverall over underwear, socks, and tennis shoes. Additionally, the harvesters wore short-sleeved shirt, and long pants under the coveralls due to cold weather. The underwear (T-shirt and briefs) were used as inner dosimeters, while coveralls were used as outer dosimeters. Additionally, they wore baseball caps, forearm gauntlets of canvas and cotton or canvas gloves. Inhalation exposure was monitored using a personal air pump with a flow rate of 1 L/min through a cassette with a pre-filter followed by Chromosorb 102 sorbent, and workers were assumed to breathe at 1.5 m³/hr. Urine was collected from each worker one day prior to use and for four days after handling Chlorpyrifos. Urine was analyzed for 3,5,6-TCP, and the higher value of either the kinetic or stoichiometric method was used to calculate exposure. Replicates in each work category were examined for pre-study TCP levels greater than post-exposure TCP levels, and those replicates were excluded from further consideration. Harvesters had no detectable residues on the inner dosimeter, so half the limit of detection was assumed for estimating dermal exposure.

Hose-End Sprayers and Hudson Sprayer (Rosenheck, 2000)

This PD-biomonitoring study involved the consecutive evaluation of PD and biomonitoring. Exposure was determined using the PD approach, followed by a biomonitoring phase in which the same individuals made further applications approximately 5 days later. Individuals within a handler scenario were monitoring first using cotton long johns worn under short sleeve shirt and short pants, and the same individuals within a use scenario were subsequently biomonitored. Three methods of application frequently used by homeowners were monitored:

- Hose-end sprayer with a ready-to-use (RTU) formulation; 11 handlers.
- Hose-end sprayer with an emulsifiable concentrate (EC) formulation; 12 handlers.
- Hudson pump-up type hand sprayer with wand; 10 handlers.

Each person using the hose-end sprayers applied 0.5 lb of active ingredient (AI) of Diazinon in a 946-mL container to approximately 5,000 square feet of turf. Hudson sprayer users mixed, loaded, and applied 0.021 lb AI of Diazinon EC to house perimeters, spot lawn treatments, ornamentals, and shrubs. All volunteers wore a T-shirt, shorts, socks, and shoes. All monitoring was conducted in North Carolina in 1999, and replicate duration was 18–122 minutes, depending on method of application. Urine was collected for one day before and four days after use; it was analyzed for G-27550, a Diazinon-specific metabolite.

Groundboom Applicators and Mixer/Loader/Applicators (Selman, 1996)

Groundboom applicators (n=7), mixer/loader/truck tenders (n=8), and mixer/loader/applicators (M/L/A, n=4) were biomonitored for urinary metabolites following use of Atrazine on corn in the Midwest. The workers in the study handled between 148 to 3450 lb Atrazine over a three day monitoring period during the early part of the pre-corn planting period during which the product is typically applied. The biomonitoring phase consisted of collection of urine samples on at least one day before being monitored and during each day of Atrazine use over the three days of monitoring. Replicate analyses of PD were conducted on the same workers on the first and second days, and the results averaged by

worker. The metabolite excretion data were adjusted for the fraction of dose excreted as chlorotriazines in humans to estimate the Atrazine absorbed dose. Workers wore long-sleeved shirts, long pants, and occasionally a sweatshirt in cold weather. The inner dosimeters consisted of 100% cotton T-shirts and 100% cotton briefs. Hand exposure was measured using a 0.01% Aerosol OT hand wash followed by a distilled water hand rinse. Head and neck exposure was estimated using two patches attached to a baseball cap. Inhalation exposure was measured using a filter and vapor collection tube attached to a personal air-sampling pump.

Groundboom Mixer-loader-applicators (Chester et al, 1989)

Fourteen vehicle groundboom mixer/loader/applicators were monitored concurrently with PD and biological monitoring during use of Fluazifop-P-butyl in the Netherlands. They handled, on average, 7.2 kg (3.8 to 14.6 kg) [15.8 lb (9.5 to 32 lb)] Fluazifop during a typical day's use of the product in field crops. They wore standardized dosimeters consisting of 100% cotton coveralls over cotton T-shirt. Soap and water handwashes were performed whenever the subjects wanted to wash their hands. There was additional wearing of sweatshirt (pullover) and pants by three subjects during colder weather. Inhalation exposure was not measured because this was assumed to be negligible for hydraulic groundboom application of an insignificantly volatile compound. Eight subjects complied with the label requirement for use of the chemical resistant gloves; none of the subjects elected to wear the label-required safety goggles, although one wore a faceshield. Twenty-four hour urine samples were collected from all subjects for a total of 11 days, including the day before the use of the product. Urine aliquots were analyzed for the metabolite FI and creatinine as a check on the completeness of collection.

Backpack mixer-loader-applicators (Findlay, 1998)

Twenty mixer-loader-applicators were monitored concurrently with PD and biological monitoring during use of Diquat with hand-held backpack sprayers in banana plantations in Guatemala. The amounts of Diquat handled ranged from 0.29 to 0.38 kg (0.64 to 0.84 lb) during a typical day's use. Standardized dosimeters were used consisting of 100% cotton long-sleeved shirts and trousers. A soap and water handwash method was used to measure hand exposure whenever the subjects wanted to wash their hands so as not to interfere with biological monitoring phase. Inhalation exposure was measured using Institute of Occupational Medicine (IOM) inhalable fraction samplers attached to personal sampling pumps worn by the subjects. Protective gloves and faceshield were provided for use during mixing and loading the product in accordance with the product label recommendation, with which there was generally good compliance. Twenty-four hour urine samples were collected by each subject over a 7 day period, including the day before the day of use of the product. This period was based on the urinary elimination half-life determined in a human volunteer dosing study. Aliquots were analyzed for unchanged Diquat and creatinine as a check on completeness of urine collection.

Data from the biomonitoring studies summarized above are shown in Tables 2–3. It is important to note that the data from some of the biomonitoring studies (e.g., Knuteson, 1999; Honeycutt and Day, 1994; and Chester et al., 1989) contain results from individuals whose

work practices were apparently less careful than other individuals in these studies (or had verified accidents) resulting in much higher exposures on one or more body regions relative to other members of their cohort. Results from those individuals were included in the geometric mean values shown in Tables 2–3, even though they represent the upper extreme for those scenarios monitored. Additionally, there were studies in which individual handlers appeared to have no exposure (i.e., their post-handling excretion of the analyte was less than prior to exposure) such as Knuteson (1999) and Shurdut *et al.* (1993). These values were excluded as unrealistically low, and were probably due to work exposure shortly before the study. The concurrent PD from those individuals was also excluded, so that there was always the same number of PD and biomonitoring results in a given study. By retaining highly exposed individuals, it tested the limits of the comparison of PD to biomonitoring.

B. Dermal Passive Dosimetry Extrapolation to Whole Body

Two primary methods of dermal PD in conjunction with biomonitoring were utilized in the studies summarized in Tables 3, 5 and 6. All of the dermal exposure estimates in Tables 3 and 5 included hand wash and a face/neck wipe or head patch to estimate face/neck exposure. The most straight-forward sampling method to test exposure to the remaining body was where the same individual or group was tested consecutively. For example, Rosenheck (2000) used WBD under typical residential clothing (short-sleeve shirt and short pants) to measure exposure that would have occurred to bare lower legs and arms, and under a single layer of clothing to assess pesticide that penetrated or was not covered by typical residential clothing, and a few days later biomonitoring the same individuals wearing only residential clothing without WBD. A variant of this method used co-located individuals wearing a single layer of WBD or a bathing suit to measure exposure to the same treated carpet, and both groups were biomonitoring (Krieger *et al.*, 2000). A completely different design used in several studies involved concurrent PD and biomonitoring in the same individuals all of whom wore normal work clothing over T-shirt or T-shirt and briefs (Chester *et al.* 1989; Honeycutt and Day, 1993, 1994; Murphy *et al.*, 1998; Knuteson *et al.*, 1999; Shurdut *et al.*, 1993; and Selman, 1996). Scenario-specific clothing penetration was assessed by taking the ratio of residues measured on the T-shirt to residues on the work shirt minus lower arms. This clothing penetration factor was then applied to body areas covered by a single layer of clothing (e.g., lower arms or legs), and that dermal exposure was added to exposure measured on T-shirt and briefs, face and hand washes to obtain total dermal exposure. No attempt was made to account for clothing penetration (also known as pass through) in estimating dermal exposure from areas covered by a T-shirt and briefs dosimeter. However, clothing penetration was accounted for when only a single layer covered the skin.

Table 2 Proprietary Study Conditions and Passive Dosimetry Description

Study Reference ^a	Company Reference ID #	Scenario	Pesticide	Dosimeter Type: Outer (Inner)	Handwash solvent/ Volume (mL)	Number of Handwashes	Workday monitored (hr)	Inhalation monitoring method	Clothing Penetration (%)	PD Reference Page Numbers
Honeycutt, 1994	91-101HE	Liquid M/L ^b , airblast	Chlorpyrifos	Coverall ^c + (TS ^d + brief), hat patch	0.008% DSS ^e →H ₂ O/ 250 each	2-3	7.6-9.8	Personal pump + sorbent (Chromosorb 102)	0.082	72-73, 299
Honeycutt, 1994	91-101HE	Applicator, Airblast	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% DSS→H ₂ O/ 250 each	2-3	5.9-9.6	Personal pump + sorbent (Chromosorb 102)	0.082	301
Honeycutt, 1994	91-101HE	Cleanup, Airblast	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% DSS→H ₂ O// 250 each	1-2	0.4-1.1	Personal pump + sorbent (Chromosorb 102)	0.082	303
Knuteson, 1994	HEA97038	Liquid M/L, aerial	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.004% Emcol ^f →H ₂ O/ 250 each	1	0.66-1.5	Personal pump + sorbent (Chromosorb 102)	6.2±10.5	16, 21, 33, 37, 38
Shurdut, 1993	HEH2.1-1-182	Liquid or WP ^g M/L	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% Emcol→H ₂ O/ 250 each	1	0.7-1.5	Personal pump + sorbent (Chromosorb 102)	7.0-8.9	22, 113-114
Shurdut, 1993	HEH2.1-1-182	Applicator, Ground-boom	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% Emcol→H ₂ O/ 250 each	??	3.8-5.3	Personal pump + sorbent (Chromosorb 102)	7.0-8.9	113

Table 2 (cont.): Proprietary Study Conditions and Passive Dosimetry Description

Study Reference ^a	Company Reference ID #	Scenario	Pesticide	Dosimeter Type: Outer (Inner)	Handwash solvent/ Volume (mL)	Number of Handwashes	Workday monitored (hr)	Inhalation monitoring method	Clothing Penetration (%)	PD Reference Page Numbers
Shurdut, 1993	HEH2.1-1-182	Scout, Low crops	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% Emcol→H ₂ O/ 250 each	??	3.9-4.1	Personal pump + sorbent (Chromosorb 102)	7.0-8.9	115
Murphy, 1998	HEH 311	Granular M/L/A ^h	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% DSS→H ₂ O/ 250 each	??	3.1-5.9	Personal pump + sorbent (Chromosorb 102)	3.5±1.9	11, 13-14, 24- 26,31
Honeycutt, 1993	91-102HE	Citrus pruner, harvester	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% DSS→H ₂ O/ 250 each	2	6.2-7.6	Personal pump + sorbent (Chromosorb 102)	4.0, harvester 5.0, dry 12.3 damp pruners	40, 41, 62,63, 118-120,125, 128,130, 131, 265, 266
Rosenheck, 2000	1063-00	Hose end, RTU and hand pump	Diazinon	(Long johns), face/neck wipes	0.01% DSS/ 250 x 2	1	0.3-2.0	Personal pump + sorbent (XAD-2)	Not measured	9-15
Chester, 1989	TMF 3487	Tractor groundboom Field crops MLA Netherlands	Fluazifop	100% cotton coverall over cotton T-shirt, cotton-polyester socks	Proprietary 'Simple' soap/ 1L wash, 200mL aliquots taken	Variable (1-5), depending on when the workers wanted to wash their hands	3-8	Not monitored	5-12, 41	Chester et al (1989)

Table 2 (cont.): Proprietary Study Conditions and Passive Dosimetry Description

Study Reference ^a	Company Reference ID #	Scenario	Pesticide	Dosimeter Type: Outer (Inner)	Handwash solvent/ Volume (mL)	Number of Handwashes	Workday monitored (hr)	Inhalation monitoring method	Clothing Penetration (%)	PD Reference Page Numbers
Findlay, 1998	RR-97-004B	Backpack hydraulic nozzles Guatemala	Diquat	100% cotton long-sleeved shirt and long pants	Proprietary 'Simple' soap/ 1L wash	2, the first at break, the second at the end of work	Variable 4.6-5.4 h	Personal air sampling with IOM samplers	10-13	Findlay (1998)
Selman, 1996 (Amendment 1)	ABR-95133	Tractor-mounted application to corn, USA	Atrazine	cotton/ polyester sweatshirt (Cold weather) over cotton/ polyester long-sleeved shirt and cotton pants (100% cotton T-shirt and brief); head patches.	0.01% 'Aerosol OT' ⁱ 200→200 distilled water 400 ml total volume.	2-3 samples/ subject	Variable, typical work days	Personal pump, cellulose ester filter and Chromosorb 102 sorbent	10%	Selman & Rosenheck (1996) Selman (1996) (Amendment 1)

^a Reference citations use only the first author's last name to conserve space

^b M/L = mixer/loader

^c Workers wore short-sleeve shirt and long pants that were not analyzed for Chlorpyrifos under the coveralls and over the T-shirt and briefs

^d TS = T-Shirt

^e DSS = dioctyl sodium succinate (anionic surfactant)

^f Emcol = Proprietary surfactant

^g WP = wettable powder

^h M/L/A = mixer/loader/applicator

ⁱ Aerosol OT = dioctyl sodium succinate

Table 3: Proprietary Study Results for Estimated Absorbed Dosage from Passive Dosimetry and Biomonitoring

Study Reference	Scenario	Pesticide	Number ^a of Replicates	Dermal Dosage (µg/kg) ^b	Inhalation Dosage (µg/kg) ^c	Estimated Absorbed Dosage (µg/kg) ^d	Biomon. Dosage (µg/kg) ^e	Ratio ^f PD:BM	Reference Page Numbers ^g
Honeycutt, 1994	M/L	Chlorpyrifos	12/15	2.0	0.13	2.2	5.4	0.41	125, 287, 299, 318, 326
Honeycutt, 1994	Applicator	Chlorpyrifos	11/14	2.9	0.33	3.5	6.7	0.52	288, 301, 320, 327
Honeycutt, 1994	Cleanup	Chlorpyrifos	10/15	0.37	0.010	0.38	0.55	0.69	289, 303, 322, 328
Knuteson, 1994	M/L	Chlorpyrifos	11/15	0.34	0.23	0.68	0.71	1.0	70-72
Shurdut, 1993	M/L	Chlorpyrifos	9/9	3.9	0.34	4.9	7.5	0.65	117, 120, 122
Shurdut, 1993	Applicator	Chlorpyrifos	8/9	0.61	0.84	1.5	1.9	0.78	116, 119, 123
Shurdut, 1993	Scout	Chlorpyrifos	8/10	0.48	0.17	0.67	1.3	0.53	118, 121, 124
Murphy, 1998	M/L/A	Chlorpyrifos	12/16	0.027	0.10	0.14	0.30	0.47	45, 50, 51
Honeycutt, 1993	Citrus harvester	Chlorpyrifos	5/5	0.053	0.18	0.17	0.36	0.48	267, 286
Honeycutt, 1993	Citrus pruner, dry	Chlorpyrifos	5/5	0.29	0.50	0.79	6.3	0.13	268, 287
Honeycutt, 1993	Citrus pruner, wet	Chlorpyrifos	5/5	1.3	0.80	2.1	2.8	0.74	267, 286
Rosenheck, 2000	Hose end sprayer	Diazinon	12/12	1.0	0.070	1.2	1.0	1.2	46
Rosenheck, 2000	RTU hose end	Diazinon	11/11	0.32	0.26	0.63	0.84	0.76	47
Rosenheck, 2000	Hand pump	Diazinon	10/10	0.11	0.039	0.17	0.40	0.42	48

Table 3 (cont.): Proprietary Study Results for Estimated Absorbed Dosage from Passive Dosimetry and Biomonitoring

Study Reference	Scenario	Pesticide	Number ^a of Replicates	Dermal Dosage (µg/kg) ^b	Inhalation Dosage (µg/kg) ^c	Estimated Absorbed Dosage (µg/kg) ^d	Biomon. Dosage (µg/kg) ^e	Ratio ^f PD:BM	Reference Page Numbers ^g
Chester, 1989	Groundboom MLA,	Fluazifop butyl	14/14	5.6	NA ^h	5.3	3.1	1.8	Tables 8, 9
Findlay, 1998	Backpack MLA	Diquat	20/20	204	0.070	0.65	0.08	8.6	19-22
Selman, 1996	groundboom ML	Atrazine	7/7	1.3	0.054	1.4	0.81	1.8	10-24 (Amendmt 1)
Selman, 1996	groundboom MLT	Atrazine	7/7	2.5	0.13	2.8	0.77	3.7	10-24 (Amendmt 1)
Selman, 1996	groundboom MLA	Atrazine	4/4	5.1	0.12	5.3	1.6	3.2	10-24 (Amendmt 1)
Selman, 1996 ⁱ	groundboom ML	Atrazine	7/7	0.41	0.016	0.44	0.61	0.71	10-24 (Amendmt 1)
Selman, 1996 ⁱ	groundboom MLT	Atrazine	7/7	1.3	0.070	1.5	0.56	2.7	10-24 (Amendmt 1)
Selman, 1996 ⁱ	groundboom MLA	Atrazine	4/4	4.3	0.10	4.5	3.9	1.1	10-24 (Amendmt 1)

^a Only replicates where post-application exposures were greater than pre-application based on biomonitoring were used. The first number indicates the number of replicates used, the second is the number of replicates actually monitored.

^b Geometric mean absorbed dermal dosage derived by applying dermal absorption factor from Table 1.

^c Geometric mean inhalation dosage based on respiratory protection (if used) and assuming 100% uptake and retention.

^d Total of dermal + inhalation absorbed dose by replicate, then averaged as geometric mean.

^e Excluding replicates where post-exposure excretion was less than pre-exposure or with aberrant excretion patterns.

^f Ratio PD:biomonitoring = ratio of PD/biomonitoring dosage

^g Key page numbers in the reviewed reference document supporting exposure methods or estimates.

^h NA = not measured

ⁱ Data also quoted in terms of µg/lb a.i. because 2 or 3 days of product use were monitored, during which PD was used on 2 occasions and biomonitoring covered the 3 days continuously. Consequently it is considered feasible to express the data in this way because it is difficult to ascertain the daily absorbed dose of Atrazine from the composite biomonitoring data.

Although many of the proprietary studies of concurrent PD and biomonitoring were conducted according to GLP and are of more recent vintage, there is a wealth of information in the open literature on the subject. Following are some examples.

C. Published Studies Involving PD and Biomonitoring Measurements of Exposure

Open Pour Groundboom M/L/A (Grover et al., 1986)

Eight farmers in Saskatchewan applied 2,4-D while wearing two layers of cotton clothing. Patches were placed underneath the clothing to estimate dermal exposure to covered areas and an outer chest and back patch were used to estimate exposure to face and neck. Hands were washed once at the end of the day with a sodium bicarbonate solution. Total urine output was collected from each participant for 4-7 days post exposure. One of the 8 replicates was excluded (subject F) due to an unrealistically high (1.7 gram) dermal exposure that apparently was attributable to one of the outer dosimeters and had no corollary high biomonitoring output.

Open Pour Groundboom MLA (Chester and Hart, 1986)

Thirteen subjects were monitored consecutively using biological monitoring and then PD during mixing, loading and application of Fluazifop butyl with vehicle-mounted groundboom application equipment in Canada. Three other subjects were also monitored during mixing and loading only. Their data are not included in this assessment because PD was conducted only during the first, interim and final mixing/loading, and so the data are not directly comparable with the biologically monitored absorbed dose. The subjects each handled approximately 132 lb active ingredient during application to approximately 300 ac. The biological monitoring phase was conducted first, involving collection of 24-hour urine samples for 9 days, including the day before use of the product. Aliquots were analyzed for the major metabolite Fl. The absorbed doses of Fluazifop-butyl were estimated using the human pharmacokinetic data described previously. The potential and actual dermal exposures were measured using synthetic 'Tyvek' coveralls incorporating a hood, and gloves as dosimeters. Inhalation exposure was not measured because it was considered to be negligible for a compound of low volatility applied with hydraulic application equipment. The biological monitoring absorbed dose data for subject number 1 were excluded from the comparison because it was known that he had provided incomplete urine samples.

Table 4: Published Study Conditions and Passive Dosimetry Description

Study Reference ^a	Scenario	Pesticide	Dosimeter Type: Outer (Inner)	Handwash solvent/ Volume (mL)	Number of Handwashes	Workday monitored (hr)	Inhalation monitoring method	Clothing Penetration (%)	PD Reference Page Numbers
Grover, 1986	Open pour groundboom M/L/A ^a	2,4-D	(Patches)	0.9% NaHCO ₃	1	1-14.5	none	NR ^b	75, 79, 81
Chester, 1986	Open pour groundboom M/L/A, M/L ^c	Fluazifop butyl	WBD coverall with hood, socks	Gloves	NA ^d	Variable but typical duration for region	none	NR ^a	142-148

^a M/L/A = mixer/loader/applicator

^b NR = No Record

^c M/L = mixer/loader

^d NA = Not applicable

Table 5: Published Study Results for Estimated Absorbed Dosage from Passive Dosimetry and Biomonitoring

Study Reference	Scenario	Pesticide	Number ^a Replicates	Dermal Dosage (µg/kg) ^b	Inhalation Dosage (µg/kg) ^c	Estimated Absorbed Dosage (µg/kg) ^d	Biomon. Dosage (µg/kg) ^e	Ratio PD:BM ^f	Reference Page Numbers ^g
Grover, 1986	Open pour groundboom M/L/A	2,4-D	7/8	33.8	NA	33.8	14.3	2.4	79
Chester & Hart, 1986	Open pour groundboom M/L/A, ML	Fluazifop-butyl	10 M/L/A; 3 M/L ^h	7.9	NA	7.9	5.8	1.4	146

NA - Not included in data analysis because of units of expression – mg/kg ai that could not be converted to mg or µg

^a Only replicates where post-application exposures were greater than pre-application based on biomonitoring were used. The first number indicates the number of replicates used, the second is the number of replicates actually monitored.

^b Geometric mean absorbed dermal dosage derived by applying dermal absorption factor from Table 1.

^c Geometric mean inhalation dosage based on respiratory protection (if used) and assuming 100% uptake and retention.

^d Total of dermal + inhalation absorbed dose by replicate, then averaged as geometric mean.

^e Excluding replicates where post-exposure excretion was less than pre-exposure or with aberrant excretion patterns.

^f Ratio PD:biomonitoring = ratio of PD/biomonitoring dosage

^g Journal page number where data is found

^h Key page numbers in the reviewed reference document supporting exposure methods or estimates.

D. Published Post-Application Exposure Monitoring Studies Conducted with Concurrent PD and Biomonitoring

In addition to pesticide handler exposure monitoring studies, there are numerous published post-application exposure monitoring studies conducted with concurrent PD and biomonitoring. These studies started as early as 1954 with apple harvesters (Batchelor and Walker, 1954), but reliable studies where the whole body was adequately represented by the patch dosimetry configuration recommended by EPA's 1986 guidelines did not occur until the 1980s. Beginning in the 1990s several concurrent WBD and biological monitoring studies have also been conducted as summarized in Table 6.

Several studies have been conducted using structured activity (e.g., Jazzercise) in which volunteers participated in aerobic exercises on a treated surface for intervals of approximately 20 minutes (Ross et al., 1990). None of these studies have monitored individual inhalation exposure, and in the case of Chlorpyrifos, it has been demonstrated that inhalation exposure potential during the 20 minutes of surface contact is negligible [i.e., with maximum air concentrations of $14 \mu\text{g}/\text{m}^3$ (Ross et al., 1992), the exposure from inhalation would constitute $\sim 0.1 \mu\text{g}/\text{kg}$ assuming a breathing rate of 29 L/min and 100% uptake and retention]. In the studies summarized here, volunteers either wore dosimetry clothing and were concurrently biomonitoring or individuals were monitored side by side (a cohort wearing dosimetry garments and another wearing minimal clothing). Following are short narrative descriptions of those studies accompanied by Table 6 that summarizes results from this genre of studies.

Williams et al., 2003

A commercial formulation of Cyfluthrin was broadcast applied using a calibrated wheeled system to the surface of nylon carpet and allowed to dry. Seven male volunteers wore a single cotton sock and cotton shorts and participated in a structured activity program (Jazzercise). Following exposure, the participants provided the sock and shorts for extraction and analysis. Only the socks were used for quantifying dermal dose. Whole body exposure was estimated using the value for sock divided by 0.12 which represents the fraction on a single sock from several WBD studies (Ross et al., 1990; Krieger et al., 2000; Selim and Krieger, 2006) divided by average participant body weight of 85 kg. They also collected their urine 12 hours pre-exposure and 72 hours post-exposure. Urine was analyzed for the biomarker, 4-fluoro-3-phenoxybenzoic acid.

Krieger et al., 2000

Total release foggers containing 1% Chlorpyrifos were applied to nylon carpet indoors. Two groups of volunteers (one group of 13 wearing cotton WBD and the other group of 21 wearing bathing suits) reentered the room following a two-hour drying interval. Each group exercised on the treated carpet using Jazzercise. The WBD were collected and analyzed for Chlorpyrifos. Both groups provided 24-hour pre-exposure and 72-hour post-exposure total urine collections. Urines were refrigerated during the 24-hour collection intervals and were analyzed for TCP. This study design allowed for testing penetration through WBD by clearly demonstrating an increase in excretion over pre-exposure. The ratio of biomonitoring dose for individuals wearing WBD to those wearing minimal clothing gives a good indication of

penetration through a single layer of WBD (15 %) and is consistent with the value assumed for other studies not using both inner and outer dosimeters.

Williams et al., 2004

A mobile spray cart was used to uniformly apply 0.5% formulated Chlorpyrifos to new nylon carpets. While carpets dried, 21 volunteers wearing one cotton sock and cotton shorts were randomly assigned to two groups. One group was allowed to sit and rest while the other group performed aerobic Jazzercise in an untreated area to induce sweating. At this point, both groups performed a low impact Jazzercise routine on the treated carpet. Following the surface contact, each participant provided the socks and shorts for analysis of Chlorpyrifos. Only the socks were used for quantifying dermal dose. Whole body exposure was estimated using the value for sock divided by 0.12 which represents the fraction on sock from several WBD studies (Ross et al., 1990; Krieger et al., 2000; Selim and Krieger, 2006). Complete urine was collected 12 hours prior to exposure and through 5 days post-exposure and analyzed for TCP. Following a two-week hiatus, volunteers participated in a cross-over design in which the resting participants were those that had previously sweated and vice versa. Samples were collected as in the first part of the study.

Table 6: Post Application Reentry Exposure Studies Using Jazzercise with Concurrent PD and Biomonitoring

Study Reference	Pesticide	Number of Subjects ^a	Dose from dosimetry garment(s) ($\mu\text{g}/\text{kg}$) ^b	Estimated Absorbed Dose ($\mu\text{g}/\text{kg}$) ^c	Biomonitoring Absorbed Dose ($\mu\text{g}/\text{kg}$)	Ratio PD:BM
Williams, 2003	Cyfluthrin	7/7	42 ^c	0.51	0.094	5.3
Krieger, 2000	Chlorpyrifos	11/13	110 ^c	0.34 ^f	0.80	0.43
Williams, 2004	Chlorpyrifos	41/41	69 ^d	2.1	1.8	1.2

^a Only replicates where post-application exposures were greater than pre-application based on biomonitoring were used. The first number indicates the number of replicates used, the second is the number of replicates actually monitored.

^b The estimated absorbed dose from passive dosimetry was the value estimated for a whole body and divided by body weight.

^c Value from previous column multiplied by dermal absorption fraction.

^d Whole body exposure was estimated using the value for (sock \div 0.12, fraction on sock from Ross et al., 1990; Krieger et al., 2000; Selim and Krieger, 2006) divided by average participant body weight.

^e Dosimetry garments included gloves, socks and long Johns.

^f Absorbed dose = WBD dose \times 0.15 clothing penetration factor.

E. Exclusion of Proprietary and Published PD-Biomonitoring Studies from Quantitative Evaluation

Of studies reviewed, there were more in Table 7 and others mentioned below that were excluded from further quantitative analysis than in Tables 2, 4 and 5 combined. The basis for the exclusion criteria recommendation for studies with human/primate dermal absorption less than 1% was a practical recognition of the difficulty in establishing a validated LOQ that is sufficiently low to allow consistent detection (i.e., so that a majority of urine samples taken 1-2 days post exposure would have quantifiable levels). Several studies were examined that helped confirm this criterion. Some of those studies are listed in Table 7 because estimates of dosage from biomonitoring based on half the LOQ would substantially exceed the estimated PD dosage; therefore actual metabolite presence in urine was questionable. Examples include Chester et al., 1991; Findlay et al., 2000; Wojeck et al., 1983; Lavy et al., 1992; Krieger et al., 1996 and Cowell et al., 1991.

Some published studies on paraquat involving concurrent PD and biomonitoring were excluded primarily because the urinary concentrations of paraquat were less than the LOQ (e.g. Wojeck et al. 1983; Chester et al. 1993). The point of these observations is that the analytical sensitivity determines whether the absorbed dose estimated via PD is less than, greater than, or equivalent to the biomonitoring dose estimated by use of half the LOQ and urine volumes. Other studies e.g., Staiff et al., 1975 and Forbess et al., 1982 were not included in Table 7 because their urine LOQ was too high to measure the dose measured by passive dosimeters. In another example, the urinary LOQ was adequate, but failed to consistently measure exposure in the 2 of 11 workers that had detects (van Wendel de Joode et al., 1996).

Most of the studies listed in Table 7 were done with patch dosimetry. It has been hypothesized that patch dosimetry will tend to overestimate dermal exposure more than WBD (Ross et al., 2001) for a variety of reasons. However, to our knowledge, there has been no definitive two-cohort (side by side) or concurrent patch and WBD study conducted to test the hypothesis. Chester and Ward, (1983) conducted a study to examine the concordance of patch dosimetry and WBD done concurrently. Results of that study show that in 2 or 3 scenarios, the results are comparable, but in one, the patch dosimetry grossly underestimates results from WBD. Moreover, in general it has been shown that the patch dosimetry data from PHED tends to overestimate absorbed dose estimates obtained from biomonitoring using the same pesticide handling equipment and formulation type (Ross et al., 2006b). For this reason and others (some evident in Table 7) related to the age of the patch studies, these older studies may be useful to support an hypothesis or be used in the absence of more recent data, but should not be relied upon in preference to more recent, higher quality data. Further, as pointed out by Chester and Ward (1983) and Fenske (1990), dermal deposition over a body region represented by a patch is not uniform and patch placement to optimally capture exposure varies between work activities.

Other older studies similarly using patch dosimetry, hand washes and air monitoring have demonstrated that PD overestimates biomonitoring with pesticides having diverse physicochemical properties such as alachlor (Dubelman and Cowell, 1989), EPTC (Knaak et al., 1989), and malathion (Fenske, 1988). Despite exclusion from quantitative comparison of PD versus biomonitoring of a number of published and proprietary concurrent PD/biomonitoring studies shown in Table 7, for the most part these studies also support the hypothesis that PD does not underestimate biomonitoring. Among those excluded studies was a potentially relevant work by Fenske (1988) that involved concurrent PD with patches placed per Subdivision U on the outside of clothing and biomonitoring for M/L and applicators making airblast applications of malathion to citrus. Because individual data for each handler were not published it was not possible to analyze these data in the same manner as other studies discussed here. Further, because the dermal data were not normalized to body surface area represented by each patch and all locations were not included in the data calculations the data were incomplete. Despite these limitations, the author did find statistically significant correlations between patches and biomonitoring.

Table 7: Examples of Supporting Studies that Were Excluded for Various Reasons

Study	Scenario	Pesticide	Biomonitoring	Dermal Method	Inhalation Method	Reason for Exclusion
Cowell, 1987	Groundboom M/L/A	Alachlor	yes	Patches	None	No hand/inhalation monitoring, incomplete reporting (e.g., legs)
Cowell, 1991	Open pour, Hose reel MLA	Dithiopyr	yes	Patches, hand wash	Personal pump + sorbent (silica)	Extremely low primate dermal absorption rate that could not be verified from original data
Fenske, 1988	Airblast M/L, Applicator	Malathion	yes	Patches, Fluorescent	None	Incomplete reporting, no individual data
Bernard, 2001	Turf reentry	Chlorpyrifos	yes	WBD	None	Post exposure biomon was only slightly larger than pre
Krieger, 1996	Indoor reentry	Borax	yes	WBD	None	Post exposure biomon was not significantly larger than pre
Rotondaro, 1992a	Airblast or Groundboom Applicator	Vinclozolin	yes	T-shirt and briefs, forearm, face/neck wipe	Personal pump + fiber filters	No primate metabolism or dermal absorption
Rotondaro, 1992b	Aerial Applicator	Vinclozolin	yes	T-shirt and briefs, forearm, face/neck wipe	Personal pump + fiber filters	No primate metabolism or dermal absorption
Dubelman, 1989	Groundboom M/L, M/L/A	Alachlor	yes	Patches	None	No hand/inhalation monitoring, clothing penetration not calc'd
Lavy, 1980	Helicopter, backpack, mist blower	2,4,5-T	yes	Patches	Personal pump + sorbent	Some dermal samples lost, and no hand, lower arm, lower leg samples

Table 7 (cont.): Examples of Supporting Studies that Were Excluded for Various Reasons

Study	Scenario	Pesticide	Biomonitoring	Dermal Method	Inhalation Method	Reason for Exclusion
Wojeck, 1981	Airblast M/L and Applictr	Ethion	yes	Patches	Respirator pads	Fingers on cotton dosimeters not measured, no lower leg measure
Knaak, 1989	Groundboom M/L/A	EPTC	yes	Patches	Personal pump + sorbent	No primate metabolism or dermal absorption
Selim, 2006	Indoor reentry	Pyrethrin	yes	WBD	Area monitoring	Individual subject data not available
Chester, 1991	Groundboom MLA, ML	Tralkoxydim	yes	WBD	Not monitored	Exposed urine metabolite concentration \leq LOQ
Findlay, 2000	Airblast MLA	Lambda Cyhalothrin	yes	WBD	Personal pump, IOM/ filter	Many urinary metabolites concentrations \leq LOQ and variable
Chester, 1993	Backpack ML & A	Paraquat	yes	WBD	Not monitored	All urinary Paraquat concentrations $<$ LOQ
Wojeck, 1983	Groundboom – low and high level A	Paraquat	yes	Patches, hand rinse or cotton gloves	Respirator and filter cartridge	Range and central tendency PD only, and not possible to calculate daily exposure; With exception of one sample, urinary concentrations $<$ LOQ.
Lavy, 1992	Applicators, weeders and scouts	Glyphosate	yes	Patches, hand wash	Not monitored	All urine concentrations $<$ LOQ
Van der Jagt, 2004	M/L/A hand pump spray	Chlorpyrifos	yes	WBD	Personal pump, IOM/ filter	Post exposure urine concentration $<$ pre

VI. VALIDATION METHODS

The purpose of this section is to describe the possible ways in which validation of PD with biological monitoring may be accomplished. Occupational or residential exposure to pesticides during use and re-entry into treated areas for specific activities can be measured using PD and biological monitoring concurrently or consecutively in the same individuals and results compared.

A. Statistical Treatment of PD/biomonitoring Data

Typically, exposure monitoring results tend to be distributed log-normally (Kromhout and Vermeulen, 2001), so the best indication of the average population exposure from a particular study is the geometric mean. With the unique studies under examination in which passive dosimetry and biomonitoring have been conducted concurrently, the most appropriate comparison between methods for the same study may be the average exposure estimated using the geometric mean. In this particular case, the influence of any individual exposure (whether low or high with respect to the population mean) will have a direct corollary in the concurrent exposure measurement. Thus, if the measure of dermal exposure is high for a particular individual, one would expect if the passive dosimetry method reflects true exposure that the corresponding absorbed dose measurement for the biomonitoring component would also be high. The key test is whether passive dosimetry is representative of the absorbed dose determined through biomonitoring across a variety of exposure scenarios.

B. Validation of the Dermal Absorption Factor Influence

Association of PD/biomonitoring Ratio with Study Dermal Absorption Values

The results obtained from the 14 concurrent PD and biomonitoring studies were used to investigate the association between the PD/biomonitoring ratio and the dermal absorption factor used in each study (see Table 1). This was done using a type of linear regression of log PD/biomonitoring ratio on dermal absorption. That is:

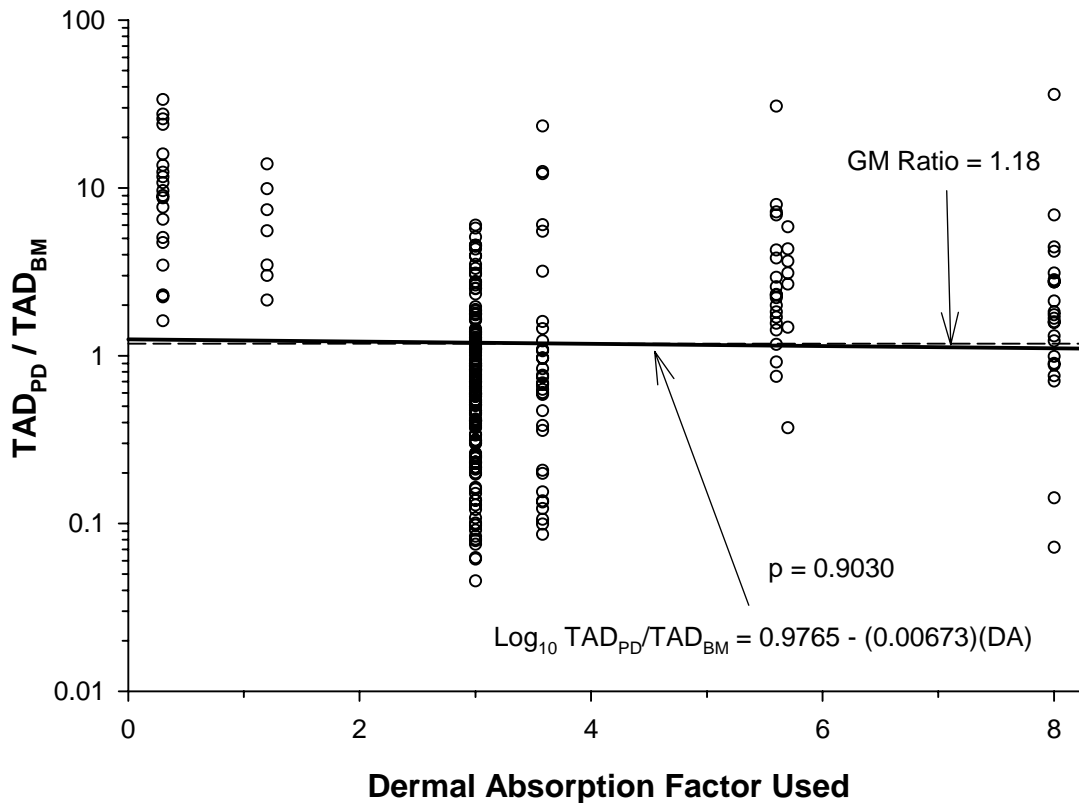
$$(1) \quad \text{Log } R_{ijk} = \alpha + \beta \times (\text{DA}_i) + A_i + B_{ij} + C_{ijk}$$

Where R_{ijk} is the PD/biomonitoring ratio for individual k of scenario j in study i . DA_i is the dermal absorption factor used in study i . The intercept and slope of the regression line are just α and β , respectively. The extra terms A_i , B_{ij} , and C_{ijk} , are necessary to account for random study, scenario, and replicate effects, respectively. In simpler regression analyses these 3 random effects would just be lumped together into “residual error”.

The results of this regression are summarized in Figure 1. There is no significant linear trend ($p=0.9030$) and the regression line is almost identical to the overall geometric mean of 1.18 (the dashed line in Figure 1). This result appears reasonable. Figure 2 shows the result of using the log of dermal absorption in the regression. In this case the regression line suggests a negative trend of log PD/biomonitoring with log DA. However, the slope is still not

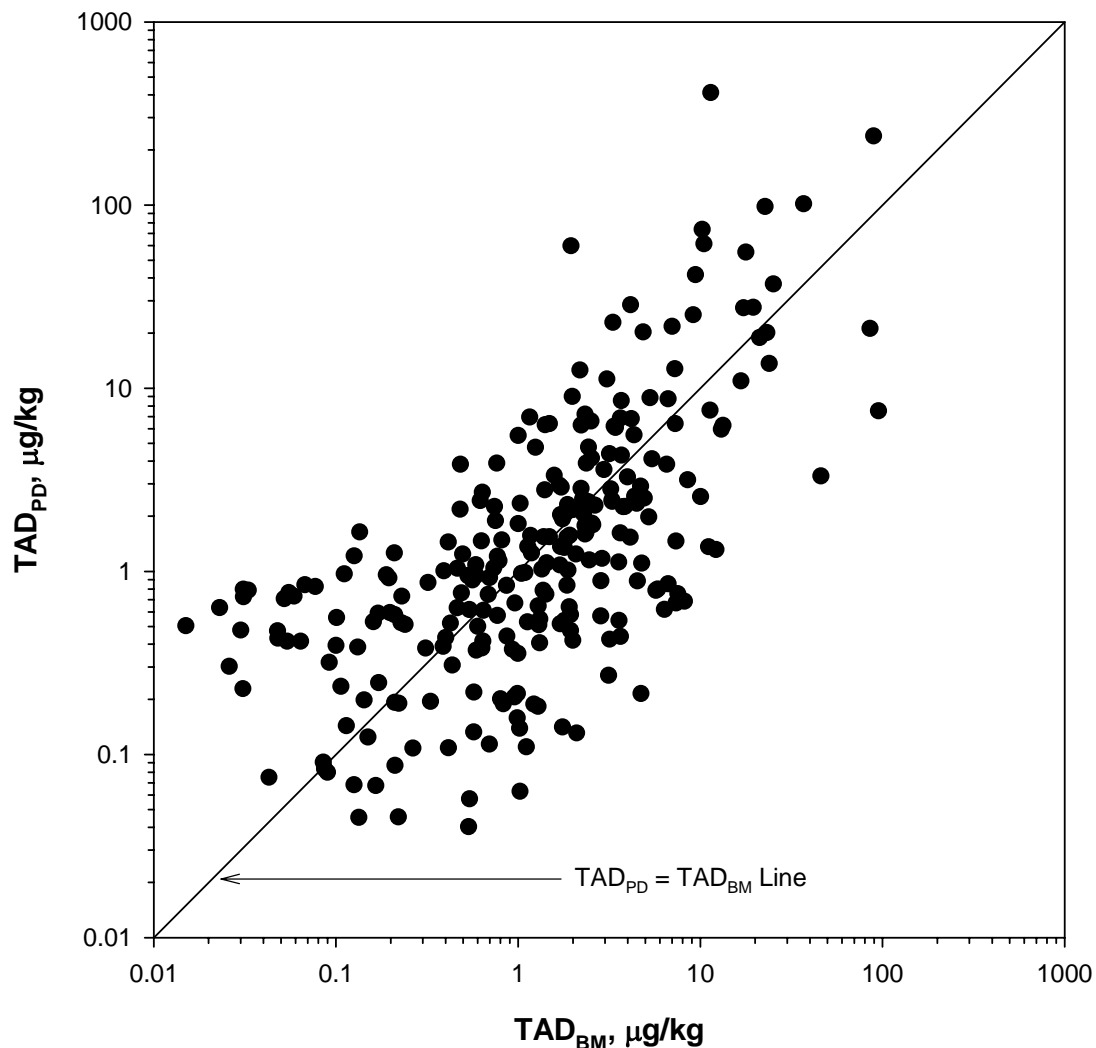
statistically significant from 0. The apparent trend is driven almost entirely by a single study using a dermal absorption factor of 0.3%. Consequently, there is no evidence in these data that the PD/biomonitoring ratio is associated with the dermal absorptions assumed in the particular studies.

Figure 1: Association of PD/biomonitoring Ratio with Dermal Absorption



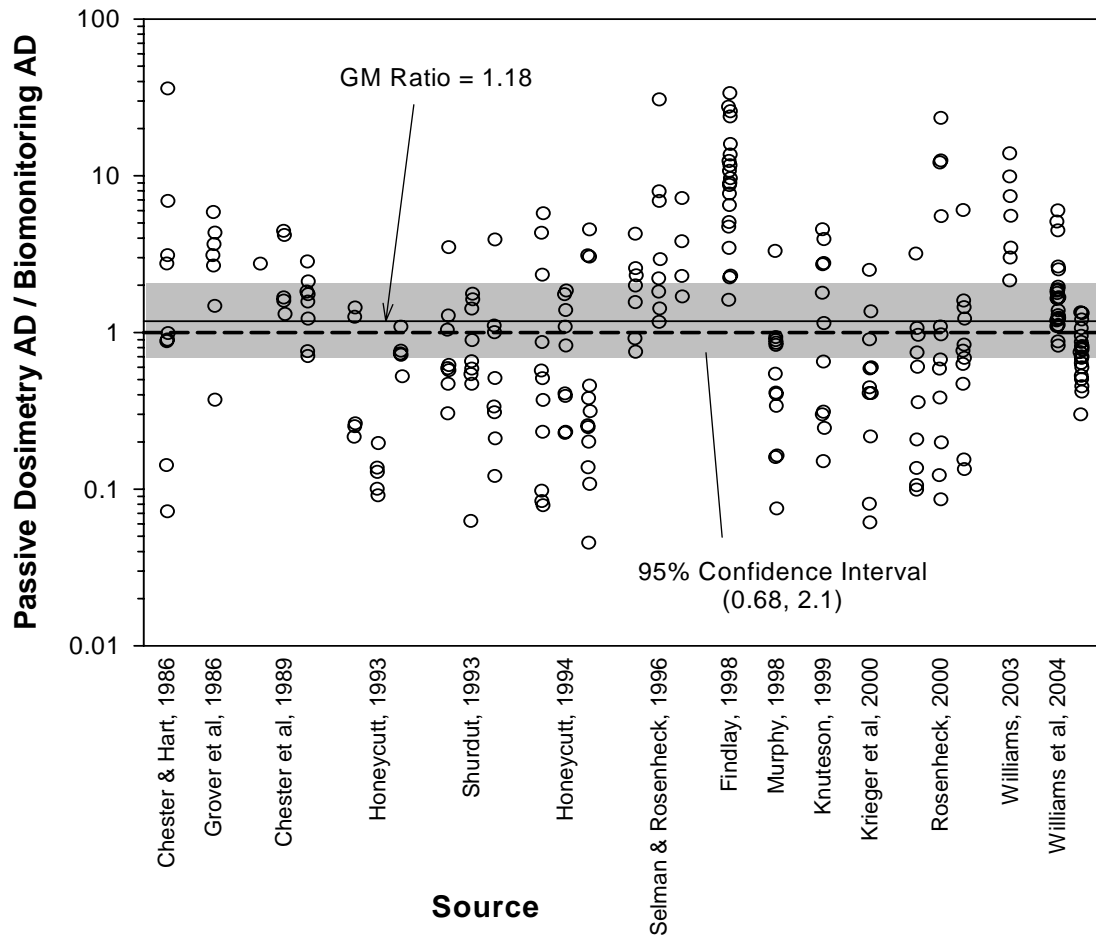
As shown in Figure 2, the two estimates of total absorbed dose are strongly correlated. The correlation between the logarithms of TAD_{PD} and $TAD_{biomonitoring}$ is 0.653 ($p < 0.0001$). The Spearman (or rank) correlation between TAD_{PD} and $TAD_{biomonitoring}$ is 0.672 ($p < 0.0001$).

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Figure 2: Plot of Passive Dosimetry on Biomonitoring for Individuals

The following statistical analysis is a comparison of the ratios of the individual worker absorbed doses (PD)/(biomonitoring). A ratio of one indicates equivalence of the two methods. The following figure shows all the individual PD/biomonitoring ratios. These data are grouped by study and (when necessary) by scenario within study. The studies are arranged in chronological order of the reference. Shown in Figure 3 is a graphic presentation of results for each individual whose mean results are presented in Tables 3, 5 and 6.

Figure 3: Ratio of Absorbed Dose from Passive Dosimetry to Biomonitoring by Individual



The solid black line is the overall geometric mean ratio (1.18) and the shaded green area indicates the 95% confidence interval for the geometric mean (0.67, 2.1). Since this interval includes 1 (the dashed line), there is no evidence of any overall bias in the PD-derived absorbed dose compared with that derived from biomonitoring.

These results were obtained using a variance components analysis on the log of the individual PD/biomonitoring ratios. More specifically, the following model was fitted to the data:

$$\text{Log } R_{ijk} = \text{Log GM} + A_i + B_{ij} + C_{ijk}$$

Where R_{ijk} is the PD/biomonitoring ratio for individual k of scenario j in study i . The terms A_i , B_{ij} , and C_{ijk} , represent random sources of variation coming from studies, scenarios within studies, and individual replicates within scenarios, respectively. So, in words, the above model is simply:

$$\text{Log PD/biomonitoring} = \text{Log GM} + \text{Study Effect} + \text{Scenario Effect} + \text{Individual Effect}$$

In addition to the GM and confidence intervals given above, this analysis also indicated that much of the variation in individual PD/biomonitoring ratios (38%) comes from differences between studies. Variation between replicate individuals accounts for most of the remaining variation (56%). Only 6% of the variation in PD/biomonitoring ratios comes from differences between the scenarios within a study. These results are certainly reflected in the figure above.

The between-individual variation is probably reflecting the ‘background’ variation that would always be encountered regardless of any bias in PD absorbed dose estimates. It’s a combination of individual differences and measurement variation in both PD and biomonitoring doses. The strong study-to-study differences, however, suggest that any given study could have strong biases in PD absorbed dose relative to the biomonitoring absorbed dose. However, such biases do not appear to favor either PD or BD overall. Such a pattern is commonly observed when there are study-specific imperfections in various ‘adjustments’ made (e.g. in this case to estimate absorbed dose). Study-specific biases in the analytical processing could also be a contributing factor. In any event, this study effect appears to operate the same on all individuals in a particular study, regardless of the scenario monitored.

C. Insignificance of the Dosimetry “Pass Through” Component of Exposure

Despite the outer and inner dosimetry, and occasionally use of impermeable gloves, there might be still measurable biomonitoring dose that exceeds the IE. If the biomonitoring actually measures an absorbed dose, then this biomonitoring dose must have been in part absorbed despite the presence of the partial dosimetry and so was not captured or intercepted by it. It could only have arisen through dermal or inhalation absorption, or incidental oral ingestion. Should part of the biomonitoring dose be factored back into the PD exposure estimate to give a more precise value for the express purpose of comparing the estimates of absorbed dose given by the two methods? The OECD guidance document states that estimates of actual dermal exposure in the variant of the whole body method should include the dose estimated to have been absorbed dermally (OECD, 1997). The decision depends upon the work activity and whether the dermal route is significant or perhaps the predominant route of exposure and absorption, e.g. for vehicle groundboom hydraulic downward application. The concurrently measured dermal biomonitoring dose could have arisen through:

- penetration via the outer dosimeter to underlying skin not covered by an inner dosimeter, e.g. lower legs or forearms;
- penetration via the outer dosimeter though a T-shirt to underlying skin, e.g. torso;
- absorption via the hands in between serial hand washes, or from residual material on the hands not removed by the hand wash;
- absorption via the face/neck area similar to the hand wash issue above.

At least some of the uncertainty of “dosimeter pass-through” was eliminated in the older PD studies where foil-backed patches were used, because with this configuration, the full amount of both outer and inner dose was fully intercepted.

The biomonitoring dose resulting from hand, face/neck or body parts covered by dosimeter clothing: $\text{biomonitoring}_{\text{TAD}} - \text{AID}$ (AID derived from IE measurement), could be added to the measured dosimetry clothing dermal exposure value. The distribution of dermal exposure indicated by the dermal PD might provide insight into the relative contributions of the different body sites to total actual dermal exposure.

Inclusion of the biomonitoring dose fraction attributable to absorption from skin areas covered by outer dosimeters in the estimate of total dermal exposure may be necessary because the porosity of the dosimetry clothing is frequently greater than the dermal absorption of the active ingredient, thereby leaving residual active ingredient on the skin surface beneath the outer dosimeter. This dermal exposure is the partial source of the biomonitoring dermally absorbed dose and is not captured or intercepted by the partial clothing PD.

If the hand wash data indicate that hands are a significant contributor to dermal exposure and thus absorption, inclusion of the biomonitoring dose fraction attributable to absorption from the hands in the estimate of total dermal exposure is also necessary. The key difference between the body areas washed and those covered by dosimeter clothing is that the hand and face are typically directly exposed.

An estimate of dosimetry garment pass through can be derived as follows:

$$\text{Pass Through} = (\text{Biomonitoring} - \text{AID}) - (\text{ODE} \times \text{CPF} + \text{IDE}) \times \text{DA} \quad [6]$$

Given the relative uncertainties all possible means of validation of PD with biomonitoring were investigated using the data available, in the ways described above. However, regarding the dosimetry pass through issue, it is clear from examining Figure 2 or 3 that about half of the data points lay below the line, suggesting that there may be a component of pass through. On the other hand, half lay above the line which would give negative numbers for pass through. Further complicating this approach is that for some data, the inhalation component alone exceeds the biomonitoring dose. Overall, these data suggest that dosimetry pass through is not a significant issue. Two concurrent PD: biomonitoring studies conducted with only a single outer dosimetry layer allow one to calculate the “pass through” that occurs through whole body dosimetry garments and it falls in the range of 8-15% (Krieger et al., 2000; Findlay, 1998), which is basically the same range measured for clothing penetration in many other PD studies (Ross et al., 2006c).

D. Conservative Biases in Both Passive Dosimetry and Biomonitoring

Contributing to conservatism (tendency to overestimate exposure) in the PD studies was the practice of taking the simple ratio of inner to outer dosimeters as an estimate of clothing penetration (e.g., Shurdut, 1993 and a majority of the other studies where it was utilized) rather than the more rigorous (and correct) method of dividing the inner dosimeter residue by the outer plus inner residues. The net difference between these two methods is typically less than 10%.

It is noteworthy that inhalation dosimetry as frequently interpreted by regulators tends to be upper bound. Several studies reviewed here used the old default value of 29 L/min respiration rate. In some cases the inhalation exposure exceeded the exposure estimated from biomonitoring, even when results were adjusted for physiologically compatible respiration rates.

Another point worth mentioning is that the dermal absorption factor usually applied to mixer-loader-applicator exposure data is that defined for the dilute spray material, i.e. the higher percent value derived from a relevant dermal absorption study. This is done in the interests of conservatism and also because it is not possible to distinguish the relative contributions from exposure to the concentrated formulated product and the diluted product.

A conservative bias not often considered is that many workers wear underwear. By adding another layer of clothing (which is not included in the estimates of protection when estimating exposure from PD), the true dermal dose is reduced by up to 10-fold to the body regions covered by underwear that represents approximately half the total body surface area.

Biomonitoring for some pesticides is conservative, because the workers (especially reentry, but also M/L and applicators or reentering consumers) can contact the prehydrolyzed pesticide. A pertinent example is Chlorpyrifos and hydrolysis to TCP. The TCP can probably be absorbed through the skin equal to or greater than the parent Chlorpyrifos based on structural similarity to triclopyr (Carmichael, 1989; Barr and Angerer, 2006). In some studies (e.g., Krieger et al., 2000) the background was not subtracted from daily collection of urine, also making those results conservative.

Biomonitoring data have been used historically as validation of PD. However, biomonitoring extrapolated to dermal dose may tend to overestimate handler dermal exposure for two reasons (Duggan *et al.*, 2003):

1. The biomonitored moiety typically represents a hydrolysis product of the parent chlorpyrifos can have greater environmental persistence, allowing more contact by humans.
2. Biomonitoring integrates all routes of exposure including dietary, non-dietary ingestion, incidental contact, inhalation, and dermal. The non dietary ingestion during and after PD monitoring and incidental contact with contaminated machinery following PD monitoring both contribute unknown but potentially significant biomonitored exposure.

VII. CONCLUSIONS

Use of PD in the 1950s through 1970s was instrumental in producing a dramatic reduction in acute pesticide illness in both handlers and reentry workers (Maddy et al., 1990) based on rudimentary knowledge of routes of exposure and particular regions of the body that tended to be the most highly exposed (e.g., hands). Beginning in the 1980s, the quantitative risk assessment paradigm adopted by regulators required not just preventing acute illness, but also proving quantitatively that exposures would not approach the toxicological no-effect level.

This change in the risk paradigm required a change in the way PD measurements were made to reflect the refinements in dose estimates that were required.

Because it is difficult to isolate and validate particular dermal dosimetry methods, the best validation is a comparison of the sum of PD methods against the biomonitored dose. The data examined (both proprietary and public) demonstrates an excellent correlation between PD and biomonitoring. Passive dosimetry as a measure of dosage appears to be consistent with biomonitoring with no bias, i.e., there is no tendency to over or under estimate exposure.

In this report, 14 concurrent or consecutive PD-biomonitoring studies were quantitatively evaluated and 18 different methods of application or reentry scenarios for 8 different active ingredients for which measured human kinetics and dermal absorption data existed. This evaluation demonstrated that the total absorbed dose (or daily dosage) estimated using PD for important handler and reentry scenarios is generally similar to the measurements for those same scenarios made using human urinary biomonitoring methods. Further, this is strongly supported by statistical analysis of individual worker PD: biomonitoring ratio and variance within and between studies. The PD techniques currently employed yield a reproducible, standard methodology that accurately and reliably quantifies exposure and does not underestimate daily absorbed dose. Based on these observations, PD has been successfully validated by biomonitoring.

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