

US EPA ARCHIVE DOCUMENT

Antimicrobials Exposure Assessment Task Force (AEATF) II

Introduction and Background



INTRODUCTION

- AEATF's primary purpose is to generate exposure data to support EPA's development of improved exposure assessments for antimicrobial (biocide) risk analyses and associated regulatory decision-making
- A secondary objective is to provide data to other regulatory agencies (Canada PMRA, EU, BPD) for their assessments and decision-makings



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INTRODUCTION

AEATF overview:

- Represents a coordinated effort between ACC and EPA
 - Preliminary talks in 2003
 - Development talks starting in 2004
- Includes multinational regulatory authority input and involvement (EPA, CDPR, PMRA, EU, OECD)



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INTRODUCTION

AEATF overview:

- \$10 Million program (initial estimate)
- 43 participating companies representing the antimicrobials value chain (active producers to end-user formulators)
- Addresses 19 different exposure scenarios



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New Antimicrobial Exposure Data Are Needed

- Existing antimicrobial exposure data are very limited
 - In response to a 1986 EPA Antimicrobial Data Call-In, ACC Task Force (AEATF I) conducted the “CMA Antimicrobial Exposure Assessment study”
 - The CMA study provided the first exposure data for antimicrobials, but has many limitations (low numbers of individuals monitored, high detection limits and only 8 activities monitored)
 - EPA currently uses the CMA study data in conjunction with Pesticide Handlers Exposure Database (PHED) to conduct most risk assessments for most registered antimicrobial active ingredients
- Paucity of existing data prompted the EPA request for new data
 - In more than 8 Re-registration Eligibility Decision documents issued since 2005, EPA has requested replacement data for the CMA study
 - The need for additional exposure data was confirmed by the EPA’s Scientific Advisory Panel (SAP) in January 2007

Key Role of AEATF Data Development Effort

- AEATF II is a state-of-the-art exposure assessment program that will provide exceptional data for registrant and EPA decisions
- Cost overruns and delays threaten the scope and the viability of this program
- AEATF II wants to continue working with the EPA to find workable solutions to maintain the viability of this valuable program



Introduction

- Antimicrobial pesticides have two major uses:
 - Protect inanimate objects (for example material preservatives in floors and walls), industrial processes or systems, surfaces, water, or other chemical substances from contamination, fouling, or deterioration caused by bacteria, viruses, fungi, protozoa, algae, or slime
 - Disinfect, sanitize, reduce, or mitigate growth or development of microbiological organisms



Examples of Antimicrobial Uses



AEATF Program Scope

Use Patterns

1. Agricultural Premises and Equipment
2. Food Handling/Storage Establishments Premises and Equipment
3. Commercial, Institutional & Industrial Premises and Equipment
4. Residential and Public Access Premises
5. Medical Premises and Equipment
6. Human Drinking Water Systems
7. Industrial Process Water Systems
8. Material Preservatives
9. Antifoulant Coatings
10. Wood Preservatives
11. Swimming Pools
12. Aquatic Areas

Application Methods

1. Aerosol Spray
2. High Pressure Spray
3. Low Pressure Spray
4. Pour Liquid
5. Pump Liquid
6. Pour Solid
7. Place Solids
8. Mop
9. Wipe
10. Fogging
11. Brush
12. Roller
13. Airless Spray
14. Flood
15. Immersion
16. Dip
17. Soak
18. Impregnated
19. Pressure Treatment



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Data Needs - Brief History: AEATF I – CMA “Pependorf Study”

- Response to the 1986 U.S. EPA Antimicrobial Data Call-In;
- 1988 – 1992 sponsored by 20 companies under the auspices of CMA Biocides Panel
- How have the data been used?
 - Exposure data from this study, combined with PHED data and models, enabled continued registration and re-registration of over 120 antimicrobial active ingredients and many end-use products
- Strengths
 - Provided first generic data for antimicrobials
 - Generic data served as the foundation for handler unit exposures
- Limitations
 - High detection limits (0.002 to 3 $\mu\text{g}/\text{cm}^2$; AEATF II target 0.003 $\mu\text{g}/\text{cm}^2$)
 - Low number of monitoring units (min = 3)
 - Limited number of representative antimicrobial scenarios (application methods) studied (n = 8)

Data Needs Identified by EPA

- In various Re-Registration Eligibility Decisions issued during 2005 and 2006, EPA has stated:

“... the risk assessment noted deficiencies in the surrogate dermal and inhalation exposure data available from the Chemical Manufacturers Association (CMA) data base. Therefore, the Agency is requiring confirmatory data to support the uses assessed with the CMA exposure data within this risk assessment.”
- PHMB. September 2005. EPA739-R-05-003
- Benisothiazoline-3-one. September 2005. EPA739-R-05-007
- Para-Tertiary-Amylphenol, Potassium Sodium Salt. January 2005. EPA738-R-05-001
- Azadioxabicyclooctane. September 2005. EPA739-R-05-010
- Chlorine Dioxide and Sodium Chlorite. August 2006. EPA738-R-06-007
- Pine Oil. October 2, 2006. (publication number unavailable)
- Aliphatic Alkyl Quaternaries (DDAC). August 2006. EPA739-R-06-008
- Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC). August 2006. EPA7389-R-06-009

EXPOSURE DATA NEEDS (cont.)

Antimicrobial exposure-related data needs have been clearly identified and justified by OPP/AD

- Confirmatory and new data requirements indicated in many EPA Registration Eligibility Decision Documents (RED)
- Need confirmed by the EPA's Science Advisory Panel (SAP)
- Data needs for "next generation" generic exposure database very apparent with antimicrobial chemicals and more pronounced than with most agricultural scenarios

Antimicrobials Are Unique

- Many of the exposure scenarios for antimicrobials are not shared with AHETF (Agricultural Handlers Exposure Task Force) (e.g., mopping or wiping, etc.)
- Even similar (shared) scenarios have different exposure potential as explained later (e.g., pour liquid)
- The selection process for antimicrobial surrogate active ingredients (a.i.s) to be used for generating generic data has special considerations:
 - High reactivity and/or low concentrations of antimicrobials require that sensitive analytical methods be available for surrogate chemicals. This limits the number of a.i.s that can be studied.
- Opportunities for conducting antimicrobial studies are limited
 - e.g., Limited access to *in situ* locations, limited opportunities where selected surrogate chemicals are being used

Quantitative Objective

- Primary quantitative objective is the same for both Task Forces:
 - Reasonable (practical) estimates of the ‘middle’ and ‘upper’ values of normalized exposure (e.g., arithmetic mean, 95th percentile of a reference distribution)
 - These values are then compared to critical toxicology endpoints for a given unique antimicrobial chemical (i.e., risk is function of hazard & exposure)
- Some users of these data might also wish to explore the relationship between exposure and the amount of AI handled (or components such as “duration of task”). While such relationships can always be examined, the range of AaiH for most anti-microbial scenarios is too small to guarantee statistical power. Thus, no such objectives are formally included in the program design.

AEATF Study Design Considerations

- **Categories of antimicrobial exposure scenarios:**
 - Indoor studies involving simple, repetitive tasks
 - e.g., mop application, wipe application, aerosol application, immersion/dip/soak, spray application, liquid pouring, solid pouring
 - some of these scenario tasks are similar for both Task Forces, e.g., open pouring of liquids, albeit with different environmental and product use conditions, i.e., outdoors versus indoors, large versus small quantities
 - commonality of environmental and task conditions permits the use of simulated environments and semi-scripted (or synthetic) monitoring events to ensure diversity
 - Indoor studies involving more complex, multi-tasking
 - e.g., wood treatment, metal working fluids
 - unique environmental and task conditions require *in situ* studies, albeit with semi-scripted study designs to ensure diversity

Application Scenario has the Greatest Impact on Exposure

- Many AEATF scenarios (e.g., mopping, wiping) occur in various indoor locations (e.g., hospitals, hotels, residences), wherein repetitive tasks are performed, with a similar range of environmental conditions (surface types and configurations, temperature, humidity, air exchange rate)
- The existing CMA antimicrobial exposure monitoring study involving nine application methods (largely repetitive task scenarios) concluded that:
 - *“the hypothesis was validated that exposures for a given application method would not vary significantly among end-use settings; therefore, the application method is a greater determinant of exposure than is the setting”*

Environmental and Product Use Considerations

- Reasons for proposed semi-scripted, simulated AEATF study designs:
 - Existing antimicrobial exposure data have a large number of non-detects on inner dosimeters, despite upper-bound usage; therefore it is not feasible to use significantly less product to extend the range lower.
 - Limiting upper-bound usage are ergonomic considerations e.g., heat stress, limits of endurance and the practical upper limits of area covered by an individual using hand-held equipment in a day. These factors taken together dictate a range of ~5-fold for amount used in a particular use scenario.
 - The large number of non-detects on inner dosimeters further dictates that to meaningfully estimate dermal exposure, the outer dosimeter values must be used with an appropriate data-derived clothing penetration factor.

'Sampling' Methods

- The most recent HSRB issue is the necessity of incorporating random sampling in the program design.
 - This requires careful consideration of the appropriateness, practical feasibility, and cost implications for AEATF studies.
- Very large monitoring costs result in relatively small numbers of monitoring events per scenario (e.g., 15-20)
- As much diversity as possible is needed among the set of monitoring events
- Sampling is not from an existing population of handler-days
 - Synthetic handler-days in simulated environments are used to obtain a broad representation of future exposure conditions.
 - A diverse selection of volunteers are needed perform scenario-related tasks
 - Diversity is also (potentially) increased by using multiple experimental locations (e.g., buildings & monitoring dates)
- This is viewed as a set of synthetic handler-days that represent future exposures under a set of diverse conditions

Random Sampling

- Issue: Should subjects (and even buildings used for simulated environments) be a probability sample?
 - Is there much advantage in a small random sample of subjects from a localized population when the environments and monitoring conditions are synthetic?
 - Random + Synthetic → Synthetic
 - Listing activities are costly and random sampling could result in less subject diversity
 - Increased time required for conduct of random sampling-based studies

Random Sampling

- Incremental cost and time requirements versus realized benefits
 - Previous 875-series guideline cost (study phase only) = 15K per ME
 - Previous 875-series guideline total cost (includes analytical method development, database development, quality assurance, development of SOPs, legal and program management costs, etc.) = 30K per ME
 - Revised purposive-diversity based sampling total cost = 45K per ME
 - Random sampling based total cost = 63K per ME

Participation/Volunteer Rates

- Review of previous studies and task force expertise suggests that site/subject participation rates (from the entire population) would be extremely small
 - For example, less than 5% response rate was observed for potential study site selection in previous CMA study. This low response rate was also observed in a recently conducted AEATF survey re: information and cooperation for the brush/roller “painting scenario study.
- Even if a random sample of subjects were desirable, small participation rates and self-selected volunteers lessen its ability to represent the subject population
- In addition, ethical issues arise when incentives are provided to overcome refusal to participate

Purposive 'Sampling' is a Commonly Employed Characteristic of Regulatory Studies

- Exposure monitoring studies are typically not designed as random samples for cost and other practical reasons (time requirement, response rate issues).
- Purposive-type (non-random sampling-based) studies have routinely served as the basis for applied pesticide exposure and risk analyses (worker and consumer) conducted by EPA, CA EPA, PMRA, European regulatory authorities and the regulated community over the past 30 years.
- EPA 875 Series and OECD exposure monitoring guidelines support purposive sampling study designs.

Purposive Studies:

Role in Regulatory Agency Risk Analysis & Decision-Making

- Purposive sampling has often been necessary in exposure monitoring studies for regulatory purposes:
 - Precedence (purposive-type pesticide exposure monitoring studies):
 - CA DPR sponsored-studies measuring worker exposure
 - Studies conducted in Europe
 - Industrial hygiene studies sponsored by OSHA, NIOSH and private industry
 - Pesticide registrant-sponsored studies measuring worker exposure
- But, for large scale studies and surveys, probability-based sampling is necessary:
 - National Human Exposure Assessment Survey (NHEXAS)
 - Product use and activity pattern surveys (e.g., REJV, NHAPS, NOPES)
 - Dietary intake surveys (e.g., USDA's CSFII)

Re-Cap of Study Monitoring Methods and Design Elements

- Studies will be conducted in accordance with U.S. EPA GLPs, 875 Series Guidelines, and regulations providing for the protection of human subjects involved in research, 40 CFR Part 26
- Protocols are also consistent with OECD guidelines and are reviewed by EU competent authorities
- Key antimicrobial study design considerations:
 - Allocation of resources to address diverse array of use patterns and application methods
 - Scenarios often involve indoor environments
 - Some scenarios involve handling small amounts (e.g., mopping, aerosol spraying)
 - Use of surrogate a.i.s with analytical methods that minimize non-detects
 - Use of semi-scripted tasks in an appropriate indoor location provides a means of ensuring diversity
 - Low site/participant response rate requires substantial effort to achieve desired diversity and sample size