General Questions for Proposed February 17, 2009 HSRB Meeting: Session on Space Insect Repellent Studies Involving Human Subjects

Questions from HSRB Working Group:
Celia B. Fisher (HSRB Chair), Jan Chambers and Michael Lebowitz
January 6, 2009

EPA Responses in bold italics

Environmental Questions:

1. What are the environmental (temperature, wind, time of day, humidity, proximity to water/plants, size and type of space) and human factors (height/weight; gender, age, ethnicity, density of humans in space) that can affect insect behavior and repellent efficacy relevant to space treatment studies?

   All the environmental and human factors affecting efficacy testing of topically applied repellents may affect efficacy testing of spatial repellents as well.

2. What factors need to be considered for test spaces with respect to size of area in which the test is conducted? How is the most appropriate test area determined?

   The test area should be populated by feeding mosquitoes. The size of the test area should be somewhat larger than the expected area claimed to be protected in proposed labeling—enough larger to show a decline in efficacy near the periphery. The appropriate shape of a test area and the placement of the emitter within that space depend on the nature of the emitter and judgments concerning likely patterns of consumer use.

3. Does the number of human subjects within testing environments of different sizes affect insect activity? Does the number of subjects in a given area affect product efficacy or the measurement of product efficacy?

   Yes, the number of humans within an area is likely to affect insect activity. EPA believes that the likely pattern of consumer use of spatial repellents is to protect a relatively small area with at least several people in it – a patio or deck, for example, when entertaining. Thus we prefer a test design that involves at least several people.

4 Are there any other special considerations regarding insect behavior in such studies that require inclusion in protocols?

   EPA knows of no special considerations regarding insect behavior that would apply uniquely to the design of efficacy tests for spatial repellents.

Study Design Questions:

5 How is the location of open spaces typically selected? How many different or similar types of sites are appropriate to assess generalizability?

The 1999 guidelines call for selecting spaces according to the guidance provided therein for field tests of topical repellents—i.e., two locations representing different habitats with adequate pest pressure.

6 What are common spatial dispensing devices? How are they related to the nature of the product dispensed (e.g., gas, suspended liquid, smoke)? What are design or measurement challenges for different dispensing devices and products?

The principal dispensing devices regulated as pesticides are:

- ***coils, which smolder and release smoke,***
- ***Candles or torches containing a repellent released in smoke,***
- ***lamps or other devices which use heat to volatilize a repellent contained in a mat, pad or cartridge,***
- ***devices that use fan to disperse repellent vapors from an impregnated plastic or other source, and***
- ***impregnated paper emitters that passively release a repellent through volatilization at ambient temperatures.***

EPA registers as a pesticide the product as it is sold in channels of trade—the coil, the cartridge for the lamp or the vibrating device, or the impregnated paper emitter. The effective form of the repellent is as a smoke or a vapor.

Because either smoke or vapor will move at the mercy of the wind, the greatest measurement challenge is how best to take the direction and speed of the wind into account in assessing the size and shape of the area protected.

7. What type of dosimetry data is required to determine amount of product application used in testing? How is discharge time determined? What are the relative design merits of the experimenter or subject discharging the repellent?

Dosimetry data comparable to that needed for topically applied repellents is generally not necessary for spatial repellents. The rate of release of the repellent smoke or vapor depends mainly on the emitting device and the physical properties of the active ingredient, not on who lights the coil or turns on the lamp or removes the emitter from its sealed pouch.

Discharge time—roughly comparable to duration of protection for a spatial repellent—can be measured by static air sampling devices, without human subjects.

8. How are outcomes measured in these studies? How are insect knockdown and mortality effects measured? Are both knockdown and landings/bites usually measured in the same study? What is the difference in knockdowns vs bites in terms of information regarding product efficacy/effectiveness?

   Repellent testing normally relies on measuring landings or bites; space repellents can be tested by subjects wearing protective clothing through which mosquitoes cannot bite, using landings as the endpoint of concern. Efficacy of insect toxicants is not tested using human subjects.

9. What is the difference with respect to measurement in assessing efficacy of the active ingredient and effectiveness of the formulation?

   When EPA requires efficacy testing, the material tested is the formulated product. All the ingredients in a formulated product may affect its efficacy; data can be extrapolated only from one tested formulation to another that is essentially the same.

   EPA only registers active ingredients (in the form of technical products) for use in the manufacture of other pesticides—a use for which efficacy data on the active ingredient is not required or meaningful.

Sample Size and Statistics Questions:

10. Depending on the outcome measure, what are best practices with respect to human sample size? What is the sample size norm in the field? How is determination of sample size related to square feet of test area? What is the best way to determine power for these studies?

    Most testing of spatial repellents has involved a cluster of three to six subjects arrayed around the emitting device according to a geometric design defined in the protocol. Both the number of subjects in the array and the specific geometric design vary from one study to another. Opinions differ concerning how a replicate should be defined. EPA believes that a replicate consists of one execution of a protocol comparing treated and untreated landing counts on multiple subjects arrayed around the repellent emitter. Some have argued that each subject should be considered a replicate.

11. What are best practices with respect to statistical analysis? How is censored data handled?

    Data censoring has been an issue when subjects in tests of topically applied repellents do not experience efficacy failure in a test of Complete Protection Time (CPT). Spatial repellents are likely to be tested for Relative Protection (RP) over a

shorter period of time, and data censoring would not be expected. Methods for calculating relative protection are well established.

12. What are the pros and cons of various endpoints (e.g. ending the study after a set number of hours, waiting until the first landing/bite, other) to assess product efficacy (e.g. to meet assumptions for appropriate statistical analyses)?

    Endpoints are chosen to suit the kind of testing being done. If space repellents are tested for relative protection, testing continues for the time defined in the protocol for both treated and untreated scenarios, and would not be ended by an event (landing or bite) indicating failure of complete protection.

    The FIFRA SAP in 2000 advised that testing repellents for relative protection was more statistically robust than testing for CPT. Since then, however, EPA has favored testing of topically applied repellents for CPT to lower the risk to subjects of bites. Spatial repellents can be tested without exposing subjects to bites, and thus the relative protection design can be employed safely.

Human Subjects Questions

13. Why are human subjects necessary for such studies if the outcome measures are knockdowns or mortality?

    Human subjects are not required for testing in which the endpoint measured is insect knockdown or mortality. In addition, work is underway to develop protocols for spatial repellent efficacy testing that would count mosquitoes caught in traps arrayed around the repellent emitter rather than mosquitoes landing on human subjects, but significant technical issues remain to be resolved. EPA encourages the ongoing efforts to address these issues.

14. What are the potential risks to treated subjects (e.g. inhalation, dermal effects)? What are exclusion criteria in subject selection to avoid such risks? How is the degree of risk related to dosage, ingredient, formulations, aerosol pressure?

    Subjects participating in efficacy testing of a spatial repellent will be exposed to the repellent vapor at low concentrations in the ambient air, both via inhalation and via contact with exposed skin. Assuming subjects are protected during the test by coveralls, hats, and face nets, the level of dermal exposure would be low. The concentration of the vapor will depend on the release rate of the emitter, ambient conditions including wind speed and direction, and the location of the subject relative to the emitter. The potential effects of exposure to the vapor will depend on the specific active ingredient.

    FIFRA requires that EPA does not register any pesticide without knowing enough about the properties and toxicity of the product to be able to conclude that it will

not, in use, cause unreasonable adverse effects. EPA would not register a space repellent determined in the course of risk assessment to pose a potential risk to users when used as directed, and would not permit testing with human subjects of a product with uncharacterized risks to subjects or with properties to which some potential subjects might be particularly vulnerable.

15. What is the methodological rationale for continuous versus intermittent exposure? How do human risks differ for these types of exposures? Will exposure start at the beginning of the test period immediately after release of the product?

    The objective of the test proposal the Board will probably see in April is to measure relative protection. In both the treated and untreated scenarios, all test subjects will wear full-coverage protective clothing and will be at negligible risk of bites. The endpoint to be measured is mosquito landings on the protective coveralls. Subject exposures in the treated scenario to the repellent (in the form of vapor in the ambient air) will begin shortly after placement of the test emitters, from which the repellent will be released continuously at a steady rate throughout the test. Each execution of the test is designed to be completed in about one hour; during that period exposure to the vapor in ambient air would be continuous.

    Other testing of other products or for other purposes might propose a different pattern of exposure.

16. If the test agent has properties to repel or destroy an insect, what is the relationship (if any) to a related mechanism of action to humans?

    The potential for a repellent or insect toxicant to affect humans is a principal concern in EPA's risk assessments, normally addressed through review of a wide range of animal studies required to support registration. It is not an element in review of efficacy studies.