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## Col. Raj Gupta's Responses to Discussion Questions

### DISCUSSION QUESTIONS FOR MOSQUITO REPELLENT STUDIES

The Human Studies Review Board (HSRB or Board) has discussed and provided advice to EPA on scientific and ethical issues related to the conduct of field studies to evaluate the efficacy of mosquito repellent products. The HSRB has reviewed both proposals for new field studies and the results of completed studies. The HSRB has noted that, although there are many similarities across studies, not all studies employ the same study design. The HSRB has identified several methodological issues for which additional background information would assist the Board in its evaluation of such studies.

#### ***BACKGROUND***

Currently, EPA requires all pesticide products that claim to repel mosquitoes to provide data on the duration of efficacy under field conditions at two biologically distinct sites. These data are derived from human research with subjects who have been treated with the repellent formulations in the field. The Agency evaluates the duration of repellent efficacy for a subject by calculating the time from application of the repellent to the occurrence of an event indicating an efficacy failure. Historically, for field studies of mosquito repellency, EPA has used the "first confirmed bite" as an indication of efficacy failure on a test subject. Several recent studies have shifted to the "first confirmed landing with intent to bite;" EPA has accepted this alternative endpoint. A "confirmed landing" on a test subject is a mosquito landing followed by a second landing on the same subject within a specified period of time (usually 30 minutes) after the initial landing.

Field studies typically involve 6 – 10 subjects who have been treated with a defined amount of the test material. Each subject is then regularly and repeatedly exposed to ambient mosquito populations for a fixed interval of time until the subject experiences an efficacy failure followed by a confirmation with the specified period of time. Mosquito landing pressure (representing intent to bite) at a site is monitored by concurrently exposing untreated subjects to mosquito landings. A study is considered valid only if there are at least a specified minimum number of mosquito landings on untreated subjects during each exposure interval.

On October 25, 2007, the HSRB will discuss scientific aspects of the design of field studies to assess the efficacy of mosquito repellents. For this meeting the Board has requested consultants to provide specialized information or assistance to the Board. The Board is particularly interested in the frequency, duration and timing of exposure of subjects to potential mosquito landings. The Board requests each consultant to respond briefly to the series of questions below. Please send the responses to the HSRB Chair and Designated Federal Official (DFO) at least one week before the meeting—i.e., by no later than October 18. All responses will subsequently be provided to the other consultants, the HSRB members, and EPA staff for their review, and will be posted on [www.regulations.gov](http://www.regulations.gov) under docket ID number, EPA-HQ-ORD-2007-0942. HSRB consultants will be available at the meeting to discuss their responses and address questions from the Board. The questions for Board consultant consideration are provided below:

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### *DISCUSSION QUESTIONS*

- What do data show about the variability of the time intervals between first and subsequent landings in mosquito repellent field trials?

**The literature indicates that the time intervals between first and subsequent bites/landing is quite variable and depends on several factors such as skin temperature, blood content and circulation, hairs on skin surface, and density of mosquito population. Normally first 5-15 minutes is sufficient for a mosquito to find the host and land/bite**

- What is the current scientific understanding of how factors other than repellent efficacy could affect the likelihood that an initial event—a mosquito landing or mosquito bite—would be “confirmed” by another similar event within 30 minutes? Please address at least these factors:
  - Characteristics of mosquito populations

**The mosquito population densities vary widely and there is a lack of coordination and agreement among investigators on mosquito population sizes or landing/biting rates. It has been shown that insect populations of different density do not provide equivalent estimates of protection time when the test method used depends on fixed endpoint for protection time such as first (or second) observed bite. This may be because the first (or second) insect bite in a small test population represents a less extreme position in the tolerance distribution than the first (or second) bite in a large population.**

- o Characteristics of test sites

**Weather conditions, test site terrain, vegetation, and proximity to human dwellings probably can affect the mosquito host seeking and landing/biting behavior. It has been shown that temperature plays an important role on the effectiveness and persistence of repellents. Protection periods of the repellents tested decreased by an average of 7.6 minutes for each increase of 1° C in ambient temperature.**

- o Characteristics of test subjects

Dr Strickman has adequately address the test subject characteristics in his response

- o Characteristics of test methods

**In bioassay test methods the responses of the mosquito population to the test material are determined over time/application. Test method design and observation/collection techniques have the potential of significantly impacting the study results. Factors such as test exposure skin surface between control and treated subjects, restricting exposure**

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of control subject to beginning and end of the test, by preventing actual bites and counting landings instead, and selective application of treatments or selection of control subjects. Such shortcuts or substitutions inevitably lead to ambiguity in the data obtained because the biting activity of a mosquito population is in a constant state of flux in course of any repellent field test.

It is suggested that the ideal test methods incorporating or simulating activities of the end user application/protection from mosquito landing/bites may provide beneficial and relevant information.

- Can the impact of such factors on the likelihood or timing of an initial and confirming event be predicted? Can it be quantified?

In repellent studies, procedures for recoding landing/bites may be either continuous recording, meaning that the observer records the occurrence and time of each landing/bite from the beginning to the end of the method, or time sampling, meaning that the observer records the occurrence of landing/biting periodically during the method. In repellent studies the initial and confirming event (landing/bites) cannot be predicted.