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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 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:

DISCUSSION QUESTIONS

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

- 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
  - Characteristics of test sites
  - Characteristics of test subjects
  - Characteristics of test methods

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

At its June 27 - 29, 2007 meeting the Board learned that different designs with different "length-biased" sampling for mosquito repellent field studies are in use. One design exposes subjects to potential mosquito landings for one minute of every 15 minutes; another design exposes subjects to potential mosquito landings for five minutes of every 30 minutes. The DFO is separately providing a CD containing the background materials for the June 27 – 29, 2007 HSRB meeting. The protocols are loaded on the CD. These designs have different "length-biased" sampling.

- What is the methodological rationale for the two different designs?

- Which design is used more widely in the field? Why?

- Can potential effects of variation in the pattern of intermittent exposure on the results of efficacy testing be isolated from the effects of other variables? If so, can the direction or magnitude of the effects be predicted? How might these influences be analyzed and accounted for in collecting, reporting and analyzing repellent efficacy data?

Dr. Matt Kramer, a USDA statistician who has served as a consultant, has suggested that the precision of estimates of Complete Protection Time (CPT) in repellent testing could be significantly increased by defining a failure of efficacy as the mean time from treatment to a series of several landings or bites. He has stated:

> The precision of CPT increases when it is estimated beyond time to [First Confirmed Bite] FCB or FCLanding. How well CPT can be estimated

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depends on the distribution of so many bites beyond FCB. The number of mosquitoes that will bite (*n*) will determine results of the test. Each person in the field should be his/her own control; that way it is possible to know *n* per person, and reduce person-to-person variability.

If using the mean time to the first 5 bites, the SE will decrease proportionally as *n* increases ($n = 5$ in this case). That is equivalent to an increase in the power of the test of 5 times. This method allows for detecting formulation differences near the CPT.

- Does this approach, indeed, increase the precision of estimates of CPT markedly without requiring additional subjects?

- If so, would this increased precision justify the incremental risk to the subjects resulting from their exposure to a great?

- Is it practical to test long-lasting repellents to the point of five landings?

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