

US EPA ARCHIVE DOCUMENT

**Extract from HSRB Final Report of April 2008 Meeting
25 June 2008**

(Discussion of ICR Protocol A-382, originally on pp. 27-30)

p. 27 **ICR Protocol: A382**

Science

Charge to the Board

If the proposed research described in ICR's proposed picaridin protocol is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling stable flies?

Board Response

Protocol A382 outlined a laboratory test to evaluate the efficacy of picaridin against stable flies when applied dermally as a 20% cream or spray product. The purpose of the study was clearly defined (i.e., efficacy testing), and the use of human subjects was adequately justified. Briefly, the proposed study will involve a total of 13 subjects, 12 of whom are designated for treatment with the picaridin spray and cream, with one additional subject designated as the negative control. The negative control will be selected at random and serves to establish the aggressiveness of each cage of stable flies to be used in the test. The first phase of the planned study will determine the average dose applied under normal use conditions, but will not exceed 4 mg/cm². The second phase of the study is the repellency test in which subjects' arms will be treated with measured amounts of both products (one product on each forearm), after which they will expose their treated forearms to stable flies for a 5 minute period every half hour for up to 10 hours. The submitted protocol proposed to use the time to first confirmed bite on both arms (both products) as the quantitative measure of repellent efficacy. The Sponsor provided a thorough statistical justification for the protocol design, including the determination that a minimum of 7 subjects would be required to achieve a 95% confidence interval for assessing protection up to 8 hours with a \pm 2-hour confidence limit.

There was general consensus that the protocol was well written and a sound scientific rationale was provided. There were several minor issues that were identified during the course of the HSRB discussion, representing issues that can easily be addressed in a revised protocol. These included: (1) clarifying the protocol to specify that there are 13 subjects, representing 1 negative control and 12 treated individuals; (2) providing some information as to what activities are permitted during the 25 minute intervals when subjects are not actively on test and specifying what activities are precluded by being involved in the test; (3) ensuring the

- p. 28 accuracy of the margin of exposure (MOE) assuming a maximum application rate of 4 mg/cm²; and (4) recommending that the Sponsor design the test to randomize the treatment modalities (spray or cream) on the left and right arms and to ensure that the professional staff involved in the conduct of the study are blinded to the treatments. The HSRB recommends that these modifications should be made to the protocol and study conduct.

There were however, three additional matters concerning the protocol design for which there was additional board discussion and more significant changes recommended to the proposed study. These issues were as follows:

1. It was noted during the Board's discussion that the Sponsor specified that the subject pool was exclusively Caucasian. There was concern as to whether the results obtained from such a constrained population could be generalized to other races, and there was a minority, but strongly voiced opinion that the protocol was not scientifically sound given this limitation. The HSRB recommended that the subjects used in this study should not be homogeneous, but rather, that there should be diversity across the subjects used for the test. The Board did not provide a specific recommendation on how diverse the test population should be, but suggested that, at a minimum, it should reflect the diversity of the region from which the possible subjects are drawn. The Board agreed that the Sponsor must address this scientific issue prior to executing the study.
2. OPP staff recommended that a positive control be used in this study, suggesting that it would improve the overall scientific validity of the test. In its discussion, the HSRB concluded that the inclusion of a positive control was not essential to the protocol, and the Board recommended against requiring a positive control in the study.
3. The protocol was designed to evaluate repellent efficacy using the accepted paradigm of time to first confirmed bite for each treatment (cream or spray product). As such, this design would result in a total of 4 bites per subject upon loss of repellency (first bite to be followed by a confirming bite for each treatment). In consideration of the biology of stable flies, there was general consensus among the HSRB that the study would be scientifically valid if the time to first bite, requiring only one bite per treatment, was used as the endpoint for evaluating the efficacy of the repellent.

HSRB Consensus and Rationale

If amended in a manner consistent with the Board's concerns and recommendations, and with particular modification to subject ethnicity, the protocol ICR A382 studying the efficacy of two formulations of picaridin for repelling stable flies would be sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of these formulations against stable flies.

Ethics

Charge to the Board

If the proposed research described in ICR's proposed picaridin protocol is revised as suggested in EPA's review, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Response

The Board concurred with the factual observations of the ethical strengths and weaknesses of the proposed study, as detailed in the EPA's Science and Ethics Review (Carley and Sweeney 2008).

Overall, this is a well written protocol, consent document, and application, answering many of the questions that HSRB has asked when reviewing in other studies. The risks to study participants were minimal and were justified by the likely societal benefits, including data on the efficacy of these new formulations as repellents against stable flies.

The 20% concentration of picaridin in the products to be used in this study is "higher than the marketed and EPA-registered formulation." Based on toxicological data currently available, however, picaridin has low acute toxicity. The potential risks include irritation or allergic response to the product. Individuals known to be sensitive to insect repellents or skin care products are excluded from the study. In addition, subjects will be monitored for signs of reaction to the products during the dosimetry portion of the study as well as during the repellent phase of the study.

While stable fly bites are acutely painful, the flies are not known to transmit any diseases to humans. Individuals known to be sensitive to stable fly bites are excluded from the study. Topical lotions and rubbing alcohol will be available to subjects to help relieve the itching from the bites.

The study protocol also included several mechanisms designed to minimize coercive recruitment and enrollment, compensation (\$11/hour, time-and-a-half over 9 hours) was not considered to be so high as to unduly influence participation, and minors and pregnant or lactating women were explicitly excluded from enrolling (pregnancy being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test "shortly before any treatment with a test article"). The potential stigmatization resulting from study exclusion was minimized by the use of 'alternate' participants, allowing for volunteers to withdraw or be excluded from participating without unduly compromising their confidentiality.

Several ethical issues were raised, and can be categorized as they relate to the Belmont Principles of Respect for Persons, Beneficence and Justice. The Board concluded that all of the issues could be addressed with additional explanations or minor protocol modifications. Concerns were raised relating to the Justice principle. Subjects greater than 70 years of age are excluded without adequate justification. Subjects who cannot "read, speak, and understand English" are also excluded, without a description of how that will be assessed or a justification of why reading English is required for this study. The recruitment pool of potential subjects is overwhelmingly Caucasian. While ICR will "look for recruits from the Afro-American

p. 30 community,” there are no plans presented to assure racial/ethnic diversity of the study population, which would be more appropriate given that these products, if marketed, will be marketed to the general diverse population.

Issues related to the Respect for Persons principle include the requirement that women not of child-bearing potential, such as women who have had a hysterectomy or who are post-menopausal, are nevertheless required to undergo a pregnancy test. Some HSRB members found this disrespectful, but a minority of other members did not.

While most issues related to the Beneficence principle were addressed, the question of whether or not the stable flies to be used in this study would be given bovine blood at any time prior to the study remained unanswered. Because bovine blood carries with it a potential risk to humans of Creutzfeld-Jacob disease or exposure to bovine leukemia virus, the Board recommended that this question of whether or not the stable flies would receive bovine blood prior to their opportunity to bite human volunteers and the attendant risks be addressed. In addition, the scientific issue of using unblinded ICR staff to measure the outcome variable (stable fly bites) may jeopardize the scientific validity of the study, and thus alter the risk-benefit assessment. The HSRB recommended randomizing which product is applied to which arm, and using a blinded evaluator to measure the outcome variable.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that, if the protocol is revised as suggested by EPA and the HSRB, the study submitted for review by the Board meets the applicable requirements of 40 CFR 26, subparts K and L.