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ELECTRONIC SUBMISSION TO THE DOCKET

October 17, 2007

Dr. Paul Lewis
Designated Federal Officer
Human Studies Review Board
United States Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

RE: Submission of Written Comments for Inclusion in the Upcoming Meeting of the Human Studies Review Board, October 24-26, 2007;
EPA Docket ID: **EPA-HQ-ORD-2007-0942**

Dear Dr. Lewis:

On behalf of the sponsor and the principal investigator (ICR), we are formally submitting these written comments in response to the Agency's ethics review, dated September 24, 2007, for the proposed research protocol evaluating the efficacy of two EPA-registered mosquito repellents in the laboratory (ICR Protocol ID: G0590607001A117). This proposed research is scheduled to be reviewed at the upcoming meeting of the Human Studies Review Board later this month. Since this submission is being made by the October 17, 2007 cutoff date, we are formally requesting that a copy of these written comments be distributed prior to the meeting to each member of the Board and its consultants for this meeting. Representatives of the principal investigator will also bring a sufficient number of copies to the meeting for distribution.

In an attempt to more effectively address the issues on which the principal investigator and sponsor are commenting, each issue is identified by a heading prior to the discussion. All of these issues were identified by the Agency in its science and ethics review. This proposed research is submitted in order to support label claims of protection against West Nile Virus vector species on currently registered repellent products. As a result of prior correspondence with the Agency, this study is necessary to compliment the field data previously submitted and reviewed. Where field study data are used quantitatively to determine a protection time for use on a product label, this laboratory study is to be used qualitatively to determine the effectiveness of the product against a West Nile Virus vector species. Study parameters (i.e. test subject pool size, standard dose and determination of repellency failure by time to first confirmed bite) are maintained in this proposed research for consistency with the field studies.

General Findings

The Agency identified several specific issues in the protocol and informed consent document (ICD) that will be amended and/or explained further in the next revision of the protocol and ICD.

The control and subject raw data collection forms (pages 32 and 33 of the August 8, 2007 submission) will identify the subject only by code/initials and the blank for subject signature will be amended to "Test Subject's Code/Date." The Agency noted that approved product labels should be appended to the protocol. Approved labeling for the repellent products being tested will be included in the revised protocol as an appendix. Additionally, to conform to current Agency practice, the term "Protection Time" will be changed to read "Complete Protection Time." ICR concurs with the Agency's current guideline recommendation regarding the use of 200 mosquitoes per cage and will amend the protocol accordingly.

The Agency's review also noted that it appears inconsistent to measure the attractiveness of a subject when an inclusion factor in the ICD is to have been previously bitten by a mosquito. The requirement for test subjects to verify that they have been previously bitten by mosquitoes helps ICR to eliminate subjects known to be hypersensitive to mosquito bites. The determination of attractancy allows ICR to verify that all test subjects are attractive to mosquitoes on the day of testing prior to applying test articles. ICR will amend the protocol to include a data collection sheet in the final report verifying the results of the preliminary landing verification for all test subjects.

Statistical Design

The Agency's ethics review cited that the description of how data is to be analyzed is incomplete or requires additional clarification. ICR has recently contracted an outside statistician to assist in the preparation of a statistical design for the analysis of study data that this proposed research will generate. ICR will be prepared to discuss and clarify the intended statistical method during public comments at the upcoming Board meeting.

Benefits of the Proposed Research

The Agency's ethics review cites that the current discussion of benefits of the proposed research pertains to the testing of new insect repellent formulations rather than the specific testing of currently EPA-registered products for efficacy against potential West Nile Virus (WNV) vector species of mosquitoes. The protocol and the ICD will be amended to reflect that while there are no direct individual benefits to the research, societal benefits from this type of study will provide the public with more diversity in insect repellents that repel WNV vector species as well as repellent formulations that are DEET alternatives. Also to be amended to the protocol and ICD, in the case of this type of study, using laboratory-reared *Culex* mosquitoes will prevent any potential for disease transmission compared to conducting such a study in a field setting.

Balance of Risks & Benefits and Risk Minimization

The Agency's ethics review cites that repellency failure on the basis of insect landings would promote risk minimization compared to the current methodology of measuring repellency failure by a first confirmed bite (FCB). ICR and the sponsor prefer that the test parameters of this proposed laboratory research remain consistent with the parameters of field studies that have previously been submitted to support these product registrations. The numerous field studies employed a standard dose of 1.67 mg/cm^2 and measured repellency failure by Time to First Confirmed Bite. In addition, ICR and the sponsor believe that the evaluation of repellency based on protection from bites rather than landings is a more reliable and rigorous method to

determine repellency failure and, therefore, effectiveness.

ICR would like to stress that although subject attractancy and mosquito aggressiveness are established through measured landings, subjects at that time are not treated with any test material and that in order to promote risk minimization and ensure minimal mosquito bites, only landings are used. During the study, subjects treated with test material are protected from bites until repellency failure.

The protocol and ICD will be amended to reflect that Time to First Confirmed Bite will be used as the endpoint for repellency failure 1) on the basis of having consistency with previously conducted field studies with the same repellent formulations, as well as 2) there being no risk of disease transmission from laboratory-reared mosquitoes.

Subject Selection

The Agency's ethics review notes that there are discrepancies in the eligibility criteria and subject selection in the protocol and informed consent document. Control subjects will be selected at random using one method (drawing a name by lot). The criterion regarding the requirement for test subjects to wear jeans and heavy socks is an appropriate safety measure as the study is conducted in ICR's insectary and stray insects may be present. Additionally, the reference to "total pool of test subjects" in the study protocol refers to the total pool of enrolled subjects for the study in question as opposed to the entire database of potential study volunteers. When revising the protocol and informed consent document, ICR will provide clarification across the protocol and ICD for the eligibility criteria as well as for the elements aforementioned.

Informed Consent Process

The Agency's ethics review notes that there are discrepancies in the recruitment and informed consent process in the protocol and informed consent document. ICR will clarify and expand the discussion of the recruitment and informed consent process when revising the protocol and informed consent document after the Board has given its recommendations at the upcoming meeting. Greater sensitivity will be given to how study participants and potential study participants are distinguished in the revised documents. In addition, ICR will clarify how the informed consent process is conducted and that any interested participant can have the opportunity to visit ICR's Baltimore office to answer questions.

In Summary

Many of the issues discussed in these comments will be amended to the protocol and/or amended in the revised informed consent document. Based on experience, by incorporating comments by the Agency's ethics review, we have created a protocol that will efficiently, effectively, and safely evaluate the repellency of West Nile Virus vector species of these currently registered insect repellent products. The sponsor and ICR look forward to the Board's evaluation of the proposed research and its recommendations. We would like to thank the Board for its time in evaluating and deliberating the aspects of this proposed research and commend each member for his or her service.

Representatives from ICR will be present at the upcoming Board meeting on October 24-26, 2007 to give public comment on the proposed research and answer any of the Board's questions. If you have any questions or require additional information or clarification in the mean time, please feel free to contact either of the following individuals:
Nick Spero of ICR at (410) 747-4500, e-mail at nspero@icrlab.com or
Micah Reynolds of *toXcel, LLC* at (703) 335-5670, e-mail at micah@toxcel.com.

Sincerely,

Micah Reynolds
Associate Scientist