Extracts Relevant to WPC-001
From HSRB 13 June 2007 Draft Report of April 2007 Meeting

From Summary (p. 2)

Mosquito Repellent Efficacy Protocol WPC-001

Scientific Considerations

- The Board raised several concerns about sample size, sample size considerations for dropouts, statistical analysis and dose for WPC-001 that should be addressed. If the recommendations provided by EPA and those suggested by the Board are followed, protocol WPC-001 appears likely to generate scientifically valid data to assess the efficacy of the test products against mosquitoes. In addition, the protocol would satisfy the scientific criteria recommended by the HSRB, namely, producing important information that cannot be obtained except by research with human subjects, and having a clear scientific objective and study design that should produce adequate data to test the hypothesis.

Ethical Considerations

- The Board concurred with the initial assessment of the Agency that, with minor revisions, the protocol WPC-001 submitted for review would meet the applicable requirements of §40CFR26, subparts K and L.

From Report (pp. 27-29)

Mosquito Repellent Efficacy Protocol WPC-001

Charge to the Board

a. If the proposed research described in Protocol WPC-001 from Carroll-Loye Biological Research 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 mosquitoes?

Board Response to the Charge

This protocol intends to test the mosquito repellent efficacy of a new formulation containing reduced concentration of an active ingredient oil of lemon eucalyptus. The issue then is not really a concern for product safety since (i) EPA does seem to have relevant data for the product with higher concentration and (ii) there is no indication of other ingredients being added or altered in this newer formulation. In this regard, the protocol justifies the need for a human study to reliably assess the efficacy of this newer formulation. The proposed studies are essentially un-blinded, to be conducted in two sites.

The various essential elements of the protocol relating to study rationale, dose selection, endpoint selection, and methods are described adequately, and appear appropriate. Concerns/limitations regarding participant selection and statistical analysis remain, however.

- *Sample size*: From the standpoint of statistical power, six treated and one untreated subject as a sample size sufficient to demonstrate a significant treatment effect at $P<0.05$ is questionable. The justification provided by the investigator is not convincing. The Board recommended reference to information in the results of completed studies to determine adequate sample size.
- *Sample size considerations for dropouts.* In previous studies, subjects dropped out at different points potentially confounding the quantification of the CPT. Considering the current practice, the sponsor should present two different analyses, one using the current practice based on the normality assumption and the other using the Kaplan-Meier method. Also the analysis should be presented in two different ways based on the current definition for the CPT and the one based on the first LIBE without the confirmation within 30 minutes as a sensitivity analysis on the CPT definition.
- *Statistical analysis*: Using the standard that a distribution in which the mean is greater than three standard deviations above zero may be regarded as effectively normal, it is sensible to compute and report the normal 95% confidence interval in this study.
- *Dose*: The dosimetry computed should be compared with toxicology benchmarks to ensure that the investigator is not proceeding with the efficacy testing (even though the Board does not expect unusual results) – doing dosimetry and applying those in further studies without knowing how the applied dose compares to the toxicology/safety benchmark doses.

HSRB Conclusion and Rationale

The Board raised several concerns about sample size, sample size considerations for dropouts, statistical analysis and dose for WPC-001 that should be addressed. If the recommendations provided by EPA and those suggested by the Board are followed, protocol WPC-001 appears likely to generate scientifically valid data to assess the efficacy of the test products against mosquitoes. In addition, the protocol would satisfy the scientific criteria recommended by the HSRB, namely, producing important information that cannot be obtained except by research with human subjects, and having a clear scientific objective and study design that should produce adequate data to test the hypothesis.

Charge to the Board

b. If the proposed research described in Protocol WPC-001 from Carroll-Loye Biological Research 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 to the Charge

The Board concurred with the factual observations of the ethical strengths and weaknesses of the protocol, as described in the EPA's Ethics Review. In general, the Board concluded that the research proposed in WPC-001, with minor revisions, would meet the applicable requirements of 40 CFR Part 26, subparts K and L.

The risks to study participants are minimal and have been minimized appropriately. These risks are justified by the likely societal benefits of the study, including the generation of data on the efficacy of a eucalyptus-based insect repellent that may be viewed by many as an important alternative for individuals sensitive to the smell of other commercially available mosquito repellents. Safety monitoring procedures are in place for the management of possible side effects or adverse events.

While the Board was generally supportive of the proposed research, it did raise several concerns. First, as noted by the Board at its January 2007 meeting concerning similar research by Dr. Carroll, the selection of field sites continues to be an issue.

To minimize the risk that study participants would be exposed to arthropod-borne illness, field tests ideally should be conducted only in areas where known vector-borne diseases have not been detected by county and/or state health or vector-control agencies for at least one month. If there is uncertainty as to whether vector-borne illness are present in the geographic region where field studies are to be conducted (e.g., arthropod-borne illnesses have been detected previously at a distant site but state or local vector-control authorities have determined that the seasonal transmission of these diseases is effectively concluded), it is recommended that investigators trap landing mosquitoes or other vectors for pooled serologic or nucleic acid-based testing. Such testing would allow research participants to be warned of their potential exposure to vector-borne pathogens, and allow them to seek appropriate testing and treatment if necessary.

Secondly, the Board expressed concerns about plans to recruit research subjects in Florida, as these recruitment procedures were not described adequately in the protocol and supporting materials. If the investigators do not plan to recruit research subjects in Florida, this change should be made in the protocol and consent materials.

Finally, the Board raised questions about the informed consent procedures for control subjects. Since control subjects would be presented with higher risks than treated subjects, the informed consent procedures should modified to more clearly explain the risks to control (untreated) research subjects.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that, with minor revision, the protocol WPC-001 submitted for review would met the applicable requirements of §40CFR26, subparts K and L.