*** DRAFT FOR REVIEW BY THE HUMAN STUDIES REVIEW BOARD ****

Background for the Human Studies Review Board

In order to register mosquito repellents with the U.S. Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), study sponsors need to conduct efficacy testing in support of their labeling claims. Consumers generally use mosquito repellents outdoors. To ensure the efficacy of these products in environments similar to those in which consumers use the repellents, the Office of Pesticide Programs (OPP) has required field testing to date. With the occurrence of US-based cases of the Zika virus, OPP wants to discuss this generic topic with the Human Studies Review Board (HSRB) now to determine if the HSRB has any comments on OPP's intended approach prior to EPA providing guidance to study sponsors in the near future.

OPP's Proposal

The EPA is proposing to continue testing insect repellents in the field for all mosquito species required to support efficacy claims on pesticide labels. Because of the limited distribution within the U.S. of Zika virus in natural *Aedes* spp. mosquito populations, the substantial monitoring efforts that are occurring and likely to continue, and the measurement endpoint in repellent studies being mosquito landings and not bites, the Agency believes from a science perspective that the risk of subjects contracting Zika in repellent studies is low and can be avoided by testing in areas where Zika virus has not been detected in the local mosquito population. The Agency believes that testing mosquito repellents in the field represents the most realistic use conditions, and provides the highest level of confidence that the efficacy claim on the product label is accurate.

The Agency does not believe that laboratory testing of mosquito repellents is the best replication of real-world conditions. The Agency does not have a validated lab protocol for which results can be translated to field efficacy with regard to protection time. Therefore, the duration of repellency for a given species when tested in the lab may be different than the duration found in the field. The difference in protection time between the lab and field tests could result in label claims suggesting greater protection and thereby giving consumers a false sense of safety.

There are several factors that can affect measurement of protection time in the laboratory and the field including environmental conditions (heat/humidity, level of transpiration); test subject variability (which will not change between lab or field); mosquito species (with increased variability among field data), and type of formulation (i.e., lotion or spray). Reduced product evaporation or lotion breakdown rates tend to overestimate efficacy inside testing cages because of the unique cage microenvironment. However, based on the type of product being tested (i.e., volatility of the active ingredient, concentration of the active ingredient, and type of formulation) worst-case scenarios could be created inside cages under semi-field conditions that result in more conservative measurements of protection time, and prevent any exposure of test subjects to the risk of Zika transmission. However, the Agency does not know of any semi-field tests that have been validated to show how conservative the measurement of protection time in semi-field tests would be in relation to field tests. If monitoring shows that the presence of Zika virus in natural populations of *Aedes* spp. mosquitoes is expanding rapidly such that testing in areas without Zika virus is not possible, or EPA determines that a product requires biting as the endpoint to determine efficacy, the Agency may consider alternatives to field tests for products claiming to repel Zika vectors.

If EPA continues to require field testing of mosquito repellents, OPP would like to place the following limitations on such field studies:

1. Field testing can only occur in locales where the Zika virus has not been detected by county or state health staff, mosquito abatement district staff and/or federal agencies. The study sponsor must confirm and document no earlier than 48 hours prior to each testing day that Zika has not been detected at or within the county encompassing the intended test site.

2. EPA is also considering asking study sponsors to apply the following exclusion criteria in addition to the criteria traditionally used; the following subjects would be excluded from these studies: (a) Males who plan on becoming fathers; and (b) Women who intend to become pregnant. Pregnant or nursing women are already prohibited from participating in intentional exposure human research studies. EPA's motivation for the additional criteria is the recognition that Zika infection during pregnancy can cause serious birth defects and is associated with other pregnancy problems; also, the Zika virus can be transmitted through sex in addition to the bite of an infected *Aedes* species mosquito.

Consent forms should include information about the Zika virus and its transmission. The training session which subjects attend should highlight the connection between Zika and the inclusion/exclusion criteria.

Questions for the HSRB

1. Does the HSRB agree with OPP's proposed approach from both a scientific perspective and an ethics perspective?

2. Does the HSRB have any comments on the proposed approach or ideas for additional limitations on such field tests? Please share those comments.

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