Hasmukh Shah
Manager, Biocides Panel
American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22209

Dear Dr. Shah:

I am writing in response to your letter of November 16, 2007, concerning the Agency's process for reviewing the results of human research conducted according to a research plan and protocols that have previously undergone review by EPA and the Human Studies Review Board (HSRB). Specifically you request on behalf of the Antimicrobial Exposure Assessment Task Force II (AEATF) that EPA:

- "provide written assurance that it will accept an 'intentional dosing' study report without regard to whether the HSRB subsequently raises new or different considerations than those discussed at the time of the study protocol's approval;

- "provide written assurance that it will accept an 'observational' study report without regard to whether the Agency subsequently raises new or different considerations than those discussed at the time of the study protocol's approval;

- "provide written assurance that a final report of an exposure monitoring study ('intentional dosing' or 'observational') conducted in conformity with an EPA- and/or HSRB-approved protocol will be accepted by the Agency, when submitted, and considered in any regulatory decision process."

As you know, the research proposed by the AEATF to measure the exposure received by people who mix, load, or apply pesticides (handler exposure) constitutes "research with human subjects" and therefore is covered by EPA regulations in 40 CFR part 26.

Most of the AEATF's proposed studies are expected to meet the definition of "research involving intentional exposure of human subjects," and EPA's regulations require, among other things, that sponsors and investigators of such research submit a description of their proposed research (together with appropriate supporting materials) to EPA. See 40 CFR 26.1125. The regulation also provides that once EPA has reviewed such proposed research, the Agency must submit the materials to the HSRB for both science and ethics review. 40 CFR 26.1601. The Agency must then transmit the HSRB's comments on the proposed research to the submitter. This process is called "protocol review."

Some of the AEATF's proposed research will likely fall outside the scope of the regulatory definition of "research involving intentional exposure," and thus outside the scope of the regulatory requirement for protocol review. Such research may also be called "observational."

After the required protocol review, the sponsor and investigator may proceed with the conduct of the research according to the EPA-approved protocol. If the results of human research (either from research involving intentional exposure of human subjects or from observational research) are submitted to EPA, the regulation requires that the report contain certain information necessary for the Agency to evaluate the ethical conduct of the research. See 40 CFR 26.1303. After receiving and reviewing a complete submission, if the Agency decides to rely on data from research involving intentional exposure of human subjects, the regulations require EPA to submit the results of the completed study to the HSRB for review and require the HSRB to address both scientific and ethical aspects of the conduct of the research. 40 CFR 26.1602 and 26.1603. This process is called "study review." The rule does not require study review by the HSRB for "observational studies."

We understand your concern to be that EPA, after considering any comments from the HSRB, may indicate that a research proposal (protocol) is acceptable, but that EPA may subsequently reject the results of research conducted according to the research proposal / protocol. EPA cannot, of course, provide an unqualified guarantee that we will always accept data so long as the research was carried out according to the approved protocol. We believe, however, that it would be unfair to researchers for the Agency to reject data that are generated from carrying out a study in accordance with its approved test protocol, simply because different methodologies could have been used. Therefore, our practice and intention is to accept scientific data and information, developed following EPA-reviewed and approved test protocols, unless we determine that the data simply are not scientifically reliable (e.g., unacceptably high variability in the recovery rate of residues) or that the study was conducted in a manner that does not comply with EPA regulations for the protection of human research subjects. We also recognize that executing a protocol exactly as written is not always possible and that investigators often must make minor changes to the way in which they execute a protocol. If such changes do not affect either the ethical conduct of the study or the scientific reliability of the results, then they would not be a basis for rejecting the data. Note, however, that no changes to approved human research can be implemented without IRB approval except to address an apparent immediate hazard to subjects. See 40 CFR §26.1108(a)(4). Investigators do not have the discretion to decide for themselves whether IRB review of a change to an approved protocol is required.

We share your interest in obtaining new, more reliable data on handler exposure and are confident that the proposed research plan and protocols under development by the AEATF will ultimately result in the generation of such information. We look forward to continuing to work together on this effort.

Sincerely,

Debra E. Edwards, Ph. D.
Director
Office of Pesticide Programs