UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

April 14, 2006

MEMORANDUM

Subject: Transmittal of materials for review by the Human Studies Review Board.

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Office of Science Advisor (8105R)

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The Agency's Human Studies Review Board (HSRB) is scheduled to meet May 2-4, 2006, to address scientific and ethical issues surrounding human toxicity studies involving two pesticide active ingredients, carbofuran and methyl isothiocyanate (MITC), and chromium, a constituent of wood preservative products. (Wood preservatives are regulated as pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act.) By this memo the Office of Pesticide Programs (OPP) is transmitting to the HSRB the documents discussed below.

On March 21, 2006, the Agency sent to the HSRB materials containing background information regarding EPA review policies and approaches and the newly-effective amended rules for protecting human subjects of research. These materials may also be useful in preparing for this HSRB meeting.

DOCUMENTS PROVIDED TO THE HUMAN STUDIES REVIEW BOARD (HSRB) FOR THE MAY 2-4, 2006 MEETING

Introduction

The Pesticide Registration Improvement Act (PRIA) requires that EPA complete its decision-making process on certain types of applications to register a pesticide product within specified amounts of time after receiving the application for registration. In addition, PRIA established deadlines for EPA to complete "reregistration" of pesticide active ingredients that are contained in pesticide products initially registered before 1984. Reregistration involves the systematic reexamination of older pesticides, applying contemporary scientific and regulatory standards. When a pesticide active ingredient is approved for use on food, EPA combines reregistration with the tolerance reassessment process mandated by the Food Quality Protection Act of 1996 (FQPA).

Both MITC and carbofuran are undergoing reevaluation in the reregistration process. EPA is considering the human health risks of chromium both in its reregistration program and as part of its review of an application for registration pending under FIFRA and PRIA.

Types of Documents Provided to the Human Studies Review Board (HSRB) for the May 2 - 4, 2006 Meeting

For each of the human studies under consideration, the Agency has provided the Board members with the complete study report and any supplements available to the Agency. Each of these studies is assigned a unique identifier, the Master Record Identifier or MRID, which OPP uses to manage documents in its archive. When a company submits multiple documents pertaining to a single study, each document is assigned a unique MRID as it is received and catalogued. Thus a study with several supplements, such as the MITC study to be discussed at this meeting, may be associated with several MRIDs.

For each study the Agency has provided a review of the ethical conduct of the study. Each ethics review identifies any deficiencies noted in the conduct of the specific study compared to both current ethical standards and the ethical standards prevailing at the time the research was performed. EPA has intentionally deferred making a final determination of whether an individual study satisfies the ethical standards for acceptability in 40 CFR sections 26.1704 – 26.1706, pending the advice of the Board.

For most studies, the Agency develops documents, called Data Evaluation Records (DERs), containing a scientific review of the study; the Board has been provided with one or more DERs for carbofuran and MITC. DERs contain summaries of the study design, methods and results, describe potential deficiencies, and provide conclusions about the usefulness of the study in risk assessment.

In addition to the DERs, OPP has prepared a "Weight of Evidence" (WOE) memorandum for carbofuran and MITC discussing the differences and similarities between the human and animal responses to each chemical and characterizing the usefulness of the human toxicity studies for human health risk assessment. The WOE memos express the Agency's current scientific conclusions on which the Agency is soliciting the Board's comments. To maintain the historical record of review, EPA may, in some cases, include a DER for a study that expresses scientific conclusions differing from those in the WOE document.

For chromium, EPA has provided a set of documents which contain similar information to DERs and WOEs, but which have a slightly different format and presentation, due to the procedural history of the EPA's review of this chemical. As noted above, chromium is a constituent in wood preservative products. EPA has concern about the potential for chromium to elicit an allergic response in sensitized individuals who come in contact with residues remaining in products made from wood that has been treated with chromium-containing wood preservatives. To assess the risk of potential dermal exposure, EPA reviewed, among other information, a study involving intentional exposure of sensitized subjects to different levels of chromium, (Nethercott 1994). This assessment was one of the first assessments of this kind performed by OPP, and it raised significant scientific issues. Accordingly, EPA prepared a background document for its independent, peer review advisory committee, the FIFRA Scientific Advisory Panel (SAP). The SAP is a federally chartered advisory committee of scientific experts who provide advice to EPA on scientific issues arising in connection with the regulation of pesticides. We are providing a copy of the materials given to the SAP for its review, as well as a copy of the SAP's final report. After receiving the SAP's recommendations, EPA sought review and comment from other Agency scientists through the steering committee of EPA's internal Science Policy Council (SPC) to ensure consistency across programs in the approach to regulating substances that are skin sensitizers. Using the advice of the SAP and the steering committee of the SPC, OPP developed a memorandum describing how OPP intended to use the results of the Nethercott study to derive a sensitization Reference Dose. This memorandum, developed in the Antimicrobials Division Toxicity Endpoint Selection Committee (ADTC), is analogous to the WOE documents generated by HED.

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Carbofuran; EPA Reg.#279-2875 (Furadan 75 WP) and EPA Reg. #279-2876 (Furadan 4 F); also FMC 35001 4 EC (unregistered Carbofuran analog).
16. Carbofuran – Data Evaluation Record – acute human dermal study (1978) with carbofuran. Memo from Amal Mahfouz to Jay Ellenberger dated June 26, 1981. Carbofuran; EPA Reg.#279-2875 (Furadan 75 WP) and EPA Reg. #279-2876 (Furadan 4 F); also FMC 35001 4 EC (unregistered Carbofuran analog).
17. Carbofuran – Discussion of Outside Peer Review Comments on the Carbofuran RfD, Memo from William Burnam to Tina Levine dated September 11, 1997.
18. Carbofuran – Human Studies Review Board: CARBOFURAN Weight of Evidence Presentation of Human and Animal Toxicity Studies
19. MITC – Russell, M.J. and Rush, T.I. (1996) Methyl Isothiocyanate: Determination of human olfactory detection threshold and human no observable effect level for eye irritation. Sensory Testing Laboratory, University of California at Davis. Report No. RR 96-049B. September 10, 1996 MRID 44400401.
20. MITC – Supplementary material for Russell et al. (1996). MRIDs 46546601, 46558201, and 46584901.
21. MITC – Ethics review by John Carley, April 13, 2006
22. MITC – Data Evaluation Record, Special Study: Human Eye Irritation and Odor Threshold. MRIDs 44400401, 46546601, 46558201, and 46584901.
23. MITC – Human Studies Review Board: Weight of Evidence Discussion for Methyl-isothiocyanate (MITC), April 13, 2006