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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

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MEMORANDUM

DATE: March 23, 2001

SUBJECT: Triphenyltin Hydroxide: Report of the Hazard Identification Assessment Review Committee: Reconsideration on the need for a developmental immunotoxicity study and sustaining the requirement for the developmental neurotoxicity study.

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Note: This report addresses specific issues related to the need for developmental immunotoxicity and neurotoxicity studies for triphenyltin hydroxide (TPTH) that were discussed at the January 11, 2001 special HIARC meeting. The selection of toxicity endpoints and FQPA issues were not discussed or impacted at this meeting. Please refer to the previous HIARC report (HED Document No.: 012972 and dated November 13, 1998) for the selection of the toxicity endpoints, FQPA and other issues.

1. Recommendations

On January 11, 2001 the HIARC convened to reconsider the need for a developmental immunotoxicity study with the fungicide triphenyltin hydroxide as well as to recommend if the developmental neurotoxicity study should be conducted at this time or to wait until the results of the acute and subchronic neurotoxicity studies have been conducted and reviewed.

In summary, the HIARC recommended that:

1. The requirement for the developmental immunotoxicity study should be RESERVED since there is currently no validated protocol for this study type. However, the registrant must conduct immunotoxicity studies (series 870.7800) that includes: (1) antibody plaque-forming cell (PFC) assay or ELISA assay; (2) Natural Killer (NK) cells activity assay; and (3) enumeration of splenic or peripheral blood total B cells, total T cells, and T cell subpopulations using flow cytometry.

2. The developmental neurotoxicity study should be conducted without waiting for the completion and review of the acute and subchronic neurotoxicity studies.

2. **Background**:

The previous (HED Doc. No.: 012972, November 13, 1998) HIARC assessment of triphenyltin hydroxide (TPTH) recommended that since immunotoxicity is a more significant endpoint than neurotoxicity that a special developmental *immunotoxicity* (DIT) study with TPTH be presented to assess the potential for TPTH to affect the immune system in fetal and/or neonatal rats. This DIT study was to follow the same dosing procedure as the guidelines for a developmental *neurotoxicity* (DNT) study. At the time that the HIARC report was prepared it was determined that a developmental *neurotoxicity* (DNT) study was not required. However, the Data-Call-In for DNT studies included TPTH (November 15, 1999) because TPTH belongs to a class of chemicals (organotins) known to be neurotoxic. Therefore, the registrant was informed that a DNT study is required for TPTH. Subsequently, it was suggested that the DNT study be conducted to include extra animals so that the immune system could also be assessed as a satellite study.

The registrant has submitted a protocol for the development *neurotoxicity* (DNT) without inclusions for immunotoxicity testing and this protocol has been reviewed by the DNT Protocol Review Committee. The Committee's report is provided as an attachment. The registrant has indicated that there would be problems in selecting the dose levels for a study primarily designed as a DNT study that would include special provisions and extra animals to also assess for immunotoxicity. This is because the dose levels that will need to be tested in order to detect a neurological response are much *higher* than the dose levels that are already known to potentially affect the immune system at least in adult rats. For example, TPTH did not demonstrate obvious neurotoxicity at dose levels of ~6.2 mg/kg/day although some effects on endocrine activity were evident in the rat chronic study. TPTH has been shown to affect immunoglobulin levels in the rat subchronic (~0.33 mg/kg/day) and chronic feeding studies and mouse subchronic feeding study (~0.75 mg/kg/day). The NOAEL and LOAEL are 2 (0.1 mg/kg/day) and 5 ppm (0.25 mg/kg/day) for decreases in white blood cell counts (a potential indicator of immunotoxicity). Thus, when subchronic and chronic studies in rats are considered, immunotoxicity does occur at dose levels much lower than any indications of neurotoxicity.

The registrant has further indicated that there are no guidelines issued for addressing DIT endpoints and that to date they have not been successful in designing a DIT study.

3. **Discussion of Specific Issues**

I. Developmental Immunotoxicity Study

The HIARC determined that the need for a developmental immunotoxicity study should be RESERVED because there is no acceptable guideline or validated protocol for assessing the rat in a developmental immunotoxicity study.

However, since TPTH has been shown to suppress white blood cell counts, reduce spleen and thymus weights and decrease antibody (IgG, IgM, IgA) production in rodents, the potential of immunotoxicity of TPTH should be further investigated. The HIARC recommenced that TPTH be assessed for potential immunotoxicity using the new immunotoxicity testing guideline (870.7800) that includes (1) antibody plaque-forming cell (PFC) assay or ELISA assay; (2) Natural Killer (NK) cells activity assay; and (3) enumeration of splenic or peripheral blood total B cells, total T cells, and T cell subpopulations using flow cytometry.

II Developmental Neurotoxicity Study

It was suggested that since the conventional guideline studies conducted with TPTH did not show any obvious signs of neurotoxicity, that the developmental neurotoxicity (DNT) study should follow the acute and subchronic neurotoxicity studies. In particular, the studies in adults could provide important data on neurotoxic effects and on dosing with TPTH that could be used to improve the design of the DNT study.

The HIARC concluded that this was not appropriate because the DNT study might show qualitative effects not seen in the studies in adults and because it would considerably delay the conduct of the DNT study. Furthermore, the registrant has already submitted general protocols for the adult and the DNT studies, and reviews of these protocols have been provided to the registrant.