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

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OPP

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

17-DEC-1998

MEMORANDUM

SUBJECT: ***TRIPHENYLTIN HYDROXIDE (TPTH)*** **- Report of the FQPA Safety Factor Committee.**

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Sarah Law, Risk Assessor
Reregistration Action Branch 3
Health Effects Division (7509C)

PC Code: 083601

The Health Effects Division (HED) FQPA Safety Factor Committee met on November 30, 1998 to evaluate the hazard and exposure data for TPTH and made two separate recommendations. The Committee recommended that the FQPA safety factor (as required by Food Quality Protection Act of August 3, 1996) be **retained in chronic dietary risk assessments and reduced (to 3x) in acute dietary risk assessments** for this pesticide.

I. HAZARD ASSESSMENT

1. Determination of Susceptibility

(I) Developmental Toxicity

The Hazard Identification Assessment Review Committee (HIARC) determined that the available Agency Guideline studies indicated no increased susceptibility of rats or rabbits, quantitatively or qualitatively, to *in utero* exposure to TPTH. In the prenatal developmental toxicity study in rats, no evidence of developmental toxicity was seen even in the presence of maternal toxicity. In the prenatal developmental toxicity study in rabbits, developmental toxicity was seen at a higher dose than that causing maternal toxicity (*Memorandum:* J. Doherty to C. Scheltema dated November 13, 1998).

(ii) Reproductive Toxicity

There was evidence of increased susceptibility to the offspring following pre-/postnatal exposure in the two-generation reproduction study in rats. In this study, offspring toxicity was manifested as decreased live litter size; decreased liver and spleen weights at a dose lower than that which caused parental systemic toxicity characterized as decreased body weight.

(iii) Immunotoxicity.

TPTH is considered as an agent that may cause immunotoxicity. The toxicity endpoint for deriving the chronic dietary RfD is based on decreases in white blood cells. Additionally, decreases in immunoglobulin levels were observed in long-term feeding studies with rats and mice.

(iv) Evidence of Endocrine Disruption

TPTH is considered to affect the endocrine system. There has been discussion between the registrants and the Agency regarding the design of some special studies to assess the potential for TPTH to affect the hormone levels in an attempt to demonstrate and characterize the possible relationship between TPTH, hormonal effects, and the development of pituitary and testicular tumors.

2. Adequacy of Toxicity Database

The toxicity data base for TPTH is lacking acute and subchronic neurotoxicity studies in rats, however, these studies are not critical for hazard characterization for FQPA since the available guideline studies do not indicate *specific* neurotoxicity with TPTH (subchronic and chronic studies in rats and dogs, multi-generation reproduction study in rats, and other studies with TPTH do not indicate obvious neurotoxicity). Although TPTH is related to a chemical class that is known to cause neurotoxicity (trimethyl and triethyl tin are known neurotoxins and are used as positive controls in neurotoxicity studies), the neurotoxicity of the alkyl and aryl substituted tin derivatives is apparently influenced by

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the size of the substitutes. As the chain length increases or gets bulkier (substitution of an aryl group in place of the alkyl), the propensity of the chemical to cause neurotoxicity diminishes (as is the case of TPTH).

The HIARC required a developmental immunotoxicity study which will evaluate immunotoxicity, a potential toxic effect of TPTH to which fetuses and neonates may be specially susceptible, in place of a developmental neurotoxicity study.

II. EXPOSURE ASSESSMENT

1. Dietary (Food) Exposure Considerations

Tolerances for residues of the fungicide, TPTH, are established at 0.05 ppm in/ on raw agricultural commodities including pecans, potatoes, sugar beet roots, milk, and meat [40 CFR 180.236]. Parent TPTH, and metabolites, DPTH (diphenyltin hydroxide) and MPTH (monophenyltin hydroxide), are excluded in Codex MRLs.

Typically, TPTH can be applied to potatoes at a maximum rate of 3 oz. ai/A, 4-6 times a year (depending upon the rate); To sugar beets at a maximum rate of 4 oz. ai/A, 3-6 times per year (depending upon the rate; submission proposes increase to at 5 applications at 4 oz. ai/A); and to pecans at a maximum rate of 6 oz. ai/A, 10 times per year.

Residues do transfer to meat/milk (sugar beet tops) and tolerances are currently established at 0.05ppm. These tolerances, however, will need to be adjusted to higher levels (0.1 ppm for milk fat and 2.0 ppm for liver).

There are no PDP or FDA monitoring data for TPTH. There is information available from BEAD on % crop treated. The source of the information for TPTH is quantitative usage analysis (QUA). Percent crop treated is approximately 50% for pecans, 25% for potatoes, and 30% for sugar beets.

The HED Dietary Risk Evaluation System (DRES) was used to assess the risk from acute and chronic dietary exposure to TPTH residues in food. The chronic analysis was performed using percent crop treated (%CT) information and anticipated residues (ARs). The acute analysis assumed 100 %CT and tolerance level residues.

2. Dietary (Drinking Water) Exposure Considerations

A comprehensive fate review of TPTH was not complete at the time of this meeting. A preliminary review of the existing data indicates that TPTH is relatively non-persistent to moderately persistent in soil. TPTH is not susceptible to hydrolysis or photolysis and is relatively insoluble in water. Microbial degradation appears to be the dominant route of dissipation. An accurate determination of K_d or K_{oc} via a batch adsorption experiment is not available for TPTH. This information is essential for estimating the leaching potential of the compound. There is sufficient information to estimate a K_{oc}, however estimations of this nature should be used with caution. Based on the estimated K_{oc} TPTH

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is not expected to leach to groundwater. However, in soils were TPTH does not rapidly degrade there is potential for transport of TPTH bound to soil via runoff due to irrigation or rain events.

There are no monitoring data available for TPTH, therefor Tier I Estimated Environmental Concentrations (EECs) are calculated using GENEEC (surface water) and SCI-GROW (ground water) based on the maximum application rate for TPTH of 0.375 lb ai × 10 applications per year on pecans.

3. Residential Exposure Considerations

There are currently no registered residential uses for TPTH, therefore, this type of exposure to infants and children is not expected.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. FQPA Safety Factor Recommendation

The Committee recommended two different FQPA Safety Factors: 3x for acute dietary risk assessments and 10x for chronic dietary assessments.

2. Rationale for the FQPA Safety Factor

The Committee made these recommendations for the FQPA Safety Factor for TPTH because:

1. There was evidence of increased susceptibility to the offspring following pre- and/or postnatal exposure in the two-generation reproduction study in rats. Offspring toxicity was observed at a dose lower than parental systemic toxicity.

2. TPTH is considered to affect the endocrine system and there is concern for the possible relationship between TPTH, hormonal effects, and the development of pituitary and testicular tumors.

3. TPTH is considered as an agent that may cause immunotoxicity. The chronic dietary RfD is based on decreases in white blood cells and both the rat and mouse chronic feeding and/or oncogenicity studies indicate decreases in immunoglobulins.

4. HIARC required a developmental toxicity study that evaluates immunotoxicity, a potential toxic effect of TPTH to which fetuses and neonates may be specially susceptible, in place of a developmental neurotoxicity study.

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3. Population Subgroups for Application of the Safety Factor

Acute Dietary Assessment: The Committee determined that the FQPA Safety Factor can be **reduced to 3x** for acute dietary risk assessment for **All Populations which include Infants and Children** because the increased susceptibility was seen only in the offspring of parental animals receiving repeated oral exposures (two-generation reproduction toxicity study) and not seen following *in utero* exposures (developmental studies). Thus the increased susceptibility concern was for chronic dietary exposure. The application of the 3x safety factor to the acute dietary exposure assessment is based on the concern for the potential immunotoxic effects which resulted in the requirement for a developmental immunotoxicity study (data gap).

Chronic Dietary Assessment: The Committee determined that the FQPA Safety Factor should be **retained (10x)** for chronic dietary risk assessment for **All Populations which include Infants and Children** because increased susceptibility to the offspring was seen following repeated oral exposures in the two generation reproduction study in rats.

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FQPA Safety Factor Committee Meeting
30NOV1998
Chemical: TPTH

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