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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 28, 1999

MEMORANDUM

SUBJECT: *IMAZALIL* - Report of the FQPA Safety Factor Committee.

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

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

TO: Sue Hummel, Branch Senior Scientist
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Health Effects Division (7509C)

PC Code: 111901

The Health Effects Division (HED) FQPA Safety Factor Committee met on September 20, 1999 to evaluate the hazard and exposure data for imazalil and recommended that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) be retained at 10x when assessing chronic dietary exposure and reduced to 3x for when assessing acute dietary exposure to this pesticide.

1

I. HAZARD ASSESSMENT

(*Memorandum:* A. Khasawinah to S. Hummel dated June 29, 1999; HED Doc. No. 013539)

1. Adequacy of Toxicity Database

At the time of this FQPA SFC meeting, the toxicology database for imazalil was considered to be adequate according to the Subdivision F Guideline requirements for a food-use chemical.

However, the FQPA Safety Factor Committee recommended that a developmental neurotoxicity study in rats be conducted due to concern for neurobehavioral effects in offspring following prenatal exposure to imazalil which were reported in a published literature study conducted in mice (Tanaka 1995). In addition, imazalil is structurally related to compounds which are known neurotoxicants including triadimefon and triademenol.

In response to the FQPA SFC recommendation, the HIARC met on September 28, 1999 to re-evaluate the requirement for the developmental neurotoxicity study. HIARC concluded that the following studies are required to complete the database for imazalil due to concern for the neurobehavioral effects reported in the published literature (Tanaka, 1995): acute neurotoxicity study in rats; subchronic neurotoxicity study in rats; and developmental neurotoxicity study in rats.

2. Determination of Susceptibility

The data submitted to the Agency, as well as those from the published literature do not demonstrate increased sensitivity of rats, mice, or rabbits to *in utero* exposure to Imazalil. In the prenatal developmental toxicity studies, the developmental effects in fetuses occurred at or above doses that caused maternal toxicity.

However, qualitative evidence of increased susceptibility was found following pre-/postnatal exposure to imazalil in the 2-generation reproduction study in rats. In this study, the offspring toxicity (pup mortality from birth to day 4) was seen in the presence of minimal maternal toxicity (decreases in body weight/body weight gain and increased liver vacuolation in males) at the same dose.

3. Published Literature

Tanaka, T. 1995. *Reproductive and Neurobehavioral effects of Imazalil Administered to Mice*. Toxicology 9 (3): 281-288. The results of this study (summarized below) suggest that neurobehavioral effects can occur in mice exposed prenatally to imazalil in their diet.

II. EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

1. Dietary (Food) Exposure Considerations
(*Correspondence:* D. Hrdy to B. Tarplee dated Sept. 13, 1999)

Tolerances are established for combined residues of the fungicide imazalil and its alcohol metabolite in or on several foods considered to be highly consumed by infants and children including: bananas, barley, citrus, cottonseed, and wheat; and milk and meat. Tolerance levels for these commodities range from 0.01 - 10 ppm (40 CFR 180.413). Codex MRLs for residues of imazalil in/on plant commodities are currently defined in terms of imazalil *per se*, and as such are not compatible with U.S. tolerances.

Residues of imazalil are systemic and, if present, will not be removed by routine preparation (e.g., washing, peeling, etc.). Residues are expected to transfer to meat and milk, for which tolerances are established.

Data sources for imazalil include residue data from field trial studies and monitoring data from the USDA Pesticide Data Program. Information on percent crop treated (%CT) has also been requested from the Biological and Economic Analysis Division (BEAD).

The HED Dietary Exposure Evaluation Model (DEEM) is used to assess the risk from acute and chronic dietary exposure to imazalil residues in food. At the time of this meeting, these analyses were not complete however, it is expected that these analyses will be highly refined using ARs from field trial and monitoring data and %CT information as it is available. These refinements would result in a more realistic depiction of acute and chronic dietary food exposure resulting from the use of imazalil.

2. Dietary (Drinking Water) Exposure Considerations
(*Correspondence:* L. Liu to B. Tarplee dated Sept. 13, 1999)

The environmental fate database for imazalil is adequate for the characterization of drinking water exposure. Based on these data, imazalil is unlikely to contaminate surface and ground waters since this chemical is considered to be persistent but immobile.

No water monitoring data are available for imazalil, therefore Tier I drinking water Estimated Environmental Concentrations (EECs) were estimated using the GENEEC (GENeric Expected Environmental Concentration model) model for surface water and SCI-GROW (Screening Concentration In Ground Water) for ground water based on the seed treatment use for wheat and barley. These models are considered to be screening tools which tend to overestimate the concentrations expected in the environment.

3. Residential Exposure Considerations
(*Correspondence:* S. Tadayon to B. Tarplee dated Sept. 1, 1999)

There are currently no recreational, residential, or other public (non-occupational) uses registered for imazalil.

3

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. FQPA Safety Factor Recommendation

The Committee recommended that the FQPA safety factor for protection of infants and children (as required by FQPA) should be retained at 10x when assessing chronic dietary exposure and reduced to 3x for when assessing acute dietary exposure to this pesticide.

2. Rationale for Requiring the FQPA Safety Factor

The FQPA SFC concluded that the FQPA safety factor is required because:

- the toxicology database for imazalil is incomplete (acute, subchronic, and developmental neurotoxicity studies are required);
- there is qualitative evidence of increased susceptibility following pre-/postnatal exposure to imazalil in the 2-generation reproduction study in rats (developmental toxicity was seen in the presence of minimal maternal toxicity at the same dose); and
- there is concern for neurobehavioral effects in offspring following prenatal exposure to imazalil which were reported in a published literature study conducted in mice (Tanaka 1995).

3. Application of the Safety Factor - Population Subgroups / Risk Assessment Scenarios

When assessing **Acute Dietary Exposure,** the safety factor can be **Reduced to 3x** for **All Population Subgroups** since there are data gaps for the acute, subchronic, and developmental neurotoxicity studies. (The increased susceptibility seen in offspring after repeated oral exposures in the 2-generation reproduction study has no bearing on acute exposure scenarios.)

When assessing the **Chronic Dietary Exposure,** the safety factor should be **Retained at 10x** for **All Population Subgroups** since there is concern for increased susceptibility of the young demonstrated after repeated oral exposures in the 2-generation reproduction study (which is designed to assess the effects of the pesticide on *male and female* reproductive processes, from egg and sperm production and mating through pregnancy, birth, nursing, growth and development, and maturation); and since there are data gaps in the toxicology database for the acute, subchronic, and developmental neurotoxicity studies in rats.

FQPA SAFETY FACTOR COMMITTEE MEETING

20SEPT1999

IMAZALIL

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