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

014552

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

April 30, 2001

MEMORANDUM

SUBJECT: *MESOTRIONE*: 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: Sarah Levy, Risk Assessor
Registration Action Branch 1
Health Effects Division (7509C)

PC Code: 122990

The Health Effects Division (HED) FQPA Safety Factor Committee met on April 16, 2001 to evaluate the hazard and exposure data for mesotrione and recommended that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) be retained at 10x in assessing the risk posed by this chemical.

1

I. HAZARD ASSESSMENT

(*Correspondence:* D. Nixon to B. Tarplee dated 04/04/01)

1. Adequacy of Toxicity Database

The toxicology data base for mesotrione is not complete since the HIARC recommended that a developmental neurotoxicity study in mice be submitted to better assess the effects of tyrosinemia on the developing nervous system. Acceptable studies in the mesotrione data base include: prenatal developmental studies in rats and mice; multi-generation reproduction studies in rats and mice; and acute and subchronic neurotoxicity studies in rats. The prenatal developmental study in rabbits was determined to be unacceptable. The HIARC determined that another rabbit study was not needed since an increased susceptibility of fetuses *in utero* has been demonstrated and a new study would not likely provide additional information for FQPA and/or hazard identification.

2. Determination of Susceptibility

There is quantitative evidence of increased susceptibility demonstrated in the oral prenatal developmental toxicity studies in rats, mice, and rabbits. Delayed ossification was seen in the fetuses at doses below those at which maternal toxic effects were noted. Maternal toxic effects in the rat were decreased body weight gain during treatment and decreased food consumption and in the rabbit, abortions and GI effects. No maternal toxic effects were noted in the mouse.

There is quantitative evidence of increased susceptibility demonstrated in the multi-generation reproduction study in mice. The young exhibited significant tyrosinemia and ocular discharge at doses below those at which parental toxic effects were noted. The parental effects were tyrosinemia and increased kidney weights.

Quantitative evidence of increased susceptibility was not demonstrated in the multi-generation reproduction study in rats since no NOAEL was established for parental or offspring systemic toxicity, but there is evidence of a qualitative increase in susceptibility since tyrosinemia observed in the young was much more severe than that observed in the adults (HED Doc. No. 014536).

II. EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

1. Dietary (Food) Exposure Considerations

Mesotrione is proposed for use on all varieties of field corn, including production seed corn, and silage corn; use is prohibited on sweet corn and popcorn. The HED Metabolism Assessment Review Committee (MARC) concluded that for the tolerance expression and risk assessment purposes, the residue of concern in/on field corn is

mesotrione *per se*. There is no likelihood of transfer of residues to meat and/or milk. The ruminant and poultry metabolism data support a Section 180.6(a)(3). There are no Codex MRLs for mesotrione.

The petitioner submitted one field trial study with this petition. There are no monitoring data or percent crop treated information available for mesotrione.

The HED Dietary Exposure Evaluation Model (DEEM) is used to assess the risk from acute and chronic dietary exposure to mesotrione residues in food. It is expected that these analyses will be conducted using tolerance level residues and 100% crop treated (unrefined).

The Committee recognizes that further refinement to the dietary food exposure analyses may be required as the risk assessment is developed. Therefore, provided the final dietary food exposure assessment does not underestimate the potential risk for infants and children, the safety factor recommendations of this Committee stand.

2. Dietary (Drinking Water) Exposure Considerations
(*Memorandum:* A. Clem to B. Tarplee dated 04/09/01)

The environmental fate database for mesotrione is adequate for characterization of drinking water exposure. These data indicate that the parent compound has high potential for leaching and runoff, however is relatively short-lived. The HED MARC concluded that for risk assessment purposes, the residue of concern in drinking water is mesotrione *per se*.

Although the registrant has submitted two interim reports on a prospective groundwater monitoring (PGM) study at a site in Michigan, there are currently no available monitoring data for mesotrione. Drinking water screening concentrations for humans potentially exposed to mesotrione in surface water are estimated from the GENEEC tier 1 environmental screening model (Version 1.2, 5/3/95). Ground water screening concentrations are estimated from the SCI-GROW Regression Model (Version 1.0, 11/12/97).

The Committee recognizes that further refinement to the dietary water exposure analyses may be required as the risk assessment is developed. Therefore, provided the final dietary water exposure assessment does not underestimate the potential risk for infants and children and is inclusive of all degradates of toxicological concern, the safety factor recommendations of this Committee stand.

3. Residential Exposure Considerations
(*Correspondence:* D. Nixon to B. Tarplee dated 04/04/01)

Mesotrione currently has no registered or proposed residential uses. Callisto™, (containing 40% ai), will be used for pre- and post-emergence selective contact and

3

residual control of broadleaf weeds in all varieties of field corn, including production seed corn, and silage corn.

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 for mesotrione.

2. Rationale for Retaining the FQPA Safety Factor

The FQPA SFC concluded that the FQPA safety factor be **retained** at 10x because:

- there is quantitative evidence of increased susceptibility of the young exposed to mesotrione in the prenatal developmental toxicity studies in mice, rats, and rabbits and in the multigeneration reproduction study in mice;
- there is qualitative evidence of increased susceptibility of the young exposed to mesotrione in the multigeneration reproduction study in rats; and
- a developmental neurotoxicity study is required to assess the effects of tyrosinemia on the developing nervous system exposed to mesotrione.

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

The Committee recommended that a safety factor of **10x** should be applied to **All Population Subgroups for All Exposure Durations** since there is evidence of increased susceptibility following pre- and postnatal exposure in three species and a developmental neurotoxicity study is required.

4/

FQPA SAFETY FACTOR COMMITTEE MEETING

APRIL 16, 2001
MESOTRIONE

Name	Division/Branch
	HED
Debbie McCall	RD
Jonathan Becker	BEAD
Dennis Edwards	AD
Sarah Levy	HED/RAB1
Jeffrey Herndon	HED/RAB1
Dana Vogel	HED/RAB1
William Hazel	HED/RAB1
Jim Stone	RD
ALEX CLEM	EFED/ERB3
David Nixon	HED/RAB1
	EFED
Ray Kent	HED/nnB4
Jon Fleuchaus	OGC
Susan Makris	HED/TOX
Jess Rowland	HED/SIMB
	HED/SIMB