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SCIENTIFIC DATA REVIEWS
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR NO. 0050587

March 21, 2002

MEMORANDUM

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

FROM: Carol Christensen, Acting Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

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

TO: Jennifer Tyler, Risk Assessor
Registration Action Branch 1
Health Effects Division (7509C)

PC Code: 128879

The Health Effects Division (HED) FQPA Safety Factor Committee (SFC) met on March 4, 2002 to evaluate the hazard and exposure data for triflumizole and determined, based upon reliable data, that use of a 3X additional safety factor will protect the safety of infants and children when assessing the risks posed by this pesticide.

I. HAZARD ASSESSMENT

(*Correspondence:* D. Nixon to C. Christensen dated February 28, 2002)

A. Adequacy of the Toxicology Database

The toxicology data base for triflumizole is not complete to assess increased susceptibility to infants and children. Acceptable studies include: 1) developmental studies in rats and rabbits and 2) multi-generation studies in rats. The Hazard Identification Assessment and Review Committee (HIARC) has determined that data gaps exist and that acute and subchronic neurotoxicity studies be required in order to better characterize the neurological effects seen in the acute oral and inhalation and rat chronic studies. The decision to request a DNT study is reserved pending the submission and review of these studies. The toxicology data base was reviewed by the Hazard Science Assessment Review Committee (HIARC) on February 7, 2002.

B. Determination of Susceptibility

There is qualitative evidence of increased susceptibility demonstrated in the oral prenatal developmental toxicity studies in rats. Developmental toxicity resulted in fetal death as compared to maternal toxicity which included decreases in body weight gain and food consumption and increases in placental, spleen and liver weights at the same dosages.

No quantitative or qualitative evidence of increased susceptibility was demonstrated in the prenatal developmental toxicity studies in rabbits or the multi-generation reproduction studies in rats. In the rabbit developmental studies, 24-hour fetal survival was decreased at the highest dose tested. This endpoint is not a recommended guideline parameter and is generally believed to have limited value in the assessment of development toxicity; rather, it is more an indicator of fetal endurance in the absence of critical maternal care, following removal from the uterus. The HIARC did not consider this effect to be a measurement of treatment-related effects on fetal viability and, thus, did not consider it to be relevant to the assessment of fetal susceptibility. There was no evidence of quantitative or qualitative susceptibility in the 2-generation reproduction study in rats. In that study, increased gestation length was observed at the study LOAEL. In rats, this alteration in normal reproductive function can result in equally adverse consequences (*i.e.*, mortality) in both dams and offspring.

C. Degree of Concern and Residual Uncertainties

Although there was evidence of qualitative susceptibility following *in utero* exposures to rats, there is no residual uncertainty because: 1) the fetal deaths observed in the prenatal developmental toxicity study in rats occurred in the presence of maternal toxicity; 2) these effects are seen in only one species; 3) a well characterized dose-response relationship was clearly demonstrated in the prenatal developmental toxicity studies conducted in rats and rabbits, and in the two-generation reproduction study in rats; 4) a clearly defined NOAEL/LOAEL was established for maternal and developmental toxicities in these three studies; 5) the developmental NOAEL and endpoint from the prenatal developmental toxicity study in rats was selected for establishing the acute Reference Dose (RfD) for dietary risk assessment of females 13-50 and therefore would be protective of the effects of concern for this population subgroup; and 6) a database uncertainty factor of 3x for lack of acute and subchronic neurotoxicity studies is applied for acute and chronic dietary risk assessments.

The acute and subchronic neurotoxicity studies were identified as data gaps based on the evidence of clinical signs of neurotoxicity seen in the acute oral (mice and rats) and inhalation (rat) studies and inhibition of plasma cholinesterase activity at the highest dose tested in the chronic rat study. An uncertainty factor of 3x (as opposed to a higher value) was deemed to be adequate by the FQPA SFC because: 1) in the acute studies, clinical signs were seen at very high doses; these signs resolved within 24 hours and no treatment-related effects were seen in the surviving animals; 2) in the chronic study, cholinesterase inhibition was seen during the first year, but not in a consistent manner; while plasma inhibition was seen in both sexes, erythrocyte was inhibited in males but not in females at the highest dose tested, no inhibition of brain cholinesterase activity was seen in either sex at any dose level, 3) there was no evidence of neurotoxicity in the subchronic studies in mice or rats; 4) there was no evidence of neuropathology in the database; and 5) the doses used in risk assessments are significantly lower than the doses that induced the clinical signs following acute exposure or cholinesterase inhibition following repeated exposures. (Note: The HIARC agreed with the FQPA SFC assignment of a database uncertainty factor of 3X to be used in the derivation of the RfD.)

II. EXPOSURE ASSESSMENT

A. Dietary (Food) Exposure Considerations
(*Correspondence:* J. Tyler to C. Christensen dated February 28, 2002)

Triflumizole is a fungicide used on many crops consumed by infants and children including apples, pears, and grapes. It is likely that quantifiable residues will be found in

food. Multiple foliar applications can be made at rates ranging from 0.125 to 0.5 lb ai/A/application. The proposed labels do not indicate the maximum number of applications per season, but specifies maximum rates ranging from 1.0 to 3.0 lb ai/A/season. It may be applied at 7-21 day intervals. The PHI's range from 0 to 120 days.

Permanent tolerances are established under 40 CFR §180.476(a) for the combined residues of triflumizole and its metabolites containing the 4-chloro-2-trifluoromethylaniline moiety, calculated as parent compound, in/on apples, pears, and grapes. In addition, permanent tolerances for livestock commodities have been established under 40 CFR §180.476(b) for the combined residues of triflumizole, the metabolite 4-chloro-2-hydroxy-6-trifluoromethylaniline sulfate, and other metabolites containing the 4-chloro-2-trifluoromethylaniline moiety, in/on milk; eggs; meat, fat, and meat byproducts (mbyp) of cattle, goats, hogs, horses, and sheep; and in/on meat, and mbyp of poultry. There are currently no Codex MRL's established for triflumizole residues in/on crop commodities.

The results of the submitted confined and field rotational crop studies indicate that residues of triflumizole are systemic. Percent of crop treated information has not been requested for triflumizole. Triflumizole is registered for use on apples, grapes, and pears, and is being proposed for use in cherries, cucurbits, strawberries and hazelnuts. In addition, there are tolerances for residues on meat, milk, poultry and egg commodities. A tier 1, acute and chronic dietary exposures assessments will be performed using tolerance level residues and assuming 100% crop treated for all registered and proposed uses. Significant contributors to the diet of infants and children include milk as well as apple and grape commodities (whole fruit, juice, and juice concentrates).

B. Dietary (Drinking Water) Exposure Considerations
(*Correspondence:* S. Ramasamy to C. Christensen dated February 28, 2002)

The environmental fate data for triflumizole is adequate to characterize drinking water exposure. Based on available data, triflumizole degradation appears to be controlled mainly by photolysis, and to a lesser degree, by hydrolysis in acidic and alkaline aquatic conditions and possibly by aerobic metabolism in soil. Overall, the fate studies suggest that triflumizole is unlikely to be persistent and has moderate mobility characteristics. The fate data on degradates are not available except for mobility study for FD-1-1, the degradate found in hydrolysis and soil photolysis, which identified that FD-1-1 is more mobile than the parent compound (Koc: 33.6-961.2). The residues of concern in the drinking water exposure assessment are triflumizole and all metabolites containing the 4-chloro-2-trifluoromethylaniline moiety.

The drinking water exposure assessment for triflumizole was based on Tier I modeling. The Tier I model, FIRST (version 1.0) was used to estimate drinking water concentrations of triflumizole in surface water. The index reservoir concentrations for the proposed use of triflumizole assessed use on cherries at the maximum application rate of 0.5 lb with 6 days intervals and 6 applications per season. Tier I modeling (SCIGROW, version 1.0) for triflumizole application assumed use on cherries as well. Currently, no monitoring data from surface or ground water are available for estimating triflumizole concentrations in drinking water.

Triflumizole is a fungicide and the formulation product, Procure 50 WS is proposed for the treatment of powdery mildew, blossom blight, fruit rot and leaf spot in cherries and powdery mildews on strawberries and cucurbits. Terraguard 50W is proposed for the treatment of foliar diseases, such as leaf spot, powdery mildew, rust, and scab on ornamental plants. Terraguard LS is a new formulation product proposed for use as foliar spray to all landscape grown ornamental trees, shrubs and vines, a large variety of grasses and broadleaved weeds. The potential for population exposure to triflumizole residues would mainly be in areas where crops are treated with this fungicide. Exposure from aerial applications is expected to be higher than ground applications.

C. Residential Exposure Considerations
(*Correspondence:* M. Dow to C. Christensen dated February 28, 2002)

Triflumizole is registered for use on residential trees, shrubs and vines. There are no residential lawn or turf uses. It is HED's judgement, as expressed in the Exposure SAC policy that such uses result in no greater than negligible exposure to infants and children. Therefore, post-application exposure assessment is not necessary.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

A. FQPA Safety Factor Recommendation

For the reasons set forth below, the FQPA SFC recommends that OPP depart from the default 10X additional safety factor and instead use a different additional safety factor of 3X. This recommendation is based on reliable data supporting the findings set forth below.

1. Traditional Additional Safety Factor Addressing Data Deficiencies

Based on the HIARC recommendation, the FQPA SFC recommends use of a 3X additional safety factor to address the data deficiency for acute and sub-chronic neurotoxicity studies. The rationale as to why reliable data support the safety of using a 3X to address this data deficiency is discussed above in § I.3.

2. Special FQPA Safety Factor

Taking into account the HIARC recommendation regarding the data deficiency, the FQPA SFC recommends that no Special FQPA Safety Factor is necessary to protect the safety of infants and children in assessing triflumizole exposure and risks.

3. Rationale and Findings Regarding Recommendation on Special FQPA Safety Factor

a) The Committee concluded that the no Special FQPA safety factor was needed because:

i. There was no quantitative or qualitative evidence of increased susceptibility in the rabbit fetuses following *in utero* exposure or the rat following pre- and post-natal exposure,
ii. There was evidence of qualitative susceptibility in the developmental rat study, however, as discussed in Section I. 3, there are no residual uncertainties, and the use of the developmental NOAEL and the endpoint for the acute RfD for females 13-50 would would be protective of the pre-natal toxicity following an acute dietary exposure.
iii. The toxicological database is incomplete, however an additional database uncertainty factor of 3x is applied for acute and chronic dietary risk assessments to account for this uncertainty, and
iv. In the exposure database, there are no residual uncertainties identified. The dietary food and drinking water exposure assessments incorporates conservative (Tier I) assumptions like 100 percent of the crop treated, and there are no residential exposures anticipated with the use of this chemical.

b. Application of the FQPA Safety Factor (Population Subgroups / Risk Assessment Scenarios)

The FQPA safety factor recommendation is for a 3X traditional safety factor to address data deficiencies and no additional Special FQPA safety factor. The 3x traditional safety factor should be applied to derivation of the acute and chronic RfD. No other FQPA safety factor would be appropriate for triflumizole.

c. Summary of FQPA Safety Factors

Summary of FQPA Safety Factors for Triflumizole				
	LOAEL to NOAEL (UF_L)	Subchronic to Chronic (UF_S)	**Incomplete Database (UF_{DB})**	Special FQPA Safety Factor (Hazard and Exposure)
Magnitude of Factor	1x	1x	**3x**	1x
Rationale for the Factor	NOAELs were used.	Chronic data available	**Lack of acute and sub-chronic neurotoxicity studies**	No residual concerns regarding pre- or post-natal toxicity or completeness of the toxicity or exposure database
Endpoints to which the Factor is Applied	Not Applicable	Not Applicable	**Acute and chronic dietary**	Not Applicable

FQPA SAFETY FACTOR COMMITTEE MEETING

March 4th, 2002

TRIFLUMIZOLE

Name	Division/Branch
Ed Zager	HED
Jess Rowland	HED/SMS
Susan Makris	HED/TOX
Jennifer K. Tyler	HED/RAB1
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