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MEMORANDUM

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

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

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

TO: Pamela Hurley, Toxicologist
Registration Action Branch II
Health Effects Division (7509C)

PC Code: 099050

The Health Effects Division (HED) FQPA Safety Factor Committee met on November 26, 2001 to evaluate the hazard and exposure data for acetamiprid and recommended that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) be reduced to 3x in assessing the risk posed by this chemical.

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I. HAZARD ASSESSMENT

(*Correspondence:* P. Hurley to C. Christensen dated November 14, 2001)

1. Adequacy of Toxicity Database

The toxicological data base is adequate for FQPA consideration. The following acceptable studies are available: acute and subchronic neurotoxicity studies, developmental toxicity studies in rats & rabbits and a two-generation reproduction study.

2. Determination of Susceptibility

There is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure in the developmental studies. In the rat, an increase in the incidence of shortening of the 13th rib was observed in fetuses at the same dose as the dams, which exhibited reduced mean body weight, body weight gain and food consumption and increased liver weights. No developmental toxicity was observed in the rabbit at dose levels that induced effects in the does: body weight loss and decreased food consumption.

In the multi-generation reproduction study, qualitative evidence of increased susceptibility of rat pups is observed. While the toxic effects in parental animals were based upon a decrease in mean body weight, body weight gain and food consumption, significant reductions pup weights in both generations, reductions in litter size, and viability and weaning indices among F_2 offspring as well as significant delays in the age to attain vaginal opening and preputial separation were observed in the offspring. The offspring effects are considered to be more severe than the parental effects and thus provides evidence for a qualitative increase in susceptibility.

3. Requirement of a Developmental Neurotoxicity Study

A developmental neurotoxicity study is required due to a structure-activity relationship to other known neurotoxicants and due to evidence of neurotoxicity (decreased locomotor activity) in the acute mammalian neurotoxicity study.

II. EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

1. Dietary (Food) Exposure Considerations

(*Correspondence:* M. Doherty to C. Christensen dated November 14, 2001)

Rhône-Poulenc Ag Company (now Aventis Cropscience) has petitioned the Agency to register the new chloronicotinyl insecticide acetamiprid {N1-[(6-chloro-3-pyridyl)methyl]-N2-cyano-N1-methylacetamidine} on cotton, leafy

vegetables, cole vegetables, fruiting vegetables, citrus, pome fruits, grapes, and canola and mustard seed. The insecticide acetamiprid is formulated as a wettable powder, ready-to-use solution, and a water soluble packet. It may be apply as a seed treatment, foliar broadcast, or a direct foliar spray for the control of insects. Application rates range from 0.1-0.6 lb a.i./Acre. Acetamiprid may be applies 1-5 times per season with PHI's ranging from 7-28 days. This is a new chemical and no other registrations exist in Canada or Mexico.

On November 13, 2001, the HED Metabolism Assessment Review Committee met and concluded that the residue of concern in plants is acetamiprid *per se* and the residues of concern in livestock are acetamiprid and the metabolite IM-2-1.

There are no monitoring data or percent crop treated information available for this chemical. Aventis has submitted adequate field trials for cotton, leafy vegetables (lettuce, spinach, celery), pome fruits (apple, pear), canola seed, mustard seed, Brassica leafy vegetables (cabbage, broccoli, mustard greens), grapes, citrus (orange, grapefruit, lemon), and fruiting vegetables (peppers, eggplant, tomato). Adequate cattle and poultry feeding studies have also been submitted.

Field trials resulted in finite residues for all commodities except canola and mustard seed. Residue values ranged from approximately 0.06 ppm (undelinted cotton seed) to 20 ppm (cotton gin byproducts). Residues of acetamiprid in mustard and canola seed were less than the LOQ of 0.01 ppm. Secondary residues of concern are likely to occur in ruminants. Appropriate ruminant tolerances range from 0.1 ppm for milk to 0.3 ppm for tissues. There are no secondary residues expected in poultry (category 3 of 40 CFR 180.6(a)).

The HED Dietary Exposure Evaluation Model (DEEM) is used to assess the risk from acute and chronic dietary exposure to acetamiprid residues in food. The DEEM analyses are expected to be unrefined (Tier 1) using tolerance level residues assuming 100% crop treated which results in an overestimation of dietary exposure.

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 includes the metabolic residue of concern and does not underestimate the potential risk for infants and children, the safety factor recommendations of this Committee stand.

2. Dietary (Drinking Water) Exposure Considerations
(*Correspondence:* C. Sutton to C. Christensen November 20, 2001)

The environmental fate database is complete for FQPA consideration and risk assessment. Acetamiprid is a mobile, rapidly biodegradable compound in most soils. Acetamiprid is expected to be moderately to highly mobile in most soils and aquatic sediments. The primary degradation pathway is aerobic soil metabolism, with three major degradates (IM-1-2, IM-1-4, and IC-0) formed in most of the systems studied. An additional major degradate (IM-1-5) was observed in only one of the aerobic soil systems studied. Acetamiprid is stable to hydrolysis at environmental temperatures, and photodegrades relatively slowly in water. A determination of photostability on soil was not conclusive, but the rapid aerobic metabolism of the compound in soil renders it likely that photodegradation on soil is not a significant fate process for the degradation of the compound in the environment. Acetamiprid is metabolized moderately rapidly in aerobic aquatic systems, but is only slowly metabolized in anaerobic aquatic systems. For drinking water, the MARC concluded that acetamiprid *per se* is the residue of concern for risk assessment purposes.

Monitoring data were not available for this chemical. Modeling was conducted to determine EECs using the models SCI-GROW (Screening Concentrations in Ground Water) and FIRST (FQPA Index Reservoir Screening Tool). The scenario utilized for modeling was the application of acetamiprid, formulated as a wettable powder (70% active ingredient; Assail™ brand 70WP), to pome fruits by airblast orchard spray at four applications of 0.15 lb a.i./A, for a total seasonal application of 0.60 lb a.i./A.

The FQPA SF 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, the safety factor recommendations of this Committee stand.

3. Residential Exposure Considerations
(*Correspondence:* M. Collantes to C. Christensen dated November 15, 2001)

Pristine ™ contains 0.006% of the active ingredient, acetamiprid, formulated as a 32 ounce ready-to-use hand held aerosol trigger spray bottle. Acetamiprid has non-occupational residential uses (ornamentals, flowers, and garden vegetables, citrus and pome fruit trees), around the home where children and infants could be exposed. According to the label, Pristine is sprayed on the top and bottom of leaf surfaces until wet. Applications may be repeated at 7-day intervals during a 4 month period (April - July). Depending on the crop site, four to five applications may be made per season. The application rate has been calculated as 0.000125 lb ai /gallon.

PHED data was used to estimate handler unit exposure for aerosol application. This PHED scenario was the only aerosol scenario which would reflect a similar exposure.

The aerosol scenario actually represents insecticide crack and crevice treatment; however, data confidence was high. A carbaryl-specific residential handler study, (*Carbaryl Mixer/loader/Applicator Exposure Study during application of RP-2 Liquid (21%) Sevin ® Ready to Use Insect Spray or Sevin ® 10 Dust to Home Garden Vegetables. EPA MRID 444598-01*) which quantified exposure applications to gardens was used to determine handler unit exposures for a ready-to-use trigger sprayer. The carbaryl study was submitted in support of the registration of acetamiprid and was used in the carbaryl RED. The HED Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments: *Section 3.1 Handler Inhalation and Dermal Potential Dose from Pesticides Applied to the Garden* was used to assess dermal and inhalation handler MOEs as well as post-application exposure to infants and toddlers. A dermal absorption factor of 30% is used in the assessment.

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 reduced to 3x for the assessment of acetamiprid.

2. Rationale for Reducing the FQPA Safety Factor

The FQPA Committee determined that the safety factor is necessary when assessing the risk posed by acetamiprid because:

1. There is qualitative evidence of increased susceptibility following pre-/postnatal exposure to acetamiprid in the 2-generation reproduction study in rats.

However, the Committee concluded that the safety factor could be reduced to **3x** for acetamidprid because:

1. The toxicology database is complete;
2. There is no quantitative or qualitative evidence of increased susceptibility following *in utero* exposure to rats and rabbits;
3. The dietary (food and water) and residential exposure assessments will not underestimate the potential exposures for infants, children, and/or women of childbearing age; and,
4. The requirement of a developmental neurotoxicity study is **not** based on criteria reflecting special concern for the developing fetuses or young which are generally used for requiring a DNT study - *and* a safety factor (*e.g.*, neuropathy in adult animals; CNS malformations following prenatal exposure; brain weight or sexual maturation changes in offspring; and/or functional changes in offspring) - and, therefore, does not warrent an FQPA safety factor.

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

The safety factor is required for **All Population Subgroups** when assessing **Chronic Dietary Exposures** as **well as when assessing residential exposure by all exposure durations - short-term, intermediate-term, and long-term** to address the concern for the effects seen following pre-/postnatal exposure to acetamiprid in the 2-generation reproduction study in rats.