

10 field trials to support the requested tolerance of 0.1 ppm.

ii. *Leaf petiole subgroup 4B.*

Interregional Research Project Number 4 received a request from Florida, Michigan, Oregon, California, and Ohio, for the use of trifloxystrobin on celery. Interregional Research Project Number 4 performed nine field trials to support the requested tolerance of 2.0 ppm.

B. Toxicological Profile

1. *Acute toxicity.* Studies conducted with the technical material of trifloxystrobin:

- *Rat.* Acute oral toxicity study with a lethal dose (LD)₅₀ >5,000 milligrams/kilogram (mg/kg).
- *Mouse.* Acute oral toxicity study with a LD₅₀ >5,000 mg/kg.
- *Rabbit.* Acute dermal toxicity study with a LD₅₀ >2,000 mg/kg.
- *Rat.* Acute dermal toxicity study with a LD₅₀ >2,000 mg/kg.
- *Rat.* Acute inhalation toxicity study with a lethal concentration (LC)₅₀ >4.65 milligrams/liter (mg/L).
- *Rabbit.* Eye irritation study showing slight irritation (toxicity category III).
- *Rabbit.* Dermal irritation study showing slight irritation (toxicity category IV).
- *Guinea pig.* Dermal sensitization study with the Buehler's method showing negative findings.
- *Guinea pig.* Dermal sensitization study with the maximization method showing some positive findings.

2. *Genotoxicity.* No genotoxicity activity is expected of trifloxystrobin under *in vivo* or physiological conditions. The compound has been tested for its potential to induce gene mutation and chromosomal changes in five different test systems. The only positive finding was seen in the *in vitro* test system (chinese hamster V79 cells) as a slight increase in mutant frequency at a very narrow range (250 – 278 micrograms/milliliter (μg/ml) of cytologic and precipitating concentrations (compound solubility in water was reported to be 0.61 μg/ml; precipitate was visually noted in culture medium at 150 μg/ml). The chemical was found to be non-mutagenic in the *in vivo* system or all other *in vitro* systems. Consequently, the limited gene mutation activity in the V79 cell line is considered a nonspecific effect under non-physiological *in vitro* conditions and not indicative of a real mutagenic hazard.

3. *Reproductive and developmental toxicity.* FFDCA section 408 provides that EPA may apply an additional safety factor for infants and children in the case of threshold effects to account for

prenatal and postnatal toxicity and the completeness of the data base. Based on the current toxicological data requirements, the data base on trifloxystrobin relative to prenatal and postnatal effects for children is complete.

In assessing the potential for additional sensitivity of infants and children to residues of trifloxystrobin, data were considered from teratogenicity studies in the rat, rabbit, and a 2-generation reproduction studies in the rat. The teratogenicity studies are designed to evaluate adverse effects on the developing embryo as a result of chemical exposure during the period of organogenesis. Reproduction studies provide information on effects from chemical exposure on the reproductive capability of mating animals and systemic and developmental toxicity from *in utero* exposure.

In the rat teratology study, reductions in body weight gain and food consumption were observed in the dam at ≥100 mg/kg. No teratogenic effects or any other effects were seen on pregnancy or fetal parameters except for the increased incidence of enlarged thymus, which is a type of variation, at 1,000 mg/kg. The developmental no observed adverse effect level (NOAEL) was 100 mg/kg.

In the rabbit teratology study, body weight loss and dramatically reduced food consumption were observed in the dam at ≥250 mg/kg. No teratogenic effects or any other effects were seen on pregnancy or fetal parameters except for the increase in skeletal anomaly of fused sternebrae–3 and –4 at the top dose level of 500 mg/kg. This finding is regarded as a marginal effect on skeletal development that could have resulted from the 40–65% lower food intake during treatment at this dose level. The developmental NOAEL was 250 mg/kg.

In the 2-generation rat reproduction study, body weight gain and food consumption were decreased at ≥750 ppm, especially in females during lactation. Consequently, the reduced pup weight gain during lactation (≥750 ppm) and the slight delay in eye opening (1,500 ppm) are judged to be a secondary effect of maternal toxicity. No other fetal effects or any reproductive changes were noted. The low developmental NOAEL, 50 ppm (5 mg/kg), seen in this study was probably due to the lack of intermediate dose levels between 50 and 750 ppm. Based on an evaluation of the dose-response relationship for pup weight at 750 ppm and 1,500 ppm, the NOAEL should have been nearly ten-fold higher if such a dose was available.

Based on all these teratology and reproduction studies, the lowest NOAEL for developmental toxicity is 5 mg/kg while the lowest NOAEL in the subchronic and chronic studies is 2.5 mg/kg/day (from the rat chronic study). Therefore, no additional sensitivity for infants and children to trifloxystrobin is suggested by the data base.

4. *Subchronic toxicity.* In subchronic studies, several mortality related changes were reported for the top dose in dogs (500 mg/kg) and rats (800 mg/kg). At these dose levels, excessive toxicity has resulted in body weight loss and mortality with the associated and nonspecific changes in several organs (such as atrophy in the thymus, pancreas, bone marrow, lymph node, and spleen) which are not considered specific target organs for the test compound.

In the dog, specific effects were limited to hepatocellular hypertrophy at ≥150 mg/kg and hyperplasia of the epithelium of the gall bladder at 500 mg/kg. Target organ effects in the rat were noted as hepatocellular hypertrophy (≥200 mg/kg) and the related liver weight increase (≥50 mg/kg). In the mouse, target organ effects included single cell necrosis (≥300 mg/kg) and hypertrophy (1,050 mg/kg) in the liver and extramedullary hematopoiesis (≥300 mg/kg) and hemosiderosis in the spleen (1,050 mg/kg).

In general, definitive target organ toxicity, mostly in the liver, was seen at high feeding levels of over 100 mg/kg for an extended treatment period. At the lowest observed adverse effect level (LOAEL), no serious toxicity was observed other than mostly non-specific effects including a reduction in body weight and food consumption or liver hypertrophy.

5. *Chronic toxicity.* The liver appears to be the major primary target organ based on the chronic studies conducted in mice, rats, and dogs. It was identified as a target organ in both the mouse and the dog studies with trifloxystrobin. However, no liver effect was seen in the chronic rat study which produced the lowest NOAEL of 2.5 mg/kg based on reduced body weight gain and food consumption seen at higher dose levels.

The compound did not cause any treatment-related increase in general tumor incidence, any elevated incidence of rare tumors, or shortened time to the development of palpable or rapidly lethal tumors in the 18-month mouse and the 24-month rat studies. Dosages in both studies were sufficient for identifying a cancer risk. In the absence of carcinogenicity, a reference dose