FILE NAME: company.wpt (7/1/2005) (xml)
Template Number P25

ATTENTION:

All commodity terms must comply with the Food and Feed Commodity Vocabulary database (http://www.epa.gov/pesticides/foodfeed/).

All text in blue font (instructions for preparing the document), should be removed prior to sending the document to the Federal Register Staff. Instructional text and prompts in green font should also be removed.

COMPANY FEDERAL REGISTER DOCUMENT SUBMISSION TEMPLATE (1/1/2005)

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INSTRUCTIONS: **Please utilize this outline in preparing tolerance petition documents. In cases where the outline element does not apply please insert "NA-Remove" and maintain the outline. The comment notes that appear on the left margin represent hidden typesetting codes designed to expedite the processing of the Federal Register document. Please do not remove or alter these comment notes or change the margins, font, or format in your document. Simply replace the instructions that appear in italics and brackets, i.e., "[*insert company name*]," with the information specific to your action.**

TEMPLATE:

[Insert company name]

[Insert petition number]

EPA has received a pesticide petition (**[insert petition number]**) from **[Bayer CropScience]**, **[P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC 27709]** proposing, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180.

Options (pick one)

1. by establishing a tolerance for residues of
~~2. to establish an exemption from the requirement of a tolerance for~~

[trifloxystrobin] in or on the raw agricultural commodity **[grass, forage]** at **[10]** parts per million (ppm) and **[grass, hay]** at **[14.0]** ppm. EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism.* **[The metabolism of trifloxystrobin in plants (cucumbers, apples, wheat, sugar beets and peanuts) is well understood. Identified metabolic pathways are substantially similar in plants and animals (goat, rat and hen). EPA has determined that trifloxystrobin parent and its metabolite CGA-321113 are the residue of concern for tolerance setting purposes.]**

2. *Analytical method.* **[A practical analytical methodology for detecting and measuring levels of trifloxystrobin in or on raw agricultural commodities has been submitted. The limit of detection (LOD) for each analyte of this method is 0.08 ng injected, and the limit of quantitation (LOQ) is 0.02 ppm. The method is based on crop specific cleanup procedures and determination by gas chromatography with nitrogen-phosphorus detection.]**

3. *Magnitude of residues.* **[**A total of five field trials (four harvest and one decline) were conducted to measure the magnitude of the total trifloxystrobin residue in/on grass forage, hay, straw, and seed following four foliar spray applications of FLINT Fungicide at a target rate of 0.125 lb ai/acre/application. In the four harvest trials, forage, hay, straw, and seed samples were collected immediately following the fourth application (0-day pre-harvest interval (PHI)). In a single decline trial, forage, hay, straw, and seed samples were collected at four intervals which began immediately after the fourth application (0-day PHI) and continued at PHIs of 7, 14, and 21 days.

The total trifloxystrobin (trifloxystrobin and trifloxystrobin acid) residue was quantitated in grass forage, hay, straw, and seed by liquid chromatography/mass spectrometrymass spectrometry (lc/ms-ms) using stable -labeled isotopes as internal standards. The limit of quantitation (LOQ) was 0.01 ppm in grass forage, hay, straw, and seed. The highest average field trial (HAFT) total trifloxystrobin residue found in/on forage, hay, straw, and seed harvested at a 0-day PHI was 7.70 ppm, 10.78 ppm, 11.68 ppm, and 16.88 ppm, respectively.**]**

B. Toxicological Profile

1. *Acute toxicity.* **[<u>Studies conducted with the technical material of trifloxystrobin</u>:**

rat acute oral toxicity study with a LD_{50} >5000 mg/kg

mouse acute oral toxicity study with a LD_{50} >5000 mg/kg
rabbit acute dermal toxicity study with a LD_{50} >2000 mg/kg
rat acute dermal toxicity study with a LD_{50} >2000 mg/kg
rat acute inhalation toxicity study with a LC_{50} >4.65 mg/L
rabbit eye irritation study showing slight irritation (Category III)
rabbit dermal irritation study showing slight irritation (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. *Genotoxicty.* **[No genotoxic 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 µg/ml) of cytotoxic 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 pre- and post-natal toxicity and the completeness of the database. Based on the current toxicological data requirements, the database on trifloxystrobin relative to pre- and post-natal 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 and the 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 1000 mg/kg. The developmental NOEL 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 NOEL 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 (1500 ppm) are judged to be a secondary effect of maternal toxicity. No other fetal effects or any reproductive changes were noted. The low developmental NOEL, 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 1500 ppm, the NOEL should have been nearly ten-fold higher if such a dose was available.

Based on all these teratology and reproduction studies, the lowest NOEL for developmental toxicity is 5 mg/kg while the lowest NOEL 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 (1050 mg/kg) in the liver and extramedullary hematopoiesis (≥300 mg/kg) and hemosiderosis in the spleen (1050 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 LOEL, 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 NOEL 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 approach is appropriate for quantitation of human risks.]

6. *Animal metabolism.* **[Trifloxystrobin is moderately absorbed from the gastrointestinal tract of rats and is rapidly distributed. Subsequent to a single oral dose, the half life of elimination is about 2 days and excretion is primarily via bile. Trifloxystrobin is extensively metabolized by the rat into about 35 metabolites, but the primary actions are on the methyl ester (hydrolysis into an acid), the methoxyimino group (O-demethylation), and the methyl side chain (oxidation to a primary alcohol). Metabolism is dose dependent as it was almost complete at low doses but only about 60% complete at high doses.**

In the goat, elimination of orally administered trifloxystrobin is primarily via the feces. The major residues were the parent compound and the acid metabolite (CGA-321113) plus its conjugates. In the hen, trifloxystrobin is found as the major compound in tissues and in the excreta, but hydroxylation of the trifluormethyl-phenyl moiety and other transformations, including methyl ester hydrolysis and demethylation of the methoxyimino group, are also seen. In conclusion, the major pathways of metabolism in the rat, goat, and hen are the same.]

7. *Metabolite toxicology.* **[Metabolism of trifloxystrobin has been well characterized in plants, soil, and animals. In plants and soil, photolytically induced isomerization results in a few minor metabolites not seen in the rat; however, most of the applied materials remained as parent compound as shown in the apple and cucumber studies. All quantitatively major plant and/or soil metabolites were also seen in the rat. The toxicity of the major acid metabolite, CGA-321113 (formed by hydrolysis of the methyl ester), has been evaluated in cultured rat hepatocytes and found to be 20-times less cytotoxic than the parent compound. Additional toxicity studies were conducted for several minor metabolites seen uniquely in plants and/or soil. The studies indicate that these metabolites, including CGA-357261, CGA-373466, and NOA-414412, are not mutagenic to bacteria and are of low acute toxicity (LD_{50} >2000 mg/kg). In conclusion, the metabolism and toxicity profiles support the use of an analytical enforcement method that accounts for parent trifloxystrobin.]**

8. *Endocrine disruption.* **[Trifloxystrobin does not belong to a class of chemicals known for having adverse effects on the endocrine system. Developmental toxicity studies in rats and rabbits and reproduction study in rats gave no indication that trifloxystrobin might have any effects on endocrine function related to development and reproduction. The subchronic and chronic studies also showed no evidence of a long-term effect related to the endocrine system.]**

C. Aggregate Exposure

1. *Dietary exposure.* **[Assessments, using the DEEM FCID Version 2.0, 1994-1996,98 CSFII software, were conducted to evaluate potential risks due to chronic and acute dietary exposure of the U.S. population and selected population subgroups to residues of trifloxystrobin. These analyses cover all registered crops plus the pending uses on barley, oats sweet corn and grasses grown for seed.**

The EPA has established an acute Population Adjusted Dose (aPAD) of 2.5 mg/kg/day for acute dietary risk assessments based on a NOAEL of 250 mg/kg bwt/day from a rabbit developmental toxicity study and an uncertainty factor or 100. For chronic dietary analyses, the EPA established a chronic Population Adjusted Dose (cPAD) of 0.038 based on a NOAEL of 3.8 from a rat reproductive toxicity study and and uncertainty factor of 100.

Results from the acute and chronic dietary exposure analyses described below demonstrate a reasonable certainty that no harm to the overall U.S. population or any population subgroup will result from the use of trifloxystrobin on currently registered uses plus the pending uses on barley, oats, sweet corn, and grasses grown for seed.]

i. *Food.* **[For food, a Tier 1 acute and a Tier 2 chronic dietary exposure assessments were performed. Acute exposure, expressed at the 95th percentile of exposure, was 0.55% of the aPAD for females 13-49 years old (only population subgroup of concern). The chronic exposure was 2.5% cPAD for the total US population and 13.5% cPAD for the most sensitive population, children 1-2 years old.]**

ii. *Drinking water.* **[The DEEM software was also used to calculate acute and chronic drinking water levels of concern (aDWLOC and cDWLOC). The aDWLOC was 74,598 and the cDWLOC was 1,297 for the total US population and 329 for the most sensitive population subgroup, children 1-2 years old. These values are above realistic estimated concentrations of trifloxystrobin and its metabolites in drinking water as published in the *Federal Register* (68 FR 53297). Therefore, there is reasonable certainty that exposure from**

trifloxystrobin will not result in harm to the adult U.S. population, females 13-49, or infants and children.]

2. *Non-dietary exposure.* **[As published in the *Federal Register* (68 FR 53297), the EPA considered chronic, short term and intermediate term risk from residential uses of tebuconazole. The EPA determined that the risk did not exceed the Agency's level of concern.]**

D. Cumulative Effects

[EPA has determined, as published in the *Federal Register* (68 FR 53297), that unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, trifloxystrobin does not appear to produce a toxic metabolite produced by other substances. Therefore EPA has not assumed that trifloxystrobin has a common mechanism of toxicity with other substances.]

E. Safety Determination

1. *U.S. population.* **[Based on the information supplied under Aggregate Exposure describe above, there is reasonable certainty that exposure from trifloxystrobin will not result in harm to the adult U.S. population.]**

2. *Infants and children.* **[Based on the information supplied under Aggregate Exposure describe above, there is reasonable certainty that exposure from trifloxystrobin will not result in harm to infants and children.]**

F. International Tolerances

[No Codex MRLs or MRLs in other countries have been established for trifloxystrobin in or on grasses grown for seed.]