

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:**

**Valent U.S.A. Company**

**5f7016**

EPA has received a pesticide petition (5f7016) from [Valent U.S.A. Company], [1600 Riviera Ave., Walnut Creek, CA 94596-8025] 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

[fluopicolide] in or on the raw agricultural commodity [Grape at 2 parts per million (ppm), Raisin at 6 ppm, Vegetable, leafy, except brassica, group 4 at 20 ppm, Vegetable, fruiting, group 8 at

**0.8 ppm, Vegetable, cucurbit, group 9 at 0.4 ppm, Potato at 0.02 ppm, Sweet potato, roots at 0.02 ppm, Wheat forage at 0.2 ppm, Wheat grain at 0.02 ppm, Wheat hay at 0.5 ppm, and Wheat straw at 0.5ppm.** 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 fate of fluopicolide in plants is clearly understood. Metabolism studies were conducted with grapes, potato, and lettuce. The metabolic profile of fluopicolide was similar in all three crops and demonstrated that fluopicolide is degraded by oxidation and hydrolysis. The primary residue found in all crops, and the only residue of concern, is the parent molecule fluopicolide. ]

**2. Analytical method.** [A practical analytical method utilizing liquid chromatography and mass spectrometry detection is available and has been validated for detecting and measuring levels of fluopicolide in and on crops. The validated limit of quantitation is 0.01 ppm.]

**3. Magnitude of residues.** [Residue data for the use of fluopicolide on the commodities listed within this notice has been submitted.]

#### *B. Toxicological Profile*

**1. Acute toxicity.** [ A battery of acute toxicity studies places technical fluopicolide in toxicity category IV. No evidence of sensitization was observed in guinea pigs. In an acute neurotoxicity study in rats, only statistically lower body temperature was observed 6 hours after dosing at the limit dose of 2000 mg/kg. No other treatment-related changes were noted in the study, and the NOAEL was considered to be 100 mg/kg. ]

**2. Genotoxicity.** [ Fluopicolide has been evaluated for genotoxicity using a battery of tests, including bacterial reverse mutation tests, a mammalian cell gene mutation (HPRT) assay, an *in vivo* mouse micronucleus assay, an *in vitro* chromosome aberration test, and an *in vivo* unscheduled

DNA synthesis test. The weight of evidence from all of these assays shows that fluopicolide is not genotoxic.]

### *3. Reproductive and developmental toxicity. [*

- i. In a developmental toxicity study in rats gavage dosed from gestation days 7 to 20 at levels of 0, 5, 60 or 700 mg/kg/day, evidence of maternal and fetal toxicity was observed at 700 mg/kg/day, the highest dose tested. The maternal and fetal NOAEL was 60 mg/kg/day based on statistically lower body weights in dams and fetuses, and skeletal findings in fetuses that included delayed ossification of some bones and slight increases in the incidence of various rib and thoracic vertebrae anomalies.
- ii. In a developmental toxicity study with rabbits, pregnant animals were given oral doses of 0, 5, 20 or 60 mg/kg/day on gestation days 6 to 28. At the high dose, 15 animals were sacrificed following spontaneous abortions and 3 animals were found dead. The few surviving animals in this group had live fetuses at cesarean sectioning but other than lower fetal weight and crown/rump length, no treatment-related findings were observed upon external, visceral and skeletal examinations of these fetuses. The NOAEL for maternal and fetal toxicity was 20 mg/kg/day.
- iii. In a 2-generation reproductive toxicity study, fluopicolide was administered to rats at dietary levels of 0, 100, 500, or 2000 ppm. The NOAEL was 500 ppm (equivalent to 26 and 33 mg/kg/day for males and females, respectively) for developing offspring and for parental/systemic toxicity. The LOAEL was 2000 ppm based on decreased body weight and organ weight changes in both F0 and F1 adults and F1 and F2 pups. The reproductive NOAEL was 2000 ppm. ]

### *4. Subchronic toxicity. [*

Ninety-day feeding studies were conducted in dogs, mice and rats.

- i. No evidence of toxicity was observed in dogs up to the limit dose of 1000 mg/kg/day. The NOAEL in dogs is 1000 mg/kg/day.
- ii. In 90-day feeding studies in both CD-1 and C57BL/6 mice, liver was the only target organ identified with hepatocellular hypertrophy seen at dietary levels of 320 ppm and higher. The NOAEL in C57BL/6 mice was 200 ppm (equivalent to 37.8 and 52.8 mg/kg/day in males and females, respectively).
- iii. In a 90-day rat study with dietary levels of 100, 1400 and 20,000 ppm, the maximum tolerated dose (MTD) was exceeded at 20,000 ppm based on body weight gain of 30 to 40% below control. The target organs identified in rats were the liver (centrilobular hypertrophy) in both sexes and the kidneys in males (accumulation of hyaline droplets, single cell death at the proximal tubule epithelium, slight foci of basophilic tubules and granular casts) at 1400 ppm and 20000 ppm. The NOAEL was 100 ppm, equivalent to 7.4 and 8.4 mg/kg/day, in males and females, respectively.
- iv. In a subchronic neurotoxicity study, rats were treated with 0, 200, 1400 or 10000 ppm in the diet for 13 weeks. The NOAEL for systemic toxicity is 1400 ppm (107 mg/kg/day in males and 125 mg/kg/day in females) based on findings in the liver and kidney. There were

no neurotoxicity findings. The NOAEL for neurotoxicity is 10,000 ppm (781 mg/kg/day in males and 866 mg/kg/day in females).

iii. In a subchronic dermal toxicity study, male and female rats were treated with fluopicolide at dose levels of 0, 100, 250, 500 and 1000 mg/kg/day. There were no effects at any dose level. The NOAEL of the study is 1000 mg/kg/day.]

#### 5. Chronic toxicity. [

i. Lower body weight gain at the limit dose of 1000 mg/kg/day was the only treatment-related effect noted in a 52-week dog study performed at 70, 300, and 1000 mg/kg/day by gavage. Thus, the NOAEL in dogs was established at 300 mg/kg/day.

ii. Chronic toxicity/carcinogenicity was assessed in rats at dietary levels of 50, 200, 750 and 2500 ppm. The NOAEL was 200 ppm (8.4 mg/kg/day in males and 10.8 mg/kg/day in females) based on microscopic changes in the liver and kidneys similar to those observed in the 90-day rat study. No evidence of carcinogenicity was observed in rats up to 2500 ppm.

iii. The oncogenic potential of fluopicolide was investigated in C57BL/6 mice at dietary levels of 0, 50, 400, or 3200 ppm. Significantly lower body weight gain was seen at 3200 ppm in conjunction with a slight decrease in food consumption. Increased liver weight and centrilobular hepatocellular hypertrophy were observed at 400 and 3200 ppm in both sexes. In addition at 3200 ppm, an increased incidence of hepatocellular adenomas was noted in both sexes, but the incidence of hepatocellular carcinomas was not affected. The NOAEL was 50 ppm (equivalent to 7.9 and 11.5 mg/kg/day in males and females, respectively). Subsequent mechanistic work demonstrated a marked transient hepatocellular proliferation, which returned to control levels after 28 days of treatment. This was accompanied by a clear induction of total cytochrome P-450 and related enzymes.

These results parallel findings with Phenobarbital, which has a well understood threshold-based mechanism of rodent tumor formation commonly known to be of no relevance to humans. ]

#### 6. Animal metabolism. [

The animal metabolism of fluopicolide is well understood. Fluopicolide is rapidly absorbed and excreted when administered to rats and the resulting tissue residues are very low. The metabolic pathway for fluopicolide is similar in rodents, goats and hens. Metabolism in livestock proceeded primarily via hydroxylation and hydrolysis.]

#### 7. Metabolite toxicology. [

Four metabolites (AE C653711, AE C657188, AE C657378, and AE 1344122) were identified as low-level plant and/or soil metabolites of fluopicolide. Several of the metabolites were identified at low levels in the rat following fluopicolide or AE C653711 administration and were therefore covered by the tox studies conducted with the parent molecule. All compounds were tested for acute, subchronic (28-day) and genetic toxicity and AE C653711 and AE C657188 were additionally studied in *in vivo* ADME studies. All were found to be

equally or less toxic than the parent molecule itself. These metabolites are therefore considered not toxicologically relevant to the overall assessment of fluopicolide human health..

]

#### **8. Endocrine disruption.** [

The toxicology database for fluopicolide is current and complete. No special studies to evaluate the potential endocrine effects of fluopicolide have been conducted. However, the studies in this database include evaluation of the potential effects on reproduction and development, and an evaluation of the pathology of the endocrine organs following short- or long-term exposure. These studies revealed no endocrine-related effects.]

### **C. Aggregate Exposure**

**1. Dietary exposure.** [An assessment was conducted to evaluate potential risks due to chronic and acute dietary exposure of the U.S. population subgroups to residues of fluopicolide. This analysis covers all pending crop uses. ]

#### **i. Food.** [

**Acute:** No appropriate toxicological endpoint attributable to a single exposure was identified in the available toxicology studies conducted with fluopicolide. Since no acute toxicological endpoints could be established, the acute aggregate risk is considered to be negligible.

**Chronic:** Chronic assessments were conducted to evaluate potential risks due to chronic dietary exposure to the U.S. population and selected population subgroups to residues of fluopicolide. This analysis was conducted using the Cumulative and Aggregate Risk Evaluation System (CARES) using actual field trial residue and estimated percent crop treated. ]

#### **ii. Drinking water.** [

**Acute:** Since no acute toxicological endpoints could be established, the acute aggregate risk is considered to be negligible.

**Chronic:** A tier II PRZM/EXAMS assessment was conducted to determine the EECs in the standard EPA pond and the EDWCs in the Standard Index Reservoir associated with fluopicolide on crops. The EXPRESS, PRZM/EXAMS shell was used to conduct the modeling. The worst case scenario was used in the drinking water exposure assessment and a refined chronic drinking water exposure risk analysis was conducted using the CARES Water Wizard.

]

*2. Non-dietary exposure.* [There is a potential residential exposure to adults applying , and adults and children entering residential turf areas treated with fluopicolide. Based on the application of fluopicolide to residential turf, conservative estimates of exposure were calculated for both children and adults. All estimates resulted in calculated margins of exposure in excess of 100.]

#### *D. Cumulative Effects*

[Section 408(b)(2)(D)(v) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider “available information” concerning the cumulative effects of a particular pesticide’s residues and “other substances that have a common mechanism of toxicity”. EPA does not have, at this time, available data to determine whether fluopicolide has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, EPA has not assumed that fluopicolide has a common mechanism of toxicity with other substances.]

#### *E. Safety Determination*

##### *1. U.S. population.* [

**Acute:** No appropriate toxicological endpoint attributable to a single exposure was identified in the available toxicology studies conducted with fluopicolide. Since no acute toxicological endpoints could be established, the acute aggregate risk is considered to be negligible.

**Chronic:** The aggregate risk of the US population to fluopicolide was determine and the resultant exposure value was expressed in terms of margin of exposure (MOE), which was calculated by dividing the no observable adverse effect level (NOAEL) by the exposure for each population subgroup. In addition, exposure was also expressed as a percent of the chronic reference dose (%cRfD). The results of the chronic dietary and drinking water exposure and risk analyses presented here, demonstrate that there is a reasonable certainty that no harm will result to the U.S. population or sensitive sub-populations, including infants and children, from chronic dietary exposure resulting from the proposed uses of fluopicolide.]

##### *2. Infants and children.* [

**Acute:** No appropriate toxicological endpoint attributable to a single exposure was identified in the available toxicology studies conducted with fluopicolide. Since no acute toxicological endpoints could be established, the acute aggregate risk is considered to be negligible.

**Chronic:** The results of the chronic dietary and drinking water exposure and risk analysis demonstrate that there is a reasonable certainty that no harm will result to the U.S. sub-populations of infants and children from chronic dietary exposure resulting from the proposed uses of fluopicolide. The percentile of chronic dietary exposure (food) was highest among children 1 to 2 years of age. The percentile of chronic drinking water exposure was highest

among infants "0" years of age. The percentile aggregate chronic exposure from food and water was highest among infants "0" years of age.

The maximum chronic exposure from food and water for each population sub-group was estimated to be less than 1 % of the c-PAD.]

*F. International Tolerances*

[There are no CODEX tolerances for residues of fluopicolide]