

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 180.510 by establishing tolerances for residues of pyriproxyfen, 2-[1-methyl-2-4-phenoxyphenoxy]ethoxypyridine] in or on the following raw agricultural commodities:

1. *PP 2E6416* proposes the establishment of tolerances for atemoya, biriba, cherimoya, custard apple, ilama, soursop, and sugar apple at 0.20 parts per million ppm (ppm).

2. *PP 2E6425* proposes the establishment of tolerances for fig at 0.30 ppm, and fig, dried at .1 ppm.

3. *PP 2E6428* proposes the establishment of tolerances for avocado, black sapote, canistel, mamey sapote, mango, papaya, sapodilla, and star apple at 1.0 ppm.

4. *PP 2E6436* proposes the establishment of a tolerance for okra at 0.02 ppm.

EPA has determined that the petitions contain 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 support granting of the petitions. Additional data may be needed before EPA rules on the petitions. This notice includes a summary of the petitions prepared by Valent USA Corporation.

A. Residue Chemistry

1. *Plant metabolism.* The major metabolic pathways in plants is aryl hydroxylation and cleavage of the ether linkage, followed by further metabolism into more polar products by further oxidation and/or conjugation reactions. However, the bulk of the radiochemical residue on raw agricultural commodities samples remained as parent. Comparing metabolites detected and quantified from cotton, apple, tomato, goat, hen, and rat shows that there are no significant aglycones in plants which are not also present in the excreta or tissues of animals. The residue of concern is best defined as the parent, pyriproxyfen.

2. *Analytical method.* The extraction methodology has been validated using aged radiochemical residue samples from metabolism studies. The methods have been validated in cottonseed, apples, soil, and oranges at independent laboratories. EPA has successfully validated the analytical methods for analysis of cottonseed, pome fruit, nutmeats, almond hulls, and fruiting vegetables. The limit of detection of pyriproxyfen in the methods is 0.01 ppm which will allow monitoring of

food with residues at the levels proposed for the tolerances.

3. *Magnitude of residues.* The magnitude of residues for pyriproxyfen is adequately understood for the proposed commodities.

B. Toxicological Profile

1. *Acute toxicity.* An assessment of toxic effects caused by pyriproxyfen is discussed in Unit II.B. of the **Federal Register** dated April 4, 2001 (FRL-6772-4) (66 FR 17883).

2. *Animal metabolism.* The absorption, tissue distribution, metabolism and excretion of ¹⁴C-labeled pyriproxyfen were studied in rats after single oral doses of 2 or 1,000 milligrams/kilograms body weight (mg/kg/bwt) (phenoxyphenyl and pyridyl label), and after a single oral dose of 2 mg/kg/bwt, phenoxyphenyl label only, following 14 daily oral doses at 2 mg/kg/bwt of unlabelled material. For all dose groups, most 88–96% of the administered radiolabel was excreted in the urine and feces within 2 days after radiolabeled test material dosing, and 92–98% of the administered dose was excreted within 7 days. Seven days after dosing, tissue residues were generally low, accounting for no more than 0.3% of the dosed ¹⁴C. Radiocarbon concentrations in fat were the higher than in other tissues analyzed. Recovery in tissues over time indicates that the potential for bioaccumulation is minimal. There were no significant sex or dose-related differences in excretion or metabolism.

3. *Metabolite toxicology.* The potential for chronic toxicity is adequately tested by chronic exposure to the parent at the maximum tolerated dose and consequent chronic exposure to the internally formed metabolites. Seven metabolites of pyriproxyfen, 4'-OH-pyriproxyfen, 5'-OH-pyriproxyfen, desphenyl-pyriproxyfen, POPA, PYPAC, 2-OH-pyridine and 2,5-diOH-pyridine, have been tested for mutagenicity, via Ames assay, and acute oral toxicity to mice. All seven metabolites were tested in the Ames assay with and without S9 at doses up to 5,000 micrograms per plate or up to the growth inhibitory dose. The metabolites did not induce any significant increases in revertible colonies in any of the test strains. Positive control chemicals showed marked increases in reverting colonies.

The acute toxicity to mice of 4'-OH-pyriproxyfen, 5'-OH-pyriproxyfen, desphenyl-pyriproxyfen, POPA, and PYPAC did not appear to markedly differ from pyriproxyfen, with all metabolites having acute oral lethal dose (LD₅₀) values greater than 2,000 mg/kg/bwt. The two pyridines, 2-OH-

pyridine and 2,5-diOH-pyridine, gave acute oral LD₅₀ values of 124 (male) and 166 (female) mg/kg/bwt, and 1,105 (male) and 1,000 (female) mg/kg/bwt, respectively.

4. *Endocrine disruption.* While specific tests, uniquely designed to evaluate the potential effects of pyriproxyfen on mammalian endocrine systems have not been conducted, the toxicology of pyriproxyfen has been extensively evaluated in acute, sub-chronic, chronic, developmental, and reproductive toxicology studies including detailed histopathology of numerous tissues. The results of these studies show no evidence of any endocrine-mediated effects and no pathology of the endocrine organs. Consequently, Valent concludes that pyriproxyfen does not possess estrogenic or endocrine disrupting properties applicable to mammals.

C. Aggregate Exposure

1. *Dietary exposure—i. Food.* An evaluation of chronic dietary exposure including both food and drinking water has been performed for the U.S. population and various sub-populations including infants and children. No acute dietary endpoint and dose was identified in the toxicology data base for pyriproxyfen, therefore, the Valent Corporation concludes that there is a reasonable certainty of no harm from acute dietary exposure.

Chronic dietary exposure to pyriproxyfen residues was calculated for the U.S. population and 25 population subgroups assuming tolerance level residues, processing factors from residue studies, and 100% of the crop-treated. The analyses included residue data for all existing uses, pending uses, and proposed new uses.

ii. *Drinking water.* Since pyriproxyfen is applied outdoors to growing agricultural crops, the potential exists for pyriproxyfen or its metabolites to reach ground water or surface water that may be used for drinking water. Because of the physical properties of pyriproxyfen, it is unlikely that pyriproxyfen or its metabolites can leach to potable ground water. To quantify potential exposure from drinking water, surface water concentrations for pyriproxyfen were estimated using Generic Expected Environmental Concentration (GENEEC) 1.3.

2. *Non-dietary exposure.* Pyriproxyfen is currently registered for use on residential non-food sites. Pyriproxyfen is the active ingredient in numerous registered products for flea and tick control. Formulations include foggers,