

**FEDERAL REGISTER DOCUMENT SUBMISSION TEMPLATE
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Sipcam Agro USA, Inc.

[PP#9F6023 and PP#6F7084]

In 1999 the U.S. EPA received pesticide petitions (**PP#9F6023 and PP#6F7084**) from Sipcam Agro USA, Inc., 300 Colonial Center Parkway, #230, Roswell, GA 30076, proposing, pursuant to section 408(d) of the Federal Code, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180.557 by establishing tolerances for residues of tetraconazole in or on the raw agricultural commodities:

- peanut, nutmeat at 0.03 [subsequently amended to 0.05]; and
- peanut, refined oil at 0.1 [subsequently amended to 0.15]; and
- pecan at 0.05 parts per million (ppm).

A separate but related petition (PP#5F6971) has proposed tolerances for residues of tetraconazole in/on poultry (eggs/fat/liver/meat/meat byproducts) resulting from the feeding of peanut and soybean meal. 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 supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant and animal metabolism.* In plants and animals, the metabolism of tetraconazole is adequately understood for the purposes of establishing the proposed tolerances. Tetraconazole metabolites include 1,2,4-triazole, and two conjugates, triazolylalanine and triazolyl acetic acid, which are common to the triazole derivative fungicides. Based on the available metabolism and toxicology data, parent tetraconazole is proposed to be considered as the residue of concern in plant and animal matrices.

2. *Analytical method.* In plants and animals, the residue of concern, parent tetraconazole, can be determined using High Pressure Liquid Chromatography (HPLC) with a Mass Spectrometer (MS) detector. The proposed limit of quantitation (LOQ) for the method is 0.01 ppm for pecan and peanut raw and processed commodities. The poultry petition (PP#5F6971) has defined LOQs for tetraconazole at 0.02 ppm for poultry meat, fat, byproducts, liver, and 0.01 ppm for egg, which are likewise relevant to the peanut tolerance proposal.

3. *Magnitude of the residues.* A magnitude of study was conducted at a total of twelve field sites to evaluate the magnitude of the residues of tetraconazole on peanut raw agricultural commodities following seven applications of Eminent 125SL at 0.107 lbs of

active ingredient (ai) per acre, with treatments throughout the growing season until 14 days prior to digging. Residues of tetraconazole on peanut nutmeats ranged from nondetectable (<0.010) to 0.0344 ppm [HAFT] among thirty-four samples taken from the twelve field sites. A subset of dissipation samples taken from one of the field sites demonstrated that the magnitude of tetraconazole residues remained unchanged in peanut nutmeats as the preharvest interval ranged from zero (0) to sixty (60) days. A processing study conducted upon bulked peanut nutmeats taken from one of the field sites determined that residues of tetraconazole concentrated in peanut refined oil by a factor of 3.3.

A magnitude of residue study was conducted among a total of five field sites to evaluate the magnitude of the residue of tetraconazole on pecans following eight applications of Eminent 125SL at 0.133 lbs active ingredient per acre, with treatments throughout the growing season until 30 days prior to harvest. Residues of tetraconazole on pecans ranged from non-detectable (<0.010) to 0.02 ppm [HAFT] among twelve samples taken from the field sites. A subset of dissipation samples taken from one of the field sites demonstrated that the magnitude of tetraconazole residues remained unchanged and non-detectable in pecans as the preharvest interval ranged from zero (0) to sixty (60) days.

B. Toxicological Profile

The toxicological database for tetraconazole is complete. The EPA's assessments of potential exposure and risks associated with the proposed tolerances are categorized as follows:

1. *Acute toxicity.* Acute oral lethal dose (LD)₅₀ = 1,031 milligrams/kilogram (mg/kg) (toxicity category III); acute dermal LD₅₀ < 2,000 mg/kg (toxicity category III); acute inhalation lethal concentration (LC)₅₀ = 3.66 mg/liter (toxicity category IV); primary eye irritation - clear by 72 hours (toxicity category III); primary skin irritation - slight irritation (toxicity category IV); and dermal sensitization - negative.

2. *Genotoxicity.* A battery of mutagenicity studies yielded negative results in *Salmonella typhimurium*, cultured Chinese hamster ovary (CHO) cells, and mouse lymphoma cells. There was no evidence of clastogenicity in vitro or in vivo and tetraconazole did not induce unscheduled DNA synthesis in human HeLa cells.

3. *Reproductive and developmental toxicity.* A two-generation reproduction study was conducted in rats at dietary concentrations of 0, 10, 70 or 490 ppm. The LOAEL for parental toxicity was 70 ppm, equivalent to 4.9/5.9 (male/female) mg/kg/day based on increased mortality in P generation females. The NOAEL was 10 ppm, equivalent to 0.7/0.8 (M/F) mg/kg/day. The LOAEL for off spring toxicity was 490 ppm (40.6 mg/kg/day from the P generation female intake) based on decreased litter weight and mean pup weight in litters of all generations before weaning and increased relative liver weights at weaning in both sexes of all litters. The NOAEL was 70 ppm (5.9 mg/kg/day). The LOAEL for reproductive toxicity was 70 ppm, equivalent to 4.9/5.9 (M/F) mg/kg/day based on increased mean gestation duration in P generation parental females and related evidence of compound toxicity in the parturition process. The NOAEL was 10 ppm (0.7 mg/kg/day for males and 0.8 for females).

A developmental toxicity study was conducted using rats gavaged with doses of 0, 5, 22.5, and 100 mg/kg/day from days 2 through 15 of gestation. The maternal toxicity LOAEL was 100 mg/kg/day based on decreased body weight gain, and food consumption and increased liver and kidney weights. The maternal toxicity NOAEL was 22.5 mg/kg/day. Developmental toxicity was noted at 100 mg/kg/day and consisted of an increased incidence of small fetuses, and supernumerary ribs. The LOAEL and NOAEL for developmental toxicity were 100 and 22.5 mg/kg/day, respectively.

A developmental toxicity study was conducted using rabbits gavaged with doses of 0, 7.5, 15, or 30 mg/kg/day. The maternal toxicity NOAEL was 13 mg/kg/day, and LOAEL was 30 mg/kg/day, based upon decreased body weight gain. The developmental toxicity NOAEL was 30 mg/kg/day and the LOAEL was not established.

4. *Subchronic toxicity.* Ninety-day feeding studies were conducted in rats and mice. The rat study was conducted at dietary concentrations of 0, 10, 60, or 360 ppm. The NOAEL was 4.1/5.5 (M/F) mg/kg/day. The LOAEL was 23.9/28.7 (M/F) mg/kg/day, based on single liver cell degeneration in males, and increased SGPT and SGOT, decreased BUN levels, increased absolute and relative liver weights and presence of hepatocellular single cell necrosis in females. The mouse study was conducted at dietary concentrations of 0, 5, 25, 125, or 625 ppm. The NOAEL was 4 (M/F) mg/kg/day. The LOAEL was 16/20 (M/F) mg/kg/day, based on single liver cell degeneration in males, and increased SGPT and SGOT, decreased BUN levels, increased absolute and relative liver weights and presence of hepatocellular single cell necrosis in females.

5. *Chronic toxicity.* A two year combined chronic toxicity/carcinogenicity study was conducted in rats at dietary concentrations of 0, 10, 80, 640 or 1280 ppm. The NOAEL was 3.4/4.4 (M/F) mg/kg/day. The LOAEL was 27.7/39.4 (M/F) mg/kg/day, based upon histopathology of the bone (osseous hypertrophy of the cranium/parietal bone), pale and thickened incisors, and decreased absolute and relative adrenal and pituitary weights in males; decreased body weight (at terminal sacrifice) in females. No treatment-related increases in tumor incidence were observed.

A 52-week chronic toxicity study was conducted in dogs at dietary concentrations of 0, 22.5, 90 or 360 ppm. The NOAEL was 0.73/0.82 (M/F) mg/kg/day. The LOAEL was 27.7/39.4 (M/F) mg/kg/day, based upon increased absolute and relative kidney weights and histopathological changes in the male kidney.

6. *Carcinogenicity.* An 80 week mouse oncogenicity study was conducted at dietary concentrations of 0, 10, 90, 800, or 1250 ppm. The NOAEL was 1.4/1.5 (M/F) mg/kg/day. The LOAEL was 12/14.5 (M/F) mg/kg/day, based upon increased liver weights and hepatocellular vacuolation in both sexes and increased kidney weights in males. Treatment-related increased incidences of combined benign and malignant liver tumors in both sexes were observed.

7. *Animal metabolism.* The nature of tetraconazole residues is adequately understood. Tetraconazole is extensively metabolized very quickly and eliminated from the body by fecal and urinary routes.

8. *Metabolite toxicology.* 1,2-4-Triazole is the major metabolite identified in urine and feces with minor amounts of triazole acid and alcohol. The most conservative toxicology endpoint for 1,2,4-triazole is 15 mg/kg/day, based on body weight decreases in male rats in the reproduction study.

9. *Endocrine disruption.* Tetraconazole did not affect endocrine organs or tissues, nor were there any indications of effects on fetal development in either rats or rabbits, or on reproductive performance in rats. Therefore, at doses likely to be encountered, tetraconazole is not likely to be an endocrine disruptor.

C. Aggregate Exposure

1. *Dietary exposure.* Using 100% crop treated scenarios and existing sugar beet, milk, cattle, horse, goat, and sheep tolerances, plus the proposed peanut, pecan, soybean and poultry tolerances, acute dietary exposure to tetraconazole from food occupies only 0.5% of the aPAD (0.225 mg/kg at UF = 100) for females 13 to 49 years old, the only population subgroup for which an acute toxicity endpoint was determined. Using the same exposure assumptions, chronic dietary exposure from food to tetraconazole occupies 3.9% and 11.1% of the cPAD (0.0073 mg/kg/day at UF = 100) for the U.S. population and the most sensitive subpopulation, non-nursing infants, respectively. The estimated aggregate cancer risk from dietary exposure from the proposed use on peanuts would not change the previously calculated oncogenic risk of 0.21×10^{-6} , a value that falls within the Agency's acceptable risk standard for cancer in the range of $<1 \times 10^{-6}$.

i. *Food.* The cRfD and aRfD values of 0.0073 mg/kg bw and 0.225 mg/kg bw, respectively, were used to assess risk from dietary exposure. Tier 1 dietary risk assessments indicate that the highest chronic and acute exposures never exceed 11.1% and 0.5% (at the 99.9th percentile of exposure) for the cRfD and aRfD, respectively.

ii. *Drinking water.* The standard EPA Mississippi soybean PRZM/EXAMS modeling scenario with index reservoir (IR) was used to conservatively estimate concentrations of tetraconazole in drinking water resulting from a proposed use on soybeans, which also applies to the presently proposed use on peanuts. The drinking water estimated concentrations (DWECS) from the Mississippi soybean scenario model were 2.19 ppb (acute), 0.578 ppb (chronic) and 0.441ppb (30 year lifetime average). These are 6 to 28 times greater than the highest level of tetraconazole “detected” in Minnesota surface water, which was 0.075 ppb (1/2 limit of quantitation). Thus, the Mississippi DWECS were used to assess dietary risks from exposure to drinking water for uses on soybeans and peanuts. The DWECS are lower than the lowest drinking water level of comparison (DWLOC) values of 6,720 ppb (acute), 69 to 249 ppb (chronic), and 1.516 ppb (cancer). When DWLOC values are not exceeded by DWEC values it can be concluded that dietary risks from exposure to drinking water are acceptable.

2. *Non-dietary exposure.* Tetraconazole is currently not registered or proposed for use on any residential non-food site. Therefore, residential exposure to tetraconazole residues would be through dietary exposure only.

D. Cumulative Effects

EPA has not determined that a common mechanism of toxicity pertains to tetraconazole as compared with any other substance.

E. Safety Determination

1. *U.S. population.* Based on the exposure assumptions described above and on the completeness of the toxicology database, it can be concluded that total aggregate exposure from food and water to the U.S. population and all evaluated population subgroups from tetraconazole exposure from all proposed uses will be below 100% of the RfDs. EPA generally has no concerns for estimated exposures below 100% of the RfD, since the RfD represents the level at or below which daily aggregate exposure will not pose an appreciable risk to human health. Thus it can be concluded that there is reasonable certainty that no harm will result from aggregate exposure to tetraconazole residues for registered and proposed uses, including the presently proposed use on peanuts.

2. *Infants and children.* In assessing the potential for additional sensitivity of infants and children to residues of tetraconazole, the data from developmental toxicity studies in both the rat and rabbit and a two generation reproduction study in rats have been considered. These toxicity studies indicate the offspring are not more sensitive and all developmental and reproductive effects were secondary to maternal toxicity. Thus infants and children are protected, and an additional uncertainty factor pertaining to infants and children is not warranted.

F. International Tolerances

Maximum residue levels (MRL) have been established for tetraconazole in the following countries (in ppm).

Belgium: sugar beet root, 0.05; wheat grain, 0.05; wheat straw, 2.0.

France: apple, 0.2; barley grain, 0.02; grape, 0.2; wine, 0.01; sugar beet root, 0.05; wheat grain, 0.02.

Italy: apple, 0.5; artichoke, 0.2; barley grain, 0.1; courgette, 0.2; cucumber, 0.2; grape, 0.5; melon, 0.05; peach, 0.2; pear, 0.2; pepper, 0.2; tomato, 0.2, watermelon, 0.05; wheat grain, 0.05

Portugal: apple, 0.3; grape, 0.2; melon, 0.1; peach, 0.2; pear, 0.3; strawberry, 0.2; sugar beet root, 0.05.

Spain: apple, 0.2; artichoke, 0.05; cucurbit fruit & edible peel, 0.2; nectarine, 0.2; peach, 0.2; pear, 0.2; sugar beet leaves, 0.3; sugar beet root; 0.05; tomato, 0.1.

United Kingdom: barley grain, 0.2; barley straw, 10; oat grain, 0.1; oat straw, 2; wheat grain, 0.05; wheat straw, 5.

Czech Republic: apple, 0.5; grape, 0.05

Hungary: apple, 0.2; grape, 0.5; sugar beet root & leaves, 0.5; sugar beet root, 0.1; wheat grain, 0.05; wheat straw, 3.

Poland: apple, 0.5; cereal grain, 0.05; cereal straw, 3; cucumber edible peel, 0.2.

Japan: wheat, 0.05; barley, 0.2 other cereal grain, 0.1; sugar beet, 0.5; artichoke, 0.2; tomato, 1; cucumber, 0.5; pumpkin (including squash), 1; oriental cucurbitaceous vegetables, 0.2; apple, 0.5, Japanese pear, 0.5, pear, 0.5 quince, 0.5 peach, 0.3, nectarine, 0.2; apricot, 0.2; Japanese plum (including prune); 0.2; cherry, 0.2; strawberry, 2; watermelon, 0.2, melon, 0.2; makuwauri, 0.2; grape, 0.5; tea, 20.