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ISAGRO S.p.A.

[5F6971]

EPA has received a pesticide petition (**[5F6971]**) from Isagro S.p.A., Centro Uffici San-Edifico D-ala 3, Via Caldera, 21-20153 Milan, Italy 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.:

1. by establishing a tolerance for residues of

tetraconazole in or on the raw agricultural commodities: soybean, seed at 0.1, aspirated grain fractions (AGF) and refined oil at 0.5; and poultry, meat, liver, byproducts, egg at 0.01, and fat at 0.05 parts per million (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 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 most of the triazole 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 methods are 0.01 ppm for soybean seed and processed commodities, and 0.02 ppm for poultry meat, fat, byproducts, liver, and 0.01 ppm for egg.

3. *Magnitude of the residues.* For soybean, a total of twenty residue trials were conducted to evaluate the magnitude of the residues of tetraconazole following two applications of Domark 230 ME at 0.09 lbs of active ingredient (ai) per acre with treatments at growth stages R3 and R5. Soybean mean and relative standard deviation residue for all sites was 0.022 ppm ± 0.0125 ppm with a maximum residue of 0.068 ppm. Soybean seed residues concentrated in AGF and refined oil by factors of 5.8 and 4.6, respectively.

For poultry, a total of 10 birds each were dosed at 0.077, 0.231, and 0.77 mg ai/kg (equivalent to 2, 6, and 20x the anticipated soybean residue dietary burden). Residues at the lowest dose were 0.038 ppm for fat, <0.01 ppm for meat, liver, and kidney, and <0.005 for egg.

B. Toxicological Profile

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*. Numerous mutagenicity studies were conducted with tetraconazole and no genotoxic effects were reported,

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 = 70 ppm, equivalent to 4.9/5.9 (male/female) mg/kg/day based on increased mortality in P generation females. The NOAEL = 10 ppm, equivalent to 0.7/0.8 (M/F) mg/kg/day. The LOAEL for off spring toxicity = 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 = 70 ppm (5.9 mg/kg/day). The LOAEL for reproductive toxicity = 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 is 100 mg/kg/day based on decreased body weight gain, and food consumption and increased liver and kidney weights. The maternal toxicity NOAEL is 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 = 13 mg/kg/day and LOAEL = 30 mg/kg/day, based upon decreased body weight gain. The developmental toxicity NOAEL = 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 conduced at dietary concentrations of 0, 10, 60, or 360 ppm. The NOAEL = 4.1/5.5 (M/F) mg/kg/day. The LOAEL = 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 = 4 (M/F) mg/kg/day. The LOAEL = 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 = 3.4/4.4 (M/F) mg/kg/day. The LOAEL = 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 = 0.73/0.82 (M/F) mg/kg/day. The LOAEL = 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 = 1.4/1.5 (M/F) mg/kg/day. The LOAEL = 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 reproductive study.

9. *Endocrine disruption.* Tetraconazole did not have effects on 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 in not likely to be an endocrine disruptor.

C. Aggregate Exposure

1. *Dietary exposure*. Using 100% crop treated scenarios and existing sugar beet, cattle, horse, goat, and sheep RAC tolerances and proposed soybean and poultry RAC tolerance for residue exposure assumptions, acute dietary exposure from food to tetraconazole occupies 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 most potent unit risk used for the purpose of lifetime cancer risk assessment by the Agency is $Q_1^* = 2.30 \times 10^{-2}$ in human equivalents. Using the same assumptions except for 50% and 10% crop treated scenarios for sugar beet and soybean, respectively, and mean residue exposure for soybean oil and seed, the estimated aggregate cancer risk from dietary exposure for the proposed use on soybeans is 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 the proposed use on soybeans. Extensive surface water monitoring results generated by the Minnesota Department of Agriculture were used to estimate concentrations of tetraconazole in drinking water resulting from use on sugar beets. 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 Level of Quantitation). Thus, the Mississippi DWECs were used to assess dietary risks from exposure to drinking water for uses on sugar beets and soybeans. 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 exceed 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 for use on any residential non-food site. Therefore, residential exposure to tetraconazole residues will be through dietary exposure only.

D. Cumulative Effects

EPA has not made a common mechanism of toxicity finding as to tetraconazole and any other substance. However, the Agency does have concern about potential toxicity to 1,2,4-triazole and two conjugates, triazolylalanine and triazolyl acetic acid. To support the extension of existing parent triazole-derivative fungicide tolerances, EPA conduced an interim human health assessment for aggregate exposure to 1,2,4-triazole.

Based on this assessment EPA concluded that for all exposure durations and population subgroups, aggregate exposures to 1,2,4-triazole are not expected to exceed its level of concern.

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, ISAGRO believes 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 on sugar beets and soybeans.

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 severe maternal toxicity. Thus, ISAGRO believes that infants and children are protected and that an additional uncertainty factor for 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.