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TEMPLATE:

Bayer CropScience

Petition number 3E9059

EPA has received a pesticide petition ~~([insert petition number])~~ 3E9059 from Bayer CropScience, 800 N. Lindbergh Blvd, St. Louis, MO 63167 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 by establishing a tolerance for residues of tetraniliprole, 1-(3-chloro-2-pyridinyl)-N-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-3-[[5-(trifluoromethyl)-2H-tetrazol-2-yl]methyl]-1H-pyrazole-5-carboxamide in or on the imported raw agricultural commodities of Tea, dried at 80 ppm. EPA has determined that the petition contains data or information regarding the elements set forth in section 408 (d)(2) of the FDDCA; 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 tetraniliprole is adequately understood to support the proposed tolerances. Plant metabolism studies with tetraniliprole were performed in apples, potatoes, lettuce and rice after foliar broadcast treatments, on tomato after soil drench treatment, on potato after seed piece treatment and on corn after seed treatment. Metabolism studies with tetraniliprole in rotational crops were performed in wheat, turnips and Swiss chard. The metabolism in all plants was very similar. Parent compound represented the main, and in some cases the only residue observed in the edible portion of primary and rotational crops. The only observed metabolic reaction was an intra-molecular condensation (cyclisation) leading to the formation of BCS-CL73507-N-methyl-quinazolinone (BCS-CQ63359).

2. *Analytical method.* A practical analytical method which uses high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) to quantitate residues of tetraniliprole in various crops is available for enforcement. The method limit of quantitation (LOQ) is 0.01 ppm in all matrices.

The following is a summary adapted from the Japanese Ministry of Health, Labor and Welfare (MHLW) review for the purpose of setting food standards (maximum residue levels for pesticides in food) for tetraniliprole and the accompanied crop field trial reports on tea.

Dried green tea samples were swollen with water as necessary and extracted with an acetonitrile/water/acetic acid (180:20:1) mixed solution, followed by a clean-up with a C18 cartridge or graphite carbon prior to quantification by liquid chromatograph-tandem mass spectrometer (LC-MS/MS). The method was validated for tetraniliprole in tea, dried, at the LOQ of 0.01 ppm and at other fortification levels with mean recoveries ranging from 85% to 99%.

3. *Magnitude of residues.* The following summary for tea, dried was adapted from the Japanese Ministry of Health, Labor and Welfare (MHLW) review for the purpose of setting food standards (maximum residue levels for pesticides in food) for tetraniliprole.

Six (6) decline field trials were conducted to measure the magnitude of tetraniliprole residues in/on dried green tea leaves following one application of Yeoval® Flowable. Yeoval® Flowable is a suspension concentrate formulation containing 200 g tetraniliprole/L. Yeoval® Flowable was mixed with water at a 2500X dilution rate resulting in a concentration of 0.08 g tetraniliprole/L. At each trial location, one broadcast foliar application of this solution was made in a water volume of 400 L/10a (10a = 0.1 ha or 1000 m^2) resulting in an application rate of 320 g tetraniliprole/ha.

Samples were collected at preharvest intervals (PHI) of 1, 3, 7 and 14 days. The PHI on the Yeoval® Flowable label is 7 days.

Residues in dried tea leaves from the 6 trials collected at a 7-day PHI were 22.3 ppm, 24.2 ppm, 41.7 ppm, 28.0 ppm, 25.2 ppm and 1.82 ppm. These data support the proposed import tolerance for tea, dried.

Residue in infused tea, collected from the 2 trials of dried tea leaves at a 7-day PHI, were 14.6 ppm and 19.6 ppm. These data can be referenced for consideration of tea, instant.

B. Toxicological Profile

1. *Acute toxicity.* All studies were conducted in 2013 and were fully compliant with Good Laboratory Practice (GLP). All tests were conducted in accordance with prevailing OECD, EU, US EPA and Japanese MAFF testing guidelines. The acute toxicity of tetraniliprole (89.6 % purity) was low for all routes evaluated (oral, dermal and inhalation). The rat acute oral and dermal LD_{50} was > 2000 mg/kg bwt, with no clinical signs evident in either study. The rat acute inhalation LC_{50} (4-hour) was > 5.01 mg/L, with one mortality and transient clinical signs that were reversible within 3 days. tetraniliprole was not irritating to rabbit skin and caused only slight ocular irritation (redness of the conjunctivae) which reversed within 48 hours. Evidence of skin sensitization (delayed contact hypersensitivity) was seen in a modified LLNA test (IMDS) in NMRI mice. Based on the US EPA classification, the results with the technical grade active ingredient tetraniliprole support acute toxicity categories III/IV. The acute toxicity classification of the end use formulations TETRANILIPROLE 200 SC AND FS 480 is Toxicity Category III/IV for oral, dermal, and inhalation toxicity and skin and eye irritation.

2. *Genotoxicity.* Tetraniliprole was tested for its genotoxic and mutagenic potential in a battery of *in vitro* or *in vivo* studies covering all required end-points (gene mutations, chromosomal aberrations, and DNA damage and repair). There was no indication of a genotoxic response in any of the studies conducted with or without metabolic stimulation on any of the batches on technical material tested; demonstrating that tetraniliprole technical showed no genotoxic potential in any of the batches tested.

3. *Immunotoxicity.* The results from guideline 28-day, 90-day and chronic studies in the rat, mouse and dog provide considerable information on potential immunotoxic effects of tetraniliprole obtained from hematology, lymphoid organ weights and histopathology performed as elements of general toxicity studies. These results provide no evidence that tetraniliprole is toxic to the immune system at any dose or dietary level. While these studies do not include a functional assessment of immunosuppression or otherwise satisfy all the requirements of OCSPP 870.7800, the body of information available with tetraniliprole is sufficient to demonstrate the immune system is not a target and further evaluation is not warranted.

4. *Reproductive and developmental toxicity.* The studies conducted to evaluate tetraniliprole for reproductive and developmental toxicity were performed from 2013-2015 and complied with OECD, EU, US EPA and Japanese MAFF testing guidelines and Good Laboratory Practice (GLP). These studies can be relevant for the short-term and intermediate-term risk assessments of occupational exposure.

In the rat and rabbit developmental toxicity studies, a limit dose of 1000 mg/kg/day was the NOAEL for maternal and developmental toxicity.

In the rat two-generation reproduction study, the parental and offspring LOAEL was 12,000 ppm (896/1032 mg/kg bw/day in males/females), based on decreased body weight, establishing a NOAEL of 196/211 mg/kg/day. The reproductive NOAEL

established in this study was 12,000 ppm (896/1032 mg/kg bw/day in males/females), which was the highest dietary level tested.

Based on the developmental and reproductive toxicity studies with tetraniliprole, the NOAEL of 1000 mg/kg/day from both the rat and rabbit developmental studies is considered the most relevant for occupational risk assessment. The NOAEL from the reproductive toxicity study is 196 mg/kg/day, which is consistent with the NOAEL of 126 mg/kg/day from the dog 90-day oral toxicity study.

5. *Subchronic toxicity.* The subchronic toxicity studies are relevant for assessing the intermediate-term risk of occupational workers exposed to tetraniliprole. Three 90-day oral toxicity studies were conducted; one in each of three species. In the rat 90-day dietary study, there were no adverse treatment-related effects at any dose level; therefore, the NOAEL was 608 and 723 mg/kg body weight/day in males and females, respectively. Likewise in the mouse 90-day dietary study, there were no effects in males or females at any dietary level; therefore, the NOAEL was 973 and 1224 mg/kg/day in males and females, respectively. In the 90-day dog dietary study, there was limited evidence of toxicity in males and females at the high dose (LOAEL) of 440/480 mg/kg/day, with a NOAEL of 126/138 mg/kg/day. The gastric lesions seen at the high dose in the 28-day dog study were not observed in the 90-day study. Based on the 90-day dog study, the NOAEL of 126 mg/kg/day is considered the most relevant for intermediate-term occupational risk assessment by routes of exposure other than dermal.

6. *Chronic toxicity.* Chronic toxicity studies have been conducted in the rat, mouse, and dog. There are no target organs in the chronic mouse, rat or dog studies. Effects in the rat one-year dietary study were limited to decreased body weight at the highest dietary level of 18,000 ppm (equivalent to 741/1052 mg/kg/day), with a NOAEL of 159/221 mg/kg/day. In the 18-month mouse study, there were no effects at any dietary level, with a NOAEL of 825/1073 mg/kg/day in males and females. Slight effects were evident in the one-year dog study at the highest dietary level of 12,800 ppm, to establish a NOAEL of 91.2/88.4 mg/kg/day in males and females.

There were no tumors in the mouse study. In the rat study, there was an increased incidence of uterine tumors and non-neoplastic lesions in the uterus, ovary and vagina at the high dose of 1052 mg/kg/day, with no tumors in males.

7. *Neurotoxicity.* Based on the toxicity profile of tetraniliprole in which no potential neurotoxic findings were observed, no specific neurotoxicity studies were considered to be necessary.

8. *Animal metabolism.* Following oral administration of tetraniliprole to rats, blood and plasma levels peaked approximately 1 to 4 hours after dosing followed by rapid decline. Tetraniliprole residues were distributed among blood and most of the organs and tissues with some preference for liver, kidneys and to a lesser extent glandular organs and, and fatty tissues. Absorption was uniformly low in both sexes and no significant sex related differences were observed in concentrations in blood and in organs and tissues as well as in the excretion via urine and feces. Overall, no significant sex

related differences were observed. In general, excretion of tetraniliprole residues was rapid, with feces being the predominant excretion route (98%), while renal excretion accounted for only ~2% in both male and female rats. Unchanged parent compound was the major residue observed in all cases. Metabolism of tetraniliprole in the rats was complex with hydroxylation followed by conjugation with glucuronic acid; intra-molecular condensation (cyclisation) leading to quinazolinone compounds; and oxidation and cleavage reactions observed in addition to several other minor reactions. Parent tetraniliprole was observed along with BCS-CL73507-hydroxy-N-methyl, BCS-CL73507-benzylalcohol, BCS-CL73507-despyridyl, BCS-CL73507-N-methyl-quinazolinone and many other minor metabolites. In the ruminant and poultry metabolism studies, tetraniliprole, BCS-CL73507-N-methyl-quinazolinone (ruminants), BCS-CL73507-benzylalcohol (ruminants) and BCS-CL73507-despyridyl (poultry) were the major significant metabolites observed.

9. *Metabolite toxicology.* BCS-CL73507-N-methyl quinazoline (BCS-CQ63359) is defined in both plant and animal livestock (ruminant) definition and was identified as a minor soil metabolite with a predicted PEC_{gw} value of > 0.1 µg/L < 0.75 µg/L. This metabolite is considered to have been adequately tested in the standard battery of regulatory guideline studies conducted on the parent tetraniliprole. Data from ADME studies show that BCS-CQ63359 plus derived metabolites accounts for approximately 8% of administered dose of tetraniliprole, which is very close to 10% which is normally regarded as a sufficiently high enough level to be covered by toxicological studies conducted on the parent. More importantly, significant levels of BCS-CQ63359, compared to tetraniliprole, were detected in plasma samples taken on the long-term rat, mouse and dog studies after approximately 3 and 12 months of treatment, plus after approximately 18-months in the mouse and approximately 24 months in the rat study (Table 5.8-1). These results in the rat, mouse and dog clearly show that BCS-CQ63359 has been adequately tested in the toxicology studies that were conducted with tetraniliprole.

10. *Endocrine disruption*. A steroidogenesis assay using the H295R cell line showed increased estradiol and cortisol with tetraniliprole and its main mammalian metabolite BCS-CQ63359, with no effect on progesterone or testosterone. A higher-tier uterotrophic assay performed with tetraniliprole to investigate this finding showed no evidence of estrogenic or anti-estrogenic activity *in vivo*. The standard battery of required toxicity studies includes an evaluation of the potential effects on reproduction and development, and an evaluation of the pathology of the endocrine organs following repeated or long-term exposure. In the two-generation study, there was no indication of an endocrine-mediated treatment-related response.

C. Aggregate Exposure

1. *Dietary exposure.* The toxicology database for tetraniliprole is complete for the purposes of this risk assessment and the characterization of potential human health risks to infants and children. A review of the toxicity data for tetraniliprole determined that no adverse effects were observed in the submitted toxicological studies regardless of the route of exposure, thus no dietary assessments are required.

2. *Non-dietary exposure*. A previous Human Health Risk Assessment for tetraniliprole determined that a quantitative risk assessment was not needed for residential, occupational, or aggregate exposure.

D. Cumulative Effects

At this time, there is no available information to indicate that tetraniliprole or its metabolites have a common mechanism of human toxicity with other substances. Tetraniliprole is a member of the anthranilic diamide insecticide class of chemistry. For this class of chemistry, EPA has not yet conducted a detailed review of common mechanisms to determine whether it is appropriate, or how to include these chemicals in a cumulative risk assessment. Tetraniliprole does not appear to produce a toxic metabolite produced by other substances. For the purposes of this assessment, therefore, no common mechanism of toxicity has been considered.

E. Safety Determination

1. *U.S. population.* The toxicological and exposure database for tetraniliprole is considered complete. There is potential for exposure to tetraniliprole via food and drinking water, as well as potential non-dietary exposure from the proposed uses of tetraniliprole on residential, commercial, institutional, and other turfgrass areas; golf courses; sports fields; and sod farms. However, no adverse effects were observed in the submitted toxicological studies for tetraniliprole regardless of the route of exposure. Therefore, quantitative dietary (food and drinking water), occupational, residential post-application, and aggregate exposure assessments were not conducted. A qualitative human health risk assessment has been conducted to support the proposed uses of tetraniliprole. No risks of concern have been identified. Therefore, there is a reasonable certainty that no harm will occur to the US Population from dietary and non-dietary exposure to residues of tetraniliprole.

2. *Infants and children*. The toxicological and exposure database for tetraniliprole is considered complete. There is potential for exposure to tetraniliprole from food and drinking water, as well as potential non-dietary exposure to children and toddlers from the proposed uses of tetraniliprole on residential, commercial, institutional, and other turfgrass areas; golf courses; sports fields; and sod farms. However, no adverse effects were observed in the submitted toxicological studies for tetraniliprole regardless of the route of exposure. A qualitative risk assessment showed no risks of concern for infants and children. Therefore, there is a reasonable certainty that no harm will occur to infants and children from dietary and non-dietary exposure to residues of tetraniliprole.

F. International Tolerances.

International tolerances have been established for tetraniliprole for many crops in various countries. The proposed tolerance in tea, dried, is from the cooperation between the Japan Ministry of Agriculture, Forestry and Fisheries (J-MAFF) and Japan Tea Export Promotion Council. The establishment of a tolerance for the imported commodity of tea, dried, will facilitate trade with Japan and other countries.