

- Leafy vegetables, group 4 at 2.0 ppm
- Head and stem brassica vegetables, subgroup 5A at 1.0 ppm.
- Leafy brassica vegetables, subgroup 5B at 2.0 ppm.

7. PP 1E6349 proposes to establish tolerances for imported green and roasted coffee beans and instant coffee at 0.05 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.

#### A. Residue Chemistry

1. *Plant metabolism.* The primary metabolic pathways of thiamethoxam in plants (corn, rice, pears, and cucumbers) were similar to those described for animals, with certain extensions of the pathway in plants. Parent compound and CGA-322704 were the major residues in all crops. The metabolism of thiamethoxam in plants and animals is understood for the purposes of the proposed tolerances. Parent thiamethoxam and the metabolite, CGA-322704, are the residues of concern for tolerance setting purposes.

2. *Analytical method.* Syngenta Crop Protection Inc. has submitted practical analytical methodology for detecting and measuring levels of thiamethoxam in or on raw agricultural commodities. The method is based on crop specific cleanup procedures and determination by liquid chromatography with either ultraviolet (UV) or mass spectroscopy (MS) detection. The limit of detection (LOD) for each analyte of this method is 1.25 nanogram (ng) injected for samples analyzed by UV and 0.25 ng injected for samples analyzed by MS, and the limit of quantitation (LOQ) is 0.005 ppm for milk and juices and 0.01 ppm for all other substrates.

3. *Magnitude of residues.* IR-4 has submitted complete residue data for thiamethoxam on succulent beans, sunflower seed, peppermint and spearmint tops and stone fruits. Syngenta has submitted complete residue data for the proposed imported coffee, pecan, leafy vegetable, head and stem brassica vegetables, leafy brassica vegetables. Details of the Syngenta residue data on these crops were provided in previously published Notices of Filing.

#### B. Toxicological Profile

1. *Acute toxicity.* The acute oral LD<sub>50</sub> for thiamethoxam in the rat is 1,563 milligrams/kilogram body weight (mg/kg bwt). The acute dermal LD<sub>50</sub> of thiamethoxam is >2000 mg/kg bwt. Thiamethoxam is non-toxic at atmospheric concentrations of 3.72 mg/L. Thiamethoxam is minimally irritating to the eye, non-irritating to skin and is not a dermal sensitizer.

In an acute neurotoxicity screening study in rats (OPPTS Harmonized Guideline 870.6200), the no observed adverse effect level (NOAEL) was 100 mg/kg/day with a NOAEL of 500 mg/kg/day based on drooped palpebral closure, decrease in rectal temperature and locomotor activity and increase in forelimb grip strength (males only). At higher dose levels, mortality, abnormal body tone, ptosis, impaired respiration, tremors, longer latency to first step in the open field, crouched over posture, gait impairment, hypo-arousal, decreased number of rears, uncoordinated landing during the righting reflex test, slight lacrimation (females only) and higher mean average input stimulus value in the auditory startle response test (males only).

2. *Genotoxicity.* In gene mutation studies with *S. typhimurium* and *E. coli* (OPPTS Harmonized Guidelines, 870.5100 and 870.5265), there was no evidence of gene mutation when tested up to 5,000 µg/plate and there was no evidence of cytotoxicity.

In a gene mutation study with chinese hamster V79 cells at hypoxanthine guanine phosphoribosyl transferase (HGPRT) focus (OPPTS Harmonized Guideline 870.5300) there was no evidence of a gene mutation when tested up to the solubility limit.

In a CHO cell cytogenetics study (OPPTS Harmonized Guideline 870.5375) there was no evidence of chromosomal aberrations when tested up to cytotoxic or solubility limit concentrations.

An *in vivo* mouse bone marrow micronucleus study (OPPTS Harmonized Guideline 870.5395) was negative when tested up to levels of toxicity in whole animals; however, there was no evidence of target cell cytotoxicity. An unscheduled DNA synthesis (UDS) assay (OPPTS Harmonized Guideline 870.5550) was negative when tested up to precipitating concentrations.

3. *Reproductive and developmental toxicity.* A prenatal developmental study in the rat (OPPTS Harmonized Guideline 870.3700) resulted in maternal and developmental NOAELs of 30 mg/kg/day and 200 mg/kg/day,

respectively. The maternal lowest observed adverse effect level (LOAEL) is 200 mg/kg/day based on decreased body weight, body weight gain and food consumption. The developmental LOAEL was 750 mg/kg/day based on decreased fetal body weight and an increased incidence of skeletal anomalies.

A prenatal developmental study in the rabbit (OPPTS Harmonized Guideline 870.3700) resulted in maternal and developmental NOAELs of 50 mg/kg/day. The maternal and developmental LOAEL is 150 mg/kg/day. The maternal LOAEL is based on maternal deaths, hemorrhagic discharge, decreased body weight and food intake during the dosing period. The developmental LOAEL is based on decreased fetal body weights, increased incidence of post-implantation loss and a slight increase in the incidence of a few skeletal anomalies/variations.

In a reproduction and fertility effects study in rats (OPPTS Harmonized Guideline 870.3800), the parental/systemic NOAEL is 1.84 (males), 202.06 (females) mg/kg/day; the reproductive NOAEL is 0.61 (males), 202.06 (females) mg/kg/day and the offspring NOAEL is 61.25 (males), 79.20 (females) mg/kg/day. The parental/systemic LOAEL is 61.25 (males), not determined (females) mg/kg/day based on increased incidence of hyaline change in renal tubules in F0 and F1 males. The reproductive LOAEL is 1.84 (males), not determined (females) mg/kg/day based on increased incidence and severity of tubular atrophy observed in testes of the F1 generation males. The offspring LOAEL is 158.32 (males), 202.06 (females) mg/kg/day based on reduced body weight gain during the lactation period in all litters.

4. *Subchronic toxicity.* A 90-day oral toxicity study in rats (OPPTS Harmonized Guideline 870.3100) resulted in a NOAEL of 1.74 males and 92.5 (females) mg/kg/day. The LOAEL is 17.64 (male) and 182.1 (female) mg/kg/day based on increased incidence of hyaline change of renal tubules epithelium (males), fatty change in adrenal gland of females, liver changes in females, all at the LOAEL.

A 90-day oral toxicity study in mice (OPPTS Harmonized Guideline 870.3100) resulted in a NOAEL of 1.41 (males) and 19.2 (females) mg/kg/day. The LOAEL was 14.3 (male) and 231 (female) mg/kg/day based on increased incidence of hepatocellular hypertrophy. At higher dose levels: Decrease in body weight and body weight gain, necrosis of individual hepatocytes, pigmentation of Kupffer cells, and lymphocytic infiltration of the