

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 petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism.* In plants, the metabolism of clothianidin is adequately understood for the purposes of establishing these proposed tolerances. Unchanged, parent clothianidin was the predominant residue in all crop matrices (14.4% to 64.5% in corn, 66.1% to 96.6% in tomatoes, 4.3% to 24.4% in sugar beets and 24.3% to 63.3% in apples), with the exception of sugar beet leaves. In sugar beet leaves, the main components were the methylguanidine and thiazolylmethylguanidine metabolites, accounting for 28.6% and 27.7% respectively. All metabolites found in plants were also found in the animal metabolism studies. In animals, parent clothianidin was the major component in liver, muscle and fat. Based on the available metabolism data, parent clothianidin, TZG, TZU, and ATMG-Pyr are proposed to be considered as the residues of concern in livestock matrices.

2. *Analytical method.* In plants and plant products, the residue of concern, parent clothianidin, can be determined using high performance liquid chromatography (HPLC) with electrospray mass spectroscopy (MS/MS) detection. In an extraction efficiency testing, the plant residues method has also demonstrated the ability to extract aged clothianidin residue.

In animal matrices, the residues parent clothianidin, TZG, TZU, and ATMG-Pyr can also be determined using HPLC with electrospray MS/MS detection. In an extraction efficiency testing, the animal residues method has also demonstrated the ability to extract aged clothianidin, TZG, TZU, and ATMG-Pyr residues.

Although, the plant and animal residues LC-MS/MS method is highly suitable for enforcement method, an LC-UV method has also been developed which is suitable for enforcement (monitoring) purposes in all relevant matrices.

3. *Magnitude of residues.* For apples, a total of 13 field trials were conducted to evaluate the magnitude of the residues of clothianidin in apples. Apple trees were treated with clothianidin at a rate of 0.2 lb active ingredient (a.i./acre). The highest average field trial residue found was 0.174 ppm in apple at 7 days pre-

harvest interval (PHI). The apple processing study conducted at the exaggerated rate of 3X rate indicated no concentration in any processed commodities including apple juice and wet pomace. A residue decline study was conducted, and an estimated half-life value was obtained at 5.9 days.

For pears, a total of seven field trials were conducted to determine the residue level in pear following one single treatment with clothianidin at a rate of 0.2 lb a.i./acre. The highest average field trial clothianidin residue was 0.163 ppm in pears. A residue decline study was conducted, and an estimated half-life value was obtained at 11.5 days for pears.

B. Toxicological Profile

1. *Acute toxicity.* The acute oral lethal dose (LD)₅₀ was >5,000 milligrams/kilogram body weight (mg/kg bwt) for both male and female rats. The acute dermal LD₅₀ was greater than 2,000 mg/kg bwt in rats. The 4-hour inhalation liquid chromatography (LC)₅₀ 6.14 milligrams per liter (mg/L) for male and female rats. Clothianidin was not irritating to rabbit skin or eyes and did not cause skin sensitization in guinea pigs.

2. *Genotoxicity.* Extensive mutagenicity studies were conducted with clothianidin. Based on the weight of evidence clothianidin was considered negative for genotoxicity.

3. *Reproductive and developmental toxicity.* In a two-generation reproduction study, rats were administered dietary levels of 0, 150, 500 and 2,500 ppm. The no observed adverse effect level (NOAEL) for reproductive parameters was 2,500 ppm. The NOAEL for developmental effects was 500 ppm based on decreased pup weights and the parental NOAEL and 150 ppm based on the decreased body weights.

A developmental toxicity study was conducted in rats with clothianidin using dose levels of 0, 10, 50 and 125 mg/kg bwt by gavage. The NOAEL for maternal toxicity was established at 10 mg/kg bwt and for developmental effects it was >125 mg/kg bwt. Additionally, a developmental toxicity was conducted with rabbits treated orally by gavage at 0, 10, 25, 75 and 100 mg/kg bwt. The NOAEL for maternal toxicity was 10 mg/kg bwt and for developmental toxicity it was 75 mg/kg bwt.

Developmental toxicity studies showed no primary developmental toxicity and no teratogenic potential was evident.

4. *Subchronic toxicity.* 90-day feeding studies were conducted in rats and

dogs. The rat study was conducted at dietary levels of 0, 150, 500 and 3,000 ppm and the dog study was conducted at 0, 325, 650 and 1,500 ppm. The NOAELs were established at 500 ppm for rat and 650 ppm for the dog.

5. *Chronic toxicity.* A two-year combined rat chronic/oncogenicity conducted at dietary levels of 0, 150, 500, 1,500 and 3,000 ppm demonstrated a NOAEL of 150 ppm based on reduced weight gains and non-neoplastic histomorphological changes. A 78-week mouse oncogenicity study conducted at dose levels of 0, 100, 350, 1,250, and 2,000, and 1,800 ppm for males and females, respectively, revealed NOAEL of 350 ppm based on reduced body weight gains and increased incidence of hypercellular hypertrophy. No evidence of oncogenicity was seen in the rat or the mice. A 52-week chronic toxicity study in dogs conducted at dietary levels of 0, 325, 650, 1,500 and 2,000 ppm revealed on overall NOAEL of 325 ppm based on slight decrease in ALT.

6. *Animal metabolism.* The nature of the clothianidin residue in livestock is adequately understood. In animals, parent clothianidin was the major component in liver, muscle and fat. Based on the available metabolism data, parent clothianidin, TZG, TZU, and ATMG-Pyr are proposed to be considered as the residues of concern in livestock matrices.

7. *Metabolite toxicology.* Eight *in vivo* metabolites of clothianidin identified in the rat were investigated for acute oral endpoint mutagenic activity. None of the metabolites were mutagenic either with or without activation and the lethal dose (LD)₅₀ values range from <500 to >2,000 mg/kg, showing low to moderate toxicity.

8. *Endocrine disruption.* All guideline studies conducted to characterize toxicological profile showed no endocrine related toxicity or tumorigenicity. No effects on T₃, T₄, TSH were observed in the subchronic rat study. In a two-generation reproduction study in rat; and rat and rabbit teratology studies, clothianidin did not show reproductive or teratogenic effects. The extensive data base shows that clothianidin has no endocrine properties.

C. Aggregate Exposure

1. *Dietary exposure.* The acute reference dose (aRfD) of 0.6 mg/kg bwt/day (acute NOAEL with a 100-fold uncertainty factor) was used to assess acute dietary exposure.

Seed treatment use. Bayer has conducted an acute dietary exposure Tier 2 assessment estimating the percent of the aRfD and corresponding margins