

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.* The metabolic pathway of butafenacil in cotton after defoliation applications is understood. The data support the selection of the residue of concern for tolerance setting.

2. *Analytical method.* Syngenta Crop Protection, Inc. has submitted practical analytical methodology for detecting and measuring levels of butafenacil in or on raw agricultural commodities. This method is based on crop-specific cleanup procedures and determination by liquid chromatography with a liquid chromatography/mass spectroscopy (LC/MS) detector. The limit of quantitation is 0.01 ppm for butafenacil for all crops tested, including cotton. The limit of quantitation for metabolites is also 0.01 ppm except for cotton gin trash where the limit of quantitation is 0.05 ppm. The analytical method was validated by determination of recoveries for fortified samples.

3. *Magnitude of residues.* A residue program was performed with butafenacil on the full geography required to support use on cotton.

B. Toxicological Profile

1. *Acute toxicity.* Butafenacil technical and the 100 EC formulation (0.83 lb active ingredient/gallon (ai/gal) have very low order of acute toxicity by oral, dermal, and inhalation exposure routes. Butafenacil technical is mildly irritating to the eye and non-irritating to the skin. The 100 EC formulation is moderately irritating to the eye and skin. Neither the technical nor the formulation are skin sensitizers. The rat dermal LD₅₀ is >5,000 milligram/kilogram (mg/kg). The rat dermal LD₅₀ is >4,000 mg/kg and the rat inhalation LD₅₀ is >5.1 milligrams per liter (mg/L) air. The end-use formulation of butafenacil has a similar low acute toxicity profile.

2. *Genotoxicity.* Butafenacil has been tested for its potential to induce gene mutation and chromosomal changes in five different test systems. Butafenacil technical did not induce point mutations in bacteria (ames assay in *salmonella typhimurium* or *escherichia coli*), and was not genotoxic in an *in vitro* unscheduled DNA synthesis assay in rat hepatocytes. Chromosome aberrations were not observed in an *in vitro* test using Chinese hamster ovary cells and there were no clastogenic or aneugenic effects on mouse bone marrow cell *in vivo* in a mouse micronucleus test. There was a

borderline positive response in the gene mutation test in V79 cells *in vitro* at the highest concentration in the presence of metabolic activation, which proved to be cytotoxic. This effect was considered to be an isolated finding and not to be of relevance when assessing the overall mutagenic potential of butafenacil. To substantiate this finding, a corresponding *in vivo in-vitro* DNA repair study on rat hepatocytes was performed. The results of this test show no mutagenic potential of butafenacil. Consequently, it can be concluded that butafenacil is not genotoxic.

3. *Reproductive and developmental toxicity.* In rat and rabbit teratology studies there was no evidence of teratogenicity. Delayed fetal development was apparent only at maternally toxic doses of butafenacil technical in rabbits. In the rabbit study (with doses of 0, 10, 100, 1,000 mg/kg), 1,000 mg/kg/day caused a mean body weight loss from days 12 to 16, decreased food consumption during the dosing period and an increase in the incidence of post-implantation loss, almost exclusively in the form of early resorptions. This increase in post-implantation loss, which was restricted to the top dose, was considered to be secondary to the maternal toxicity occurring at this dose level, and not a direct effect by butafenacil. Slightly reduced fetal body weights at 1,000 mg/kg/day were considered secondary to maternal effects. The incidence and type of external, visceral and skeletal findings were not affected by treatment. There was no indication of developmental toxicity in rabbit offspring at 100 mg/kg/day. The no observed adverse effect level (NOAEL) for both maternal and developmental toxicity was established at 100 mg/kg/day in rabbits.

In the rat teratogenicity study 0, 10, 100, 1,000 mg/kg, there was no observation of maternal toxicity. Body weight and food consumption were comparable in all groups. Reproduction and fetal parameters were not impaired. The incidence and type of external, visceral and skeletal findings were comparable in all dose groups. No treatment-related findings were noted. In conclusion, butafenacil was not teratogenic and not toxic to the progeny. Maternal parameters were not affected. The NOAEL for both maternal and developmental toxicity was >1,000 mg/kg/day, the highest dose level tested.

In a rat multi-generation study, butafenacil technical was administered in feed at concentrations of 0, 30, 300, or 1,000 ppm. The dose in mg/kg/day spans a wide range over the duration of the study as animals gain weight and go

through gestation and lactation. The ranges are 1.5–3.3, 15.5–31.9, and 50.9–101.6 for males and 1.7–6.3, 16.8–65.4, and 49.8–215.8 mg/kg/day for females at the 30, 300, or 1,000 ppm dietary levels, respectively. Butafenacil had no effect on reproductive parameters for either the F0 or F1 generation of parent animals. Parental body weight gain and food consumption were reduced at 300 and 1,000 ppm in both the F0 and F1 males and in F1 females. Increased incidence of liver pathology was observed in males and females in the F0 and F1 generations, including bile duct hyperplasia in both sexes at 300 and 1,000 ppm, hepatocellular hypertrophy in males at 1,000 ppm, and foci of necrosis in both sexes at 1,000 ppm and males at 300 ppm. Body weight gain was reduced during the lactation period at 300 and 1,000 ppm in offspring of the F0 generation and at 1,000 ppm in offspring of the F1 generation.

In conclusion, the NOAEL for systemic toxicity in both sexes and both generations of rats was 30 ppm (range = 1.5–3.3 mg/kg/day in males and 1.7–6.3 mg/kg/day in females). The grand mean test item intake (mean of all weekly means for both sexes, both generations, all time points) at this dose level was 2.48 mg/kg/day. There were no effects on the reproductive parameters and the NOAEL for reproductive toxicity was >1,000 ppm. Offspring effects were observed only at dose levels that also produced parental toxicity. There is no evidence that developing offspring are more sensitive than adults to the effects of butafenacil.

4. *Subchronic toxicity.* In a 90-day subchronic neurotoxicity study in rats, butafenacil was not neurotoxic when administered in the diet for 13 weeks at concentrations resulting in average daily test substance intakes of 0, 7.8, 23.5, or 74.4 mg/kg/day for males or at 0, 8.7, 26.0, or 78.9 mg/kg/day for females. There were no treatment-related neurobehavioral or motor activity effects, no macroscopic findings and no microscopic findings in central or peripheral nervous tissue. All animals survived until scheduled sacrifice and there were no treatment-related clinical observations. Histopathology of the liver revealed effects in animals of both sexes from the top dose group. In addition, one male at 23.5 mg/kg/day showed single cell necrosis of hepatocytes. In conclusion, subchronic dietary administration of butafenacil to rats did not produce neurotoxic effects at any dose level. The NOAEL for liver toxicity was 7.8 mg/kg/day for males and 26.0 mg/kg/day for females.

5. *Chronic toxicity.* Butafenacil technical was not oncogenic in rats or