UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

Date: JULY 31-2003

Subject: Butafenacil (PC Code 122004). Section 3 Registration for Application of Butafenacil to Cotton. **HED Human Health Risk Assessment.** Barcode D291514. Case 294136. Submission S601297.

From: Thomas Bloem, Chemist, Registration Action Branch 1 (RAB1)
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Through: Dana Vogel, Acting Branch Senior Scientist
RAB1/HED (7509C)

To: Jim Tompkins/Dennis Szuhay
Registration Division (PM Team 25)

Syngenta Crop Protection submitted a petition proposing the application of butafenacil (1,1-dimethyl-2-oxo-2-(2-propenyloxy)ethyl 2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl] benzoate) to cotton as a harvest aid. A summary of the estimated human health risks resulting from the requested butafenacil use is provided in this document. The risk assessment was provided by Tom Bloem and Mary Clock-Rust of RAB1, hazard assessment was provided by Robert Zendzian, of the Toxicology Branch; the residue chemistry assessment and dietary exposure assessment were provided by Tom Bloem of RAB1; the occupational and residential exposure assessments were provided by Mark Dow of RAB1; and the drinking water assessment was provided by Jose Melendez of the Environmental Fate and Effects Division (EFED).

1.0 EXECUTIVE SUMMARY

Butafenacil is a new herbicide belonging to the uracil chemical class. Butafenacil is intended for use as a cotton defoliant. The petitioner states that butafenacil inhibits protoporphyrinogen oxidase which leads to membrane destruction and cell death. Butafenacil is a new active ingredient with no feed/food or residential uses.

Hazard Assessment:

A complete toxicology database on this chemical has been submitted. Butafenacil has low acute toxicity in the rat by the oral, dermal or inhalation routes (acute toxicity Categories III and IV). It is toxic in the rat following repeated oral feeding in studies of 21 days or longer but not following dermal dosing up to 28 days at 1000 mg/kg/day. Compared to toxicity feeding studies in rats, butafenacil is more toxic in mouse feeding studies. It is significantly less toxic in oral dosing studies in dogs.

Subchronic toxicity caused by butafenacil is characterized primarily by hematological effects such as, decreased hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV), and increased red cell volume, and increased incidence of bone marrow hypercellularity. These effects were observed at the LOAEL of 62.3 mg/kg/day. Chronic administration caused liver and kidney effects. In the mouse oncogenicity study, enlarged livers with increased weights, were associated with hepatic microscopic lesions including Kupffer cell hyperplasia, inflammatory cell infiltration, and single cell necrosis in both sexes and deposits of lipofuscin in males were observed at the LOAEL of 6.96 mg/kg/day.

Based on the submitted studies, butafenacil produced no reproductive or developmental toxicity in rats or rabbits. Butafenacil is not neurotoxic in acute or 90-day neurotoxicity studies. There was no evidence of neurotoxicity in any other study throughout the data base.

Butafenacil did not produce tumors in the rat chronic/oncogenicity study nor in the mouse oncogenicity study. HIARC concluded that, based on the weight of the evidence, butafenacil is not mutagenic. Further, butafenacil is classified as "not likely to be carcinogenic to humans."

Toxicity data for the metabolites of butafenacil have also been evaluated. Overall, the information from these studies demonstrate no mutagenicity concerns and indicate that the metabolites are less toxic than the parent material.

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision:

The Hazard Identification and Assessment Review Committee (HIARC) met on 6/18/03 to select endpoints for risk assessment and to evaluate the potential for increased susceptibility of infants and children from exposure to butafenacil according to the February 2002 OPP 10X guidance document. The special Food Quality Protection Act (FQPA) Safety Factor (SF) was reduced to 1x based on toxicological considerations by HIARC (7/11/03; TXR # 0052030), the conservative residue assumptions used in the chronic dietary exposure risk assessment, the completeness of the residue chemistry and environmental fate databases and the lack of the potential for residential exposures (evaluated by the risk assessment team).

An endpoint attributable to a single exposure (dose) was not available in the data base including

the developmental toxicity studies. Since the increase in post-implantation loss in the rabbit teratology study was observed only at the limit dose (1000 mg/kg/day) in two dams, this endpoint was determined to be inappropriate for quantitation and risk for the general population or the subgroup, females, 13-50. The chronic reference dose (cRfD) was calculated by dividing the no-observed adverse effects level (NOAEL) by 100 (10X for interspecies extrapolation and 10X for intraspecies variation). Since the special FQPA SF has been reduced to 1X, the chronic population adjusted dose (cPAD) is equal to the cRfD. HIARC concluded that quantitation of dermal risk is not required due to lack of concern for systemic toxicity at the limit-dose following repeated dermal exposures as well as lack of concern for developmental toxicity. Since an oral study was selected for all durations of inhalation exposure, a 100 % inhalation absorption factor was used in the route-to-route extrapolation. The level of concern for occupational inhalation exposures are for margins of exposure (MOEs) <100. Endpoints selected for risk assessments that are pertinent to this action are summarized below.

Exposure Scenario	Dose	Study/Effect
Chronic Dietary	Oral NOAEL=1.2 mg/kg/day UF=100 cRfD=0.012 mg/kg/day	Mouse oncogenicity study; lowest-observed adverse effects level (LOAEL) is 6.96 based on enlarged livers with increased weights and hepatic microscopic lesions.
Short-term and Intermediate-term Inhalation	Oral NOAEL= 18.8 mg/kg/day LOC =MOE of 100	90-day rat feeding study; LOAEL is 62.3 mg/kg/day based on decreased hemoglobin and other blood parameters.

UF=uncertainty factor; LOC= level of concern

***Exposure Assessment*:**

Residential Exposure: Butafenacil is proposed for agricultural use on cotton only. No uses resulting in residential exposure are expected.

Dietary Exposure: The HED Metabolism Assessment Review Committee (MARC) concluded that the residues of concern in cotton for risk assessment purposes are butafenacil, the [2+2] cycloaddition dimer of butafenacil, and CGA-293731. The residue of concern for tolerance enforcement purposes is butafenacil, *per se*. A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 1.30), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII; 1994-1996 and 1998). The chronic analysis assumed tolerance level residues or maximum field trial residues (residues of concern for tolerance expression and risk assessment are different), 100% of crops are treated, and used DEEM™ (ver. 7.73) default concentration factors for all commodities. The chronic dietary food exposure estimates to butafenacil were less than HED's level of concern (<100% cPAD) for the general US population and all population subgroups (<1% cPAD for all population subgroups).

Drinking Water Exposure: As recommended by the MARC, EFED provided HED with upper bound estimates of the concentrations of butafenacil and its major transformation product, CGA-293731, that might be found in surface water and groundwater resulting from the use of butafenacil on cotton. The Tier I Estimated Environmental Concentrations (EECs) for butafenacil and CGA-293731 were calculated using FIRST (for surface water) and SCIGROW (for ground water) at the maximum application rate of 0.141 lb a.i./A/season. Since an acute assessment was not performed, chronic drinking water estimates were used: 0.00095 ppb for ground water and 0.049 ppb for surface water.

Occupational Exposure Estimates: Based upon the proposed use as a cotton defoliant,

occupational handlers may be exposed to butafenacil through mixing/loading (open-pour) the liquid formulation, applying butafenacil using open-cab, ground-boom machinery, and applying using fixed wing aircraft. Since HIARC did not identify dermal endpoints of concern, worker exposure and risks were estimated based on inhalation exposure only. Chemical-specific exposure data were not available to assess pesticide handler exposure. Therefore, surrogate data from the Pesticide Handler Exposure Database (PHED), Version 1.1 (August, 1998) were used to estimate mixer/loader and applicator exposure. MOEs for occupational handlers ranged from 11,000 to 194,000, and were not of concern to HED. Postapplication inhalation exposure is expected to be negligible, and since dermal endpoints were not identified, postapplication risks were not assessed.

Aggregate Exposure Assessment: The currently proposed uses for butafenacil include only agricultural use sites. No residential uses are proposed. Therefore, when addressing aggregate exposures, only the dietary pathways of food and drinking water were considered. Butafenacil is classified as "not likely to be carcinogenic to humans;" therefore, an aggregate cancer risk assessment was not performed. Because an endpoint of concern attributable to a single oral dose was not selected, only chronic exposures are considered. Estimates of chronic exposure from food were taken from the chronic dietary exposure assessment. Monitoring data for residues of butafenacil in drinking water are not available; therefore, HED calculated Drinking Water Levels of Comparison (DWLOCs) to estimate aggregate exposure. Based on dietary exposure estimates and default values for body weight and water consumption, the population subgroups for Children (aged 1-2, 3-5 and 6-12 years old) have the lowest, and therefore worst-case, DWLOC values of 120 ppb. Because this DWLOC is greater than both the surface water EEC (0.049 ppb) and ground water EEC (0.00095 ppb), HED is reasonably sure that aggregate exposure to the residues of concern for butafenacil will not exceed our level of concern.

Recommendation for Tolerances and Registration: The HED Hazard Identification Assessment Review Committee (HIARC) requested a 28-day inhalation toxicity study as a condition of registration. However, based on the low volatility and low inhalation toxicity (Category IV) of butafenacil and inhalation margins of exposure (MOEs) >1000 for the proposed uses in this risk assessment, butafenacil qualifies for a waiver of the 28-day inhalation toxicity study for the proposed uses [HED Standard Operating Procedure (SOP) 2002.01: *Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies*, 08/15/02]. **The requirement for the 28-day inhalation toxicity study is waived for this action only.** If in the future, requests for new uses or formulations are submitted that may result in a significant change in either the toxicity profile or exposure scenarios, HED will reconsider this data requirement.

Provided the petitioner submits a revised Section F, proposes and validates a livestock enforcement method, and EPA's analytical chemistry laboratory is able to validate the proposed livestock and plant enforcement methods, HED concludes that the toxicology, residue chemistry, and occupational/ residential databases are sufficient for a conditional registration and establishment of permanent tolerances listed below. The tolerance expression for cotton is for butafenacil (1,1-dimethyl-2-oxo-2-(2-propenyloxy)ethyl 2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl] benzoate) and the tolerance expression for the livestock commodities is for butafenacil and CGA-293731 (1-carboxy-1-methylethyl 2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl] benzoate).

Cotton, undelinted seed	0.50 ppm
Cotton, gin byproducts	10 ppm
*Liver	0.50 ppm
*Kidney	0.05 ppm

* = cattle, goat, hog, horse, sheep

An unconditional registration may be established upon the submission of the following data:

- cottonseed (412 days), cotton gin byproduct (504 days), cotton hull (321 days), cotton meal (323 days), and cotton oil (432 days) frozen storage stability data (butafenacil and CGA-293731)
- ruminant feeding study

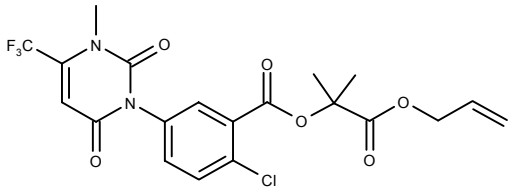
2.0. PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

The information pertaining to the physical chemical properties of butafenacil was taken from summary information submitted with the residue chemistry database (product chemistry reviews have not been completed). Butafenacil has a high vapor pressure and relatively high water solubility.

2.1 Identification of Butafenacil

CAS Chemical Name:	1,1-dimethyl-2-oxo-2-(2-propenyloxy)ethyl 2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl] benzoate
Common Name:	butafenacil
Chemical Type:	herbicide
Chemical Family:	uracil
PC Code No.:	122004
CAS Registry No.:	134605-64-4
Empirical Formula:	$C_{20}H_{18}ClF_3N_2O_6$
Molecular Weight:	473.5

2.2 Structural Formula of Butafenacil



2.3 Physical and Chemical Properties of Butafenacil

Physical State:	white powder
Vapor Pressure:	5.5×10^{-11} mm Hg
Water Solubility:	10 mg/l
Octanol/Water Partition Coefficient, Log K_{ow}:	3.19
Melting Point:	113 C
Density:	1.37 g/ml

3.0 HAZARD CHARACTERIZATION

References:

BUTAFENACIL - Report of the Hazard Identification Assessment Review Committee. R. Zendzian. 07/11/2003. TXR No. 0052030

Mechanism of Toxicity SARC Second Report: Butafenacil (PC Code: 122004). R. Zendzian. 07/21/2003. TXR No. 0052037.

Butafenacil - Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Decision Document. Meeting date: 2-July-2003. T. Bloem. 07/16/2003. TXR No. 0052048

3.1. Hazard Profile

The existing toxicological database for butafenacil supports the establishment of permanent tolerances for residues of butafenacil in/on cotton and livestock commodities. There is high confidence in the hazard endpoints and dose-response assessments conducted for this chemical.

Butafenacil is a new chemical proposed as an herbicide for defoliation of cotton. A complete toxicology database on this chemical has been submitted; however, HIARC requested submission of a 28-day inhalation toxicity study that is required to address the concern for repeated inhalation exposure based on the proposed use pattern (this study was subsequently waived). Butafenacil acts as an inhibitor of the enzyme protoporphyrinogen oxidase in plants and animals. This enzyme catalyzes the last step in the production of porphyrin a common component of the chlorophyll and hemoglobin molecules. In the animal, this inhibition blocks the production of hemoglobin and erythrocytes. A build up of precursors of porphyrin and liver toxicity occur secondary to this inhibition.

Butafenacil has low acute toxicity in the rat by the oral, dermal or inhalation routes. It is toxic in the rat following repeated oral feeding in studies of 21 days or longer but not following dermal dosing up to 28 days at 1000 mg/kg/day. Compared to toxicity studies in rats, It is more toxic in mouse feeding studies. It is significantly less toxic in oral dosing studies in the dog.

Subchronic toxicity caused by butafenacil is characterized primarily by hematological effects such as decreased hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), increased red cell volume, and increased incidence of bone marrow hypercellularity. These effects were observed at the LOAEL of 62.3 mg/kg/day. Chronic administration caused liver and kidney effects. In the mouse oncogenicity study, enlarged livers with increased weights were associated with hepatic microscopic lesions including Kupffer cell hyperplasia, inflammatory cell infiltration and single cell necrosis in both sexes and deposits of lipofuscin in males were observed at the LOAEL of 6.96 mg/kg/day.

Butafenacil showed no reproductive toxicity in the rat or rabbit teratology studies nor in the rat two generation reproduction study. Butafenacil is not neurotoxic in the acute or 90-day neurotoxicity studies. There was no evidence of neurotoxicity in any other study throughout the data base.

Butafenacil did not produce tumors in the rat chronic/oncogenicity study nor in the mouse oncogenicity study. HIARC concluded that, based on the weight of the evidence, butafenacil is not mutagenic. It is classified as “not likely to be carcinogenic to humans.”

Table 1. Acute Toxicity of Butafenacil

Guideline number	Study Type	MRID	Results	Toxicity Category
870.1100	Acute Oral	45394533	LD_{50} >5000 mg/kg male & female	IV
870.1200	Acute Dermal	45394608	LD_{50} >2000 mg/kg male & female	III
870.1300	Acute Inhalation	45394610	LC_{50} >5.10 mg/L	IV
870.2400	Primary Eye Irritation	45394612	ocular irritation resolved within 96 hours	III
870.2500	Primary Skin Irritation	45394614	not an irritant	IV
870.2600	Dermal Sensitization	45394616	not a sensitizer	NA

Table 2. Toxicity Profile for Butafenacil

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-day oral (dietary) toxicity rodents (rat)	MRID 45394619, 45394720 (1996) 0, 20, 100, 300, 1000, or 4000 ppm [0/0, 1.2/1.4, 6.1/7.1, 18.8/20.6, 62.3/69.3, or 243.2/281.8 mg/kg/day (M/F)] Acceptable/guideline	NOAEL = 300 ppm (18.8/20.6 mg/kg/day M/F) LOAEL = 1000 ppm (62.3/69.3 mg/kg/day M/F), based on decreased body weight gains, decreased hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, increased red cell volume, increased bone marrow hypercellularity; increased bilirubin and urobilinogen; increased alanine aminotransferase; hepatocyte necrosis; inflammatory liver cell infiltration
870.3100 90-day oral (dietary) toxicity in rodents (mouse)	MRID 45394727, 45394719 (1996) (reviewed in DER for MRID 45394625) 0, 1, 3, 10, 30, or 100 ppm [0/0, 0.12/0.18, 0.42/0.67, 1.27/1.98, 4.11/5.67, or 13.8/20.1 mg/kg/day (M/F)] Acceptable/guideline	NOAEL = 30 ppm (4.11/5.67 mg/kg/day M/F) LOAEL = 100 ppm (13.8/20.1 mg/kg/day M/F), based on hepatic histopathology: fatty change, glycogen deposition, and hypertrophy in both sexes
870.3150 90-day oral (capsule) toxicity in non-rodents (dog)	MRID 45394620, 45394726 (1996) 0, 25, 200, or 1000 mg/kg/day Acceptable/guideline	NOAEL = 200 mg/kg/day M/F LOAEL = 1000 mg/kg/day M/F, based on decreases in MCV and MCH in males; increases in RDW, HDW, platelets and triglycerides in males; and hemosiderosis in spleen and liver and extramedullary hematopoiesis the spleen in males
870.3200 28-day dermal toxicity (rat)	MRID 45394621 (1996) 0, 10, 100, or 1000 mg/kg/day Acceptable/guideline	NOAEL = 1000 mg/kg/day LOAEL = not determined

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700a Prenatal developmental toxicity in rodents (rat)	MRID 45394622,45394621 (1996) 0, 10, 100, or 1000 mg/kg/day Acceptable/guideline	Maternal NOAEL = 1000 mg/kg/day Maternal LOAEL = not determined Developmental NOAEL = 1000 mg/kg/day Developmental LOAEL = not determined
870.3700b Prenatal developmental toxicity in non-rodents (rabbit)	MRID 45394623, 45394722, 45394728 (1996) 0, 10, 100, or 1000 mg/kg/day Acceptable/guideline	Maternal NOAEL = 100 mg/kg/day Maternal LOAEL = 1000 mg/kg/day based on decreased body weight gains and food consumption during the treatment period, and on blood-stained vaginal discharge (related to total litter loss) in two doses Developmental NOAEL = 100 mg/kg/day Developmental LOAEL = 1000 mg/kg/day based on increased early resorptions and post-implantation loss
870.3800 2-generation reproduction and fertility effects	MRID 45394624, 45394624 (1998) 0, 30, 300, or 1000 ppm [0/0, 2.4/2.5, 23.8/25.2, or 79.6/83.8 mg/kg/day (M/F)] Acceptable/guideline	Parental/systemic NOAEL = 30 ppm (2.4/2.5 mg/kg/day M/F) Parental/systemic LOAEL = 300 ppm (23.8/25.2 mg/kg/day M/F), based on decreased body weights and food consumption and on increased incidences of bile duct hyperplasia and liver necrosis in males and females of both generations Offspring NOAEL = 300 ppm (23.8/25.2 mg/kg/day M/F) Offspring LOAEL = 1000 ppm (79.6/83.8 M/F), based on decreased pup body weight and body weight gain in both generations Reproductive NOAEL = 30 ppm (2.4/2.5 mg/kg/day M/F) Reproductive LOAEL = 300 ppm (23.8/25.2 mg/kg/day M/F) based on an increase in the number of days to mating in both generations
870.4100b 1-yr chronic oral (capsule) toxicity (dog)	MRID 45394734 (1998) 0, 20, 100, 500, or 1000 mg/kg/day Acceptable/guideline	NOAEL = 500 mg/kg/day M/F LOAEL = 1000 mg/kg/day M/F, based on decreased body weight gain in males, decreased MCV, MCH, and MCHC; increased thrombocytes and red cell volume distribution width; hepatic histopathology: glycogen disposition, inclusion bodies in cytoplasm, and pigment disposition in both sexes, and focal vaculolation in females
870.4200b 18-mo carcinogenicity dietary study (mouse)	MRID 45394625 (1996) 0,1, 3, 10, or 60 ppm [0/0, 0.12/0.13, 0.36/0.37, 1.17/1.20, or 6.96/6.59 mg/kg/day (M/F)] Acceptable/guideline	NOAEL = 10 ppm (1.17/1.20 mg/kg/day M/F) LOAEL = 60 ppm (6.96/6.59 mg/kg/day M/F), based on enlarged livers with increased weights, and hepatic microscopic lesions including Kupffer cell hyperplasia, inflammatory cell infiltration, and single cell necrosis in both sexes and on deposits of lipofuscin in males No evidence of carcinogenicity

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4300 Combined 2-yr chronic/carcinogenicity dietary study (rat)	MRID 45426401 (1998) 0, 10, 30, 100, or 300 ppm [0/0, 0.39/0.44, 1.14/1.30, 3.76/4.43, 11.4/13.0 mg/kg/day (M/F)] Acceptable/guideline	NOAEL = 100 ppm (3.76/4.43 mg/kg/day M/F) LOAEL = 300 ppm (11.4/13.0 mg/kg/day M/F), based on minimal hepatic abnormalities in the females, including a fatty change and increased mitotic activity No evidence of carcinogenicity
870.5100 *In vitro* bacterial gene mutation	MRID 45394701 (1997) Initial: 0, 61.73, 185.19, 555.56, 1666.67 or 5000 µg/plate with/without S9-mix. Confirmatory assay: 0, 312.50, 625.00, 1250.00, 2500.00 and 5000.00 µg/plate with/without S9-mix Acceptable/guideline	Negative in a reverse gene mutation assay in strains TA98, TA100, TA102, TA1535, TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* in the presence and absence of mammalian metabolic activation
870.5300 *In vitro* mammalian cells in culture	MRID 45394708 (1996) Initial test: 0, 9.2593, 27.7778, 83.3333, 250.0000 µg/mL without S9-mix; 0, 3.7037, 11.1111, 33.3333, 100.0000 µg/mL with S9-mix Confirmatory test: 31.2500, 62.5000, 125.0000, 250.0000 µg/mL without S9-mix and to concentrations of 12.5000, 25.0000, 50.0000, 100.0000 µg/mL with S9-mix Acceptable/guideline	Evidence of borderline induction of mutant colonies in presence of S9 in a mammalian cell gene mutation assay at the HGPRT locus of Chinese hamster V79 cells
870.5375 *In vitro* mammalian cytogenetics	MRID 45394711 (1996) Initial: 0, 15.63, 31.25, 62.5, 125.0 or 250.0 µg/mL with/without S9-mix Confirmatory : 0, 31.25, 62.5, 125.0 or 250.0 µg/mL with/without S9-mix Acceptable/guideline	Negative. No evidence of increase in chromosome aberrations over background
870.5395 *In vivo* mammalian cytogenetics - micronucleus assay (mouse)	MRID 4539714 (1995) 0, 1250, 2500, 5000 mg/kg Acceptable/guideline	Negative. No increase in frequency of micronucleated polychromatic erythrocytes
870.5550 Other genotoxicity - unscheduled DNA synthesis - *in vivo/ in vitro*	MRID 45394716 (1997) 0, 1250, 2500, or 5000 mg/kg Acceptable/guideline	Negative. No evidence of induction of UDS; no indications of induction of DNA damage.
870.5550 Other genotoxicity - unscheduled DNA sysnthesis - *in vitro*	MRID 45394715 (1995) Initial: 0, 0.98, 1.96, 3.91, 7.82, 15.63 or 31.25 µg/mL Confirmatory: 0, 1.563, 3.125, 6.25, 12.5, 25 or 50 µg/mL Acceptable/guideline	Negative. No evidence of induction of UDS; no indications of induction of DNA damage in primary rat hepatocytes in culture.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.6200a Acute neurotoxicity screening battery (rat)	MRID 45394717, 45394724 (1998) 0 or 2000 mg/kg Acceptable/guideline	NOAEL = 2000 mg/kg LOAEL = Not determined No evidence of neurotoxicity
870.6200b Subchronic neurotoxicity screening battery (rat)	MRID 45394718 (1996) 0, 100, 300, or 1000 ppm [0/0, 7/8, 21/24, or 72/76 mg/kg/day, M/F] Acceptable/guideline	NOAEL = 300 ppm 21/24 mg/kg/day M/F LOAEL = 1000 ppm 72/76 mg/kg/day M/F, based on liver histopathology and decreased motor activity at week 13 in the males No evidence of neurotoxicity
870.7485 Metabolism and pharmacokinetics (rat)	MRID 45394530, 45394531 (1997) 0.5 or 100 mg/kg) of [phenyl-^{14}C]CGA-276854 Acceptable/guideline	Overall recovery of administered radioactivity exceeded 95%, most (74-93%) of which was eliminated in the feces. Approximately 4-15% of the administered radioactivity was excreted in the urine over 168 hours while tissue residues were negligible, thereby implying limited absorption. No radioactivity was detected in expired air. Excretion of radioactivity was >90% complete by 48 hours. Up to six components were detected in the urine of rats from both dose groups, the most prevalent being an hydrolysis product, CGA-293731 which represented >90% of urinary radioactivity. Urinary elimination of metabolites was quantitatively greater in female rats than in males. Only minor amounts (near detection limits) of parent compound were detected in the urine of high-dose males. Based upon biliary elimination, ~74-79% of the dose entered the hepatobiliary pathway but was eliminated via the feces. An increase in parent compound in feces of the high-dose group was indicative of saturated absorption and/or saturated metabolism, but could not be definitively resolved due to the absence of biliary elimination studies at the high dose. Biliary elimination studies revealed that approximately 60-64% of the administered low dose was detected in 0-4 hour pooled bile samples and that the majority of fecal radioactivity could be attributed to biliary metabolites
Mechanistic studies	MRID 45394723 (1994) Acceptable/non-guideline	Effects on enzymes of cultured mouse, rat, and/or human hepatocytes involved with heme biosynthesis
	MRID 45394729 (2000) Acceptable/non-guideline	Effects on liver microsomal and plasma protox activity and its metabolic conversion
	MRID 45394730 (2000) Acceptable/non-guideline	Effects on porphyrin profile in rats; treatment induced porphyria, consisting of accumulation of selected porphyrins in the liver, spleen, and plasma and increased excretion in urine and feces
	MRID 45394731 (2000) Acceptable/non-guideline	Test substance interferes with heme biosynthesis in rats, as evidenced by dose-dependent, pronounced porphyria in the liver, spleen, and plasma; increased porphyrin excretion, and decreased activity of various isoenzymes of the hepatic microsomal cytochrome P450 system

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
	MRID 45394732 (2000) Acceptable/non-guideline	Test substance interferes with heme biosynthesis in mice, as evidenced by dose-dependent, pronounced porphyria in the liver, spleen, and plasma; increased porphyrin excretion, and decreased activity of various isoenzymes of the hepatic microsomal cytochrome P450 system
	MRID 45394733 (2000) Acceptable/non-guideline	Effects on porphyrin profile in mice; treatment induced porphyria, consisting of accumulation of selected porphyrins in the tissue and plasma, and increased excretion of heme precursors

Toxicity of Metabolites/Degradates: Additional toxicology studies conducted on metabolites of butafenacil were submitted to the Agency and are summarized in Table 3. **Overall, the information from these studies demonstrate no mutagenicity concerns and indicate that the metabolites are less toxic than the parent material following 28-days of repeated exposures to rats.**

Butafenacil acts as an inhibitor of the enzyme protoporphyrinogen oxygenase (protox) in plants and animals. The petitioner submitted an *in vitro* toxicity study investigating the inhibitory effects of butafenacil, CGA-293731, CGA-293730, and CGA-380963 on protox from mouse, rat, human, and dog plasma and liver mitochondrial fractions (MRID 45394729). Butafenacil was a potent inhibitor of protox activity in mouse liver mitochondrial fractions. When compared to the parent compound, CGA-293731 was about 5- to 6-fold less potent protox inhibitor in the mouse, rat, and dog liver and 2- to 3-fold less potent in human liver. CGA-293730 and CGA-380963 were essentially without inhibitory effect. The petitioner also submitted a 28-day rat oral toxicity study in which separate groups were dosed with butafenacil, CGA-293730, or CGA-380963 (MRID 45394735). The LOAEL for butafenacil (21.2/22.6 mg/kg/day (male/female)) was substantially lower than that for CGA-293730 (815.9/964.0 mg/kg/day (male/female)) with the target organs for both compounds being the hemopoetic system, liver, and kidney. A LOAEL for CGA-380963 was not observed (highest dose tested - 767.3/824.3 mg/kg/day (male/female)).

CGA-293730 and CGA-380963 were identified as major residues in the rotational crop and/or environmental fate studies. However, based on the demonstrated mode of toxicity for butafenacil in animals (inhibition of protox) and the demonstrated lack of protox inhibition by CGA-293730 and CGA-380963, despite the structural similarities to parent, the MARC concluded that CGA-293730 and CGA-380963 were not of concern. Since CGA-356925, a major metabolite found in rotational crops, is structurally similar to CGA-380963 (CGA-356925 = N-demethylated CGA-380963), the MARC concluded that this compound is not of concern.

Based on the available toxicity data and the structural similarities to butafenacil, the MARC concluded that CGA-293731 warrants inclusion as a residue of concern but is not likely to be more toxic than parent (CGA-293731 is a major rat metabolite). The [2+2] cycloaddition dimer of butafenacil was identified as a residue of concern in cotton. The MARC concluded that the dimer is likely to be hydrolyzed to CGA-293731 and a cyclobutane derivative of butafenacil in the same way that butafenacil is hydrolyzed to CGA-293731. As a result, the MARC concluded that the identified dimer warrants inclusion as a residue of concern but is not likely to be more

toxic than parent.

Table 3. Toxicity Profile for Butafenacil Metabolites

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3050 28-day oral (dietary) toxicity rodents (rat) - comparison of technical and plant metabolites	MRID 45394735 (1999) 0, 300, 2000, or 10000 ppm **CGA-276854** (butafenacil technical): 0/0, 21.2/22.6, 148.4/156.0, or 766.9/745.5 mg/kg/day (M/F) **CGA-293730** (plant metabolite): 0/0, 24.4/26.0, 139.4/150.6, or 815.9/964.0 (M/F) **CGA-380963** (plant metabolite): 0/0, 25.0/25.7, 142.6/162.2, or 767.3/824.3 (M/F) Acceptable/guideline	CGA 276854 (butafenacil technical): NOAEL =Not determined LOAEL = 300 ppm (21.2/22.6 mg/kg/day M/F), based on increased urobilinogen and bilirubin in males CGA 293730 (plant metabolite): NOAEL = 2000 ppm (139.4/150.6 mg/kg/day, M/F) LOAEL = 10000 ppm (815.9/964.0 mg/kg/day, M/F), based on minimal histological changes of the liver of both sexes and kidneys of the females CGA 380963 (plant metabolite): NOAEL = 10000 ppm (767.3/824.3 mg/kg/day, M/F) LOAEL = Not determined
870.5100 *In vitro* bacterial gene mutation	**CGA-293730** MRID 45394703 (1998) 0, 312.5, 625, 1250, 2500 or 5000 µg/plate with/without S9-mix. Acceptable/guideline	Negative in a reverse gene mutation assay in strains TA98, TA100, TA102, TA1535, TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* in the presence and absence of mammalian metabolic activation
870.5300 *In vitro* mammalian cells in culture	**CGA-293730** MRID 45394710 (1999) Initial test: 0, 111.11, 333.33, 1000, or 3000 µg/mL with/without S9-mix Confirmatory test: 375, 750, 1500 or 3000 µg/mL with/without S9-mix	Negative for induction of mutant colonies in the presence and absence of metabolic activation in a mammalian cell gene mutation assay at the HGPRT locus of Chinese hamster V79 cells
870.5375 *In vitro* mammalian cytogenetics	**CGA-293730** MRID 45394712 (1999) 0, 750, 1500, 3000 µg/mL with/without S9-mix Acceptable/guideline	Negative. No evidence of increase in chromosome aberrations over background in the presence and absence of activation in Chinese hamster ovary (CHO-CCL 61) cell cultures
870.5100 *In vitro* bacterial gene mutation	**CGA-380963** MRID 45394702 (1998) 0, 312.5, 625, 1250, 2500 or 5000 µg/plate with/without S9-mix. Acceptable/guideline	Negative in a reverse gene mutation assay in strains TA98, TA100, TA102, TA1535, TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* in the presence and absence of mammalian metabolic activation
870.5300 *In vitro* mammalian cells in culture	**CGA-380963** MRID 45394709 (1999) Initial test: 0, 92.5926, 277.7778, 833.3333, or 2500 µg/mL with S9-mix 0, 111.1111, 333.3333, 1000, or 3000 µg/mL without S9-mix Confirmatory test: 250, 500, 1000 or 2000 µg/mL with S9-mix 375, 750, 1500 or 3000 µg/mL without S9-mix Acceptable/guideline	Negative for induction of mutant colonies in the presence and absence of metabolic activation in a mammalian cell gene mutation assay at the HGPRT locus of Chinese hamster V79 cells

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5375 *In vitro* mammalian cytogenetics	**CGA-380963** MRID 45394713 (1999) 0, 1250, 2500, 5000 µg/mL with/without S9-mix Acceptable/guideline	Negative. No evidence of increase in chromosome aberrations over background in the presence and absence of activation in Chinese hamster ovary (CHO-CCL 61) cell cultures
870.5100 *In vitro* bacterial gene mutation	**CGA-98166** MRID 45394704 (1999) 0, 312.5, 625, 1250, 2500 or 5000 µg/plate with/without S9-mix. Acceptable/guideline	Negative in a reverse gene mutation assay in strains TA98, TA100, TA102, TA1535, TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* in the presence and absence of mammalian metabolic activation
870.5100 *In vitro* bacterial gene mutation	**CGA-356925** MRID 45394705 (1999) 0, 312.5, 625, 1250, 2500 or 5000 µg/plate with/without S9-mix. Acceptable/guideline	Negative in a reverse gene mutation assay in strains TA98, TA100, TA102, TA1535, TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* in the presence and absence of mammalian metabolic activation
870.5100 *In vitro* bacterial gene mutation	**CGA-368220** MRID 45394707 (1999) 0, 312.5, 625, 1250, 2500 or 5000 µg/plate with/without S9-mix. Acceptable/guideline	Negative in a reverse gene mutation assay in strains TA98, TA100, TA102, TA1535, TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* in the presence and absence of mammalian metabolic activation
870.5100 *In vitro* bacterial gene mutation	**CGA-380950** MRID 45394706 (1999) 0, 312.5, 625, 1250, 2500 or 5000 µg/plate with/without S9-mix. Acceptable/guideline	Negative in a reverse gene mutation assay in strains TA98, TA100, TA102, TA1535, TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* in the presence and absence of mammalian metabolic activation

3.2 FQPA Considerations

On June 18, 2003, the HED HIARC evaluated the potential for increased susceptibility of infants and children from exposure to butafenacil according to the February 2002 OPP 10X guidance document. The HIARC concluded that the toxicology database was complete for FQPA purposes and that there are no residual uncertainties for pre-/post-natal toxicity (Memo, R. Zendzian, 07/11/03; TXR No. 0052030). Based on the hazard data, the HIARC recommended the special FQPA SF be reduced to 1x. The butafenacil risk assessment team evaluated the quality of the exposure data; and, based on these data, recommended that the special FQPA SF be reduced to 1x. The recommendation is based on the following:

Hazard

- There is no quantitative or qualitative evidence of increased susceptibility of rat and rabbit fetuses to *in utero* exposure in developmental studies or to *in utero* and postnatal exposure to rats in the two-generation reproduction study.
- There are no concerns or residual uncertainties for pre- or postnatal toxicity.
- The toxicological database is complete for the assessment of toxicity and susceptibility following pre- and/or postnatal exposures. No clinical signs of neurotoxicity or neuropathology were observed in the data base, and the developmental neurotoxicity study was not required.

Exposure

- There are no residual concerns regarding pre- or post-natal toxicity or completeness of the toxicity or exposure database.
- The dietary food exposure assessment is Tier 1, screening level, which is based on tolerance level residues and assumes 100% of all crops will be treated with butafenacil. By using these screening level assessments, actual exposures/risks will not be underestimated.
- The dietary drinking water assessment utilizes water concentration values generated by models and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations which will not likely be exceeded.
- There are currently no registered residential uses of butafenacil.
- These assessments will not underestimate the exposure/risks posed by current or proposed uses of butafenacil.

3.3 Dose-Response Assessment

The Mechanism of Toxicity Assessment Review Committee (MTARC) reviewed the submitted mechanistic data for butafenacil and also considered the issue of whether the dog is a more appropriate model for risk assessment than the rodent (memo; R. Zendzian, 07/11/03; TXR No. 000052030). The committee concluded that although the mechanism is substantiated, the available information is not sufficient to mandate using the results of the dog studies for selection of doses for risk assessment rather than that of the mouse and the rat. Therefore, the most sensitive species (rodent) is utilized in the risk assessment.

Acute Dietary Endpoint: An endpoint attributable to a single exposure (dose) was not available in the data base including the developmental toxicity studies. Since the increase in post-implantation loss in the rabbit teratology study was observed only at the limit dose (1000 mg/kg/day) in two dams, this endpoint was determined to be inappropriate for quantitation and risk for the general population or the subgroup, females, 13-50.

Chronic Dietary Endpoint: The mouse oncogenicity study was used to select the endpoint for establishing the cRfD of 0.012 mg/kg/day. The NOAEL of 1.2 mg/kg/day was based upon enlarged livers with increased weights, and hepatic microscopic lesions (including Kupffer cell hyperplasia, inflammatory cell infiltration, and single cell necrosis in both sexes, and deposits of lipofuscin in males) at the LOAEL of 6.96 mg/kg/day. A 100-fold uncertainty factor (10x for interspecies extrapolation and 10x for intraspecies variation) was incorporated into the cRfD. The special FQPA SF of 1x is applicable for the chronic-dietary risk assessment. Thus, the cPAD is 0.012 mg/kg/day.

Carcinogenicity: The HIARC classified butafenacil as "not likely to be carcinogenic to humans" by all routes of exposure, based upon negative studies in rats and mice; therefore, a cancer risk assessment is not required.

Short-/Intermediate-Term Incidental Oral Endpoint: Short- and intermediate-term incidental oral endpoints were selected from the 90-day subchronic feeding study in rats. The NOAEL of 18.8 mg/kg/day was based upon decreased hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, increased red blood cell volume distribution width, and increased incidence of bone marrow hypercellularity at the LOAEL of 62.3 mg/kg/day.

Although the NOAEL for the 90 day mouse study was lower than the 90 day rat, the HIARC selected the 90 day rat for short- and intermediate- term risk assessments based on the following rationale. The treatment related effects observed in the 90-day dietary study in mice consisted of histopathological findings in the liver (fatty change, glycogen deposition, and hypertrophy). These findings at the HDT represent early stages of hepatic toxicity which were considered by the HIARC to be non-adverse and not appropriate for dose and endpoint selection for risk assessment. However, for butafenacil, these findings in the mouse were considered to demonstrate a progression of the toxicity with long-term dietary exposure. In that study, a LOAEL of approximately 7 mg/kg/day was observed, based on more severe, and clearly adverse hepatic lesions (i.e., single cell necrosis). In the rat, effects noted in the 13-week dietary study at the LOAEL of 62.3/69.3 mg/kg/day (in M/F) included hepatocytic necrosis and inflammatory liver cell infiltration, with a NOAEL of 18.8/20.6 mg/kg/day in males/females. Therefore based on clearly adverse effects in hepatic histopathology, the HIARC selected the 90-day dietary study in rats to provide a solid endpoint and dose for short-intermediate-term risk assessment.

The endpoint of concern is appropriate for the population of concern (infants and children) and the durations of exposure. Although the NOAEL (1.2 mg/kg/day) in the mouse oncogenicity study is lower, the NOAEL (18.8 mg/kg/day) in the rat study was selected because consistent alterations in clinical chemistry values were observed in rats in the subchronic and chronic studies. In the mouse study, the LOAEL is based on increases in organ weights and histopathological lesions of the liver which are known to occur after long-term exposure and thus these endpoints are not appropriate for short- and intermediate-term exposure periods.

Dermal Endpoints: Quantification of dermal risk assessment is not required due to lack of concern for dermal, systemic or developmental toxicity.

Short- and Intermediate-Term Inhalation Endpoints: Short- and intermediate-term inhalation endpoints were selected from the 90-day subchronic feeding study in rats. The NOAEL of 18.8 mg/kg/day was based upon decreased hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, increased red blood cell volume distribution width, and increased incidence of bone marrow hypercellularity at the LOAEL of 62.3 mg/kg/day. The endpoint of concern is appropriate for the population of concern (infants and children) and the durations of exposure.

Long-Term Inhalation Endpoint: The mouse oncogenicity study was used to select the endpoint for long-term inhalation risk assessment. The NOAEL of 1.2 mg/kg/day was based upon enlarged livers with increased weights, and hepatic microscopic lesions (including Kupffer cell hyperplasia, inflammatory cell infiltration, and single cell necrosis in both sexes, and deposits of lipofuscin in males) at the LOAEL of 6.96 mg/kg/day. The proposed use pattern for butafenacil is not expected to result in long-term inhalation exposure; therefore, this risk assessment was not performed.

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 4.

Table 4. Endpoints Selected by HIARC for Butafenacil Risk Assessment

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General population including infants and children)	None	NA	An endpoint attributable to a single dose is not available in the data base.
Chronic Dietary (All populations)	NOAEL= **1.2** mg/kg/day UF = **100** **Chronic RfD** = **0.012** mg/kg/day	FQPA SF = **1** **cPAD** = chronic RfD / FQPA SF = **0.012** mg/kg/day	**Mouse Oncogenicity Study** The LOAEL is 6.96 mg/kg/day, based on enlarged livers with increased weights, and hepatic microscopic lesions including Kupffer cell hyperplasia, inflammatory cell infiltration, and single cell necrosis in both sexes and on deposits of lipofuscin in males.
Short-Term Incidental Oral (1-30 days)	NOAEL= **18.8** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** = NA	**90-day rat feeding study** The LOAEL for this study is 62.3 mg/kg/day, based on decreased hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, increased red cell volume distribution width, and increased incidence of bone marrow hypercellularity.
Intermediate-Term Incidental Oral (1-6 months)	NOAEL= **18.8** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** = NA	**90-day rat feeding study** The LOAEL for this study is 62.3 mg/kg/day, based on decreased hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, increased red cell volume distribution width, and increased incidence of bone marrow hypercellularity.
Dermal (All durations)	NA	NA	Quantification of dermal risk assessment is not required due to lack of concern for dermal, systemic or developmental toxicity.
Short-Term Inhalation (1 to 30 days)	Oral NOAEL= **18.8** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational = 100**	**90-day rat feeding study** The LOAEL for this study is 62.3 mg/kg/day based on decreased hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, increased red cell volume distribution width, and increased incidence of bone marrow hypercellularity.

Intermediate-Term Inhalation (1 to 6 months)	Oral NOAEL= **18.8** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** = **100**	**90-day rat feeding study** The LOAEL for this study is 62.3 mg/kg/day, based on decreased hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, increased red cell volume distribution width, and increased incidence of bone marrow hypercellularity.
Long-Term Inhalation (>6 months)	Oral NOAEL= **1.2** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** = **100**	**Mouse Oncogenicity Study** The LOAEL is 6.96 mg/kg/day, based on enlarged livers with increased weights, and hepatic microscopic lesions including Kupffer cell hyperplasia, inflammatory cell infiltration, and single cell necrosis in both sexes and on deposits of lipofuscin in males.
Cancer (oral, dermal, inhalation)	NA	NA	Classified as "not likely to be carcinogenic to humans."

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

* The reference to the special FQPA SF refers to any additional SF retained due to concerns unique to the FQPA.

3.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, butafenacil may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

References:

Tier I Estimated Environmental Concentrations of Butafenacil, and Total Butafenacil Residues, for use in Human Health Risk Assessment (DP Barcode D287459). J. Melendez. 07/10/2003.

Butafenacil. Registration for Use on Cotton. Summary of Analytical Chemistry and Residue Data. D289180. T. Bloem. 07/17/2003.

Butafenacil (122004). Chronic Dietary Exposure Assessment. DB Barcode: D291621. Submission S601297. Case 294136. T. Bloem. 07/18/2003.

4.1 Summary of Registered Uses

There are no registered food/feed or residential uses for butafenacil.

4.2 Summary of Proposed Uses

The petitioner is proposing application of a 0.83 lb ai/gal EC formulation of butafenacil to cotton as a harvest aid. The submitted label adequately describes the proposed use pattern. Table 5 is a summary of the proposed application scenario.

Table 5. Summary of the Proposed Butafenacil Use on Cotton

App. Timing, Type, and Equip.	Formulation (EPA Reg. No.)	App. Rate (lb ai/acre)	RTI (days)	PHI (days)	Use Directions and Limitations
harvest aid; broadcast foliar application; ground or aerial equipment	Inspire™ EC; 0.83 lb ai/gal (100-xxx)	2 x 0.069-0.083	7	3	• maximum seasonal use rate of 0.152 lb ai/acre • minimum application volumes of 5 and 10 gal/acre are specified for aerial and ground application, respectively • the following adjuvants may be used at the indicated final concentration: 0.25% non-ionic surfactant, 2.5% crop oil concentrate, or 0.125% silicone-based surfactant • do not rotate to any food/feed crop other than cotton for 240 days after last application • apply only after all bolls have matured, at least 60% of the bolls are open, and there are not more than four nodes between the highest first position cracked boll and the highest first position harvestable boll

4.3 Dietary Exposure/Risk Pathway

4.3.1 Residue Profile

Background: Syngenta Crop Protection submitted a petition proposing the application of butafenacil to cotton as a harvest aid. In conjunction with this use, Syngenta is proposing the establishment of permanent tolerances for residues of butafenacil and its metabolites, CGA-293730 and CGA-293731, expressed as parent, in/on the following commodities: cottonseed at 0.5 ppm and cotton gin byproducts at 13.0 ppm.

Nature of the Residue - Cotton: The qualitative nature of butafenacil residues in cotton is understood based upon an adequate cotton metabolism study. Based on the observed metabolite profile in cotton, butafenacil forms a [2+2]cycloaddition dimer which the petitioner stated was photo-metabolite formed on the plant surface. To a lesser extent, the parent compound also undergoes hydrolysis to form CGA-293731 and CGA-293730, which can be subsequently esterified to form the ethylene glycol ester of CGA-293731 and ethyl ester of CGA-293730. The MARC concluded that the residues of concern in cotton, for risk assessment purposes, are butafenacil, the [2+2] cycloaddition dimer of butafenacil, and CGA-293731. The residue of concern for tolerance enforcement purposes is butafenacil *per se* (D291620, T. Bloem, 16-Jul-2003).

Nature of the Residue - Livestock: The qualitative nature of butafenacil residue in livestock is understood based upon adequate ruminant and poultry metabolism studies. In both goats and hens, the primary route of metabolism for butafenacil involves the hydrolysis of butafenacil to CGA-293731. Minor metabolic processes include the hydrolysis, hydroxylation, N-demethylation (poultry only), and/or glucuronic acid conjugation (ruminants only) of CGA-293731 to form a variety of minor metabolites (CGA-293730, P1, P1-D, P5, and P6) and the oxidation of the allylic ester moiety of the parent to form a glycerol ester (P2). The MARC reviewed the poultry and ruminant metabolism studies and concluded that the residues of concern in livestock, for tolerance enforcement and risk assessment purposes, are butafenacil and CGA-293731 (D291620, T. Bloem, 16-Jul-2003).

Magnitude of the Residue - Cotton: The petitioner submitted a cotton magnitude of the residue study conducted at the maximum proposed application rate and minimum PHI. Provided the petitioner validates the cottonseed (412 days) and cotton gin byproduct (504 days) frozen storage intervals (butafenacil and CGA-293731), HED concludes that the available field trial data support tolerances for residues of butafenacil in/on cotton, seed and cotton, gin byproduct of 0.50 ppm and 10 ppm, respectively. A revised Section F should be submitted.

Provided the petitioner validates the cotton seed (330 days), oil (432 days), meal (323 days), and hull (321 days) frozen storage intervals (butafenacil and CGA-293731), the submitted cottonseed processing study is adequate and indicates that residues of butafenacil do not concentrate in cottonseed processed commodities. Since the average butafenacil processing factors for cottonseed hulls (0.20x), meal (0.40x) and oil (0.22x) were less than 1, separate tolerances are not required for these commodities.

Magnitude of the Residues - Livestock: No ruminant or poultry feeding studies were submitted with the current petition. The maximum theoretical dietary burden (MTDB) for livestock are 0.13 ppm for poultry, 0.10 ppm for hog, 3.81 ppm for beef cattle, and 3.92 ppm for dairy cattle. Based on the total radioactive residues (TRR) in poultry commodities from the metabolism study (≤0.295 ppm), in which hens were dosed for 8 days at levels equivalent to 85.4 ppm in the diet (657x MTDB), quantifiable residues in poultry commodities are unlikely (40 CFR 180.6(a)(3); a poultry feeding study is unnecessary). Based on the TRR in ruminant commodities from the goat metabolism study (liver - 4.440 ppm; kidney - 0.413 ppm; fat - 0.010 ppm; muscle - 0.010 ppm; and milk - 0.007 ppm), in which goats were dosed for 4 consecutive days at levels equivalent to 76-112 ppm in the diet (19x), quantifiable residues are unlikely in fat, muscle, and milk (40 CFR 180.6(a)(3)). However, quantifiable residues in liver and kidney are likely (77-83% of the TRR was identified as CGA-293731). Therefore, a ruminant feeding study is requested. Based on the goat metabolism study, HED concludes that tolerances for the combined residues of butafenacil and CGA-293731 in liver (cattle, goat, hog, horse, and sheep) and kidney (cattle, goat, hog, horse, and sheep) of 0.50 ppm and 0.05 ppm, respectively, are appropriate.

Magnitude of the Residue in Rotational Crops: The petitioner submitted a confined rotational crop study conducted at ~0.22 lbs ai/acre (1.4x the maximum proposed rate for cotton). Based on the metabolic profile observed in the representative rotational crops, the metabolite profile in rotational crops is similar to primary crops. Butafenacil undergoes hydrolysis to form CGA-293731 and CGA-293730. These two metabolites undergo N-demethylation of the uracil ring to form CGA-380950 and CGA-356925. CGA-293730 also undergoes reduction of the uracil ring double bond to yield CGA-380963. Based on the enzymatic and acidic hydrolysis, metabolites CGA-380950 and CGA-380963 may also be present as conjugates. Based on the confined rotational crop study, field rotational crop study (see below), and toxicological considerations, the MARC determined that the residue of concern in rotational crops, for purposes of tolerance expression and risk assessment, is butafenacil (D291620, T. Bloem, 19-Jul-2003).

The petitioner also submitted a field rotational crop study which indicated that residues of butafenacil, CGA-293730, and CGA-293731 were <0.01 ppm in/on turnip, lettuce, and wheat planted 240 days after soil treatment at 0.268 lb ai/acre (1.7x the maximum proposed seasonal application rate). Based on these data, HED concludes that the petitioner's proposed 240-day plant-back interval (PBI) for all crops excluding cotton, is appropriate (no tolerances are required).

Analytical Enforcement Method - Plants: The petitioner proposed Syngenta Method 131-99 for enforcement of the proposed cotton tolerances (adequate validation, independent laboratory validation (ILV), and radiovalidation data has been submitted). HED forwarded the method to EPA's analytical chemistry laboratory for petition method validation (PMV; D285016, T. Bloem, 27-Feb-2003). A successful PMV is necessary before this method can be employed as an enforcement method. The petitioner is requested to submit a confirmatory method and an interference study (interference study will demonstrate that other pesticides registered for application to cotton do not interfere with quantitation of butafenacil). If the petitioner proposes a confirmatory method which employs a mass selective detector (MSD) and monitors three structurally significant ions (m/z > 91), then an interference study is not necessary.

Analytical Enforcement Method - Livestock: The petitioner has not proposed a method for enforcement of the recommended ruminant liver and kidney tolerances. The petitioner should propose an enforcement method and submit adequate validation, ILV, and radiovalidation. Upon submission and acceptance of these data, HED will forward the method to the analytical laboratory for PMV. Successful completion of each of these steps is necessary before the proposed method can be employed as an enforcement method.

Multiresidue Methods: Butafenacil and its two metabolites, CGA-293730 and CGA-293731, were evaluated using FDA Multiresidue Protocols. Butafenacil was tested using Protocols C, D, and E. CGA-293730 and CGA-293731 were tested using Protocols B and C. Butafenacil was not recovered through FDA multiresidue methods Protocols D and E (Protocols D and E with Florisil column cleanup; recovery without Florisil column clean-up was not tested). However, depending on the fortification level, CGA-293730 and CGA-293731 could be partially or completely recovered from corn forage using Method 402 E2/C1a/C1b/C1c. These data were forwarded to the U.S. FDA for further evaluation (D288449, T. Bloem, 27-Feb-2003).

International Harmonization of Tolerances: Canada, Codex, and Mexico do not have maximum residue limits (MRLs) for residues of butafenacil in/on cotton. Therefore, harmonization is not an issue.

Tolerance Summary: The proposed and recommended tolerances for residues of butafenacil (cotton commodities) and butafenacil and CGA-293731 (livestock commodities) are listed in Table 6.

Table 6. Tolerance Summary for Butafenacil

Proposed Tolerance[1]		Recommended Tolerance[2]	
Commodity Definition	**Tolerance (ppm)**	**Commodity Definition**	**Tolerance (ppm)**
Cottonseed	0.5	Cotton, Seed	0.50
Cotton by-products	13	Cotton, gin byproducts	10
Liver[3]	not proposed	Liver[1]	0.50
Kidney[3]	not proposed	Kidney[1]	0.05

[1] proposed tolerance expression - butafenacil, CGA-293731, CGA-293730

[2] recommended tolerance expression (plants) - butafenacil; recommended tolerance expression (livestock) - butafenacil and CGA-293731.

[3] cattle, goat, hog, horse, sheep

Residues to be Used in the Dietary Exposure Assessment: The residues of concern in cotton for risk assessment purposes are butafenacil, the [2+2] cycloaddition dimer of butafenacil, and CGA-293731 (residues of concern for tolerance expression is butafenacil). Residues of the dimer were not determined in the magnitude of the residues studies. The cotton metabolism study indicated that the dimer was present in cottonseed at concentrations 0.25-0.62x that of butafenacil. Based on the maximum butafenacil concentration in cottonseed of 0.37 ppm, the maximum expected concentration of the dimer in cottonseed is 0.23 ppm. Combining the maximum butafenacil (0.37 ppm) and CGA-293731 (0.06 ppm) concentrations from the field trials with expected maximum residue of the dimer (0.23 ppm), a maximum combined residue of combined butafenacil, dimer, and CGA-293731 in/on cotton seed of 0.66 ppm is attained (this figure was used in the dietary exposure assessment and in the ruminant dietary burden analysis). Since the dimer possesses the same chemical moieties as the parent, HED concludes that the

dimer will have a nearly identical K_{ow} as that of the parent and is likely to have similar cotton processing factors as the parent.

4.3.2 Dietary Exposure Analyses

The HIARC did not select an endpoint of concern attributable to a single oral dose for any population subgroup (including infants and children), and butafenacil has been classified as "not likely" to be a human carcinogen according to EPA *Proposed Guidelines for Carcinogen Risk Assessment* (10-Apr-1996). Therefore, acute and cancer dietary exposure analyses were not conducted.

Butafenacil chronic dietary exposure assessments were conducted using DEEM-FCID™, Version 1.30), which incorporates consumption data from USDA's CSFII, 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food-form is summed with the residue consumption estimates for all other food/food-forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

DEEM-FCID™ (Ver. 1.30) estimates the dietary exposure for the U.S. population and various population subgroups. Based on an analysis of 1994-96, 98 CSFII consumption data which took into account dietary patterns and number of survey respondents, HED determined that the following population groupings were appropriate for regulatory purposes (only the exposure estimates for these populations are reported in this document): U.S. Population, all infants (<1 year old), children 1-2 years old, children 3-5 years old, children 6-12 years old, youth 13-19 years old, females 13-49 years old, adults 20-49 years old, and/or adults 50+ years old.

4.3.2.1 Chronic Dietary Exposure Analysis

The chronic dietary exposure analysis assumed tolerance level residues or maximum field trial residues (residues of concern for tolerance expression and risk assessment are different), 100% crop treated, and DEEM (ver. 7.73) default concentration factors were used for all commodities. The chronic dietary food exposure estimates for butafenacil were less than HED's level of concern (<100% cPAD) for the general US population and all population subgroups (<1% cPAD for all population subgroups).

Table 7. Summary of Results from Chronic Dietary Exposure Analysis for Butafenacil

Subgroups	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.000041	<1
All Infants (< 1 year old)	0.000014	<1
Children 1-2 years old	0.000097	<1
Children 3-5 years old	0.000104	<1
Children 6-12 years old	0.000069	<1
Youth 13-19 years old	0.000036	<1
Adults 20-49 years old	0.000033	<1
Females 13-49 years old	0.000030	<1
Adults 50+ years	0.000031	<1

4.4 Water Exposure/Risk Pathway

Environmental Fate Assessment: The major routes of dissipation for butafenacil are aerobic and anaerobic metabolism (half-life <5 days), and, to a lesser extent, hydrolysis under alkaline conditions (half-life 100-117 days at pH 7; half-life <2 days at pH 9). The major transformation products found in the aerobic soil metabolism studies were CGA-293730, CGA–293731, and CGA-380963, approximately in that order (all >10% of the applied). Three terrestrial field dissipation studies confirm that butafenacil is short-lived and that it does not last long enough to leach to subsurfaces (half-life of 1-3 days). Despite this, it has been found that the total residues of butafenacil plus the three major transformation products are very persistent. Under anaerobic conditions, the degradation products CGA-98166 and trifluoroacetone (a volatile compound) were observed. Of these transformation products, the ones found in the field at measurable amounts were the aerobic soil metabolites. Of them, CGA-293730 and CGA-380963 appeared to be important leachers.

Ground and Surface Water EECs: The MARC concluded that the residues of concern in drinking water are butafenacil and CGA-293731 (D291620, T. Bloem, 16-Jul-2003). The metabolites CGA-293730 and CGA380963 were not included as a residues of concern in drinking water because they are believed to be of lower toxicity. Since ground or surface water monitoring data were not available to calculate quantitative aggregate exposure, EFED provided Tier I ground (SCI-GROW) and surface water (FIRST) EECs for butafenacil and CGA-293731. Both models were conducted using the cotton application scenario (0.141 lb ai/acre/season). The upper bound confidence value (90^{th} percentile) was used in FIRST, and the median value for SCIGROW. CGA-293731 reached a maximum of 66.71% of the applied parent in one aerobic soil metabolism study. It was simulated by multiplying the label application rate by 66.71%. It is noted that by selecting the highest percentage observed out of four studies, the results are likely overestimations (particularly of the peak values), and represent upper-bound estimates of the concentrations that might be found in surface waters and ground waters due to the use of butafenacil on cotton at the maximum application rate. The resulting ground and chronic surface water EECs are shown below in Table 8.

Table 8. Modeling Results for Use of Butafenacil and CGA-293731 on Cotton

Parameter	Butafenacil	CGA-293731	Combined Parent+Metabolite
FIRST 1.0 Peak Untreated Surface Water Concentration (ppb)	0.216 ppb	1.14 ppb	1.36 ppb
FIRST 1.0 Annual Average Untreated Surface Water Concentration (ppb)	0.0012 ppb	0.048 ppb	0.049 ppb
SCIGROW Ground Water Concentration (ppb)	$2.8x10^{-5}$ ppb	$9.2x10^{-4}$ ppb	0.00095 ppb

4.5 Residential/Non-Occupational Exposure Pathway

Butafenacil is not proposed or registered for residential application. However, spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from ground application. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT® computer model to its risk assessments for pesticides applied by air, orchard air-blast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

The currently proposed uses for butafenacil include only agricultural use sites. No residential uses are proposed. Therefore, when addressing aggregate exposures, only the dietary pathways of food and drinking water were considered. Because an endpoint of concern attributable to a single oral dose was not selected, only chronic exposures are considered. Butafenacil is classified as "not likely to be carcinogenic to humans;" therefore, an aggregate cancer risk assessment was not performed.

5.1 Chronic Aggregate Risk Assessment

Estimates of exposures from food were taken from the DEEM™ results described above (Section 4.3.2). These exposure estimates are based on tolerance level residues and the conservative assumption of 100% crop treated and should be considered unrefined.

To address exposure to residues of butafenacil in drinking water, HED has calculated DWLOCs. These values are the maximum concentration of a chemical that might occur in drinking water after taking into account exposures to residues from other pathways and sources. The DWLOCs are compared against the modeled EECs provided by EFED (see Section 4.4). DWLOC values that are greater than the EECs indicate that aggregate exposures are unlikely to exceed HED's level of concern.

As shown in Table 9, the DWLOCs for the general US population and all of the representative population subgroups modeled by DEEM-FCID are greater than both the surface water and ground water EECs. Because of the degree of difference between the DWLOCs and the EECs, and the unrefined status of the dietary exposure estimates, HED believes that aggregate chronic exposure to butafenacil associated with the requested use on cotton is unlikely to result in chronic aggregate risks that exceeds HED's level of concern.

Table 9. Chronic Aggregate Exposures to Butafenacil Residues

Population	cPAD (mg/kg/day)	Chronic Food Exposure (mg/kg/day)	Max Chronic Water Exposure[1] (mg/kg/day)	Ground Water EEC[2] (ppb)	Surface Water EEC[2] (ppb)	Chronic DWLOC[3] (ppb)
General U.S. Population	0.012	0.000041	0.012	0.00095	0.049	420
All Infants (< 1 year old)		0.000014	0.012			120
Children 1-2 years old		0.000097	0.012			120
Children 3-5 years old		0.000104	0.012			120
Children 6-12 years old		0.000069	0.012			120
Youth 13-19 years old		0.000036	0.012			360
Adults 20-49 years old		0.000033	0.012			420
Females 13-49 years old		0.000030	0.012			360
Adults 50+ years old		0.000031	0.012			420

[1] maximum chronic water exposure (mg/kg/day) = cPAD (mg/kg/day) - chronic food exposure from DEEM (mg/kg/day); no res. exp.

[2] Parent plus CGA-293731; FIRST and SCI-GROW modeling EECs (Tier 1); cotton application scenario - 1 x 0.141 lb ai/acre; maximum proposed rate

[3] DWLOC(µg/L) = (allowable water exposure (mg/kg/day) x body weight (kg) x 1000 µg/mg) ÷ (water consumption (liters)) Consumption = 1 L/day for populations <13 years old and 2 L/day for populations ≥ 13 years old. Default body weights = 70 kg for general US population and adult males, 60 kg for youth and females ≥ 13 years old, and 10 kg for all others. Values are

rounded to 2 significant figures.

6.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether butafenacil has a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to butafenacil and any other substances and butafenacil does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that butafenacil has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

7.0 OCCUPATIONAL EXPOSURE AND RISK ASSESSMENT

Reference:

Butafenacil - Exposure/Risk Assessment for Pesticide Handlers and Agricultural Workers from the Proposed Use of Butafenacil on Cotton. M. Dow. D291514. 21-July-2003.

7.1 Handler Exposure and Risk Assessment

Based upon the proposed use patterns, HED believes that there are three pesticide handler activities that should be assessed as being the most highly exposed and they are: a mixer/loader using liquid, open-pour technique; an applicator using open-cab, ground-boom machinery; and an applicator using fixed wing aircraft.

Private (i.e., grower) applicators may perform both functions, that is, load and apply the material. HED Science Advisory Council for Exposure (ExpoSAC) Policy 12 (29 March 2000) directs that although the same individual may perform both tasks, they shall be assessed separately. By separating the two job functions, HED determines the most appropriate levels of personal protection equipment (PPE) for each aspect of the job without requiring the applicator to wear unnecessary PPE that may be required for the mixer/loaders (e.g., chemical resistant gloves may only be necessary during the pouring of a liquid formulation)."

Chemical specific data were not available with which to assess pesticide handler exposure. Therefore, surrogate data from studies in the PHED, Version 1.1 (August 1998) Surrogate Exposure Guide were used to estimate mixer/loader and applicator exposure. The label directs pesticide handlers to wear long sleeved shirt, long pants, shoes plus socks, chemical resistant gloves such as barrier laminate, butyl rubber or Viton and protective eyewear (goggles or face shield).

There is a possibility for commercial handlers to have intermediate-term exposure (1-6 months) to butafenacil because cotton is planted over large acreage. The short-, intermediate-, and long-term

inhalation toxicological endpoints identified by HIARC for use in risk assessment are identical (18.8 mg a.i./kg bw/day). Therefore, the estimated MOEs presented in Table 10 are adequately protective of all durations of exposure.

Table 10. Inhalation Exposure and Risks to Pesticide Handlers Applying Butafenacil to Cotton

Unit Exposure[1] mg a.i./lb handled	Application Rate[2] lb a.i. handled/A	Units Treated[3]	Average Daily Dose[4] mg/kg bw/day	Margin of Exposure[5]
Mixer/Loader -Liquid - Open Loading Supporting Aerial Operations				
Inhalation 0.0012 HC	0.083	1200	0.0017	11,000
Applicator - Ground-boom - Open Cab				
Inhalation 0.00074 HC	0.083	200	0.000175	110,000
Applicator -Aerial				
Inhalation 0.000068 MC	0.083	1200	0.0000967	190,000

1. Unit Exposure = mg a.i./lb a.i. handled; taken from the Pesticide Handler's Exposure Database PHED Surrogate Exposure Guide version 1.1; August 1998; HC = high confidence data; MC = Medium Confidence Data
2. Application Rate from proposed label booklet for Inspire™ EC Cotton Defoliant
3. Acres Treated from ExpoSAC SOP 9.1 Rev. 25 SEP 01
4. Average Daily Dose (ADD) = Unit Exposure * Application Rate * Units Treated ÷ 70 kg body weight. NOAEL taken from a 28 day rat study where effects were changes in hematology and liver necrosis. Inhalation absorption assumed 100%.
5. Margin of Exposure (MOE) = No Adverse Effect Level (NOAEL) ÷ ADD. NOAEL =18.8 mg a.i./kg bw/day.

An MOE of 100 is adequate to protect pesticide handlers. Since MOE's > 100, the proposed use does not exceed HED's level of concern.

7.2 Post-Application Exposure and Risk Assessment

It is possible that agricultural workers may experience post-application exposure to dislodgeable foliar pesticide residues by re-entering treated fields. In this case, since the HIARC did not identify dermal toxicological endpoints, dermal post-application exposure and risk assessment are not necessary. The proposed label lists a 12-hour restricted entry interval (REI). In view of this REI , the MOEs estimated for pesticide handlers and the high vapor pressure (5.5×10^{-11} mm Hg) of butafenacil, HED believes post-application inhalation exposure from the proposed use will be negligible and an assessment is not necessary.

7.3 Restricted-Entry Intervals (REIs)

Butafenacil is classified in Acute Toxicity Categories III and IV. Therefore, the proposed Worker Protection Standard (WPS) interim REI of 12 hours is adequate to protect agricultural workers re-entering treated fields.

7.4 Incidents

Butafenacil is a new active ingredient being proposed for use. Therefore, no incident data are available.

8.0 RESIDUE CHEMISTRY AND TOXICOLOGY DEFICIENCIES

8.1 Residue Chemistry

- revised Section F
- successful PMV of the petitioner proposed cotton enforcement method
- propose a ruminant liver and kidney enforcement method and submit adequate validation, ILV, and radiovalidation; upon submission and acceptance of these data, HED will forward the method to the analytical laboratory for PMV; successful completion of each of these steps is necessary before the proposed method can be employed as an enforcement method
- cottonseed (412 days), cotton gin byproduct (504 days), cotton hull (321 days), cotton meal (323 days), and cotton oil (432 days) frozen storage stability data (butafenacil and CGA-293731)
- ruminant feeding study

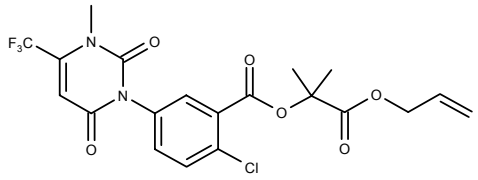
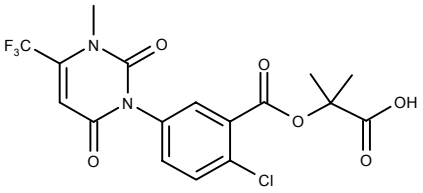
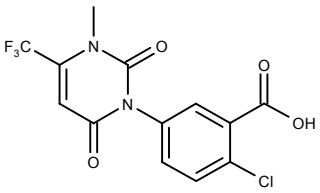
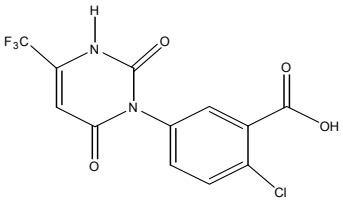
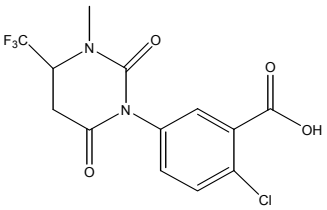
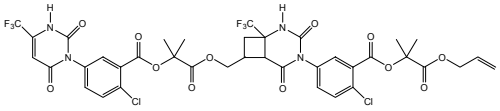
8.2 Toxicology

- The HED Hazard Identification Assessment Review Committee (HIARC) requested a 28-day inhalation toxicity study as a condition of registration. However, based on the low volatility and low inhalation toxicity (Category IV) of butafenacil and inhalation margins of exposure (MOEs) >1000 for the proposed uses in this risk assessment, butafenacil qualifies for a waiver of the 28-day inhalation toxicity study for the proposed uses [HED Standard Operating Procedure (SOP) 2002.01: *Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies*, 08/15/02]. **The requirement for the 28-day inhalation toxicity study is waived for this action only.** If in the future, requests for new uses or formulations are submitted that may result in a significant change in either the toxicity profile or exposure scenarios, HED will reconsider this data requirement.

Attachment 1: Structures of Butafenacil and Metabolites

cc: R. Zendzian, T. Bloem, Mark Dow, Mary Clock-Rust
RDI: Branch (31-July-2003)
M. Clock-Rust:810J:CM#2:(703)308-2718:7509C:RAB1

Attachment 1: Structures of Butafenacil and Metabolites

Common name, Company Code, and Chemical name	Chemical structure
Butafenacil (CGA-276854) 1,1-dimethyl-2-oxo-2-(2-propenyloxy)ethyl 2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl] benzoate	
CGA-293731 1-carboxy-1-methylethyl 2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl] benzoate	
CGA-293730 2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2H)-pyrimidinyl] benzoic acid	
CGA-356925	
CGA-380963	
Butafenacil dimer ([2+2] cycloaddition product; petitioner identified this as a photo-metabolites)	
CGA-98166