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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

March 10, 1997

MEMORANDUM

SUBJECT: **Chlorfenapyr - 129093**: Health Effects Division Risk Characterization for Use of the New Chemical Chlorfenapyr in/on Cotton (5F4456).

PRATS Case Number: 286152
PRATS DP Barcode numbers: D225998, D229102, & D232519

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The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate toxicology and residue chemistry data and conduct dietary and worker risk assessments to estimate the risk to human health that will result from the use of the new chemical chlorfenapyr in/on cotton.

A summary of the findings and an assessment of human risk resulting from the proposed use of chlorfenapyr are provided in this document. The hazard assessment was provided by Guruva B. Reddy, D.V.M., Ph.D. of Toxicology Branch I; the product and residue chemistry data review by Gary F. Otakie, P.E. of Chemistry Branch 1 - Tolerance Support; the dietary risk assessment by Brian Steinwand of the Science Analysis Branch; the drinking water exposure assessment by R. David Jones, Ph.D.

of the Risk Characterization and Analysis Branch and the occupational exposure assessment by Carol Lang of the Occupational and Residential Exposure Branch.

I. EXECUTIVE SUMMARY

HED has reviewed toxicology and residue chemistry data submitted by the American Cyanamid Company in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and 40 CFR §158, to support pending registrations containing the new active ingredient (ai) chlorfenapyr for a technical product and two end-use product liquid formulations for use as an insecticide in/on cotton.

The HED RfD/Peer Review Committee considered the No Observed Effect Level (NOEL) in the 1-year neurotoxicity study (MRID 43492833) of 2.6 mg/kg/day to be the appropriate end-point for establishing the reference dose (RfD) for chlorfenapyr. An uncertainty factor (UF) of 100 was applied to account for interspecies extrapolation and intraspecies variability. The chronic toxicity/carcinogenicity study in mice (MRID 43492838) suggest a compound-related effect on the central nervous system (CNS) and skin lesions. In addition, the acute neurotoxicity study (MRID 43492829) in the rat revealed myelinopathic alterations. Therefore, the RfD/Peer Review Committee recommended that an additional modifying factor (MF) of 10 be used until the potential for developmental neurotoxicity is determined and the lesions are better characterized. On this basis the RfD was calculated to be 0.003 mg/kg/day utilizing the 1000-fold uncertainty factors. The Committee also recommended that a developmental neurotoxicity study be conducted.

In the rat chronic toxicity/carcinogenicity study (MRID 434292837) there were increased trends in the incidence of hepatocellular adenomas, hepatocellular adenomas and/or carcinomas combined, malignant histiocytic sarcomas and testicular interstitial cell tumors in males rats. In female rats there were significant increasing trends in endometrial stromal polyps. Significant difference is pair-wise comparison of fibroadenomas at low dose and carcinomas at the mid-dose existed for female rats. There was no evidence of tumorigenic potential in mice. Based on these findings, the RfD/Peer Review Committee referred the chemical to the HED Cancer Peer Review Committee (CPRC) for in depth consideration.

CPRC met to discuss and evaluate the weight-of-the-evidence on chlorfenapyr with particular reference to its carcinogenic potential. In accordance with the EPA proposed Guidelines for Carcinogenic Risk Assessment (April 10, 1996), chlorfenapyr was characterized as "cannot be determined, suggestive". The consensus of the CPRC to characterize the weight of evidence for chlorfenapyr as "cannot be determined, suggestive" was based on the absence of persuasive evidence; increases in tumors occurred with significant positive trends only, mainly at the highest dose and only in rats. There was also no apparent concern for mutagenic activity and a lack of structure-activity data.

Toxicological endpoints of concern have been identified for acute dietary exposure and short term, intermediate term and chronic (other than cancer) occupational or residential exposure. HED recommends the following endpoints be used for risk assessment purposes. The NOEL from the acute neurotoxicity study (MRID 43492829) in rats of 45 mg/kg/day for acute dietary risk assessments. The NOEL from the 28-day dermal toxicity study (MRID 43492831) of 100 mg/kg/day for short-

and intermediate term occupational or residential risk assessments. The NOEL of 3 mg/kg/day from the combined chronic toxicity/carcinogenicity study (MRID 43492838) in mice for chronic (non-cancer) occupational or residential risk assessments. Since the toxicology endpoint to be used for chronic (non-cancer) occupational or residential risk assessments was selected from an oral study, for dermal exposure scenarios a dermal absorption factor of 5% should be used. The LC50 from the acute inhalation study (MRID 42770209) is 1.9 mg/L (Toxicity Category III) for chlorfenapyr technical. Therefore, an inhalation risk assessment is not required.

Tolerances for chlorfenapyr of 0.50 ppm in/on cottonseed and 0.01, 0.15, 0.01, and 0.10, respectively for milk, milk fat, meat, and fat of cattle, goats, hogs, horses, and sheep were recommended for dietary risk assessments. A residue value of 0.3 ppm was recommended for the dietary risk assessment for meat byproducts of cattle, goats, hogs, horses and sheep. A ratio of 6X the proposed parent tolerance level (0.05 ppm) in ruminant meat byproducts was recommended to account for metabolite residues per the HED Metabolism Committee. Cotton gin byproduct field trial data has not been submitted. In the absence of this required data, HED recommends a tolerance of 2.00 ppm as a realistic worst case estimate of parent residues in cotton gin byproducts. Six additional field trials are required to obtain residue data on cotton gin byproducts. Tolerances for poultry commodities are not required for the proposed cotton use.

A note in the tolerance expression of the revised Section F and 40 CFR for animal commodities is required indicating that the parent is serving as a marker for metabolite residues in meat byproducts. For this reason the meat byproduct tolerance should be listed separately in the Code of Federal Regulations.

A chronic dietary exposure analysis was performed. The chronic analysis showed that exposure from the proposed tolerance for use in/on cotton for non-nursing infants less than 1 year old (the subgroup with the highest exposure) would be 76% of the RfD, while the exposure for the general U.S. population would be 23% of the RfD. A chronic drinking water analysis showed that chronic exposure from drinking water to children would be no greater than 30% of the RfD, while the exposure for the general U.S. population would be no greater than 10% of the RfD. **Therefore, the combined exposure of chronic dietary and drinking water to chlorfenapyr would be no greater than 106% of the RfD for children, while the combined exposure for chronic dietary and drinking water for the general U.S. population would be 33% of the RfD.**

The drinking water values were developed for use in eco-risk assessment and represent a reasonable upper-bound estimate for eco-risk assessment. It is expected they represent an even more substantial overestimate for human health risk assessments. The chronic dietary analysis is also an upper-bound estimate of dietary exposure with all residues at tolerance level and 100 percent of the commodity assumed to be treated with chlorfenapyr. Therefore, even without refinements, HED does not consider the combined aggregate chronic dietary/drinking water risk to exceed the level of concern.

The Margin of Exposure (MOE) is a measure of how closely the anticipated exposure comes to the NOEL. The Agency is not generally concerned unless the MOE is below 100 when the NOEL is based upon data generated in animal studies. The 100 accounts for interspecies extrapolation and intraspecies variability. However, an additional 10-fold MF is considered appropriate for chlorfenapyr

due to the lack of understanding of the toxicity with regard to the developing young. Therefore, at this time HED's level of concern is for MOEs below 1000 for chlorfenapyr.

MOEs were calculated for acute dietary and aggregate acute dietary/drinking water risk as well as short term and intermediate term occupational risk. HED does not anticipate that there will be chronic exposure to the worker for the proposed use of chlorfenapyr on cotton. The pending registration for use of chlorfenapyr on cotton should not result in any residential exposure.

For use of chlorfenapyr on cotton, acute dietary MOEs ranged from 3,000 to greater than 10,000. Aggregate acute dietary/drinking water MOEs range from 4,500 to 8,000. MOEs for short- and intermediate term occupational risk range from 1,800 to greater than 10,000. The MOEs for the use of chlorfenapyr on cotton are above HED's level of concern for all exposure scenarios.

The residue chemistry and toxicological data base are adequate to support a conditional registration for the use of chlorfenapyr on cotton in terms of human health risk. HED recommends a developmental neurotoxicity study and six additional field trials be required as a condition of registration.

The registrant must also submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether chlorfenapyr share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for chlorfenapyr need to be modified or revoked.

II. BACKGROUND

Chlorfenapyr is a member of a new class of chemicals known as pyrroles. Technical chlorfenapyr (EPA File Symbol 241-GAA) is to be formulated into two liquid formulations for use as an insecticide, Pirate with 30.83% ai (EPA File Symbol 241-GAT) and Alert with 21.44 % ai (EPA File Symbol 241-GAI). Both Pirate and Alert are intended for use on cotton, with Pirate for use East of the Rocky Mountains, and Alert for use West of the Rocky Mountains. 5F4456 is the petition number associated with the request for permanent tolerances in/on cotton.

Chlorfenapyr is to be applied by ground boom or aerial application with a maximum application rate of 1.05 lbs ai/acre/season. Pirate can be applied at a maximum one-time application rate of 0.35 lbs ai/acre with a maximum of three applications. Alert can be applied at a maximum one-time application rate 0.34 lbs ai/acre with a maximum of three applications.

III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

Chemical Name: [4-bromo-2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile]

Common Name: Chlorfenapyr

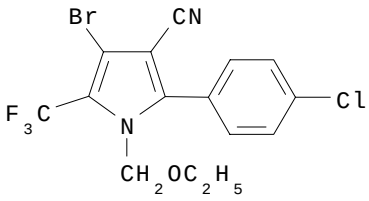
PC Code Number: 129093

CAS Registry No.: 122453-73-0

Empirical Formula: $C_{15}H_{11}BrClF_3N_2O$

Molecular Weight: 407.6

Structural Formula:



Physical and Chemical Properties for Chlorfenapyr	
Color	light tan or light yellow
Physical State	powdered solid
Odor	characteristic of halides and ketones
Melting Point	melting point apparatus 100-101° C
Boiling Point	n/a; TGAI is a solid
Density, Bulk Density, or Specific Gravity	0.543 g/ml tapped bulk density 0.355 g/ml untapped bulk density
Solubility	Solvent — Solubility at 25°C deionized water 0.12 mg/ml water, pH 4 0.13 mg/l water, pH 7 0.14 mg/l water, pH 10 0.12 mg/l hexane 0.89 g/100 ml methanol 7.09 g/100 ml acetonitrile 68.4 g/100 ml toluene 75.4 g/100 ml acetone 114 g/100 ml dichloromethane 141 g/100 ml
Vapor Pressure	<1.0 x 10-7 mm hg at 25 ° C
Dissociation Constant	since there are no ionizable groups in the chlorfenapyr structure, no dissociation will occur (PAI)
Octanol/Water Partition Coefficient	Kow = 67,670 (log Kow = 4.83) at 25 ° C
pH	7.16; 1% aqueous slurry at 24 ° C
Stability	stable at 25 ° C for 24 months, 37 ° C for 12 months, and 45 ° C for 3 months.

Physical and Chemical Properties for Chlorfenapyr	
Oxidizing or Reducing Action	unreactive to oxidizing or reducing agents; no reaction was observed when exposed to tap water, 1% monoammonium phosphate, 0.01M aqueous potassium permanganate and zinc foil.
Flammability	TGAI is a solid
Explodability	not sensitive to an impact of 2 kg/cm at room temperature; one exotherm at 183 ° C with a heat release of -350 kJ/kg in differential thermal analysis; dust did not ignite at any concentration or ignition delay time test; classified as Class 0 dust (impact, differential thermal analysis, and dust explositivity assays)
Storage Stability	stable for one year under outdoor storage conditions (GC and HPLC assays).
Viscosity	TGAI is a solid
Miscibility	TGAI is a solid
Corrosion Characteristics	no corrosion observed after 12 months storage in a polyethylene bag or a VELOSTAT (non-conductive plastic) bag inside a fiberpak

B. Human Risk Assessment

1. HAZARD ASSESSMENT

a. Acute Toxicity

i. Acute Toxicity of Technical Grade Chlorfenapyr

TEST	RESULTS	CATEGORY
Oral LD50 - rat MRID 42770207 & 42884201	441 mg/kg, males 1152 mg/kg, females 626 mg/kg, combined	II*
Oral LD50 - mouse MRID 43492828	45 mg/kg, males 78 mg/kg, females 55 mg/kg, combined	I
Dermal LD50 - rabbit MRID 42770208	> 2000 mg/kg	III
Inhalation LC50 - rat MRID 42770209	0.83 mg/l, males > 2.7 mg/l, females 1.9 mg/l, combined	III
Eye irritation - rabbit MRID 42770210	Corneal opacity, iritis, and conjunctivitis present at 48 hours. At 72 hours iritis was resolved. All rabbits were normal by Day-7.	III
Dermal irritation - rabbit MRID 42770211	non-irritating	IV
Dermal sensitization - guinea pig MRID 42770212	non-sensitizer	

* Based on the most sensitive sex

ii. Acute Toxicity of Chlorfenapyr Metabolites

TEST	RESULTS	CATEGORY
Metabolite - AC 303,268 Oral LD50 - Rat MRID 43492824	27.0 mg/kg, males 29.4 mg/kg, females 28.7 mg/kg, combined	I
Metabolite - AC 312,094 Oral LD50 - Rat MRID 43492825	>5,000 mg/kg, males >5,000 mg/kg, females >5,000 mg/kg, combined	IV
Metabolite - AC 322,250 Oral LD50 - Rat MRID 43492826	>5,000 mg/kg, males 2,500 mg/kg, females	III
Metabolite - AC 325,195 Oral LD50 - Rat MRID 43492827	776 mg/kg, males 1367 mg/kg, females	III

b. Subchronic Toxicity

i. Subchronic Oral Toxicity in Rats

A subchronic oral toxicity study in rats (MRID 42770219) was conducted with chlorfenapyr technical. Chlorfenapyr was administered in feed to rats at dose levels of 0, 150, 300, 600, 900 or 1200 ppm (measured intake of 0, 11.7, 24.1, 48.4, 72.5 or 97.5 mg/kg/day, respectively) for 90 days. At 600 ppm, males had a decreased body weight gain and increased relative liver weights, while females exhibited decreased hemoglobin (HGB) and increased absolute/relative liver weights. At 900 ppm, body weight gain and food consumption in males/females, red blood cell (RBC) numbers, percent hematocrit (HCT) and percent HGB in females were decreased. At the same dose level, platelets, alkaline phosphatase (ALK) in males, absolute/relative liver weights in females, relative liver weights in males and absolute/relative spleen weights in males and females were increased. At 1200 ppm, male rats exhibited decreased activity, ataxia, anorexia, chromodacryorrhea and dark brown material around nose. Additionally, in males/females, body weight gains, feed consumption, RBC numbers, %HCT and %HGB decreased and platelet counts, blood urea nitrogen (BUN) in males, ALK levels in males/females, absolute/relative liver and splenic weights in females and absolute/relative splenic weights and relative liver weights in males were increased. The Lowest Effect Level (LEL) of 48.4 mg/kg/day (600 ppm) is based on decreased body weight gain and increased relative liver weight in males and decreased HGB and increased absolute/relative liver weights in females. The NOEL is 24.1 mg/kg/day (300 ppm).

ii. Subchronic Oral Toxicity in Mice

In a subchronic oral toxicity study in mice (MRID 43492830) chlorfenapyr technical was administered to mice at dietary dose levels of 0, 40, 80, 160, or 320 ppm (average 0, 7.1, 14.8, 27.6,

or 62.6 mg/kg/day, respectively, for males; 0, 9.2, 19.3, 40.0, or 78.0 mg/kg/day, respectively, for females) for 91 days. Male mice fed chlorfenapyr at 80 ppm, and male and female mice fed chlorfenapyr at 160 or 320 ppm exhibited a toxic response to the test compound. Two mice died prior to the termination of the study; one male and one female dosed at the 320 ppm level died after only 2 days of feeding. In male mice, hepatic cell hypertrophy was observed in the 80, 160, and 320 ppm treatment groups. Male mice in the 160 or 320 ppm treatment groups had increased relative liver and spleen weights. Male mice in the 320 ppm treatment group had lower body weight gain, and increased hematocrit values and RBC counts compared to the controls. In female mice, hepatic cell hypertrophy occurred in animals in the 160 and 320 ppm treatment groups. Female mice in the 320 ppm treatment group had lower body weight gain, increased white blood cell (WBC) counts, and increased relative liver weights compared to the controls. Spongiform encephalopathy was noted in the brain and myelin of the spinal cord of both males and females receiving the 320 ppm treatment level. The LEL is 14.8 mg/kg/day (80 ppm) for male mice and 40.0 mg/kg/day (160 ppm) for female mice, based on hepatic cell hypertrophy in ≥ 20% of the test animals at this treatment level. The NOEL is 7.1 mg/kg/day (40 ppm).

iii. Subchronic Oral Toxicity in Dogs

In a subchronic oral toxicity study in dogs (MRID 42770220) chlorfenapyr technical was administered to dogs for 13 weeks at doses of 0, 60, 120 or 247 ppm (0, 2.16, 4.23 or 6.1 mg/kg/day, respectively). The 247 ppm was based on concentration of chlorfenapyr in the diet of 300 ppm from Day 1 - 14, 240 ppm from Day 15 - 25 and 200 ppm from Day 25 - 93 (5.2, 5.9 and 7.2 mg/kg/day, respectively). At the high dose of 247 ppm there was a significant reduction in body weight gain, feed efficiency, and increased emaciation. The LEL is 6.1 mg/kg/day (247 ppm), based on reduced body weight gain and feed efficiency and emaciation. The NOEL is 4.23 mg/kg/day (120 ppm).

iv. Twenty-eight Day Dermal Toxicity Study in Rabbit

In a 28 day repeated dose dermal toxicity study (MRID 43492831) chlorfenapyr technical was applied to the shaved skin of rabbits at dose levels of 0, 100, 400, or 1000 mg/kg for 6 hours/day, 5 days/week for 4 weeks. Rabbits of both sexes in the 400 and 1000 mg/kg treatment groups exhibited statistically significant and concentration-related increases in serum cholesterol, relative liver weights, and cytoplasmic vacuolation of the liver. The vacuolation of the liver was minimal to slight for male and female rabbits in the 400 mg/kg treatment groups, and minimal to moderately severe for the 1000 mg/kg treatment groups. In addition, female rabbits in the 1000 mg/kg treatment group exhibited a statistically significant increase in serum alanine aminotransferase concentrations. No differences were observed between rabbits in the 100 mg/kg treatment groups and the control groups. The LEL is 400 mg/kg for both sexes, based on changes in liver chemistry and morphology. The NOEL is 100 mg/kg.

c. Chronic Toxicity and Carcinogenicity

i. Chronic Oral Toxicity Dogs

In a chronic toxicity study (MRID 43492834), chlorfenapyr technical was administered to dogs in the diet at dose levels of 0, 60, 120, or 240 ppm (0, 2.1, 4.0, or 8.7 mg/kg/day, respectively, for

males; 0, 2.3, 4.5, or 10.1 mg/kg/day, respectively, for females) for 52 weeks. Body weights and body weight gains were depressed in both sexes treated at 240 ppm, with more pronounced differences observed in the females. Body weights and body weight gains of both sexes treated at 60 or 120 ppm were comparable to those of the controls. No treatment-related effects were observed on the survival, clinical signs, ophthalmology, hematology, clinical chemistry or urinalysis parameters, organ weights or gross and microscopic pathology at any dose level. The LEL is 8.7 mg/kg/day (240 ppm), based on decreased body weights and body weight gains. The NOEL is 4.0 mg/kg/day (120 ppm).

ii. Chronic Toxicity/Carcinogenicity Study in Rats

In a chronic toxicity/carcinogenicity study [MRID 434292837 (main), 434292836 (range-finding)], chlorfenapyr technical was administered to rats in the diet at dose levels of 0, 60, 300, or 600 ppm (0, 2.9, 15.0, or 30.8 mg/kg/day, respectively in males; 0, 3.6, 18.6, or 37.0 mg/kg/day, respectively in females) for 104 weeks. Chronic toxicity observed in males and females at 300 and 600 ppm included slight to moderate non-neoplastic centrilobular to midzonal or diffuse hepatocellular enlargement in males and females. At the 300 and 600 ppm levels in both sexes, there were significant increases in mean liver-to-body weight ratios at 12 months and in 600 ppm rats at 24 months. There was an increased incidence of malignant histiocytic sarcoma in male rats in the 600 ppm group compared to controls. Rats in this study probably could have tolerated higher dosing due to the low mortality at 600 ppm; however, there were non-neoplastic lesions in the liver and significantly decreased body weight gains in treated groups. The LEL for systemic toxicity is 15.0 and 18.6 mg/kg/day for males and females, respectively (300 ppm) based on liver toxicity. The NOEL is 2.9 and 3.6 mg/kg/day for males and females, respectively (60 ppm) based on liver toxicity.

iii. Chronic Toxicity/Carcinogenicity Study in Mice

In a chronic toxicity/carcinogenicity study [MRID 43492838 (main), 43492830 (range-finding)], chlorfenapyr technical was administered to mice in the diet at dose levels of 0, 20, 120, or 240 ppm (0, 2.8, 16.6, or 34.5 mg/kg/day, respectively, in males; 0, 3.7, 21.9, or 44.5 mg/kg/day, respectively, in females) for 80 weeks. Chronic toxicity observed in males and females at 120 and 240 ppm included decreased body weight gains, non-neoplastic brain vacuolation primarily in the white matter of the corpus callosum, tapetum, hippocampus, and cerebellum. Body weight gains decreased in males and females in the 120 and 240 ppm treatment groups by the end of study. Males and females at 240 ppm also exhibited vacuolation of the spinal cord and optic nerve. Treatment-related gross pathological changes, including skin ulceration and scabbing, occurred in males and females at the 240 ppm level, and scabbing occurred in males at 120 ppm. At the doses tested, there was no treatment-related increase in tumor incidence when compared to controls. The LEL for systemic toxicity is 16.6 and 21.9 mg/kg/day in males and females, respectively (120 ppm) based on decreased body weight gains, brain toxicity and scabbing of the skin (males). The NOEL is 2.8 and 3.7 mg/kg/day for males and females, respectively (20 ppm).

d. Developmental Toxicity

i. Developmental Toxicity in Rats

In a developmental toxicity study in rats (MRID 42770221/42884202), chlorfenapyr technical was administered to pregnant rats by oral gavage in 0.5% carboxymethylcellulose at dose levels of 0, 25, 75 or 225 mg/kg/day from days 6 through 16 of gestation. Maternal toxicity was noted in the form of a dose-related decrease in body weight gain in the mid and high dose groups, a dose-related decrease in relative feed consumption in the mid and high dose groups and a decrease in water intake in the high dose group. Therefore, the LEL for maternal systemic toxicity is 75 mg/kg/day, based on reduced body weight gain, reduced relative feed intake and reduced water consumption. The NOEL for maternal systemic toxicity is 25 mg/kg/day.

Developmental toxicity was not observed either in the form of maternal cesarean section observations or fetal external, visceral or skeletal malformations and variations. Therefore, the LEL for developmental (pup) toxicity is greater than 225 mg/kg/day and the NOEL is greater than or equal to 225 mg/kg/day (highest dose tested).

ii. Developmental Toxicity Study in Rabbits

In a developmental toxicity study (MRID 42770222) pregnant rabbits received either 0, 5, 15 or 30 mg/kg/day chlorfenapyr technical in 0.5% carboxymethylcellulose by oral gavage from gestation days 7 to 19, inclusive. At 15 mg/kg/day there was decreased body weight gain during the treatment period. At 50 mg/kg/day in a rangefinding study there was mortality and possibly some neurologic signs. The LEL for maternal systemic toxicity is 15 mg/kg/day, based upon reduced body weight gain during treatment. The NOEL for maternal systemic toxicity is 5 mg/kg/day. There was no evidence of developmental toxicity at any dose. The NOEL for developmental (pup) toxicity is greater than 30 mg/kg/day (highest dose tested).

e. Reproductive Toxicity

i. Reproductive Toxicity Study in Rats

In a 2-generation reproduction study [MRID 434292836 (main), 434292835 (range-finding)], chlorfenapyr technical was administered continuously in the diet to rats at concentrations of 0, 60, 300, or 600 ppm (0, 5, 22, or 44 mg/kg/day, respectively, based on body weight and food consumption during pre-mating periods) for two successive generations (1 litter/generation). P_1 and F_1 males were mated after approximately 16 and 23 weeks of treatment, respectively. P_1 females were fed the test diets for approximately 19 weeks; mating was initiated at 10 weeks. F_1 pups were weaned on the same test diet fed their parents. F_1 females were fed the test diets for approximately 23 weeks; mating was initiated at 11 weeks.

In the 600 ppm male treatment group, the pre-mating weight gains of P_1 and F_1 animals were lower than for control animals ($p < 0.05$). In the 600 ppm female treatment group, the pre-mating weight gains of P_1 and F_1 females were lower than control animals (significant only in the F_1 generation). Mean weights of F_1 and F_2 pups in the 600 ppm treatment group at weaning were lower than for control animals. Pup deaths during lactation days 0-4 were significantly higher in the F_2 litters from the 600 ppm treatment group. In the 300 ppm treatment group, mean body weight and body weight gains in P_1 males during the pre-mating period were lower than control animals. The mean body weight gains of F_1 males, and of P_1 and F_1 females were similar to the controls. The mean lactational weight

gain of F_1 and F_2 pups in the 300 and 600 ppm treatment groups were significantly lower than the controls, although the mean weights of pups at birth were comparable to controls. At weaning, the mean weights of F_1 and F_2 pups in the 300 and 600 ppm groups were significantly lower than controls; this is considered a reproductive effect. No changes in reproductive performance were seen in either males or females of the parental generations. At 60 ppm, there were no adverse effects on the parental generations, there were no neonatal effects of toxicological importance, and there were no effects on reproductive performance. The LEL for parental toxicity was 22 mg/kg/day (300 ppm), based on pre-mating effects on parental weight gain. The parental NOEL was 5 mg/kg/day (60 ppm). The LEL for reproductive toxicity was 22 mg/kg/day (300 ppm), based on decreased lactational weight gains. The reproductive NOEL was 5 mg/kg/day (60 ppm).

f. Neurotoxicity

i. Acute Neurotoxicity Study in Rats

In an acute neurotoxicity study (MRID 43492829), chlorfenapyr technical was dissolved in 0.5% carboxymethylcellulose and administered once, via gastric intubation in a dosing volume of 10 ml/kg/dose, to rats at dose levels of 0, 45, 90, or 180 mg/kg. All rats were observed for 2 weeks following dosing. The rats were evaluated for reactions in functional observational battery and motor activity measurements pretest and on study days 1, 8, and 15. In addition, five rats per group were examined for neuropathologic lesions.

Two males and two females in the 180 mg/kg dose group died within 7 hours of dosing, possibly as a result of accidental injury during treatment. Surviving rats in this dose group exhibited changes in gait, locomotion, and arousal, and 20-30% of the males and females were lethargic on the day of treatment. In the 90 mg/kg dose group, 20% of the males were lethargic on the day of treatment. No dose-related effects on body weights, food consumption, neurobehavioral observations, or gross or histological post mortem examinations were noted. The LEL is 90 mg/kg, based on lethargy of the rats on the day of treatment. The NOEL is 45 mg/kg.

ii. One-Year Dietary Neurotoxicity Study in Rats

In a one-year dietary neurotoxicity study (MRID 43492833), chlorfenapyr technical was administered in the diet at 0, 60, 300, or 600 ppm (52-week average 0, 2.6, 13.6, or 28.2 mg/kg/day, respectively, for males; 0, 3.4, 18.0, or 37.4 mg/kg/day, respectively, for females) to rats for 52 weeks, followed by a 16-week recovery period during which the remaining rats were fed the control diet. The rats were evaluated for reactions in functional observational battery followed by motor activity measurements 1 week before the test diets were provided; 4, 8, 13, 26, 39, and 52 weeks after the first day of exposure; and 13 weeks after the cessation of treatment. A portion of the rats in each treatment group were sacrificed for neuropathological examination following 13 or 52 weeks of exposure, or 16 weeks of recovery.

In the 600 ppm dose group, both sexes exhibited statistically significant decreases in average body weights, body weight gains, absolute and relative feed consumption, feed efficiency, and water consumption (males only). Neurohistological examination of males sacrificed after 13 weeks of exposure revealed myelin sheath swelling in the spinal nerve roots compared to the controls. At 52

weeks, a more generalized myelinopathic process consisting of vacuolar myelinopathy, vacuolation, and/or mild myelin sheath swelling, was found. This process was not associated with myelin or axon degeneration and was not evident in rats sacrificed after 16 weeks of recovery. In the 300 ppm dose group, both sexes exhibited decreases in average body weights, body weight gains, feed efficiency, absolute feed consumption (females only) and water consumption (males only) at various times during the exposure period and body weight gains were reduced (non-significantly) for males during recovery. The myelinopathic observations described in the 600 ppm group males were also found in the 300 ppm group of rats after 13 and 52 weeks exposure but were less severe and at a lower incidence. In the 60 ppm dose group rats, minimum myelin sheath swelling was seen in the Gasserian ganglia of one male at 52 weeks and spinal nerve roots of three males after 13 weeks of exposure. The toxicologic importance of these findings is equivocal since swelling in the spinal nerve roots was absent in the 60 ppm group after 52 weeks. Neuropathological changes were confined to males; females were not affected. The LEL is 13.6 mg/kg/day (300 ppm) based on the presence of myelinopathic alterations in the 300 ppm group male rats, decreased average body weights, body weight gains, feed efficiency, absolute feed consumption (females) and water consumption (males). The NOEL is 2.6 mg/kg/day (60 ppm).

g. Mutagenicity

i. Mutagenicity Testing of Technical Grade Chlorfenapyr

Study	Results
Gene Mutation-Ames MRID 42770223	Negative for reverse mutation in S. typhimurium strains TA 98, TA 100, TA 1535, TA 1537, TA 1538 and E. coli strain WP2 uvrA- exposed up to cytotoxicity (50 μg/plate, +/- S9)
Chinese hamster ovary (CHO) cell HGPRT gene mutation MRID 42770224	Independently performed tests were negative up to a cytotoxic and precipitating concentration (500 µg/mL) in the presence of S9 activation or the solubility limit (250 µg/mL) without S9 activation.
In vivo micronucleus assay MRID 42770225	The test was negative in mice administered single oral gavage doses of 7.5-30 mg/kg (males) or 5-20 mg/kg (females). Clinical toxicity (deaths in males and diarrhea in females) was seen at the highest dose tested. There was, however, no evidence of cytotoxicity for the target organ.
In vitro CHO cell chromosome aberration assay MRID 43492843	The test was negative up to 100 µg/mL -S9 or 25 µg/mL +S9; higher doses with or without S9 activation were cytotoxic.
In vitro Chinese hamster lung (CHL) fibroblasts chromosome aberration assay MRID 43492839	The test was negative up to a precipitating level without S9 activation (225 µg/mL) or a concentration range of 3.5-14.1 µg/mL +S9. Higher S9-activated doses ($\geq$ 28 µg/mL) were cytotoxic.
Repair in vitro (UDS) MRID 42770226	Negative for inducing unscheduled DNA synthesis in primary rat hepatocyte cultures exposed up to severely toxic concentrations ($\geq$ 30 μg/ml).

ii. Mutagenicity Testing of Chlorfenapyr Metabolites

Study	Results
Metabolite CL 303,268 Salmonella typhimurium/Escherichia coli reverse gene mutation assay MRID 43492840	Independently performed tests with a chlorfenapyr metabolite and impurity: 4-bromo-2-(p-chlorophenyl)-5-(trifluoromethyl)-pyrrole-3-carbonitrile (100.3%) were negative up to a cytotoxic dose (5 µg/plate +/-S9) with all S. typhimurium strains and to the solubility limit (250 µg/plate +/-S9) with E. coli. Salmonella typhimurium/Escherichia coli reverse gene mutation assay
Metabolite CL 312,094 Salmonella typhimurium/Escherichia coli reverse gene mutation assay MRID 43492841	Independently performed tests with the chlorfenapyr impurity: 2-(6-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-pyrrole-2-carbonitrile (96.3%) were negative in all strains up to insoluble concentrations (≥ 250 µg/plate -S9; ≥ 500 µg/plate +S9).
Metabolite CL 322,250 Gene Mutation - Ames MRID 43492842	Independently performed tests with a chlorfenapyr metabolite: 3-bromo-5-(p-chlorophenyl)-4-cyano-pyrrole-2-carboxylic acid (89%) were negative up to doses (≥ 1000 µg/plate -S9; 2500 µg/plate +S9) that were cytotoxic to all S. typhimurium strains. Compound precipitation was seen at the highest concentration tested (5000 µg/plate +/-S9) with E. coli.

The available mutagenicity studies clearly indicate that chlorfenapyr is neither mutagenic in bacterial or mammalian cells nor clastogenic in cultured mammalian cells in vitro or in male and female mice in vivo. There was also no evidence of genotoxicity in primary rat hepatocytes.

h. Metabolism

i. Metabolism Study in Rats

In a metabolism study (MRID 43492844), [2-pyrrole-^{14}C] or [phenyl-^{14}C] chlorfenapyr was administered to rats by oral gavage at dose levels of 20 mg/kg/day as a single dose or following a 14-day pre-treatment with non-radioactive chlorfenapyr, or at 200 mg/kg as a single dose.

Low recoveries of the radioactive dose in urine and tissues indicate limited absorption of chlorfenapyr by rats. The radioactivity in urine from the high dosed rats was about half that from the single and multiple-low dosed rats. More than 80% of the doses were eliminated in the feces. Most of the radioactivity was eliminated in the feces and urine within 48 hours of dosing. After 7 days, 89-121% of the dosed radioactivity was recovered. At sacrifice, female rats had greater (about twice) recovery of radioactivity in the carcass, blood, and fat at all doses than did males. The highest recovery of radioactivity from a single organ was from the liver (0.15-0.48% of dose).

Metabolite extraction and identification accounted for 72-91% of the radioactive doses. The parent was the major radioactive compound found in excreta, accounting for approximately 40-70% of the administered doses. Minor amounts of eight primary and conjugated metabolites and four unidentified isolated components were detected, each at less than 10% of the dosed radioactivity. Liver and kidney contained several primary and conjugated metabolites and only minor levels of the parent compound ($\leq$8.3% of the radioactivity in the sample). Based on
the metabolites identified, the major deposition route of orally administered chlorfenapyr is fecal excretion of unaltered parent compound. Other pathways include cleavage of the ethoxymethyl side-chain, followed by de-alkylation and ring hydroxylation, and some degree of conjugation of the de-alkylated, ring-hydroxylated metabolite. The two rings of the molecule are not cleaved. Metabolites are excreted primarily in urine; accumulation in tissues is minimal.

2. DOSE RESPONSE ASSESSMENT

a. Reference Dose and Safety Consideration for Infants and Children under FQPA

The Food Quality Protection Act (FQPA) requires that pesticide regulatory review incorporate an assessment of potential hazards to infants and children and include additional safety factors, of up to 10 fold when warranted, for the protection of these sensitive subpopulations.

The HED RfD/Peer Review Committee met on July 18, 1996 to discuss and evaluate the existing toxicology database for chlorfenapyr, discussed in the Hazard Assessment section above. An ad hoc group of six members met a second time on October 9, 1996 to consider additional data requirements based on the conclusions of the first RfD/Peer Review Committee meeting.

In the rat chronic toxicity/carcinogenicity study (MRID 434292837) there were increased trends in the incidence of hepatocellular adenomas, hepatocellular adenomas and/or carcinomas combined, malignant histiocytic sarcomas and testicular interstitial cell tumors in males rats. In female rats there were significant increasing trends in endometrial stromal polyps. Significant difference is pair-wise comparison of fibroadenomas at low dose and carcinomas at the mid-dose existed for female rats. There was no evidence of tumorigenic potential in mice. To discuss these findings, the RfD/Peer Review Committee referred the chemical to the HED CPRC for in depth consideration.

The chronic toxicity/carcinogenicity study in mice (MRID 43492838) suggest a compound-related effect on the central nervous system (CNS) and skin lesions. In addition, the acute neurotoxicity study (MRID 43492829) in the rat also revealed myelinopathic alterations. Although the toxicology database is adequate to support a permanent tolerance and Section 3 registration of the chemical, the RfD/Peer Review Committee recommended that an additional MF of 10 be used until the potential for developmental neurotoxicity is determined and the lesions are better characterized.

The Committee also recommended that a special developmental neurotoxicity study be conducted based upon the effects of a spongyform myelopathy seen in the brain and spinal cord of treated rats and mice. The registrant should conduct a mechanistic study to determine the cause/relationship of CNS/myelinopathic alterations to neurotoxicity (including developmental). The Ad Hoc Committee considered the following modifications to the developmental neurotoxicity study protocol are necessary: A 90 day treatment period for males and females prior to the routine developmental phase required

in the developmental neurotoxicity study guidelines is needed. The dams would deliver their pups and come off treated feed at day 10 post-delivery. Normal testing as required in the developmental neurotoxicity study guidelines would then commence. Further, the Ad Hoc Committee and the Toxicology Branch consider it necessary to characterize the nature of the vacuoles reported in the previous studies and any found in the presently proposed study. The treated males would be used to assist in this characterization. This information may well play a great role in assessing the potential risk of this chemical. It is strongly recommended that the registrant contact the Toxicology Branch prior to initiating the study in order to discuss dose selection and study protocol.

The RfD/Peer Review Committee of July 18, 1996 considered the NOEL in the 1-year neurotoxicity study (MRID 43492833) of 2.6 mg/kg/day to be the appropriate end-point for establishing the RfD for chlorfenapyr. The Ad Hoc Committee also considered the 2.6 mg/kg/day to be the appropriate end-point for establishing the RfD until additional data is submitted and reviewed. An UF of 100 was applied to account for interspecies extrapolation and intraspecies variability. Because of the type of lesions, the lack of understanding of the cause, and possible further unknown toxicity with regard to the developing young, an additional 10-fold MF is considered appropriate for this chemical. On this basis the RfD was calculated to be 0.003 mg/kg/day with a 1000-fold UF/MF.

b. Carcinogenicity Classification

The HED CPRC met on September 25, 1996 to discuss and evaluate the weight-of-the-evidence on chlorfenapyr with particular reference to its carcinogenic potential. In the rat chronic toxicity/carcinogenicity study (MRID 434292837) there were increased trends in the incidence of hepatocellular adenomas, hepatocellular adenomas and/or carcinomas combined, malignant histiocytic sarcomas and testicular interstitial cell tumors in males rats. In female rats there were significant increasing trends in endometrial stromal polyps. Significant difference is pair-wise comparison of fibroadenomas at low dose and carcinomas at the mid-dose existed for female rats. There was no evidence of tumorigenic potential in mice.

In accordance with the EPA proposed Guidelines for Carcinogenic Risk Assessment (April 10, 1996), chlorfenapyr was characterized as "cannot be determined, suggestive". The consensus of the CPRC to characterize the weight of evidence for chlorfenapyr as "cannot be determined, suggestive" was based on the absence of persuasive evidence; increases in tumors occurred with significant positive trends only, mainly at the highest dose and only in rats. Chlorfenapyr was not associated with increases in tumors in mice and, there was no apparent concern for mutagenic activity and an absence of structure-activity data. There is no human data for chlorfenapyr.

c. Other Toxicity Endpoints

Based upon a review of the toxicology database for chlorfenapyr, by the Toxicology Endpoint Selection (TES) Committee on July 24, 1996, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. For more information on studies discussed in this section refer to the Hazard Assessment section of this document.

i. Dermal Absorption

A dermal absorption study was not available. Therefore, a dermal absorption value of 5% has been calculated based on the route-to-route extrapolation using the maternal NOEL of 5 mg/kg/day from the developmental toxicity study (MRID 42770222) in rabbits and the systemic NOEL of 100 mg/kg/day from the 28-day dermal toxicity study (MRID 43492831) in rabbits. This dermal absorption value will be used ONLY for chronic (non-cancer) occupational or residential risk assessments since an oral study was selected as an endpoint for this exposure scenario. The dermal absorption factor is not needed for the short- and intermediate term exposure risk assessments since the endpoint of concern identified was selected from the 28-day dermal toxicity study.

ii. Acute Dietary Endpoint (One Day)

An acute dietary endpoint of concern was identified. The NOEL of 45 mg/kg/day from the acute neurotoxicity study (MRID 43492829) in rats was selected as the endpoint to be used for acute dietary risk assessments. An UF/MF of 1000 is considered appropriate for this chemical. The UF is based on 100 to account for interspecies extrapolation and intraspecies variability and an additional 10-fold MF for the lack of understanding of the
toxicity with regard to the developing young.

iii. Short- and Intermediate Term Occupational or Residential (Dermal) Exposure

Short term (1-7 days) and intermediate term (7 days to several months) endpoints of concern were identified. The NOEL of 100 mg/kg/day from the 28-day dermal toxicity study (MRID 43492831) in rabbits was selected as the endpoint to be used for both short- and intermediate term risk assessments. An UF/MF of 1000 is considered appropriate for this chemical. The UF is based on 100 to account for interspecies extrapolation and intraspecies variability and an additional 10-fold MF for the lack of understanding of the toxicity with regard to the developing young.

iv. Chronic (Non-Cancer) Occupational or Residential (Dermal) Exposure

A chronic term endpoint of concern was identified. The NOEL of 3 mg/kg/day from the combined chronic toxicity/carcinogenicity study (MRID 43492838) in mice was selected as the endpoint to be used for chronic (non-cancer) occupational or residential risk assessments. An UF/MF of 1000 is considered appropriate for this chemical. The UF is based on 100 to account for interspecies extrapolation and intraspecies variability and an additional 10-fold MF for the lack of understanding of the toxicity with regard to the developing young.

Since the toxicology endpoint to be used for chronic (non-cancer) occupational or residential risk assessments was selected from an oral study, for dermal exposure scenarios the dermal absorption factor of 5% must be used for risk assessments.

v. Inhalation Exposure (Any Time Period)

The LC50 from the acute inhalation study (MRID 42770209) is 1.9 mg/L (Toxicity Category III) for chlorfenapyr technical. Therefore, risk via the inhalation route is not a concern at this time and no endpoint of concern was identified.

3. DIETARY EXPOSURE AND RISK CHARACTERIZATION

a. Dietary Exposure - Food Sources

i. Plant Metabolism

The nature of the residue in cotton is adequately understood based on data submitted by American Cyanamid (MRID 42770234 and 43492853) depicting the metabolism of [2-pyrrole-^{14}C]-labeled and uniformly ring labeled [phenyl-^{14}C]chlorfenapyr in cotton. Each test substance was formulated as a suspension concentrate and applied to field-grown cotton plants once a week for 5 consecutive weeks. Foliage was sampled immediately following the first, third and fifth applications. At 28 days following the fifth application, all mature open cotton bolls were harvested and cottonseeds were removed by ginning.

Total radioactive residues (TRR) were determined in foliage and cottonseed samples by liquid scintillation spectroscopy (LSS) following combustion. The limit of detection was 0.01 ppm. Samples were then extracted and hydrolyzed for identification of residues.

The parent compound chlorfenapyr, was the major radioactive component in cottonseeds (59.3-67.7% of the TRR). ^{14}C-residues in cottonseed oil and non-extractable residues accounted for <3.2% of the TRR and 9.7-11.1% of the TRR, respectively.

The HED Metabolism Committee (6/20/96) has determined that for plant commodities the chlorfenapyr permanent tolerance expression should be in terms of parent only. Use of only parent residues is acceptable for chlorfenapyr dietary risk assessments on plant commodities based on the parent comprising such a high percentage of the residue.

ii. Animal Metabolism

Poultry

The nature of the residue in poultry is adequately understood based on data submitted by American Cyanamid (MRID 42770236 and 43492854) depicting the metabolism of uniformly ring-labeled [phenyl-^{14}C]- and [2-pyrrole-^{14}C]-labeled chlorfenapyr in laying hens orally dosed at high (14.52-15.04 ppm) and low (3.02-3.10 ppm) doses for seven consecutive days. These doses correspond to 28X and 134X the proposed maximum daily dietary burden. Radioactive residues ranged from 0.02 ppm in muscle to 1.31 ppm in liver. The TRR in eggs increased from <0.01 ppm to 0.42 ppm by day 7.

The data indicate that laying hens metabolize [phenyl-^{14}C0- and [pyrrole-^{14}C]chlorfenapyr in a similar manner yielding similar metabolites. The primary residue found in muscle and fat was the

parent. In addition to the parent numerous chlorfenapyr metabolites have been identified. In eggs the parent and its N-dealkylation metabolite, CL 303,268 [i.e. pyrrole-3-carbonitrile, 4-bromo-2-(p-chlorophenyl)-5-(trifluoromethyl)-] are present at the highest level. In liver and kidney the parent, and metabolites CL 303,268, CL 152,835/M-6 (i.e. acetic acid,{[2-(p-chlorophenyl)-3-cyano-5-(trifluoromethyl)pyrrol-1-yl]methoxy}-) and CL 325,157/M-6A (i.e. acetic acid, {[3-bromo-5-(p-chlorophenyl)-4-cyano-2-(trifluoromethyl)pyrrol-1-yl]methoxy}-) were present at the highest levels.

In the HED Metabolism Committee Meeting of 6/20/96 it was noted that based on the proposed use on cotton, tolerances on poultry commodities are not required. However, poultry was addressed in the event that future proposed uses for this new chemical require tolerances on poultry commodities. It was determined that for poultry commodities (excluding meat byproducts) the chlorfenapyr permanent tolerance expression should be in terms of parent only. Use of only parent residues is acceptable for chlorfenapyr dietary risk assessments on poultry commodities (excluding meat byproducts). For poultry meat byproducts the chlorfenapyr permanent tolerance expression should be in terms of parent only. However, chlorfenapyr dietary risk assessments on poultry meat byproducts should include the four metabolites, CL 303,268, CL 325,195, CL 152,835, and CL 325,157 as well as the parent (CL 303,630). The poultry meat byproduct risk assessment will use a factor (i.e. ratio parent plus metabolites/parent) multiplied by the parent based tolerance determined from the residue levels of the five moieties in the poultry metabolism studies.

Ruminants

The nature of the residue in ruminants is adequately understood based on data submitted by American Cyanamid (MRID 42770235 and 43492855) depicting the metabolism of ^{14}C-chlorfenapyr in lactating goats dosed orally once a day for seven days. The low and high doses represented a daily feeding level of 3.0 and 17.9 ppm for [phenyl-^{14}C]chlorfenapyr and 3.16 ppm and 16.4 ppm for [2-pyrrole-^{14}C]-chlorfenapyr. These doses represent 10X and 58X the proposed maximum daily dietary burden.

The distribution of TRR in milk and tissues from both groups were similar. In the high dose group, the TRR in milk increased from 0.03 to 0.07 ppm by day 7. Radioactive residues ranged from 0.03-0.05 ppm in muscle to 1.45-1.46 ppm in liver.

Residues found consist primarily of the parent in muscle, fat and milk. In addition to the parent numerous chlorfenapyr metabolites were identified. In the liver and kidney the metabolites CK\L 325,195 [i.e. 2-pyrrolidine-3-carbonitrile, 2-(p-chlorophenyl)-5-hydroxy-4-oxo-5-(trifluoromethyl)-} and CL 322,250 {i.e. Pyrrole-2-carboxylic acid, 3-bromo-5-(p-chlorophenyl)-4-cyano-] were present at the highest level as well as the parent, other metabolites and conjugates.

In the HED Metabolism Committee Meeting of 6/20/96 it was determined that for ruminant commodities (excluding meat byproducts) the chlorfenapyr permanent tolerance expression should be in terms of parent only. Use of only parent residues is acceptable for chlorfenapyr dietary risk assessments on ruminant commodities (excluding meat byproducts). For ruminant meat byproducts the chlorfenapyr permanent tolerance expression should be in terms of parent only. However, chlorfenapyr dietary risk assessments on ruminant meat byproducts should include the two metabolites CL 303,268, and CL 325,195 as well as the parent (CL 303,630). The ruminant meat byproduct risk

assessment will use a factor (i.e. ratio parent plus metabolites/parent) multiplied by the parent based tolerance determined from the residue levels of the three moieties in the ruminant metabolism studies.

iii. Residue Analytical Method- Plants

Adequate analytical methods for chlorfenapyr in cottonseed are available to support the proposed permanent tolerances (MRID 43492856).

A satisfactory method trial has been conducted by EPA's Analytical Chemistry Laboratory for Method M 2216 for chlorfenapyr in/on cottonseed with minor revisions required. Residues of chlorfenapyr are extracted from cottonseed with a methanol/water mixture and cleaned up using C-18 solid phase extraction. Quantitation is done using gas chromatography equipped with electron capture detector and a mega bore capillary column. The revised analytical method with the recommended revisions (M 2216.01) has been submitted. The method limit of quantitation is 0.05 ppm but method sensitivity is reported at 0.005 ppm. A GC/MS confirmatory method (M 2418) has also been submitted.

Multiresidue data for chlorfenapyr were submitted. Protocols A and B were not applicable to chlorfenapyr. In Protocol C, chlorfenapyr gave a good response and a good peak with the electron capture detector on three different GC columns. In Protocol D, using pears as a nonfatty food representative the 5% OV-101 column gave the greatest sensitivity at 0.05 and 0.50 ppm. In Protocol E, chlorfenapyr eluted well on Florisil in both the ethyl ether/petroleum ether system and the alternate hexane/acetonitrile/methylene chloride system and gave excellent recovery.

iv. Residue Analytical Method - Animals

Three different analytical methods for chlorfenapyr residues in milk, muscle/fat and liver/kidney are available to support the proposed permanent tolerances (MRID 43492857).

M 2395 - Parent residues are isolated from milk and purified using acetone precipitation, methylene chloride partition and solid phase extraction techniques. Residues are measured using gas chromatography (GC) with electron capture detection and residues are calculated as parent by direct comparison of sample peak height to that of an external standard. The validated sensitivity of the method is 10 ppb.

M 2398 - Parent residues are extracted from muscle with methanol and from fat with acetonitrile. Residues are isolated by hexane partition and purified using solid phase extraction techniques. Residues are measured using GC with electron capture detection and calculated as parent by direct comparison of sample height to that of an external standard. The validated sensitivity of the method is 10 ppb.

M 2405 - Parent residues are extracted from cattle liver and kidney tissues with acetonitrile. Residues are isolated by hexane partition and are purified using solid phase extraction techniques. Residues are measured using GC with electron capture detection and calculated as parent by direct comparison of sample height to that of an external standard. The validated sensitivity of the method is 50 ppb.

v. Storage Stability

Storage stability data (MRID 43492858) were submitted. HED concludes that chlorfenapyr is stable in cottonseed up to 23 months when stored frozen. Considering the stability of chlorfenapyr in cottonseed stored frozen up to 23 months HED also concludes that storage stability data on cottonseed processed fractions stored frozen up to four months as in the original processing study are not required. The storage stability data indicate that chlorfenapyr is stable in milk up to 3 months when stored frozen and up to four days when stored in a refrigerator. Additional data from the ruminant feeding study were provided to indicate the fat and muscle samples were analyzed within 42 rather than 90 days. Since the HED Metabolism Committee has decided that only the parent needs to be regulated, storage stability data on metabolites are not required.

vi. Magnitude of the Residue - Meat, Milk, Poultry and Eggs

An acceptable ruminant feeding study (MRID 43492859) has been submitted. Female non-pregnant Holstein dairy cows were dosed for 28 days at 0, 0.66, 2.19, or 6.81 mg per kg feed (i.e. ppm) on a dry matter basis of chlorfenapyr with capsules using a balling gun. Whole milk was collected twice daily and composited into a daily sample. The highest chlorfenapyr residue levels from the ruminant feeding study occurred in fat tissue at approximately 9X (6.81/0.77 ppm) residue levels in muscle tissue. Furthermore, the ^{14}C goat milk fat study verified that chlorfenapyr concentrates in milk fat as well.

Residue data are not currently available on chlorfenapyr in cotton gin byproducts. However, based on a best estimate of possible residues in cotton gin byproducts the tolerances for chlorfenapyr in ruminant commodities should be: milk, 0.01 ppm; milk fat, 0.15 ppm; meat of cattle, goats, hogs, horses, and sheep, 0.01 ppm; fat of cattle, goats, hogs, horses and sheep, 0.10 ppm; and meat byproducts of cattle, goats, hogs, horses and sheep, 0.05 ppm. A tolerance of 0.3 ppm is recommended for the dietary risk assessment for meat byproducts of cattle, goats, hogs, horses and sheep. A ratio of 6X the proposed parent tolerance level (0.05 ppm) in ruminant meat byproducts is recommended to account for metabolite residues per the HED Metabolism Committee. A note in the tolerance expression of the revised Section F and 40 CFR for animal commodities is required indicating that the parent is serving as a **marker** for metabolite residues in meat byproducts. For this reason the meat byproduct tolerance should be listed separately in the Code of Federal Regulations.

A poultry feeding study has not been required by HED since the highest single residue from the poultry metabolism study (i.e. 0.79 ppm M-6A in the liver) occurred at a dosage level of 15.9 ppm (i.e. 145X) so that the highest expected residue in poultry at 0.79 ppm/145 or 0.005 ppm would likely not be detectable. Therefore, residues of chlorfenapyr are not likely to be found in poultry commodities, based on the feeding levels of the metabolism studies and the resulting residues. Accordingly, tolerances on poultry commodities are not required.

vii. Magnitude of the Residue - Crop Field Trials/Processed Commodities

Cotton Field Trials

American Cyanamid submitted data (MRID 42770238) from seven tests conducted in 1991 in AR(1), CA(1), LA(2), MS(2), and TX(1) and one test conducted in 1992 in LA depicting residues of chlorfenapyr in/on cottonseeds following the last of five foliar broadcast applications of the 2 and 3 lb/gal EC formulations each at 0.4 lb ai/acre/application. Additional residue field trial data (MRID No. 43482860) were submitted from ten field trials conducted in 1992 in AR(1), CA(1), LA(2), MS(2), TX(1), AL(1), SC(1) and GA(1) depicting residues of chlorfenapyr in/on cottonseeds following the last of five foliar broadcast applications of the 3 lb/gal EC formulations each at 0.4 lb ai/acre/application.

Residues of chlorfenapyr were ≤0.32 ppm and ≤0.31 ppm in/on cottonseed samples harvested 21 and 28 days, respectively following the last of five foliar broadcast applications of 3 lb/gal EC formulations each at 0.4 lbs ai/acre or approximately 2x the proposed current maximum seasonal application rate of 1.05 lbs ai/acre/season.

The cottonseed field trial data are adequate to support the proposed permanent tolerance for chlorfenapyr of 0.5 ppm in/on cottonseed harvested 21 days following the last of 5 foliar broadcast applications of chlorfenapyr not to exceed a total seasonal maximum application rate of 1.05 lb ai/acre.

Residue data on cotton gin byproducts (RAC) are required for chlorfenapyr. Cotton gin byproducts include the plant residues from ginning cotton, and consist of burrs, leaves, stems, lint, immature seeds, and sand or dirt. Cotton must be harvested by commercial equipment (stripper and mechanical picker) to provide an adequate representation of plant residue for the ginning process. At least 3 field trials for each type of harvesting (stripper and picker) are needed, for a total of 6 field trials. These data may be provided on a conditional basis.

In the absence of the required cotton gin byproduct field trial data HED recommends a tolerance of 2.00 ppm as a realistic worst case estimate of parent residues in cotton gin byproducts. The tolerance of 2.00 ppm is based on the results of the cottonseed processing study (MRID 44084002) discussed below, where parent residues in linters and linter motes were 1.80 and 2.13 ppm, respectively after processing delinted cottonseed with parent residues of <0.05 ppm. In the absence of the required cotton gin byproduct field trial data HED will use 2.00 ppm as a realistic worst case estimate of parent residues in cotton gin byproducts. The petitioner has committed to conduct six field trials during the 1997 season to obtain residue data on cotton gin byproducts.

Cottonseed Processing

Cottonseed processing data (MRID 42770238, 43492861, and 43482860) were submitted depicting the concentration of residues of chlorfenapyr in cottonseed processed commodities. No concentration of parent residues (average level of 0.30 ppm in ginned cottonseed) occurred in crude/refined cottonseed oil or hulls. Accordingly, separate tolerances for cottonseed processed commodities are not required.

viii. Confined Rotational Crops

The confined crop rotation study (MRID 43492851) indicates that residues of chlorfenapyr and or metabolites CL 312094 and CL 325195 at 0.01-0.02 ppm are possible in rotated crops with a 30

day plant back interval. However, since the study was conducted at approximately 2X the current proposed use rate of 1.05 lb ai/acre/season with application made to bare ground (a worst case), at a plant back interval of 60 days or later all residue components in all rotated crops should be less than 0.01 ppm. Accordingly, at the current proposed use rate of 1.05 lb ai/acre/season field rotational crop studies are not required provided the end use product label contains the following restrictions:

- Do not plant root crops within 60 days of last application.
- For all other crops do not plant within 30 days of last application.

b. Dietary Exposure - Drinking Water

Based on review of environmental fate data (requirements listed under 40 CFR § 158.290) by EPA's Environmental Fate and Effects Division (EFED), chlorfenapyr is considered immobile and has a relatively high affinity for soil. This is predicted by laboratory batch equilibrium studies using four different soils (median soil organic carbon adsorption coefficient, Koc, of about 11,500 mL/g) which confirmed the absence of significant leaching in a total of five terrestrial field dissipation studies in four states. Judging from laboratory study only, a major soil metabolite, AC 312,094 (median Koc of about 2200), is also not expected to be a groundwater concern. Therefore, in spite of its persistence in the environment, chlorfenapyr is not expected to be a groundwater concern. The mobility characteristics exhibited by this compound in both the laboratory and field are not those generally associated with compounds found in groundwater.

However, chlorfenapyr does present surface water concerns. Persistent chemicals that have a strong affinity for soil can move to surface water with eroded sediments. Tier II Estimated Environmental Concentrations (EEC's) were estimated by Siroos Mostaghimi of the Surface Water Section of EFED/Environmental Fate and Ground Water Branch (EFGWB) to estimate exposure of chlorfenapyr from surface water.

Two scenarios were used for modeling: a Mississippi site, which represents a scenario with high potential for runoff; and a Texas site, which represents a scenario with a moderate potential for runoff. Tier II EEC uses a single high exposure site for the use of pesticide on a particular crop. The weather and agricultural practices were simulated at the sites for 36 years so that the probability of an EEC occurring at those sites can be estimated. The following assumptions were made for the application of chlorfenapyr on cotton:

- The chemical is applied aerially. At the application time 75% of the chemical applied reaches the field.
- 5% of the applied chlorfenapyr reached surface water at application time due to aerial spray drift.
- The other 20% either remained airborne or deposited on the ground beyond the pond.

The agricultural field model PRZM 2 and the water quality model EXAMS are used to calculate Tier II EEC's. The values represent an upper bound estimate of the concentration in an edge-of-the-field

pond with no outlet. The field is 10 hectares in size and the pond is one hectare, two meters deep. The values have estimated return frequency of one in ten years at that site.

The recommended values for drinking water exposure for use in human health risk assessment for surface water are 11 μg/L for acute drinking water exposure and 9 μg/L for chronic drinking water exposure. Using these exposure numbers the dietary exposure calculation for water are as follows:

Adult Exposure = (chemical concentration in μg/L in consumed water)(10^{-3} mg/μg)(2 L/day) ÷ (70 kg body weight)

Children Exposure = (chemical concentration in μg/L in consumed water)(10^{-3} mg/μg)(1 L/day) ÷ (10 kg body weight)

Subgroup/Exposure Scenario	Exposure to Chlorfenapyr from Drinking Water (Surface Water) mg/kg/day
Adult/Acute Exposure	3×10^{-4}
Adult/Chronic Exposure	3×10^{-4}
Children/Acute	1×10^{-4}
Children/Chronic	9×10^{-4}

c. Dietary Risk Characterization

i. Acute Dietary

An acute dietary risk assessment is required for chlorfenapyr. The NOEL of 45 mg/kg/day from the acute neurotoxicity study (MRID 43492829) in rats was selected as the endpoint to be used for acute dietary risk assessments. HED's detailed acute analysis estimates the distribution of single-day exposures for the overall U.S. population and certain subgroups. The analysis evaluates individual food consumption as reported by respondents in the USDA 1977-78 Nationwide Food Consumption Survey (NFCS) and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of chlorfenapyr in the commodity supply.

The MOE is a measure of how closely the anticipated exposure comes to the NOEL and is calculated as a ratio of the NOEL to the exposure (NOEL/exposure = MOE). The Agency is not generally concerned unless the MOE is below 100 when the NOEL is based upon data generated in animal studies. The 100 accounts for the interspecies extrapolation and intraspecies variability. However, an additional 10-fold MF is considered appropriate for chlorfenapyr due to the lack of understanding of the toxicity with regard to the developing young. Therefore, for chlorfenapyr, HED's level of concern is for MOEs that are below 1000.

For use of chlorfenapyr on cotton the MOEs (>99 percentile exposure estimate) for all subgroups was greater than 3000 and therefore indicates there is no acute dietary concern.

Subgroup	NOEL (mg/kg/day)	Exposure (mg/kg/day)	MOE*
General U.S. Population	45	0.005	9000
Infants (< 1 year)	45	0.015	3000
Children (1-6 years)	45	0.01	4500
Females (13+ Years)	45	0.003	> 10000
Males (13+ Years)	45	0.003	> 10000

* MOE = NOEL/exposure

ii. Chronic Dietary Risk

A chronic dietary risk assessment is required for chlorfenapyr. The RfD used for the chronic dietary analysis is 0.003 mg/kg bwt/day.

Tolerances for chlorfenapyr of 0.50 ppm in/on cottonseed and 0.01, 0.15, 0.01, and 0.10, respectively for milk, milk fat, meat, and fat of cattle, goats, hogs, horses, and sheep were used for this dietary risk assessment. A residue value of 0.3 ppm was used for the dietary risk assessment for meat byproducts of cattle, goats, hogs, horses and sheep. A ratio of 6X the proposed parent tolerance level (0.05 ppm) in ruminant meat byproducts is used to account for metabolite residues per the HED Metabolism Committee. Cotton gin byproduct field trial data have not been submitted. In the absence of this required data, HED recommends a tolerance of 2.00 ppm as a realistic worst case estimate of parent residues in cotton gin byproducts. Tolerances for poultry commodities are not required for the proposed cotton use.

A chronic exposure analysis was performed using tolerance level residues and 100 percent crop treated information to estimate the Theoretical Maximum Residue Contribution (TMRC) for the general population and 22 subgroups. The chronic analysis showed that exposure from the proposed tolerance for use in/on cotton for non-nursing infants less than 1 year old (the subgroup with the highest exposure) would be 76% of the RfD, while the exposure for the general U.S. population would be 23% of the RfD.

This chronic analysis for chlorfenapyr is a upper-bound exposure estimate of dietary exposure with all residues at tolerance level and 100 percent of the commodity assumed to be treated with chlorfenapyr. Therefore, even without refinements, HED does not consider the chronic dietary risk to exceed the level of concern.

iii. Aggregate Acute Dietary/Drinking Water Risk

To determine aggregate acute dietary/drinking water risk, a MOE approach is used where the total acute exposure from the diet and drinking water is compared to the acute dietary endpoint of concern, the NOEL of 45 mg/kg/day. An aggregate acute dietary/drinking water MOE greater than 1000 is considered appropriate for chlorfenapyr. Since the MOEs for both the general population and children are greater than 1,000, the use of chlorfenapyr in/on cotton demonstrates no aggregate acute dietary/drinking water risk concern.

Subgroup	NOEL (mg/kg/day)	Exposure-Diet (mg/kg/day)	Exposure-Water (mg/kg/day)	MOE*
General Population	45	0.005	0.0003	8,000
Children	45	0.01	0.0001	4,500

* MOE = NOEL/exposure

This aggregate acute dietary/drinking water analysis for chlorfenapyr is a high exposure estimate that assumes acute exposure via the diet and drinking water at the same time. It is very unlikely such a scenario would occur. Therefore, HED has high confidence that the aggregate acute dietary/drinking water risk is minimal for use of chlorfenapyr on cotton.

iv. Aggregate Chronic Dietary/Drinking Water Risk

The chronic drinking water risk is calculated as a percent of the RfD taken up by drinking water. The following calculation is used:

%RfD = (Exposure from Water mg/kg/day) ÷ (RfD mg/kg/day) x 100

In order to determine the percent of the RfD taken up by drinking water for use of chlorfenapyr on cotton the exposure estimates are taken from the Dietary Exposure - Drinking Water section above and the RfD of 0.003 mg/kg/day is used. The chronic analysis showed that chronic exposure from drinking water to children would be no be greater than 30% of the RfD, while the exposure for the general U.S. population would be 10% of the RfD. **Therefore, the combined exposure of chronic dietary and drinking water to chlorfenapyr would be no greater than 106% of the RfD for children, while the combined exposure for chronic dietary and drinking water for the general U.S. population would be 33% of the RfD.**

The drinking water values were developed for use in eco-risk assessment and represent a reasonable upper-bound estimate for eco-risk assessment. It is expected they represent an even more substantial overestimate for human health risk assessments. The chronic dietary analysis is also an upper-bound estimate of dietary exposure with all residues at tolerance level and 100 percent of the commodity assumed to be treated with chlorfenapyr. Therefore, even without refinements, HED does not consider the combined aggregate chronic dietary/drinking water risk to exceed the level of concern.

4. OCCUPATIONAL AND RESIDENTIAL EXPOSURE AND RISK CHARACTERIZATION

a. Occupational Exposure

For risk assessment purposes the average farm size is considered to be 666 acres. This is an estimate of maximum acreage treated. This is representative of the maximum acreage in cotton in Fresno County, California. The average acres in cotton per farm in the United States is 315; California is the state producing the most cotton, with a state average of acres in cotton per farm of 453 acres; Fresno County is the county in California with the highest acres in cotton per farm at 666 acres. The

source of this information is the U.S. Department of Commerce, 1992 Census of Agriculture, Volume 1, Geographic Area Series, Part 51 (U.S. Summary and State Data), and Part 5 (California, State and County Data).

HED's occupational exposure estimates are also based on the assumptions in following table:

Assumptions for Worker Exposure Assessments

Factors	Quantities/Units
Applicator body weight	70 kg
Mixer/loader body weight	70 kg
Application rate (air/ground)	0.35 lb ai/acre (Pirate) 0.34 lb ai/acre (Alert)
Acres treated per day (air)	482 acres[1]
Acres treated per day (ground)	88 acres[1]
Number of Farms Treated by Professional Chemical Operator	Ground: 2 (default value) Air: 10 (default value)
Mixer/loader unit exposure from the Pesticide Handlers Exposure Database (PHED), (In support of aerial or groundboom application; liquid; open mixing; with coveralls [Pirate only], long pants, long-sleeved shirt, and gloves).	(Pirate) 17.5 µg/lb ai handled[2] (Alert) 23.0 µg/lb ai handled
Applicator unit exposure from PHED (Aerial application; liquid; enclosed cockpit; with long pants, long-sleeved shirt, no gloves).	5.0 µg/lb ai handled[3]
Applicator unit exposure from PHED (Groundboom application; liquid; open cab; with long-pants, long-sleeved shirt, and gloves).	14.0 µg/lb ai handled[3]
Personal protective equipment (PPE), per label.	**For Pirate:** Coveralls over short-sleeved shirt and short pants; chemical-resistant gloves, chemical-resistant footwear plus socks, chemical-resistant headgear for overhead exposure, and chemical-resistant apron when cleaning equipment, mixing, or loading. **For Alert:** Long-sleeved shirt and long pants; chemical-resistant gloves; shoes plus socks.

[1] Assumptions of the acreage treated per day given the application methods and finish spray quantities stated in the labels are provided by Dr. Yuen-shaung Ng, Biological and Economic Exposure Division (refer to C. Lang memo of 2/12/97).
[2] Source: Pesticide Handlers Exposure Database V1.1, run "LIQ1.OPN.MLOD" for mixer/loader, groundboom and aerial, liquid, open pour, with and without coveralls, long pants, long sleeves, gloves.
[3] Source: Pesticide Handlers Exposure Database V1.1, "Best Available" Surrogate Exposure Table, dated 7/25/96: page 5 for applicators, groundboom, liquid, open cab, long pants, long sleeves, gloves; page 9 for applicator, aerial, liquid, enclosed cockpit, long pants, long sleeves, no gloves (pilots are not required to wear gloves).

The Mixer/Loader worker exposure estimate below for Pirate DOES reflect use of an arithmetically calculated protection factor for use of coveralls. For mixer/loaders there are no two-layered (coveralls over pants and shirt) values in the Pesticide Handlers Exposure Database (PHED), Version 1.1. for the liquid/open mixing scenario. HED estimates that the additional coveralls will provide an additional 50% reduction in exposure. In order to estimate the reduction in exposure that coveralls would provide, the upper arm, chest, back, forearms, thighs and lower legs values were reduced by 50%. Mixer/Loader

exposure estimates for Alert were made based on use of long sleeved shirts, long pants, shoes, socks, and gloves.

Data were not available to estimate worker exposure for application of Pirate via groundboom with use of coveralls. Further, available PHED, Version 1.1 data are based on use of long pants, long-sleeved shirt rather than the short pants, short-sleeved shirt recommended on the label. The estimate found below for this scenario is a conservative estimate and worker exposure for this scenario with use of coveralls would be expected to be somewhat less. Application of Alert via groundboom is based on use of long sleeved shirts, long pants, shoes, socks, and gloves. The aerial applicator exposure estimate does not represent the use of coveralls or gloves, as pilots in enclosed cabs are exempt from use of certain Personal Protective Equipment (PPE).

The following calculations were used to determine the expected worker exposures resulting from the handling and application of chlorfenapyr to cotton.

Mixer/loaders - Groundboom
lbs ai applied/acre x number of acres treated/day = lbs ai/day
µg/lb ai handled (PHED, Version 1.1) x lbs ai/day = µg ai/day ÷ 70 kg bw = µg ai/kg bw/day. µg ai/kg bw/day ÷ 1000 = mg ai/kg bw/day

Applicators - Groundboom
lbs ai applied/acres x number of acres treated/day = lbs ai/day
µg/lb ai handled (PHED, Version 1.1) x lbs ai/day = µg ai/day ÷ 70 kg bw = µg ai/kg/bw/day. µg ai/kg bw/day ÷ 1000 = mg ai/kg bw/day

Mixer/loaders - Aerial
lbs ai applied/acres x number of acres treated/day = lbs ai/day
µg/lb ai handled (PHED, Version 1.1) X lbs ai/day = µg ai/day ÷ 70 kg bw = µg ai/kg bw/day. µg ai/kg bw/day ÷ 1000 = mg ai/kg bw/day

Applicators - Aerial
lbs ai applied/acres x number of acres treated/day = lbs ai/day
µg/lb ai handled (PHED, Version 1.1) X lbs ai/day = µg ai/day ÷ 70 kg bw = µg ai/kg bw/day. µg ai/kg bw/day ÷ 1000 = mg ai/kg bw/day

Worker Exposures Resulting from the Use of Chlorfenapyr to Cotton

Job Function	Average Dermal Daily Dose for Pirate mg ai/kg bw/day	Average Dermal Daily Dose for Alert mg ai/kg bw/day
Mixer/loaders (ground)	8×10^{-3}	10×10^{-3}
Applicators (ground)	6×10^{-3}	6×10^{-3}
Mixer/loaders (air)	42×10^{-3}	54×10^{-3}

Worker Exposures Resulting from the Use of Chlorfenapyr to Cotton		
Applicators (air)	12 x 10^{-3}	12 x 10^{-3}

b. Residential Exposure

The pending registration for use of chlorfenapyr on cotton should not result in any residential exposure.

c. Occupational Risk Characterization

As discussed above the TES Committee identified endpoints of concern for short term, intermediate term, and chronic occupational or residential exposure. The short- and intermediate term endpoints are derived from a 28-day dermal toxicity study in rabbits; the NOEL is 100 mg/kg/day. The chronic endpoint is derived from a combined chronic toxicity/oncogenicity study in mice; the NOEL is 3 mg/kg/day.

The Agency does not generally have an occupational or residential concern unless MOEs are below 100 when the NOEL is based upon data generated in animal studies. The 100 accounts for interspecies extrapolation and intraspecies variability. However, an additional 10-fold MF is considered appropriate for chlorfenapyr due to the lack of understanding of the toxicity with regard to the developing young. Therefore, for chlorfenapyr HED's level of concern is for MOEs that are below 1000.

Chronic exposure is not expected for use of chlorfenapyr on cotton, hence a chronic risk assessment will not be done. The TES Committee does not consider workers to be at risk from inhalation exposure due to the low toxicity of the chemical. Consequently, an inhalation worker risk assessment will not be performed.

The table below summarizes HED's estimates for MOEs for total worker exposure for applicators and mixer/loaders for the proposed use of chlorfenapyr on cotton. These estimates are based on the assumptions outlined in the Occupational Exposure section above.

Worker Risk from Exposure to Chlorfenapyr for Use on Cotton

Job Function	NOEL (mg/kg/day)	Average Dermal Daily Dose for **Pirate** mg ai/kg bw/day	Average Dermal Daily Dose for **Alert** mg ai/kg bw/day	Dermal Short & Intermediate-Term MOE* for **Pirate** and (**Alert**)
Mixer/loaders (ground)	100	8 x 10^{-3}	10 x 10^{-3}	>10,000 (10,000)
Applicators (ground)	100	6 x 10^{-3}	6 x 10^{-3}	>10,000 (>10,000)
Mixer/loaders (air)	100	42 x 10^{-3}	54 x 10^{-3}	2,300 (1,800)

Worker Risk from Exposure to Chlorfenapyr for Use on Cotton				
Applicators (air)	100	12×10^{-3}	12×10^{-3}	8,300 (8,300)

* MOE = NOEL/exposure

Both short term and intermediate term occupational exposure are likely for the following reasons. With an average of 666 acres per farm in Fresno County, California, a worker treating that entire acreage may do so over a period of 7 and 1/2 days if application is by groundboom, and approximately 1 and 1/2 days if application is by air. Additionally, HED estimates that a Professional Chemical Operator may treat 2 farms in an area by groundboom and 10 farms in an area by air. These noted factors may increase a worker's exposure significantly over time above the estimates of occupational exposure cited. However since all MOEs reported are higher than 1000, HED anticipates risk to the worker will be minimal for these exposure scenarios.

5. CUMULATIVE EFFECTS

Section 408 of FQPA 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." While the Agency has some information in its files that may be helpful in determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodology to resolve the scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will enable it to develop and apply policies for evaluating the cumulative effects of chemicals having a common mechanism of toxicity. At present, however, the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments.

In the case of chlorfenapyr, HED has not yet determined whether or how to include this chemical in a cumulative risk assessment. This tolerance determination therefore does not take into account common mechanism issues. After EPA develops a methodology for applying common mechanism of toxicity issues to risk assessments, the Agency will develop a process (either as part of the periodic review of pesticides or otherwise) to reexamine those tolerance decisions made earlier.

On this basis, the registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether chlorfenapyr share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for chlorfenapyr need to be modified or revoked.

IV. DATA REQUIREMENTS

A. Toxicology

A special developmental neurotoxicity study should be conducted. The registrant should conduct a mechanistic study to determine the cause/relationship of CNS/myelinopathic alterations to

neurotoxicity (including developmental). The following modifications to the developmental neurotoxicity study protocol are necessary. A 90 day treatment period for males and females prior to the routine developmental phase required in the developmental neurotoxicity study guidelines is needed. The dams would deliver their pups and come off treated feed at day 10 post-delivery. Normal testing as required in the developmental neurotoxicity study guidelines would then commence. Further, it necessary to characterize the nature of the vacuoles reported in the previous studies and any found in the presently proposed study. The treated males would be used to assist in this characterization. This information may well play a great role in assessing the potential risk of this chemical. It is strongly recommended that the registrant contact the Toxicology Branch prior to initiating the study in order to discuss dose selection and study protocol.

B. Residue Chemistry

Residue data on cotton gin byproducts (RAC) are required for chlorfenapyr. Cotton gin byproducts include the plant residues from ginning cotton, and consist of burrs, leaves, stems, lint, immature seeds, and sand or dirt. Cotton must be harvested by commercial equipment (stripper and mechanical picker) to provide an adequate representation of plant residue for the ginning process. At least 3 field trials for each type of harvesting (stripper and picker) are needed, for a total of 6 field trials.

V. LABEL REQUIREMENTS

The label must contain the following crop rotation restrictions:

- Do not plant root crops within 60 days of last application.
- For all other crops do not plant within 30 days of last application.

The label should contain a restriction that applications of chlorfenapyr do not exceed a total seasonal maximum application rate of 1.05 lb ai/acre.

As required by the Worker Protection Standard (WPS), the PPE that applicators and other handlers must wear for use of the end-use product Pirate (30.83% ai) are:

- Coveralls over short-sleeved shirt and short pants
- Chemical-resistant gloves such as barrier laminate or butyl rubber of nitrile rubber or polyvinyl chloride (PVC) or viton neoprene
- Chemical-resistant footwear plus socks
- Chemical-resistant headgear for overhead exposure
- Chemical-resistant apron when cleaning equipment, mixing, or loading.

The minimum PPE required for early entry into treated areas that involves contact with anything that has been treated, such as plants, soil or water for use of the end-use product Pirate are:

- Coveralls over short-sleeved shirt and short pants
- Chemical-resistant gloves such as barrier laminate or butyl rubber of nitrile rubber or polyvinyl chloride (PVC) or viton neoprene
- Chemical-resistant footwear plus socks

- Chemical-resistant headgear for overhead exposure.

The PPE that applicators and other handlers must wear for use of the end-use product Alert (21.44%) are:

- Long-sleeved shirt and long pants
- Chemical-resistant gloves such as barrier laminate or butyl rubber of nitrile rubber or polyvinyl chloride (PVC) or viton neoprene
- Shoes plus socks.

The minimum PPE for early entry into treated areas that involves contact with anything that has been treated, such as plants, soil or water for use of the end-use product Alert are:

- Coveralls
- Chemical-resistant gloves such as barrier laminate or butyl rubber of nitrile rubber or polyvinyl chloride (PVC) or viton neoprene
- Shoes plus socks.

The restricted-entry interval (REI) is 12 hours for both pending end-use products.

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