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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 12-Feb-1998

SUBJECT: **Chlorfenapyr - 129093**: Health Effects Division Risk Characterization for Use of the Chemical Chlorfenapyr (Alert, EPA File Symbol 5905-GAI) in/on Citrus (6F04623). Case: 287132. Barcode: D221320

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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 chlorfenapyr in/on citrus.

American Cyanamid Company has petitioned for permanent tolerances for residues of the insecticide/miticide chlorfenapyr [4-bromo-2-(chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile] as follows:

Citrus . . . 0.5 ppm

Chlorfenapyr is also known as Pirate, Alert, CL 303,630 or AC 303,630. A temporary tolerance has been established in/on cottonseed at 0.5 ppm. Temporary tolerances of 0.5 ppm have also been proposed for oranges and lemons (PP#5G04507). In conjunction with PP#5F04456, HED has determined that the following meat and milk tolerance are required to support the proposed use on citrus:

Milkfat	0.15 ppm	Milk	0.01 ppm
Fat*	0.10 ppm	Meat*	0.01 ppm
Meat by-products*	0.05 ppm		

* of beef, goat, swine, horse, and sheep

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 Marion Copley, D.V.M. of RAB1; the product and residue chemistry data review by Gary F. Otakie, P.E. of CEB2 and George Kramer, Ph.D. of RAB1; the dietary risk assessment by Andrew Rathman of RAB1; the drinking water exposure assessment by R. David Jones, Ph.D. and Siroos Mostaghimi of EFED; the occupational exposure assessment by Julianna Cruz of RAB1.

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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 registration containing the active ingredient (ai) chlorfenapyr for a technical product and the end-use product liquid formulation (Alert, EPA File Symbol 5905-GAI) for use as an insecticide in/on citrus.

The HED RfD/Peer Review Committee (revised document dated 11/21/97) considered the No Observed Effect Level (NOEL) in the 1-year rat neurotoxicity study (MRID 43492833) of 2.6 mg/kg/day to be the appropriate end-point for establishing the reference dose (RfD) for chlorfenapyr *[also supporting this endpoint are similar central nervous system (CNS) lesions and skin lesions observed in the mouse carcinogenicity study (NOEL 2.8 mg/kg/day)*(MRID 43492838)*]*. An uncertainty factor (UF) of 100 was applied to account for interspecies extrapolation and intraspecies variability. In addition, the acute neurotoxicity study (MRID 43492829) in the rat revealed myelinopathic alterations. FFDCA section 408 provides that EPA shall apply an additional 10-fold margin of exposure (safety) for infants and children in the case of threshold effects to account for pre-and post-natal toxicity and the completeness of the data base unless EPA determines that a different margin of safety will be safe for infants and children. Since chlorfenapyr has produced CNS lesions in several studies in both rats and mice, the RfD/Peer Review Committee recommended that the additional FQPA Factor of 10 be retained 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 factor (UF). The Committee also recommended that a developmental neurotoxicity study be conducted.

In the rat chronic toxicity/carcinogenicity study (MRID 43492837), 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 in pair-wise comparison of fibroadenomas at the 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 (9/25/96) 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 of carcinogenicity; 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. Structure-activity data were not available.

Toxicological endpoints of concern have been identified for acute dietary exposure and short- and intermediate-term dermal and inhalation exposures. HED recommends the following endpoints be used for risk assessment purposes: 1) The NOEL from the acute neurotoxicity study (MRID 43492829) in rats of 45 mg/kg/day for acute dietary risk assessments; 2) 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.

A chronic dietary exposure analysis was performed using **anticipated residue** values (derived from averages of field trial results). The chronic analysis showed that exposure from the proposed tolerance for use in/on citrus for non-nursing infants less than 1 year old (the subgroup with the highest exposure) would be 26% of the RfD, while the exposure for the general U.S. population would be 12% of the RfD. Based on the chronic dietary (food) exposure and using default body weights and water consumption figures, chronic levels of concern (LOC) for drinking water were calculated. For **chronic** exposure, based on an adult body weight of 70 kg and 2 L consumption of water per day, HED’s level of concern from chronic exposure in drinking water is 92 µg/L. For children (10 kg and consuming 1 L water/day), the level of concern for drinking water is 22 µg/L. Because the estimated chronic drinking water exposure for chlorfenapyr is 9 µg/L, potential residues in drinking water are not greater than HED's level of concern. **Therefore, the combined exposure of chronic dietary and drinking water exposure to chlorfenapyr would be no greater than 100% of the RfD for children or the general U.S. population.**

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 chronic risk assessments. The chronic dietary analysis is also an overestimate of dietary exposure as 100 percent of the commodity was assumed to be treated with chlorfenapyr. Therefore, even without further refinements, HED does not consider the combined aggregate chronic dietary/drinking water risk to exceed the level of concern.

Based on the existing toxicological database, 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 citrus. There are no existing uses of chlorfenapyr which would result in any residential exposure. The pending registration for

use of chlorfenapyr on citrus should not result in any residential exposure.

For use of chlorfenapyr on citrus, acute dietary MOEs ranged from 4,500 to 9,000. MOEs for short- and intermediate term occupational risk range from 6,300 to greater than 40,000. Based on the acute dietary (food) exposure and using default body weights and water consumption figures, acute levels of concern (LOC) for drinking water were calculated. For **acute** drinking water exposure for adults, the level of concern is 1220 µg/L; and for children, 350 µg/L. Because the estimated acute drinking water exposure for chlorfenapyr is 11 µg/L, potential residues in drinking water are not greater than HED's level of concern. The MOEs for the use of chlorfenapyr on citrus are thus above HED's level of concern for all exposure scenarios.

The residue chemistry and toxicological data bases are adequate to support <u>time-limited</u> tolerances and a <u>conditional</u> registration for the use of chlorfenapyr on citrus in terms of human health risk. HED recommends that: 1) commitment to perform a developmental neurotoxicity study; 2) establishment of meat and milk tolerances; 3) proposed tolerances for citrus processed commodities; 4) submission of a new version of the proposed analytical enforcement method for citrus with the revisions recommended by ACL; 5) commitment to conduct post-application exposure monitoring; **and** 6) commitment to perform 11 additional field trials be required as a condition of registration. To provide for the periodic evaluation of the anticipated residues, the Agency will require under Section 408(b)(2)(E) residue data be submitted every five years as long as the proposed tolerances remain in force.

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 5905-GAI). Only Alert is intended for use on citrus. Petitions are pending for the use in/on cotton (5F4456) and imported oranges and lemons (6E04683).

Alert is intended for use in/on citrus fruit trees. In the United States, there are four states which grow a majority (at least 99.9%) of all the citrus fruits with in the nation: Arizona, California, Florida, and Texas. Out of the four states, Florida has the most

acreage allotted for citrus fruits; which is 71.53% (887,904.0 acres) of the total U.S. acreage (1,241,320.0) allotted for citrus fruit trees. The predominant types of citrus fruits grown in all four states are: grapefruits, lemons, limes, oranges, tangelos, and tangerines. The above data is from the 1992 Census of Agriculture, Volume - 1, Parts 3, 5, 9, 43B, & 51.

III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

1. Identification of Active Ingredient

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

Common Name: Chlorfenapyr

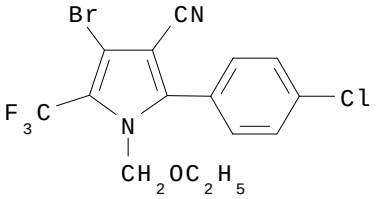
PC Code Number: 129093

CAS Registry No.: 122453-73-0

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

Molecular Weight: 407.6

Structural Formula:



2. Physical and Chemical Properties

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

Physical and Chemical Properties for Chlorfenapyr	
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	K_{ow} = 67,670 (log K_{ow} = 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.
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 LD_{50} - rat MRID 42770207 & 42884201	441 mg/kg, males 1152 mg/kg, females 626 mg/kg, combined	II*
Dermal LD_{50} - 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 LD_{50} - Rat MRID 43492824	27.0 mg/kg, males 29.4 mg/kg, females 28.7 mg/kg, combined	I
Metabolite - AC 312,094 Oral LD_{50} - Rat MRID 43492825	>5,000 mg/kg, males >5,000 mg/kg, females >5,000 mg/kg, combined	IV
Metabolite - AC 322,250 Oral LD_{50} - Rat MRID 43492826	>5,000 mg/kg, males 2,500 mg/kg, females	III
Metabolite - AC 325,195 Oral LD_{50} - 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 were 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 Rabbits

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/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 43492837 (main), 43492836 (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).

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. 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). In a range finding study (doses of 0,

12.5, 25, 50, 100 or 200 mg/kg/day) there was mortality and possibly some neurologic signs (including excess salivation and impaired righting reflexes) in those rabbits that died at 50 mg/kg/day and above.

e. Reproductive Toxicity

In a 2-generation reproduction study [MRID 43492836 (main), 43492835 (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. 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 (≥ 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 (≥ 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.

g. Metabolism

In a metabolism study (MRID 43492844), [2-pyrrole-14C] or [phenyl-14C] 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 (≤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.

h. 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 a 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).

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 oral 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.

j. Other Toxicological Considerations (special studies)

None

2. Dose Response Assessment

a. Special Sensitivity to Infants and Children

EPA generally defines the level of appreciable risk as exposure that is greater than 1/100 of the no observed effect level in the animal study appropriate to the particular risk assessment. This 100-fold uncertainty (safety) factor/margin of exposure (safety) is designed to account for inter-species extrapolation and intra-species variability. FFDCA section 408 provides that EPA shall apply an additional 10-fold margin of safety for infants and children in the case of threshold effects to account for pre-and post-natal toxicity and the completeness of the data base unless EPA determines that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA risk assessments either directly through use of a margin of exposure analysis or through using uncertainty (safety) factors in calculating a dose level that poses no appreciable risk to humans.

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. There is a revised RfD document dated 11/21/97.

i. Adequacy of data

Acceptable prenatal toxicity studies in rats and rabbits with chlorfenapyr have been submitted to the Agency. There are no data gaps for the assessment of the effects of chlorfenapyr following *in utero* exposure, however a developmental neurotoxicity study has been requested (see developmental neurotoxicity section below). An acceptable reproductive toxicity study in rats with chlorfenapyr is also available. There are no data gaps for the assessment of the effects of chlorfenapyr to young animals following early postnatal exposure (see the following executive summaries).

(a) 83-3a Prenatal Developmental Study - Rat

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).

This study is classified **acceptable (guideline)** and satisfies the guideline requirement for a developmental study in the rodent (83-3a).

(b) 83-3b Prenatal Developmental Study - Rabbit

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 range finding 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).

The developmental toxicity study in the rabbit is classified **acceptable (guideline)** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3 (b)) in rabbit.

(c) 83-4 Two-Generation Reproduction Study - Rat

In a 2-generation reproduction study [MRID 43492836 (main), 43492835 (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).

The two-generation reproduction study in the rat is classified **acceptable (guideline)** and satisfies the guideline requirement for a two-generation reproduction study (OPPTS 870.3800; §83-4) in rat.

ii. Susceptibility issues

The existing data demonstrated no indication of increased sensitivity of rats and/or rabbits to *in utero* exposure to chlorfenapyr. The NOELs for maternal toxicity (in the existing developmental studies) were always less than or equal to the NOELs for fetal toxicity. The existing data demonstrated no indication of increased sensitivity of rats and/or rabbits to early post natal exposure to chlorfenapyr. The NOEL for systemic toxicity was always less than the NOELs for reproductive toxicity. **However**, since this chemical has a demonstrated potential for central nervous system lesions, the

RfD Committee determined that there was inadequate evidence to be sure that increased sensitivity to infants or children did not exist.

iii. Uncertainty Factor

The Committee determined that for chlorfenapyr, the additional 10-fold FQPA Factor for the protection of infants and children should be retained for lack of understanding of the cause, and possible further unknown neurotoxicity with regard to the developing young. The Committee considered that "unusual toxic properties raise concerns regarding the adequacy of the standard margin/factor."

iv. Recommendation for a developmental neurotoxicity study

The RfD Committee also recommended that a special developmental neurotoxicity study be conducted based upon the effects of a spongyform myelopathy and/or vacuolation seen in the brain and spinal cord of treated rats and mice. They concluded that the registrant should also 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 considered 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 play a role in assessing the potential risk of this chemical. It is strongly recommended that the registrant contact the HED prior to initiating the study in order to discuss dose selection and study protocol. It should be noted that the Registrant has requested modifications to the protocol of the neurotoxicity study. This request is currently under consideration by HED.

b. Reference Dose (RfD)

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. There is a revised RfD document dated 11/21/97.

In the rat chronic toxicity/carcinogenicity study (MRID 43492837), 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 in pair-wise comparison of fibroadenomas at the 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 this issue for chlorfenapyr 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 1 year neurotoxicity study (MRID 43492833) and acute neurotoxicity study (MRID 43492829) both in the rat also revealed CNS/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 the additional FQPA Factor of 10 be retained 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 (see details above).

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 *[also supporting this endpoint are similar central nervous system lesions and skin lesions observed in the mouse carcinogenicity study (NOEL 2.8 mg/kg/day)*(MRID 43492838)*]*. 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, the additional 10-fold FQPA Factor is retained and considered appropriate for this chemical. On this basis the RfD was calculated to be 0.003 mg/kg/day with a 1000-fold UF.

c. Carcinogenic 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 43492837) 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. Structure-activity data were not available. There is no human data for chlorfenapyr. Dietary risk concerns due to long-term consumption of chlorfenapyr residues are adequately addressed by the DRES chronic exposure analysis using the RfD.

d. 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 oral 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.

e. Other Toxicological 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. There is a revised TES document dated 11/21/97. For more information on studies discussed in this section refer to the Hazard Assessment section of this document.

i. Acute Dietary (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 of 1000 is considered appropriate for this chemical. The UF is based on 100 to account for interspecies extrapolation and intraspecies variability and the 10-fold FQPA Factor for the lack of understanding of the toxicity with regard to the developing young.

ii. Short and Intermediate Term Occupational (dermal)

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 of 1000 is considered appropriate for this chemical. The UF is based on 100 to account for interspecies extrapolation and intraspecies variability and the 10-fold FQPA Factor for the lack of understanding of the toxicity with regard to the developing young.

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 indicating low toxicity by this route. However, if there is a concern for high exposure via this route, a risk assessment may be required. With the exception of the acute inhalation toxicity study, there are no inhalation toxicity studies available for selection of a dose and endpoint for inhalation exposure risk assessment. An oral NOEL should be used for risk assessment if needed, applying an inhalation absorption factor of 100%.

iii. Chronic Occupational (Non-Cancer)

A chronic term endpoint of concern was identified. The NOEL of 3 mg/kg/day from the one year neurotoxicity study in rats (MRID 43492833) and the combined chronic toxicity/carcinogenicity study (MRID 43492838) in mice for chronic (non-cancer) occupational or residential risk assessments (rounded from 2.6 and 2.8 mg/kg/day, respectively). An UF of 1000 is considered appropriate for this chemical. The UF is based on 100 to account for interspecies extrapolation and intraspecies variability and the 10-fold FQPA Factor for the lack of understanding of the toxicity (neurotoxicity) 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.

TABLE 1. Summary of Toxicological Endpoints for Chlorfenapyr

Exposure Duration	Exposure Route	Endpoint and Toxicological Effect
Acute	Dietary	NOEL: 45 mg/kg/day (neurotoxicity signs of lethargy in males in an acute neurotoxicity study rats) Acceptable MOE = 1000 (includes FQPA Factor)
Short-Term (1-7 days) Occupational/Residential	Dermal	NOEL: 100 mg/kg/day (increased cholesterol, relative liver weights and cytoplasmic vacuolation of the liver in male and females in a 28-day dermal toxicity study in rabbits) Acceptable MOE = 1000 (includes FQPA Factor)
Intermediate-Term (one week to several months) Occupational/Residential	Dermal	NOEL: 100 mg/kg/day ((increased cholesterol, relative liver weights and cytoplasmic vacuolation of the liver in male and females in a 28-day dermal toxicity study in rabbits) Acceptable MOE = 1000 (includes FQPA Factor)
Chronic-Term (greater than several months) Occupational/Residential	Dermal	NOEL: 3 mg/kg/day (decreased body weight gains brain lesions (vacuolation) and/or scabbing of the skin in a 1 year neurotoxicity study in rats and a chronic/carcinogenicity study in mice) Acceptable MOE = 1000 (includes FQPA Factor)
[All time periods]	[Inhalation]	No concern
Cancer	Dietary/Dermal/ Inhalation	Classified as “cannot be determined, suggestive”. A cancer endpoint was not identified for use in risk assessment. Use the RfD.
Chronic (non-cancer)	Dietary	NOEL: 3 mg/kg/day (decreased body weight gains brain lesions (vacuolation) in a 1 year neurotoxicity study in rat, supported by CNS lesions and scabbing of the skin in a chronic/carcinogenicity study in mice)

3. Dietary Exposure and Risk Assessment/Characterization

a. Dietary Exposure (Food Sources)

i. Directions for Use

Chlorfenapyr is formulated as Alert 2SC Insecticide-Miticide (EPA Est. No. 5905-GA-01) which contains 21.44% chlorfenapyr and 78.56% inert ingredients. Alert is applied when pest pressure appears during spring, summer and fall. The maximum application rate is 0.35 lbs. ai/A. The seasonal maximal use rate is 1.05 lbs. ai/A with a minimum retreatment interval of 80 days.

The application volume is 50-1000 gal/A. Spray oils may be used with a minimum of 0.5% v/v oil. The PHI is 7 days.

The label contains a restriction against the grazing and the feeding of cover crops to livestock.

ii. Nature of the Residue - Plants

The nature of the residue in citrus is adequately understood based on data submitted by American Cyanamid (MRID 436221-01) depicting the metabolism of [pyrrole-^{14}C]-labeled and uniformly ring labeled [phenyl-UL-^{14}C] chlorfenapyr in oranges. Metabolism of chlorfenapyr proceeds via: 1) N-dealkylation of the parent compound to CL 303,268; and 2) oxidation of CL 303,268 to CL 322,250.

In the citrus metabolism study, the test substance was formulated as a suspension concentrate and applied to navel orange trees at a rate of 0.66 lbs. ai/A (2X) in the field. A total of three applications were made, with the second and third applications performed 98 and 154 days after the first. Oranges were harvested 7 days prior the final application (-7 days PHI) and 7, 14, and 28 days after the final application.

Total radioactive residues (TRR) were determined in tissues by combustion. Samples were then extracted and hydrolyzed for identification of residues.

Chlorfenapyr *per se* was the major radioactive component in oranges (71-77% of the TRR in the 7 day PHI samples). Other minor metabolites included CL 303,268, accounting for a maximum of 3% of the TRR; CL 322,250, accounting for a maximum of 1% of the TRR; and CL 325,195, accounting for a maximum of 2% of the TRR. A total of 74-78% of the TRR was identified in the 7 day PHI. Unidentified peaks, none of which exceeded 0.01 ppm, accounted for up to 20.2% of the TRR.

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.

iii. Nature of the Residue - Livestock

No new studies were submitted with this petition.

The nature of the residue in ruminants is adequately understood based on data submitted by American Cyanamid (MRID#s 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 the TRR in milk and tissues from both groups was 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 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 CL 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. 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.

iv. Residue Analytical Methods

Plants:

Adequate analytical methods for chlorfenapyr in citrus are available to support the proposed permanent tolerances (MRID 43622102).

A satisfactory method trial has been conducted by EPA's Analytical Chemistry Laboratory (ACL) for Method M 2284 for chlorfenapyr in/on citrus with minor revisions required. Orange samples are extracted by homogenization in a methanol/water mixture. Solids are removed by filtration. After clean-up by C-18 solid phase extraction, quantitation is done using gas chromatography with electron capture detector and fused silica capillary column. **A new version of the analytical method with the recommended revisions has not been submitted**. The method limit of quantitation is 0.05 ppm. A GC/MS confirmatory method has also been submitted.

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). A satisfactory method trial has been conducted by EPA's Analytical Chemistry Laboratory for the subject animal commodity chlorfenapyr methods (i.e. M 2405 for cattle liver, M 2398 for cattle muscle and M2395.01 for cows milk).

M 2395.01 - 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 2398.01 - 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. Multiresidue Methods

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 acceptable recovery.

vi. Storage Stability Data

Storage stability data (MRID 43835902) were submitted. Samples of oranges with field-incurred residues were stored frozen at < -10°C. Samples were maintained frozen and two subsamples were removed and analyzed for residues of chlorfenapyr using the proposed enforcement method after 12, 18, and 24 months. Each analysis included one freshly fortified control. The average recovery in the stored sample, after correction for the recovery in the freshly-fortified control was 96-99%. The results demonstrate that residues of chlorfenapyr are stable during storage in fresh oranges for up to 24 months. Residues of chlorfenapyr are also considered to be stable during frozen storage in cottonseed for up to 23 months and in cotton processed fractions for up to 4 months (Memo, G. Otakie 5/9/96). The data for processed cotton storage stability were translated to processed citrus commodities.

The RAC samples from the field residue and processing studies were stored for a maximum of 13 months; and the processed fraction, 3 months. Processed citrus samples were stored frozen less than that of the cotton processed samples. Storage stability is thus not an issue for this petition.

vii. Crop Field Trials

American Cyanamid submitted citrus residue data (MRID # 43622101 and 43835903).

<u>Oranges</u>:

A total of six orange residue trials were conducted in 1992 and 1993. These trials were located in Regions 3 (3 trials), 6 (1 trial), and 10 (2 trials). Two trials were conducted in 1992. Chlorfenapyr (3SC formulation) was applied post-bloom, 90 days prior to harvest and 7 days prior to harvest at a rate of 1.8 lbs. ai/A per application (1.7X). The spray volume was 500 gal/A. Oil was added to the finished spray at a rate of 0.5%. Samples were harvested 0, 7. 14, and 21 days PHI. Four trials were conducted in 1993. Chlorfenapyr (2SC formulation) was

applied post-bloom, 90 days prior to harvest and 7 days prior to harvest a rate of 0.9 lbs. ai/A (0.9X) or 1.8 lbs. ai/A per application (1.7X). The spray volume was 89-100 gal/A. Samples were harvested 0, 7, 14, 21, and 28 days PHI. The varieties used in these trials were all either Navel or Hamlin (a common sweet variety). Sample analysis for chlorfenapyr was performed using the proposed enforcement method. The method was validated over a range of 0.05-1.0 ppm. The average concurrent recovery was 87.2 ± 7.7% (n=26). Analysis of the treated samples showed that the maximum chlorfenapyr residue at 7 days PHI was 0.24 ppm at 0.9X and 0.68 at 1.7X.

Lemons:

A single lemon residue trial was conducted in 1993 in CA. Chlorfenapyr (2SC formulation) was applied post-bloom, 90 days prior to harvest and 7 days prior to harvest at a rate of 0.9 lbs. ai/A (0.9X0 or 1.8 lbs. ai/A per application (1.7X). The spray volume was 100 gal/A. Oil was added to the finished spray at a rate of 0.5%. Samples were harvested 0, 7, 14, 21, and 28 days PHI. Sample analysis for chlorfenapyr was performed using the proposed enforcement method. The method was validated over a range of 0.05-0.5 ppm. The average concurrent recovery was 90.0 ± 8.5% (n=2). Analysis of the treated samples showed that the chlorfenapyr residue at 7 days PHI was 0.33 ppm at 0.9X and 0.58 at 1.7X.

A single lemon residue trial was conducted in 1994 in CA. Chlorfenapyr (2SC formulation) was applied starting post-bloom and ending 7 days prior to harvest at a rate of 0.3 lbs. ai/A (0.9X) per application. The spray volume was 99-101 gal/A. Oil was added to the finished spray at a rate of 0.5%. Samples were harvested 7 days PHI. Sample analysis of chlorfenapyr was performed using the proposed enforcement method. The method was validated over a range of 0.05-2.0 ppm. The average concurrent recovery was 96 ± 1% (n=2). Analyses of the treated samples showed that the chlorfenapyr residue at 7 days PHI was 0.30 ppm.

Grapefruit:

A total of four grapefruit residue trials were conducted in 1993 and 1994. These trials were located in Regions 3 (2 trials) and 10 (2 trials). One trial was conducted in 1993. Chlorfenapyr (2SC formulation) was applied starting post-bloom and ending 7 days prior to harvest at a rate of 0.3 lbs. ai/A or 0.6 lbs. ai/A per application (0.9X or 1.7X). The spray volume was 100 gal/A. Oil was added to the finished spray at a rate of 0.5%. Samples were harvested 0, 7, 14, 21, and 28 days PHI. Three trials were conducted in 1994. Chlorfenapyr (2SC formulation) was applied starting post-bloom and ending 7 days prior to harvest at a rate of 0.3 lbs. ai/A (0.9X). The spray volume was 65-100 gal/A. Samples were harvested 7 days PHI. The varieties used in these trials included Ruby Red and

Marsh White. Sample analysis for chlorfenapyr was performed using the proposed enforcement method. The method was validated over a range of 0.05-1.0 ppm. The average concurrent recovery was 93 ± 8% (n=12). Analyses of the treated samples showed that the maximum chlorfenapyr residues at 7 days or longer PHI were 0.27 ppm at 0.9X and 0.64 at 1.7X.

The petitioner has provided the results of six orange trials located in Regions 3 (3 trials), 6 (1 trial) and 10 (2 trials); four grapefruit trials located in Regions 3 (2 trials) and 10 (2 trials); and two lemon trials, located in Region 10. The maximum chlorfenapyr residues observed at ≈1X were 0.24 ppm in oranges, 0.27 ppm in grapefruit and 0.33 ppm in lemons. The number and distribution do not correspond to that required for a citrus crop group tolerance: 12 orange trials located in Regions 3 (8 trials), 6 (1 trial) and 10 (3 trials); six grapefruit trials located in Regions 3 (3 trials), 6 (1 trial) and 10 (2 trials); and five lemon trials, located in Regions 3 (1 trial) and 10 (4 trials) (*EPA Residue Chemistry Test Guidelines, OPPTS 860.1500 Crop Field Trials, August 1996*). As these trials were initiated prior to the issuance of our guidelines and the observed residue values are relatively low and very consistent between crops and sites, HED could recommend in favor of **time-limited** tolerances while the additional data are generated.

For a permanent tolerance, the petitioner should submit an additional six orange trials located in Regions 3 (5 trials) and 10 (1 trial); two grapefruit trials located in Regions 3 (1 trials) and 6 (1 trial); and three lemon trials, located in Regions 3 (1 trial) and 10 (2 trials). Data should be provided for commercially important varieties (i.e, blood, navel and common or sweet oranges). Note that residue data for sour oranges are required only for setting tolerances on oranges *per se* while sweet oranges are a representative commodity for the citrus crop group. The label includes instructions for both concentrated (50-100 gal/A) and dilute sprays (above 100 gal/A). Residue data must be provided for side-by-side trials using both dilute and concentrated sprays **or** the total number of trials must be evenly divided between dilute and concentrated applications as specified in *EPA Residue Chemistry Test Guidelines, OPPTS 860.1500 Crop Field Trials, August 1996.*

viii. Processed Food/Feed

A study on the residues of chlorfenapyr processed products in citrus was submitted (MRID# 43622104).

Oranges were grown in CA in 1994. A single application of Alert was made to trees at a rate of 4.0 lbs. ai/A (11X the per application rate, 4X the seasonal rate). The spray volume was 97 gal/A. A single bulk sample was harvested from the treated plot 7 days after application. An analytical sample was also

harvested and shipped to Cyanamid. The bulk sample was shipped to the National Food Lab (Dublin, CA) at ambient temperature. Five subsamples were removed for analysis. The oranges were processed into juice, wet pulp, dry pulp, molasses and oil. Sample analysis for chlorfenapyr was performed using the proposed enforcement method. The method was validated over a range of 0.01-50 ppm. The average concurrent recovery was 92 ± 13% (n=12). Analyses of the treated samples showed that the chlorfenapyr residues concentrate in oil and dried pulp.

Chlorfenapyr residues concentrated in oil (70X) and dried pulp (2.4X). Until adequate residue data are available, HED is unable to comment on the expected residue levels in processed commodities in regards to a permanent tolerance petition. However, a conclusion can be reached in regards to a potential **time-limited** tolerance petition. Based on the observed concentration factors, the maximum expected residues in citrus oil are 2.6 ppm and in dried citrus pulp, 0.9 ppm. These values were calculated by using the highest average field trial (HAFT) after adjustment for the 0.9X application rate. Tolerances of 3 ppm for citrus oil and 1.0 ppm dried citrus pulp are required for **time-limited** tolerances on citrus.

ix. Meat, Milk, Poultry, Eggs

Meat and Milk:

No new studies were submitted with this petition.

An acceptable ruminant feeding study (MRID 43492859) has been submitted and reviewed in conjunction with PP#5F04456 (Memo, G. Otakie 2/6/96). 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.

Based on the estimated maximum dietary burden of 0.22 ppm, meat and milk tolerances are required for this petition (quantifiable residues are found at the 10X level, 2.2 ppm). Based on extrapolation of the results to the 1X level, the appropriate chlorfenapyr tolerances when considering the citrus use only are:

Milkfat (reflection 0.01 ppm in whole milk)	--	0.15 ppm
Fat*	--	0.05 ppm
Meat*	--	0.01 ppm

*of cattle, goats, horses, hogs and sheep

These tolerances are equal or lower than those required for the proposed use on cotton (PP#5F04456). **The meat and milk tolerances proposed in PP#5F04456 must thus be established prior to our recommending in favor of citrus tolerances.** This conclusion is applicable to both permanent and time-limited tolerances.

Poultry:

As there are not poultry feed items associated with this petition, issues related to the magnitude of the residue in poultry RACs are not germane.

x. Water, Fish, and Irrigated Crops - Not applicable

xi. Food Handling - Not applicable

xii. Confined Accumulation in Rotational Crops

As grove crops are not rotated, the nature and magnitude of the residue in rotational crops are not applicable to this petition.

xiii. Field Accumulation in Rotational Crops

As grove crops are not rotated, the nature and magnitude of the residue in rotational crops are not applicable to this petition.

xiv. Tolerance Reassessment Table - Not Applicable

xv. Anticipated Residues

Citrus: For oranges, all 7-day-PHI residue data were normalized to a 1X application rate and averaged, resulting in an anticipated residue of 0.21 ppm. The maximum normalized value, 0.40 ppm, was used for the acute risk assessment. In the citrus processing study, the concentration factor for orange juice was 0.02X. The anticipated residue for orange juice is thus 0.0047 ppm (0.21 ppm x 0.02). Anticipated residue were not calculated for other citrus commodities as oranges and orange juice are the primary contributors to the dietary exposure.

Meat and Milk: Anticipated residues in meat and milk were calculated using a reasonable animal diet to calculate exposure to livestock (Table 2). Cotton gin byproducts were used in this calculation instead of dried citrus pulp as it is unlikely that both feed items would be included in the same diet and residues are higher in cotton gin byproducts.

Table 2. Anticipated Dietary Burden for Beef and Dairy Cattle.

Feed Item	Tolerance/ %DM	% in Diet[1]		Anticipated Dietary Burden[2]	
		Beef	Dairy	Beef	Dairy
Grains	n/a	30	20	0	0
Forages	n/a	30	30	0	0
Hay	n/a	25	35	0	0
Cottonseed	0.57	10	10	0.06	0.06
Cotton gin byproducts	2.22	5	5	0.11	0.11
Total				**0.17**	**0.17**

[1] Based on a reasonable cattle diet which includes cotton commodities (Memo, C. Swartz 4/3/97)

[2] The anticipated dietary burden is calculated by multiplying the tolerance/%DM by the % of the feed item in the diet.

The dosing levels used in the ruminant feeding study correspond to 4X, 13X and 40X the anticipated dietary. Based on this information, and based on the residues found in meat, meat by-products, fat and milk in the ruminant feeding study (Table 3), the anticipated residues in livestock commodities to be used in the chronic dietary risk assessments are shown below:

meat	0.0013 ppm
liver	0.0014 ppm
meat by-products (except liver)	0.0006 ppm
fat	0.017 ppm
milk	0.0027 ppm
milk fat	0.040 ppm

Note: The milk fat residue is based on the anticipated residue in whole milk (0.0027 ppm) multiplied by a concentration factor of 15X. Anticipated residue values of 0.0036 and 0.0084 ppm, respectively were used for the dietary risk assessment for meat byproducts and liver of cattle, goats, hogs, horses and sheep. A ratio of 6X the calculated parent anticipated residue levels in ruminant meat byproducts and liver was used to account for metabolite residues per the HED Metabolism Committee.

Table 3- Maximum residues in cow tissues following 28 days of administration of chlorfenapyr at dietary burdens of 0.66, 2.19 and 6.81 ppm.

Tissue	Maximum Residues (ppm) at Dietary Burden of:		
	0.66 ppm	2.19 ppm	6.81 ppm
Milk	<0.010	0.035	0.042
Liver	<0.050	<0.050	0.054
Kidney	<0.050	<0.050	<0.050
Muscle	<0.010	0.017	0.022
Fat	0.067	0.429	0.597

For acute dietary risk assessment, anticipated residues (AR) in blended commodities, such as processed commodities (such as orange juice), may be used; however, tolerance level residues should be used for fat, meat by-product, and meat of cattle, goats, hogs, horses and sheep [milk is a blended commodity, and therefore an anticipated residue value may be used].

Table 4 - Summary of Chlorfenapyr Anticipated Residues for Dietary Risk Assessment (Chronic and Acute Endpoints) based on field-trial data

Commodity	Recommended Tolerance (ppm)	Chronic Anticipated Residue for DRES Run (ppm)	Acute Anticipated Residue for DRES Run (ppm)
Oranges	0.5	0.21	0.40
Orange Juice	0.5	0.0047	0.0047
Meat	0.01	0.0013	0.01
Meat by-products (except liver)	0.05	0.0036	0.30
Liver	0.05	0.0084	0.30
Fat	0.10	0.017	0.10
Milk Fat	0.15	0.040	0.040
Milk	0.01	0.0027	0.0027

To provide for the periodic evaluation of the anticipated residues, the Agency will require under Section 408(b)(2)(E) residue data be submitted every five years as long as the proposed tolerances remain in force.

b. Dietary Exposure (Drinking Water Source)

i. Ground 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, K_{oc}, 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 K_{oc} 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.

ii. Surface Water

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 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 (cotton), which represents a scenario with high potential for runoff; and a Texas site (citrus), 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:

- 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 was 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.

c. Dietary Risk Assessment and Characterization

i. Chronic 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.

Anticipated residue values for chlorfenapyr of 0.40 ppm in/on oranges and 0.0027, 0.40, 0.0013, and 0.017, respectively for milk, milk fat, meat, and fat of cattle, goats, hogs, horses, and sheep were used for this dietary risk assessment.

Anticipated residue values of 0.0036 and 0.0084 ppm, respectively were used for the dietary risk assessment for meat byproducts and liver of cattle, goats, hogs, horses and sheep. A ratio of 6X the calculated parent anticipated residue levels in ruminant meat byproducts and liver was used to account for metabolite residues per the HED Metabolism Committee. Tolerances for poultry commodities are not required for the proposed citrus use.

Chronic dietary exposure estimates (DRES) for chlorfenapyr are summarized in Attachment III (run dated 10/28/97). The DRES analysis utilized the anticipated residues calculated from field-trial data for all orange and animal commodities. The proposed and established chlorfenapyr tolerances result in an Anticipated Residue Contribution (ARC) that is equivalent to the following percents of the RfD:

U.S. Population (48 States)	12%
Hispanics	13%
Non-Hispanic Others	13%
Non-Nursing Infants (<1 year old)	26%
Females (13+ years, pregnant)	10%
Females (20+ years, not pregnant, not nursing)	11%
Females (13+ years, nursing)	13%
Children (1-6 years old)	24%
Children (7-12 years old)	16%

The subgroups listed above are: (1) the U.S. population (48 states); (2) infants and children; and, (3) the other subgroups for which the percentage of the RfD occupied is equal to, or greater than, that occupied by the subgroup U.S. population (48 states).

This chronic analysis for chlorfenapyr is an over-estimate of dietary exposure with 100 percent of the commodity assumed to be treated with chlorfenapyr. Therefore, even without all possible refinements, HED does not consider the chronic dietary risk to exceed the level of concern.

ii. Carcinogenic Risk

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. Dietary risk concerns due to long-term consumption of chlorfenapyr residues are adequately addressed by the DRES chronic exposure analysis using the RfD.

iii. Acute Dietary Risk

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, the additional 10-fold FQPA Factor 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 citrus the MOEs (>99 percentile exposure estimate) for all subgroups were greater than 1000. Therefore, no acute dietary concern is indicated. This acute analysis for chlorfenapyr is an over-estimate of dietary exposure with 100 percent of the commodity assumed to be treated with chlorfenapyr and tolerance-level residues. Therefore, even without all possible refinements, HED does not consider the acute dietary risk to exceed the level of concern.

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

* MOE = NOEL/exposure

iv. Drinking Water Risk (Acute and Chronic)

OPP has calculated drinking water levels of concern (DWLOCs) for **acute** exposure to chlorfenapyr in surface and ground water for U.S. population and children. Procedures for Drinking Water Exposure and Risk Assessments, 11/26/97 and Interim Guidance for Conducting Drinking Water Exposure Estimates, 12/2/97). They are 1220 and 350 ppb, respectively. For **chronic** (non-cancer and cancer) exposure to chlorfenapyr in surface and ground water, the drinking water levels of concern are 92 and 22 ppb for U.S. population and children, respectively. To calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from the DRES analysis) was subtracted from the ratio of the acute NOEL (used for acute dietary assessments) to the “acceptable” MOE for aggregate exposure to obtain the acceptable acute exposure to chlorfenapyr in drinking water. To calculate the DWLOC for chronic (non-cancer) exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DRES) was subtracted from the RfD to obtain the acceptable chronic (non-cancer) exposure to chlorfenapyr in drinking water. DWLOCs were then calculated using default body weights and drinking water consumption figures.

Estimated maximum concentration of chlorfenapyr in surface water is 11 ppb. Estimated average concentration of chlorfenapyr in surface water is 9 ppb. *Note: For the purposes of the screening-level assessment, the maximum and average concentrations in ground water are not believed to vary significantly.* The maximum estimated concentrations of chlorfenapyr in surface and ground water are less than OPP’s levels of concern for chlorfenapyr in drinking water as a contribution to acute aggregate exposure. The estimated average concentrations of chlorfenapyr in surface and ground water are less than OPP’s levels of concern for chlorfenapyr in drinking water as a contribution to chronic aggregate exposure. Therefore, taking into account the present uses and uses proposed in this action, OPP concludes with reasonable certainty that residues of chlorfenapyr in drinking water (when considered along with other sources of exposure for which OPP has reliable

data) would not result in unacceptable levels of aggregate human health risk at this time.

OPP bases this determination on a comparison of estimated concentrations of chlorfenapyr in surface waters and ground waters to back-calculated "levels of concern" for chlorfenapyr in drinking water. These levels of concern in drinking water were determined after OPP has considered all other non-occupational human exposures for which it has reliable data, including all current uses, and uses considered in this action. The estimates of chlorfenapyr in surface and ground waters are derived from water quality models that use conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of chlorfenapyr on drinking water as a part of the aggregate risk assessment process.

Calculation:

$$DWLOC_{chronic\ or\ acute}\ (\mu g/L) = \frac{(chronic\ or\ acute)\ water\ exposure\ (mg/kg/day)\ x\ (body\ weight)}{consumption\ (L)\ x\ 10^{-3}\ mg/\mu g}$$

d. Statement of the adequacy of the dietary exposure data base to assess infants' and children's exposure

The dietary (food and water) exposure data base for chlorfenapyr is adequate to assess infants' and children's exposure.

4. Occupational Exposure and Risk

a. Occupational Exposure

i. Summary of Use Patterns and Formulations: Occupational

The information in Table 5, below is taken from the label for Alert, and other sources as cited.

Table 5 - Registration Request for Use of Alert in/on citrus fruits.

Factors	Comments
Crop to be treated	Citrus fruits
Pests	Citrus Thrips, mites (Citrus rust two-spotted spider, False spider, Citrus bud), Citrus leafminer, & Citrus cutworm.
Application methods	Airblast application.

Factors	Comments
Maximum application rate	**Maximum one-time applications:** Alert: 0.35 lbs ai/A **Maximum per season with multiple applications:** Alert: 1.05 lbs ai/A
Maximum number of applications	Three
Percent Absorption	Not applicable for short and intermediate term occupational exposure as toxicology endpoints for those scenarios are derived from a dermal toxicity study.
Average Acreage of Application per Day	20 acres[1]
Manufacturer	American Cyanamid Company

[1] The estimate of maximum acreage used in this assessment of worker exposure is representative of the maximum standard acreage for Airblast on citrus fruit trees.

Acute toxicity endpoints are established for the active ingredient 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 for both short- and intermediate-term exposures is 100 mg/kg/day. The chronic endpoint is derived from a 1-year neurotoxicity study in rats and a combined chronic toxicity/oncogenicity study in mice; the NOEL for chronic exposure is 3 mg/kg/day. Risk assessments are required for short-term, intermediate-term, and chronic exposure, where appropriate. This active ingredient will not be used over several months, hence a chronic exposure assessment is not required.

TYPE OF TOXICITY	TOXICITY CATEGORY	
	Active ingredient	Alert (21.44% ai)
Acute Oral	II	III
Acute Dermal	III	III
Acute Inhalation	III	III
Primary Eye	III	IV
Primary Dermal	IV	IV
Dermal Sensitization	Not a sensitizer	Not a sensitizer

ii. Handler Exposures and Assumptions

HED's exposure assessment is based on the assumptions in Table 6.

Table 6. Assumptions for Worker Exposure Assessments

Factors	Quantities/Units
Applicator body weight	70 kg
Mixer/loader body weight	70 kg
Application rate (Airblast)	0.35 lb ai/A (Alert)
Acres treated per day (Airblast)	20 acres[1]
Mixer/loader unit exposure from the Pesticide Handlers Exposure Database (PHED), (In support of Airblast application; liquid; open mixing; with long pants, long-sleeved shirt, and gloves).	(Alert) 23.0 µg/lb ai handled[2]
Applicator unit exposure from PHED (Airblast application; liquid; open cab; with long-pants, long-sleeved shirt, and gloves).	159.0 µg/lb ai handled[3]
Personal protective equipment (PPE), per label.	**For Alert:** Long-sleeved shirt and long pants; chemical-resistant gloves; shoes plus socks.

[1] Standard assumptions of the acreage treated per day given the application method and ground speed.
[2] Source: Pesticide Handlers Exposure Database V1.1, Surrogate Exposure Guide (May 97): page 19, for mixer/loaders, Airblast, liquid, open mixing, with, long pants, long sleeves, gloves.
[3] Source: Pesticide Handlers Exposure Database V1.1, Surrogate Exposure Guide (May 97): page 25 for applicators, Airblast, liquid, open cab, long pants, long sleeves, gloves.

iii. Post-Application Exposures & Assumptions - Occupational

During the harvesting of citrus fruits (which is considered to be a high exposure activity), there is a potential for significant post-application exposure to the harvesters.

iv. Mixer/Loader/Application Exposure Assessment

Table 7, below, summarizes the HED/RAB1 estimates for total worker exposure for applicators and mixer/loaders in the

proposed use of chlorfenapyr, the active ingredient in the insecticide/miticide, Alert, on citrus. These estimates are based on the assumptions outlined in Table 6.

Table 7. Worker Exposure to Alert Insecticide

Job Function	Average Dermal Daily Dose for chlorfenapyr mg ai/kg bw/day	Dermal Short & Intermediate-Term MOE
Applicators	0.0159	6,300
Mixer/loaders	0.0023	43,000

MOE = NOEL/ADD (where NOEL = 100 mg/kg/day)

The exposure estimates in Table 7 are based on treatment of 20 acres per day by airblast.

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

Applicators - Airblast

$$0.35 \text{ lbs ai applied/acre} \times 20 \text{ # acres treated/day} = 7 \text{ lbs ai/day}$$

$$159.0 \ \mu g/lb \text{ ai handled (PHED, Version 1.1)} \times 7 \text{ lbs ai/day} = 1113 \ \mu g \text{ ai/day}$$

$$\frac{1113 \ \mu g \text{ ai/day}}{70 \text{ kg bw}} = 15.9 \ \mu g \text{ ai/kg bw/day}$$

$$\frac{15.9 \ \mu g \text{ ai/kg bw/day}}{1000 \ \mu g} = 0.0159 \text{ mg ai/kg bw/day}$$

Mixer/Loaders - Airblast

$$0.35 \text{ lbs ai applied/acre} \times 20 \text{ # acres treated/day} = 7 \text{ lbs ai/day}$$

$$23.0 \ \mu g/lb \text{ ai handled (PHED, Version 1.1)} \times 7 \text{ lbs ai/day} = 161.0 \ \mu g \text{ ai/day}$$

$$\frac{161.0 \ \mu g \text{ ai/day}}{70 \text{ kg bw}} = 2.3 \ \mu g \text{ ai/kg bw/day}$$

$$\frac{2.3 \ \mu g \text{ ai/kg bw/day}}{1000 \ \mu g} = 0.0023 \text{ mg ai/kg bw/day}$$

v. Post-Application Exposure Assessment

The petitioner did not provide post-application exposure sampling data.

b. Occupational Risk Assessment/Characterization

i. Risk from Dermal and Inhalation Exposures

The Agency does not generally have an occupational 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. FFDCA section 408 provides that EPA shall apply an additional 10-fold margin of safety for infants and children in the case of threshold effects to account for pre-and post-natal toxicity and the completeness of the data base unless EPA determines that a different margin of safety will be safe for infants and children. The additional 10X is considered appropriate for chlorfenapyr due to lack of understanding of the toxicity with regard to the developing young. Therefore, HED's level of concern for chlorfenapyr are for MOEs that are below 1000.

Chronic exposure is not expected for use of chlorfenapyr on citrus fruit trees, hence a chronic risk is not required at this time. Also, HED 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 is not required at this time.

Table 7 summarizes HED's estimates for MOEs for total worker exposure for Applicators and Mixer/Loaders for the proposed use of chlorfenapyr on citrus fruit trees. These estimates are based on the assumptions outlined in sections II and III, above.

Both short- and intermediate-term occupational exposures are likely for the use of chlorfenapyr based on seasonal applications being recommended when pest pressure appears during spring summer and fall. Because there is a preharvest interval of seven day, it is anticipated that post-application reentry exposure is also likely following chlorfenapyr. Although MOEs are greater than 1000 for applicators wearing personal protective equipment (PPE), citrus harvesting is a high exposure resulting in similar or greater exposure without the use of PPE.

The PPE for handlers, required by the label for Alert is summarized in Table 6. The PPE requirements as represented on the label for Alert are in compliance with the Worker Protection Standard (WPS).

Based on an assumption within this risk assessment that there are no uses resulting in residential exposures, a restriction should be incorporated in the registrant's label: this insecticide/miticide is not for residential use.

ii. Risk From Post-Application Exposures

Because there are endpoints of concern, there is a potential for exposure to harvesters, the petitioner should conduct post-application exposure monitoring so that an effective/efficient

occupational risk assessment/ characterization can be conducted based on actual sampling results. These data should consist of dermal and inhalation exposure monitoring (875 Part B Guidelines 875.2400 and 875.2500 respectively (formerly 133-3 and 133-4)) and dislodgeable foliar residue dissipation 875.2100 (formerly 132-1a).

iii. Restricted Entry Interval

Based on the TOX Category, the appropriate REI is 12 hours. The Alert label is in compliance with the REI of 12 hours.

iv. Incident Reports

There were two incidents noted in REFS concerning chlorfenapyr, but it was used intentionally for suicide in Japan.

c. Statement of the adequacy of the residential exposure data base to assess infants' and children's exposures

The registration for use of chlorfenapyr on citrus fruit trees should not result in residential exposure, because it is only applied to commercial citrus groves.

5. Aggregate Exposure and Risk Assessment/Characterization

a. Acute Aggregate Exposure and Risk

From the acute dietary (food only) risk assessment, a high-end exposure estimate of 0.01 mg/kg/day was calculated for females 13+ years, the general U.S. population, infants (< 1 year) and children (1-6 years). This exposure yields a dietary (food only) MOE of 4500 for these population subgroups. The maximum estimated concentrations of chlorfenapyr in surface and ground water are less than OPP's levels of concern for chlorfenapyr in drinking water as a contribution to acute aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of chlorfenapyr in drinking water do not contribute significantly to the aggregate acute human health risk at the present time considering the present uses and uses proposed in this action.

OPP bases this determination on a comparison of estimated concentrations of chlorfenapyr in surface waters and ground waters to levels of concern for chlorfenapyr in drinking water. The estimates of chlorfenapyr in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts

of chlorfenapyr on drinking water as a part of the aggregate acute risk assessment process.

b. Short- and Intermediate-term Aggregate Exposure and Risk

Chlorfenapyr is currently registered for use only on cotton. Therefore, no residential exposure (short- or intermediate-term) is anticipated and a short- and intermediate-term aggregate risk assessment is not required.

c. Chronic Aggregate Exposure and Risk

For the U.S. population, 12% of the RfD is occupied by dietary (food) exposure. Because chlorfenapyr is currently used only on cotton, no chronic residential exposure is anticipated. The estimated average concentrations of chlorfenapyr in surface and ground water are less than OPP's levels of concern for chlorfenapyr in drinking water as a contribution to chronic aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of chlorfenapyr in drinking water do not contribute significantly to the aggregate chronic human health risk at the present time considering the present uses and uses proposed in this action.

OPP bases this determination on a comparison of estimated concentrations of chlorfenapyr in surface waters and ground waters to levels of concern for chlorfenapyr in drinking water. The estimates of chlorfenapyr in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of chlorfenapyr on drinking water as a part of the aggregate chronic risk assessment process.

6. Other Food Quality Protection Act (FQPA) Considerations

a. Cumulative Risk

Section 408 of FQPA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency considers "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.

b. Endocrine Disruption

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...". The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disrupter effects.

c. Determination of Safety (U.S. Population, Infants, and Children)

The acute dietary (food only) MOE for females 13+ years old (accounts for both maternal and fetal exposure) is 4500. This MOE calculation was based on the neurotoxicity NOEL in rats of 45 mg/kg/day. This risk assessment assumed 100% crop treated for all treated crops consumed, resulting in a significant over-estimate of dietary exposure. Despite the potential for exposure to chlorfenapyr in drinking water, HED does not expect the acute aggregate exposure to exceed HED's level of concern.

The large acute dietary MOE calculated for females 13+ years old provides assurance that there is a reasonable certainty of no harm for both females 13+ years and the pre-natal development of infants.

Using the exposure assumptions described above, HED has concluded that the percentage of the RfD that will be utilized by chronic dietary (food only) exposure to residues of chlorfenapyr ranges from 5 percent for nursing infants less than one year old, up to 26 percent non-nursing infants less than one year old. Despite the potential for exposure to chlorfenapyr in drinking water, HED does not expect the chronic aggregate exposure to exceed 100% of the RfD. Since there are no residential uses of chlorfenapyr, no chronic residential exposure is anticipated. HED concludes that there is a reasonable certainty that no harm will result to infants and children from chronic aggregate exposure to chlorfenapyr residues.

7. Data Requirements

a. Toxicology

The registrant should conduct a developmental neurotoxicity study to determine the cause/relationship of CNS/myelinopathic alterations to neurotoxicity. The requirement for a mechanistic portion is currently being reconsidered based on a recent submission by the registrant.

b. Residue Chemistry

The petitioner should submit six additional orange residue trials located in Regions 3 (5 trials) and 10 (1 trial); two grapefruit trials located in Regions 3 (1 trial) and 6 (1 trial); and three lemon trials, located in Regions 3 (1 trial) and 10 (2 trials).

Chlorfenapyr residues concentrated in oil (70X) and dried pulp (2.4X). Until adequate residue data are available, HED is unable to comment on the expected residue levels in processed commodities in regards to a permanent tolerance petition. Time-limited tolerances for these commodities are required.

Based on an estimated maximum dietary burden of 0.22 ppm, meat and milk tolerances are required for this petition (quantifiable residues are found at the 10X level in the feeding study). The meat and milk tolerances proposed in PP#5F04456 must thus be established prior to HED recommending in favor of the proposed citrus tolerances.

The petitioner should submit a new version of the proposed analytical enforcement method for citrus with the revisions recommended by ACL.

To provide for the periodic evaluation of the anticipated residues, the Agency will require under Section 408(b)(2)(E) residue data be submitted every five years as long as the proposed tolerances remain in force.

c. Occupational/Residential Exposure

The petitioner should conduct post-application exposure monitoring so that an effective/efficient occupational risk assessment/characterization can be conducted based on actual sampling results. These data should consist of dermal and inhalation exposure monitoring (875 Part B Guidelines 875.2400 and 875.2500 respectively (formerly 133-3 and 133-4)) and dislodgeable foliar residue dissipation 875.2100 (formerly 132-1a).

ATTACHMENTS

I. Acute DRES analyses for chlorfenapyr.

II. Chronic DRES analyses for chlorfenapyr.

cc: PP#6F04623, Kramer, Chun, Copley, Cruz, R.F.
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