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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 10-MAR-2003

SUBJECT: **PP# 7F4716. Chlorfenapyr On Fruiting Vegetables Grown In Greenhouses. Health Effects Division (HED) Risk Assessment.** DP Barcode D275052. Chemical No. 129093. Case 287746. Submission S597379.

FROM: George F. Kramer, Ph.D., Chemist
Jessica Kidwell, Environmental Protection Specialist
Jennifer R. Tyler, Chemist
Mark I. Dow, Ph.D., Biologist
Registration Action Branch 1 (RAB1)/HED (7509C)

THROUGH: G. Jeffrey Herndon, Branch Senior Scientist
RAB1/HED (7509C)

TO: Marion Johnson/Ann Sibold, PM team 10
Registration Division (RD) (7505C)

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational/residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the registered and proposed uses of the insecticide/miticide chlorfenapyr [4-bromo-2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile] formulated as Chlorfenapyr® SC (EPA File Symbol No. 241-GAI). Chlorfenapyr® is a soluble concentrate (SC) product which contains 21.44% active ingredient (ai) or 2.0 lbs of ai per gallon. Chlorfenapyr is a member of a new class of chemicals known as pyrroles.

A summary of the findings and an assessment of human-health risk resulting from the proposed uses of chlorfenapyr are provided in this document. The risk assessment and the residue chemistry data review were provided by George Kramer (RAB1), the occupational/residential exposure assessment by Mark Dow (RAB1), the dietary exposure assessment by Jennifer Tyler (RAB1), and the hazard characterization by Jessica Kidwell (RAB1).

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Recommendations for Tolerances/Registration

Provided that revised Sections B & F and a revised analytical enforcement method are submitted, the toxicological, residue chemistry and occupational exposure databases support the establishment of a **conditional registration** and **permanent** tolerances for residues of chlorfenapyr *per se* in/on the following raw agricultural commodities (RACs):

Vegetable, fruiting, group 8 . . . . . 1.0 ppm

Registration should be made conditional upon submission of the following data:

Chemistry:

1) Additional field residue data from a small variety of tomato.

Toxicology:

1) A developmental-neurotoxicity (DNT) study: The DNT should be conducted to determine the cause/relationship of potential CNS/myelinopathic alterations to neurotoxicity in the developing young.

2) An acceptable 28-day dermal-toxicity study in the rat (not rabbit): The 28-day dermal-toxicity study in the rabbit was re-classified by the 01/21/03 HIARC as Unacceptable/Guideline due to incomplete histopathological evaluation. Histopathology was not performed on the minimum number of tissues as set forth in the guidance (870.3200), including brain tissue. Although the study was previously considered Acceptable, based on a re-evaluation of the database, the HIARC determined that the very limited histopathological examination is considered a significant deficiency. The HIARC has requested a new 28-day dermal-toxicity study in the rat, not the rabbit, which should include a full histopathological examination, including the brain and spinal cord.

3) A 90-day inhalation-toxicity study in the rat: A subchronic inhalation-toxicity study was requested to characterize the direct effects of chlorfenapyr on the pulmonary system and any systemic effects via the inhalation route. This study should also include brain histopathology.

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1.0 EXECUTIVE SUMMARY

Chlorfenapyr is the first commercial pesticide to be derived from a class of microbially-produced compounds known as halogenated pyrroles. Synthesized in 1988 from a naturally-produced chlorinated pyrrole, chlorfenapyr is being used in at least 32 countries, including the United States. Chlorfenapyr is a "pro-insecticide;" i.e., it requires activation through metabolism. The parent compound is converted to the N-dealkylated metabolite, which functions as an uncoupler of oxidative phosphorylation at the mitochondria (http://www.pwrc.usgs.gov/resshow/Albers/albers1.htm). There are currently no tolerances established for residues of chlorfenapyr. However, there are pending uses on cattle (ear-tag application) and imported citrus fruits.

Hazard Assessment

Chlorfenapyr has moderate acute toxicity via the oral route (Toxicity Category II) and low acute toxicity (Toxicity Category III) via the dermal and inhalation routes of exposure. It is a mild eye irritant, but it is not a dermal irritant or sensitizer. The nervous system is the primary target of chlorfenapyr in rats and mice. Subchronic and chronic dietary administration of chlorfenapyr to rats (males only) and mice (both sexes) induced neurohistological changes (vacuolar myelinopathy) in the white matter of the brain, spinal cord, and/or spinal nerve roots. The 80-week carcinogenicity study in mice exhibited a dose- and compound-related effect on the central nervous system (CNS) (brain vacuolation), as well as vacuolation of the spinal cord and optic nerve at the high dose. In the subchronic mouse study, spongiform encephalopathy was noted in the white matter of the brain and myelin of the spinal cord in both sexes at the high dose. The chronic neurotoxicity study in rats revealed dose-related myelinopathic alterations in the CNS (brain, spinal cord, and spinal nerve roots) in male rats only. In the subchronic rat feeding study, spongiform myelinopathy (moderate) was noted in the brain and spinal cord of male rats. In an acute neurotoxicity study, the rats in the high-dose group exhibited some neurobehavioral changes at functional observation battery (FOB) testing on the day of dosing. Subchronic and chronic toxicity studies in the dog showed generalized effects on body weight/body weight gain. Emaciation and decreased food efficiency were also seen in the subchronic dog study. Body weight decrements were also noted in the rat and/or mouse subchronic, chronic, and carcinogenicity studies, as well as in the developmental and reproduction studies. Changes in hematology parameters consistent with anemia were also noted in the subchronic and chronic toxicity/carcinogenicity rat studies.

In accordance with the EPA *Proposed Guidelines for Carcinogenic Risk Assessment* (April 10, 1996), chlorfenapyr was characterized as "cannot be determined, suggestive," based on the increases in tumors in the rat only, which were not considered to be persuasive, but could not be dismissed. The classification was based on significant trends in liver tumors (adenomas and combined adenomas/carcinomas, due mainly to adenomas), malignant histiocytic sarcomas, and testicular cell tumors in male rats and uterine polyps in female rats seen at the highest dose. No tumors were seen in male or female mice. A Q_1* was not established. **The 2003 HIARC clarified, but did not change, the ambiguous 1996 cancer classification of "cannot be determined, suggestive." The HIARC indicated that, according to EPA's July 1999 *Draft Guidelines for Carcinogen Risk Assessment*, the current classification category of**

"Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" was a better description of the intent of the 1996 Cancer Peer Review Committee. 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.

There is no evidence (qualitative or quantitative) for increased susceptibility following *in utero* exposure in the developmental toxicity studies in rats and rabbits or pre-/post-natal exposure in the two-generation reproduction study in rats. In both the rat and rabbit developmental toxicity studies maternal toxicity included decreased body weight gain. No developmental toxicity was noted in rats up to the highest dose tested (HDT, 225 mg/kg/day). Developmental toxicity in rabbits (increased post implantation loss) occurred at a higher dose than maternal toxicity. In the 2-generation reproduction study in rats, parental and offspring toxicity included body weight decrements at similar doses. No reproductive effects were noted up to the HDT.

Dose-Response Assessment

On January 21, 2003, the HED HIARC reviewed the recommendations of the toxicology reviewer for chlorfenapyr with regard to the acute and chronic reference doses (aRfDs and cRfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to chlorfenapyr was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the February 2002 OPP 10X Guidance Document. The **special FQPA SF** was reduced to **1X** based on toxicological considerations by the HIARC (**Memo, J. Kidwell, 04-MAR-2003, TXR No. 0051606Ç),** the conservative residue assumptions used in the dietary exposure risk assessments, and the completeness of the residue chemistry database (evaluated by the risk assessment team). In addition, the HIARC concluded that a DNT study is required for chlorfenapyr and that a **database uncertainty factor (UF_{DB}) of 10X** is required for the acute and chronic dietary exposure scenarios, until the data are received and evaluated.

Risk assessments were conducted for the following specific exposure scenarios listed below. The aRfDs for the general population and females 13-50 years old subgroups were calculated by dividing the no-observed-adverse-effect-levels (NOAELs) by 1000 [10X for interspecies extrapolation, 10X for intraspecies variation; and 10X database uncertainty factor (UF_{DB}) for the lack of a DNT study]. The cRfD was calculated by dividing the NOAEL by 1000 [10X for interspecies extrapolation, 10X for intraspecies variation and 10X database uncertainty factor (UF_{DB}) for the lack of a DNT study]. Since the special FQPA SF has been reduced to 1X, the acute and chronic population adjusted doses (aPAD and cPAD) are equal to the aRfDs and cRfD, respectively. Since oral studies were selected for all durations of dermal and inhalation exposure, a 5% dermal-absorption factor and a 100% inhalation absorption factor are used in the route-to-route extrapolation. The level of concern for occupational dermal and inhalation exposures are for MOEs <100. For the occupational exposure assessment, dermal and inhalation exposure estimates can be combined because same effects were observed in these routes of exposure.

Exposure Scenario	Dose	Endpoint	Study/Effect
Acute dietary (General Population)	NOAEL = 45 mg/kg/day	aRfD and aPAD = 0.045 mg/kg/day	Acute Neurotoxicity study in rats/ Lethargy in male rats
Acute dietary (Females 13-50 years old)	NOAEL = 15 mg/kg/day	aRfD and aPAD = 0.015 mg/kg/day	Developmental toxicity study in rabbits/ Increased post-implantation loss
Chronic dietary	NOAEL = 2.6 mg/kg/day	cRfD and cPAD = 0.003 mg/kg/day	Chronic Neurotoxicity Study in rats/ Presence of myelinopathic alterations in the CNS in male rats and decreased average body weights, body weight gains, food efficiency, absolute food consumption (females), and water consumption (males) Supporting this endpoint are similar central nervous system lesions and skin lesions observed in the mouse carcinogenicity study (NOAEL = 2.8)
Short- and intermediate-term dermal	Oral NOAEL = 3.9 mg/kg/day	Target MOE = 100 (occupational)	90-Day feeding study in dogs/ Emaciation, decreased body weight gains, and decreased food efficiency
Short- and intermediate-term inhalation	Oral NOAEL = 3.9 mg/kg/day	Target MOE = 100 (occupational)	

Margin of Exposure (MOE) for Occupational/Residential Risk Assessments: A MOE of 100 is required for short-, intermediate-, and long-term occupational risk assessments for both dermal and inhalation routes of exposure.

Occupational Exposure and Risk Assessment

Chlorfenapyr is applied to greenhouse fruiting vegetables by the use of a variety of hand-held types of equipment. Of these various types of equipment, the highest occupational pesticide-handler exposure results from the use of high-pressure hand-wand equipment. Estimates of exposure and risk are presented for a mixer/loader/applicator using high-pressure hand-wand equipment. Chemical-specific data were not available with which to assess occupational pesticide-handler exposure. Therefore, surrogate data from studies in the Pesticide Handler Exposure Database Version 1.1 (PHED, Surrogate Exposure Guide, August 1998) are used to estimate exposure and risk to a mixer/loader/applicator. Since the dermal and inhalation toxicological endpoints are the same, the estimated dermal and inhalation exposures are combined (i.e., summed) to calculate the resulting MOE. MOEs $\geq$ 100 are adequate to protect occupational pesticide handlers. In this case, the resulting MOE is > 100 and, therefore, below HED's level of concern. Since the short- and intermediate-term toxicological endpoints are the same, the resulting estimated risk is the same for short- and intermediate-term exposures.

Post-application exposure and risk are estimated for agricultural workers. Post-application agricultural activities identified by the Agricultural Re-Entry Task Force (ARTF) and HED are

utilized in conjunction with transfer coefficients (TCs) identified by HED to estimate post-application exposure. No compound-specific data were available to estimate worker exposure. Therefore, standard procedures were used which assume 20% of the maximum application rate is available as foliar-dislodgeable residue on the day of treatment. Estimated day-0, screening-level MOEs exceed 100 and are, therefore, not of concern to HED.

Residential Exposure and Risk Assessment

There are no existing or proposed uses of chlorfenapyr which would result in residential exposures.

Dietary Risk Estimates (Food Only)

Separate, unrefined, Tier 1 acute dietary exposure assessments [using tolerance-level residues and assuming 100% crop treated (CT) for all registered and proposed commodities, and default Dietary Exposure Evaluation Model (DEEM™) Version 7.76 processing factors for all commodities except citrus juices] were conducted for females 13-49 years old and the general U.S. population and various population subgroups. These assessments conclude that the acute dietary exposure estimates are below HED's level of concern (<100% aPAD) at the 95th exposure percentile for females 13-49 years old (15% aPAD), and the general U.S. population (6% of the aPAD) and all other population subgroups. The most highly exposed population subgroup (other than females 13-49 years old) is children 1-2 years old, at 12% of the aPAD.

An unrefined, Tier 1 chronic dietary exposure assessment [using tolerance-level residues and assuming 100% CT for all registered and proposed commodities, and default DEEM™ Version 7.76 processing factors for all commodities except citrus juices] was conducted for the general U.S. population and various population subgroups. These assessments conclude that the chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (24% of the cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-2 years old, at 47% of the cPAD.

Drinking Water

There are no existing or proposed uses of chlorfenapyr which would result in contamination of drinking water.

Aggregate Risk Estimates

As there are no existing or proposed uses of chlorfenapyr which would result in contamination of drinking water or residential exposures, no aggregate-exposure risk assessment was not performed.

Recommendations for Tolerances/Registration

Provided that revised Sections B & F and a revised analytical enforcement method are submitted, the toxicological, residue chemistry and occupational exposure databases support the establishment

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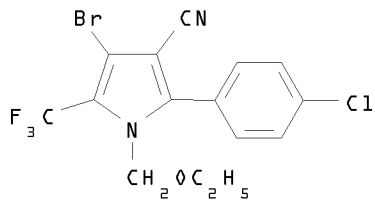
2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1 Identification of Active Ingredients

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

2.2 Structural Formula



2.3 Physical and Chemical Properties

The review of product chemistry data associated with this petition is under the purview of the RD. However, the following data for chlorfenapyr were reported in a previous HED memorandum (memo, Kramer, *et al.*, 2/12/98, D221320):

Vapor Pressure: <1.0 x 10^{-7} mm hg at 25°C

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

Octanol/Water Partition Coefficient: log K_{ow} = 4.83 at 25°C

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Chlorfenapyr is an insecticide/miticide and a member of the class of chemicals known as pyrroles. The toxicology database for chlorfenapyr is basically complete, with the exception of three studies which were requested by the HIARC. These include a DNT study, an acceptable 28-day dermal-toxicity study in the rat, and a 90-day inhalation-toxicity study in the rat. Chlorfenapyr has moderate acute toxicity via the oral route (Toxicity Category II) and low acute toxicity (Toxicity Category III) via the dermal and inhalation routes of exposure. It is a mild eye irritant but it is not a dermal irritant or sensitizer.

The CNS is the primary target of chlorfenapyr in rats and mice. Subchronic and chronic dietary administration of chlorfenapyr to rats (males only) and mice (both sexes) induced neurohistological changes (vacuolar myelinopathy) in the white matter of the brain, spinal cord, and/or spinal nerve roots. The 80-week carcinogenicity study in mice exhibited a dose- and

compound-related effect on the CNS (brain vacuolation), as well as vacuolation of the spinal cord and optic nerve at the high dose. In the subchronic mouse study, spongiform encephalopathy was noted in the white matter of the brain and myelin of the spinal cord in both sexes at the high dose. The chronic neurotoxicity study in rats revealed myelinopathic alterations in the CNS (brain, spinal cord, and spinal nerve roots) in male rats only. Myelin sheath swelling of spinal nerve roots was noted with dose-related incidences in treated males after both 13 and 52 weeks. The vacuolar myelinopathy was not associated with myelin or axon degeneration and was reversible following 16 weeks recovery. In the subchronic rat feeding study, spongiform myelinopathy (moderate) was noted in the brain and spinal cord of male rats. Although these cellular changes did not demonstrate a clear dose-response and did not affect clinical signs such as ataxia or locomotor activity, they are considered treatment-related because the findings are consistent with those seen in the chronic neurotoxicity rat study (males only), and the subchronic and carcinogenicity mouse studies (both sexes). In an acute neurotoxicity study, the rats in the high-dose group exhibited some neurobehavioral changes at FOB testing on the day of dosing. The findings seen in both sexes included changes in gait, locomotion, arousal and lethargy (top two doses) on the day of treatment.

Subchronic and chronic toxicity studies in the dog showed generalized effects on body weight/body weight gain. Emaciation and decreased food efficiency were also seen in the subchronic dog study. Body weight decrements were also noted in the rat and/or mouse subchronic, chronic, and carcinogenicity studies, as well as in the developmental and reproduction studies. Changes in hematology parameters consistent with anemia were also noted in the subchronic and chronic toxicity/carcinogenicity rat studies.

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studies maternal toxicity included decreased body weight gain. No developmental toxicity was noted in rats up to the HDT (225 mg/kg/day). Developmental toxicity in rabbits (increased post implantation loss) occurred at a higher dose than maternal toxicity. In the 2-generation reproduction study in rats, parental and offspring toxicity included body weight decrements at similar doses. No reproductive effects were noted up to the HDT.

In a rat metabolism study, fecal excretion was the major route of elimination (80% of recovered radioactivity), with low recoveries of the radioactive chlorfenapyr in urine and tissues, indicating limited absorption. Most of the radioactivity was eliminated within 48 hours of dosing. Female rats had greater (about twice) recovery of radioactivity in the carcass, blood, and fat at all doses than did males. Parent compound was the major radioactive component found in excreta, accounting for approximately 40-70% of the administered doses. Minor amounts of eight primary and conjugated metabolites and four unidentified isolated components were detected, each at less than 10% of the dosed radioactivity. Liver and kidney contained several primary and conjugated metabolites and only minor levels of the parent compound ($\leq$8.3% of the radioactivity in the sample). Based on the metabolites identified, the major deposition route of orally administered chlorfenapyr is fecal excretion of unaltered parent compound. Other pathways include cleavage of the ethoxymethyl side-chain, followed by de-alkylation and ring hydroxylation, and some degree of conjugation of the de-alkylated, ring-hydroxylated metabolite. The two rings of the molecule are not cleaved. Metabolites are excreted primarily in urine; accumulation in tissues is minimal.

Table 1. Acute Toxicity Data on Technical Grade Chlorfenapyr

Guideline/ Study Type	MRID#	Results	Toxicity Category
870.1100 Oral LD_{50} - rat	42770207 42884201	441 mg/kg, males 1152 mg/kg, females 626 mg/kg, combined	II*
870.1200 Dermal LD_{50} - rabbit	42770208	> 2000 mg/kg	III
870.1300 Inhalation LC_{50} - rat	42770209	0.83 mg/l, males > 2.7 mg/l, females 1.9 mg/l, combined	III
870.2400 Primary Eye Irritation - rabbit	42770210	Corneal opacity, iritis, and conjunctivitis present at 48 hours. At 72 hours, iritis was resolved. All rabbits were normal by Day 7.	III
870.2500 Primary Dermal Irritation - rabbit	42770211	Non-irritating	IV
870.2600 Dermal Sensitization - guinea pig	42770212	Non-sensitizer	Not applicable

*Based on most sensitive sex.

Table 2. Toxicity Profile of Chlorfenapyr

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rats	42770219 (1993) Acceptable/guideline 0, 150, 300, 600, 900, 1200 ppm 0, 11.7, 24.1, 48.4, 72.5, 94.5 mg/kg/day	NOAEL = 24.1mg/kg/day LOAEL = 48.4, based on spongiform myelopathy in the brain and spinal cord of male rats, decreased body weight gain and increased relative liver weight in males and females, increased absolute liver weight in females, and decreased hemoglobin in females.
870.3100 90-Day oral toxicity mouse	43492830 (1994) Acceptable/guideline 0, 40, 80, 160, 320 M: 0, 7.1, 14.8, 27.6, 62.6 mg/kg/day F: 0, 9.2, 19.3, 40, 78 mg/kg/day	NOAEL = 27.6/40, M/F LOAEL = 62.6/78, M/F, based on reduced body weights/body weight gains, and spongiform encephalopathy in both sexes.
870.3150 90-Day oral toxicity dog	42770220 (1993) Acceptable/guideline 0, 60, 120, ~247* ppm M: 0, 2.1, 3.9, 6.7 mg/kg/day F: 0, 2.2, 4.5, 6.8 mg/kg/day *high dose animals received 300 ppm during days 1-15, 240 ppm during days 15-25, and 200 ppm during days 25-93	NOAEL = 3.9/4.5 mg/kg/day, M/F LOAEL = 6.7/6.8 mg/kg/day, M/F, based on emaciation, decreased body weight gains, and decreased food efficiency.
870.3200 21/28-Day dermal toxicity rabbit	43492831 (1993) Unacceptable/guideline due to incomplete histopathological examination 0, 100, 400, 1000 mg/kg/day	NOAEL = 100 mg/kg/day LOAEL = 400 mg/kg/day, for both sexes, based on changes in liver chemistry and morphology.
870.3700a Prenatal developmental rat	42884202 (1993) Acceptable/guideline 0, 25, 75, 225 mg/kg/day	Maternal NOAEL = 25 mg/kg/day Maternal LOAEL = 75 mg/kg/day, based on decreased body weight gain and relative food consumption during treatment. Developmental NOAEL ≥225 mg/kg/day Developmental LOAEL = not identified

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700b Prenatal developmental rabbit	42770222 (1993) Acceptable/guideline 0, 5, 15, 30 mg/kg/day	Maternal NOAEL = 5 mg/kg/day Maternal LOAEL = 15 mg/kg/day, based on decreased body weight gain during treatment. Developmental NOAEL = 15 mg/kg/day Developmental LOAEL = 30 mg/kg/day, based on increased post implantation loss.
870.3800 2-Generation Reproduction and fertility effects rat	43492836 (1994) Acceptable/guideline 0, 60, 300, 600 ppm Premating doses for P_1 males/females: 0/0, 4.5/5.0, 22.2/24.5, 44/44.6 mg/kg/day Premating doses for F_1 males/females: 0/0, 4.4/5.1, 22.5/25.6, 44.6/50.7 mg/kg/day	Parental systemic NOAEL = 4.4-4.5 mg/kg/day, M Parental systemic LOAEL = 22.2-22.5 mg/kg/day, M, based on decreased absolute body weight/body weight gains of P1 males during premating. Offspring systemic NOAEL = 4.4-5.1 mg/kg/day Offspring systemic LOAEL =22.2-25.6 mg/kg/day, based on decreased pup weights at weaning. Reproductive NOAEL ≥44-50.7 mg/kg/day Reproductive LOAEL: not identified
870.4100b Chronic toxicity dog	43492834 (1994) Acceptable/guideline 0, 60, 120, 240 ppm M: 0, 2.1, 4.0, 8.7 mg/kg/day F: 0, 2.3, 4.5, 10.1 mg/kg/day	NOAEL = 4.0/4.5 mg/kg/day, M/F LOAEL = 8.7/10.1 mg/kg/day, M/F, based on decreased body weight/body weight gains.
870.4200b Carcinogenicity mouse	43492838 (1994) Acceptable/guideline 0, 20, 120, 240 ppm M: 0, 2.8, 16.6, 34.5 mg/kg/day F: 0, 3.7, 21.9, 44.5 mg/kg/day	NOAEL = 2.8/3.7 mg/kg/day, M/F LOAEL = 16.6/21.9 mg/kg/day, M/F, based on decreased body weight gains, brain vacuolation, and scabbing of the skin (males). No evidence of carcinogenicity.
870.4300 Combined Chronic/ carcinogenicity in rat	43492837 (1994) Acceptable/guideline 0, 60, 300, 600 ppm M: 0, 2.9, 15.0, 30.8 mg/kg/day F: 0, 3.6, 18.6, 37 mg/kg/day	NOAEL = 15 mg/kg/day, males LOAEL = 30.8 mg/kg/day, males, based on anemia NOAEL = 3.6 mg/kg/day, females LOAEL = 18.6 mg/kg/day, females, based on decreased body weight/body weight gain. Classification: "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" based on significant trends in liver tumors (adenomas and combined adenomas/carcinomas), malignant histiocytic sarcomas, and testicular cell tumors in male rats and uterine polyps in female rats seen at the highest dose.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5100 Bacterial reverse mutation	42770223 (1993) Acceptable/Guideline	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).
870.5300 *In vitro* mammalian cell gene mutation in Chinese hamster ovary cells (CHO/HGPRT)	42770224, 43187601 (1993) Acceptable/Guideline	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.
870.5375 *In vitro* mammalian chromosome aberration (CHO)	43492843 (1994) Acceptable	The test was negative up to 100 µg/ml -S9 or 25 µg/ml +S9; higher doses with or without S9 activation were cytotoxic.
870.5385 In vitro chromosome aberration assay in Chinese hamster lung (CHL) cells	43492839 (1994) Acceptable/Guideline	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.
870.5395 Mammalian micronucleus (mouse)	42770225, 43187602 (1993, 1994) Acceptable/Guideline	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 HDT. There was, however, no evidence of cytotoxicity for the target organ.
870.5550 Unscheduled DNA synthesis	42770226 (1993) Acceptable/Guideline	Negative for inducing unscheduled DNA synthesis in primary rat hepatocyte cultures exposed up to severely toxic concentrations (≥ 30 µg/ml).
870.6200a Acute neurotoxicity screening battery rat	43492829 (1994) Acceptable/guideline 0, 45, 90, 180 mg/kg	NOAEL = 45 mg/kg/day LOAEL = 90 mg/kg/day, based on lethargy in male rats on the day of treatment.
870.6200a Chronic neurotoxicity rat	43492833 (1994) Acceptable/Guideline 0, 60, 300, 600 ppm M: 0, 2.6, 13.6, 28.2 mg/kg/day F: 0, 3.4, 18, 37.4 mg/kg/day	NOAEL = 2.6/3.4 mg/kg/day, M/F LOAEL = 13.6/18 mg/kg/day, M/F, based on the presence of myelinopathic alterations in the CNS in male rats and decreased average body weights/body weight gains, food efficiency, absolute food consumption (females) and water consumption (males).

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics rat	43492844 (1994) Acceptable/guideline 20, 200 mg/kg/day	Low recoveries of the radioactive dose in urine and tissues indicate limited absorption of CL 303,630 by rats. The radioactivity in urine, as a percent of administered dose, 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 and parent compound accounted for 72-91% of the radioactive doses. Parent compound was the major radioactive component 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.

3.2 FQPA Considerations

On January 21, 2003, the HED HIARC evaluated the potential for increased susceptibility of infants and children from exposure to chlorfenapyr according to the February 2002 OPP 10X guidance document. The HIARC concluded that the toxicology database was complete for FQPA purposes and that there are no residual uncertainties for pre-/post-natal toxicity (Memo, J. Kidwell, 04-MAR-2003, TXR No. 0051606Ç). Based on the hazard data, the HIARC recommended the special FQPA SF be reduced to 1X. The chlorfenapyr risk assessment team evaluated the quality of the exposure data and, based on these data, recommended that the special FQPA SF be reduced to 1X. The recommendation is based on the following:

- There is no evidence (qualitative or quantitative) of increased susceptibility of rat or rabbit fetuses to *in utero* exposure in developmental toxicity studies. There is no evidence

(qualitative or quantitative) of increased susceptibility of rat offspring in the multi-generation reproduction toxicity study.

- There are no concerns or residual uncertainties for pre- and post-natal toxicity in the available developmental and 2-generation reproduction toxicity studies.
- The toxicological database is complete for FQPA evaluation.
- The conservative residue assumptions used in the dietary exposure risk assessments, and the completeness of the residue chemistry database.

In addition, the HIARC concluded that a DNT study is required for chlorfenapyr based on the presence of neuropathology (CNS lesions) and neurotoxic signs seen in adult rats (males) and mice (both sexes). In accordance with *the 2002, OPP Guidance Document on Determination of the Appropriate FQPA SF(s) in Tolerance Assessment*, the HIARC concluded that aUF_{DB} of 10X is required until the data are received and evaluated. The HIARC does not have sufficient reliable data justifying the selection of a factor lower than the default 10X value for this data gap.

A summary of the FQPA SFs chosen for chlorfenapyr are listed in Table 3.

Table 3. Summary of FQPA SFs for Chlorfenapyr

	LOAEL to NOAEL (UF_L)	Subchronic to Chronic (UF_S)	Incomplete Database (UF_{DB})	Special FQPA SF (Hazard and Exposure)
Magnitude of Factor	1X	1X	10X	1X
Rationale for the Factor	Not required	Not required	Lack of DNT study	Not required
Endpoints to which the Factor is Applied	Not Applicable	Not Applicable	Acute and Chronic dietary; Residential exposures	Not Applicable

3.3 Dose-Response Assessment

Acute Dietary Endpoint: The developmental toxicity study in the rabbit was used to select the endpoint for establishing the aRfD of 0.015 mg/kg for females 13-50 years old. The LOAEL of 30 mg/kg was based upon increased post-implantation loss. A 1000-fold uncertainty factor (10X for interspecies extrapolation, 10X for intraspecies variation, 10X for lack of a DNT study) was incorporated into the NOAEL of 15 mg/kg/day to derive the aRfD. The special FQPA SF of 1X is applicable for the acute dietary risk assessment. Thus, the aPAD is 0.015 mg/kg.

The acute neurotoxicity study in the rat was used to select the endpoint for establishing the aRfD of 0.045 mg/kg for the general population. The LOAEL of 90 mg/kg was based on lethargy in male rats. A 1000-fold uncertainty factor (10X for interspecies extrapolation, 10X for intraspecies variation, 10X for lack of a DNT study) was incorporated into the NOAEL of 45 mg/kg/day to derive the aRfD. The special FQPA SF of 1X is applicable for the acute dietary risk

assessment. Thus, the aPAD is 0.045 mg/kg.

Chronic Dietary Endpoint: The chronic neurotoxicity study in the rat was used to select the endpoint for establishing the cRfD of 0.003 mg/kg/day. The NOAEL of 2.6 mg/kg/day was based upon the presence of myelinopathic alterations in the CNS in male rats and decreased average body weights, body weight gains, food efficiency, absolute food consumption (females), and water consumption (males). Supporting this endpoint are similar CNS lesions and skin lesions observed in the mouse carcinogenicity study (NOAEL = 2.8 mg/kg/day). A 1000-fold uncertainty factor (10X for interspecies extrapolation, 10X for intraspecies variation, and 10X for lack of a DNT study) was incorporated into the cRfD. The special FQPA SF of 1X is applicable for the chronic dietary risk assessment. Thus, the cPAD is 0.003 mg/kg/day.

Carcinogenicity: In accordance with the EPA *Proposed Guidelines for Carcinogenic Risk Assessment* (April 10, 1996), chlorfenapyr was characterized as "cannot be determined, suggestive," based on the increases in tumors in the rat only, which were not considered to be persuasive, but could not be dismissed. The classification was based on significant trends in liver tumors (adenomas and combined adenomas/carcinomas, due mainly to adenomas), malignant histiocytic sarcomas, and testicular cell tumors in male rats and uterine polyps in female rats seen at the highest dose. No tumors were seen in male or female mice. A Q_1* was not established. **The 2003 HIARC clarified, but did not change, the ambiguous 1996 cancer classification of "cannot be determined, suggestive." The HIARC indicated that, according to EPA's July 1999 *Draft Guidelines for Carcinogen Risk Assessment*, the current classification category of "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" was a better description of the intent of the 1996 Cancer Peer Review Committee.** A cancer risk assessment is not required.

Short-Term Incidental Oral Endpoint: A short-term incidental oral endpoint was selected from the 90-day feeding study in the dog. The NOAEL of 3.9 mg/kg/day was based upon emaciation, decreased body weight gains, and decreased food efficiency seen at the LOAEL of 6.7 mg/kg/day. These effects were noted in the first several weeks of the study. This study and endpoint are appropriate for the population of concern (infants and children) and the route and duration of exposure.

Intermediate-Term Incidental Oral Endpoint: An intermediate-term incidental oral endpoint was selected from the 90-day feeding study in the dog. The NOAEL of 3.9 mg/kg/day was based upon emaciation, decreased body weight gains, and decreased food efficiency seen at the LOAEL of 6.7 mg/kg/day. This study and endpoint are appropriate for the population of concern (infants and children) and for the route and duration of exposure. In addition, this dose is protective of the CNS lesions seen in the chronic neurotoxicity study in rats at 13 weeks at a dose of 13 mg/kg/day and in the subchronic rat and mouse studies at 48.4 mg/kg/day and 62/78 mg/kg/day, respectively.

Dermal Penetration: A dermal-absorption study was not available. Based on its physical form, molecular weight, partition coefficient value, and water solubility, chlorfenapyr is unlikely to be readily absorbed through the human skin. Therefore, the dermal absorption of chlorfenapyr was

estimated to be ~5%.

Short-Term Dermal Endpoint: A short-term dermal endpoint was selected from the 90-day feeding study in the dog. The NOAEL of 3.9 mg/kg/day was based upon emaciation, decreased body weight gains, and decreased food efficiency seen at the LOAEL of 6.7 mg/kg/day. These effects were noted in the first several weeks of the study. This study and endpoint are appropriate for the population of concern (general population, including infants and children) and the duration of exposure. Since the dose identified for the short-term dermal exposure is from an oral study, route-to-route extrapolation should include conversion of the oral equivalents, using a 5% dermal-absorption rate. [Note: The HIARC reclassified the 28-day dermal-toxicity study in the rabbit (MRID 43492831) as Unacceptable/Guideline due to incomplete histopathological examination, and, therefore, did not select the dermal study for risk assessment.]

Intermediate-term Dermal Endpoint: An intermediate-term dermal endpoint was selected from the 90-day feeding study in the dog. The NOAEL of 3.9 mg/kg/day was based upon emaciation, decreased body weight gains, and decreased food efficiency seen at the LOAEL of 6.7 mg/kg/day. This study and endpoint are appropriate for the population of concern (general population, including infants and children) and for the route and duration of exposure. In addition, this dose is protective of the CNS lesions seen in the chronic neurotoxicity study in rats at 13 weeks at a dose of 13 mg/kg/day and in the subchronic rat and mouse studies at 48.4 mg/kg/day and 62/78 mg/kg/day, respectively. Since the dose identified for the intermediate-term dermal exposure is from an oral study, route-to-route extrapolation should include conversion of the oral equivalents, using a 5% dermal-absorption rate. [Note: The HIARC reclassified the 28-day dermal-toxicity study in the rabbit (MRID 43492831) as Unacceptable/Guideline due to incomplete histopathological examination, and, therefore, did not select the dermal study for risk assessment.]

Long-term Dermal Endpoint: A long-term dermal endpoint was selected from the chronic neurotoxicity study in the rat. The NOAEL of 2.6 mg/kg/day was based upon the presence of myelinopathic alterations in the CNS in male rats and decreased average body weights, body weight gains, food efficiency, absolute food consumption (females), and water consumption (males). Supporting this endpoint are similar CNS lesions and skin lesions observed in the mouse carcinogenicity study (NOAEL = 2.8 mg/kg/day). Since the dose identified for the long-term dermal exposure is from an oral study, route-to-route extrapolation should include conversion of the oral equivalents, using a 5% dermal-absorption rate.

Short-term Inhalation Endpoint: A short-term inhalation endpoint was chosen from the 90-day feeding study in the dog. The NOAEL of 3.9 mg/kg/day was based upon emaciation, decreased body weight gains, and decreased food efficiency seen at the LOAEL of 6.7 mg/kg/day. These effects were noted in the first several weeks of the study. This study and endpoint are appropriate for the population of concern (general population, including infants and children) and the duration of exposure. An inhalation absorption factor of 100% should be applied.

Intermediate-term Inhalation Endpoint: An intermediate-term inhalation endpoint was chosen from the 90-day feeding study in the dog. The NOAEL of 3.9 mg/kg/day was based upon emaciation, decreased body weight gains, and decreased food efficiency seen at the LOAEL of

6.7 mg/kg/day. This study and endpoint are appropriate for the population of concern (infants and children) and for the route and duration of exposure. In addition, this dose is protective of the CNS lesions seen in the chronic neurotoxicity study in rats at 13 weeks at a dose of 13 mg/kg/day and in the subchronic rat and mouse studies at 48.4 mg/kg/day and 62/78 mg/kg/day, respectively. An inhalation absorption factor of 100% should be applied.

Long-term Inhalation Endpoint: A long-term inhalation endpoint was selected from the chronic neurotoxicity study in the rat. The NOAEL of 2.6 mg/kg/day was based upon the presence of myelinopathic alterations in male rats and decreased average body weights, body weight gains, food efficiency, absolute food consumption (females), and water consumption (males). Supporting this endpoint are similar CNS lesions and skin lesions observed in the mouse carcinogenicity study (NOAEL = 2.8 mg/kg/day). An inhalation absorption factor of 100% should be applied.

MOE for Occupational/Residential Risk Assessments: An MOE of 100 is required for short-, intermediate-, and long-term occupational risk assessments for both dermal and inhalation routes of exposure. An MOE of 1000 is required for residential risk assessments for all routes of exposure for any duration. The target MOE of 1000 for residential risk assessments includes the conventional 100X UFs and an additional 10X database uncertainty factor for the lack of the DNT study. For short-/intermediate-/long-term dermal and inhalation exposures, the following route-to-route extrapolation was followed: the inhalation (using 100% absorption) and dermal (using 5% absorption) exposures were converted to equivalent oral doses, combined, and then compared to their respective oral NOAELs since all of the dermal and inhalation endpoints are based on oral equivalents.

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

Table 4. Summary of toxicological dose and endpoints for chlorfenapyr for use in human risk assessment[1].

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)	NOAEL = 15 mg/kg UF = 1000 **ARfD** = 0.015 mg/kg	FQPA SF = 1X **aPAD** = aRfD / FQPA SF = 0.015 mg/kg	**Developmental Toxicity Study - Rabbit** LOAEL = 30 mg/kg/day based on increased post-implantation loss.
Acute Dietary (General population including infants and children)	NOAEL = 45 mg/kg UF = 1000 **ARfD** = 0.045 mg/kg	FQPA SF = 1X aPAD = aRfD / FQPA SF = 0.045 mg/kg	**Acute Neurotoxicity Study - Rat** LOAEL = 90 mg/kg/day based on lethargy in male rats.
Chronic Dietary (All populations)	NOAEL= 2.6 mg/kg/day UF = 1000 **CRfD** = 0.003 mg/kg/day	FQPA SF = 1X **cPAD** = cRfD / FQPA SF = 0.003 mg/kg/day	**Chronic Neurotoxicity Study - Rat** LOAEL = 13.6/18 mg/kg/day, M/F, based on the presence of myelinopathic alterations in the CNS in male rats and decreased average body weights, body weight gains, food efficiency, absolute food consumption (F), and water consumption (M). **Supporting this endpoint** are similar CNS lesions and skin lesions observed in the mouse carcinogenicity study (NOAEL = 2.8).
Short-Term Oral (1-30 days)	Oral study NOAEL= 3.9 mg/kg/day	**Residential** LOC for MOE =1000 **Occupational** = NA	**90-Day Feeding Study - Dog** LOAEL = 6.7/6.8 mg/kg/day, M/F, based on emaciation, decreased body weight gains, and decreased food efficiency.
Intermediate-Term Oral (1- 6 months)	Oral study NOAEL= 3.9 mg/kg/day	**Residential** LOC for MOE =1000 **Occupational** = NA	**90-Day Feeding Study - Dog** LOAEL = 6.7/6.8 mg/kg/day, M/F, based on emaciation, decreased body weight gains, and decreased food efficiency.
Short-Term Dermal (1 to 30 days)	Oral study NOAEL= 3.9 mg/kg/day (dermal-absorption rate = 5%)	**Residential** LOC for MOE =1000 **Occupational** = 100	**90-Day Feeding Study - Dog** LOAEL = 6.7/6.8 mg/kg/day, M/F, based on emaciation, decreased body weight gains, and decreased food efficiency.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Intermediate-Term Dermal (1 to 6 months)	Oral study NOAEL= 3.9 mg/kg/day (dermal-absorption rate = 5%)	**Residential** LOC for MOE =1000 **Occupational** = 100	**90-Day Feeding Study - Dog** LOAEL = 6.7/6.8 mg/kg/day, M/F, based on emaciation, decreased body weight gains, and decreased food efficiency.
Long-Term Dermal (>6 months)	oral study NOAEL= 2.6 mg/kg/day (dermal-absorption rate = 5%)	**Residential** LOC for MOE =1000 **Occupational** = 100	**Chronic Neurotoxicity Study - Rat** LOAEL = 13.6/18 mg/kg/day, M/F, based on the presence of myelinopathic alterations in the CNS in male rats and decreased average body weights, body weight gains, food efficiency, absolute food consumption (F), and water consumption (M). **Supporting this endpoint** are similar CNS lesions and skin lesions observed in the mouse carcinogenicity study (NOAEL = 2.8).
Short-Term Inhalation (1 to 30 days)	Oral study NOAEL= 3.9 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE =1000 **Occupational** = 100	**90-Day Feeding Study - Dog** LOAEL = 6.7/6.8 mg/kg/day, M/F, based on emaciation, decreased body weight gains, and decreased food efficiency.
Intermediate-Term Inhalation (1 to 6 months)	Oral study NOAEL= 3.9 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE =1000 **Occupational** = 100	**90-Day Feeding Study - Dog** LOAEL = 6.7/6.8 mg/kg/day, M/F, based on emaciation, decreased body weight gains, and decreased food efficiency.
Long-Term Inhalation (>6 months)	inhalation (or oral) study NOAEL=2.6 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE =1000 **Occupational** = 100	**Chronic Neurotoxicity Study - Rat** LOAEL = 13.6/18 mg/kg/day, M/F, based on the presence of myelinopathic alterations in the CNS in male rats and decreased average body weights, body weight gains, food efficiency, absolute food consumption (F), and water consumption (M). **Supporting this endpoint** are similar CNS lesions and skin lesions observed in the mouse carcinogenicity study (NOAEL = 2.8).

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Cancer (oral, dermal, inhalation)	Classified as "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential." A cancer risk assessment is not required.		Dietary/Dermal/Inhalation

[1] UF = uncertainty factor, FQPA SF = FQPA SF, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure =, LOC = level of concern

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

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

4.1 Summary of Proposed Uses

The proposed formulation is Chlorfenapyr SC® (EPA File Symbol No. 241-GAI) which contains 21.44% active ingredient (ai) or 2.0 lbs of ai per gallon. The petitioner provided a specimen label describing the proposed uses of chlorfenapyr on greenhouse-grown fruiting vegetables (including tomato, tomatillo, ground cherry, peppers, eggplant, and pepinos). The formulation is to be applied as a foliar spray at 0.10-0.20 lb ai/A/application in sufficient water for complete coverage. Up to three applications may be made during a crop growing season, with 5-7 day retreatment intervals (RTIs), for a maximum seasonal rate of 0.6 lb ai/A. The proposed preharvest interval (PHI) is 0 days. The label specifies that it is not to be applied through any type of irrigation system or as an ultra low-volume (ULV) spray, or to consecutive crops in a greenhouse structure. It may be tank mixed with other spray products, once compatibility of the mixture is established.

Conclusion

The proposed use directions for the 2 lb/gal SC formulation (EPA File Symbol No. 241-GAI) are **not** adequate to allow HED to assess whether or not the submitted residue data reflect the maximum residues likely to occur in fruiting vegetables grown under greenhouse conditions. Due to deficiencies in the residue trial data (see below), the following interim label restriction is appropriate until additional data are obtained: "Do not use on tomatoes with a diameter of less than one inch." **The petitioner should submit a revised Section B** with this restriction.

4.1.1 Residue Profile

Background

American Cyanamid Company has submitted an amended petition for the establishment of a permanent tolerance for residues of the insecticide/miticide chlorfenapyr in/on:

Fruiting vegetables . . . . . 1.5 ppm

The transmittal letter of the subject petition explains that the proposed uses of chlorfenapyr on fruiting vegetables are now being limited to those grown in greenhouses; previous petitions on tomatoes (PP#5G04574) and fruiting vegetables (PP#6F4716) reflect applications of chlorfenapyr on field-grown crops. There are currently no tolerances established for residues of chlorfenapyr. However, there are pending uses on cattle (ear-tag application) and imported citrus fruits. Per RD's request, these uses were included in the acute and chronic dietary exposure assessments (personal communication between M. Johnson and G. Kramer, 1/23/03). Time-limited tolerances (in conjunction with a Section 18 registration on cotton) were previously established for residues of chlorfenapyr in/on: cottonseed (0.5 ppm); cotton gin byproducts (2.0 ppm); fat* (0.10 ppm); mbyp* (0.3 ppm); meat* (0.01 ppm); milk (0.01 ppm); and milk fat (0.15 ppm) [40 CFR §180.513(b); expired 1/31/01].

* of cattle, goats, hogs, horses, and sheep

Nature of the Residue

The nature of the residue in plants is adequately understood based on acceptable metabolism studies conducted on cotton, citrus, lettuce, potato, and tomato (PP#3G4224, DP Barcode D192275, 5/20/93, G. Otakie; PP#5G4507, DP Barcode D215017, 8/8/95, G. Kramer; PP#5G4523, DP Barcode D215977, 3/21/96, G. Otakie; and PP#5G04574, DP Barcode D218766, 2/1/96, G. Kramer). Metabolism of chlorfenapyr proceeds via: 1) N-dealkylation of the parent compound and 2) oxidation of the dealkylated metabolite. The HED Metabolism Committee (DP Barcode D227383, 6/25/96, G. Otakie) has determined that the terminal residue of concern in plants is chlorfenapyr *per se* which is the regulated residue in 40 CFR §180.513.

There are no livestock feed items associated with fruiting vegetables; therefore, the nature of residues in livestock is not pertinent to this petition.

Residue Analytical Methods

The proposed enforcement method is M 2427, a gas chromatography/electron capture detection (GC/ECD) method with an limit of quantitation (LOQ) of 0.05 ppm. Method M 2427 has been subjected to a successful independent laboratory validation (ILV) as well as an acceptable radiovalidation using samples obtained from lettuce and tomato metabolism studies. A version of this method, M 2284 was sent to EPA's Analytical Chemistry Branch (ACB) in Beltsville, MD for a petition method validation (PMV) on oranges and citrus oil. Although the PMV was successful, minor revisions were required. A new version of the analytical method with the recommended revisions has not been submitted. HED's review of PP#6F4716 (DP Barcode D226458, 11/20/96, R. Cook) concluded that method M 2427 is adequate for data collection and tolerance enforcement purposes pending submission of the rewritten method M 2284. Since M 2427 is similar to M 2284, the petitioner should rewrite Method M 2427 following the ACL comments regarding M 2284. The rewritten method M 2427 should be submitted.

Multiresidue Method (MRM)

The data requirement for Multiresidue Methods is satisfied pending FDA review and acceptance of the MRM results (PP5F4456, 2/1/96, G. Otakie). The petitioner previously submitted MRM recovery data for chlorfenapyr through FDA Protocols A through E. Protocols A and B were not applicable to chlorfenapyr. In Protocol C, chlorfenapyr gave a good response 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.

Crop Field Trials

Greenhouse trials were conducted on tomatoes, bell peppers, and Jalapeno peppers. The 2 lb/gal SC formulation of chlorfenapyr was foliarly applied five times to these crops, with a 5-day retreatment interval, at 0.18-0.21 lb ai/A per application for a total rate of ~1.0 lb ai/A (~1.7x the maximum proposed seasonal rate of 0.6 lb ai/A for greenhouse-grown fruiting vegetables). At the proposed 0-day PHI, residues of chlorfenapyr were 0.23-0.34 ppm in/on treated tomatoes, 0.31-0.39 ppm in/on treated bell peppers, and 0.60-0.65 ppm in/on treated Jalapeno peppers. Supporting data showed that residues generally declined with a corresponding increase in the PHI.

The maximum residues of chlorfenapyr in/on representative commodities of fruiting vegetables that were observed from the current study are substantially lower than the proposed crop group tolerance of 1.5 ppm. The greenhouse trials were conducted at an exaggerated rate of ~1.7x. However, the per application rate was 1x and the retreatment interval was in accordance with label. The exaggerated rate is thus a result of two extra applications. As the residues at harvest would result primarily from the applications closest to harvest, HED concludes that the residue data can be used to support the proposed use. However, the petitioner failed to provide data from a small variety of tomato. The petitioner is, therefore, requested to provide residue data (including residue decline data) from a greenhouse trial on tomatoes using small variety such as cherry or grape reflecting the maximum proposed seasonal rate of 0.6 lb ai/A. In the situation where tomato field trial data do not include the cherry tomato variety, the HED Science Advisory Council for Chemistry (ChemSAC) concluded that the following interim label restriction is appropriate until data are obtained (Minutes of 5/3/00 ChemSAC Meeting):

"Do not use on tomato varieties with a diameter of less than one inch when mature."

The petitioner should submit a revised Section B with this restriction. The available greenhouse data support a tolerance of 1.0 ppm for residues of chlorfenapyr in/on "Vegetable, fruiting, group 8." **The petitioner should submit a revised Section F.**

Processed Food/Feed

American Cyanamid previously submitted an acceptable tomato processing study (MRID

43753604) which was reviewed under PP#5G4574. The study showed that chlorfenapyr residues did not concentrate in juice (reduction factor of 0.3x) and puree (reduction factor of 0.9x) and concentrated marginally in paste (1.8x). However, as greenhouse-grown tomatoes are not utilized for processing (B. Schneider, personal communication), these data are not relevant to the proposed use.

Meat, Milk, Poultry, Eggs (MMPE)

There are no feed commodities associated with the proposed use on fruiting vegetables. Therefore, data depicting magnitude of residues in livestock commodities are not pertinent to this petition.

Confined and Field Accumulation in Rotational Crops

For the purpose of this proposed use (limited to greenhouse-grown crops), rotational crop studies are not required. It is noted that the proposed formulation prohibits the application of chlorfenapyr to consecutive crops in a greenhouse structure.

International Harmonization of Tolerances

There are no established Codex, Canadian, or Mexican maximum residue levels (MRLs) for chlorfenapyr on fruiting vegetables; therefore, harmonization of MRLs and U.S. tolerances is not an issue at this time.

4.1.2 Dietary Exposure Analysis

Chlorfenapyr acute and chronic dietary exposure assessments were conducted using Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.3), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

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

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic (Tier 1 or Tier 2) exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic (Tier 3/4) assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In accordance with HED policy, per capita exposure and risk are reported for all tiers of analysis. However, for Tiers 1 and 2, significant differences in user vs. per capita exposure and risk are identified and noted in the risk assessment.

HED's level of concern is when the exposure is greater than 100% of the PAD. That is, estimated exposures above this level are of concern, while estimated exposures at or below this level are not of concern. The DEEM™ analyses estimate the dietary exposure of the U.S. population and 26 population subgroups. The results reported in Table 5 are for the U.S. Population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, males 20-49, and adults 50+ years old.

4.1.2.1 Acute Dietary Exposure Analysis

Unrefined, Tier 1 acute dietary exposure assessments [using tolerance-level residues and assuming 100% CT for all registered and proposed commodities, and default DEEM™ Version 7.76 processing factors for all commodities except citrus juices] were conducted. The HED HIARC selected separate acute dietary endpoints for females 13-50 years old and the general U.S. population (including infants and children). Therefore, two separate acute dietary exposure assessments were performed for females 13-49 years old and for the general U.S. population and various population subgroups. These assessments conclude that the acute dietary exposure estimates are below HED's level of concern (<100% aPAD) at the 95th exposure percentile for females 13-49 years old (15% aPAD), and the general U.S. population (6% of the aPAD) and all other population subgroups. The most highly exposed population subgroup (other than females 13-49 years old) is children 1-2 years old, at 12% of the aPAD.

4.1.2.2 Chronic Dietary Exposure Analysis

An unrefined, Tier 1 chronic dietary exposure assessment [using tolerance-level residues and assuming 100% CT for all registered and proposed commodities, and default DEEM™ Version 7.76 processing factors for all commodities except citrus juices] was conducted for the general U.S. population and various population subgroups. This assessment concludes that the chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (24% of the cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-2 years old, at 47% of the cPAD.

Table 5. Summary of Dietary Exposure and Risk for Chlorfenapyr.

Population Subgroup	Acute Dietary[1]		Chronic Dietary[2]	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	0.002624	6.0	0.00706	24
All Infants (< 1 year old)	0.001380	3.0	0.000311	10
Children 1-2 years old	0.005354	12	0.001409	47
Children 3-5 years old	0.004636	10	0.001234	41
Children 6-12 years old	0.003204	7.0	0.000861	29
Youth 13-19 years old	0.002114	5.0	0.000585	20
Adults 20-49 years old	0.002410	5.0	0.000630	21
Females 13-49 years old	0.002310	15	0.000592	20
Adults 50+ years old	0.002497	6.0	0.000662	22

1. Acute dietary endpoint of 0.015 mg/kg/day applies to females 13-49 years old only; acute dietary endpoint of 0.045 mg/kg/day applies to the general U.S. population (including infants and children).
2. Chronic dietary endpoint of 0.003 mg/kg/day applies to the general U.S. population and all population subgroups.

4.2 WATER EXPOSURE/RISK PATHWAY

There are no existing or proposed uses of chlorfenapyr which would result in contamination of drinking water.

4.3 RESIDENTIAL EXPOSURE/RISK PATHWAY

There are no registered or proposed uses of chlorfenapyr which result in residential exposures. HED has previously addressed the issues of possible residential exposures to chlorfenapyr when used according to label directions, either as a termiticide or as a crack and crevice treatment (Memo, M. Dow, DP Codes 238777, 255715, 255758, 277150, 16 OCT 01). HED concluded that there is essentially no incidental-oral or dermal exposures. Also, because of the low vapor pressure of chlorfenapyr, inhalation exposure should be negligible.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

As there are no existing or proposed uses of chlorfenapyr which would result in contamination of drinking water or residential exposures, no aggregate-exposure risk assessment was not performed.

6.0 CUMULATIVE RISK

The FQPA (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED did not perform a cumulative risk assessment as part of this tolerance action for chlorfenapyr because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of chlorfenapyr. For purposes of this tolerance action, EPA has assumed that chlorfenapyr does not have a common mechanism of toxicity with other substances.

On this basis, the petitioner 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 shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for chlorfenapyr need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with chlorfenapyr, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on January 16, 2002 (67 FR 2210-2214) and is available from the OPP Website at:

http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf

In the guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the *"Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity"* (64 FR 5795-5796, February 5, 1999).

7.0 OCCUPATIONAL EXPOSURE

The American Cyanamid Company has requested registration of the compound chlorfenapyr for use on fruiting vegetables (tomato, tomatillo, ground cherry, pepper, eggplant, and pepinos) grown in greenhouses. The proposed product is Chlorfenapyr® SC Insecticide-Miticide for Use on fruiting vegetables in greenhouses. The product is a 2.0 pound active ingredient per gallon SC liquid.

The proposed label for EPA Reg. No. 241-GAI indicates that the product is a Restricted Use Product (RUP) "For retail sale to, and use only by Certified Applicators or persons under the direct supervision of a Certified Applicator, and only for those uses covered by the Certified Applicator's certification." See Table 6 for a summary of the proposed new use.

Table 6. Summary of Proposed New Use of Chlorfenapyr on Fruiting Vegetables in Greenhouses

Formulation	2.0 lb a.i./gal SC
Use Site	greenhouse (fruiting vegetables)
Method of Application	high-pressure hand wand assumed
Pest	armyworms, pinworms, hornworms, loopers, two-spotted spider mite, thrips
Application Rate	0.10 - 0.20 lb a.i./A; 6.5 - 13 fl oz/100 gal
Frequency/Timing	5 - 10 day spray interval; maximum 3 applications per crop growing cycle - may not be applied to consecutive crops in a greenhouse structure.
REI	12 hour
PHI	none - may be applied on day of harvest
Manufacturer	American Cyanamid Company

For the proposed use, it is likely that chlorfenapyr will be applied with any one of several spray technologies. HED believes that a high-pressure hand wand is likely to result in the highest exposures to applicators. The proposed product may not be applied as an ultra low-volume

application and may not be applied in any type of irrigation system. The label directs that: "Apply specified dosage using sufficient water to obtain uniform and complete coverage of foliage."

Based upon the proposed labeling, HED expects that only certified professional applicators, or persons under their direct supervision (pesticide handlers), will be exposed via mixing, loading or applying the material. Further, based on label restrictions, HED believes that typically, pesticide handler exposures are likely to be short-term, that is 1-30 days. However, the HED Science Advisory Council for Exposure (ExpoSAC) directs that it may be possible for commercial handlers to be exposed to intermediate-term (1-6 months) exposures. In this case, the toxicological endpoints are the same for short- and intermediate-term exposures; therefore, the risks to short- and intermediate-term exposures are the same.

7.1 HANDLER EXPOSURE

No chemical-specific data were available with which to assess potential human exposures from handling (i.e., mixing, loading and applying) or for exposures due to re-entry to a treated area to perform agricultural activities such as harvesting, pruning, tying, etc. As such, the handler estimates of exposure are based upon the PHED, Surrogate Exposure Guide, August 1998. Assumptions include the use of maximum label rates of application. HED policy dictates that estimates of exposure be presented for "baseline" which consists of a single layer of work clothing (i.e., long pants, long sleeved shirt and shoes plus socks) and **without** the use of protective gloves. HED also presents estimates of exposure for "baseline" clothing **in addition** to protective gloves or any other Personal-Protective Equipment (PPE) or engineering controls that might be necessary or appropriate.

The proposed label indicates that applicators and other handlers must wear long-sleeved shirt, long pants, chemical-resistant gloves such as barrier laminate or butyl rubber or nitrile rubber or polyvinyl chloride or viton neoprene and shoes plus socks. See Table 7 for a summary of exposure and risk to commercial pesticide handlers applying chlorfenapyr to fruiting vegetables in greenhouses.

The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the PHED Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand held operations, all handling activities are assumed to be effected by the same individual. The available monitoring data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, groundboom tractors, or air-blast sprayers, the applicator exposures are assessed and presently separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of PPE for each aspect of the job without requiring the applicator to wear unnecessary PPE that may be required for a mixer/loader (e.g., chemical resistant gloves may only be necessary during the pouring of a liquid formulation).

Table 7. Estimated Exposures and Risks to Pesticide Handlers Applying Chlorfenapyr to Fruiting Vegetables in Greenhouses					
Unit Exposure[1]	**Application Rate[2]**	**Units Treated[3]**	**Avg. Daily Dose[4]**	**NOAEL[5]**	**MOE[6]**
Mixer/Loader/Applicator - Liquid Open Pour-High Pressure Handwand					
Dermal: SLNG not avail SLWG 2.5 LC Inhal. 0.120 LC	13.0 fl oz/100 gal	1000 gal/day	Dermal: NG not avail WG 0.00363 Inhal 0.00348	3.9	550

1. Unit Exposure = mg a.i./lb a.i. handled; taken from the Pesticide Handler's Exposure Database PHED Surrogate Exposure Guide version 1.1; August 1998; Dermal: SLNG = Dermal exposure from single layer of work clothing NO gloves; SLWG = Dermal exposure from single layer clothing WITH gloves; Inhal. = Inhalation exposure (assumes 100% absorption); Dermal exposure is adjusted for dermal absorption. The HIARC identified dermal absorption to be 5 %. LC = Low-Confidence data.
2. Application Rate from proposed Chlorfenapyr SC label Reg. No. 241-GAI; 2.0 lb a.i./gal ÷ 128 fl oz/gal = 0.015625 lb a.i./fl oz; 0.015625 lb a.i./fl oz * 130 fl oz/day = 2.03 lb a.i./day
3. Units Treated are from ExpoSAC Policy No 9 Rev. 5 July, 2000.
4. Average Daily Dose (ADD) (mg a.i./kg bw/day) = Unit Exposure * Application Rate * Units Treated * 0.05 ÷ 70 kg body weight. Dermal absorption = 5 %. (See footnote 2)
5. NOAEL = No Observed Adverse Effect Level (mg a.i./kg bw/day); Short- and Intermediate-term Dermal **and** inhalation NOAEL = 3.9 mg a.i./kg bw/day from a 90-day oral study in the dog.
6. MOE = NOAEL ÷ ADD. ADD = **Dermal** + **Inhalation**

HED's level of concern is for MOEs <100. For commercial pesticide handlers in this case, MOEs are greater than 100 and are, therefore, not of concern to HED.

7.2 POST-APPLICATION WORKER EXPOSURE

A number of post-application agricultural activities may occur for fruiting vegetables which include hand harvest, pruning, staking, thinning, training, tying, scouting and weeding. The highest TC identified by the ExpoSAC is 1000 cm²/hr for several activities related to tomatoes, eggplant and pepper. HED does not have data regarding TCs of pepinos, tomatillos and ground cherries but assumes they are similar to those presented for tomatoes. In this case, HED uses the TC of 1000 cm^2/hr for estimating post-application exposure on day zero after application. This is taken from the ExpoSAC Policy No. 003 (Revised 7 August 2000). The following convention may be used to estimate post-application exposure:

Surrogate Dislodgeable Foliar Residue
DFR = application rate * 20% available as dislodgeable residue * 4.54 x 10^8 µg/lb * 2.47 x 10^{-8} A/cm^2

and the Average Daily Dose
ADD = DFR (µg/cm^2)* TC (cm^2/hr) * hr/day * 0.001 mg/µg * 1/70 kg bw ∴

0.2 lb a.i./A * .20 * 4.54^8 µg/lb * 2.47^{-8} A/cm² = 0.45 µg/cm^2 ∴

0.45 µg/cm^2 * 1000 cm^2/hr * 8 hr/day * 0.001 mg/µg * 5 % dermal absorption * 1/70 kg bw = 0.00256 mg/kg bw/day

Since **MOE** = NOAEL ÷ ADD then 3.9 mg/kg bw/day ÷ 0.00256 mg/kg bw/day = **1500**.

Since HED's level of concern is for MOEs <100 and since the estimated day-0, screening-level MOE is > than 100, the post-application dermal exposure is not of concern to HED.

HED does not expect any post-application agricultural operations will occur until after the restricted-entry interval (REI). At that point in time, sprays are expected to have dried. The vapor pressure of chlorfenapyr is < 1.0 x 10^{-7} mm Hg at 25 C°. HED expects any inhalation exposure that might occur will be negligible; therefore, assessment of post-application inhalation exposure is not necessary.

7.3 REI

Chlorfenapyr is classified in Acute Toxicity Category III for Acute Dermal, Acute Inhalation, and Primary Eye Irritation. It is classified as Category IV for Primary Skin Irritation and it is not a Skin Sensitizer. Therefore, the interim Worker Protection Standard REI of 12 hours is sufficient to be protective of agricultural workers reentering treated sites.

7.4 INCIDENTS

OPP's Incident Data System (22 JAN 03) lists 6 incidents of unknown certainty, all occurring in 1993 and involving domestic animals.

8.0 DEFICIENCIES / DATA NEEDS

8.1 Chemistry

1. Revised Section B.
2. Revised Section F.
3. Additional field residue data from a small variety of tomato.
4. Revision of analytical method for plants.

8.2 Toxicology

1. A DNT study: The DNT should be conducted to determine the cause/relationship of potential CNS/myelinopathic alterations to neurotoxicity in the developing young.
2. An acceptable 28-day dermal-toxicity study in the rat (not rabbit): The 28-day dermal-toxicity study in the rabbit was re-classified by the 01/21/03 HIARC as Unacceptable/Guideline due to incomplete histopathological evaluation. Histopathology was not performed on the minimum number of tissues as set forth in the guidance (870.3200), including brain tissue. Although the study was previously considered

Acceptable, based on a re-evaluation of the database, the HIARC determined that the very limited histopathological examination is considered a significant deficiency. The HIARC has requested a new 28-day dermal-toxicity study in the rat, not the rabbit, which should include a full histopathological examination, including the brain and spinal cord.

3. A 90-day inhalation-toxicity study in the rat: A subchronic inhalation-toxicity study was requested to characterize the direct effects of chlorfenapyr on the pulmonary system and any systemic effects via the inhalation route. This study should also include brain histopathology.

9.0 LIST OF REFERENCES

Chlorfenapyr: Second Report of the Hazard Identification Assessment Review Committee, 04-MAR-2003, TXR No. 0051606

Chlorfenapyr. Acute and Chronic Dietary Exposure Assessments for Requests for Tolerances on Fruiting Vegetables Grown in Greenhouses. 19-FEB-2003. DP Barcode: D279174

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