United States Environmental Protection Agency | Prevention, Pesticides And Toxic Substances (7505C) | EPA-730-F-00-001 January, 2001

Pesticide Fact Sheet

Chlorfenapyr
Reason for Issuance: New Chemical Registration
Date Issued: January, 2001

Description of the Chemical

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

Chemical Class: Pyrroles (new)

Common Name: Chlorfenapyr, AC 303,630

Trade Name: Pylon Miticide-Insecticide

EPA Chemical Code (OPP Chemical Code): 129093

Chemical Abstracts Service (CAS) Number: 122453-73-0

Year of Initial Registration: January, 2001

Pesticide Type: Insecticide, Miticide

Manufacturer: BASF Corporation
P.O. Box 400
Princeton, NJ 08543-0400

Use Patterns and Formulations

Application Sites:	Ornamental Crops in Commercial Greenhouses, non-food use
Types of Formulation:	For manufacturing use; and as a foliar spray to ornamental crops in greenhouses
Target Pest:	For greenhouse ornamentals: mites, caterpillar pests, thrips, and fungus gnats
Use Patterns:	Foliar spray on ornamental crops grown in greenhouses

Science Findings

Summary Statement:

Chlorfenapyr is a member of a new class of chemicals -- the pyrroles. The compound is a pro-insecticide, i.e. the biological activity depends on its activation to another chemical. Oxidative removal of the N-ethoxymethyl group of chlorfenapyr by mixed function oxidases forms the compound CL 303268. CL 303268 uncouples oxidative phosphorylation at the mitochondria, resulting in disruption of production of ATP, cellular death, and ultimately organism mortality.

Chlorfenapyr has not been previously registered in the United States. However, it has been used on cotton (under the trade name Pirate) under Sec. 18 of the Federal Insecticide Fungicide and Rodenticide Act (FIFRA).

The use on ornamental crops grown in greenhouses is a non-food use so there will be no dietary exposure. Since there are no residential uses of chlorfenapyr, no chronic residential exposure is anticipated.

EPA has completed a review of the toxicological data submitted for this chemical. There are no data gaps for this use pattern.

EPA has determined, for occupational exposure to chlorfenapyr, that an MOE below 100 would be of concern to the Agency. For the commercial greenhouse use on ornamentals, the MOEs for occupational exposure ranged from 100 for long-term post-application activities to 2200 for short-intermediate dermal exposure for mixer/loader/applicators. The long-term MOE for mixer/loader/applicators was calculated to be 580. Thus no MOE exceeded levels of concern. Further, the MOE of 100, calculated for a post-application irrigation scenario, is likely to overestimate exposure for the following reasons: the estimates of potential exposure do not take into account resistance management practices specified on the label (such as no more than 2-3 consecutive applications); and these estimates assumed an 8 hour work day, which is likely an overestimate for irrigation activities.

The Agency has previously considered and decided not to register outdoor use on cotton because of persistence and concern about bird reproductive effects. However, unlike outdoor uses, the greenhouse use is not expected to result in outdoor residues, drift or runoff. Thus, the Agency expects no wildlife exposure and or other significant environmental exposure or risk.

Chemical Characteristics

Technical Grade.

Physical:	powdered solid
Color:	light tan or light yellow
Odor:	characteristic of halides and ketones
Melting Point:	melting point 100-101E C
pH:	7.16; 1% aqueous slurry at 24 E C
Density:	0.543 g/ml tapped bulk density
Empirical Formula:	$C_{15}H_{11}BrClF_3N_2O$, mw 407.6
Vapor Pressure:	<1.0 x 10-7 mm hg at 25 E C

Solubility:	Solvent	Solubility at 25EC
	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

Dissociation Constant	since there are no ionizable groups in the chlorfenapyr structure, no dissociation will occur
Octanol/Water Partition Coefficient	Kow = 67,670 (log Kow = 4.83) at 25 E C

Pylon Miticide-Insecticide (21.4% chlorfenapyr)

Physical State	liquid
pH:	7.1
Oxidation/reduction incompatibility	oxidizer
Explodability	not explosive
Corrosion characteristics	non-corrosive
Density/relative density bulk density	1.11 g/cc

Human Health Assessment

1. TOXICOLOGY CHARACTERISTICS

Acute Toxicity:

1. Technical. The technical is categorized as Tox Category II based on the results of an acute oral test with the rat. The signal word is danger. Note that both a rat and a mouse study are available for the acute oral studies with the technical. EPA

has determined that when both are available, the rat studies are routinely used to compare relative toxicity across different labels for a given chemical.

Guideline No.	Study type	Results	Tox Category
81-1	Acute Oral(LD50)	Rat: 441 mg/kg, males 1152 mg/kg, females 626 mg/kg, combined	II
81-1	Acute Oral(LD50)	Mouse: 45 mg/kg, males 78 mg/kg, females 55 mg/kg, combined	I
81-2	Acute Dermal (LD50)	Rabbit: > 2000 mg/kg	III
81-3	Acute Inhalation (LC50)	rat: 0.83 mg/l, males > 2.7 mg/l, females 1.9 mg/l, combined	III
81-4	Primary Eye Irritation	rabbit: Corneal opacity, iritis, and conjunctivitis present at 48 hours. At 72 hours iritis was resolved. All rabbits were normal by Day-7.	III
81-5	Primary Skin Irritation	rabbit: non-irritating	IV
81-6	Dermal Sensitization	guinea pig: non-sensitizer	

2. Formulated Product (Pylon Miticide-Insecticide). The formulated product is Tox Category III based on the oral, dermal, and inhalation study results. The signal word is Caution.

Guideline No.	**Study type**	**Results**	
81-1	Acute Oral Toxicity in Rats	Acceptable. LD_{50} = 560 mg/kg, males, 567 mg/kg, females	III
81-2	Acute Dermal Toxicity in Rabbits	Acceptable. LD_{50} > 2000 mg/kg, males and females	III

Guideline No.	Study type	Results	Tox Category
81-3	Acute Inhalation Toxicity in Rats	Waived. Data requirements satisfied by AC 303,630 3SC Formulation (32% a.i.).	III
81-4	Primary Eye Irritation in Rabbits	Acceptable. Slight-to-moderate redness of conjunctivae, and slight ocular discharge were present at 1 hour. All signs of irritation had resolved by 24 hours. It was considered practically non-irritating.	IV
81-5	Primary Dermal Irritation in Rabbits	Acceptable. Slight erythema was observed at 1 hour and persisted in 1 rabbit at 24 hours. All signs of irritation had resolved by 48 hours.	IV
81-6	Dermal Sensitization in Guinea Pig	Waived. Data requirements satisfied by Chlorfenapyr tech. and AC 303,630 3SC Formulation (32% a.i.).	Not a sensitizer

Subchronic Toxicity

i. Subchronic Oral Toxicity in Rats. Rats were fed chlorfenapyr in feed at doses of 0, 150, 300, 600, 900 or 1200 ppm (0, 11.7, 24.1, 48.4, 72.5 or 97.5 mg/kg/day, respectively) for 90 days. The NOAEL (the no observed adverse effects level) is 300 ppm (24.1 mg/kg/day). The lowest observed adverse effect level (LOAEL) is 600 ppm (48.4 mg/kg/day) based on the following effects: males had a decreased body weight gain and increased relative liver weights, while females exhibited decreased hemoglobin (HGB) and increased absolute/relative liver weights. More severe effects occurred at higher doses.

ii. Subchronic Oral Toxicity in Mice. Mice were administered chlorfenapyr 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. The NOAEL is 7.1 mg/kg/day (40 ppm). The LOAEL 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. More severe effects occurred at higher doses.

iii. Subchronic Oral Toxicity in Dogs. Chlorfenapyr 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 LOAEL is 6.1 mg/kg/day (247 ppm), based on reduced body weight gain and feed efficiency and emaciation. The NOAEL is 4.23 mg/kg/day (120 ppm).

iv. Twenty-eight Day Dermal Toxicity Study in Rabbits. Chlorfenapyr 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. The NOAEL is 100 mg/kg. The LOAEL is 400 mg/kg for both sexes, based on changes in liver chemistry and morphology (structure and form). More severe effects were observed at higher doses.

Chronic Toxicity/Carcinogenicity

i. Chronic Oral Toxicity Dogs. Chlorfenapyr 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. The LOAEL is 8.7 mg/kg/day (240 ppm), based on decreased body weights and body weight gains. The NOAEL is 4.0 mg/kg/day (120 ppm). 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.

ii. Chronic Toxicity/Carcinogenicity Study in Rats. 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. The NOAEL is 2.9 and 3.6 mg/kg/day for males and females, respectively (60 ppm). The LOAEL for systemic toxicity is 15.0 and 18.6 mg/kg/day for males and females, respectively (300 ppm) based on liver toxicity. More severe effects were observed at higher doses.

iii. Chronic Toxicity/Carcinogenicity Study in Mice. Chlorfenapyr 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. The NOAEL is 2.8 and 3.7 mg/kg/day for males and females, respectively (20 ppm). The LOAEL 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). More severe effects occurred at higher doses.

Developmental Toxicity

i. Developmental Toxicity in Rats. Chlorfenapyr was administered to pregnant rats by oral gavage at dose levels of 0, 25, 75 or 225 mg/kg/day from days 6 through 16 of gestation. The NOAEL for maternal systemic toxicity is 25 mg/kg/day. The LOAEL for maternal systemic toxicity is 75 mg/kg/day, based on reduced body weight gain, reduced relative feed intake and reduced water consumption. 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 LOAEL for developmental (pup) toxicity is greater than 225 mg/kg/day and the NOAEL is greater than or equal to 225 mg/kg/day (highest dose tested).

ii. Developmental Toxicity Study in Rabbits. Pregnant rabbits received 0, 5, 15 or 30 mg/kg/day chlorfenapyr by oral gavage from gestation days 7 to 19. The LOAEL for maternal systemic toxicity is 15 mg/kg/day, based upon reduced body weight gain during treatment. The NOAEL for maternal systemic toxicity is 5 mg/kg/day. There was no evidence of developmental toxicity at any dose. The NOAEL for developmental (pup) toxicity is greater than 30 mg/kg/day (highest dose tested).

Reproductive Toxicity

Two generation rat reproduction study. Chlorfenapyr 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, for two successive generations (1 litter/generation). The LOAEL for parental toxicity was 22 mg/kg/day (300 ppm), based on pre-mating effects on parental weight gain. The parental NOAEL was 5 mg/kg/day (60 ppm). The LOAEL for reproductive toxicity was 22 mg/kg/day (300 ppm), based on decreased lactational weight gains. The reproductive NOAEL was 5 mg/kg/day (60 ppm).

Mutagenicity

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. The studies are summarized in the following table.

Study	Results
Gene Mutation-Ames	Negative for reverse mutation in S. typhimurium and E. coli exposed up to cytotoxicity (50 µg/plate, +/- S9)
Chinese hamster ovary (CHO) cell HGPRT gene mutation	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	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	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	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 ($28 µg/mL) were cytotoxic.
Repair in vitro (UDS)	Negative for inducing unscheduled DNA synthesis in primary rat hepatocyte cultures exposed up to severely toxic concentrations ($ 30 µg/mL).

Metabolism

Radioactive 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. Based on the metabolites identified, the major deposition route of orally administered chlorfenapyr is fecal

excretion of unaltered parent compound. The two rings of the molecule are not cleaved. Metabolites are excreted primarily in urine; accumulation in tissues is minimal.

Neurotoxicity

i. Acute Neurotoxicity Study in Rats. Chlorfenapyr was administered once, via gastric intubation 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. In addition, five rats per group were examined for neuropathologic lesions. No dose-related effects on body weights, food consumption, neurobehavioral observations, or gross or histological post mortem examinations were noted. The LOAEL is 90 mg/kg, based on lethargy of the rats on the day of treatment. The NOAEL is 45 mg/kg.

ii. One-Year Dietary Neurotoxicity Study in Rats. Chlorfenapyr 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. The LOAEL 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 NOAEL is 2.6 mg/kg/day (60 ppm).

Dermal Absorption

A dermal absorption study was not available. Therefore, a dermal absorption value of 5% has been calculated using the maternal NOAEL of 5 mg/kg/day from the oral developmental toxicity study in rabbits and the systemic NOAEL of 100 mg/kg/day from the 28-day dermal toxicity study in rabbits.

2. OCCUPATIONAL EXPOSURE AND RISK ASSESSMENT

a. Toxicological Endpoints for Chlorfenapyr

Summary of Toxicological Endpoints for Chlorfenapyr

Exposure Duration	Exposure Route	Endpoint and Toxicological Effect
Short-Term (1-7 days) Occupational	Dermal	NOAEL: 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).
Intermediate-Term (one week to several months) Occupational	Dermal	NOAEL: 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).
Chronic-Term (greater than several months) Occupational	Dermal	NOAEL: 2.6 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). Use a dermal absorption factor of 5% since the NOAEL is from an oral study.
Short-Term Occupational	Inhalation	NOAEL: 4.2 mg/kg/day (reduced body weight gain and feed efficiency and emaciation in a subchronic oral study in dogs). Use the inhalation absorption factor of 100% since the NOAEL is from an oral study.
Intermediate Term Occupational	Inhalation	NOAEL: 4.2 mg/kg/day (reduced body weight gain and feed efficiency and emaciation in a sub-chronic oral study in dogs).Use the inhalation absorption factor of 100% since the NOAEL is from an oral study.

Exposure Duration	Exposure Route	Endpoint and Toxicological Effect
Long-Term Occupational	Inhalation	NOAEL: 2.6 mg/kg/day (decreased body weight gains, brain lesions (vacuolation) and /or scabbing of the skin in a one year neurotoxicity study in rats and a chronic/carcinogenicity study in mice). Use the inhalation absorption factor of 100% since the NOAEL is from an oral study.
Cancer	Dermal/ Inhalation	Classified as "cannot be determined, suggestive." There was increased tumor incidence in rats only at the highest dose tested; however, this evidence was judged to be not persuasive but could not be dismissed. A Q_1* has not been established. Given the weak evidence of carcinogenicity, and the large difference between the chronic LOAEL and the cancer LOAEL, HED determined that a quantitative cancer risk assessment was not necessary for chlorfenapyr.

b. Occupational Exposure and Risk. The margin of exposure (MOE) is a measure of how closely the anticipated exposure comes to the NOAEL and is calculated as a ratio of the NOAEL to the exposure (NOAEL/exposure = MOE). For this use, the Agency is not concerned unless the MOE is below 100.

1. **Mixer/loader/applicator risk.** The following table summarizes the exposure and risk estimates for mixer/loaders and applicators from the proposed greenhouse uses for chlorfenapyr. The mixer/loader/applicator using a high pressure handwand is expected to represent the scenario with the highest potential exposure.

Occupational Risk Estimates		
Exposure Scenario	**Short-/Intermediate-term MOEs**	**Long-term MOE**
Mixer/ Loader/Applicator	2200-dermal	580
	1900-inhalation	

2. **Post Application risk.** The following table presents post application risks.

Post-application Risk Estimates		
Exposure Scenario	**Exposure duration**	**MOE**
Irrigation of ornamental plants AR = 0.64 lb ai/A	Short/Intermediate-term	150
	Long-term	100

As shown in the tables above, for the foliar spray of chlorfenapyr on ornamental crops in commercial greenhouses, all occupational MOEs are above levels of concern.

Environmental Fate and Ecological Effects Characteristics

Greenhouse use has limited opportunity for outdoor residues, drift, runoff, and wildlife exposure. Therefore, use on ornamental crops grown in enclosed commercial greenhouses is not expected to cause any significant environmental exposure or risk.

Data Gaps

There are no data gaps for this use.

Regulatory Conclusion

Under the authority of Section 3(c)(5), the Agency has determined that the database supports granting an unconditional registration for Chlorfenapyr Technical, and for

Pylon Miticide-Insecticide (21.4% chlorfenapyr), for use on ornamentals grown in commercial greenhouses.

Note that this conclusion contrasts with the Agency's previous determination that the use of chlorfenapyr on cotton would pose unreasonable adverse effects due to persistence and potential adverse effects on the reproduction of birds. The Agency finds there is no such concern with the use of this pesticide in an enclosed greenhouse environment.

For More Information

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Electronic copies of the this fact sheet are available on the Internet. See http://www.epa.gov/opprd001/factsheets/. Printed copies of this fact sheet can be obtained from EPA's National Center for Environmental Publications and Information (EPA/NCEPI), PO Box 42419, Cincinnati, OH 45242-2419, telephone 1-800-490-9198; fax 513-489-8695. For more information about EPA's pesticide registration program, please contact the Registration Division (7505C), OPP, US EPA, Washington, DC 20460, telephone 703-305-5446. For information about the health effects of pesticides, or for assistance in recognizing and managing pesticide poisoning symptoms, please contact the National Pesticides Telecommunications Network (NPTN). Call toll-free 1-800-858-7378, from 6:30 a.m. to 4:30 p.m. Pacific Time, or 9:30 a.m. to 7:30 p.m. Easter n Standard Time, seven days a week.

Information about the environmental aspects of the proposed chlorfenapyr use on cotton is available at the following internet address:
http://www.epa.gov/opprd001/chlorfenapyr/toc.htm

Paper copies of these electronic materials are available at the following location: Public Docket, Environmental Protection Agency, Rm. 119, Crystal Mall 2 (CM #2), 1921 Jefferson Davis Hwy. Arlington, VA 22202.