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

MAR 10 1997

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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

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

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

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

I. EXECUTIVE SUMMARY

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

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

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

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

mutagenic activity and a lack of structure-activity data.

Toxicological endpoints of concern have been identified for acute dietary exposure and short term, intermediate term and chronic (other than cancer) occupational or residential exposure. HED recommends the following endpoints be used for risk assessment purposes. The NOEL from the acute neurotoxicity study (MRID 43492829) in rats of 45 mg/kg/day for acute dietary risk assessments. The NOEL from the 28-day dermal toxicity study (MRID 43492831) of 100 mg/kg/day for short- and intermediate term occupational or residential risk assessments. The NOEL of 3 mg/kg/day from the combined chronic toxicity/carcinogenicity study (MRID 43492838) in mice for chronic (non-cancer) occupational or residential risk assessments. Since the toxicology endpoint to be used for chronic (non-cancer) occupational or residential risk assessments was selected from an oral study, for dermal exposure scenarios a dermal absorption factor of 5% should be used. The LC50 from the acute inhalation study (MRID 42770209) is 1.9 mg/L (Toxicity Category III) for chlorfenapyr technical. Therefore, an inhalation risk assessment is not required.

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

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

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

U.S. population would be no greater than 10% of the RfD. **Therefore, the combined exposure of chronic dietary and drinking water to chlorfenapyr would be no greater than 106% of the RfD for children, while the combined exposure for chronic dietary and drinking water for the general U.S. population would be 33% of the RfD.**

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

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

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

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

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

The registrant must also submit, upon EPA's request and according to a schedule determined by the Agency, such

information as the Agency directs to be submitted in order to evaluate issues related to whether chlorfenapyr share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for chlorfenapyr need to be modified or revoked.

II. BACKGROUND

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

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

III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

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

Common Name: Chlorfenapyr

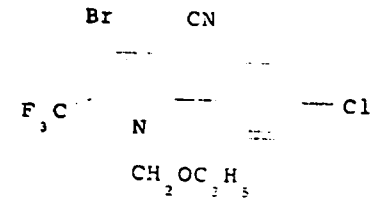
PC Code Number: 129093

CAS Registry No.: 122453-73-0

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

Molecular Weight: 407.6

Structural Formula:



Physical and Chemical Properties for Chlorfenapyr	
Color	light tan or light yellow
Physical State	powdered solid
Odor	characteristic of halides and ketones
Melting Point	melting point apparatus 100-101° C
Boiling Point	n/a; TGAI is a solid
Density, Bulk Density, or Specific Gravity	0.543 g/ml tapped bulk density 0.355 g/ml untapped bulk density
Solubility	Solvent — Solubility at 25°C deionized water — 0.12 mg/ml water, pH 4 — 0.13 mg/l water, pH 7 — 0.14 mg/l water, pH 10 — 0.12 mg/l hexane — 0.89 g/100 ml methanol — 7.09 g/100 ml acetonitrile — 68.4 g/100 ml toluene — 75.4 g/100 ml acetone — 114 g/100 ml dichloromethane — 141 g/100 ml
Vapor Pressure	<1.0 x 10-7 mm hg at 25 ° C
Dissociation Constant	since there are no ionizable groups in the chlorfenapyr structure, no dissociation will occur (PAI)
Octanol/Water Partition Coefficient	Kow = 67,670 (log Kow = 4.83) at 25 ° C
pH	7.16; 1% aqueous slurry at 24 ° C
Stability	stable at 25 ° C for 24 months, 37 ° C for 12 months, and 45 ° C for 3 months.
Oxidizing or Reducing Action	unreactive to oxidizing or reducing agents; no reaction was observed when exposed to tap water, 1% monoammonium phosphate, 0.01M aqueous potassium permanganate and zinc foil.
Flammability	TGAI is a solid
Explodability	not sensitive to an impact of 2 kg/cm at room temperature; one exotherm at 183 ° C with a heat release of -350 kJ/kg in differential thermal analysis; dust did not ignite at any concentration or ignition delay time test; classified as Class 0 dust (impact, differential thermal analysis, and dust explositivity assays)
Storage Stability	stable for one year under outdoor storage conditions (GC and HPLC assays).
Viscosity	TGAI is a solid
Miscibility	TGAI is a solid
Corrosion Characteristics	no corrosion observed after 12 months storage in a polyethylene bag or a VELOSTAT (non-conductive plastic) bag inside a fiberpak