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

MAY 30 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: PP#5F04456 - New Chemical - Chlorfenapyr (i.e. Alert/Pirate®). Insecticide/Miticide on Cotton/Oranges and Lemons/Tomatoes/Lettuce/Cabbage/Potatoes. Issues to be presented to the HED Metabolism Committee on June 20, 1996.

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THRU: Edward Zager, Acting Chief
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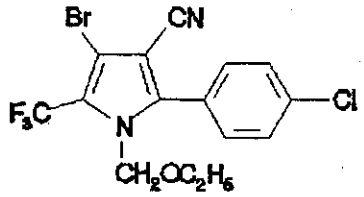
TO: The Metabolism Committee

Background

Chlorfenapyr also known as Alert/Pirate® [4-bromo-2-(chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile] is a new chemical insecticide/miticide with Experimental Use Permits and temporary tolerances for use on cotton, citrus, lettuce, cabbage and tomatoes. Proposed PHI's vary from one day on cabbage to seven days on citrus and 21 days for cotton. Temporary tolerances for the parent in/on cottonseed, oranges and lemons at 0.5 ppm and in/on milkfat, fat, meat and meat by-products of cattle, goats, horses and sheep at 0.25, 0.20, 0.01 and 0.05 ppm, respectively have been tentatively recommended by CBTS. Temporary tolerances for the parent on lettuce, cabbage and tomatoes at 0.5 ppm have also been recommended by CBTS. Although a potato metabolism study was submitted with the tomato petition no tolerance on potatoes has yet been proposed.

ALERT/PIRATE



Proposed Use

The proposed uses include multiple applications with a total seasonal application rate of approximately 1.0 lb ai/A with PHI's of 21, 7, 3, 1, and 0 days for cotton, oranges and lemons, lettuce, cabbage and tomatoes, respectively.

Plant Metabolism

Summary The majority of the TRR is extracted in the organic soluble fraction. The parent (AC 303,630) is the most prominent residue identified accounting for 75.1-76.8% in lettuce, 56-75% in citrus, 59-68% in cottonseed, 38-50% in tomato, and 74.7-86.6% in potato vine (no detectable residues in tubers) of the TRR in each crop. The parent also accounted for most of the identified residue from the confined rotational crop study with the highest residue in immature carrots (i.e. parent at 67% of the TRR). Details of the metabolism studies are discussed below. **Attachment 1** describes the proposed metabolic pathways in citrus and lettuce. Structures for plant and animal metabolites are included in **Attachment 8.**

Nature of the Residue in Cotton:

Metabolism of chlorfenapyr (Pirate/Alert) in cotton was discussed under PP#3G4224 (see 1/26/94 memo of G. Otakie). The parent was the major component identified and accounted for 63.7 and 57.7% of the TRR in cotton linters for 2-pyrrole-^{14}C and phenyl-^{14}C, respectively. American Cyanamid (1993; MRID 42770234) submitted data depicting the metabolism of [2-pyrrole-^{14}C]-labeled and uniformly ring-labeled [phenyl-^{14}C]Pirate in cotton.

The TRR in foliage and cottonseeds following five applications of [^{14}C]Pirate are presented below:

Total radioactive residues in/on cotton foliage, seed meal, and linters following five applications of [2-pyrrole-^{14}C]- or [phenyl-ring-labeled-^{14}C]Pirate at a seasonal rate of ~2 lb ai/A (2x the current proposed rate).

Matrix/Sampling Interval	[^{14}C]Pirate equivalents (ppm)	
	[2-pyrrole-^{14}C]	[phenyl-^{14}C]
Foliage 1st Application	38.49	48.30
3rd Application	93.48	102.86
5th Application	122.13	131.79
Seed Meal	0.15	0.18
Linters	0.12	0.13
Total Cottonseed	0.27	0.31

Expressed on a whole seed basis, the parent compound accounted 59.3-67.7% of the TRR (0.16-0.21 ppm). An unidentified polar metabolite (designated Unknown-1) accounted for 4.7-7.1% of the TRR (0.01 ppm) in meal and 3.4-3.5% of the TRR (<0.01 ppm) in linters. Characterization of Unknown-1 indicated that it was not conjugated to glucose and it did not contain a functional hydroxyl group. Numerous minor radioactive peaks (≤0.01 ppm) also were observed in organosoluble extracts of meal and linters.

Nature of the Residue in Oranges:

The orange metabolism study was reviewed under PP#5G04507 (see 8/8/95 memo of G.F. Kramer). Chlorfenapyr (Pirate/Alert), radiochemically labelled in the aromatic ring (phenyl-UL-^{14}C) or in the pyrrole ring (pyrrole-^{14}C) was applied to navel orange trees at a rate of 0.66 lbs. ai/A (2X) in the field. A total of three applications were made, with the second and third applications performed 98 and 154 days after the first. Oranges were harvested 7 days prior the final application (-7 days PHI) and 7, 14 and 28 days after the final application.

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

proceeds via: 1) N-dealkylation of the parent compound to CL 303,268; and 2) oxidation of CL 303,268 to CL 325,195 and CL 322,250.

Nature of the Residue in Lettuce:

The lettuce metabolism study was discussed under PP#5G04523 (see 3/21/96 memo of G. Otakie). Chlorfenapyr (Pirate/Alert), radiochemically labelled at position-2 of the pyrrole ring (2-pyrrole-C14) and uniformly labeled in the phenyl ring (phenyl-U-C14) was applied to lettuce during the later growth stage to near harvest at an application rate of 0.25 lb ai/A in five treatments at a seven day interval with the total application rate of 1.23-1.25 lb ai/A. Lettuce was sampled at 0, 3, and 7 days after the fifth application. At 0, 3, and 7 days after the last application the TRR in lettuce **with wrapper leaves** was 12.23, 13.77 and 10.06 ppm, respectively for the 2-pyrrole-C14 and 8.17, 12.74, and 9.33 ppm for the phenyl-U-C14. At 3 and 7 days after the last application the TRR in lettuce **with wrapper leaves removed** was 7.49 and 7.42 ppm, respectively for the 2-pyrrole-C14 and 5.37 and 8.89 ppm, respectively for the phenyl-U-C14.

The parent (CL 303,630) was the major component in lettuce accounting for 75.1% and 76.8% of the TRR in 2-Pyrrole-C14 and Phenyl-U-C14, respectively. Some minor metabolites were also identified and included CL 303,268, CL 312,094, and CL 325,195 accounting for a maximum of 1.3, 1.4 and 1.8% of the TRR, respectively. Unidentified unknowns accounted for up to 1.69 % of the TRR with 12 moieties.

The results of the HPLC analysis are summarized in the following Table.

Identification of Methanol Extractable Residues in Lettuce with Wrapper Leaves Collected 3 Days After the Last of 5 applications at 0.25 lb ai/A Each (1.25X).

Residue Component	2-Pyrrole-C14		Phenyl-U-C14	
	PPM	%TRR	PPM	%TRR
TRR in Lettuce	13.77		12.74	
CL 303,630	10.34	75.1	9.78	76.8
CL 303,268	0.18	1.3	0.14	1.1
CL 312,094	0.11	0.8	0.18	1.4
CL 325,195	0.17	1.2	0.23	1.8
Unknowns(No.)	1.24(7)	9.0	1.69(12)	13.3
PES	0.61	4.4	0.71	5.6

Nature of the Residue in Tomatoes: The tomato metabolism study was reviewed under PP#5G04574 (see 2/1/96 memo of G.F. Kramer). A tomato metabolism study was conducted with five applications of 0.2 lb ai/A (1X). Chlorfenapyr (Pirate/Alert) *per se* was the major component of the residue identified in tomato fruit, accounting for 50% of the TRR at 7-days PHI and 38-50% at 14-days PHI (0.02 ppm parent both cases). Unidentified peaks, none of which exceeded 0.01 ppm, accounted for up to 58% of the TRR. **Attachment 2** is a summary of of the tomato metabolism data.

Nature of the Residue In Potatoes: A potato metabolism study was submitted with the tomato petition. The parent was the major component identified in potato foliage at 0 day after four applications each at a slightly lower rate than the proposed 0.20 lb ai/A (i.e. total 0.51-0.69 lb ai/A) and there were no detectable residues (<0.003 ppm) in the potato tubers. **Attachment 3** summarizes the potato metabolism data.

Confined Crop Rotation

The confined crop rotation study was reviewed in conjunction with PP#5F04456 (see 2/6/96 memo of G. Otakie). An outdoor confined crop rotation study was conducted at Madera, California, during 1991-1992 with either chlorfenapyr (Pirate/Alert) pyrrole C14 or phenyl C14 label applied to **bare** sandy soil for five successive weeks at an application rate of 0.40 lb ai/A/application or approximately 2X the current proposed seasonal application rate of 1.05 lb ai/A. Rotational crops of leaf lettuce (leafy vegetable), carrot (root crop), barley (small grain) and soybean (legume) were planted at 31, 60, 119, and 364 days after treatment number 5 (DAY-5).

The radioactive residue in rotational crops was moderately extractable ranging from 30.0-93.4% TRR in the combined extracts for all the rotational crops. Terminal residues in the rotational crops contained the parent (CL 303,630) at <0.01-0.13, and metabolites CL 325,195 at <0.01-0.01, and CL 312,094 at <0.01-0.03 ppm, in addition to other minor extractable polar and nonpolar metabolites. **Attachment 4** summarizes the total C14 residue and characterization crop rotation data obtained. The metabolic profile was similar for both the pyrrole C14 or phenyl C14 label and the bond between the phenyl and pyrrole ring apparently remains intact.

The highest residues were 0.13 and 0.07 ppm of parent detected in immature and mature carrot root, respectively at a 31 day plant back interval. However at the 60 day plant back interval parent residues were <0.01 ppm in immature carrot. Parent residue of 0.01 ppm in lettuce at a 31 day plant back was reduced to <0.01 ppm at a 60 day plant back interval.

Field Trial Data

Residues of the parent were ≤ 0.32 ppm in/on **cottonseed** samples harvested 21 days after the last application at the 1X rate (i.e. 5 foliar application totalling 2 lb ai/A). Maximum residues of the parent in **oranges** harvested 7 days after the last application were 0.24 ppm at 0.9X and 0.68 ppm at 1.7X. Maximum residues of the parent in **lettuce** treated at 1X and harvested 3 days after the last application were 4.4 ppm with wrapper leaves and 0.23 ppm without wrapper leaves. The maximum residue of the parent in tomatoes at a 0 day PHI was 0.24 ppm.

Nature of the Residue in Animals

Metabolism of Pirate In Poultry

Metabolism of pirate in poultry was discussed under PP#3G4224 (see 1/26/94 memo of G. Otakie). To charcterize residues multiple metabolism studies were conducted. Laying hens were orally dosed with [phenyl-^{14}C]- and [pyrrole-^{14}C]Pirate at 3.02-3.10 ppm and 14.42-15.04 ppm of Pirate in the diet for seven days. The distribution of TRR in eggs and tissues from both labeled samples was similar. In the high dose groups, the TRR in eggs increased from <0.01 to 0.42 ppm by day 7. Radioactive residues ranged from 0.02 ppm in muscle to 0.52 ppm in kidney and were highest in liver (1.25-1.31 ppm).

The data indicate that laying hens metabolize [phenyl-^{14}C]- and [pyrrole-^{14}C]Pirate in a similar manner. The parent compound and eight metabolites were detected in eggs and tissues; two metabolites (AC 8508-78-BA/BB) were identified as a mixture. The total identified/characterized ^{14}C-residues accounted for 89% TRR (eggs), ≥87% TRR (liver), ≤89% TRR (kidney), 94% TRR (skin/fat), and ≥62% TRR (muscle). The petitioner identified the parent compound as the major metabolite from [phenyl-^{14}C]- and [pyrrole-^{14}C]Pirate samples in eggs (40-42% TRR, 0.16-0.17 ppm), skin/fat (79-84% TRR, 0.29-0.39 ppm), and muscle (25-31% TRR, <0.01-0.01 ppm).

In the liver and kidney, CL 303,268 was the major metabolite, which amounted to 7-17% TRR (0.09-0.21 ppm) and 17-25% TRR (0.09 ppm), respectively. To provide kidney and liver samples for metabolite identification, an additional 25 laying hens were divided into a control and two treatment groups (5 in the control and 10 in each dosage group) with the treatment groups dosed at 15.9 ppm phenyl ^{14}C or 16.9 ppm 2-pyrrole ^{14}C. A summary of the total radioactive residue TRR for the last poultry metabolism study and the highest ppm equivalents and % TRR is included in **Attachment 5**.

Based on the identity of metabolites, metabolism of Pirate takes place at the phenyl ring, and on the substituents of the pyrrole ring. Fragmentation of the two rings was not evident. Pirate undergoes extensive metabolism in the hen involving modification of the phenyl ring and the substituents of the pyrrole ring. The metabolic pathways of Pirate in the hen include N-dealkylation, dehalogenation, ring hydroxylation and oxidation of the N-alkyl group components. The metabolic pattern of Pirate in the hen is qualitatively similar to that in the goat and rat (see **Attachment 6**).

The nature of the residue in poultry is adequately understood and consists primarily of the parent in muscle and fat. In addition to the parent numerous Pirate metabolites have been identified. In eggs the parent and its N-dealkylation metabolite CL 303,268 [i.e. Pyrrole-3-carbonitrile, 4-bromo-2-(p-chlorophenyl)-5-(trifluoromethyl)-] are present at the highest level. In liver and kidney the parent, CL 303,268, CL 152,835/M-6 (i.e. Acetic acid, {[2-(p-chlorophenyl)-3-cyano-5-(trifluoromethyl)pyrrol-1-yl]methoxy}-) and CL 325,157/M-6A (i.e. Acetic acid, {[3-bromo-5-(p-chlorophenyl)-4-cyano-2-(trifluoromethyl)pyrrol-1-yl]methoxy}-) are present at the highest levels. In light of the low dietary burden for poultry from the proposed use on cotton, tolerances are not required in poultry tissues and eggs. Nevertheless, a decision is requested of the HED Metabolism Committee on which moieties should be regulated in case future uses require such tolerances.

Metabolism of Pirate in the Goat

Metabolism of Pirate in the ruminant was discussed under PP#3G4224 (see 1/26/94 memo of G. Otakie). To characterize residues multiple metabolism studies were conducted. In brief, American Cyanamid (1993; MRID 42770235) submitted data depicting the metabolism of [^{14}C]Pirate in lactating goats dosed orally once a day for seven days. The low and high doses represented a daily feeding level of 3.0 and 17.9 ppm for [phenyl-^{14}C]Pirate and 3.16 ppm and 16.4 ppm for [pyrrole-^{14}C]Pirate.

Both [phenyl-^{14}C]- and [pyrrole-^{14}C]-labeled samples showed similar distribution patterns of radioactive residues in tissues and milk. During the testing period, radioactive residues in milk samples from the low dose group remained at 0.02 ppm. In the high dose group, the TRR in milk samples increased during the test period from 0.03 ppm to 0.07 ppm. Radioactive residues were highest in liver (1.45-1.46 ppm); the ^{14}C-residues in other tissues ranged from 0.03-0.05 ppm in muscle to 0.62-0.94 ppm in kidney.

Approximately 79% of the administered radioactivity in Pirate was excreted by lactating goats in the urine and feces.

The parent compound and eight metabolites were detected in milk and tissues; two metabolites (AC 8508-78-BA/BB) were identified as a mixture. The total identified/characterized ^{14}C-residues were: ≥83% TRR (milk), ≥65% TRR (liver), ≥81% TRR (kidney), ≥92% TRR (fat), and ≥45% TRR (muscle). Pirate per se was the major metabolite detected in milk (24.7-68.4% TRR), kidney (8.3-9.6% TRR), fat (46.9-78.0% TRR), and muscle (28.7-52.0% TRR). The major metabolite detected in liver was CL 325,195 (3.9-13.5% TRR, 0.06-0.20 ppm). Unknowns 1, 2, 4, 10, and 11, accounting for <0.1-19.2% of the TRR (<0.01-0.1 ppm), were also detected. Non-extractable residues in milk and tissue samples accounted for 4.4-68.0% of the TRR (<0.01-0.24 ppm). Non-extracted ^{14}C-residues from muscle samples (52.0-68.0% TRR, 0.02-0.03 ppm) were not further examined.

The data indicated that Pirate is metabolized in lactating goats by N-dealkylation, dehalogenation, ring hydroxylation, and/or oxidation of the terminal alkyl group. Pirate is N-dealkylated to form CL 303,268, which undergoes ring hydroxylation producing CL 325,195, AC 8944-45, and AC 8508-78-BB. The terminal alkyl group of Pirate is oxidized and dehalogenated to produce AC 8805-31-2-B. All the identified metabolites contain ^{14}C-labels from the [phenyl-^{14}C]- and [pyrrole-^{14}C]Pirate, indicating no fragmentation of the phenyl and pyrrole rings during the metabolism of Pirate in goats.

A final report on the metabolism of Pirate in the goat included additional data. In addition to the low and high dose treatment group with two goats per group discussed above this report included goats treated in a second experiment, L-2461-A, to complete the identification/characterization of residues in the liver and kidney, and to provide tissue and milk for radiovalidation of the proposed analytical method.
A summary of the total radioactive residue TRR for the goat metabolism study and the highest ppm equivalents and % TRR is included in **Attachment 7**.

Pirate undergoes extensive metabolism in the goat involving modification of the phenyl ring and the substituents of the pyrrole ring. The metabolic pathways of Pirate metabolism include N-dealkylation, dehalogenation, and hydroxylation of both the phenyl and pyrrole ring, hydroxylation and oxidation of the N-alkyl group and conjugation to endogenous components. However, there is no fragmentation of the molecule. The metabolic pathway of Pirate in the lactating goat is similar to that in the laying hen and laboratory rats (see **Attachment 6**).

The nature of the residue in ruminants is adequately understood and consists primarily of the parent in muscle, fat and milk. In addition to the parent numerous Pirate metabolites have been identified. In the liver and kidney the metabolites

CL 325,195 [i.e. 2-Pyrrolidine-3-carbonitrile, 2-(p-chlorophenyl)-5-hydroxy-4-oxo-5-(trifluoromethyl)-] and CL 322,250 [i.e. Pyrrole-2-carboxylic acid, 3-bromo-5-(p-chlorophenyl)-4-cyano-] were present at the highest level as well as the parent, other metabolites and conjugates.

A decision on which moieties should be regulated is deferred to HED Metabolism Committee. The petitioner has proposed regulating only the parent for animal commodities. CBTS is not opposed to utilizing the parent as a marker compound in meat by-product tissues where it accounts for less than half the identified residue provided the HED Metabolism Committee has no objection.

Secondary Residues In Meat, Milk, Poultry and Eggs

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

Ruminant An acceptable ruminant feeding study has been submitted and appropriate tolerances in animal ruminant commodities required by CBTS (tolerances for parent only in ruminant commodities of 0.05, 0.75, 0.02, 0.50 and 0.05 ppm, respectively for milk, milk fat, meat, fat and meat byproducts of cattle, goats, hogs, horses, and sheep). Since the parent concentrates in milkfat and meat fat the highest tolerances of 0.75 and 0.50 ppm, respectively have been required for these matrices.

Analytical Methods

GC methods for detection of the parent only in plant and animal matrices have been developed.

Questions To The Metabolism Committee - re: Cholrfenapyr (i.e. Alert/Pirate®)

Plants

1. Is a permanent tolerance expression for plants containing only the parent acceptable (are there any other residues of toxicological concern)? Is use of only parent residues acceptable for dietary risk assessments for a crop such as tomatoes where the parent is 38-50% TRR?

Animals

Ruminant Commodities Excluding Meat ByProducts

2. Is a permanent tolerance expression for ruminant commodities (i.e. milk/milkfat, fat and meat; excluding meat byproducts) containing only the parent acceptable (are there any other residues of toxicological concern)? Is use of only parent residues acceptable for dietary risk assessments for ruminant commodities?

Ruminant Meat Byproducts

3. Is a permanent tolerance expression containing only the parent serving as a marker compound for metabolite residues acceptable for ruminant meat byproducts (are there any other residues of toxicological concern)? Since metabolites can account for 13-39X the parent residues in ruminant byproducts should they be included in the dietary risk assessment (i.e. a factor could be used for the risk assessment based on the ratio of the sum of all the metabolite mixtures, conjugates and metabolites of toxicological concern to the parent marker; see Attachment 7; 13X for liver and 39X for kidney includes all metabolites and mixtures)?

Poultry

4. Although tolerances on poultry commodities are not yet required based on the current proposed uses they may be required for additional new uses for this new chemical. Are the metabolism decisions for ruminant commodities applicable to poultry? If not proceed to 5. and 6.

Poultry Commodities Excluding Meat ByProducts

5. Is a permanent tolerance expression for poultry commodities (i.e. meat, fat and eggs; excluding meat byproducts) containing only the parent acceptable (are there any other residues of toxicological concern)? Is use of only parent residues acceptable for dietary risk assessments for poultry commodities?

Poultry Meat Byproducts

6. Is a permanent tolerance expression containing only the parent, serving as a marker compound for metabolite residues, acceptable for poultry meat by-products (are there any other residues of toxicological concern)? Since metabolites can account for 11-16X the parent residues in poultry meat byproducts should they be included in the dietary risk assessment (i.e. a factor could be used for the risk assessment based on the ratio of the sum of all the metabolites, to the parent marker; see Attachment 5; 13X for liver and 16X for kidney includes all metabolites and mixtures)?

Attachment 1 - Proposed metabolic pathway in citrus and lettuce (citrus from page 49 of MRID# 436221-01).

Attachment 2 - Tomatoes - Page 34 of Book one of MRID No. 437536-01.

Attachment 3 - Potatoes - Pages 36 and 40 of Book 2 of MRID No. 437536-01.

Attachment 4 - Pirate Residues in Confined Crop Rotation Study (from page 8 of MRID No. 434928-51)

Attachment 5 - Pirate Residues in Poultry Metabolism Study (from pages 6 and 9 of MRID No. 434928-54).

Attachment 6 - Pirate Animal and Fish Metabolism (page 144 from Summary of Data Submitted in Support of the Registration Application for AC 303,630 Insecticide-Miticide Technical; American Cyanamid Company; 12/9/94; no MRID No.).

Attachment 7 - Pirate Residues in Goat Metabolism Study (from pages 6 and 7 of MRID No. 434928-55).

Attachment 8 - Metabolite Structures from MRID Nos. 434928-54 and 434928-55.

cc with Attachments: Reviewer-Otakie, PP#4F4346, PP3G04198, RF, Circu, E. Haeberer.

RDI: EHaeberer:5/23/96 RLoranger:5/23/96

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