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

SEP 27 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP 5F3267. Fosetyl-Al on Citrus. Evaluation of Analytical Method and Residue Data. Accession No. 073642, RCB No. 1179

FROM: Sami Malak, Ph.D., Chemist
Tolerance Petition Section III
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU: Charles L. Trichilo, Ph.D., Chief
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Hazard Evaluation Division (TS-769)

TO: Henry M. Jacoby, PM #21
Herbicide-Fungicide Branch
Registration Division (TS-767)

The Agrochemical Divison of Rhone-Poulenc, Inc., is proposing establishment of a permanent tolerance for residues of the fungicide fosetyl-Al (Aliette™; Aluminum tris (O-ethyl-phosphonate)) in/on citrus at 0.1 ppm.

Permanent tolerances are established for residues of the fungicide aluminum tris (O-ethylphosphonate) in or on pineapple, pineapple fodder, and pineapple forage at 0.1 ppm, each (40 CFR 180.415). A request for a permanent tolerance of 10 ppm for residues of fosetyl-Al in/on fresh or green hops and a food additive tolerance of 20 ppm in/on dried hops is currently pending (PP #5F3251/FAP 5H5468, memo of R.W. Cook, 5/31/85). RCB has recommended for FIFRA Section-18 emergency exemption actions for fosetyl-Al on hops in three states (85-OR-01,85-WA-01, 85-ID-02, L. Cheng, 3/28/85).

A successful method tryout for fosetyl-Al in/on pineapple fruit was carried out in connection with PP #2F2702 (memo of E. Greer to R. W. Cook, 6/29/83). Another method tryout for Rhone-Poulenc Inc., method #163, was requested for fosetyl-Al in/on fresh (green) and dried hops in connection with PP #5F3251/FAP #5H5468 (R.W. Cook 5/23/85). Method #163 is the same method employed for residue determination of fosetyl-Al in/on citrus; however it is different than the pineapple method in the use of different solvent extraction and cleanup procedures. This method was found to be not satisfactory for enforcement purposes (R. W. Cook memo, PP #5F3251/FAP #5H5468, 8/20/85).

Conclusions

1. The metabolism of fosetyl-Al in citrus was not adequately addressed in this petition. We have previously concluded that the residue of concern is fosetyl-Al. This conclusion may be extended to include citrus.

2. A method trial, for Rhone-Poulenc method #163, is required before we can conclude that the analytical method is adequate for enforcement purposes. A method trial for method #163 was requested in connection with PP #5F3251/FA #5H5468 and was found to be not satisfactory for enforcement purposes. (Memo of R. W. Cook, 8/20/85.) The following conclusions presume a successful method trial.

2(a). RCB concludes that residues of fosetyl-Al in/on whole citrus fruit as a result of the proposed use are not likey to exceed the requested 0.1 ppm tolerance.

2(b). RCB concludes that fosetyl-Al residues do not concentrate in citrus processed fractions, therefore, no need for food additive tolerances.

3. No residue was submitted for cover crops in treated orchards. The petitioner should revise Section B by adding a grazing restriction to the proposed label as follows: "Do not allow livestock to graze on the floor of treated orchards."

4. From the submitted data and provided that the petitioner complies with the grazing restriction suggested in Conclusion #3, we expect no residues of fosetyl-Al in the feed items from this use, and there will be no problem with secondary residues in meat, milk, poultry, and eggs. The petitioner should be informed, however, that if future proposed uses of fosetyl-Al result in detectable residues in/on raw agricultural commodities or their byproducts which may be fed to livestock, animal metabolism and feeding studies will be required.

5. There are no Codex, Canadian or Mexican tolerances for fosetyl-Al in/on citrus. Therefore, no compatibility problems exist.

Recommendations

We recommend against the establishment of the proposed tolerance for the reasons cited in Conclusions 2 and 3.

For a favorable recomendation, the petitioner should be informed of the following:

1. We await a successful method tryout for citrus.

Additional Comments

The petitioner should be informed if future proposed uses of fosetyl-Al result in detectable residues in/on raw agricultural commodities or their byproducts which may be fed to livestock, animal metabolism and feeding studies will be requried to determine possible secondary residues in meat, milk, poultry, and eggs.

Detailed Considerations

Manufacturing Process

The manufacturing process of fosetyl-Al (Aliette™) has been previously discussed in connection with the Registration Standard for Aliette and it is included in Confidential Appendix A of the Standard.

Formulation

The formulation proposed for use is Aliette™ 80WP Fungicide, EPA Reg. No. 359-706, a wettable powder formulation containing 80% of the active ingredient fosetyl-Al: Aluminum tris (O-ethyl phosphonate). The formulated product Aliette™ 80WP Fungicide contains 84.2% of the technical grade material. A confidential statement of formula is included in this submission. The same formulation was reviewed in connection with PP 2F2702/FAP #3H5397 (R. W. Cook, 9/29/83), and it was concluded that all inerts in Aliette™ are cleared under 40 CFR 180.1001 (c).

Directions for Use

For control of Phytophthora foot and root rot in bearing citrus grown in all areas except California, foliar applications of fosetyl-Al (Aliette™) are to be made at each leaf flush (March, May, July, and September) at the rate of 4 lbs act/A/ application in 150-250 gallons of spray using ground equipment, for a maximum of 4 applications/season. There is a 90-day PHI.

There is no livestock grazing restriction for cover crops of treated orchards.

Nature of Residues

Plant Metabolism

The absorption, translocation, and metablishm of fosetyl-Al in grape vines and pineapples has been previously reviewed in connection with PP#2F2702/FAP3H5397(memo of R. W. Cook, 9/29/83). Quoting from this review:

"In grape vines foliarly treated with ethyl-^{14}C-fosetyl-Al, samples of treated leaves, untreated old leaves, and new growth leaves were taken over 21 days. Leaves were examined by autoradiography and extraction by washing or soaking with water + surfactant. Soaking was more effective in removing ^{14}C than washing, 87% vs. 18 to 36% by washing. Translocation of surface applied ^{14}C-fosetyl-Al to either old growth or new growth was less than 1% of total applied activity. Extraction of old and new growth showed only parent compound and traces of phosphorous acid. Parent compound was the only ^{14}C material detected by TLC. The metabolism of fosetyl-Al in grape vines proceeds through hydrolytic cleavage of the ethyl ester bond, with phosphorous acid and probably ethanol as the major plant metabolites.

In a pineapple metabolism study, pineapple crowns were treated with ethyl-^{14}C-fosetyl-Al, and sampled over 120 days. Water soluble ^{14}C-materials from acetonitrile/HCL extract were examined by HPLC ^{14}C liquid scintillation detection. Acetone extract fractions were examined by TLC and autoradiography. Radioactivity recovered from pineapples decreased steadily, showing 45, 34, 28, 15, 14, and 14% at 0, 7, 14, 28, 56, and 120 days respectively. Major detected ^{14}C materials were fosetyl-Al and ethanol, found in aqueous phase of acetonitrile/HCL extract. These two materials accounted for 38% of the 41.9% recovered in this fraction at 0 days, and 2.3% of the total ^{14}C at 120 days in the aerial portion. Bound ^{14}C and acetone/HCl/methanol extractables accounted for 0.6% and 2.9% at 0 days, and 5.6 and 5.8% at 120 days (aerial portion), respectively. Oleic acid, 1-docosanol, and 1-tetracosanol were identified. Long chain fatty acids, alcohols or esters were also present. None of these fatty materials accounted for more than 0.5% of the ^{14}C."

Citrus metabolism and fractionation studies were reported with this petition. Treatment, sampling, handling, and a fractionation study were conducted by G. Bausher, a plant physiologist with the USDA in Orlando, Florida (Ref. 82/412/BHL/AG, 6/82).

In these studies, orange and tangerine trees grown in Orlando, Florida received 3-4 foliar applications of ethyl-^{14}C-fosetyl-Al at the rate of 4 lb act/A/application beginning at postbloom, April 21, 1981 and ending on September 29, 1981. Treated plants were placed on concrete blocks with raised sides to prevent runoff. Fruits and foliage were harvested around

December 14, 1981; i.e., 76 days after last application and the fruits were immediately processed. The results of the processing studies and residue distribution in the foliage are discussed under Residue Data.

In the residue characterization study conducted by Rhone Poulenc Researchers, the whole truit and peel of oranges and tangerines were extracted first in water, then in acetone and finally in acidified methanol. The aqueous extracts of the whole fruit and the juice were buffered to pH3 to inhibit the breakdown of foestyl-Al to phosphoric acid and ethanol. Quantitation was accomplished by the use of ion pair liquid chromatography on C18 bonded silica. The radioactivity present in the different extracts and liquid chromatography elements was measured by liquid scintillation.

The results of residue characterization in the various samples are shown in the Table 1:

Table 1 - Characterization of the Radioactivity (ppm)*

Sample	Oranges Whole fruit	Oranges Peel	Tangerines Whole fruit	Tangerines Peel
Aqueous Extracts	1.9	27.5	9.8	9.8
Acetone Extracts	0.1	11.4	2.6	2.6
Methanol/HCL Extracts	0.2	4.0	1.9	1.9
Residual Cake (insoluble)	0.6	11.7	7.6	7.6

* Calculated as fosetyl-Al equivalents.

The aqueous extracts from whole fruit and the peel contained approximately 67 and 50% of the radioactivity, respectively. Chromatographic characterization of the nature of the residues in the aqueous extracts showed that the extract is made largely of fosetyl-Al and glucose where glucose makes about 50% and 75% of the radioactivity in the whole fruit and fruit juice, respectively. The identity of the glucose was established using the following liquid chromatographic conditions: ion pairs with tetrabutylammonium hydroxide in acid medium on C18 bonded silica, ion pairs with cetrimide (hexadecyltrimethylammonium hydroxide) in neutral medium on C18 bonded silica, and C811 shodex ion pack.

The presence of ^{14}C in large formations of glucose is perhaps an indicative that the carbon group of fosetyl-Al is largely integrated into the normal plant metabolism. This study, however, did not address the question of fosetyl-Al metabolism in plants. Therefore, we are unable to arrive at a conclusion from this study, as to the nature of fosetyl-Al residues in plants. RCB has previously concluded, in connection with PP Nos. 2F2702 and 5F3251, that the residue consists of the parent compound, fosetyl-Al, phosphorous acid, and ethanol and that the residue of concern in plants is fosetyl-Al. This conclusion may be extended to include those in citrus.

Animal Metabolism

No information is available on the metabolism of fosetyl-Al in animals (See also under Meat, Milk, Poultry, and Eggs).

Analytical Methods

The analytical method employed for residue determination of fosetyl-Al in/on citrus is Rhone-Poulenc, Inc., Method No. 163, dated May 1983 and bearing the designation REF No. 83/403/BHL/AG and ASD No. 83/019. The method, authored by Somma, N. et. al., is entitled, "Determination of fosetyl-Al Aluminum Tris (O-Ethyl Phosphonate) in/on Citrus Fruit and Fractions by Phosphorous Specific Flame Photometric gas Chromatography." The method is discussed in connection with PP #5F3251 and a method tryout was requested in/on fresh (green) and dried hops (R. W. Cook, 5/23/85). This method, however, was found to be not satisfactory for enforcement (R. W. Cook memo, PP#5F3251/FAP#5H5468, 8/10/85).

Briefly, the method involves extraction of the whole fruit or peel in a 50/50 mixture of 0.1 N hydrochloric acid and acetonitrile. The extract is cleaned up by alumina column chromatography. The eluate is evaporated, and acetic acid is added to the residue. The liberated O-ethyl phosphonic acid is esterified with diazomethane to obtain the corresponding methyl ester, which is detected by phosphorous specific flame photometric gas chromatography, and the results calculated as fosetyl-Al. The limit of detection for whole fruit, peels, and juice was reported to be 0.05 ppm.

Whole grapefruit and orange samples fortified at levels from 0.05-8.0 ppm had recoveries from 84-97%, averaging 90%. Grapefruit and orange peels fortified at levels from 0.05-80.0 ppm had recoveries from 82-96%, averaging 90%. Non fortified control samples had no fosetyl-Al residues (< 0.05 ppm). Sample chromatgrams were included.

We will withhold our conclusions on the adequacy of the method pending the results of a method tryout for enforcement of the proposed tolerances in citrus.

R. W. Cook memo, PP #5F3251, 5/23/85).

Residue Data

Data submitted were reported by C. Guyton and A. Guardigli of Rhone-Poulenc, Inc. in a report dated June, 1985, and bearing the designations REF. No. 85/BHL/163/AG and ASD No. 85/128. This report is entitled, "Fosetyl-Al Residue Data on Bearing Citrus and Processed Citrus Fractions."

Residue data reflect five replicated orange trials from Texas, Florida, and California, three grapefruit trials from Texas and California and one lemon trail from California. Field tests were conducted during 1982-1984 in which mature trees received 4-5 applications of Aliette (fosetyl-Al) at the rate of 4-25 lb act/A/application for a total of 16 (1x) to 65 (4x) lb act/A/season. The PHI's varied from 0 to 143 days. Whole fruit samples were collected during February, 1983, shipped on ice, then stored in a freezer (0°F) until analyzed two months later during April, 1983. The storage interval of 8 weeks from harvest to analysis does not appear unduly long, and we are not raising questions on this issue. Some of the samples were processed and analyzed for residues, the results of which are discussed below. Whole fruit samples were analyzed for the parent compound using analytical method No. 163 described under Analytical Methods. Sample chromatograms are included.

A summary of the available residue data is shown in Table 2.

Table 2 - Residues of Fosetyl-Al in/on Citrus

Location	Rate lb act/A	No. of Applications	PHI (days)	Residues (ppm)
		ORANGES		
CA	4	4	30	0
	4	4	30	0
	4	4	61	0
FL	4	4	69	0
	4	4	98	0
TX	10	4	143	0
	10 + 25	4 + 1	0	1.11
		GRAPEFRUIT		
CA	4	4	30	0
TX	10	4	143	0
	10	4	143	0
	10 + 25	4 + 1	0	2.92
	10 + 25	4 + 1	0	1.99
		LEMONS		
CA	4	4	56	0

It can be seen from Table 2 that only 3 samples of fosetyl-Al-treated oranges and grapefruit to carry detectable residues (1.11, 1.99, and 2.92 ppm); all reflected 0-day PHI and an exaggerated rate of 4x. No fosetyl-Al residues (< 0.05 ppm) were detected in any of the samples with four treatments at 4 lbs/ act/A/treatment and a PHI of 30-98 days. The proposed use is calls for treatments at 4 lb act/A/ application and a PHI of 90 days.

From the available data RCB concludes, pending a successful method tryout, that fosetyl-Al residues in/on citrus will not exceed the proposed tolerance of 0.1 ppm.

When the whole citrus fruit and various fractions of oranges were fortified with fosetyl-Al at levels from 0.05 to 5.0 ppm, recovery ranged from 67 to 129%, averaging 93%.

A processing study by C. Guyton and A. Guardigli was included in this report. Aliette was applied to mature orange trees grown in Florida using two applications at the exaggerated rate of 40 lb act/A/(10x). The fruits were harvested immediately after last application (0-day PHI) and shipped on frozen ice to the University of Florida where samples were stored in a freezer (0°F) until processed. Representative subsamples from each substrate were analyzed using method #163 described under Analytical Methods. The following is a summary of the processing study as reported by C. Guyton of Rhone-Poulenc:

Commodity Analyzed	Fosetyl-Al Residues (ppm)
Oranges, unwashed	2.09
Oranges, washed	0.46
Chopped peel	0.13
Peel fruits	0.17
Finisher pulp	0.00
Dried peel	0.75
Pressed liquor	0.18
Fruit juice	0.00
Molasses	0.31
Oil	0.00

From the available data, it is apparent that fosetyl-Al does not concentrate in any of the processed commodities of oranges.

A radiolabeled fractionation study, conducted by G. Bausher of the USDA, is discussed here. Treatments and handling are discussed under Plant Metabolism. In this study, citrus oil was extracted from the peel using hexane. The hexane extracts were dried in a flash evaporator, whereas all other samples were dried in an oven at 60°C. Dried samples were then combusted and fosetyl-Al residues were determined using LSC. Results of this study, calculated as fosetyl-Al equivalents, were reported as follows:

Commodity Analyzed	Fosetyl-Al Residues (ppm) Oranges	Fosetyl-Al Residues (ppm) Tangerines
Whole fruit	1.43	0.52
Juice	0.24	0.04
Pulp	0.76	0.13
Seeds	4.55	0.52
Peel	2.73	1.95
Hexane-washed peel (dried)	23.80	7.92
Citrus oil	NA 1/	3.29
Animal feed 2/	5.65	1.16

1/ NA = not available.
2/ A mixture of dried peel, pulp, and seeds.

From the available data, it is apparent that fosetyl-Al concentrates in the wet and dry peel and animal feed of oranges by a factor of 1.9, 16.6, and 4.0x, respectively. No data are available for citrus oil. In tangerines, the concentration factor for wet and dry peel, animal feed, and citrus oil were calculated at 3.8, 15.2, 2.2 and 6.3x, respectively.

A second radiolabeled fractionation study, utilizing samples as those processed by G. Bausher of the USDA, was conducted by Rhone-Poulenc researchers (see also under Plant Metabolism). In this study, extraction and quantitation were accomplished in a manner similar to those of G. Bausher of the USDA. Results of this study, calculated as fosetyl-al equivalents, were reported by Laurent, M., et. al., of Rhone-Poulenc as follows:

	Fosetyl-Al Residues (ppm)	
Commodity Analyzed	Oranges	Tangerines
Whole fruit	2.8	1.2
Juice	0.7	0.25
Hexane-washed peel	54.7	22.0
Animal feed	12.7	3.2
Citrus oil	0.2	0.2

The data show that fosetyl-Al concentrates in the orange peel and animal feed by a factor of 19.5 and 4.5x, respectively; and those in tangerines by a factor of 18.3 and 2.7x, respectively.

In the two radiolabeled fractionation studies discussed above, the average concentration factor for wet and dry citrus peel, animal feed, and citrus oil was calculated at 2.9, 17.4, 3.4, and 6.3x, respectively.

When a comparison is made between the radiolabeled processing studies (1x rate; 76-day PHI; hexane extraction of citrus oil, combustion, and LSC) and the chemical processing study (10x rate; 0-day PHI; and chemical method of analysis using method #163) in which no concentration of fosetyl-Al was found in/on citrus processed fractions, one can conclude that the chemical method of analysis is more reliable and acceptable since it determines the parent compund, fosetyl-Al whereas, the radiolabeled studies determine the ^{14}C-pool in these commodities.

RCB concludes, pending the completion of a successful method tryout, that fosetyl-Al per se does not concentrate in/on the various fractions of the citrus fruit.

Selected leaf samples from the radiolabeled study, by G. Bausher of the USDA, were analyzed by combustion for residues of fosetyl-Al. The results are given below:

Sampling	^{14}C-fosetyl-Al Equivalent Residues in Leaves (ppm) Oranges	Tangerines
After 1st treatment - 4/21/81	137.3	3.7
Prior to 2nd treatment - 6/23/81	2.2	---
Prior to 3rd treatment - 7/29/81 (old growth)	6.2	---
Prior to 3rd treatment - 7/29/81 (new growth)	0.3	---
After 3rd treatment - 9/29/81	---	85.4
Prior to 4th treatment - 9/29/81	23.3	---
After 6th treatment - 9/29/81 (76-day PHI)	98.3	---

Equivalent fosetyl-Al residues in the orange fruit harvested after the 4th treatment (76-day PHI) were determined at 2.8 ppm. From these data, it is apparent that the level of fosetyl-Al residues in whole fruit is 2.8% that in the leaves.

The petitioner should revise Section B by adding a grazing restriction to the proposed label as follows: "Do not allow livestock to graze on the floor of treated orchards."

Meat, Milk, Poultry, and Eggs

Considering the available residue data showing no detectable residue of fosetyl-Al at method sensitivity in the raw agricultural commodity, citrus fruit, and processed citrus fractions and provided that the petitioner restricts grazing of livestock in treated orchards, we are not raising questions regarding possible secondary residues in meat, milk, poultry, or eggs at this time. However, the petitioner should be informed that if future proposed uses of fosetyl-Al result in detectable residues in/on raw agricultural commodities or their byproducts which may be fed to livestock, animal metabolism and feeding studies will be required.

Other Considerations

There are no Codex, Canadian, or Mexican tolerances for fosetyl-Al in/on citrus. An International Residue Limit Status Sheet is attached.

Attachment I: Codex Sheet

cc: RF, Circu, Reviewer, EEB, EAB, FDA (Robert Thompson, RTP), TOX, RD (PM #21), SF (PP #5F3267), PMSD/ISB.
RDI: P. Errico: 9/25/85: R. D. Schmitt: 9/25/85.
TS-769: RCB: S. Malak: ejh/9/25/85: x557-7377: CM#2: RM810:7/29/85.

CHEMICAL Fosetyl-Al (Aliette) PETITION NO 5F3267

Sami Malak

CCPR NO. ____

Codex Status	Proposed U. S. Tolerances
[ ] No Codex Proposal Step 6 or above	Aluminum tris (O-ethylphosphonate)
Residue (if Step 9): ____	Residue: fosetyl-Al (parent compound).

Crop(s)	Limit (mg/kg)	Crop(s)	Tol. (ppm)
		Citrus	0.1

CANADIAN LIMIT		MEXICAN TOLERANCIA	
Residue: ____		Residue: ____	
Crop	**Limit (ppm)**	**Crop**	**Tolerancia (ppm)**
None		None	

Notes: