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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP#1F2575/1H5322 Chlorpyrifos on citrus. Evaluation of analytical Method and residue data.

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and

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Dow Chemical Company proposes tolerances for the residues of chlorpyrifos (which include the parent plus a metabolite, 3,5,6-trichloro-2-pyridinol (TCP) in or on citrus fruits (1 ppm). Food additive tolerances are proposed for dried citrus pulp (5 ppm) and citrus oil (25 ppm).

Several chlorpyrifos tolerances are established ranging from 0.01 ppm for eggs and poultry to 15 ppm for peanut hulls. Temporary tolerances are in effect for oranges and lemons both at 2.5 ppm and dried citrus pulp at 15 ppm. Many petitions are pending.

Conclusions

1. The nature of the residue is adequately understood. The residue of concern consists of chlorpyrifos plus TCP.
2. Adequate analytical methods are available for enforcement purposes.
3. Two applications to citrus per fruit year are permitted. The label does not specify a minimum interval between applications.

Either the petitioner should propose a minimum of 30 days between applications, or if this is not acceptable, then more residue data reflecting two applications (especially 2 applications of a low volume spray for which no residue data are submitted) will be needed.

- 4a The following conclusions concerning appropriate tolerance levels are contingent on the establishment of a 30 day minimum period between applications.
- 4b The proposed tolerance for citrus fruits (1 ppm) is too low. A tolerance of 2 ppm would be adequate and should be proposed.
- 4c The proposed tolerance for dried citrus pulp (5 ppm) is too low. A tolerance of 15 ppm would be adequate and should be proposed.
- 4d The proposed tolerance for citrus oil is too low. A tolerance of 40 ppm would be adequate and should be proposed.
- 4e Residue in juice and molasses are not expected to exceed the tolerance for citrus. Food additive tolerances are not needed on these commodities.
- 5a Pending tolerances for meat and milk in other petitions will accommodate any expected secondary residues that may result from the proposed use.
- 5b Since no poultry feed items are involved there will be no problem of secondary residues in poultry and eggs.
- 6. An International Residue Limit status sheet is attached. The Codex MRL (which does not include residues of TCP) for citrus fruit is 0.3 ppm. Since this proposed use will result in higher residues (up to 2 ppm) and since TCP can be a significant portion of the residue the U.S. tolerance cannot be made compatible with the Codex MRL.

Recommendation

We recommend against the proposed tolerance. For a favorable recommendation, the petitioner should submit:

- 1. A revised Section B in which a minimum time period of 30 days between applications is imposed or additional residue data reflecting 2 applications (especially data reflecting low volume applications).

2. A revised Section F in which the following tolerances are proposed.

- | | |
|----------------------|--------|
| a. citrus fruit | 2 ppm |
| b. dried citrus pulp | 15 ppm |
| c. citrus oil | 40 ppm |

A favorable recommendation is also contingent on the concurrent establishment of the meat and milk tolerances proposed with PP#OF2281.

Formulation

Lorsban 4E (EPA) Reg. No. 464-448) is proposed for use and contains 40.7% chlorpyrifos (4 lbs/gal). The inert ingredients,

[REDACTED] are cleared for use under Sec. 180.1001(c).

Technical chlorpyrifos has minimum purity of 94.0%. The manufacturing process has been described in our review of PP#4F1445 (memo of 5/3/74, A. Smith). Impurities comprise [REDACTED] of the technical material. They are [REDACTED]

[REDACTED] The remainder of the nonvolatiles (<0.04% each), consist of at least seven compounds. We do not expect the impurities in Lorsban to present a residue problem due to the high dilution rates upon application.

Proposed Use

For control of various insects and mites infesting the foliage, bark and/or fruit of citrus trees Lorsban 4E is to be applied as a dilute or concentrate ground application. The rate is (for dilute applications) is 4 to 8 ounces a.i./100 gallons of spray not to be applied at a rate in excess of 7.5 a.i./A. For concentrate sprays the same amount of chlorpyrifos is applied as for dilute sprays using appropriate application procedures. No application is to be made within 21 days of harvest. No more than two applications are to be made per fruit year. Livestock are not to be grazed in treated areas.

Nature of the Residue

Plant

No metabolism studies were submitted with this petition.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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The metabolism of radiolabeled chlorpyrifos (^{14}C and ^{36}Cl) has been studied in corn and bean plants (PP#3F1306). These studies show that chlorpyrifos is translocated only to a limited degree from soil or from treated leaves. Chlorpyrifos degrades in UV light in the presence of water by dechlorination to form diols and triols which can undergo ring cleavage. Under prolonged irradiation the products were apparently carbon dioxide, ammonium carbonate and sodium chloride.

Plant metabolism (as indicated by the corn and bean studies) is via hydrolysis to ethyl 3,5,6-trichloro-2-pyridylphosphate; 3,5,6-trichloro-2-pyridylphosphate; 3,5,6-trichloro-2-pyridinol (TCP); and material postulated to be a TCP conjugate. TCP can undergo dechlorination (as observed in UV degradation) to form diols and triols which can be conjugated or incorporated into natural plant constituents.

More recently, apple and soybean metabolism studies have been submitted and reviewed (PP#OF2281, memo of 7/7/81, E. Leovey). In the apple metabolism study chlorpyrifos and TCP were observed as residues at levels of 36.3 and 5.1 - 5.6% respectively. Two metabolites were postulated to be mono-dechlorinated derivatives of chlorpyrifos from GC/MS data. The aqueous layers contained a metabolite designated B (4.9 to 5.4% of residue) which upon hydrolysis yielded TCP. The hydrolyzed insoluble material yielded metabolites C (5.2-5.7%), D (3.2 to 5.4%) and E (5.5 to 5.7%) which were not characterized due to a lack of sufficient material.

The remainder of the radioactivity was insoluble material (3.3-4.5%) and aqueous layer (1.4-1.5%). The material in the unidentified hydrolyzed fraction consisted of numerous radiolabelled compounds smeared throughout the HPLC fractions. From 90-95% of the radioactivity could be traced; the remainder was probably lost in sample handling.

The ^{14}C residue in soybeans was characterized as 17% incorporated into natural components of the oil; 2.5% chlorpyrifos; 11% TCP; 24% extracted into the aqueous layer and containing at least seven metabolites not hydrolyzable to TCP; 18% solubilized which individually constituted at most 3% of the total residue; 11% in the precipitate and deduced to be incorporated into protein and 8% remaining insoluble, according to our calculations. Unidentified metabolites were claimed to be compounds arising from the plants' natural constituents.

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In conjunction with PP#s OF2281 and 9F2270 we deferred to Toxicology Branch as to the significance of apple metabolites B, C, D, and E and the unidentified apple and soybean metabolites, particularly the water soluble metabolites. Toxicology Branch has recently concluded (Section 18 by the State of Ohio for Chlorpyrifos on soybeans, memo of 8/11/81, A. Mahfouz) that the unidentified metabolites that are water soluble are not of toxicological significance because water soluble metabolites of organophosphate insecticides are usually inactive degradation products. More recently (memo of 10/28/81, W. Dykstra) Toxicology Branch concluded that the organosoluble metabolites are not of concern. We therefore conclude that the nature of the residue in plants is adequately understood and consists of chlorpyrifos and TCP.

Animal metabolism

Metabolism in animals has been described in our review of PP#3F1306 (memo of F.D.R. Gee, 3/1/73). In rats, ^{14}C and ^{36}Cl chlorpyrifos and ^{14}C -TCP were extensively eliminated in the urine and feces. Only 1.1-25% of the dose remained in tissues with residues highest in the liver, kidney, stomach and blood. Five ppm chlorpyrifos was fed to a lactating cow for four days. The urinary metabolites were identified as diethylthiophosphate and diethyl phosphate which were 35.9 and 26.8% of the insecticide fed. No chlorpyrifos was found in milk or urine. Approximately 1.7% of the chlorpyrifos fed was found in the feces. Samples were not analyzed for TCP.

Chlorpyrifos was concluded as result of PP#3F1306 to be metabolized in animals by oxidation and hydrolysis to phosphoric acid-type compounds and TCP which may be further broken down to CO_2 . However, as a result of further information discussed in our review of PP#9F2270 we concluded that in that submission the animal metabolism of chlorpyrifos was not adequately delineated and the fate of chlorpyrifos in a lactating goat needed characterization. In conjunction with PP#OF2281 (memo of 7/7/81, E. Leovey) a goat metabolism study was submitted. Two lactating goats were orally dosed with 2,6, ring labeled ^{14}C chlorpyrifos twice a day for 10 days. Feeding levels were 15 and 19 ppm for the goats. Urine and milk were collected during feeding and tissues analyzed at the conclusion of the experiment.

Radioactive residues in tissues ranged from 0.01 ppm (bone) to 0.8 ppm (rumen). Residues in milk and muscle were 0.03 ppm; this was considered to low for further analysis. Residues at the 19 ppm feeding level were: fat 0.10 ppm; liver, 0.22 ppm; and kidney, 0.29 ppm. These residues were considered sufficient for residue characterization and were comparable to the blood levels.

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Distribution of the does in urine, feces, gut, tissues, and milk was 75.5 and 85.1%, 3.5% and 3.7%, 1.2 and 0.6%, 0.7 and 0.8% and 0.14 and 0.05% at the two feeding levels, 15 and 19 ppm respectively, for a total of 81 and 90.2%.

Urine was acidified and extracted with ether. Metabolites were partitioned into sodium bicarbonate. After acidification, residues were extracted into ether, concentrated, and analyzed by HPLC. TCP constituted at most 15.3% of the urine metabolites. A beta-glucuronide conjugate of TCP was the major urine metabolite, 80-91%. A minor metabolite was tentatively identified as S-ethyl,0-(3,5,6-trichloro-2-pyridyl)phosphorothioic acid. The results shown in the report were for a urine sample collected approximately six days into the diet. Other samples were reported to be similar (W.R. Bauriedil, Dow Chemical, April 27, 1981).

Fat was dissolved in hexane and the ^{14}C -labeled residues reportedly extracted into acetonitrile and after concentration was cleaned up again with a hexane-acetonitrile partition. Solids remaining after hexane dissolution were hydrolyzed. Residues were extracted into ether after acidification and cleaned-up by hexane acetonitrile partition. Chlorpyrifos was the major component (confirmed by GC/MS). It constituted more than 95% of the residue as determined by HPLC, and the remainder was TCP or material, particularly in the solids, which could be hydrolyzed to TCP.

Liver and kidney were blended with 50% methanol and centrifuged. The supernatant was diluted and extracted with ether-hexane which was concentrated. The residue was dissolved in methanol and analyzed by HPLC. Solids were hydrolyzed and after acidification extracted into ether. Tissues were also hydrolyzed with hot potassium hydroxide and extracted as just described followed by hexane/acetonitrile partitioning. The majority of the residue was TCP with at most 10% unidentified material. After hydrolysis more than 94% of the radioactivity was identified as TCP.

We conclude that the nature of the residue in animals is adequately understood. The residue of ~~the~~ ^{the} ~~parent~~ ^{parent} consists of the parent plus TCP.

Analytical Method

The residue data in this petition were obtained by methods similar to the PAM II method for chlorpyrifos. Chlorpyrifos and TCP are determined separately.

Chlorpyrifos

The citrus sample (whole fruit, peel or pulp) is extracted with acetone. The extract is filtered and the acetone is reduced by a Snyder column. The residue is partitioned into hexane. A hexane-acetonitrile partition and silica gel chromatographic column are used for cleanup. The solvent is removed, the residue is dissolved in acetone, then analyzed by GLC using a flame photometric detector.

Slight variations are required for the analysis of dried citrus pulp, juice, molasses, and citrus oil.

TCP

The plant sample is treated with methanol and NaOH at 130°. An aliquot of the methanol is evaporated to near dryness; the residue is taken up in water. Concentrated HCl and salt are added; the freed TCP is extracted into benzene. The benzene extract is chromatographed on an acidic alumina column using a diethyl ether/pH 6.5 buffer mix for elution. The ether eluate is partitioned with sodium bicarbonate. The bicarbonate solution is acidified and the TCP is extracted into benzene. An aliquot of the benzene solution is silylated with N,O-bis(trimethylsilyl)acetamide (BSA). The pyridinol trimethylsilyl derivative is then determined by GLC using electron capture detection.

Slight variations in this method are required for citrus oil. As the method determines total TCP, the chlorpyrifos must be determined by an independent method; the TCP is then calculated by difference.

The following check and recovery values are submitted for grapefruit:

chlorpyrifos fruit (fraction)	Check (ppm)	recovery		
		Fort. (ppm)	range (%)	Avg. (%)
whole grapefruit	0.001-0.005	0.01-1.0	71-103	86
dried citrus pulp	0.01	1.0	68	--
molasses	0.002	0.01-1.0	76-103	93
juice	0.000	0.10	75	--
oil	0.05-0.06	0.1-5.0	55-64	60

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TCP*

whole grapefruit	0.01-0.02	0.05-1.0	80-102	93.2
dried citrus pulp	0.02	0.1-1.0	81-85	83
molasses	0.006	0.05-0.1	90-100	95
juice	0.000	0.05	96-98	97
oil	0.07	0.1-4.0	88-90	89

*Samples were fortified with TCP and/or chlorpyrifos

Similar recovery and check values were submitted for lemons, oranges and tangelos.

Adequate analytical techniques are available for enforcement of the proposed tolerances.

Residue data

The residue data submitted are from experiments in California, Texas, and Florida. Treated oranges, grapefruits, tangelos and lemons were examined for residues. A variety of rates, concentrations (high or low volume) and PHIs are represented. Few data are strictly representative of the proposed use; most involve only one application. Residue data are for combined chlorpyrifos and TCP residues.

The highest residue found was 3.82 ppm (including <0.05 ppm TCP; for the purposes of determining an appropriate tolerance residues reported as <0.05 ppm are considered to be 0.05 ppm) at 14 days after application of a low volume spray to oranges (15 lb a.i./A; 30 pts Lorsban 4E/100 gal spray) during a 1975 California study. This value was discounted by the petitioner because application had been made with equipment incapable of spraying the tops of the trees. The applicator's attempts to spray the upper portion of the trees resulted in higher rates of application to the lower portion of the trees from which the samples were taken. We are therefore disregarding these data (as we did earlier in conjunction with PP#9G2168, memo of 9/24/79, A. Rathman).

The submitted data clearly show that the potential of high residues is greater when a low volume application is made. The highest combined residue found as a result of a high volume application (oranges; 0.5 lb a.i./100 gallons spray; 7.7 lb a.i./A; x2 applications; 15 day PHI) was 0.73 ppm (<0.05 ppm TCP). The highest residue found as a result of a low volume application (12.5 lb a.i./100 gal spray; 12.5 lb a.i./A; this is an exaggerated rate as the maximum amount allowed per application is 7.5 lb a.i./A) was 3.0 ppm (0.4 ppm TCP) at a 14 day PHI and 2.6 ppm (0.4 ppm TCP) at a 21 day PHI.

The data are extensive but few are strictly representative of the proposed use. The only residue data reflecting two applications were from high volume applications and were sampled 14 or 15 days after the last application (the proposed PHI is 21 days). These applications (0.5 lb a.i./100 gallon spray) resulted in residues on oranges, lemons, grapefruit and tangeloes ranging from <0.1 to 0.73 ppm, (<0.05-0.16 ppm TCP) The average being 0.45 ppm (avg. TCP found = 0.07 ppm).

The existing temporary tolerance (2.5 ppm) for chlorpyrifos on lemons and oranges is for residues resulting from up to two applications of 0.5 lb a.i./100 gal spray (or the equivalent per acre dosage applied as a low volume spray) with a zero day PHI. The petitioner now proposes a 1 ppm tolerance for residues from the same use but at a 21 day PHI. The data do not support this tolerance. We can arrive at an appropriate tolerance by translating from residue data not representative of the proposed use but are concerned about the potential cumulative affect of two applications made within a relatively short period of time. This concern would be allayed if a minimum time period between applications were imposed. We could recommend for a tolerance of 2.0 ppm provided a label restriction establishing a minimum time period of 30 days between applications is imposed.

Processing studies were carried out on oranges, tangeloes, lemons and grapefruit. For dried citrus pulp, the highest concentration factor was 5.9 x (grapefruit carrying residues of 0.33 ppm was processed into dried pulp carrying residues of 1.96 ppm). We estimate residues in citrus pulp might be as high as 12 ppm (the proposed food additive tolerance is 3 ppm). We recommend that a tolerance of 15 ppm be proposed for dried citrus pulp.

For citrus oil the maximum concentration of residues was ca. 20 x (grapefruit carrying residues of 0.33 ppm was processed into oil carrying residues of 6.7 ppm). Therefore the residues in citrus oil might be as high as 40 ppm (the proposed tolerance is 25 ppm). We recommend that a tolerance of 40 ppm be proposed for citrus oil. No other processing fraction (juice, molasses, finisher pulp, and peel frits) of any fruit showed a concentration of residues; food additive tolerances proposals are not needed for these commodities.

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Meat, Milk, poultry and eggs

A tolerance of 2.0 ppm for the meat, fat, and meat byproducts of cattle is pending (PP#OF2281; this tolerance includes residues realized as the result of a dip treatment). Since the proposed tolerance for dried citrus pulp is no higher than tolerances for other significant feed items (alfalfa hay, 15 ppm, pending; soybean straw, 15 ppm, pending; peanut hulls, 15 ppm; and tomato pomace, 15 ppm, pending) and since, in fact, residues from the feeding of dried citrus pulp were included in our calculations (PP#OF2281) to determine an appropriate meat tolerance (citrus was included because of the temporary citrus tolerance), we conclude that the pending 2.0 ppm tolerance for cattle is adequate.

By similar reasoning we conclude that the pending tolerance for milk fat (0.50 ppm reflecting no more than 0.02 ppm in whole milk) is adequate.

For the meat, fat, and meat by products of goats, horses, and sheep, tolerances of 1.0 ppm are pending. Based on cattle feeding studies most recently discussed in our review of the 9/10/81 amendment to PP#OF2881 (See memo of 11/6/81, K. Arne) we do not anticipate that the proposed tolerance would be exceeded should citrus pulp or other citrus byproducts be used as feed for these animals.

Dried citrus pulp is not an important feed item for hogs (1% of the diet) through other processing fractions may constitute up to 30% of the diet. Since no residues greater than 2 ppm are expected for these items and since the maximum amount of chlorpyrifos in a hogs diet would result from feeding 50% alfalfa hay (tolerance-15 ppm) and 50% corn forage and fodder (tolerance-10 ppm) we do not expect that the feeding of citrus processing fractions to hogs will have a significant effect on secondary residues. The pending tolerance of 0.5 ppm for the meat, fat, and meat byproducts of hogs is adequate.

As citrus and citrus byproducts are not fed to poultry, there will be no problem of secondary residues in poultry tissues and eggs.

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