1-30-81

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: JAN 30 1981

SUBJECT: PP#1G2428. Chlorothalonil on citrus. Evaluation of analytical methods and residue data.

FROM: Lynn M. Bradley, Chemist
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TO: Eugene Wilson, PM Team# 21
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and

Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: Charles L. Trichilo, Chief
Residue Chemistry Branch (TS-769)

Diamond Shamrock Corporation, Agricultural Chemicals Division, requests a temporary tolerance of 0.1 ppm on citrus and a temporary food additive tolerance of 10 ppm in citrus oil for combined residues of the fungicide 2,4,5,6-tetrachloroisophthalonitrile (chlorothalonil) and its metabolite 4-hydroxy-2,5,6-trichloroisophthalonitrile. The proposed EUP involves 725.6 lb active chlorothalonil to be used on 50 acres in Florida.

Tolerances are established for combined residues of the fungicide chlorothalonil (tetrachloroisophthalonitrile) and its metabolite 4-hydroxy-2,5,6-trichloroisophthalonitrile in or on numerous r.a.c.'s at levels ranging from 0.1 to 15 ppm (40 CFR 180.275).

A previous petition for a temporary tolerance for chlorothalonil on oranges (PP#6G1871, M. Nelson, 1/11/77) involved use as a harvest aid in combination with abscission chemicals. This tolerance (0.5 ppm) was granted and renewed on oranges and grapefruit several times. PP#0F2405 requesting a permanent tolerance on oranges and grapefruit is currently under review.

Petitions 8E2037 (spinach) and 8E2065 (dry beans) are in reject status. PP#8E2065 was rejected because of the need for meat, milk, poultry and egg tolerances.

We note here that the ADI for chlorothalonil has been reached or exceeded, according to recent TOX reviews (R. Coberly, 1/27/77).

Conclusions

1a. Data on the level of pentachlorobenzonitrile (PCBN) in technical chlorothalonil should be submitted.

1b. We are unable to conclude that residues of the impurities hexachlorobenzene (HCB) and PCBN will not present a residue problem. Residue data are needed (See conclusion 5c).

2a. The proposed 100 day PHI is not practical, as certain varieties of citrus have nearly mature fruit on the tree at the suggested time of application. Petitioner should propose a specific PHI less than 30 days (as indicated elsewhere in the petition) or else restrict the use to early maturing varieties from which fruit is completely harvested prior to blooming.

2b. Section B should state a maximum number of applications which will be made. The accompanying EUP indicates that up to 5 applications will be made, whereas Section B indicates possibly only two. Section B should be revised to reflect the use intended for the experimental program.

2c. The EUP indicates that all varieties of citrus will be treated, while Section B gives only the proposed use for oranges and grapefruit. Section B should accurately reflect the proposed experimental program.

2d. If the proposed use is indeed only for oranges and grapefruit, Section F should be so worded.

3. The nature of residue is adequately understood. The residues of concern, in plants, are parent chlorothalonil and 4-hydroxy-2,5,6-trichloroisophthalonitrile. The majority of the chlorothalonil residue in citrus is found in the peel. The impurities PCBN and HCB may also be components of the residue.

4a. Adequate analytical methodology is not available to detect residues of parent chlorothalonil in citrus. The petitioner should run a comparison study for surface extraction vs. maceration using citrus samples bearing significant levels (1 ppm or more) of weathered residues. If the surface extraction method proves less efficient, a validated method employing maceration of whole fruit will be required.

4b. Analytical methodology for determining residues of 4-hydroxy-2,5,6-trichloroisophthalonitrile in whole citrus fruit should be submitted, along with appropriate validation data. The methodology should employ maceration of the fruit.

4c. Adequate analytical methodology is available for detection of residues of 4-hydroxy-2,5,6-trichloroisophthalonitrile in meat and milk.

5a. Until the requested method comparison study is available (conclusion 4a) we are unable to conclude that the residue data submitted are valid.

5b. The proposed 0.1 ppm temporary tolerance for citrus is not adequate. In order to determine the appropriate tolerance level, residue data reflecting the maximum number of applications at the maximum proposed rate and a more practical PHI including some data for the 4-hydroxy metabolite will be required.

5c. Residue data for HCB and PCBN using an acceptable analytical method and fruit containing significant levels of chlorothalonil residues should be submitted.

5d. We are unable to draw a final conclusion regarding the adequacy of the proposed 10 ppm food additive tolerance for citrus oil until such time as an appropriate level for ora nges and grapefruit is decided on. The available processing study is considered adequate.

6a. We are unable to draw any conclusions regarding secondary residues in meat and milk until appropriate tolerance levels are determined for oranges and grapefruit and we can determine whether residues will be present in citrus pulp. If residues are present in dried citrus pulp, we tentatively conclude that secondary residues will occur in meat and milk [Sec. 180.6(a)(2)].

6b. There are no poultry feed items involved. Thus, there will be no problem with respect to secondary residues in poultry and eggs.

Recommendations

We recommend against the establishment of these temporary tolerances for the reasons outlined in Conclusions 1a, 1b, 2a, 2b, 2c, 2d, 4a, 4b, 5a, 5b, 5c, 5d and 6a. Chlorothalonil has been referred to SPRD for RPAR review.

Detailed Considerations

Manufacture

The manufacturing process for technical chlorothalonil was discussed in our review of PP#4E1502 (R. Schmitt, 11/27/74).

In PP#8E2065 (McLaughlin, 11/28/78) it is reported that hexachlorobenzene (HCB) was a contaminant [redacted] in 8% of 308 batches of technical chlorothalonil which were analyzed. Pentachlorobenzonitrile is also known to be a contaminant, but actual levels are not available. Also, we concluded that the possible presence of dioxins in the technical material was not expected to be a problem.

The levels of PCBN in technical chlorothalonil should be submitted. Available information on levels of HCB is adequate.

Residue levels of hexachlorobenzene (HCB) and pentachlorobenzonitrile (PCBN) were determined in oranges using the surface extraction method (See Analytical Methods). In two studies, oranges were treated once with 2.6 or 3.64 lb active chlorothalonil per acre in 250 gal/A and the analysis of the Bravo 500 formulation used reports 41.4% chlorothalonil, [redacted] At PHI's of 208-221 days, residues of chlorothalonil and HCB were non-detectable (<0.01 and ≤0.003 ppm, respectively); residue levels of PCBN were 0.010 - 0.022 ppm (32 samples) while control samples gave apparent residue levels of 0.012 - 0.019 ppm (6 samples). Thus residue levels of PCBN and HCB were not significantly higher than controls by this method.

IMPURITY INFO IS NOT INCLUDED

Considering the extremely long PHI used for these two studies and the questionable acceptability of the analytical methodology (see Analytical Methods) we are not able to draw any conclusions regarding HCB and PCBN levels in fruit at the much shorter PHI likely to be practical for this proposed use. Residue data for these impurities should be submitted for PHI's reflective of the proposed use, using acceptable analytical method and fruit containing significant residues of the parent compound.

Formulation

The formulation to be used is Bravo 500, which contains 4.17 lb active chlorothalonil per gallon, or 500 g/liter. This relatively new formulation was first reviewed in an amendment to PP#6F1799 dated 2/19/80 (see review of P.V. Errico, 8/13/80). All inerts are cleared under 40 CFR § 180.1001.

Another registered formulation used for some of the residue studies, Bravo 6F, contains 6 lb active chlorothalonil per gallon.

Proposed Use

For oranges and grapefruit apply 2.6-5.73 lb a.i./A in 250 - 500 gallons of water per acre between pin head stage and mid-July, depending on disease to be controlled. For control of scab a second application at 2/3 petal fall may be made. Alternatively, make only one application at 2/3 petal fall under less severe disease conditions. To control greasy spot and pink pitting, apply in combination with 0.5% oil and to control melanose, make a second application 2-3 weeks after the first.

Do not apply when mature fruit is on the tree, nor within 100 days of harvest. Do not allow livestock to graze in treated areas.

We do not consider the 100 day PHI to be a practical restriction. Certain varieties of oranges have mature or nearly mature fruit on the tree during the time suggested for application. Petitioner should propose a more reasonable PHI (not exceeding 30 days) or else indicate on the label that use is restricted to early maturing varieties.

We are unable to determine the maximum number of applications proposed - two or four. Section B should state a maximum number of applications.

The Section G of the accompanying EUP application (Proposed Experimental Program) indicates that up to 5 applications will be made at the 3.64 lb a.i./A rate, 4 applications at the 5.73 lb a.i./A rate and only 1 application at the 2.6 lb a.i./A rate. Section B of the petition should be revised to reflect the planned usage or vice versa, as treatment of citrus at 2x the rate under Section B may produce illegal residues.

Section G also indicates that all varieties of citrus will be treated, whereas Section B only gives directions for oranges and grapefruit. These two Sections should reflect essentially the same use. One or the other should be revised.

Nature of the Residue

No new metabolism data are submitted with this petition. The original review of chlorothalonil metabolism is in PP#11024 (memo of W. Cox, 5/6/71).

The residues of concern in both plants and animals consists of the parent and 4-hydroxy-2,5,6-trichloroisophthalonitrile. The 4-hydroxy metabolite is <10% of the residue in plants, but comprises the bulk of the residue in animals. Chlorothalonil residues remain on the surface of the plant and are not translocated in the aerial plant parts. The impurities HCB and PNCB may also constitute a portion of the residue.

We conclude that the metabolism of chlorothalonil is adequately understood and can be translated to citrus. The majority residues will be found in the peel.

Analytical Method

The accepted method of enforcement of determination of residues of chlorothalonil and its 4-hydroxy metabolite is described in PAM II. Residues are extracted from the crop using acidified acetone and the two components are separated on a florisil column. The 4-hydroxy metabolite is converted to its methyl ester and both components determined separately by MC- or EC-GLC. The procedure was validated on peanuts and potatoes in connection with PP#1F1024; adequate recoveries of both compounds were obtained at fortification levels of 0.3 to 5.0 ppm.

Various modifications of this procedure are used for oranges and associated commodities. Whole fruit are extensively surface-washed with methylene chloride, the residues concentrated and quantitated by ECGLC. For the pre- and after-wash, the solution is acidified and then extracted with isopropyl ether; other liquid commodities (juice, emulsion water and peel liquor) are acidified and extracted with isopropyl ether, then the 4-hydroxy metabolite is extracted from the ether with 0.4 M sodium bicarbonate. The chopped peel, peel frits, finisher pulp and dry pulp and peel are extracted with methylene chloride and filtered. Cold pressed citrus oil is extracted with hexane which is then extracted with acetonitrile and the 4-hydroxy metabolite extracted into acidic water solution. Cleanup and/or separation on either florisil or alumina columns are performed for several commodities and all residues are quantitated by ECGLC.

Control and recovery data are summarized in the following table:

commodity	chlorothalonil			4-OH-chlorothalonil		
	control (ppm)	fortification level (ppm)	recovery	control (ppm)	fortification	recovery
whole fruit	0.02 - 0.04	0.1 - 0.31	84 - 123%	-	-	-
green whole oranges	0.01 - 0.52	-	-	-	-	-
wash water	<0.01 - 0.02	0.06 - 0.14	66 - 140%	≤0.02	0.06 - 0.14	88 - 113%
chopped peel	<0.01 - 0.04	0.1 - 0.12	80 - 96%	<0.02	0.12 - 0.2	80 - 100%
peel frits	<0.01 - 0.02	0.1 - 0.12	56 - 107%	<0.02	0.12 - 0.2	80 - 93%
peel liquor	<0.01	0.12 - 0.2	83 - 97%	<0.02	0.12 - 0.2	77 - 97%
molasses	<0.01 - 0.03	0.2	80 - 100%	<0.02	0.2	90 - 105%
dry pulp and peel	<0.01 - 0.04	0.12	70 - 125%	<0.02	0.12	47 - 87%
finisher pulp	<0.01 - 0.02	0.05 - 0.12	88 - 110%	<0.02	0.12 - 0.2	90 - 110%
emulsion water	<0.01	0.12 - 0.2	57 - 112%	<0.02	0.12 - 0.2	74 - 137%
oil	0.02 - 0.10	0.4 - 2.0	82 - 103%	<0.02	0.6 - 2.0	63 - 107%
juice	<0.01	0.08 - 0.2	65 - 117%	<0.02 - 0.2	0.08 - 0.5	86 - 120%

In one study reporting residues of hexachlorobenzene (HCB) and pentachlorobenzonitrile (PCBN), two analytical methods are compared for extraction efficiency and the easier method used for the majority of HCB and PCBN residue data.

The first method involves surface extraction with methylene chloride (as above) and chromatography on a column of florisil and sodium sulfate. The HCB is eluted with 10% acetone in methylene chloride, and the chlorothalonil and PCBN eluted with methylene chloride. The solvent is dried, the samples taken up in petroleum ether with 2% paraffin oil, dried again, taken up in toluene and quantitated by EC-GC.

The second macerates the whole fruit in acetone. An aliquot of the acetone is dried, taken up in 0.4 M sodium bicarbonate and the pH adjusted to 4.5. Residues are extracted with pet. ether, dried, taken up in 10% acetone in methylene chloride, then chromatographed and quantitated as in the first method above.

A method comparison was done to investigate whether or not residues had migrated into the fruit from the peel surface.

Recovery data are reported for parent, HCB and PCBN, presumably for the surface extraction method. Orange samples fortified with 0.013 - 0.016 ppm HCB gave recoveries of 75 - 93%; with 0.025 - 0.04 ppm PCBN, 55 - 100%; with 0.03 - 0.04 ppm chlorothalonil, 75 - 133%. Control values were 0.007 ppm HCB and 0.012 - 0.019 ppm PCBN.

Duplicate samples of field treated oranges were analyzed by both methods. Residues of HCB were <0.003 ppm in both samples, levels of chlorothalonil were 0.01 ppm in both samples; levels of PCBN were 0.008 ppm by the surface extraction method and 0.019 ppm by the maceration method. Only one set of analyses are reported.

Because of the extremely low levels of chlorothalonil present in these samples, the study is not adequate to conclude that the surface extraction method is measuring the total residue of chlorothalonil or of HCB and PCBN.

The petitioner should run a comparison study for surface extraction versus maceration using citrus samples having significant levels (1 ppm or more) of weathered chlorothalonil residues. Should this study show that surface extraction does not detect residue levels with an efficiency equivalent to the maceration method, methodology which employs maceration of whole fruit will be required. HCB and PCBN determinations should be included in this study.

Methodology for determining the 4-hydroxy metabolite in whole fruit should be submitted. While we acknowledge that levels of this metabolite are likely to be quite low, methodology is readily available and the tolerance regulation is established in terms of combined residues of the two compounds.

A successful MTO was conducted on the analytical method for 4-hydroxy chlorothalonil for meat and milk in connection with PP#2F1230 (memo of B. Puma 6/27/72). Recoveries at fortification levels of 0.2 - 0.4 ppm were 61 - 76% for milk and 65 - 72% for beef kidney.

We conclude that acceptable analytical methodology is not available for enforcement of the proposed tolerance on citrus fruit. The methods used for the various processing fractions are acceptable for both parent and metabolites.

Available analytical methodology for meat and milk is adequate.

Residue Data

Three residue studies done in Florida are submitted and an additional study (also in Fla.) is available in PP#0F2405. Two varieties of oranges and two varieties of grapefruit were treated once with PHI's of up to 262 days. The 4-OH metabolite was not analyzed for.

Temple oranges were treated at 3.68, 5.72 and 7.28 lb active/A in 250-500 gal. per acre. From 1 application at 1x maximum dose rate, maximum residues were 6.02 ppm at 0 days PHI, 5.48 ppm at 7 days PHI, 2.04 ppm at 14 days, 1.48 ppm at 21 days and <0.01 ppm at 230 days. Immature green Valencia oranges treated once at 3.75, 5.25 (0.92x) and 7.5 (1.31x) lb active/A (using 6F formulation) in 250 or 500 gal per acre had residue levels of 3.52 ppm at 0 days PHI, 1.67 ppm at 7 days and 0.15 ppm at 30 days from the 5.25 lb a.i./A rate and from the 7.5 lb a.i./A rate, 6.36, 2.61 and 0.43 ppm at 0,7 and 30 days, respectively. Mature oranges had residue levels of 4.96, 2.91, 0.64 and 0.02 ppm at 0, 7, 30 and 262 days PHI from the 5.25 lb a.i./A rate, and 7.11, 5.23, 0.71 and 0.05 ppm at 0, 7, 30 and 262 days PHI from treatment at the 7.5 lb a.i./A rate. Mature oranges treated with 22.5 lb a.i./A (3.93x) in 2000 gal/A had residue levels of 5.7 ppm at 0 days PHI, 2.86 ppm at 7 days, 0.64 ppm at 30 days and 0.02 ppm at 262 days PHI. Valencias are a variety of orange which would have nearly mature fruit on the trees during the blooming period.

Ruby Red grapefruit were treated with either 3.68, 5.72 or 7.28 lb a.i./A in 250-500 gal per acre. At the 1x rate (5.72 lb/A), residue levels were 4.22 ppm at 0 days PHI, 1.09 ppm at 7 days, 0.49 ppm at 14 days, 0.15 ppm at 21 days and 0.03 ppm at 138 days PHI.

Marsh grapefruit were treated with the 6F formulation at 3.75, 5.25 and 7.5 pounds active per acre in 250-500 gal per acre or 19.5 lb active/A in 1740 gal per acre. Residue levels were 4.64, 2.46 and 0.04 ppm at 0, 7 and 201 days PHI from the 0.92x rate (5.25 lb), and 4.18, 2.75 and 0.03 ppm at 0, 7 and 201 days PHI at the 1.3x rate (7.5 lb). At the 3.4x rate (19.5 lbs in dilute spray), residues levels were 3.96, 2.0 and 0.06 ppm at 0, 7 and 201 days PHI, respectively.

None of the residue data reflect multiple applications, while at least 2 applications are recommended on the label and up to 5 applications are proposed for the accompanying Experimental Use Permit. Additionally, the proposed 100 day PHI is considered impractical. At present, we can only conclude that the proposed tolerance of 0.1 ppm on citrus is not adequate. Residue data reflecting the maximum number of applications at the maximum proposed rate will be required. Also, pending the method comparison study requested in the Analytical Methods section, we are unable to make a conclusion regarding the validity of the available residue data.

Residue data (as well as appropriate analytical methodology) for the 4-hydroxy metabolite in whole fruit will be required, since we expect considerably higher residue levels with the shorter PHI requested.

Also, petitioner should be advised that for any permanent tolerance on citrus, residue data from all major growing areas will be required. The available data from Florida do not constitute adequate geographical representation.

If the proposed use is only for oranges and grapefruit, we consider the tolerance request for citrus to be inappropriate. The EUP indicates that all citrus varieties will be treated. If the EUP is only for oranges and grapefruit, the proposed temporary tolerance should be so worded.

Processing studies are submitted for oranges, grapefruit, lemons and limes. Washed whole fruit were processed, and the following fractions were analyzed: unwashed fruit, washed fruit, prewash water, chopped peel, peel frits, peel liquor, molasses, dry pulp and peel, emulsion water, oil and juice. Washing removes 50% or more of the initial residues on citrus. On other crops, the % removal by washing is more variable.

No concentration of residues of parent was observed from any washed fruit into any fraction except the oil. Concentration of chlorthalonil residues up to 137X residues in washed fruit was reported in the oil. However the r.a.c is unwashed fruit. Maximum concentration in oil compared to unwashed fruit was up to ca. 30-40X(limes).

Residue levels of the 4-hydroxy metabolite are reported for all commodities except the whole fruit. However, except for the oil, residues of parent plus metabolite in the processing commodities are less than residues of parent on the r.a.c. (using surface extraction which, in this instance, represents a "worst case" comparison). Thus we consider the submitted processing study to be acceptable, and we conclude that residues only concentrate in the oil.

Because the appropriate tolerance level for oranges and grapefruit is not established we are unable to conclude that the proposed 10.0 ppm temporary food additive tolerance for citrus oil is adequate.

Meat, Milk, Poultry and Eggs

In the feeding study evaluated in PP#1F1024, the petitioner fed lactating cows a mixture of chlorothalonil and its hydroxy metabolite in a ratio of 125:1 at levels of 25, 75 and 250 ppm parent compound. Since residues in meat and milk were comprised solely of the hydroxy metabolite, we were unable to make any a priori conclusions as to the transfer of residues of the parent compound to meat and milk.

In PP#2F1230, there is presented an additional study wherein one cow was fed the parent compound at 250 ppm, a second cow was fed 2 ppm of the hydroxy metabolite and a third served as a control. The two cows were fed the chemicals for 44 days with milk samples taken at intervals of 2 to 6 days (average 3.1 days) and during a 15-day withdrawal period.

The second milk-out study shows that the parent compound has relatively little tendency to transfer to milk -- 0.2% of the ingested fungicide appeared in the milk as the hydroxy metabolite. Maximum residues of 1.3 ppm appeared in the milk as a result of ingesting 250 ppm in the daily ration. The results for feeding of the parent compound are in strong contrast to those for the hydroxy metabolite -- the transfer rate for the metabolite is over 100X that for the parent. From a daily feeding of 2.0 ppm of hydroxy-chlorothalonil, maximum residues of 1.54 ppm of the hydroxy metabolite are reported in the milk.

There is no particular pattern to the reported residues--however, a plateau was reached at 18 to 26 days from the feeding of each compound. During the first week of the withdrawal periods, there was little decline in residue levels in milk. Detectable residues were found in the last milk-out sample taken (15 days after last feeding).

The proposed feed uses of chlorothalonil-treated crops are categorized in Section 180.6(a)(2) since the hydroxy metabolite (even though a minor component of the residues) transfers to milk and meat even at very low levels (i.e., <0.1 ppm in the diet).

Cull citrus, cannery wastes, and various of the processing fractions (e.g., dried pulp, molasses) are livestock feed items, and may comprise up to 30% of the animal's diet.

As discussed in the Residue Data section, residues in washed oranges and their feed by-products were shown to be less than the initial residue in unwashed fruit.

In the absence of an appropriate tolerance level for citrus, we are unable to reach a final conclusion regarding residues in meat and milk.

Since neither oranges nor their by-products are items of poultry feed, we classify the proposed use within 40 CFR 180.6 (a)(3) with respect to secondary residues in poultry tissues and eggs.

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL Chlorothalonil PETITION NO 0F2405

CCPR NO. 81

Codex Status

[ ] No Codex Proposal Step 6 or above

Proposed U. S. Tolerances

Residue (if Step 9): Combined residues of Chlorothalonil & 4-hydroxy-2,5,6-trichloro-1,3-benzene dicarbonitrile, expressed as chlorothalonil

Crop(s)	Limit (mg/kg)	
citrus fruit	5 mg/kg	Step 8

(all MRLs provisional until 1981)
(temporary ADI)

Residue: 2,4,5,6-tetrachloroisophthalonitrile
~~4-hydroxy-2,5,6-trichloroisophthalonitrile~~

Crop(s)	Tol. (ppm)
oranges	0.1 ppm
grapefruit	0.1 ppm
citrus oil	10 ppm

CANADIAN LIMIT

Residue: Chlorothalonil

Crop	Limit (ppm)
none on these commodities	

MEXICAN TOLERANCIA

Residue: Chlorothalonil

Crop	Tolerancia (ppm)
none on these commodities	

Notes:

To: L. Bradley Date: 10/29/80

Petition No.: 1G2428 is assigned to you for review.

Chemical: Chlorothalonil

Commodity: citrus?

60 DDL: 12/1/80

90 DDL: 12/31/80

Please submit your completed review to me by the 60 DDL.

R. J. Hummel