RENey:SFHoward:ph:7-19-72

Evaluation for Registration for Chlorothalonil
(2,4,5,6-tetrachloroisophthalonitrile) (Daconil)
P.P.No. 2F1230
Submitted by Diamond Shamrock Chemical Corp.
Date Recd. January 7, 1972
Date Filed January 24, 1972

I. Introduction

1A Other petition 7F0599, 9F0743 and 1F1024

1B See P.P. No. 1F1024 - Evaluation of Environmental Data by Frank Sanders, 7/15/71; Reevaluation No. 2 and No. 3 by R. Ney, Dated 7/27/72 and 8/6/72.

2. This proposal is an application for Amended Registration of Bravo W-75 (Daconil) P.P. No. 2F1230

3. The Diamond Shamrock Company is proposing tolerances for the combined residues of chlorothalonil (Daconil 2787) and its metabolite (DAC 3701) (4-hydroxy-2,5,6-trichloroisophthalonitrile) at:

50 ppm in or on lima and snap bean vines
20 ppm in or on peanut vine hay, sugar beet tops and sweet corn forage
15 ppm in or on lima beans
0.2 ppm in meat, fat and meat by products of cattle, goats, hogs, horses and sheep and milk and sugarbeets.

Note: On June 14, 1972 PTD suggested the following:

	Proposed Tol.	PTD
Bean Vines	50 ppm	100 ppm or increase PHI from 7 to 14 days
Beans Snap	5 ppm	15 ppm
Meat & Milk	0.1 ppm	1 ppm
Sugarbeets	0.2 ppm	0.3 ppm
Peanuts	0.3 ppm	0.3 ppm (to include peanut hulls)

Note: On August 23, 1972 Diamond made the following label changes (677-287) (677-313)

Cucumbers - Limiting claim on target spot to Florida only.
Tomato - Deleting claim for target spot control.

4. Product

Bravo™ W-75 (wettable powder containing 75% tetrachloroiso--phthalonitrile)

Active ingredient:

Tetrachloroisophthalonitrile

Inert ingredient:

[redacted]

Total 100.0%

5. Metabolite

4-hydroxy-2,5,6-trichloroisophthalonitrile

6. The average analysis of technical chlorothalonil and the range of variation:

Tetrachloroisophthalonitrile 97.6

[redacted]

Totals 100.3

Conclusion:

Chemical Identity - The carbon composition of the empirical formula for the parent compound (tetrachloroisophthalonitrile) is incomplete by two carbon atoms.

II. Direction For Use

1. Bean (Snap): Use 3 lbs per acre (2.25 lbs A/A) in sufficient water to obtain adequate coverage. Begin applications during early bloom stage or when disease first threatens and repeat at weekly intervals or as necessary to maintain control. Do not apply within 7 days of harvest.

2. Bean (Lima): Same as for Bean (Snap) except that the dosage is 2 lbs. per acre (1.5 lbs A/A). Apply at 7 day intervals. PHI 7 days.

3. Corn (Sweet): Same as above except that the dose rate is 1 1/2 - 2 lbs. per acre (1.125 to 1.5 lbs A/A) and the pre-harvest interval is 14 days.

4. Peanuts: Use 1 - 1 1/2 lbs. per acre (0.75 to 1.125 lbs A/A). Apply Bravo W-75 in sufficient water to obtain adequate coverage. Start applications when disease first appears and repeat at 10 to 14 day intervals or as necessary to maintain control. Under severe disease conditions, use the 1 1/2 lbs. per acre rate. Do not apply within 14 days of harvest.

5. Sugar Beet: Direction use is same as for peanut. The dosage is 1 1/2 - 2 lbs. per acre (1.125 to 1.5 lbs A/A). Under severe disease conditions use 2 lbs. per acre rate. The pre-harvest interval is 10-14 days dependent upon the dose rate used.

6. Sprays in 20 to 150 gal H_2O/A for dilute sprays in and 5 to 10 gal H_2O/A for concentrate sprays.

III. Discussion of Data

1. Residue Data - Beans

A.

LIMA BEANS

Rate lbs W-75/A	Number Applications	Days from Application to harvest	Residue Range ppm
Beans only			
0	0	-	.00 - .16
1.5	10	0	.20 - .39
2.0	7	0	.00 - .05
	7	15	.00 - .13
Pod and Bean (surface extracted)			
0	0	-	.00 - .01
2.0	13	0	10.1 - 12.9

(CONTINUED)

LIMA BEANS (CONTINUED)

Rate lbs W-75/A	Number Applications	Days from Application to harvest	Residue Range ppm
Plants only			
0	0	-	.05 - 79.2
1.5	10	0	218 - 535
2.0	7	15	22.0 - 60.5

Conclusions

Residues Data: Lima Beans

1. One control blank value is unreasonably high in relation to the residue values reported for treated lima beans - 40% of the highest residue value reported. Of six blank determinations, two values ranged from 15.4 - 40%. The mean residue value reported for the control was 0.05 ppm.

2. Explanation is needed for the following:

   Number of applications (10); days from Application to Harvest (0). Although obtained data appear not to be in accordance with the direction for use with respect to preharvest interval, residue values are low.

B. Pod and Bean (surface extracted) - Conclusions:

   1. Explanation as in 2 above is needed.

C. Plants only: Conclusions:

   1. Blank values are unreasonably high in relation to the reported residue values.

   2. Data do not support time interval from last application to harvest.

   3. Significant residues appear to result on bean plants when chlorothalonil is used as directed.

D.

SUMMARY OF SUPPLEMENTAL RESIDUE DATA FOR DACONIL-2787
and its Metabolite 4-Hydroxy-2,5,6-trichloroisophthalonitrile (DAC-3701)

Rate lbs W-75/A	Number Applications	Days from Application to Harvest	Residue Range ppm
DACONIL-2787 - Lima Bean (vines)			
0	Check	-	.00 - .80
2.0	4	3	46.8 - 68.0
2.0	13	0	93.0 - 310.0
DAC-3701 - Lima Beans and Pods			
0	Check	-	.32 - .46
2.0	4	3	.80 - 1.12

*Not corrected for apparent residue in non-treated samples.

RECOVERY DATA

	ppm Added	Range ppm Recovered	% Recovery
DACONIL-2787			
Lima Beans	1.0	.87 - .98	93
DAC-3701			
Lima Beans	1.0	1.03 - 1.19	110

Conclusions:

Daconil - Lima Bean (vines)

1. Blank values are unreasonably high in relation to reported residue values.

2. Data do not adequately support the recommended time interval from last application to harvest.

3. Significant residues appear to result from the recommended use pattern.

Note: Residue values "Not corrected for apparent residue in non-treated samples."

Is the petitioner implying that Daconil-2787 and its metabolite, DAC-3701, are endogenous to lima bean vines? We need definitive chemical techniques to confirm this implication.

4. The indefinite volume of H_2O used with Daconil formulation (20-150 gallons per acre for dilute sprays and 5-10 gallons per acre for concentrate sprays) relative to the maturity of the crop may cause application rates greater than the recommended rates. Data are needed on the minimum and maximum number of gallons per acre.

5. Table on page 17 - Residue Data

   Discrepancies between residue data from major growing areas are too inconclusive to permit adequate evaluation.

   Some of the data are not supported by recovery studies. Other data are supported by inadequate recovery studies. Combined residues of Daconil and the 4-hydroxy metabolite on lima bean vine from Jackson, Tenn. are significantly high, even though residues are supported by adequate recovery data. Daconil residues on lima bean vines from Davis, Calif. are very high, varying from 93 ppm to 310 ppm with a mean value of 167 ppm. They are supported by adequate recovery studies.

E. Peanut Hay Data

SUMMARY OF SUPPLEMENTAL RESIDUE DATA FOR DACONIL-2787
and its Metabolite 4-Hydroxy-2,5,6-trichloroisophthalonitrile (DAC-3701)

Rate lbs W-75/A	Number Applications	Days from Application to Harvest	Residue Range ppm
DACONIL-2787 - Peanut Hay			
0	0	-	.00 - .09
1.5	5	4	85.0 - 96.0
1.5	5	18	12.6 - 14.0
1.5	11	4	19.4 - 23.1
1.5	11	7	5.04 - 5.88
1.5	4	16	.26 - 1.13
1.5	6	31-33	.00 - 4.37
1.5	4-6-11	45-68	.00 - 1.97
DAC-3701 - Peanut Hay			
0	0	-	.00 - .29
1.5	4-6	31-55	.00 - .58
1.5	11	4-45	.00 - .09

*Not corrected for apparent residue in non-treated samples.

RECOVERY DATA

	ppm Added	Range ppm Recovered	% Recovery
DACONIL-2787			
Peanut	1.0	.86 - 1.24	107
Hay	5.0	4.33 - 6.3	114
DAC-3701			
Peanut	0.2	.18 - 21.0	95
Hay	1.0	.84 - .96	88

Conclusions:

1. Insufficient data submitted to support the 10 to 14 day preharvest interval; preharvest intervals are either shorter or longer than the recommended 10 to 14 day PHI.

2. We need definitive test to support the petitioner implication for apparent residues in non-treated samples. Residue values were not correct for blank values.

3. Insufficient data to determine a residue decline curve.

4. Insufficient data to determine if residues will be insignificant at end of preharvest interval.

5. Data are needed on the minimum and maximum number of gallons per acre used which correspond with the maturity of the crop.

6. Data appear to reflect that when the PHI is short the parent residue is high and the metabolite residue is low. Conversely, the longer the PHI the higher the metabolite and lower parent residues.

F. Sugar Beets

Recoveries of Daconil 2787 and its metabolite DAC-3701 were done on sugar beet tops. They appear to be adequate as indicated below.

RECOVERY DATA

	ppm Added	Range ppm Recovered	% Recovery
DACONIL 2787 Sugar beets (tops only)	.40	.32 - .51	108
DAC-3701 Sugar beets (tops only)	.50	.32 - .47	76

Residue Data

Samples from treated plots were obtained from five sources. Geographical representations are considered adequate. Applications rates were varied between the proposed rate and 2 1/2 times this rate. Samples were done at 14 days interval and up to 59 days from date of application. In all cases the residue found was less than the proposed combined tolerance for Daconil and the 4-hydroxy metabolite.

Rate lbs W-75/A	Number Applications	Days from Application to Harvest	Residue Range ppm	Mean Residue ppm
DACONIL 2787 - Sugar beets (tops only)				
0	Check	-	.00- .10	.02
2.0	5	14	7.8 -17.3	10.7
2.0	4	28	.97- 3.37	1.84
2.0	6	41	.52- 2.09	.88
3.0	3	25	4.74- 6.25	5.65
3.0	4	59	.24- 3.0	1.19
DAC-3701 - Sugar beets (tops only)				
0	Check	-	.00	.00
3.0	3	25	.00	.00

Conclusion:

1. Residue data appear to be adequate for Daconil 2787 on sugar beets (top only); however, the recommended PHI should have been supported with additional data. For DAC-3701, no residues were reported for a 2 pre-harvest interval of 25 days. We need additional data to support the 14 day PHI.

G. Sweet Corn Forage

Data submitted by the petitioner are for Sweet Corn (Kernels plus Cob with Husk Removed) and Husk only. This data are inadequate. The proposal is for residues on corn forage. The petitioner defines forage as the whole corn plants cut six to eight inches above ground level which is chopped and packed into air-tight silos.

IV. Supplementary Milk and Meat Study

Background:

Portions of this data were evaluated October 20, 1970, in PP No. 1F1024 and again in the same petition, July 15, 1971. Some of the conclusions of those evaluations are reiterated here: (a) No significant DAC-2787 residues were detected in milk or tissue after 30 days of feeding at levels of 25 to 250 ppm (b) DAC-3701 (the 4-hydroxy metabolite) residues were found in milk and tissue after 30 days of feeding at levels of 25 to 250 ppm; insignificant residues of DAC-3701 were detected, however, after a withdrawal period of 21 days and (c) Feeding of DAC-3701 at levels of 0.2, 0.6 and 2.0 ppm for 30 days results in residue in both milk and tissues.

In the formal review of PP No. 1F1024 the petitioner was asked whether the residue of the metabolite (DAC-3701) in milk was the result of feeding the 4-hydroxy metabolite or was the result of chlorothalonil being metabolized to the 4-hydroxy metabolite. Since both the parent compound and the metabolite were fed together, the question could not be answered from data of the original feed study. Also, data from two sacrifice intervals between zero day and 30 day was requested. The above questions were to be answered in this Admended Petition.

To determine whether the feeding of chlorothalonil would result in residue of the 4-hydroxy metabolite in milk, a limited study was conducted. Three lactating cows were used in the study: one served as control, the second received 250 ppm chlorothalonil and the third received 2.0 ppm of the 4-hydroxy metabolite in their daily diet. Milk samples were collected and analyzed using the same GLC method as before, but with an EC detector.

The results of the limited study reflected that no residues of chlorothalonil could be detected in milk after 30 days of feeding at 250 ppm. This observation supports the "no significant residue of chlorothalonil" conclusion of the previous review. Significant residues of the 4-hydroxy metabolite were detected in milk of both

the Daconil fed cow and the cow fed the 4-hydroxy metabolite. For the chlorothalonil fed cow, values of the metabolite in milk ranged from 0.05 to 1.30 ppm in 44 days, with peak value occurring in about 8 days. For the metabolite fed cow residues of the metabolite in milk varied from 0.05 to 1.54 in 44 days. The plateau value occurred in about 20 days. During the withdrawal period, residues of the 4-hydroxy metabolite in milk declined from 0.60 - 0.19 in 15 days for the chlorothalonil fed cow and decline from 1.30 to 0.32 for the metabolite fed cow.

Conclusions:

1. The recovery study for chlorothalonil in milk is inadequate because of the 51% range between values for samples fortified at the same level.

2. Study for residues in milk is too limited. Study should have included at least six cows - two controls and duplicates for chlorothalonil and 4-hydroxy metabolite fed cows. As the data stand, no basis of comparison can be made between parallel determinations. Conclusions based on a single determination on one species of cow can be misleading.

3. What is done with the milk produced while the cows are on treated feed?

Residue in Tissue Samples

The two test animals used in the milk study were sacrificed on the 15th day of the withdrawal period. Samples of muscle, fat, liver and kidney were analyzed for residues of chlorothalonil and the 4-hydroxy metabolite. The results are reported in the table below:

TABLE VI

Residue of Chlorothalonil and its Metabolite In Tissue Samples

	Chlorothalonil			4-Hydroxy-2,5,6-trichloro-isophthalonitrile		
	Control	T-1	T-2	Control	T-1(1)	T-2(2)
Liver	.05	.05	.05	.05	.05	0.1
Kidney	.05	.05	.05	.05	0.7	1.2
Muscle	.05	.05	.05	.05	.05	.05
Fat	.05	.05	.05	.05	.05	.05

(1) Received 250 ppm chlorothalonil in daily diet for 44 days.
(2) Received 2.0 ppm 4-hydroxy-2,5,6-trichloroisophthalonitrile for 44 days.

The data show that no residue of chlorothalonil or its 4-hydroxy metabolite was detectable above that found in the control (0.05 ppm) in the muscle and fat of either test animal. Residues of 0.7 and 1.2 ppm of the 4-hydroxy metabolite were detectable in the kidney of the chlorothalonil and DAC-3701 fed cows respectively. One tenth ppm (0.1 ppm) of the 4-hydroxy metabolite was found in the liver of the DAC-3701 fed cow.

Conclusions:

1. Data are not supported by adequate recovery studies for chlorothalonil and the 4-hydroxy metabolite in tissues.

2. See conclusion 2 above for Chlorothalonil in milk.

V. The Disappearance of Chlorothalonil During Ensiling of Treated Forage

1. Use pattern for chlorothalonil results in residue of the fungicide on treated plants at the time of harvest. Since some plants forage are used in the production of silage, a study to determine the stability of Daconil during ensilaging was conducted.

   A series of chopped treated corn plants weighing 200 grams were packed into 32 ounce jars. After incubation at 27°C for various periods, duplicate samples were analyzed for their chlorothalonil and 4-hydroxy metabolite contents.

   Acid hydrolysis studies at different temperatures and time intervals were also undertaken; to assure that the degradation products of Daconil formed during the ensilaging process were not the 4-hydroxy metabolite.

2. Analytical Method

   See PP-1F1024, Section D, evaluation of the analytical method. Because tolerances has been established for Daconil and its metabolite on or in potatoes, it is, therefore, concluded that the analytical method is capable of determining residue in treated forage. However the method appears to give rise to "false positive" values for some crops - high blank values.

3. Results of the analysis of treated forage for residue of Daconil before and during ensilaging process appear to be adequate as indicated in the Table below: (Page 48).

Table I

Days Stored	Chlorothalonil Residue PPM A DCM		Chlorothalonil Residue PPM B Acidified Acetone		Mean	DAC-3701 Residue PPM
0	28.0	27.6	33.1	29.0	29.6	N.D.
7	11.0	11.3	9.0	9.0	10.0	0.5
12	3.9	4.8	5.3	5.3	4.8	-
18	3.0	3.0	2.3	2.4	2.8	-
24	3.2	2.2	2.2	-	2.2	0.5
40	2.8	-	2.8		2.8	-

Residue of chlorothalonil appears to decline during the ensilage process. The observed half-life is approximately four days over the period of 0 to 18 days. Residue decline from 30 ppm to less than 3 ppm in 18 days and remained at this level over the next 22 days of the study.

The decline of Daconil did not appear to result in the production of the 4-hydroxy metabolite nor products which could be converted to the 4-hydroxy metabolite by exhaustive acid hydrolysis within the temperature limits used in the experiments - 25 to 80°C.

Conclusions:

1. If the acid hydrolysis breakdown products of chlorothalonil are not the 4-hydroxy metabolite, then what are the breakdown or reaction products?

2. What other degradation or conversion products will the analytical method detect and determine other than the 4-hydroxy metabolite and the predicted 4-amino metabolite.

3. What are the aerobic and anaerobic organisms conversion products produced in the fermentation process in the production of silage. Will the analytical method determine these products?

VI. Reinvestigation of the Degradation of Chlorothalonil by Bovine Rumen Fluid

This study reinvestigated bovine rumen fluid conversion of chlorothalonil to the 4-hydroxy metabolite in addition to other unidentified metabolites

in the water soluble fraction of rumen fluid extract. Both normal and C^{14} labelled chlorothalonil (uniformly labelled in the benzene ring) were used in the experiments.

Results of this study showed that most of the rumen fluid converted chlorothalonil appeared as water soluble products. Basic hydrolysis of the water soluble fraction was more effective than acid hydrolysis to cause release or conversion of water soluble components to the 4-hydroxy metabolite. The hydrolytic conversion to the 4-hydroxy metabolite, however, was not significant when compared to the remainder of unidentified water soluble components.

A half life ($t_{1/2}$) of about 3.5 hours was required for Daconil decline over the first several hours of rumen fluid incubation with either normal or labelled compound. After 20 hours of incubation with rumen fluid, more than 90% of Daconil (input at 20 ppm) was consumed and about 4-5% converted to the 4-hydroxy metabolite (about .87 ppm actual). The consumed material (about 77%) appeared in the H_2O soluble fraction.

Significant findings of this study appeared to be the confirmation of chlorothalonil conversion to the 4-hydroxy metabolite by bovine rumen fluid and the observation that most of the converted chlorothalonil products were in the water soluble fraction. This probably means that a considerable amount of metabolized Daconil may be excreted in the urine or feces. This seems reasonable, since most residues in meat tissue were found in the kidney.

IV. Conclusions:

The conclusions show data to be either insufficient or inadequate to support registration of Daconil for use on the listed crops. The conclusions should be considered objections to registration.

V. Recommendation

A. Object to registration for the following reasons:

I. To support the proposed use the following information is needed on the residue data.

Lima Beans

1. Insufficient number of samples treated and harvested in accordance with labeling directions.

2. Explanation is needed for the following: Number of applications (ten); days from application to harvest (zero).

Pod and bean

1. Explanation is needed for the following: Number of applications (13); days from application to harvest (zero).

Plants Only

1. Blank values are unreasonably high in relation to the reported residue values. A control would be required to correct residues.

2. Data do not support time interval from last application to harvest.

Lima bean (vines)

1. Data do not adequately support the recommended time interval from last application to harvest.

2. Note: Residue values "not corrected for apparent residue in non-treated samples."

   We would need definitive chemical techniques to confirm the implication that Daconil is endogenous to lima bean vines.

3. Discrepancies between residue data from major growing areas are too inconclusive to permit adequate comparative evaluation.

Peanut Hay

1. Insufficient data submitted to support the 10 to 14 day preharvest interval; preharvest intervals are either shorter or longer than the recommended PHI.

2. Data do not permit an evaluation of residues decline.

3. See Note above for lima bean vines.

II. The Disappearance of Chlorothalonil During Ensiling of Treated Forage.

1. Other than the 4-hydroxy metabolite, the acid hydrolysis products of Chlorothalonil have not been identified.

2. What other degradation or conversion products will the analytical method detect and determine other than the 4-hydroxy metabolite and the predicted 4-amino metabolite.

3. Data is inconclusive as to the aerobic and anaerobic organisms conversion products produced in the fermentation process in the production of silage. If there is a decline in chlorothalonil during the ensiling of treated forage there has to be degradation or conversion products.

III. There is no way to tell if crops were treated with dilute sprays or concentrated sprays. Each application in the data must be supported by the number of gallons used per acre.

IV. In order to evaluate the data we need rainfall accumulation data up to each sampling. Soil type in each of residue sampling areas should be submitted.