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

MAY 27 1987

EXPEDITE

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 010501 - Dicofol
Rohm and Haas Response to Registration Standard
Metabolism, Methodology, and Residue Data
EPA File Symbol 707-ENE
[MRID Nos. 400420-01 to -31, RCB No. 1869]

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THRU: Charles L. Trichilo, Chief
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This review is being expedited at the request of E. Tinsworth, Director, Registration Division (see E. Tinsworth memo of 1/28/87). The expedite request includes review of plant and animal metabolism, analytical methods, and screening of residue data for residues reported on the day of application. These residue data were needed for the use of EEB in their review. The expedited due date is 5/27/87. Other data, including residue data on other crops, storage stability data, processing data, and animal feeding studies were not reviewed. Review of the balance of the studies will follow when requested by the Product Manager.

Rohm and Haas Company submits their response to the Dicofol Registration Standard (issued 12/30/83), consisting of Plant and Animal Metabolism data, Analytical Methodology, Residue Data, Storage Stability Data, Processing data, and Animal Feeding Studies. The following data have been submitted:

MRID NO.	STUDY TITLE AND REPORT NO.
400420-01	Determination of the Octanol/Water Coefficient of 14C-p,p'-Dicofol, Rohm and Haas Technical Report No. 310-86-36, A. M. Tillman (Rohm and Haas) and D. Teeter (Analytical Bio-Chemistry Laboratories), June 9, 1986.
400420-02	Determination of the Octanol/Water Coefficient of 14C-o,p'-Dicofol Rohm and Haas Technical Report No. 310-86-37, A. M. Tillman (Rohm and Haas) and D. Teeter (Analytical Bio-Chemistry Laboratories), June 9, 1986.
400420-03	A Metabolism Study of 14C-Dicofol in Grapefruit, Rohm and Haas Technical Report No. 31L-85-25, A. M. Tillman, October, 1986.
400420-04	Metabolism of 14C-p,p'-Dicofol in Cotton-seeds, Rohm and Haas Technical Report No. 310-86-69, A. M. Tillman, November 15, 1986.
400420-05	Metabolism of 14C-o,p'-Dicofol in Cotton-seeds, Rohm and Haas Technical Report No. 310-85-70, A. M. Tillman, November 15, 1986.
400420-06	Dicofol - Nature of the Residue in Lactating Dairy Goats, Rohm and Haas Technical Report No. 310-86-61, F. W. Deckert (Rohm and Haas) and L. Predmore and M. Williams (Analytical Bio-Chemistry Laboratories), April, 1986.
400420-07	Dicofol - Nature of the Residue in Laying Hens, Rohm and Haas Technical Report No 310-86-68, F. W. Deckert (Rohm and Haas), C.E. Jameson and S.R. Shaffer (Analytical Bio-Chemistry Laboratories), April, 1986.
400420-08	A Residue Analytical Method for p,p'-Dicofol and o,p'-Dicofol, Rohm and Haas Technical Report No. 310-86-74, C. K. Hofmann, November, 1986.
400420-09	Interim Report On the Stability of o,p'-Dicofol in Cottonseed Products under Frozen Storage Conditions After 18 Months,

Rohm and Haas Technical Report No. 310-86-51, R. J. Pollock (Analytical Development Corporation) and C. K. Hofmann (Rohm and Haas), October, 1986.

400420-10 Interim Report on the Stability of o,p'-Dicofol in Cottonseed Products under Frozen Storage Conditions (10 Months), Rohm and Haas Technical Report No. 310-85-46, R. J. Pollock (Analytical Development Corporation) and C. K. Hofmann (Rohm and Haas), October, 1986.

400420-11 A Study on the Stability of Dicofol and its o,p' Isomer (o,p'-Dicofol) on Citrus in A Frozen Storage Environment: One Year Report, Rohm and Haas Technical Report No. 310-86-24, C. K. Hofmann (Rohm and Haas), July, 1986.

400420-12 Kelthane Residues in Citrus, Rohm and Haas Technical Report No. 31A-86-81, Lorna S. Mazza, 1986 (date not specified).

400420-13 Kelthane Residues in Citrus, Rohm and Haas Analytical Report No. 31A-86-85, Lorna S. Mazza, 1986 (date not specified).

400420-14 Kelthane Residues in Apples, Rohm and Haas Analytical Report No. 31A-86-68, Lorna S. Mazza, 1986 (date not specified).

400420-15 Kelthane Residues in Pears, Rohm and Haas Analytical Report No. 31A-86-79, Lorna S. Mazza, 1986 (date not specified).

400420-16 Kelthane Residues in Pears, Rohm and Haas Analytical Report No. 31A-86-87, Lorna S. Mazza, 1986 (date not specified).

400420-17 Kelthane Residues in Dry Beans, Rohm and Haas Analytical Report No. 31A-86-64, Lorna S. Mazza, 1986 (date not specified).

400420-18 Kelthane Residues in Melons, Rohm and Haas Analytical Report No. 31A-86-55, Lorna S. Mazza, 1986 (date not specified).

400420-19 Kelthane Residues in Melons, Rohm and Haas Analytical Report No. 31A-86-88, Lorna S. Mazza, 1986 (date not specified).

400420-20 Kelthane Residues in Cucumbers, Rohm and Haas Analytical Report No. 31A-86-86, Lorna S. Mazza, 1986 (date not specified).

400420-21 Kelthane Residues in Squash, Rohm and Haas Analytical Report No. 31A-86-89, Lorna S. Mazza, 1986 (date not specified).

400420-22 Kelthane Residues in Pecans, Rohm and Haas Analytical Report No. 31A-86-83, Lorna S. Mazza, 1986 (date not specified).

400420-23 Kelthane Residues in Walnuts, Rohm and Haas Analytical Report No. 31A-86-84, Lorna S. Mazza, 1986 (date not specified).

400420-24 Kelthane Residues in Grapes, Rohm and Haas Analytical Report No. 31A-86-90, Lorna S. Mazza, 1986 (date not specified).

400420-25 Kelthane Residues in Cottonseed, Rohm and Haas Analytical Report No. 31A-86-76, Lorna S. Mazza, 1986 (date not specified).

400420-26 Kelthane Residues in Processed Apple Haas Technical Report No. 31D-86-48, L. S. Mazza, 1986 (date not specified).

400420-27 Kelthane Residues in Processed Cotton Rohm and Haas Technical Report No. 310-86-42, L. S. Mazza, 1986 (date not specified).

400420-28 Kelthane Residues in Processed Grape Products Rohm and Haas Technical Report No. 310-86-66 L. S. Mazza, 1986 (date not specified).

400420-29 Kelthane Residues in Processed Citrus Products Rohm and Haas Technical Report No. 310-86-67 L. S. Mazza, 1986 (date not specified).

400420-30 A Feeding Study with Cows Dosed with Technical Kelthane - Preliminary Report on the Analysis of Tissue and Milk Samples, Rohm and Haas Technical Report No. 310-86-57, A. M. Tillman (Rohm and Haas), L. Predmore and S. Shaffer (Analytical Bio-Chemistry Laboratories), November, 1986.

400420-31 A Feeding Study with Hens Dosed with Technical Kelthane - Preliminary Report on the Analysis of Tissue and Egg Samples, Rohm and Haas Technical Report No. 310-86-

56, A. M. Tillman (Rohm and Haas), C. Jameson and S. Shaffer (Analytical Bio-Chemistry Laboratories), November, 1986.

001437-04 Carbon-14 Kelthane Residues in/on Dry Beans, Rohm and Haas Technical Report No. 34F-79-25, C. Parker, 1979 (included by reference, not previously reviewed by RCB)

Residue studies were not submitted for hops, spent hops, apricots, nectarines, peaches, caneberries, cherries, plum (fresh prunes), snap beans, lima beans (succulent), tomatoes, peppers, figs, field corn, alfalfa, clover, processed tomatoes, bean forage and hay or bean cannery waste, corn forage and fodder, cottonseed forage, and cotton gin trash. These studies are still needed.

Residue studies were not submitted for mint and strawberries. However, the Registration Standard concluded that additional residue studies were not needed for mint and strawberries, provided that plant metabolism studies show that dicofol, per se is the residue of concern.

TOLERANCES

Tolerances for dicofol [1,1-bis(p-chlorophenyl)-2,2,2-trichloroethanol] have been established (40 CFR 180.163) on a variety of crops. The tolerances are expressed in terms of dicofol, per se. No tolerances have been established on meat, milk, poultry, or eggs. No food or feed additive tolerances have been established.

Registration Standard Conclusions on Tolerances

A tolerance reassessment will be performed when the Registration Standard data deficiencies are resolved. If the requested additional residue data indicate the presence of residues of DDTr in or on raw agricultural commodities resulting from the registered uses of dicofol on these raw agricultural commodities, then residue tolerances for DDTr for these commodities may be required. Two uses, for alfalfa and clover seed crops, are designated as food uses of dicofol and require tolerances under the Federal Food Drug and Cosmetic Act.

Current Conclusions on Tolerance Reassessment

This submission does not resolve Registration Standard data deficiencies. Consequently, a tolerance reassessment cannot be made at this time.

REGISTERED USES

The registered uses of dicofol products and established tolerances are summarized below. Both dilute and concentrate sprays may be used. More detail can be found in the Registration Standard.

CROP	RATE(lb ai/A)	#APPLI-CATIONS	PHI (days)	TOLERANCE (ppm)	LIMITATIONS
Hops	0.52-1.5	1 or more	7	30	feeding restriction (Rohm and Haas) not practical
Mint Hay	0.65-1.2	1	30	25	feeding restriction - hay & spent hay not practical
Apricots, Nectarines, and Peaches	1.05-3.2	1 or more	14	10	30 day interval (Rohm and Haas)
Grapefruit, Kumquats, lemons, limes, oranges, and tangerines	1.6-8.0	1 or more	7	10	follow directions of State Ag. Experiment Station
apples, crabapples, pears, and quinces	1.0-4.0	1 - 2 (Rohm and Haas-1 or more)	7	5	one label-10-14 day intervals; one label-30 day intervals Rohm and Haas-7-10 day interval
blackberries, boysenberries, dewberries, loganberries, and raspberries	0.45-1.2	1 or more	2	5	
cherries	1.2-3.2	1 or more	7	5	30 days between applications
plums (prunes)	1.4-2.0	1 or more	7	5	30 days between applications

CROP	RATE(lb ai/A)	#APPLI-CATIONS	PHI (days)	TOLERANCE (ppm)	LIMITATIONS
beans (dry), snap beans and lima beans (succulent)	0.3-1.5	not listed	7-45	5	feeding restriction
cantaloupes, melons, muskmelons, and watermelons,	0.17-1.5	1 or more	2	5	
pumpkins, winter squash,and summer squash	0.17-1.5	1 or more	2	5	feeding restriction
cucumbers	0.3-1.5 0.3-0.7	1 or more 1 or more	21 2	5	
bushnuts, butternuts, chestnuts, hazelnuts, hickory nuts,pecans, walnuts, and filberts	1.6-4.0	1 or more	14	5	feeding restriction-husks
tomatoes	0.3-1.5 0.3-0.7	1 or more 1 or more	21 2	5	feeding restriction-(not practical)
eggplants, peppers, and pimentos	0.6-1.5	1 or more	2	5	
grapes	0.45-1.5	1 or more	7	5	
figs	1.4-2.0	1 or more	7	5	feeding restriction-husks (not needed)
strawberries	0.4-2.4	2-3	2	5	10-20 days between applications

CROP	RATE(lb ai/A)	#APPLI-CATIONS	PHI (days)	TOLERANCE (ppm)	LIMITATIONS
cottonseed	0.8-1.6	1 or more	14	0.1	feeding restriction - gin trash (not practical) some labels- feeding restriction- forage (not practical)
alfalfa, clover	1.0-1.5	1 or more	-	none	grown for seed feeding restriction (not practical)
field corn*	0.74-1.5	1 or more	45	none	Do not apply after ears begin to form; feeding restriction (not practical)

*No tolerance has been issued for dicofol residues on field corn. However, uses for dicofol on field corn appear on registered State labels, and 3.2% of the total pounds of dicofol is used on field corn (memo from Bruce A. Kapner, 1/27/84).

Note: Note that the current label restrictions for hops, mint hay, tomatoes, cottonseed, alfalfa and clover grown for seed, and field corn, current label feeding restrictions are not practical. Thus label changes and residue and processing data are needed on these commodities, since there is a possibility of transfer of residues to meat, milk, poultry, and eggs.

Registration Standard Labeling Requirements

The Registration Standard stated that label restrictions will depend on data yet to be submitted and that the Agency may, after review of data to be submitted in response to the Standard, require additional revision to current labels and may impose additional label requirements.

RCB Comments/Conclusions on Registered and Proposed Uses

The registrant should be reminded that all labeled uses must be supported by residue data or the labels amended to reflect the maximum use supported by residue data. Residue data must be submitted to support the maximum number of

applications allowed on the label, or the maximum number of applications allowed on the label must be changed to reflect the use supported by the submitted residue data. A a maximum number of applications per season or a maximum quantity of pesticide to be applied per season must be specified on the label. A minimum interval between applications must be added to the labels. Product labels must be changed to allow dilute sprays and ground application only or residue data must be submitted for both dilute and concentrate sprays, ground and aerial application, as allowed on product labels. Use directions for orchards must be changed to account for the variability in tree sizes. (Several options for orchard labeling are shown in Attachment 1). Grazing restrictions must also be added for orchards. Suggested language is "Do not allow livestock to graze in treated areas or feed on orchard cover crops." Alternatively, tolerances may be proposed for orchard cover crops and grazing allowed only on orchard cover crops for which tolerances have been established.

Product labels must be changed to allow use of formulations for which residue data have been received or residue data must be supplied for each type of formulation to be used, i.e., emulsifiable concentrate (EC), wettable concentrate (WP) or Flowable Concentrate, Granular, and Dust.

No residue data on an emulsifiable concentrate formulation were submitted for apples, pears, grapes, melons, cucumbers, or squash. Data are required for the emulsifiable concentrate formulation on these crops. Alternatively, these crops may be removed from labels for EC products.

No residue data from the use of a wettable powder or flowable formulation were submitted for citrus, dry beans, pecans, walnuts, and cottonseed. Residue data are required for the wettable powder or flowable formulation on these crops. Alternatively, these crops may be removed from proposed wettable powder or flowable formulation labels.

Residue studies were not submitted for mint and strawberries. However, the Registration Standard concluded that additional residue studies were not needed for mint and strawberries, provided that plant metabolism studies show that dicofol, per se is the residue of concern.

The volume of spray used in the residue field trials was not reported in the residue field trial reports. The volume of spray must be reported for each residue field trial. Residue data will support only the volume (dilute, concentrate, ULV) and type of application for which data were supplied. (Data on dilute applications support dilute

applications on the label; data on concentrate applications support concentrate applications on the label; etc.)

Comments on Specific Crops

These comments on specific crops are related to residue data included in this submission. The submitted residue data appear to support these uses. However, additional deficiencies in the residue data may be found when the residue data are reviewed in full. (Residue data were only screened for this review.)

Citrus. At the present time, residue data appear to support up to 3 ground applications of the emulsifiable concentrate at up to 6 lb ai/A. The volume of spray (dilute, concentrate, ULV) supported by the residue field trial data is not known.

Apples. Residues reported for three applications at 3 lb ai/A exceed the established tolerance. Registered labels allow only 2 applications. No more than two applications at no more than 3 lb ai/A appear to be supported at this time. Only ground applications appear to be supported. The volume of spray supported by the residue field trial data is not known.

Pears. Reported residues exceed the established tolerance at a 14 day PHI. The residue data submitted appear to support up to 3 ground applications at 3 lb ai/A and a 21 day PHI. The volume of spray supported by the residue field trial data is not known.

Grapes. Reported residues exceed the established tolerance. The residue data submitted appear to support up to two ground applications at 1.2 lb ai/A may be used with a 21 day PHI. The volume of spray supported by the residue field trial data is not known.

Dry Beans. Residues reported from aerial applications at 1.5 lb ai/A exceed the established tolerance. From the residue data submitted, it appears that up to two ground applications at 1.5 lb ai/A may be supported. The registrant should explain why residues are increasing with increasing PHI. The volume of spray supported by the residue field trial data is not known.

Other Crops. We have tabulated the rates and formulations used for developing residue data on other crops. The rates, PHI, and type of formulation used in these residue studies are tabulated below.

Crop	Formulation	Maximum Rate	PHI (days)
Melons	4F	3 x 0.6 lb ai/A	6
	or	2 x 1.13 lb ai/A	6
Cucumbers	4F	3 x 0.6 lb ai/A	2
Squash	4F	4 x 0.6 lb ai/A	2
Pecans	MF	2 x 2 lb ai/A	7
Walnuts	MF	2 x 2 lb ai/A	7
Cottonseeds	MF	2 x 1.5 lb ai/A	30

The maximum rates tabulated above are the maximum rates that appear to be supported, pending review of the submitted residue data. These data cannot support formulations of a different type than was used in the residue field trials. Only ground or hand applications were used in generating these data. Thus, data must be submitted for aerial applications or aerial applications should be prohibited on the labels.

Formulation

There are currently two registered end use products containing dicofol, both 4 lb/gal EC. Additionally, Rohm and Haas has several pending applications for new registration of end use products: Kelthane EC (4 lb/gal), Kelthane MF (4 lb/gal EC), Kelthane 4F (4 lb/gal flowable), and Kelthane 35 (35% WP).

Manufacturing Process and Impurities

Rohm and Haas and Makhteshim Agan have submitted manufacturing processes for their dicofol technicals. These manufacturing processes have been discussed in previous Product Chemistry Reviews. The manufacturing process was discussed in general terms in the Registration Standard (12/30/83) and in Sittig. Briefly, DDT is chlorinated, producing Cl-DDT. The Cl-DDT is hydrolyzed in acidic solution, producing dicofol. Dicofol contains a mixture of isomers, approximately 1:4 o,p' to p,p', approximately the same ratio as the ratio of isomers in the DDT starting material.

Dicofol products are known to contain DDT and related impurities, including DDE, DDD, and Cl-DDT. DDT related compounds are referred to as DDTr. The Dicofol Special Review was concluded with a cancellation notice (51 FR 19508, May 29, 1986), cancelling all dicofol products unless their registrations were amended to include an upper certified limit of no more than 2.5% DDTr in the technical product. This amendment had to be submitted by June 29,

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1986. By January 1, 1989, dicofol products may contain no more than 0.1 % DDTr in the technical.

PLANT METABOLISM

No adequate plant metabolism studies for dicofol had been submitted prior to the publication of the Registration Standard. Two metabolites had previously been reported in mint oil (see PP#6F0472), 4,4'-dichlorobenzophenone, and 4,4'-dichlorobenzhydrol (MRID No. 00004321). There is some evidence for conversion of dicofol to polar metabolites (MRID No. 05006528). These polar metabolites were not identified.

Registration Standard Data Gaps

The metabolic fate of dicofol in or on plants has not been adequately demonstrated. Further testing will be required using ^{14}C dicofol to identify the metabolites and/or degradation products in the final residue.

Current Submission

Three plant metabolism studies are included in this submission.

400420-03 A Metabolism Study of 14C-Dicofol in Grapefruit, Rohm and Haas Technical Report No. 31L-85-25, A. M. Tillman, October, 1985.

400420-04 Metabolism of 14C-p,p'-Dicofol in Cottonseeds, Rohm and Haas Technical Report No. 310-86-69, A. M. Tillman, November, 1986.

400420-05 Metabolism of 14C-o,p'-Dicofol in Cottonseeds, Rohm and Haas Technical Report No. 310-85-70, A. M. Tillman, November, 1986.

Another plant metabolism study was submitted earlier, but had not been reviewed to date.

001437-04 Carbon-14 Kelthane Residues in/on Dry Beans, Rohm and Haas Technical Report No. 34F-79-25, C. Parker, 1979 (included by reference, not previously reviewed by RCB)

Grapefruit Metabolism

A recent study of the metabolism of dicofol in grapefruit was described in the report, "A Metabolism Study of 14C-Dicofol in Grapefruit," Rohm and Haas Technical

Report No. 31L-85-25, A. M. Tillman, October, 1985. MRID No. 400420-03.

Texas Ruby Red grapefruit in Homestead, FL, were individually sprayed once with 14-C-UL-dicofol , diluted with unlabeled dicofol in December, 1984. An analysis of the 14-C-dicofol was provided. The dicofol was formulated as Kelthane MF, containing 4 lb ai/gal.

Rohm and Haas had previously determined that dicofol does not translocate. (Hofmann, C.K., Mar 15, 1985, Rohm and Haas Technical Report No. 31L-85-04, " 14-C-Dicofol Translocation Studies in Citrus Plants in a Greenhouse Environment.") A copy of this report was appended to the grapefruit metabolism study. 14-C dicofol, formulated as Kelthane MF, was applied to single leaves of orange seedlings and to soil surrounding orange seedlings. Plant and soil samples were taken at 0, 1, 2, 4, 8, and 12 weeks. The treated leaf was removed and the rest of the seedling (from 1 cm above the soil) was analyzed by Liquid Scintillation (LSC). Less than 1% of the dicofol was found to translocate from the treated leaf. Less than 0.05% of the soil applied dicofol was uptaken into the plant from the soil.

Grapefruit samples were collected 0, 1, 2, 3, 4, and 5 months after treatment. The samples were shipped by Federal Express at ambient temperatures and stored in the refrigerator at 5C for 1 to 5 days until processing. Samples were processed into peel, juice, pulp, and seed and stored in the refrigerator until analysis. Most samples were analyzed shortly after collection. However, some seed and juice samples were not analyzed until August to October, 1985 (up to 10 months after sampling). Long term storage was in a freezer (-15C). Climatological data from the National Climatic Data Center were submitted.

Juice was analyzed directly by LSC. Peel, seeds, and presumably pulp were analyzed by LSC. Greater than 98.7% of the radioactivity was found in the peel at all TSI's (treatment to sampling intervals). Less than 1.4% of radioactivity was found in the juice. Less than 0.6% of the radioactivity was found in the pulp. Only one seed sample had and detectable radioactivity (LOD = 5 ppb). This further reinforces the earlier conclusion that dicofol is non-systemic.

Characterization of residues in peels was attempted. Peel samples were extracted two times with acetone. The acetone extracts were combined. Residues not extracted by acetone were referred to as "bound residue."

The acetone extracts were further purified by partitioning into petroleum ether or ethyl acetate. Reverse Phase HPLC (C-18 column) was used for analysis with a Berthold radioactivity monitor in series with a UV detector (254 nm). For samples with TSI's less than one month, 94% or more of the extract was identified as dicofol. However, the chromatograms submitted are unreadable, and RCB is unable to confirm the identification. Up to 6% of the extract was unidentified polar compounds. Acetone extracts of samples with 5 month TSI's were reported as 82-85% dicofol, 14-15% polar compounds, and 0-5% DCBP. Again, the chromatograms were unreadable. The DCBP was assumed to be due to decomposition. The polar compounds were expected to be chlorohippuric acid, dichlorobenzophenone, chlorobenzoic acid or dichlorobenzilic acid. These standards were used along with autoradiography of the TLC plates used for the separation. However, the R_f of standards of these compounds did not match those of the unidentified polar compounds on TLC plates. The unidentified polar compounds were more polar than the four aforementioned standards.

Residues not extractable by acetone comprised 25-35% of the Total Radioactive Residue (TRR) in the peel, at a 5 month TSI. The peel residue after acetone extraction was further fractionated. The method used was a "classical fractionation" scheme designed to separate citrus peel into its carbohydrate components. This scheme was described by Braddock and Crandall (1981) and by Southgate (1969). Copies of these references were appended to the grapefruit metabolism report.

This fractionation scheme is shown in Figure 1. The residue after acetone extraction is extracted with hot methanol for 1 hour. The methanol supernatant would contain sugars. The residue after methanol extraction is extracted with hot water for 30 minutes. The water supernatant would contain starch. The residue after water extraction was refluxed with 5% H_2SO_4 for 2.5 hours. The supernatant would contain sugars from hemicellulose and pectin. The residue after refluxing with dilute acid was extracted with 72% H_2SO_4. The supernatant from this treatment would contain cellulose components. The residue after treatment with concentrated acid would contain lignin. The breakdown of radioactivity in each of these fractions is shown in Table 1. Rohm and Haas presented their figures only in terms of % of the fraction (acetone extract or residue after acetone extraction) and should have presented their figures in terms of the % TRR and ppm dicofol equivalents. We have calculated residues in these terms for Table 1.

Figure 1

Scheme 1

Fractionation Scheme for Partition of ^{14}C Peel Residues into Various Carbohydrate Components

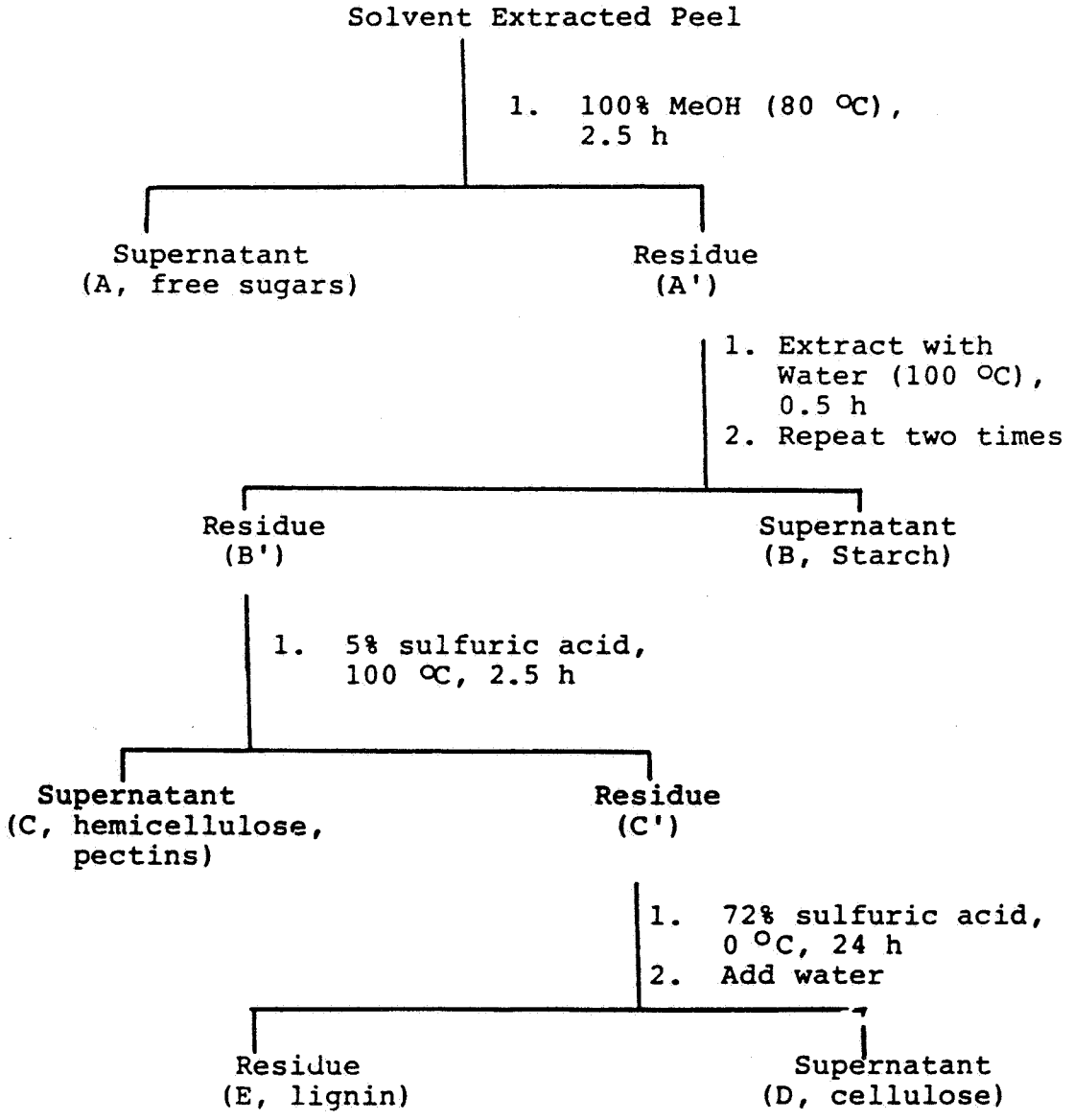

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Table 1

Extraction of ^{14}C-Dicofol Residues in Grapefruit

Fraction	% TRR	% of fraction	% TRR	ppm [3/] dicofol equivalents
Acetone extract	70			
Dicofol[1/]		80-85	58	0.58
"Polar compounds" [2/]		14-15	10	0.10
DCBP		0-5	2	0.02
Residue After Acetone Extraction	30			
Methanol Extract		7.7	2.3	0.02
Water Extract		12.4	3.7	0.04
Dilute Acid Extract		1.2	0.3	0.003
Strong Acid Extract		2.8	0.8	0.01
Residue remaining		53.0	16	0.16

[1/] Identity not confirmed. Readable chromatograms needed.

[2/] More polar than chlorohippuric acid, dichlorobenzophenone, chlorobenzoic acid or dichlorobenzilic acid.

[3/] TRR was 1.0 ppm in samples with TSI of 5 months. This figure is used in this table. The maximum residue found was 4.8 ppm at 4 month TSI.

No reported attempt was made to further identify these fractions. While this fractionation scheme would extract free sugars with methanol, there is no evidence that the radioactive portion of the methanol fraction is actually comprised of free sugars, etc. Rohm and Haas then concludes that "[t]hese results demonstrate that dicofol or a degradate of dicofol is incorporated into natural products of citrus peel." No evidence was presented to support this conclusion. Rohm and Haas notes that little is known about the synthesis of lignin, but that lignin does originate from shikimic acid, a known precursor to aromatic amino acids.

RCB Comments/Conclusions

The grapefruit metabolism study submitted is incomplete. Readable chromatograms are needed to support the identification of dicofol. Exhaustive extraction was done with polar solvents only along with acid hydrolysis as part of the fractionation scheme. However, no report of any attempt to identify the components of these fractions was reported. The various solvent fractions could have been combined, and identification of the combined fractions attempted. Additionally, non-polar solvents were not reported to have been used. However, the raw data indicate that isooctane/acetone was used as an extraction solvent. We note that the protocol included in this report suggested that heptane be used as one of the solvents for extraction. This point should be clarified. Enzyme hydrolysis was not used. Enzyme hydrolysis may have released some of the residues remaining in the peel after the various extractions. Additionally, enzyme hydrolysis of the extract(s) may have cleaved some of the conjugates present and facilitated their identification. To support the conclusion that dicofol or its degradates are incorporated into the natural products of the peel, further identification of the fractions is needed.

If TOX and EEB are not concerned about 40% of the residue being unidentified (10% or more "polar compounds"), then the requirement for further identification could be waived. However, confirmation of the identification of dicofol is still needed.

Cottonseed Metabolism

Recent studies of the metabolism of dicofol in cottonseed were described in two reports, "Metabolism of 14C-p,p'-Dicofol in Cottonseeds," Rohm and Haas Technical Report No. 310-86-69, A. M. Tillman, November, 1986, MRID No. 400420-04, and "Metabolism of 14C-o,p'-Dicofol in Cottonseeds, Rohm and Haas Technical Report No. 310-85-70, A. M. Tillman, November, 1986, MRID No. 400420-05.

Rohm and Haas indicates that Kelthane is normally applied once or twice to young cottonseed plants at the rate of 1.5 lb ai/A. Their intention was to treat cottonseed with ^{14}C dicofol twice at the rate of 1.5 lb ai/A using a formulation of Kelthane MF (o,p' and p,p'-dicofol in separate trials, and covered in separate reports). However, the mixture of labeled and unlabeled dicofol was prepared incorrectly. Instead of diluting labeled and unlabeled dicofol with the inert ingredients of Kelthane MF, the labeled and unlabeled active ingredient was apparently diluted with Kelthane MF, containing additional dicofol including both o,p' and p,p'- isomers. The report states, apparently incorrectly, that the active ingredient was diluted with technical Kelthane. Consequently, the application rate used was 2.55 lb ai/A instead of 1.5 lb ai/A (considering both o,p' and p,p' isomers). If only the isomer being studied is considered, the application rate for the first application was 2.25 lb ai/A p,p'-dicofol, and 1.6 lb ai/A o,p'-dicofol. The second application was then changed to 2.55 lb ai/A p,p'- or o,p'- dicofol. The error in formulation was not well explained in either the report or the raw data sheets. The raw data sheets merely state, "7/21/86 Determined that the Formulations group had sent us the wrong material for preparing the Kelthane formulation. The formulation was not control but contained Kelthane."

Stoneville 506 variety cotton plants were started from seeds in the greenhouse at the Rohm and Haas Mississippi research farm in Cleveland, MS. These plants were then transplanted to plots in fields on the research farm. Two plots for each study received labeled dicofol. A hand sprayer was used for the applications. Dicofol was applied to the first plot 72 and 49 days prior to harvest (when < 10% of the bolls were open). Dicofol was applied to the second plot 72 and 15 days prior to harvest (>50 % of bolls open at time of second application). In the second application, the dicofol was sprayed directly on the open bolls. Folex (merphos, tributylphosphorotrithioate) was used to defoliate the cotton. Folex was applied 3 and 1 weeks prior to harvest. The PHI for dicofol use on cotton on registered labels is 14 days. Samples were collected as follows.

Timing*	Samples Collected
60	leaves, soil
30	leaves, soil, bolls
15	leaves, soil, bolls
0	soil, bolls

*Approximate number of days to harvest

Note to PM: EAB should be alerted to the presence of soil analyses in these studies.

We note that the protocol for this study (included in the submission, but not previously submitted for review) called for collection of stem samples. The reports of these studies do not mention either the collection or the analysis of stems.

A summary of the weather conditions was included for each day the study was in progress. Samples were frozen and shipped in dry ice to Rohm and Haas Spring House Research Laboratories. Samples were stored frozen (-15C) until analysis.

Leaf samples were separated from stems and ground in a mortar and pestle with dry ice. The dry ice was removed by sublimation in the freezer overnight. Cottonseeds were obtained by hand separation of the seeds from the lint. Seeds plus lint were ground in a blender with dry ice. Hand delinted seeds were further delinted using a concentrated sulfuric acid wash, water rinse, and a lime rinse. Seeds were dried in an oven at 80C overnight. Dried seeds were ground in a blender. Samples of each of these were analyzed by combustion radioanalysis.

Delinted seed (ground) was extracted twice with hexanes and once with acetonitrile. The solvents were reduced with rotary evaporation under reduced pressure. Aliquots of the extract (referred to as the cottonseed oil extracts) were counted by liquid scintillation and analyzed by combustion radioanalysis. A limited effort was made to identify the radioactive components of the hexanes extract of the fields treated with p,p'-dicofol. The hexanes extract was purified using a silica gel sep pak. Two aliquots were analyzed, one by normal phase TLC using hexanes/methanol as the eluent, and one by reverse phase TLC using acetonitrile/water as the eluent. The plates were exposed to x-ray film and quantitated by scraping zones and counting by liquid scintillation. The report states that the majority of the activity was dicofol. However, the identity was not confirmed by another analytical technique. Additionally, we note that dicofol, FW-152 (1,1-bischlorophenyl-2,2-dichloroethanol), and dichlorobenzophenone are not resolved on the reverse phase plates, and dicofol and dichlorobenzophenone are not resolved on the normal phase TLC plates.

In the study of o,p'-dicofol, Rohm and Haas stated, "[t]he hexane extracts from cottonseeds [treated with ^{14}C-o,p-dicofol] did not contain sufficient activity for sample purification and tlc analysis. Based on the results from

the cottonseed metabolism with ^{14}C-p,p'-dicofol (Tillman, 1986), it is assumed that the hexanes extract from the o,p'-dicofol study contained parent compound."

The residue remaining after hexanes/acetonitrile extraction was separated further according to a fractionation scheme designed to separate seed samples into protein, carbohydrates, cellulose, and phytin fractions. The procedure was adapted from Rackis (1961) and Smith (1972), and is shown in Figure 2. Copies of these references were not included in the submission. The residue from the hexanes/acetonitrile extraction was further extracted with water adjusted to pH 7.4-8.0 for one hour. The extraction was repeated. The residue after water extraction was extracted with 80% aqueous ethanol for one hour. This extract was designated E-1. The residue remaining after ethanol extraction (designated S-1) was air dried, and the supernatant (E-1) concentrated by lyophilization.

The neutral water extract was acidified with 1N HCl. Some material precipitated. The mixture was centrifuged, and the supernatant (designated aqueous whey fraction) decanted. The precipitate was extracted with absolute ethanol. The supernatant was designated E-2 and the precipitate was designated S-2, and said to contain acid precipitated proteins.

The acidic aqueous fraction was adjusted to pH 8.5 with 1N NaOH, cooled, and centrifuged. The supernatant (designated E-3) was concentrated by lyophilization. The precipitate was designated S-3 and said to contain phytate-protein complexes.

Each of these extracts and solids was counted by liquid scintillation. Leaf samples were combusted and counted by liquid scintillation. The results of the counting are presented below in Tables 2 and 3.

Table 2

Leaf residues from Treatment of Cotton Plants with ^{14}C-p,p'-Dicofol

Plot	Treatment	ppm dicofol equivalents
A	first	736
	pre-second	194.9
	second	348.4
C	first	410.1
	second	- (not sampled)

Table 2, continued

Leaf residues from Treatment of Cotton Plants with ^{14}C-o,p'-Dicofol

Plot	Timing	ppm dicofol equivalents	
		Linted seed	Delinted seed
D	at harvest	1.88	1.48
F	pre-second treatment	2.19	0.53
	at harvest	2.34	1.26
D	first	484.5	
	pre-second	48.9	
	second	507.6	
C	first	140	
	second	- (not sampled)	

Table 3

Seed residues from Treatment of Cotton Plants with ^{14}C-p,p'-Dicofol

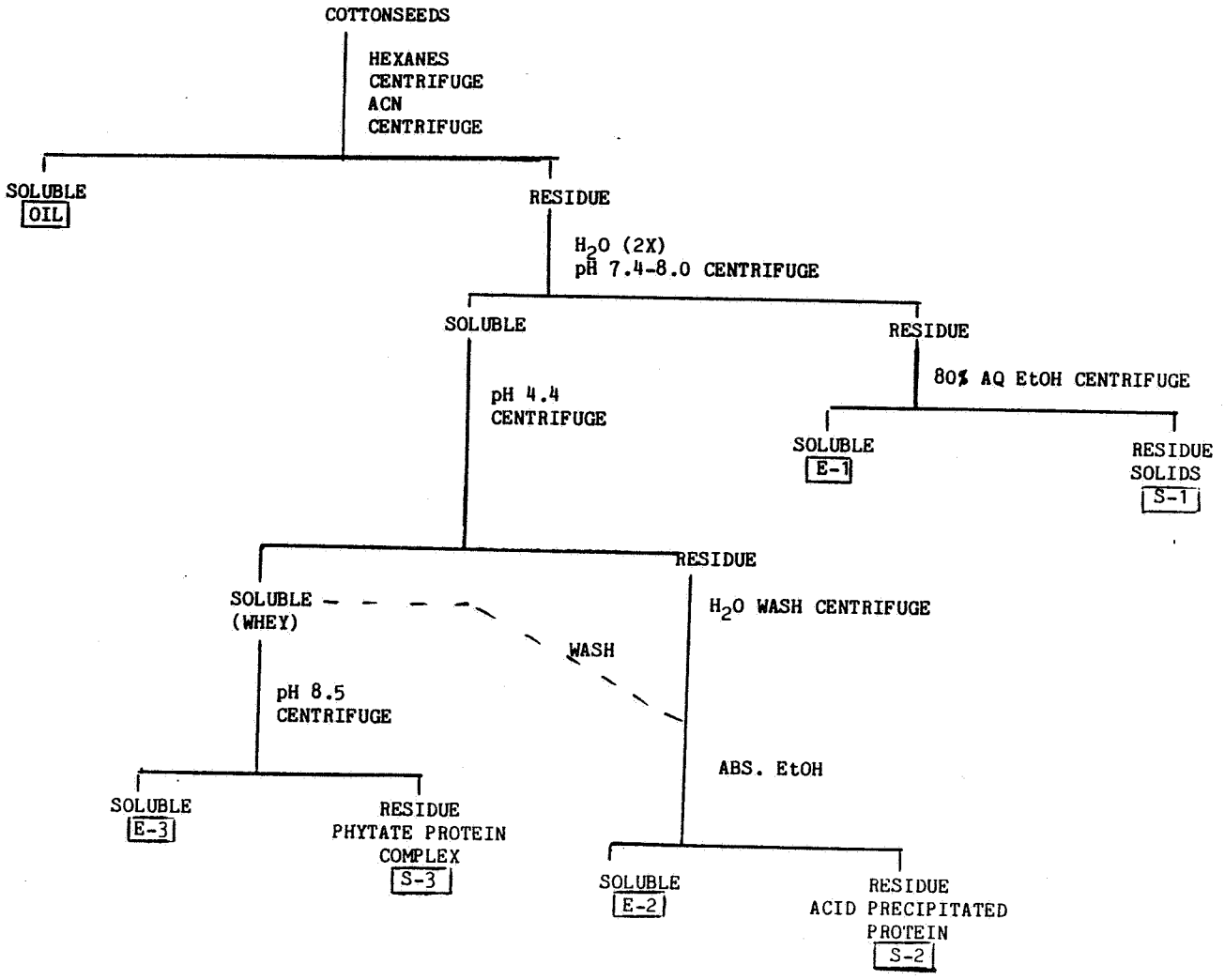
Plot	Timing	Residue (ppm dicofol equivalents)	
		Undelinted seed	Delinted seed
A	at harvest	0.529	1.05
C	pre-second treatment	11.9	4.94
	at harvest	3.76	6.88

Seed residues from Treatment of Cotton Plants with ^{14}C-o,p'-Dicofol

Plot	Timing	ppm dicofol equivalents	
		Linted seed	Delinted seed
D	at harvest	1.88	1.48
F	pre-second treatment	2.19	0.53
	at harvest	2.34	1.26

Figure 2

FRACTIONATION SCHEME FOR COTTONSEEDS



Classification of Solid Residues and Soluble Supernatants From Classical Fractionation of Cottonseeds

Solid Residue Fraction	Classification
S-1	Cellulose, Complex proteins
S-2	Acid-precipitated proteins
S-3	Phytate-Protein Complex
Soluble Supernatant Fraction	
E-1	Carbohydrates, water insoluble molecules
E-2	Compounds loosely bound to proteins
E-3	Whey proteins and carbohydrates

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Table 4

Distribution of Residues in Fractions of Cottonseed Treated with ^{14}C-p,p'-Dicofol

Fraction	Field A %TRR	Field A ppm	Field C %TRR	Field C ppm
Hexane extract	27.5	0.29	72.8	5.00
E-1	11.2	0.12	3.3	0.23
E-2	4.4	0.05	6.3	0.43
E-3	2.7	0.03	0.5	0.03
S-1	42.7	0.45	15.6	1.07
S-2	9.3	0.10	1.8	0.12
S-3	2.1	0.02	0.03	0.002

Distribution of Residues in Fractions of Cottonseed Treated with ^{14}C-o,p'-Dicofol

Fraction	Field A %TRR	Field A ppm	Field C %TRR	Field C ppm
Hexane extract	36.7	0.54	11.6	0.15
E-1	5.3	0.08	12.8	0.16
E-2	5.0	0.07	13.4	0.17
E-3	3.9	0.06	5.6	0.07
S-1	37.6	0.56	49.7	0.63
S-2	11.3	0.17	6.9	0.09
S-3	0.2	0.003	0.23	0.002

No attempt to characterize the radioactivity in any of these fractions was reported. Nothing in their report supports their conclusion that "bound residues from extracted seeds also were found incorporated into the cellulose/complex protein fraction," and "[s]ince ^{14}C-p,p'-dicofol applied to cotton plants or bolls can be found only in the seed's organic solvent extractable fraction, the remaining bound residues are due to dicofol or some degradation product of dicofol which bind to or incorporate into the cell's pool of natural products, in this case, into the cellulose/complex protein fraction." A similar conclusion was made in the report on o,p'-dicofol.

RCB Comments/conclusions

The submitted metabolism studies on cottonseed are incomplete. None of the radioactivity was unequivocably identified. Minimal effort to characterize the radioactivity in a hexane extract of cottonseeds was reported. Two and three of the standards used for comparison of R_f's did not appear to be resolved by normal phase and reverse phase TLC, respectively. Perhaps the actual photographs of these TLC plates would show better resolution than the photocopies of the photographs. However, even if the identification of dicofol as the primary residue is correct, less than 40% of the residue could be considered identified. No attempt to identify any of the activity in any other fraction was reported. Additionally, up to 50% of the radioactivity remained unextracted and no attempt at enzyme hydrolysis to release this activity was reported. Again, the term, "bound residue" was incorrectly used. See our conclusions regarding the citrus metabolism study for further discussion.

Metabolism in Dry Beans

In 1979, Rohm and Haas reported on the metabolism of ^{14}C-Kelthane in Dry Beans. The report, "Carbon-14 Kelthane REsidues in/on Dry Beans," Rohm and Haas Technical Report No. 34F-79-25, C. Parker, December 6, 1979, was included in this submission by reference. The report had been submitted to the Agency 11/8/84. Since the report had not been previously reviewed, it will be reviewed here.

A row of dry beans was sprayed twice, using a hand held boom sprayer, 15 and 43 days post-emergence, with ^{14}C-Kelthane diluted with Kelthane EC (unlabeled) at the rate of 1.5 lb ai/A. Apparently, ^{14}C-p,p'-dicofol was used. The location of the farm was not completely specified ("Newtown Farm"). Samples of foliage were collected 1, 14, and 28 days after each application. The entire crop was harvested 48 days after the second application. Samples of stems and beans + pods were collected 28 days after each application. The purpose of the study was to monitor the decline in Kelthane residues over time, and to collect samples to isolate and identify components of the residue. All samples were reportedly analyzed promptly.

Final harvested bean pods were shelled and beans were separated from the pods. Samples were ground in a blender and analyzed by combustion radioanalysis. Leaf, stem, and pod + bean samples were ground with dry ice, and then Soxhlet extracted with heptane. The extracted plant material was air dried and analyzed by combustion radioanalysis. Heptane extracts were cleaned up on Florisil

columns, eluting with 5% and 10% ethyl ether in iso-octane. One set of extracts was eluted with methanol. The methanol also removed much inactive plant material from the Florisil column.

Plant samples were analyzed by combustion radio-analysis. Sample calculations were presented for this analysis.

The residues in the heptane extracts and in the residue after heptane extraction are summarized below in Table 5. Residues in bean pods at harvest were not reported.

Table 5

Residues in Dry Bean Plant Plant Parts at Various Time Intervals

Sample	Residue (ppm dicofol equivalents)	% Extracted with heptane
1st Spray		
0 day green leaves	248.4	98.4
14 day green leaves	81.1	76.3
28 day green leaves	28.4	58.8
28 day stems	8.0	63.3
28 day pods + beans	0.18	41.2
2nd Spray		
0 day green leaves	169.3	87.9
14 day green leaves	110.4	77.5
28 day green leaves	85.5	58.3
28 day stems	37.6	67.8
28 day pods + beans	6.1	61.4
48 day dry beans (harvest)	0.31	-

The heptane extracts were analyzed by TLC using silica gel plates, and 98:2 hexane:methanol as the developing solvent. The developed plates were photographed with x-ray film, producing autoradiographs. The TLC plates were then scraped in sections and counted by liquid scintillation. dicofol (Kelthane) and dichlorobenzophenone were tentatively identified by their R_f. The identifications were not confirmed by any other analytical technique. The results were reported as % of activity in the extract (or cleaned up extract) and were not reported as % of the TRR. In cleaning up the extract, much of the activity due to polar material was lost. The results are shown in Table 6 by % of activity in the extract, and in Table 7 by % of the TRR. Harvested beans

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were not analyzed. Results are tentative, since the identifications were not confirmed by any other analytical technique.

Table 6

Quantitation by TLC Expressed as % in Extract

Extract	% Kelthane	% DCBP	% Polar Material
0 day leaves	96.6	1.2	0.7
14 day leaves	85.2	1.5	4.5
1st Spray -28 day cleaned up extracts			
Beans and Pods	94.1	1.2	1.9
Stems	97.7	0.8	0.9
Leaves	98.0	0.7	0.3
2nd Spray -28 day cleaned up extracts			
Beans and Pods	98.0	1.0	0.3
Stems	98.0	1.2	0.2
Leaves	98.1	0.8	0.2

Table 7

Quantitation by TLC Expressed as % of TRR

Extract	% Kelthane	% DCBP	% Polar Material
0 day leaves	95.1	1.2	0.7
14 day leaves	65.0	1.1	3.4
1st Spray -28 day cleaned up extracts			
Beans and Pods	4.3	0.05	0.08
Stems	47.6	0.4	0.4
Leaves	44.1	0.3	0.1
2nd Spray -28 day cleaned up extracts			
Beans and Pods	52.7	0.5	0.2
Stems	57.2	0.7	0.1
Leaves	56.3	0.5	0.1

RCB Comments/Conclusions

The Bean metabolism study is not complete. There was no reported attempt of exhaustive extraction, acid or base hydrolysis, or enzyme hydrolysis. Approximately 50% of the residue was tentatively identified as dicofol in immature beans + pods and in bean foliage by TLC. The identity of the residue was not confirmed by other techniques.

ANIMAL METABOLISM

No animal metabolism studies for dicofol had been submitted prior to the publication of the Registration Standard.

Registration Standard Data Gap

Metabolism studies indicating the nature of the residue in animals by the feeding of Kelthane are needed.

Current submission

Two animal metabolism studies were included in this submission.

400420-06	Dicofol - Nature of the Residue in Lactating Dairy Goats, Rohm and Haas Technical Report No. 310-86-61, F. W. Deckert (Rohm and Haas) and L. Predmore and M. Williams (Analytical Bio-Chemistry Laboratories), April, 1986.
400420-07	Dicofol - Nature of the Residue in Laying Hens, Rohm and Haas Technical Report No 310-86-68, F. W. Deckert (Rohm and Haas), C.E. Jameson and S.R. Shaffer (Analytical Bio-Chemistry Laboratories), April, 1986.

Metabolism in Lactating Goats

This metabolism study consists of a Rohm and Haas report which covers two studies done for Rohm and Haas by Analytical Bio-Chemistry Laboratories. Three reports for the two ABC Studies are included in the appendix to the Rohm and Haas report. (Two reports cover the second study.) The study titles are:

"Dicofol - Nature of the Residue in Lactating Dairy Goats," Rohm and Haas Technical Report No. 310-86-61, F. W. Deckert

(Rohm and Haas) and L. Predmore and M. Williams (Analytical Bio-Chemistry Laboratories), April, 1986. MRID No. 400420-06.

"Metabolism of ^{14}C-Dicofol in Lactating Dairy Goats ("First Study")," ABC Report No. 32025, L. Predmore, 11/20/84, Report to W.R. Lyman, Rohm and Haas Company.

"Metabolism of ^{14}C-Dicofol in Lactating Dairy Goats," ABC Report No. 32999, L. Predmore, 7/17/85. Report for W. R. Lyman, Rohm and Haas Company.

"^{14}C-p,p'-DDE, ^{14}C-p,p'-Dicofol, and ^{14}C-p,p'-FW-152 Residues in Goat Fat, Liver, and Milk." ABC Report No. 33897, B.M. Williams, B. Bunch, 4/14/86. Report for F. W. Deckert, Rohm and Haas Company.

The Rohm and Haas report covers two goat metabolism studies. The tissues from the first metabolism study were reportedly lost due to a freezer failure, although total radioactive residues in these tissues were reported. Milk and urine from the first study were used. Tissues from the second study only were extracted and further analyzed. Milk and urine from the second study were used in addition to milk and urine from the first study. The in-life portions of the studies were conducted by ABC laboratories. Metabolite characterization by TLC was performed by Rohm and Haas Research Laboratories. ABC Laboratories then performed additional analyses for DDE, dicofol, and FW-152 on selected milk, fat, and liver samples from the second study.

In the first metabolism study, 4 goats were used, one control, one fed 1.5 ppm for seven days with 7 day depuration, and 2 goats fed 15 ppm for seven days, and killed 24 hours after the last dose. In the second study, 3 goats were used: one control, one fed 1.5 ppm for 7 days, and one fed 15 ppm for 7 days. All goats from the second study were killed 24 hours after the last dose. A feeding level of 15 ppm would correspond to a 1x rate (See Meat, Milk, Poultry, and Eggs Section). Milk samples were collected 2 times per day, and composited by day. Urine and feces were collected daily. Fat, muscle, kidney, and liver samples were collected after sacrifice. The food intake of the goats averaged about 2 kg per day.

The elimination of radioactivity through urine, feces, and milk, was measured by liquid scintillation counting (LSC). In 7 days, 23-67% of the radioactivity was eliminated in the feces, 3-13% in the urine, and 1-3% in the milk. Total radioactive residues (TRR) found in goat milk from both studies are reported in Table 8. Residues are expressed as dicofol equivalents. Residues plateaued in milk after three to four days at approximately 0.6 ppm dicofol equivalents for

the 15 ppm feeding level. In milk, 86-91% of the TRR was extracted by acetonitrile. The limit of quantitation of the method (LOQ) was reported to be 0.001 ppm.

Table 8

^{14}C Dicofol Equivalent Concentrations in Milk by Goat, Dose, and Study Day

	Residue (ppm dicofol equivalents)				
	1.5 ppm dose level			15 ppm dose level	
Study Day	32A	32B	30A	31A	31B
1	0.013	0.022	0.070	0.010	0.21
2	0.022	0.041	0.44	0.14	0.45
3	0.023	0.042	0.67	0.28	0.55
4	0.029	0.056	0.63	0.36	0.98
5	0.034	0.056	0.57	0.41	0.64
6	0.031	0.052	0.63	0.41	0.59
7	0.030	0.0637	0.66	0.42	0.65
	Depuration of one Goat fed at 1.5 ppm				
8	0.019				
9	0.0091				
10	0.0069				
11	0.0050				
12	0.0044				
13	0.0043				
14	0.0045				

Tissue samples were solubilized and analyzed by LSC. Tissues were also extracted and analyzed by TLC and HPLC.

Milk samples were centrifuged and the solids extracted several times with acetonitrile. The extracts were analyzed by LSC. The extracts were then pooled, analyzed by LSC and by TLC.

For HPLC analysis, milk samples were extracted with methanol/ethyl ether as described in PAM I, Section 211.13H Milk; and partitioned into petroleum ether. The extract was evaporated to near dryness, reconstituted with methylene chloride:cyclohexane 1:1, and cleaned up by gel permeation chromatography (GPC) to remove high molecular weight impurities. The eluate was then evaporated to near dryness and reconstituted in methanol.

Tissue samples were extracted with acetonitrile in the presence of sodium sulfate. The extraction was repeated; however, only the first extract was analyzed by TLC.

Aliquots of the first extracts were analyzed by LSC. Extraction with other solvents, including ethyl acetate, methylene dichloride, and methanol, was attempted in preliminary experiments. Close to 100% of the TRR was extracted with acetonitrile in three extractions of all tissues except liver. Approximately 40% of the TRR was extracted from liver samples in three extractions of acetonitrile. To increase the level of radioactive residue extracted from liver, aqueous homogenates of the liver samples were prepared, acidified with HCl, and extracted with ethyl acetate or sequentially with ethyl acetate, methanol, and acetonitrile. Base hydrolysis reportedly reduced the extraction yield. Enzyme hydrolysis was not reported, and could potentially have increased the extraction of radioactive residues from liver. The percentage of the TRR extracted from each tissue for each extraction is presented in Table 9. Note that generally only the first extract was analyzed by TLC.

Table 9

Extraction of Radioactivity from Tissues

Tissue/Solvent	% of ^{14} Extracted per extract First	Second	Third	Sum
Fat/ACN	86.6	15.1	1.9	103.7
Fat/MeOH	77.3	22.6	4.3	104.2
Fat/EtOAc	67.8	32.6	7.96	108.3
Fat/MDC	105.4	14.3	2.0	121.7
omental/ACN	85.0	17.4	2.0	104.4
perirenal/ACN	79.4	17.4	2.1	98.8
Muscle/ACN	90.5	18.3	3.2	112.0
Muscle/MeOH	84.3	22.2	4.4	110.9
long. dorse/ACN	89.0	16.8	2.7	108.5
semimemb./ACN	79.5	14.2	2.7	96.4
triceps/ACN	81.7	15.8	2.5	100.0
Kidney/ACN	65.3	7.9	1.4	74.6
Liver/ACN	32.4	6.2	1.0	39.6
Liver/MeOH	40.6	10.7	2.4	53.7
Liver/EtOAc	35.2	7.6	2.5	45.3
Liver/MDC	38.7	13.8	8.3	60.8

Key to Solvents Used

ACN = acetonitrile
MeOH = methanol
EtOAc = ethyl acetate
MDC = methylene dichloride

For HPLC analysis, fat and liver samples were extracted with methylene chloride, evaporated to near dryness under nitrogen, reconstituted with methylene chloride:cyclohexane 1:1, cleaned up by gel permeation chromatography (GPC) to remove high molecular weight impurities. The eluate was evaporated to near dryness and reconstituted in methanol. Other tissue samples were not analyzed by HPLC.

For the characterization of metabolites, both one and two dimensional TLC were used. Normal phase TLC was done on both one and two dimensional silica gel plates. Reverse phase TLC was done on both one and two dimensional C18 plates. In the characterization of metabolites, a number of standards which were expected to be metabolites of dicofol were co-chromatographed with the samples. The R_f values for these standard are tabulated in Table 10 for several different TLC solvent systems. Structures and chemical names of the standards are presented in Figure 3. Fluorescent indicators and UV light were used to visualize the standards. Radioactivity was analyzed by auto-radiography. Radioactive zones were scraped and analyzed by LSC. The minimum quantifiable level (MQL) in the tissues ranged from 0.001 to 0.004 ppm (1-4 ppb), depending on the tissue. Identification was by cochromatography on one and two dimensional TLC. Additional evidence for identification of dicofol and FW 152 was by cochromatography on HPLC.

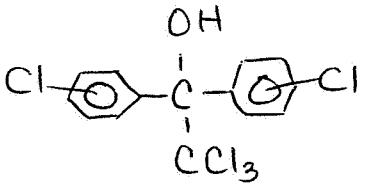
Table 10

Rf Values for Reference Standards in TLC Solvent Systems on Whatman LK5DF TLC Plates

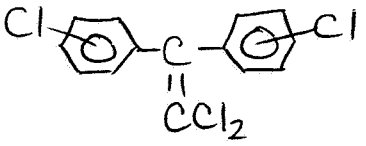
Compound	Solvent I	Solvent II	Solvent III
DDE	0.76	0.75	0.84
DBCP	0.65	0.60	0.60
Dicofol	0.35	0.47	0.64
FW-152	0.28	0.39	0.62
DCBH	0.11	0.19	0.24
CBA & CHA	0.1	0.1	0.0

Solvent I = hexanes:methanol:acetic acid (98:2:1)
Solvent II = hexanes:ethyl ether (9:1)
Solvent III = toluene:hexanes (75:25)

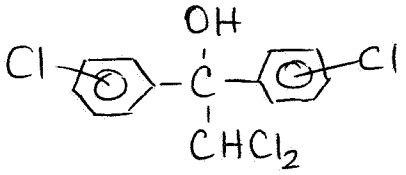
Figure 3



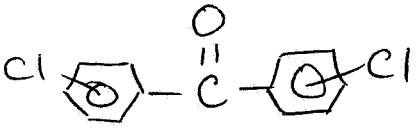
dicofol
1,1-bis(chlorophenyl)-2,2,2-trichloroethanol



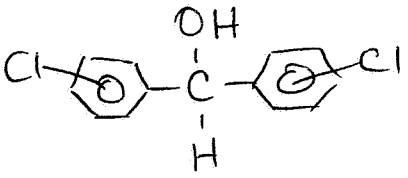
DDE
1,1-bis(chlorophenyl)-2,2-dichloroethylene



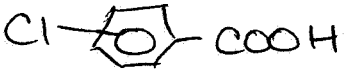
FW-152
1,1-bis(chlorophenyl)-2,2-dichloroethanol



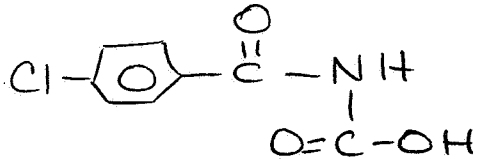
DBCP
dichlorobenzophenone



DCBH
dichlorobenzhydrol



CBA
chlorobenzoic acid



CHA
chlorohippuric acid

For the HPLC analyses, milk, liver, and fat samples were fortified with non-radioactive FW-152, dicofol, and DDE as markers for UV detection and retention time. (FW-152 is 1,1-bis (4-chlorophenyl)-2,2-dichloroethanol.) The samples were analyzed by HPLC using a C-18 column and acetonitrile/water 85:15 as the mobile phase. A UV detector at 230 nm was used along with a fraction collector. Fractions were collected every 0.5 minutes. The fractions were then analyzed by LSC.

The distribution of residues in goat tissues, milk, and excreta, expressed as percentage of total dose and as total radioactive residue (ppm dicofol equivalents) is presented in Table 11. The percentage of the residue in the extracts identified as 1,1-bis(chlorophenyl)-2,2,2-trichloroethanol (dicofol), 1,1-bis(chlorophenyl)-2,2-dichloroethanol (FW-152), dichlorobenzophenone (DCBP), and dichlorobenzhydrol (DCBH) is presented in the remainder of the columns. Total radioactive residues in goat tissues from individual goats in both studies are reported in Table 12. Residues are expressed as ppm dicofol equivalents. DDE was detected in three of the four fat samples, but not in the duplicates of these samples. In the HPLC analyses performed by ABC Laboratories, DDE was detected in one of the two liver samples, but not in the duplicate of that sample. DDE was found in one milk sample and its duplicate.

Table 11

Dicofol Metabolism in Goats

	Percent of Total 14C dose	TRR (ppm dicofol equiv.)	% of TRR				
			dicofol	FW-152	DCBP	DCBH	Unextracted
Milk	1.0-3.0	0.58	24-37	50-67	1-17	2-3	-
Fat	7.2-15	3.2	30-46	44-55	2-18	2	-
Muscle	<1-3.4	0.44	36-43	53-56	2-3	1-3	-
Kidney	<1	0.19	10	28	1	-	-
Liver	<1-1.2	1.5	0.5-2.4	27-47	0.5-0.6	<1	40-50
Urine	3.3-13		<1	1	1	14-39	
Feces	23-67		1-3	54-71	1	3-5	

Table 12

Total Radioactive Residue in Goat Tissues by Dose Level

Tissue	Residue (ppm dicofol equivalents) Depurated	1.5 ppm level	15 ppm level
Muscle			
Triceps	0.015	0.052	0.34-0.49
Semimembranosus	0.0064	0.034	0.22-0.47
Longissimus dorsi	0.020	0.063	0.44-0.77
Fat			
Perirenal	0.17	0.32	3.0-3.4
Omental	0.15	0.27	2.0-3.7
Kidney	0.0052	0.023	0.17-0.21
Heart	0.038	0.085	0.21-1.0
Liver	0.019	0.30	1.2-1.7
Gall Bladder Contents	0.034	1.1	2.2-3.0
Whole Blood	<0.003	0.0036	0.039-0.046

*Depurated goats were dosed at 1.5 ppm and depurated for 7 days.

RCB Comments/Conclusions

The major dicofol metabolite in lactating goats is FW-152. Minor metabolites are dichlorobenzophenone and dichlorobenzhydrol. Unmetabolized dicofol is also present. Little if any dicofol is metabolized to DDE in lactating goats. However, only 50% of the TRR was extracted from liver. Enzyme hydrolysis of liver was not attempted. We defer to TOX and EEB the need for additional analysis of goat liver. We note for TOX and EEB that enzyme hydrolysis could have increased the extraction of radioactive residues from liver.

Hen Metabolism

Rohm and Haas has submitted a report of the metabolism of dicofol in Laying Hens. The study is entitled, "Dicofol - Nature of the Residue in Laying Hens," Rohm and Haas Technical Report No 310-86-68, F. W. Deckert (Rohm and Haas), C.E. Jameson and S.R. Shaffer (Analytical Bio-Chemistry Laboratories), April, 1986. MRID No. 400420-07

Appended to this report were the reports from the contractor for this study, Analytical Bio-Chemistry Laboratories. ABC Laboratories conducted the in-life portions of these studies and performed specific HPLC analyses. These reports were:

"Metabolism of ^{14}C-Dicofol in Laying Hens," ABC Report No. 32480, Charles E. Jameson and Stanley R. Shaffer, March 20, 1985, report to W. R. Lyman, Rohm and Haas Company.

"Determination of ^{14}C-Dicofol, ^{14}C-ER-8, and ^{14}C-p,p'-DDE Residues in Poultry Samples From Hens Orally Dosed with ^{14}C-Dicofol for Seven Days," ABC Report No. 33000, Stanley R. Shaffer, April 25, 1985, report to W. R. Lyman, Rohm and Haas Company; also designated Rohm and Haas Technical Report No. 31L-85-12, May 2, 1985, W. R. Lyman.

Four groups of 5 hens were orally dosed for seven days with ^{14}C-dicofol at 0.1 ppm, 1.0 ppm, 10.0 ppm, and 10.0 ppm with 10 days depuration. A fifth group of hens served as controls. The hen's intake averaged 98 g of feed per day. A feeding level of 1 ppm would correspond to a 1x rate (See Meat, Milk, Poultry, and Egg Section.) Eggs were collected daily, and tissues at termination. Metabolite characterization was done at Rohm and Haas Research Laboratories. No plateau was reached in eggs in seven days of feeding. In the depurated hens, residues continued increasing for four to five days following cessation of dosing. Rohm and Haas noted that the residue levels were not linear with dose. Additional analyses by HPLC were done by ABC Laboratories.

Samples were handled the same as were the samples from the goat metabolism study, except for the HPLC analyses. The HPLC analyses of poultry tissues were done slightly differently than the HPLC analyses of goat tissues. Fat, liver, and eggs were extracted with dichloromethane, evaporated to near dryness, reconstituted with 50:50 dichloromethane:cyclohexane. The samples were cleaned up by gel permeation chromatography (GPC) to remove high molecular weight impurities, evaporated to dryness, and reconstituted with methanol. The extracts were analyzed by HPLC, using a C18 column, 85:15 acetonitrile:water as the mobile phase, and a UV detector at 230 nm. One minute fractions were collected and analyzed by Liquid scintillation counting (LSC). The limit of quantitation was reported to be 0.01 ppm in liver and whole egg, and 0.03 ppm in fat.

As in the goat metabolism study, liver samples were not fully extracted (40-51% unextracted). As in the goat metabolism study, enzyme hydrolysis was not reported. Low extractability was also reported for egg yolk (15-29% unextracted). Residues in egg whites were fully extracted. Breast muscle was 19% unextracted. Fat and thigh muscle were

close to 100% extracted. Extraction efficiencies for eggs using various solvents are presented in Table 13 and for tissues using various solvents in Table 14. The key to the solvents used is found in Table 9. Acid hydrolysis of aqueous liver homogenates increased extractability by approximately 10%. Neither base nor enzyme hydrolysis were reported. These techniques could have increased the extraction of radioactivity from tissues.

Table 13

Extraction Efficiency in Whole Eggs and Egg Yolks

Sample/Solvent	Percent of TRR Extracted by Extract			
	First	Second	Third	Sum
Whole Egg/EtOAC	66.4	13.2	3.8	83.4
Whole Egg/MeOH	67.5	16.9	4.1	88.5
Whole Egg/ACN	69.0	11.4	1.6	82.0
Egg Yolk/EtOAC	57.9	10.5	2.6	71.0
Egg Yolk/MeOH	60.7	19.6	4.7	85.0
Egg Yolk/ACN	61.1	12.8	2.5	76.4

Table 14

Extraction Efficiency in Tissues

Sample/Solvent	Percent of TRR Extracted by Extract			
	First	Second	Third	Sum
Fat/ACN	79.1	14.6	2.5	96.2
Fat/MDC	81.3	11.3	1.6	94.2
Breast Muscle/ACN	64.8	12.6	3.2	80.7
Thigh Muscle/ACN	78.9	15.3	2.5	96.7
Kidney/ACN	67.0	10.2	1.7	78.9
Liver/ACN	41.0	6.9	1.3	49.2
Liver/MeOH	46.0	12.4	3.2	61.6

The distribution of residues in hen tissues and eggs, expressed as percentage of total dose and as total radioactive residue (ppm dicofol equivalents) is presented in Table 15. The percentage of the residue in the extracts identified as dicofol, FW-152, dichlorobenzophenone (DCBP), dichlorobenzhydrol (DCBH), and unidentified polar compounds, is presented in the remainder of the columns. Tissues were also analyzed for DDE. Up to 0.1 ppm was found in whole eggs, up to 0.3 ppm in egg yolk, and up to 0.3 ppm was found in kidney. No DDE was detected in other tissues. Total radioactive residues in eggs

by dose group are presented in Table 16. Total radioactive residues in hen tissues by dose level are reported in Table 17. Residues are expressed as ppm dicofol equivalents. Identifications were confirmed by two dimensional TLC. In the HPLC analyses, ABC Laboratories did not detect any ER-8 (Cl-DDT) or DDE. The HPLC method used was not capable of distinguishing between dicofol and FW-152. Consequently, these results were not used.

Table 15

Dicofol Metabolism in Hens

	Percent of Total 14C dose	TRR (ppm dicofol equiv.)	% of TRR				
			dicofol	FW-152	DCBP	DCBH	Polars
Eggs	0.7-7.1	0.086*	13-27	9-17	44-51	-	14-24
yolk			44-66	9-29	7-14	-	9-19
white			2-4	12-20	59-66	-	18-19
Fat	0.7-6.1	0.741	73-77	10-17	4-8	1-2	-
Muscle	0.2-0.5		63	22	6	-	9
thigh		0.039					
breast		0.0085					
Kidney	0.2-0.3	0.132	34	36-38	4	2	24
Liver	0.8-0.9	0.176	2	20-33	0.5-4	1-5	10-22
(40-51% unextracted)							

*Residue in eggs on day 7

Table 16

Total Radioactive Residue in Whole Eggs by Dose Level

	Residue (ppm dicofol equivalents)			
	Dose Level			
Study Day	0.1 ppm	1.0 ppm	10 ppm	10 ppm depurated
1	<0.001	<0.001	<0.001	<0.001
2	<0.001	0.0036	0.0490	0.0365
3	n/a	0.0143	0.210	n/a
4	0.00267	0.0293	0.472	0.435
5	0.00406	0.0556	0.702	0.668
6	n/a	0.0616	1.17	n/a
7	0.00624	0.0859	1.38	1.14

Table 16, continued

Total Radioactive Residue in Whole Eggs in Depurated* Hens

Study Day	Residue (ppm dicofol equivalents) 10 ppm depurated hens
8	1.41
9	1.59
10	1.60
11	1.64
12	n/a
13	1.27
14	0.927
15	0.770
16	n/a

* Depurated Hens were dosed for 7 days and depurated for 7 days.

Table 17

Total Radioactive Residue in Hen Tissues

Tissue	Residue (ppm dicofol equivalents) Dose Level 0.1 ppm	1.0 ppm	10 ppm	10 ppm depurated
Thigh Muscle	0.00296	0.0392	0.574	0.213
Breast Muscle	<0.003	0.00836	0.166	0.0444
Fat	0.0474	0.741	11.3	3.45
Heart	0.00848	0.130	1.94	0.545
Liver	0.0190	0.176	2.02	0.603
Gizzard	0.00496	0.0746	0.596	0.410
Kidney	0.0130	0.132	2.07	0.471

RCB Comments/Conclusions

The major dicofol metabolite in laying hens is FW-152 (1,1-bis-(chlorophenyl)-2,2-dichloroethanol). Minor metabolites are dichlorobenzophenone and dichlorobenzhydrol. Unmetabolized dicofol is also present. Little if any dicofol is metabolized to DDE in laying hens. However, only 50% of the TRR was extracted from liver. Base and enzyme hydrolysis of liver were not attempted. Egg yolks were 70% extracted. Other tissues, egg whites, and whole eggs were 80 to 100% extracted. We defer to TOX and EEB the need for additional analysis of poultry liver. We note for TOX and EEB that base and enzyme hydrolysis could have increased the extraction of radioactive residues from liver.

ANALYTICAL METHODOLOGY

Prior to the publication of the Registration Standard, spectroscopic methods had been submitted for the analysis of dicofol, per se. Partial information was available on the applicability of PAM I methodology for o,p'- and p,p'- dicofol.

PAM II analytical methodology for the determination of dicofol, per se, was discussed in the Registration Standard. This methodology consists of several spectophotometric methods. These methods had been considered adequate for enforcement purposes. Dicofol is hydrolyzed to $CHCl_3$ under alkaline conditions. The $CHCl_3$ formed is determined spectrophotometrically in a Fujiwara type color reaction.

Some information is available on the applicability of PAM I multiresidue methodology. However, additional information is needed. Relative retention times for o,p'- and p,p'- dicofol on 5% OV-101 have been given. Relative retention times (RRT) on 3% OV-225, 2% DEGS, and 3% OV-17 would be helpful. Recoveries through Florisil columns have been given for p,p'- dicofol. p,p'-Dicofol is partially (50-80%) recovered through the full method from fatty foods and completely (>80%) recovered from non-fatty foods. Both o,p'- and p,p'- dicofol elute from florisil in both 6% and 15% ethyl ether in petroleum ether fractions. Information on methylene chloride elution from florisil is available only for p,p'-dicofol and is needed for o,p'-dicofol. Further information on protocol 1 is needed for o,p'-dicofol on protocol 1 and for both p,p'- and o,p'-dicofol for protocol 3. Protocols 2 and 4 would not be expected to recover dicofol.

An electron capture gas chromatographic method was submitted in connection with PP#3E1327, but was not validated (J. E. Mayes, 1/31/73). A GC method might determine metabolites of dicofol.

An HPLC analytical method had been submitted subsequent to the publication of the Registration Standard (K. Dockter, 1/22/85). The method, Rohm and Haas TR#31L-83-10, was used for the analysis of citrus. Both o,p- and p,p'- dicofol were determined, along with p,p'- isomers of several DDTr compounds.

Registration Standard Data Gap

Since there is no adequate profile of the fate of dicofol residues in or on plants and animals, no opinion can be offered about whether or not there are adequate methods to collect the residue data and to enforce the

established tolerances. When they are revised, the dicofol tolerances may have to be expressed in terms of residues of dicofol and its metabolites, or degradation products. Methods in that case will have to be available to determine the metabolites, or degradation products. If residues are identified as being different from Kelthane, per se, analytical methodology will be required to identify and quantify these residues in/on treated crops, their byproducts and incidental commodities (cover crops in orchards), and in animal tissues.

Current Submission

Final conclusions cannot be made on the adequacy of the analytical methodology to determine the residue of concern until the plant and animal metabolism of dicofol are adequately understood. In this section, methodology for o,p'- and p,p'- dicofol is discussed.

A different analytical method was included in this submission. The method was titled, "A Residue Analytical Method for p,p'-Dicofol and o,p'-Dicofol," Rohm and Haas Technical Report No. 310-86-74, C. K. Hofmann, November, 1986. (MRID No. 400420-08). The copy of this method, included in this submission is stamped, "Property of Rohm and Haas Company, Philadelphia" on every page. For that reason, the method cannot be accepted. A "clean" copy of the analytical method is required, i.e., a copy with no no claim of confidentiality.

The method involves several different sample workups, depending on the crop to be analyzed, followed by GC analysis for p,p'- and o,p'- dicofol.

The sample workup involves extraction with isooctane (orange peel, cottonseed), acetonitrile (orange pulp, whole orange), or acetone and isooctane (corn husks and cobs, corn kernels, and beans). For other crops, the workup from Rohm and Haas TR # 36-81-05 is to be followed. A copy of this report was not included, and is needed.

An aliquot of the initial extract is evaporated to an oily residue by rotary evaporation at 60C, and reconstituted with petroleum ether. The sample is partitioned into acetonitrile, and partitioned back into petroleum ether with the additional of NaCl. The pet ether extract is washed with NaCl solution, and dried with Na_2SO_4. The pet ether extract is evaporated to an oily residue and reconstituted with a known volume of pet ether. The extract is cleaned up on a florisil column. The column is eluted with 6% ethyl ether/petroleum ether. The first eluate is discarded. The

column is then eluted with 15% ethyl ether/petroleum ether. This eluate is collected, evaporated to dryness by rotary evaporation at 60C, and reconstituted with isooctane for GC analysis.

A 6' x 2 mm i.d. column, packed with 5% OV-17 on 80/100 mesh Gas Chrom Q (Supelco), is used, along with an Electron Capture Detector (ECD). The column is maintained at 200C for the analysis and then ramped to 250C, apparently to clean out the column between analyses. The injector was maintained at 240C, and the detector at 350C. The retention time of p,p'-dicofol by this method was 7.3 minutes, and the retention time of o,p'-dicofol, approximately 6.3 minutes. Peak heights were used for calculation. Recoveries were calculated by adjusting for control values. Residues were corrected for recovery. The Sensitivity of the method was reported to be 0.01 ppm for both isomers.

Recoveries were reported for a number of commodities. We note that the raw data submitted with the report were collected on different dates than the summary tables indicate. Some of the corn raw data were labeled cottonseed products. These should be explained. EAB should be alerted to the presence of soil recovery data in this report.

Recoveries reported by Rohm and Haas are summarized in Table 18. Rohm and Haas averaged recovery data for all commodities from a particular crop.

Table 18

Recoveries of Dicofol

Commodity	p,p'-dicofol average % (range)	o,p'-dicofol average % (range)
Citrus Products	95 (59-130)	94 (66-120)
fruit (unspecified)	97 (89-120)	93 (93-105)
wet peel	78 (59-96)	92 (77-106)
dry peel	102	103
oil	101	87
juice	130	120
Cottonseed Products	90 (68-125)	92 (73-126)
seed	94 (68-125)	95 (75-114)
hull	90 (90-91)	96 (91-102)
meal	83 (76-90)	90 (87-92)
refined oil	82 (75-90)	102 (77-126)
crude oil	74	83
soapstock	94 (81-106)	77 (73-81)

Table 18, continued

Recoveries of Dicofol

Commodity	p,p'-dicofol average % (range)	o,p'-dicofol average % (range)
Corn Products	88 (43-117)	94 (62-133)
kernels	92 (69-117)	
meal	97 (96-98)	
crude oil	83 (61-104)	102 (84-119)
refined oil	88 (80-96)	101 (93-119)
soapstock	88 (73-102)	76 (62-90)
flour	92 (85-100)	97 (96-99)
germ	96 (89-105)	93 (80-103)
grits	83 (83-83)	93 (89-97)
hulls	64 (43-87)	82 (68-101)
Almonds	102 (78-125)	100 (73-114)
meal	98 (78-125)	96 (73-114)
hulls	109 (101-111)	108 (101-114)
Grape Products	87 (61-157)	96 (59-153)
grapes	91 (67-157)	91 (59-153)
juice	71 (61-81)	89 (79-99)
wet pomace	95 (91-99)	125 (97-153)
dry pomace	108	113
raisins	79 (77-81)	100 (81-119)
stems	75 (73-78)	112 (73-152)
waste	63 (61-65)	64 (63-66)
wine	109 (100-118)	110 (85-136)
Beans	118	98
Pears	103 (77-122)	101 (87-116)
Cantaloupe (melon)	105 (100-112)	99 (85-111)
Cucumbers	98 (84-120)	87 (81-95)
Pecans (nuts)	101	87
Squash	112 (96-139)	105 (93-114)
Walnuts	99 (85-113)	95 (82-108)
Apples	105 (100-112)	99 (85-111)

RCB Comments/Conclusions

Final conclusions cannot be made on the adequacy of the analytical methodology to determine the residue of concern until the plant and animal metabolism of dicofol are adequately understood. Thus, any comments made on this methodology are tentative, pending resolution of metabolism issues.

A "clean" copy of the analytical method submitted in MRID No. 400420-08 is needed for further consideration. An explanation of the differing dates between the Rohm and Haas tables and the raw data is needed.

A copy of Rohm and Haas TR-36-81-05 is needed, since this method was used for some of the sample workups.

The registrant should be reminded that recovery data are needed each time the method is used (each time residue data are generated).

Additional data on the applicability of FDA multiresidue methods is needed. Relative retention times (RRT) on 3% OV-225, 2% DEGS, and 3% OV-17 would be helpful. Information on methylene chloride elution from florisil is needed for o,p'-dicofol. Further information on protocol 1 is needed for o,p'-dicofol on protocol 1 and for both p,p'- and o,p'-dicofol for protocol 3. Protocols 2 and 4 would not be expected to recover dicofol.

STORAGE STABILITY DATA

Dicofol has been reported to be unstable during storage in solution at 40C (MRID No. 05004877). No storage stability data were available for frozen storage at the time the Registration Standard was published.

Registration Standard Data Gap

All residue studies should be supported by storage stability studies of samples held in storage before analysis. Handling history of the samples should accompany all of the residue studies.

Current Submission

Storage stability data were included in this submission. However, these data will not be included in this expedited review.

FIELD RESIDUE DATA

According to the Registration Standard, the field residue data available at the time the Registration Standard was written do not support the registered uses. These data were generated between 1955 and 1965 in support of tolerance petitions. These data are inadequate by today's standards since metabolites were not considered, feeding studies were not conducted to determine transfer of residues to meat, milk, poultry, and eggs; and processing studies were not conducted on the following processed commodities: apple pomace, tomato pomace, tomato waste, citrus pulp, citrus oil, grape pomace, raisin waste, and cottonseed byproducts (meal, hulls, and oil). Most applications were not made at today's maximum registered rate, and rarely was more than one application made, although the labels allow for multiple applications. In the field residue data, available at the time the Registration Standard was written, for most crops, dicofol, per se, is the only residue reported. (Residues of chloroform, dichlorobenzophenone, and dichlorobenzhydrol were reported in the mint oil processing studies.)

Field residue data available for the preparation of the Registration Standard are found in the following petitions: PP#108 (Acc#113272), PP#154 (Acc#113391), PP#390 (Acc#114230), and PP#6F0472 (Acc#114538).

Available residue data from field trials were tabulated for the Special Review (S. Hummel, 1/14/85). The tabulated data reflected uses which are closest to the maximum registered rate and recommended PHI. The mean and range for these data, including data from a mint oil processing study are tabulated again in this memo. Note that most data reflect a single application, whereas, most labels allow multiple applications. These data are being retabulated here in Table 19 for use by EEB in their review.

Table 19

Residue Data from Petition Files

CROP	#SAMPLES	RESIDUE (ppm)	
		mean	range
hops	8	12.08	1.23-25.00
mint hay	64	25.56	10.30-92.00
spent mint hay	38	2.48	0.49-14.60
mint oil	61	4.83	0.01-31.70
peaches	21	3.24	0.13-8.30
grapefruit	18	2.33	1.12-5.00
oranges	37	1.99	1.10-3.51

Table 19, continued

Residue Data from Petition Files

CROP	#SAMPLES	RESIDUE (ppm) mean	range
apples	26	2.16	0.37-4.52
pears	10	1.17	0.22-2.60
raspberries	6	1.77	0.70-2.90
cherries	4	2.28	1.20-4.00
plums	5	0.27	0.06-0.40
beans (all types)	8	0.52	0.11-1.46
cantaloupes	5	2.26	0.60-4.20
cucumbers	12	0.55	0.01-2.30
tomatoes	10	0.38	0.01-0.77
grapes	6	1.45	0.87-2.20
figs	7	1.44	0.15-4.60
cottonseed	5	0.00	0.00-0.00
strawberries	9	0.91	0.13-3.00
corn kernels	28	0.03	0.01-0.33
corn husks	17	19.42	1.70-41.60

Residues reported in field studies of mint hay and processing studies of mint oil exceeded the established tolerance. The highest reported residue, 92.00 ppm, and the second highest reported residue, 68.00 ppm reflected a rate slightly higher than the registered rate (1.6lb ai/A). Additionally, the hay was wilted, resulting in a weight loss of 50%, according to a 7/15/66 letter from Rohm and Haas (PP#390). In this letter, Rohm and Haas also claimed that the high residues reported were resulted from using an old method of analysis which did not distinguish between chloroform and dicofol. Later studies showed much lower residues (PP#390). RCB recommended for the tolerance based on these arguments and by comparing the persistence of dicofol to DDT in PP#334 and FAP #686 (PP#6F0472, 7/25/66, G. J. Beusch). Residues were reported on corn kernels and corn husks (PP#390). No tolerance has been established for field corn.

Registration Standard Data Gaps

Although for most crops, residue data were submitted; due to the changes of application rates and pre-harvest intervals, these outdated data are not adequate to support the registered uses under present day standards, and the established tolerances are not supported.

Residue data will be required for all crops (except mint and strawberries) reflecting the maximum registered application rate, in samples taken at intervals after the application in order to establish a time lapse degradation pattern (decline curve) for the residues. The residue studies should include multiple applications, ground and aircraft application equipment, representation of formulations used, geographical representation, as well as effects of climatological conditions (rain, wind, sun, etc.).

Processing studies will be required showing the amount of residue in the processed commodities apple pomace, tomato pomace, tomato waste, citrus pulp, citrus oil, grape pomace, raisin waste, cottonseed byproducts, i.e., cottonseed meal and hulls, cottonseed oil, etc.

If a concentration of residues is indicated to the extent that the residue level exceeds that of the tolerance level established for the r.a.c., a food additive tolerance for the byproduct will be required.

Residue studies are required reflecting the registered application rate on crop feed items, i.e., forage, hays, stalks, stover, vines, cottonseed linters etc., and if residues are present, adequate tolerances should be established.

Subsequent Data Submission

Additional residue data were received from Rohm and Haas while the Special Review was in progress. These data included a citrus processing study and a residue decline study. Residues determined included dicofol and the impurities in the manufacturing process, including DDT-r impurities. These studies utilized the maximum application rate, however, usually only a single application was made. When multiple applications were made, they were made at intervals of three months, not at minimum intervals. DDT-r residues were found to be approximately 10% of total dicofol residues. Dicofol residues from single applications of widely spaced applications were reported to be 1.5 ppm in oranges and 0.7 ppm in grapefruit (sum of o,p'- and p,p'- dicofol and 5 impurities and degradates). Residues were found to concentrate in peel frits, dry pulp, and citrus oil.

Current Submission

As part of the expedited review, RCB was requested to screen the residue data submitted for zero day residues. Residue data were submitted for citrus, apples, pears, dry

beans, melons, cucumbers, squash, pecans, walnuts, grapes, and cottonseed. Residues of o,p'- and p,p' dicofol were reported at zero days for samples of grapefruit, melons, pecans, and walnuts. In no case were these zero day residues the highest reported residues. Instead of zero day residues, we will tabulate the maximum reported residue for crops of interest to EEB (L. Turner, EEB, private communication). These data are not being reviewed in detail at this time, but are only screened. This review will indicate obvious deficiencies. However, additional deficiencies may be identified in a thorough review of these data. The maximum residues reported are presented in Table 20. Comments specific to each crop are found at the end of our comments and conclusions section.

Table 20

Maximum Residues of Dicofol

Crop	Application Rate	Residue (ppm)	PHI	Formulation
Citrus	3 x 6 lb ai/A	4.17	14	MF
Apples	3 x 2.25 lb ai/A	8.9	21	4F
Pears	3 x 3 lb ai/A	10.8	6	4F
Grapes	2 x 1.2 lb ai/A	9.65	21	4F
	5 x 1.21 lb ai/A	9.7	14	4F
Dry Beans	2 x 1.5 lb ai/A	7.3	20	MF
Bean Pods	2 x 1.5 lb ai/A	31.1	40	MF

Information on Specific Crops

Citrus. Residue data were supplied from FL, CA, and TX. Three ground applications of Kelthane MF were made at 6 lb ai/A. The maximum labeled rate is unlimited applications of 8 lb ai/A. Both ground and aerial applications are permitted on the labels. No information was given regarding the volume of spray used per acre. Samples were stored up to a year before analysis. According to the Rohm and Haas Report, the maximum residue found was 3.16 ppm. However, this "maximum residue" is actually an average of three samples. The maximum residue reported was 4.17 ppm.

Apples. Three ground or hand applications of Kelthane 4F were made at the rate of 2.25 or 1.88 lb ai/A, in an unspecified volume of spray solution per acre. The lower rate was used in VA and NY. The higher rate was used in WA, NJ, MI, OR, PA, and CA. We note that data on apple pomace indicates approximately a 10 x concentration factor.

Pears. Three ground applications of Kelthane 4F were made at the rate of 3 lb ai/A. Residue data are from CA, MI, OR, and WA. The volume of spray solution used per acre was not given. The dates of application were not given. We cannot determine the interval between applications.

Grapes. Residue data were submitted from CA, OR, MI, PA, and NC. Ground applications of Kelthane 4F were made. Several application rates were used. Some field trials used two applications at 1.2 lb ai/A. Some used two applications at 2.0 lb ai/A. Some used 5 applications at 1.21 lb ai/A.

Dry Beans. Residue data are from ID, CA, and NY. Two applications of Kelthane MF were made at 1.5 lb ai/A. We note an increase in the residue reported with increasing PHI. This should be explained.

RCB Comments/Conclusions

The registrant should be reminded that all labeled uses must be supported by residue data or the labels amended to reflect the maximum use supported by residue data. Residue data must be submitted to support the maximum number of applications allowed on the label, or the maximum number of applications allowed on the label must be changed to reflect the use supported by the submitted residue data. A maximum number of applications per season or a maximum quantity of pesticide to be applied per season lmust be specified on the label. A minimum interval between applications must be added to the labels. Residue data must reflect both dilute and concentrate sprays, ground and aerial application, as allowed on product labels (or product labels changed to reflect the residue data). The volume of spray used per acre must be reported for orchard applications. Use directions for orchards must be changed to account for the variability in tree sizes. (Several options for orchard labeling are shown in Attachment 1). Grazing restrictions must also be added for orchards. Suggested language is "Do not allow livestock to graze in treated areas or feed on orchard cover crops." Alternatively, tolerances may be proposed for orchard cover crops and grazing allowed only on orchard cover crops for which tolerances have been established.

Residue data must be supplied for each type of formulation to be used, i.e., emulsifiable concentrate (EC), wettable concentrate (WP) or Flowable Concentrate, Granular, Dust. An analysis of the formulation used for the residue field trials must be submitted along with the residue data. At this time, only emulsifiable concentrates of dicofol are registered. Rohm and Haas has pending applications for registration of two emulsifiable concentrates (Kelthane EC and

Kelthane MF), a wettable powder (Kelthane 35), and a flowable concentrate (Kelthane 4F). Residue data are needed for both an emulsifiable concentrate and a wettable powder or flowable concentrate for all crops except cottonseed to support registered products and pending applications. (Cottonseed is found only on labels of emulsifiable concentrates.)

Residue data must also reflect the geographic locations where the crop is grown. The registrant may refer to "Agricultural Statistics" to determine appropriate locations for residue field trial data. For the crops for which Rohm and Haas has submitted data, residue data are needed for the following locations:

Crop	Locations from which residue data are needed
Citrus	
oranges	FL, CA, AZ, TX
grapefruit	FL, TX, CA
lemons	CA, AZ
Apples	CA, MI, NY, PA/WV, VA/NC, WA/OR
Pears	CA, NY, WA, MI
Grapes	CA, NY, WA, MI, NC
Walnuts	CA, OR
Pecans	AL/GA/LA/MS, NM/TX/OK
Dry beans	CA, ID, MI, CO, NE, ND
Summer Squash	CA, FL, TX, MI, NY/NJ/MA, GA/SC, OR
Cucumbers	CA, FL, TX, MI/OH, NY/NJ, NC/SC
Melons	TX, AZ, CA

If all submitted residue data are valid and labels are changed to reflect the maximum rates and other conditions in the submitted data, residue data will still needed for oranges from FL; for apples from NY and VA at the higher rate; for pears from NY, for walnuts from OR, for dry beans from MI, CO, NE, and ND; for summer squash from MI, NY/NJ/MA, and OR; and for cucumber from MI/OH.

Residues on many crops increased with increasing PHI. For this reason, we question the sampling techniques used. The registrant should completely describe all sampling and subsampling techniques used.

The data do not indicate whether dilute or concentrate sprays were used. This information (and volume of spray solution used per acre) is needed.

No data on an emulsifiable concentrate formulation were submitted for apples, pears, grapes, melons, cucumbers, or squash. Data are required for the emulsifiable formulation on these crops. Alternatively, these crops may be removed from labels for EC products.

No data from the use of a wettable powder or flowable formulation were submitted for citrus, dry beans, pecans, walnuts, and cottonseed. Data are required for the wettable powder or flowable formulation on these crops. Alternatively, these crops may be removed from proposed labels for wettable powder or flowable formulations.

Residue studies were not submitted for hops, spent hops, apricots, nectarines, peaches, caneberries, cherries, plum (fresh prunes), snap beans, lima beans (succulent), tomatoes, peppers, figs, field corn, alfalfa, clover, processed tomatoes, bean forage and hay or bean cannery waste, corn forage and fodder, and cottonseed forage. These studies were required by the Registration Standard, and are still needed. The PM should take appropriate action regarding the non-submission of these data.

Residue studies were not submitted for mint and strawberries. However, the Registration Standard concluded that additional residue studies were not needed for mint and strawberries, provided that plant metabolism studies show that dicofol, per se, is the residue of concern.

Comments on Specific Crops

Citrus. At the present time, residue data appear to support up to 3 ground applications of the emulsifiable concentrate at up to 6 lb ai/A. The volume of spray (dilute, concentrate, ULV) supported by the residue field trial data is not known.

Apples. Residues reported for three applications at 3 lb ai/A exceed the established tolerance. Registered labels allow only 2 applications. No more than two applications at no more than 3 lb ai/A appear to be supported at this time. Only ground applications appear to be supported. The volume of spray supported by the residue field trial data is not known.

Pears. Reported residues exceed the established tolerance at a 14 day PHI. The residue data submitted appear to support up to 3 ground applications at 3 lb ai/A and a 21

day PHI. The volume of spray supported by the residue field trial data is not known.

Grapes. Reported residues exceed the established tolerance. The residue data submitted appear to support up to two ground applications at 1.2 lb ai/A may be used with a 21 day PHI. The volume of spray supported by the residue field trial data is not known.

Dry Beans. Residues reported from aerial applications at 1.5 lb ai/A exceed the established tolerance. From the residue data submitted, it appears that up to two ground applications at 1.5 lb ai/A may be supported. The registrant should explain why residues are increasing with increasing PHI. The volume of spray supported by the residue field trial data is not known.

Other Crops. We have tabulated the rates and formulations used for developing residue data on other crops. The rates, PHI, and type of formulation used in these residue studies are tabulated below.

Crop	Formulation	Maximum Rate	PHI (days)
Melons	4F	3 x 0.6 lb ai/A	6
	or	2 x 1.13 lb ai/A	6
Cucumbers	4F	3 x 0.6 lb ai/A	2
Squash	4F	4 x 0.6 lb ai/A	2
Pecans	MF	2 x 2 lb ai/A	7
Walnuts	MF	2 x 2 lb ai/A	7
Cotton	MF	2 x 1.5 lb ai/A	30

The maximum rates tabulated above are the maximum rates that appear to be supported, pending review of the submitted residue data. These data cannot support formulations of a different type than was used in the residue field trials. Only ground or hand applications were used in generating these data. Thus, data must be submitted for aerial applications or aerial applications should be prohibited on the labels.

Processing Studies

Processing studies were submitted for apples, cotton, grapes, and citrus. Processing studies were not submitted for hops, plums, tomatoes, or beans. The PM should take appropriate action, regarding non-submission of these data. Review of the submitted processing studies will not be done as a part of this expedited review. Review of these data will follow at a later date.

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MEAT, MILK, POULTRY, AND EGGS

Registration Standard Data Gaps

Conventional animal feeding studies with large ruminants and poultry will be required to establish the extent of transfer of residues to meat and milk, poultry and eggs. These studies must be conducted at feeding levels which reflect 1x, 3x, and 10x those of the established tolerances for commodities and/or byproducts used as livestock feed, and at rates at which these commodities and/or byproducts are fed.

Current Submission

Feeding studies were submitted for cattle and poultry. These studies will not be reviewed as part of this expedited review. Review of these studies will follow. However, it should be noted that these studies cannot be accepted until the metabolism of dicofol in animals is adequately understood.

While we cannot determine appropriate tolerances for dicofol in meat, milk, poultry, and eggs; we must note that the lowest feeding levels Rohm and Haas used in their metabolism studies was much lower than the 1x feeding level we calculate based on current tolerances.

Our calculation of dietary intake of dicofol for cattle and poultry, based on current tolerances, is presented below. Note that spent hops, spent mint hay, and bean cannery waste are processed commodities, and thus, not under grower control. Therefore, feeding restrictions for these commodities on dicofol labels would not be practical.

DIETARY INTAKE OF DICOFOL IN BEEF CATTLE

Feed Item	Tolerance (ppm)	% in diet	Contribution (ppm)
Hops, spent	30	5	1.5
Mint, spent hay	25	25	6.25
Citrus pulp	10	33	3.3
Citrus molasses	10	15	1.5
Apple Pomace	5	22	1.1
			13.6 PPM

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DIETARY INTAKE OF DICOFOL IN DAIRY CATTLE

Feed Item	Tolerance (ppm)	% in diet	Contribution (ppm)
Hops, spent	30	5	1.5
Mint, spent hay	25	60	15.0
Citrus pulp	10	33	3.3
Citrus molasses	10	2	0.2
			20.0 PPM

DIETARY INTAKE OF DICOFOL IN POULTRY

Feed Item	Tolerance (ppm)	% in diet	Contribution (ppm)
Apple Pomace	5	5	0.25
Been Seed	5	15	0.45
Tomato Pomace	5	3	0.15
Grape Pomace	5	3	0.15
Cottonseed Meal	0.1	10	0.01
Soapstock	0.1	5	0.005
			1.01 PPM

OTHER CONSIDERATIONS

Compatibility with CODEX was discussed in the Registration Standard. This issue will be discussed further when the metabolism issues are resolved and the residue data reviewed in full.

CONCLUSIONS

1. A tolerance reassessment cannot be done at this time. Registration Standard data deficiencies must be resolved before a tolerance reassessment can be done. Metabolism issues must be resolved. Registered and proposed uses must be supported by residue data. Residue data deficiencies are tentative, since the residue data were screened, and not reviewed in full.

2. The directions for use on all registered labeling and all proposed labeling must be changed to reflect the uses for which residue data were submitted or residue data must be submitted for all uses on registered and proposed labels. See further discussion in Conclusion 6.

3. The metabolism of dicofol in plants is not adequately understood. The grapefruit, cottonseed, and bean metabolism

studies submitted are incomplete.

3a. For the grapefruit metabolism study, readable chromatograms are needed to support the identification of dicofol.

3b. Exhaustive extraction was done with polar solvents only along with acid hydrolysis as part of the fractionation scheme. However, no report of any attempt to identify the components of these fractions was reported. The various solvent fractions could have been combined, and identification of the combined fractions attempted. Additionally, non-polar solvents were not reported to have been used. However, the raw data indicate that isooctane/acetone was used as an extraction solvent. We note that the protocol included in this report suggested that heptane be used as one of the solvents for extraction. This point should be clarified. Enzyme hydrolysis was not used. Enzyme hydrolysis may have released some of the residues remaining in the grapefruit peel after the various extractions. Additionally, enzyme hydrolysis of the extract(s) may have cleaved some of the conjugates present and facilitated their identification. To support the conclusion that dicofol or its degradates are incorporated into the natural products of the peel, further identification of the fractions is needed.

3c. If TOX and EEB are not concerned about 40% of the residue in grapefruit being unidentified (10% or more "polar compounds"), then the requirement for further identification could be waived. However, confirmation of the identification of dicofol is still needed. TOX and EEB should be informed of our deferral.

3d. None of the radioactivity in cottonseed was unequivocally identified. Minimal effort to characterize the radioactivity in a hexane extract of cottonseeds was reported. Two and three of the standards used for comparison of R_f's did not appear to be resolved by normal phase and reverse phase TLC, respectively. Perhaps the actual photographs of these TLC plates would show better resolution than the photocopies of the photographs. However, even if the identification of dicofol as the primary residue is correct, less than 40% of the residue could be considered identified. No attempt to identify any of the activity in any other fraction was reported. Additionally, up to 50% of the radioactivity remained unextracted and no attempt at enzyme hydrolysis to release this activity was reported. Again, the term, "bound residue" was incorrectly used.

See our conclusions regarding the citrus metabolism study for further discussion.

3e. In the bean metabolism study, there was no reported attempt of exhaustive extraction, acid or base hydrolysis, or enzyme hydrolysis. Approximately 50% of the residue was tentatively identified as dicofol in immature beans + pods and in bean foliage by TLC. The identity of the residue was not confirmed by other techniques.

4. The metabolism of dicofol in lactating goats and laying hens may be considered adequately understood, depending on TOX and EEB considerations. TOX and EEB should be advised of our deferrals.

4a. The major dicofol metabolite in lactating goats and laying hens is FW-152 (1,1-bis(chlorophenyl)-2,2-dichloroethanol). Minor metabolites are dichlorobenzophenone and dichlorobenzhydrol. Unmetabolized dicofol is also present. Little if any dicofol is metabolized to DDE in lactating goats or laying hens.

4b. Only 50% of the TRR was extracted from goat liver. Enzyme hydrolysis of liver was not attempted. We defer to TOX and EEB the need for additional analysis of goat liver. We note for TOX and EEB that enzyme hydrolysis could have increased the extraction of radioactive residues from liver.

4c. Only 50% of the TRR was extracted from laying hen liver. Base and enzyme hydrolysis of liver were not attempted. Egg yolks were 70% extracted. Other tissues, egg whites, and whole eggs were 80 to 100% extracted. We defer to TOX and EEB the need for additional analysis of poultry liver. We note for TOX and EEB that base and enzyme hydrolysis could have increased the extraction of radioactive residues from liver.

5. Final conclusions cannot be made on the adequacy of the analytical methodology to determine the residue of concern until the plant and animal metabolism of dicofol are adequately understood. Thus, any comments made on methodology at this time are tentative, pending resolution of metabolism issues.

5a. A "clean" copy of the analytical method submitted in MRID No. 400420-08 is needed for further consideration. An explanation of the differing dates between the Rohm and Haas tables and the raw data is needed.

5b. m A copy of Rohm and Haas TR#36-81-05, referenced with the analytical method, is needed, since the sample workup from this method is reported to have been used.

5c. The registrant should be reminded that recovery data are needed each time the method is used (each time residue data are generated).

5d. Additional data on the applicability of FDA multiresidue methods is needed. Relative retention times (RRT) on 3% OV-225, 2% DEGS, and 3% OV-17 would be helpful. Information on methylene chloride elution from florisil is needed for o,p'-dicofol. Further information on protocol 1 is needed for o,p'-dicofol on protocol 1 and for both p,p'- and o,p'-dicofol for protocol 3. Protocols 2 and 4 would not be expected to recover dicofol.

6. RCB was requested to screen residue data for zero day residues for this expedited review. Thus, the residue data submitted were not reviewed in full. However, instead of zero day residues, RCB has tabulated the maximum residue reported for each crop where the residue reported exceeded 2 ppm. This tabulation is found in Table 20 of the body of this review. Obvious deficiencies are indicated in this review. However, additional deficiencies may be identified in a thorough review of these data. Submitted residue data included analyses for only p,p'- and o,p'- dicofol. We cannot conclude that these data are adequate until the metabolism issues and discrepancies between the residue data and labeling are resolved.

6a. The registrant should be reminded that all labeled uses must be supported by residue data or the labels amended to reflect the maximum use supported by residue data. Residue data must be submitted to support the maximum number of applications allowed on the label, or the maximum number of applications allowed on the label must be changed to reflect the use supported by the submitted residue data. A minimum number of applications per season or a maximum quantity of pesticide to be applied per season must be specified on product labels. A minimum interval between applications must be added to the labels. Residue data must reflect both dilute and concentrate sprays, ground and aerial application, as allowed on product labels (or product labels changed to reflect the residue data). The volume of spray used per acre must be reported for orchard applications. Use directions for orchards must be changed to account for the variability in tree sizes. (Several options for orchard labeling are shown in Attachment 1). Grazing restrictions must also be added for orchards. Suggested

language is "Do not allow livestock to graze in treated areas or feed on orchard cover crops." Alternatively, tolerances may be proposed for orchard crops and grazing allowed only on orchard cover crops for which tolerances have been established.

6b. Residue data must be supplied for each type of formulation to be used, i.e., emulsifiable concentrate (EC), wettable concentrate (WP) or Flowable Concentrate, Granular, and Dust. An analysis of the formulation used for the residue field trials must be submitted along with the residue data. At this time, only emulsifiable concentrates of dicofol are registered. Rohm and Haas has pending applications for registration of two emulsifiable concentrates (Kelthane EC and Kelthane MF), a wettable powder (Kelthane 35), and a flowable concentrate (Kelthane 4F). Residue data are needed for both an emulsifiable concentrate and a wettable powder or flowable concentrate for all crops except cottonseed. (Cottonseed is found only on labels of emulsifiable concentrates.)

6c. Residue data must also reflect the geographic locations where the crop is grown. The registrant may refer to "Agricultural Statistics" to determine appropriate locations for residue field trial data.

6d. If all submitted residue data are valid and labels are changed to reflect the maximum rates and other conditions in the submitted data, residue data will still be needed for oranges from FL; for apples from NY and VA at the higher rate; for pears from NY, for walnuts from OR, for dry beans from MI, CO, NE, and ND; for summer squash from MI, NY/NJ/MA, and OR; and for cucumber from MI/OH.

6e. Residues on many crops increased with increasing PHI. For this reason, we question the sampling techniques used. The registrant should completely describe all sampling and subsampling techniques used.

6f. The data do not indicate whether dilute or concentrate sprays were used. This information (and volume of spray solution used per acre) is needed.

6g. No data on an emulsifiable concentrate formulation were submitted for apples, pears, grapes, melons, cucumbers, or squash. Data are required for the emulsifiable concentrate formulation on these crops. Alternatively, these crops may be removed from labels for EC products.

6h. No data from the use of a wettable powder or flowable formulation were submitted for citrus, dry beans, pecans, walnuts, and cottonseed. Data are required for the wettable powder or flowable formulation on these crops. Alternatively, these crops may be removed from proposed wettable powder or flowable formulation labels.

6i. Residue studies were not submitted for hops, spent hops, apricots, nectarines, peaches, caneberries, cherries, plum (fresh prunes), snap beans, lima beans (succulent), tomatoes, peppers, figs, field corn, alfalfa, clover, processed tomatoes, bean forage and hay or bean cannery waste, corn forage and fodder, and cottonseed forage. These studies were required by the Registration Standard, and are still needed. The PM should take appropriate action regarding the non-submission of these data.

6j. Residue studies were not submitted for mint and strawberries. However, the Registration Standard concluded that additional residue studies were not needed for mint and strawberries, provided that plant metabolism studies show that dicofol, per se, is the residue of concern.

6k. Citrus. At the present time, residue data appear to support up to 3 ground applications of the emulsifiable concentrate at up to 6 lb ai/A. The volume of spray (dilute, concentrate, ULV) supported by the residue field trial data is not known.

6l. Apples. Residues reported for three applications at 3 lb ai/A exceed the established tolerance. Registered labels allow only 2 applications. No more than two applications at no more than 3 lb ai/A appear to be supported at this time. Only ground applications appear to be supported. The volume of spray supported by the residue field trial data is not known.

6m. Pears. Reported residues exceed the established tolerance at a 14 day PHI. The residue data submitted appear to support up to 3 ground applications at 3 lb ai/A and a 21 day PHI. The volume of spray supported by the residue field trial data is not known.

6n. Grapes. Reported residues exceed the established tolerance. The residue data submitted appear to support up to two ground applications at 1.2 lb ai/A may be used with a 21 day PHI. The volume of spray supported by the residue field trial data is not known.

6o. Dry Beans. Residues reported from aerial applications at 1.5 lb ai/A exceed the established tolerance. From the residue data submitted, it appears that up to two ground applications at 1.5 lb ai/A may be supported. The registrant should explain why residues are increasing with increasing PHI. The volume of spray supported by the residue field trial data is not known.

6p. Other Crops. We have tabulated the rates and formulations used for developing residue data on other crops. The rates, PHI, and type of formulation used in these residue studies are tabulated below.

Crop	Formulation		Maximum Rate	PHI (days)
Melons	4F		3 x 0.6 lb ai/A	6
		or	2 x 1.13 lb ai/A	6
Cucumbers	4F		3 x 0.6 lb ai/A	2
Squash	4F		4 x 0.6 lb ai/A	2
Pecans	MF		2 x 2 lb ai/A	7
Walnuts	MF		2 x 2 lb ai/A	7
Cotton	MF		2 x 1.5 lb ai/A	30

The maximum rates tabulated above are the maximum rates that appear to be supported, pending review of the submitted residue data. These data cannot support formulations of a different type than was used in the residue field trials. Only ground or hand applications were used in generating these data. Thus, data must be submitted for aerial applications or aerial applications should be prohibited on the labels.

7. Processing studies were submitted for apples, cotton, grapes, and citrus. Processing studies were not submitted for hops, plums, tomatoes, or beans. Spent hops are an animal feed item not under grower control. Thus, a feeding restriction for this commodity is impractical. With a feeding restriction for bean forage and hay, processing data are required for bean cannery waste, which is not under the control of the grower. The PM should take appropriate action, regarding non-submission of these data. Review of the submitted processing studies will not be done as a part of this expedited review. Review of these data will follow at a later date.

8. Feeding studies were submitted for cattle and poultry. These studies will not be reviewed as part of this expedited review. Review of these studies will follow. However, it should be noted that these studies cannot be accepted until TOX and EEB concur that the metabolism of dicofol in animals

is adequately understood. The registrant should note our calculations of maximum dietary intake for livestock based on current tolerances.

9. Compatibility with CODEX was discussed in the Registration Standard. This issue will be discussed further when the metabolism issues are resolved and the residue data reviewed in full.

RECOMMENDATIONS

We recommend that the registrant be informed of the remaining Registration Standard data gaps and advised to fill the data gaps. We recommend that the PM take appropriate action regarding non-receipt of required data.

We recommend that the PM inform TOX and EEB of our deferrals in conclusions 3c and 4c regarding plant and animal metabolism.

Attachment: Guidance for Orchard Spray Application
attached to all copies

cc: circu, R.F., S. Hummel, Dicofol Special Review File (S. Hummel), dicofol S.F., dicofol Reg. Standard File (Boodee)
TOX, EAB, EEB (L. Turner), SRB (B. Kapner), PMSD/ISB
RDI:EZ:5/26/87:RDS:5/26/87
TS-769:RCB:SVH:svh:CM#2:RM810:5/27/87

Guidance for Orchard Spray Application

As a guidance to any future orchard spray applications, the petitioner should incorporate one or more of the following concepts in their submissions as the means of instructing the users on how to vary the quantity of a.i./acre that is needed for different tree sizes.

Procedure 1. For High Volume (HV) Spray Applications to Orchards

Determine volume/A to spray orchard to run-off. Use so much active ingredient/ 100 gal and multiply this number by the volume/A to spray your orchard to runoff to determine the amount of active ingredient/A.

For Example:

Step 1: Use rate (determined by petitioner).....0.5 lb act/100 gal.

Step 2: To spray one acre of your orchard to run-off...300 gal/A.

Step 3: The amount of lb a.i./acre in 300 gal of water is 1.5 lb (0.5 lb act/100 gal x 300 gal/A).

Procedure 2. Estimation of Tree Row Volume (TRV) to Calculate the Gallons/A Needed to Spray to Run-off

Step 1: 43,560/between-row spacing (ft) = feet of row/acre.

Step 2: Feet of row/acre x tree height (ft) x cross-row limb spread (ft) = cu ft of TRV/acre.

Step 3: Select one of the following numbers that best indicate the canopy density of each separate orchard or block:

0.70 gal/1,000 cu ft: Trees extremely open, light visible through entire tree, less than 15 scaffold limbs/tree or young tree.

0.75 gal/1,000 cu ft: Trees very open, 18 - 21 scaffold limbs/tree, light penetration throughout tree, healthy spurs within tree canopy.

0.80 gal/1,000 cu ft: Trees well pruned, adequate light in trees for healthy spurs throughout trunk and scaffold limbs, many holes in foliage where light can be seen through tree.

0.85 gal/1,000 cu ft: Trees moderately well pruned, reasonable spur population within canopy, tree thick enough that light cannot be seen through bottom two-thirds of tree.

0.90 gal/1,000 cu ft: Trees pruned minimally, spurs inside canopy are weak due to limited light, very few holes where light can be seen through the tree.

0.95 gal/1,000 cu ft: Little or no pruning, spurs dead or very weak in canopy, very little light visible through tree.

1.00 gal/1,000 cu ft: Tree totally unpruned, extremely thick, no light visible anywhere through tree canopy, trees more than 20 ft high.

Step 4: $$\frac{\text{cu ft of TRV/acre (from Step 2)} \times \text{density (from Step 3)}}{1{,}000}$$

= gal of dilute solution to be applied/A.

Step 5: Using the volume of spray to run-off calculated in Step 4 above, calculate the lb a.i./acre using the formula of Procedure 1 (Step 3).

For Example: An orchard has rows spaced 25 ft apart, tree height is 20 ft, and cross row limb spread is 17 ft. The tree density is 0.85.

Step 1: 43,560 ft^2/25 ft = 1,742.4 ft

Step 2: 1,724.4 ft x 20 ft x 17 ft = 592.416 cu ft

Step 3: Density has been given as 0.85

scaffold limbs/tree or young tree.

Step 4: (592.416 x 0.85)/1,000 = 503.5 gal/acre

Step 5: Using the volume of spray to run-off calculated in Step 4 above, calculate the lb a.i./acre using the formula of Procedure 1 (Step 3).

Procedure 3. Estimation of Gallons of Pesticide Spray Solution per acre to Spray to Run-off or LV Application at the Full Leaf Stage of Canopy Using the following Table

Approximate number of gallons of pesticide spray liquid needed per acre for coverage at the full leaf stage of canopy development in tree fruit orchards using high volume (HV) dilute sprays and low volume (LV) concentrate sprays applied with airblast sprayers

Tree height (ft) X Tree width (ft)[b]	Spray Type	Gallons Per Acre[a] distance between tree rows (ft)												
		16	18	20	22	24	26	28	30	32	34	36	38	40
80	HV	152	136											
	LV	20[c]	17[c]											
100	HV	191	169	152										
	LV	25	22[c]	20[c]										
150	HV	256	254	229	208	191								
	LV	37	33	29	27	25								
200	HV	...[d]	...	305	277	254	235	218						
	LV	...	...	39	36	33	30	28						
250	HV	...	...	...	346	317	293	272	254	238				
	LV	...	...	...	45	41	38	35	33	31				
300	HV	...	...	...	416	381	352	327	305	286	269	254	241	229
	LV	...	...	...	53	49	45	42	39	37	35	33	31	29
350	HV	...	...	...	...	445	411	381	356	334	314	296	281	267
	LV	...	...	...	...	57	53	49	46	43	40	38	36	34
400	HV	...	...	...	...	...	469	436	407	381	359	339	321	305
	LV	...	...	...	...	...	60	56	52	49	46	44	41	39
450	HV	...	...	...	...	...	...	490	457	429	404	381	361	343
	LV	...	...	...	...	...	...	63	59	55	52	49	46	44
500	HV	...	...	...	...	...	...	...	508	476	448	424	401	381
	LV	...	...	...	...	...	...	...	65	61	58	54	52	49
550	HV	...	...	...	...	...	...	...	...	524	493	466	441	419
	LV	...	...	...	...	...	...	...	...	67	63	60	57	54
600	HV	...	...	...	...	...	...	...	...	...	538	508	481	457
	LV	...	...	...	...	...	...	...	...	...	69	65	62	59

[a] See text for full details of calculation. All values rounded to the nearest whole gallon. Based on standard dosage volumes of 0.7 gallon per 1,000 cu ft TRV for HV and 0.09 gallon for LV sprays. Trees which have a very dense foliar canopy may require slightly more spray volume than shown.

[b] Where small trees are interplanted with large trees in the same row, use only the large tree dimensions.

[c] LV applications of less than 25 gallons per acre are not generally recommended because of other factors affecting coverage.

[d] Data not given because the combination of this tree size on this planting density is unlikely.

Reference: Unrath, C. R., and T. B. Sutton. North Carolina State University, Raleigh, NC 27695. Bulletin AG 37.

The amount of a.i./acre can be calculated by using the volume of spray to run-off per acre found in the table above into the formula used in Procedure 1 (Step 3) above.

Procedure 4. For Low Volume (LV) and Ultra-low Volume (ULV) Applications to Orchards

Take the amount of a.i./A for orchard calculated from Procedure 1; the TRV estimated from Procedure 2; or the full leaf stage of canopy table from Procedure 3; and add to X gal of water/A for LV applications or Y gal of water and/or other solvent/A. X and/or Y is (are) determined by the petitioner to coincide with the proposed use. Less active ingredient/A is normally required for LV and ULV applications. The lower amount of active ingredient/A, if proposed, should be stated as a fraction of the high volume rate. Residue data must be submitted for all uses proposed on the label. Therefore, LV and/or ULV applications will not be allowed if residue data have been submitted for HV applications only.