9-29-92 R7,

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

SEP 29 1992

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#2E04018. Chlorothalonil (Bravo® 720 Agricultural Fungicide, EPA Reg. No. 50534-188) in or on Mango. Evaluation of analytical method and magnitude of residue data. MRID No. 419882-01, CBTS No. 8581, HED No. 1-2372, DP Barcode: 168809.

FROM: William D. Wassell, Chemist
Tolerance Petition Section I
Chemistry Branch I - Tolerance Support
Health Effects Division (H7509C)

THROUGH: Robert S. Quick, Section Head
Tolerance Petition Section I
Chemistry Branch I - Tolerance Support
Health Effects Division (H7509C)

TO: Hoyt L. Jamerson, PM - 43
Emergency Response and Minor Use Section
Registration Division (H7505C)

and

Toxicology Branch II
Fungicide/Herbicide Support
Health Effects Division (H7509C)

W.L. Biehn, Ph.D., Associate Coordinator, Interregional Research Project No. 4 (IR-4), State Agricultural Experiment Station, Rutgers University, New Brunswick, New Jersey on behalf of the IR-4 Project and the Agricultural Experiment Stations of Florida, Puerto Rico and the Virgin Islands requests the establishment of a tolerance for the combined residues of the fungicide chlorothalonil, [tetrachloroisophthalonitrile] and its metabolite 4-hydroxy-2,5,6-trichloroisophthalonitrile (SDS-3701) in or on the raw agricultural commodity (RAC) mango at 1.0 ppm.

Chlorothalonil is a FIFRA '88 List A pesticide active ingredient and the Chemistry Chapters of the Chlorothalonil Final Registration Standard and Tolerance Reassessment (FRSTR) have been completed (3/11/88).

Tolerances are established (40 CFR §180.275(a)) for the combined residues of the fungicide chlorothalonil and its metabolite 4-hydroxy-2,5,6-trichloroisophthalonitrile in or on various RAC's ranging from 0.05 to 15 ppm. A tolerance with regional registration is established (40 CFR §180.275(b)) for the combined residues of this fungicide and its metabolite at 2 ppm in or on mint hay.

A letter (dated 7/22/91) from Ralph P. Burton, Manager, Product Registrations, ISK Biotech Corporation to Mr. Hoyt L. Jamerson, Registration Division, authorizes the Agency to review and rely on all test data owned or submitted to the EPA by ISK Biotech for chlorothalonil, which may be necessary to support the proposed tolerance.

Conclusions:

1. The manufacturing process of chlorothalonil (technical product) has been adequately discussed in the Product Chemistry Chapter of the FRSTR (3/11/88). We have determined that the impurity hexachlorobenzene (HCB) is of concern.

2. CBTS concludes the proposed directions for use of the product on mangoes are inadequate. We request a revised Section B that includes a restriction against the grazing of livestock in treated orchards/groves as well as a restriction against the cutting of cover crops for livestock feed.

3a. Plant metabolism data were not submitted with this petition. For the purpose of this minor crop petition for mangoes only, we conclude the nature of the residue is adequately understood and the regulated residues are chlorothalonil and its 4-hydroxy metabolite.

3b. The impurity HCB is not includes in the tolerance expression. HCB can occur as a residue in chlorothalonil treated commodities. The HCB residue levels are used in calculating dietary risk considerations asociated with HCB for chlorothalonil treated commodities.

4. Animal metabolism data were not submitted with this petition. Animal feed items are not derived from mangoes. Therefore, there is no concern for animal metabolism and secondary residues of chlorothalonil in animal commodities resulting from the proposed use.

5. For the purpose of this minor crop petition only, CBTS concludes adequate methodology for the enforcement of residues resulting from the proposed use of chlorothalonil on mango does exist.

6. CBTS defers comments on the adequacy of the residue method utilized for data collection purposes until the data discrepancies cited in the Magnitude of Residue Section of this review are resolved.

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7. CBTS requests the petitioner to review the submitted data and recalculate the recovery and residue values for all samples including storage stability. It is apparent the recoveries for some of the analytes are variable and the analytical method utilized may not be suitable. If the petitioner wishes to utilize the data from these trials, we request submission of a **complete** set of chromatograms for our review.

CBTS requires at least three (3) valid mango residues trials at the maximum proposed application rate in order to evaluate the residue levels resulting from the proposed use of chlorothalonil on this fruit. Inclusion of Puerto Rico as a site for one of the three requested field trials would be desirable. The 1988 and 1990 Florida trials may be acceptable if the question raised in the Magnitude of Residue section of this review are resolved.

8. Storage stability data for chlorothalonil on mango was supplied with the magnitude of residue data. This data was not reviewed for reasons stated in the Magnitude of Residue Section of this review.

9. The International Residue Limit Status sheet is attached and there are no established Codex, Mexican or Canadian tolerances for chlorothalonil and its metabolite 4-hydroxy-2,5,6-trichloroisophthalonitrile in or on mangoes. Therefore, the establishment of the proposed tolerance on this commodity will not create compatibility problems.

Recommendations:

For reasons 2, 6, 7 and 8, stated above, CBTS can not at this time recommend for the establishment of the proposed tolerance limit of 1.0 ppm for residues of chlorothalonil and its 4-hydroxy metabolite in or on the raw agricultural commodity mango.

Note to PM: CBTS requests submission of this review in its entirety to the petitioner.

Detailed Considerations

Manufacture and Formulation:

The manufacturing process of chlorothalonil (technical product) has been adequately discussed in the Product Chemistry Chapter of the FRSTR (3/11/88). We have determined that the impurity hexachlorobenzene (HCB) is of concern.

The formulation to be used is Bravo® 720 Agricultural Fungicide (EPA Reg. No. 50534-188); this is a product of ISK Biotech Corporation of Mentor, Ohio. Bravo 720 is a broad spectrum fungicide containing 6.0 lbs active ingredient per gallon.

Proposed use:

Apply Bravo 720 to control anthracnose on mango at a rate of 2 to 3.5 pints per acre (1.5 to 2.6 lbs ai/A) in at least 100 gallons per acre. Begin applications at early bloom and repeat at 7 to 14 day intervals until early fruit development. Use the high rate and apply weekly when conditions favor disease development. A maximum of 32 pints of product (24 lbs ai/A) may be used for each growing season. Do not apply within 21 days of first harvest.

CBTS concludes the proposed directions for use of the product on mangoes are inadequate. We request a revised Section B that includes a restriction against the grazing of livestock in treated orchards/groves as well as a restriction against cutting of cover crops for feeds.

Nature of the Residue - Plants:

Plant metabolism data were not submitted with this petition. The available plant metabolism data for chlorothalonil has been extensively reviewed in the Residue Chemistry Chapter of the FRSTR (dated: 3/11/88), PP#5F3183 (see memo of S.H.Willett, 11/3/88) and PP#6E3410 (see memo of S.H.Willett, 6/22/89). In PP#6E3410, we concluded that the nature of the residue in plants is not adequately understood. We are requiring at least one additional metabolism study in order to adequately delineate the nature of the residue in plants (see memo of S.H. Willett, 9/8/89).

A metabolism study on tomatoes with ^{14}C-chlorothalonil was submitted and reviewed in conjunction with PP5F3183 (see our memo of 11/3/88, S.H. Willett). This study suggests that the residues are primarily comprised of chlorothalonil and 4-hydroxy-2,5,6-trichloroisophthalonitrile (SDS-3701). Some translocation of residues occurs from the foliage, root and possibly the fruit skin, but the residues appear to be primarily surface in nature. For the purpose of this minor crop petition for mangoes only, we conclude the nature of the residue is adequately understood and the residues of toxicological concern are chlorothalonil and its 4-hydroxy metabolite (SDS-3701) along with the impurity HCB.

Chlorothalonil and its 4-hydroxy metabolite are included in the tolerance expression for residues resulting from the use of chlorothalonil, but residue levels of HCB are considered separately. Currently, CB estimates residue levels of HCB at 0.5% of the chlorothalonil tolerance level for individual commodities. This value is utilized to estimate dietary risk associated with HCB, but additional data on HCB levels has been requested for reregistration of chlorothalonil (see our memo of 4/11/89, D.F. Edwards, Ph.D., DEB No. 4892). HCB residue data has not been requested for all commodities for which chlorothalonil is registered.

Nature of the Residue - Animal:

Animal metabolism data were not submitted with this petition. Animal feed items are not derived from mangoes. Therefore, there is no concern for animal metabolism and secondary residues of chlorothalonil in animal commodities resulting from the proposed use.

Analytical Methods - Enforcement:

Recovery of chlorothalonil via FDA Multiresidue Protocol E (PAM I 211.1 and 212.1) is complete (Pestrak data base (11/6/90)). The 4-hydroxy metabolite of chlorothalonil (SDS-3701) is not recoverable via FDA Multiresidue Protocols (Pestrak data base (11/6/90)). Recovery of the impurity HCB via FDA Multiresidue Protocols E and D (PAM I, 211.1 and 232.4) is complete.

An enforcement method for the determination of residues of chlorothalonil and its 4-hydroxy metabolite has been published in PAM II (Pesticide Reg. Sec. 180.275) as Method I. Additionally, we have recommended for a method entitled "General Analytical Procedure for the Determination of Residues of Chlorothalonil (SDS-2787), SDS-3701, SDS-46851, HCB and PCBN on Selected Crops" to be published in PAM II as this appears to be a better methodology than the currently published method (see memo of W.T. Chin, Ph.D., 2/22/91). This method has not yet appeared in PAM II.

For the purpose of this minor crop petition only, CBTS concludes adequate methodology for the enforcement of residues resulting from the proposed use of chlorothalonil on mango does exist.

Analytical Methods - Data Collection:

The analytical portions of the 1988 and 1990 residue studies were conducted at the IR-4 Southern Region Analytical Laboratory, University of Florida, Gainesville, FL. The analytical method utilized for the determination of chlorothalonil, SDS-3701 (4-hydroxy-2,5,6-trichlorophthalonitrile), SDS-46851 (3-carboxytrichlorobenzamide), HCB (hexachlorobenzene) and PCBN (pentachlorobenzonitrile) in or on mangoes was a slightly modified version of Fermenta Method 1321-86-0046-CR-000. Briefly, the residues are extracted by blending the samples with acidic acetone. After filtering, the extract is split into aliquots of equal volume. Residues of chlorothalonil, HCB and PCBN are extracted from one of the aliquots while the residues of SDS-3701 and SDS-46851 are extracted from the other aliquot. The chlorothalonil, HCB and PCBN are extracted from the aliquot with petroleum ether. A solvent exchange to methylene chloride is performed and the extract is cleaned by liquid/solid chromatography utilizing florisil. A solvent exchange to toluene is performed and the extract is analyzed by GC. The acetone is evaporated from the other aliquot of the aqueous extract. The residues of SDS-3701 and SDS-46851 are extracted from this aliquot by sequential partitioning with petroleum ether and diethyl ether after adjusting the pH of the extract first to 4.5 and then to less than 1.

The extracted residues are methylated with 3-methyl-1-*p*-tolyltriazene. A solvent exchange to methylene chloride is performed and the extract is cleaned by liquid/solid chromatography utilizing florisil. A solvent exchange to toluene is performed and the residues in both extracts are quantitated by gas chromatographic analysis equipped with a ^{63}Ni electron capture detector and a fused silica capillary column.

Field and storage stability samples were analyzed concurrently with fortified control samples at various levels. The results of the concurrent fortifications will not be discussed at this time as the data contained many errors (see Magnitude of Residue Section of this review for a detailed discussion).

CBTS defers comments on the adequacy of the residue method utilized for data collection purposes until the data discrepancies cited in the Magnitude of Residue Section of this review are resolved.

Note to IR-4: Analyses for chlorothalonil metabolite SDS-46851 (3-carboxytrichlorobenzamide) and the impurity PCBN (pentachlorobenzonitrile) are not necessary for future chlorothalonil submissions.

Magnitude of Residue: (MRID No. 419882-01)

Field trials were conducted in Florida in 1987 (3 trials), 1988 (1 trial) and 1990 (1 trial) with chlorothalonil on mango in order to produce treated crop samples for residue analysis. In the 1987 trials, two trials were conducted with seven applications at a rate of 1.3 lbs ai/A (total dosage: 9.1 lbs ai/A) and one trial was conducted with eight applications at a rate of 1.3 lbs ai/A (total dosage: 10.4 lbs ai/A). These trials do not approximate the maximum proposed use rate (applications at 1.5 to 2.6 lbs ai/A at 7 to 14 day intervals with a maximum dosage of 24 lbs ai/A) and are not considered adequate to determine the residue levels resulting from the proposed use. The data for these trials was not extensively reviewed and will not be discussed in this review.

In the 1988 trial, chlorothalonil was applied to mango nineteen times at a rate of 1.64 pts/A (1.23 lbs ai/A, total dosage: 23.4 lbs ai/A) with approximately 7 days between applications. In the 1990 trial, chlorothalonil was applied to mango sixteen times at a rate of 3.5 pts/A (2.6 lbs ai/A, total dosage: 41.6 lbs ai/A) with approximately 7 days between applications. Applications in both trials were made with an air blast sprayer utilizing 250 gallons of spray per acre.

The petitioner submitted approximately 500 pages of data for these two trials (Volume 4 of 4). The data includes chromatograms and data work sheets for most of the analyses. We performed a spot check of some of the work sheets and compared them to the chromatograms; this revealed **many** errors. Some of these errors include:

1. The standard curve was forced through the origin by inclusion of a 0,0 point in the curve. All data should be recalculated without the 0,0 point in the calibration curve.

2. Sample 880187B (page 1053 and 1054 of 1569) contained residues above the method quantitation limit of HCB and PCBN. This sample was the untreated control sample which was fortified and analyzed concurrently with residue samples to determine the method recoveries. All fortifications of this sample should be recalculated to correct for the apparent residue level.

3. In numerous instances, some calibration standards were not included in the calculations, i.e. page 1065 of 1569, the 0.02 ppm PCBN standard was not utilized. Another example is page 1064 of 1569; the 0.012 ppm HCB standard was not utilized. When these standards are included and the 0,0 point is not included in the calculations, the recoveries are approximately 30% less than what was reported. We can find no justification for leaving these points out of the calibration curve.

4. A note included on page 1045 of 1569 reads: "data not used[,] bad peak separation". The chromatography for these samples does not look any worse than the chromatography for the other SDS-46851 analyses and we can find no justification for leaving out this data.

5. Samples 880189 and 880189 contain detectable residues of approximately 0.1 ppm SDS-46851. This data is contained on page 1079 of 1569; the data was not used due to "bad peak separation". This sample was subsequently extracted and reanalyzed (Page 1178 of 1569); the chromatograms for this sample and calibration standard contain peaks that were not integrated properly because the integration function of the integrator was turned off too early in the run.

6. Recoveries for the metabolites SDS-3701 and SDS-46851 are highly variable and the method may not be suitable to determine these compounds.

7. In numerous instances, certain chromatograms were not included in the report. If the petitioner desires to supply us with the chromatograms from the study, a complete set should be supplied and not an almost complete set.

CBTS requests the petitioner to review the submitted data and recalculate the recovery and residue values for all samples including storage stability. It is apparent the recoveries for some of the analytes are variable and the analytical method utilized may not be suitable. If the petitioner wishes to utilize the data from these trials, we request submission of a **complete** set of chromatograms for our review.

CBTS requires at least three (3) valid mango residues trials at the maximum proposed application rate in order to evaluate the residue levels resulting from the proposed use of chlorothalonil on this fruit. Inclusion of Puerto Rico as a site for one of the three requested field trials would be ideal, but not completely necessary.

Note to IR-4: Recalculation of SDS-46851 and PCBN data are not necessary. While HCB data are not required for all commodities in reregistration, but as the data are available and may enhance the accuracy of the estimation of the dietary risk from HCB residues resulting from the proposed use of chlorothalonil, we request the HCB data to be recalculated.

Storage Stability: (MRID Nos. 418087-01)

Storage stability data for chlorothalonil on mango was supplied with the magnitude of residue data. This data was not reviewed for reasons stated in the Magnitude of Residue Section of this review.

Meat, Milk, Poultry and Eggs:

Animal feed items are not derived from mangoes. Therefore, there is no concern for animal metabolism and secondary residues of chlorothalonil in animal commodities resulting from the proposed use.

Other Considerations:

The International Residue Limit Status sheet is attached and there are no established Codex, Mexican or Canadian tolerances for chlorothalonil and its metabolite 4-hydroxy-2,5,6-trichloroisophthalonitrile in or on mangoes. Therefore, the establishment of the proposed tolerance on this commodity will not create compatibility problems.

Attachment: IRL Status Sheet
cc: WDWassell, RF, Circ., PP#2E04018, chlorothalonil SF, chlorothalonil Rereg. File
RDI: RS Quick: 9/28/92; RA Loranger: 9/29/92.
H7509C:CBTS:WDWassell:wdw:CM#2:Rm 804U:(703)305-6135:1/10/92.
Disk: WDW-1, File: WDW-25

INTERNATIONAL RESIDUE LIMIT STATUS

F. Kutz 2/5/92

CHEMICAL Chlorothalonil

CODEX NO. 81

CODEX STATUS:

☑ No Codex Proposal Step 6 or above (on Mango)

Residue(if Step 8): parent

Crop(s)	Limit (mg/kg)

PROPOSED U.S. TOLERANCES:

Petition No. PP 1E 04018

RCB Reviewer W.D. Wassell

Residue: parent & its metabolite 4-hydroxy-2,5,6-trichloroisophthalonitrile

Crop(s)	Limit (mg/kg)
Mango	1.0

CANADIAN LIMITS:

☑ No Canadian limit (on mango)

Residue: parent

Crop(s)	Limit (mg/kg)

MEXICAN LIMITS:

☑ No Mexican limit (on mango)

Residue:

Crop(s)	Limit (mg/kg)

NOTES: