CBTS
7-22-96

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 07/22/96

SUBJECT: **PP#6E4672. CHLOROTHALONIL** in/on **PISTACHIOS.**
Review of Request for Permanent Tolerance.

DP Code:	D223399	Chem#:	081901
Trade Name:	Bravo 720	Caswell#:	215B (HCB, 477)
EPA Reg #:	50534-188	40 CFR:	180.275
Class:	Fungicide	MRID#:	439241-00, -01
Rereg Case:	0097	Priority:	6

TO: Debbie McCall, Acting Team Leader
RS/RCAB/HED (7509C)

FROM: M. Nelson, W. Dykstra, C. Lewis
PIRAT/RCAB/HED (7509C)

THRU: Michael Metzger, Acting Chief
RCAB/HED (7509C)

INTRODUCTION

The petitioner, Interregional Research Project No. 4 (IR-4), on behalf of the Agricultural Experiment Station of Arizona and the Arizona and California Pistachio Growers Associations, proposes the establishment of a tolerance for the combined residues of the fungicide chlorothalonil and its metabolite 4-hydroxy-2,5,6-trichloroisophthalonitrile (expressed as chlorothalonil) in or on the raw agricultural commodity (rac) pistachios at 0.2 ppm.

Tolerances for said combined residues on various rac's are listed under 40 CFR §180.275(a,b).

Chlorothalonil is a List A chemical for reregistration. The Reregistration Eligibility Document (RED) is scheduled for FY96 completion (Case# 0097). The HED Chapter was finished 2/13/96.

RECOMMENDATION

Dietary exposure estimates for chlorothalonil and its contaminant, hexachlorobenzene, are below HED's level of concern. **Provided** the Bravo 720 label is amended to restrict application to closed cab airblast equipment; to impose a 4-day restricted entry interval (REI); and to specify additional personal protective equipment (PPE; all mixers and loaders to wear chemical-resistant gloves and a chemical-resistant apron), occupational exposure estimates will also be below HED's level of concern. **Contingent** upon incorporation of these label revisions, PIRAT recommends favorably for the establishment of the proposed tolerance for the combined residues (per 40 CFR 180.275a) of chlorothalonil in or on pistachios at 0.2 ppm.

CONCLUSIONS

Hazard Assessment

1. Occupational Exposure Endpoint Selection

a) Short-Term Risk

1) Chlorothalonil. For short-term MOE calculations, the TES (Toxicology Endpoint Selection) Committee recommended use of the LEL of 175 mg/kg/day in the 3-month feeding study in male Fischer 344 rats (MRID# 40243702). The LEL was based on the renal and gastric histological lesions observed within 4 days of dosing. A NOEL was not established. The lesions appear to be precursors to kidney and forestomach neoplasms observed in the chronic study. This endpoint is used with an MOE of 300.

2) Hexachlorobenzene (HCB). There is no toxicological endpoint identified in the RED for short-term exposure to HCB.

b) Intermediate-Term Risk

1) Chlorothalonil. For intermediate-term MOE calculations, the TES Committee recommended use of the NOEL of 1.5 mg/kg/day from the 13-week feeding study in rats (MRID#s 00127842, 00127843, 00127851, 00127852, and 00147943). At the LEL of 3.0 mg/kg/day, there were increased numbers of irregular intracytoplasmic inclusion bodies in the proximal convoluted tubules of all males.

2) HCB. There is no toxicological endpoint identified in the RED for intermediate-term exposure to HCB.

c) Chronic Risk

A chronic worker exposure scenario has not been identified for this action and a toxicological endpoint was not selected for chlorothalonil or HCB.

d) Cancer Risk

1) Chlorothalonil Q_1^* = 7.66 x 10^{-3} $(mg/kg/day)^{-1}$. Chlorothalonil has been classified as a Group B2 (probable human carcinogen) chemical by the HED Cancer Peer Review Committee based upon female rat renal (adenoma and/or carcinoma) tumor rates. A 3/4 scaling factor was used to determine the Q_1^* from the rat data.

2) HCB Q_1^* = 1.02 $(mg/kg/day)^{-1}$. HCB, an impurity in chlorothalonil, is also classified as a Group B2 chemical (probable human carcinogen) based on positive results in hamsters and rats.

e) Dermal Penetration

1) Chlorothalonil. The dermal penetration for chlorothalonil has been determined to be 5% in a rat dermal penetration study.

2) HCB. The dermal penetration of HCB is estimated at 26% (per the HED Chapter of the Chlorothalonil RED).

2. Dietary Endpoint Selection

a) Acute Risk

1) Chlorothalonil = 175 mg/kg/day. The LEL of 175 mg/kg/day (only dose tested) from the 3-month rat study (MRID# 40243702) should be used for evaluating acute dietary risk to all subgroups. This endpoint will be used with an uncertainty factor of 300 (based on renal and gastric lesions observed in male Fischer 344 rats within four days of testing). This recommendation is from the TES Document dated 10/10/95.

2) HCB. No acute dietary endpoints have been identified.

b) Chronic Risk

1) Chlorothalonil RfD = 0.018 mg/kg/day. The RfD for chlorothalonil was established based on a 2-year dog feeding study (MRID# 00114034) with a NOEL of 1.8 mg/kg/day and an uncertainty factor of 100 (based on increased urinary bilirubin levels and kidney vacuolated epithelium at 3.5 mg/kg/day). RfD/Peer reviewed 1/27/94 and 5/18/95.

2) HCB RfD = 0.0008 mg/kg/day. The RfD for HCB is based on the NOEL of 0.08 mg/kg/day from a 130-week feeding study in rats (MRID# not available). At the LEL of 0.29 mg/kg/day, there was hepatic centrilobular basophilic chromogenesis. An uncertainty factor of 100 was used to account for inter-species extrapolation and intra-species variability. HED reviewed 5/5/88; Agency verified 5/26/88.

c) Cancer Risk

1) Chlorothalonil Q_1^* = 7.66 x 10^{-3} $(mg/kg/day)^{-1}$. Chlorothalonil is classified as a Group B2 (probable human carcinogen) chemical by the HED Carcinogenicity Peer Review Committee based on female rat renal (adenoma, carcinoma) tumor rates (memo of E. Rinde, 7/20/88). The dose levels used in the rat study (MRID# not available) were 0, 40, 80, and 175 mg/kg chlorothalonil. Corresponding tumor rates in female rats were 0/60, 2/60, 7/61, and 19/59 and did not display statistically significant differential mortality. The 3/4 scaling factor was used to determine the human Q_1^* from the rat data.

2) HCB Q_1^* = 1.02 $(mg/kg/day)^{-1}$. HCB was classified as a Group B2 (probable human carcinogen) chemical by both HED (9/28/87) and the Agency (6/22/88) based on data sets which showed significant increases in tumor incidence in two species, hamsters and rats. The Q_1^* was calculated in the memo of W. Burnam dated 6/21/95.

Occupational Exposure

1. Acute data for this formulation were not provided to PIRAT. Therefore, no determination can be made as to whether the proposed work clothing and personal protective equipment (PPE) appearing on the label are in compliance with the Worker Protection Standard (WPS).

2. Acute data for the technical are available. The restricted entry interval (REI) of 24 hours appearing on the label is not in compliance with the WPS. WPS requires a 48-hour REI. However, the HED Chapter of the Chlorothalonil Reregistration Eligibility Document (RED) recommends a 4-day REI for fruit orchards (hand-labor). Therefore, **PIRAT recommends a 4-day REI for pistachios. The label should be revised to reflect this recommendation.**

3. Occupational exposure assumptions and estimates of exposure are summarized in Tables 1 and 2, respectively. PIRAT has conducted estimates of exposure for mixer/loaders wearing a single layer of clothing, gloves, and dust/mist respirator. For applicators using airblast equipment, estimates of

exposure have also included use of a second layer of clothing. The label (EPA Reg No. 50534-188) provided with this petition requires applicators and other handlers to wear long-sleeved shirt and pants, waterproof gloves, shoes plus socks, protective eyewear, and a dust/mist respirator. The HED Chapter of the RED also requires all mixers and loaders to wear chemical-resistant gloves and a chemical-resistant apron in addition to baseline protection. **PIRAT recommends that mixers and loaders of chlorothalonil intended for use on pistachios wear the work clothing and PPE appearing on the label plus that required by the RED (HED Chapter). In addition, based on the low (MOE=57) intermediate-term MOEs (see Table 2) for applicators using open cab airblast equipment, even while wearing a second layer of clothing (MOE=62), PIRAT recommends use be restricted to applications by closed cab airblast equipment (MOE=650).**

PIRAT contacted Jerry Baron, IR-4 (908-932-9575) concerning the feasibility of requiring closed cabs when applying chlorothalonil with airblast equipment. Mr. Baron stated that, in California, the majority of growers already use closed cab equipment. Based on his contacts, he felt that growers not having closed cab equipment would probably be willing to utilize the technology in order to apply chlorothalonil.

The label provided with this petition is a liquid formulation; however, WP formulations of chlorothalonil are also available. Included in Table 2 for informational purposes only are estimates of exposure for mixer/loaders of a wettable powder (WP). Intermediate-term MOEs for mixer/loaders of WPs are an unacceptably low < 100 (47).

An assessment has also been conducted for the contaminant hexachlorobenzene (HCB). Estimates of exposure are summarized in Table 3. Based on the HED Chapter of the RED for chlorothalonil, PIRAT has assumed 0.02% contamination (based upon a dislodgeable residue study) and 26% dermal absorption of HCB.

Dietary Exposure

1a. The nature of the residue in plants is adequately understood. The regulable residue is chlorothalonil and its metabolite 4-hydroxy-2,5,6-trichloroisophthalonitrile (SDS-3701), as stated in 40 CFR 180.275. HCB is a contaminant of concern.

1b. The nature of the residue in animals is not germane to this review as no feed items are associated with pistachios and the grazing of livestock in treated areas is prohibited.

2. Adequate analytical methodology (GLC-ECD) is available in PAM II to enforce the tolerance expression. A copy of the data collection method (GLC-ECD) is in MRID# 439241-01.

3. The residue data are adequate to support the proposed tolerance of 0.2 ppm for the regulable residue in/on pistachios.

4. Although chlorothalonil is classified as a Group B2 (probable human carcinogen) chemical, Delaney issues do not apply as no processed commodities are derived from pistachios.

5. Secondary residues are not expected in meat, milk, poultry, or eggs from the proposed use because there are no feed items and the grazing of livestock in treated areas is prohibited.

6. Dietary exposure estimates (DRES) for chlorothalonil (chronic, acute, cancer) and HCB (chronic, cancer), and the anticipated residue information utilized, are provided as Attachments. Runs assumed 100% crop treated.

   a) Chronic Dietary Risk

      i) Chlorothalonil. For the subgroup, US population (48 states), published tolerances currently occupy <0.5% of the RfD. The proposed new pistachios tolerance will not contribute to the RfD. If all other pending tolerances are included, a total 7.3% of the RfD will be occupied.

      For the subgroup most highly exposed to chlorothalonil, non-nursing infants (< 1 year old), published tolerances currently occupy <0.8% of the RfD. The proposed new pistachios tolerance will not contribute to the RfD. If all other pending tolerances are included, a total 37.5% of the RfD will be occupied.

      ii) HCB. For the subgroup, US population (48 states), published tolerances currently occupy <0.01% of the RfD. The proposed new pistachios tolerance will not contribute to the RfD. If all other pending tolerances are included, a total 0.05% of the RfD will be occupied.

      For the subgroup most highly exposed to HCB, children (1-6 years old), published tolerances currently occupy <0.02% of the RfD. The proposed new pistachios tolerance will not contribute to the RfD. If all other pending tolerances are included, a total <0.07% of the RfD will be occupied.

   b) Acute Dietary Risk

      i) Chlorothalonil. The acute dietary exposure effects of concern are renal and gastric lesions. For each of

the most highly exposed subgroups, infants (< 1 year old) and children (1-6 years old), the Margin Of Exposure (MOE) value is calculated to be 875.

ii) HCB. No acute dietary endpoints have been found.

c) Dietary Cancer Risk

i) Chlorothalonil. Chlorothalonil tolerances (published plus new proposed on pistachios plus all others pending) result in a cancer risk of 1.1 X 10^{-6} (using anticipated residues) for the US general population (48 states). This number is derived from the DRES printout (chronic run) in the following manner:

- The run includes both parent + SDS-3701 metabolite.
- SDS-3701 has not been found to be a carcinogen.
- The pending tolerances on meat and milk are based on SDS-3701 only (no measurable residues of parent are expected in meat or milk).
- For dietary cancer risk purposes, the contribution from meat and milk is subtracted from the total, since the meat and milk residues are due solely to the non-carcinogen SDS-3701.
- The total residues (10.05 x 10^{-6}) minus the total SDS-3701 residues in meat and milk (8.91 x 10^{-6}) equals 1.1 x 10^{-6} as the dietary cancer risk.

ii) HCB. HCB residues (HCB is a contaminant in chlorothalonil) due to the chlorothalonil published, pending, and the proposed new tolerance on pistachios result in a dietary cancer risk of 3.7 x 10^{-7} for the US general population (48 states).

d) Anticipated Residues

i) The chronic/cancer DRES runs for both chlorothalonil and HCB incorporated the anticipated residue information on crops with established tolerances as provided to DRES by CBRS (memo of W. Smith, 6/13/95). For pistachios, an anticipated residue value (0.068 ppm, based on field trials) was used for chlorothalonil; 0.05% (0.0001 ppm) of the chlorothalonil tolerance level was used for HCB. (0.05% is the maximum certified limit for HCB residues permitted in chlorothalonil formulations.)

ii) The acute run did not use any anticipated residues.

DETAILED CONSIDERATIONS

Occupational Exposure

Table 1. Occupational Exposure Assumptions	
PARAMETER	**ASSUMPTION**
Pesticide Handlers Exposure Database (PHED), Version 1.1, Unit of Exposure From Best Available Surrogate Exposure Table (BASET, 5/29/96)	Mixer/Loader (all liquid formulations, open mixing, single layer clothing plus gloves): Dermal = 43.0 µg/lb ai handled (0.0086 µg/lb ai HCB based on 0.02% contamination), Inhalation (corrected for dust/mist respirator) = 0.242 µg/lb ai handled (0.00005 µg/lb ai HCB based on 0.02% contamination).
	Mixer/Loader (wettable powder, open bag, single layer clothing plus gloves): Dermal = 160.0 µg/lb ai handled (0.032 µg/lb ai HCB based on 0.02% contamination), Inhalation (corrected for dust/mist respirator) = 8.68 µg/lb ai handled (0.00174 µg/lb ai HCB based on 0.02% contamination).
	Applicator - Ground (airblast, open cab, single layer clothing plus gloves): Dermal = 254.4638 µg/lb ai applied (0.0509 µg/lb ai HCB based on 0.02% contamination), Inhalation (corrected for dust/mist respirator) = 0.8931 µg/lb ai applied (0.00018 µg/lb ai HCB based on 0.02% contamination).
	Applicator - Ground (airblast, open cab, two layers of clothing plus gloves): Dermal = 232.0912 µg/lb ai applied (0.04642 µg/lb ai HCB based on 0.02% contamination), Inhalation (corrected for dust/mist respirator) = 0.8931 µg/lb ai applied (0.00018 µg/lb ai HCB based on 0.02% contamination).
	Applicator - Ground (airblast, closed cab, single layer clothing plus gloves): Dermal = 16.0 µg/lb ai applied (0.0032 µg/lb ai HCB based on 0.02% contamination), Inhalation = 0.4 µg/lb ai applied (0.00008 µg/lb ai HCB based on 0.02% contamination).
Work Clothing and PPE	Single layer of clothing, gloves, and a dust/mist respirator ± coveralls
Percent Absorption	Dermal: 5 % (Tox value), HCB 26% (Tox value) Inhalation: 100 % (default value)
Application Type	ground-airblast
Minimum Finish Spray	Ground: 100 gal/A
Maximum Application Rate	4.5 lb ai/A
Maximum Applications Per Year	5
Acres Treated/Day (Y. NG,BEAD)	Ground: 30 acres
Average Farm Size	115 acres (Based on personal communication with Jerry Baron IR-4)
Duration of occupational exposure	Intermediate (1 week to several months)

Table 1. Occupational Exposure Assumptions	
PARAMETER	**ASSUMPTION**
Worker Weight	70 kg (based on Tox endpoint)
Number of Farms Treated by PCO (Professional Chemical Operator)	Ground: 2

Table 2. Occupational Exposure and Risk Assessment (chlorothalonil)[a]					
Worker	**Average Daily Dose[b] Dermal + Inhalation (ug/kg/day)**	**Average Annual Daily Dose[c] Dermal + Inhalation (ug/kg/day)**	**Short-Term MOE[d]**	**Intermediate MOE[e]**	**Cancer Risk[f]**
Ground Mixer/Loader All liquids	4.6	0.5	38,000	330	1.9×10^{-6}
Ground Mixer/Loader Wettable powder/open bag	32.2	3.4	5,400	47	1.3×10^{-5}
Ground Applicator - Open cab	26.3	2.7	6,700	57	1.0×10^{-5}
Ground Applicator - Open cab + coveralls	24.1	2.5	7,300	62	9.5×10^{-6}
Ground Applicator - Closed cab	2.3	0.2	76,000	650	7.6×10^{-7}

[a] MOEs are expressed to two significant figures.

[b] Average Daily Dose (ADD) = PHED unit exposure x % absorption x application rate x acres treated/day ÷ kg body weight.

[c] Average Annual Daily Dose (AADD) = ADD x number of days to treat average field x number applications/year x number of farms treated by PCO ÷ 365 days/year.

[d] Short-Term Occupational Exposure MOE = NOEL/ADD (where NOEL = 175 mg/kg/day).

[e] Intermediate Occupational Exposure MOE = NOEL/ADD (where NOEL = 1.5 mg/kg/day).

[f] Cancer Risk: Q_1^* approach: Q_1^* x AADD x 35/70 (35 years of work in a 70 year lifetime) (where $Q_1^* = 0.0076 (mg/kg/day)^{-1}$).

Table 3. Occupational Exposure and Risk Assessment (HCB)[a]			
Worker	Average Daily Dose[b] Dermal + Inhalation (ng/kg/day)	Average Annual Daily Dose[c] Dermal + Inhalation (ng/kg/day)	Cancer Risk[d]
Ground Mixer/Loader All liquids	4.4	0.5	2.6×10^{-7}
Ground Mixer/Loader Wettable powder/open bag	19.4	2.0	1.0×10^{-6}
Ground Applicator - Open cab	25.9	2.7	1.4×10^{-6}
Ground Applicator - Open cab + coveralls	23.6	2.5	1.3×10^{-6}
Ground Applicator - Closed cab	1.8	0.2	1.0×10^{-7}

[a] MOEs are expressed to two significant figures.

[b] Average Daily Dose (ADD) = PHED unit exposure x % absorption x application rate x acres treated/day ÷ kg body weight.

[c] Average Annual Daily Dose (AADD) = ADD x number of days to treat average field x number applications/year x number of farms treated by PCO ÷ 365 days/year.

[d] Cancer Risk: Q_1^* approach: Q_1^* x AADD x 35/70 (35 years of work in a 70 year lifetime) (where $Q_1^* = 1.02$ (mg/kg/day)$^{-1}$)

Dietary Exposure

Table 4. Summary of Product Label, Analytical Methodology, Storage Stability, Residue Results, and CODEX	
PARAMETER	PERTINENT INFORMATION
CHEMICAL	Chlorothalonil
FORMULATION	BRAVO® 720 Agricultural Fungicide (EPA Reg. No. 50534-188, a flowable concentrate containing 6.0 lbs chlorothalonil ai/gal; ISK Biosciences Corporation, registrant). BRAVO formulations may contain up to a maximum of 0.05% of the manufacturing impurity, HCB.
CROP	Pistachios
FOR CONTROL OF	Shoot & panicle blight, blossom & shoot blight, late blight, leaf blight
TYPE APPLICATION	Broadcast foliar spray (≥100 gpa) via ground equipment, using sufficient spray to provide thorough coverage of the tree canopy.
# APPLICATIONS	Not stated (5 under maximum rate conditions)
TIMING	Apply when trees begin to blossom, then re-apply at full bloom. If conditions are favorable for late blight or leaf spot infections, repeat applications at 4-week intervals.
RATE/A/APPLICATION	Up to 6 pts (4.5 lbs ai) (applied as 2-3 pts BRAVO/100 gals spray)

Table 4. Summary of Product Label, Analytical Methodology, Storage Stability, Residue Results, and CODEX	
PARAMETER	**PERTINENT INFORMATION**
RATE/A/SEASON	Up to 30 pts (22.5 lbs ai)
RESTRICTIONS	14-Day PHI. Do not allow livestock to graze in treated areas. Do not apply BRAVO through any type of irrigation equipment.
ANALYTICAL METHOD TYPE/VALIDATION	Data collection method was GLC-ECD ("General Analytical Procedure for the Determination of Residues of Chlorothalonil, SDS-3701, SDS-46851, HCB, and PCBN on Selected Crops", Document No. 3136-88-0138-MD-001,Fermenta ASC Corp., copy in MRID# 439241-01). Only chlorothalonil, SDS-3701, and HCB were determined. The limit of quantitation is 0.01 ppm for chlorothalonil and SDS-3701 and 0.003 ppm for HCB. Analytical recoveries ranged 70-104% of fortified amounts (0.01-0.25 ppm, chlorothalonil (n=8) and SDS-3701 (n=8); 0.003 and 0.015 ppm, HCB (n=7)). Representative chromatograms are provided.
FREEZER STORAGE STABILITY	No validation data are provided for pistachios, which were stored (-20°C, 17 months) prior to analysis. However, the Residue Chemistry Chapter for the RED (W. Smith, 6/13/95, D201522) states that residues of SDS-3701 and HCB are stable during frozen storage for up to 4 years in/on carrots, celery, cherries, cucumbers, peanuts, potatoes, soybeans, tomatoes, and wheat grain. Residues of chlorothalonil are stable under the same conditions in the above commodities except for an apparent decline of approximately 9% per year in peanuts. These findings are adequate (by translation) to validate the frozen storage of pistachio nutmeats.
RESIDUE DATA MRID#	439241-01 (PP#6E4672)
PERFORMING LAB	IR-4 Western Region Residue Laboratory, University of California, Davis
RESIDUE RESULTS	Three field trials (AZ-1, CA-2; 1992) were conducted. BRAVO 720 was applied to pistachio trees at initial bloom, full bloom, and at approximately 28-day intervals up to 14 days prior to harvest. A total of 5 applications was made, each at the maximum rate of 6 pts (4.5 lbs ai)/A by airblast ground sprayer (using 35-110 gals water/A). This is the maximum use (30 pts/A/season) proposed by the label. Nuts were harvested, dehulled, and the nutmeats were maintained in frozen storage (-20°C, 17 months) until extraction/analysis. Control nutmeat samples contained no detectable residues (<0.01 ppm chlorothalonil or SDS-3701; <0.003 ppm HCB). Treated nutmeat samples contained no detectable residues of SDS-3701 (<0.01 ppm) or HCB (<0.003 ppm) and <0.01-0.14 ppm (0.068 ppm, average) of chlorothalonil. These data support the proposed 0.2 ppm tolerance on pistachios for the regulable residue.
CODEX	There are no CODEX, Canadian, or Mexican MRLs for chlorothalonil on pistachios.
LETTER OF AUTHORIZATION	Letter of 7/4/95, ISK Biosciences Corporation (registrant), provides authorization for the Agency to refer to and cite all ISK's relevant test data to support IR-4's petition.

ATTACHMENTS: DRES Analyses (Chronic, Acute, Cancer; Anticipated Residue Information; 6/26/96 and 7/19/96)

cc (with Att.): M. Nelson, H. Jamerson (RD), B. Steinwand (SAB).

cc (w/o Att.): W. Dykstra, C. Lewis, PIRAT, M. Clock (RCAB), TOX (A. Levy), Caswell# 215B, PP#6E4672 (CBTS), OREB (#81901).

RDI:PIRAT:07/18/96 **[mjn file: CHLO-PIS.IR4]**