3-2-82 RCB

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

QUICK
Anne
File petition

MEMORANDUM MAR 2 1982

DATE: FEB 25 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Petition No. 2F2602; EPA Reg. No. 677-313; Proposed Tolerance for Chlorothalonil in/on Stone Fruits.
Acc. # 070461 CASWELL #215B

FROM: George W. Robinson, D.V.M. GWR 2/25/82
Review Section #1
Toxicology Branch/HED (TS-769) RCB 3/1/82

TO: Henry M. Jacoby, PM #21
Registration Division (TS-767)

THRU: Orville E. Paynter, Ph.D. for OEP
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Petitioner: Diamond Shamrock Corporation
1100 Superior Avenue
Cleveland, Ohio 44114

Action Requested:

The petitioner proposes the establishment of a tolerance for the residues of the fungicide Chlorothalonil (2,4,5,6-tetrachloroisophthalonitrile) and its methabolite (4-hydroxy-2,5,6-trichloroisophthalonitrile) in or on the raw agricultural commodity Stone Fruits at 0.2 ppm. This crop grouping includes apricots, cherries, nectarines, peaches, plums and prunes. The petitioner also applies to amend the chlorothalonil pesticide product Bravo® 500 registration to include added uses on stone fruits.

Conclusion:

Existing toxicity data will support the establishment of a tolerance for the combined residues of the fungicide Chlorothalonil and its 4-OH metabolite in or on the raw agricultural commodity Stone Fruits at 0.2 ppm.

Previously Submitted Toxicity Data:

Following is a brief summary of numerous toxicological reviews conducted on the diversified toxicity data submitted by the registrant to support the safety of its requested tolerances on food and feed.

1. Technical Chlorothalonil

   a. Acute oral, rat, LD_{50} > 10,000 mg/kg.
   b. Acute oral, dog, LD_{50} > 5,000 mg/kg.
   c. Acute dermal, rabbit, LD_{50} > 10,000 mg/kg.
   d. Acute inhalation, rat, LC_{50} > 4.7 mg/L.
   e. Primary eye irritation, rabbit - corneal opacity persists at day 7; severe irritation.
   f. 2-year feeding, dog, NOEL = 60 ppm.
   g. 2-year feeding, rat, NOEL = 60 ppm (HDT); no oncogenicity.
   h. 3-generation reproduction, rat, NOEL = 15,000 ppm (reproduction); NOEL = 1,500 ppm (lactation).
   i. Teratogenicity, rabbit, NOEL = 62.5 mg/kg (HDT).
   j. Mutagenicity studies:

      1. Cell transformation, newborn rat, negative.
      2. Mammalian cell gene point mutation, negative.
      3. Ames, negative.
      4. In vitro mammalian point mutation, negative.
      5. DNA repair, negative except that it may interfere with DNA repair in TA-1538 cells.

   k. Oncogenicity, NCI-carcinogenic in male and female Osborne-Mendel rats, but not in B_6 C_3 F_1 mice at 10,126 ppm (HDT).

2. Metabolite (4-hydroxy-2,5,6-trichloroisophthalonitrile)

   a. Acute oral, rat, LD_{50} = 332 (422, male; 242, female) mg/kg.
   b. Acute oral, dog, LD_{50} = 100 mg/kg.
   c. 4-month feeding, rat, NOEL = 100 ppm.
   d. 90-day feeding, dog, NOEL < 50 ppm.
   e. Teratogenicity, rabbit, terata NOEL > 5 mg/kg (HDT).
   f. 3-generation reproduction, rat, NOEL not established.
   g. Mutagenicity studies

      1. Host-mediated assay, mouse, negative.
      2. In vivo cytogenetic, mouse, negative.
      3. Dominant lethal, mouse, negative but a significant increase in early deaths at week 3 of mating (spermatid stage) was noted at 6.5 mg/kg/day.
      4. Dominant lethal, rat, negative at 8 mg/kg/day for 5 days.

3. Bravo 500

A formulation containing 40.76% chlorothalonil (toxicity data reviewed by C.A. Rodriquez 11/30/78).

a. Acute oral, rat, LD_{50} = 4.2 g/kg
b. Acute dermal, rabbit, LD_{50} > 20.0 g/kg.
c. Primary dermal irritation, rabbit, PIS = 1.3/8.0
d. Primary eye irritation, rabbit, severe eye irritation, corneal opacity persisted at 7 days.
e. Acute inhalation, rat, LC_{50} > 7.16 mg/L for 4 hours.

Existing Tolerances:

Tolerances for the combined residues of chlorothalonil and its 4-OH metabolite have been established under 40 CFR 180.275 for a variety of raw agricultural commodities as listed on the attached computer printout.

The toxicology data considered in support of this proposed tolerance include: acute oral studies in the rat (LD_{50} > 10,000 mg/kg) and dog (LD_{50} > 5,000 mg/kg), a 2-year dog feeding study with a no-observed-effect-level (NOEL) of 60 ppm, a 2-year rat feeding study (NOEL of 60 ppm), a 3-generation rat reproduction study (NOEL of 15,000 ppm), a teratogenicity study in rabbits (NOEL of 62.5 mg/kg), and a series mutagenic studies (cell transformation in newborn rats, mammalian gene point, in vitro mammalian point mutation, Ames, and DNA repair) with negative results except for a finding that chlorothalonil may interfere with DNA repair in TA-1538. Also, a study by the National Cancer Institute (NCI) concluded chlorothalonil was not carcinogenic in B_6 C_3 F_1 mice at a feeding level of 10,126 ppm.

Acceptable Daily Intake Data:

Current	85.58%	0.7703 mg/day (1.5 kg)
Occupied	85.17%	0.7665 mg/day (1.5 kg)
Difference	0.41%	0.0038 mg/day

The present Acceptable Daily Intake (ADI) of 0.015 mg/kg/day is based on the 2-year dog feeding study with a NOEL of 60 ppm and a safety factor of 100. Based on this ADI, the Maximum Permissable Intake (MPI) is 0.9 mg/day for a 60-kg person. The requested tolerance will utilize 0.41% of the ADI, increasing the occupied ADI from 85.17% to 85.58%. The incremental residue contribution to the theoretical maximum residue contribution (TMRC) of 0.0038 mg/day (1.5 kg diet) is less than 1% of the TMRC. (See FR Vol. 44, No. 93, May 11, 1979).

Oncogenic risk analysis indicates that the oncogenic potential from these residues is less than 10^{-6} at the upper limit on risk based on an oncogenicity study in rats reported by National Cancer Institute, study #NCI-66-TR-41 (memo of 1/18/80, D. Ritter; risk analysis by R. Gardner).

Chlorothalonil was referred to SPRD for RPAR review (memo of D. Ritter, 12/26/78).

Other Considerations:

Of 308 batches of technical chlorothalonil which were analyzed, 8% contained an average of [redacted] hexachlorobenzene (HCB) as a technical impurity. No residues of HCB were detected in almonds after use of Bravo 500 containing [redacted] HCB (memo of N. Dodd, RCB, 11/17/81).

The Bravo 500 label contains the precautionary statements "DO NOT allow livestock to graze in treated areas. DO NOT feed hay or threshings from treated fields to livestock".

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

File last updated 2/18/82

ACCEPTABLE DAILY INTAKE DATA

Dog NOEL mg/kg	Dog NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
1.500	60.00	100	0.0150	0.9000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Celery(26)	15.000	0.29	0.06438
Broccoli(19)	5.000	0.10	0.00766
Brussel Sprouts(20)	5.000	0.03	0.00225
Cabbage,sauerkraut(22)	5.000	0.74	0.05519
Cauliflower(27)	5.000	0.07	0.00537
Cucumbers,inc pickl(46)	5.000	0.73	0.05442
Melons(92)	5.000	2.00	0.15023
Onions,green(107)	5.000	0.11	0.00843
Pumpkin,inc squash(131)	5.000	0.11	0.00843
Beans,snap(12)	5.000	0.98	0.07358
Summer Squash(155)	5.000	0.03	0.00225
Tomatoes(163)	5.000	2.87	0.21561
Passion fruit(112)	3.000	0.03	0.00135
Carrots(24)	1.000	0.48	0.00720
Corn,sweet(40)	1.000	1.43	0.02145
Onion(dry bulb)(106)	0.500	0.72	0.00537
Peanuts(115)	0.300	0.36	0.00161
Potatoes(127)	0.100	5.43	0.00814
Papayas(109)	15.000	0.03	0.00675
Bananas(7)	0.050	1.42	0.00107
Parsnips(111)	1.000	0.03	0.00045

MPI	THRC	% ADI
0.9000 mg/day(60kg)	0.7012 mg/day(1.5kg)	77.91

****

Unpublished,Tox Approved 6E1841,1887,2037,2065,0F2405,6G1813

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Mustard Greens(99)	15.000	0.06	0.01380
Turnip Greens(166)	15.000	0.03	0.00675
Escarole/endive(56)	6.000	0.03	0.00270
Chicory(32)	6.000	0.03	0.00270
Beets(14)	1.000	0.17	0.00261
Turnips(165)	1.000	0.05	0.00077
Spinach(150)	42.000	0.05	0.03219
Citrus Fruits(33)	0.010	3.81	0.00057
Almonds(1)	0.050	0.03	0.00002
Beans;dry edible(10)	0.100	0.31	0.00047
Soybeans (oil)(148)	0.200	0.92	0.00275

MPI	THRC	% ADI
0.9000 mg/day(60kg)	0.7655 mg/day(1.5kg)	85.17

****

Current Action -- PP# 2F2602

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Stone Fruits(151)	0.200	1.25	0.00374

MPI	TMRC	% ADI
0.9000 mg/day(60kg)	0.7703 mg/day(1.5kg)	85.56

****

Other Pending Tolerances PP# 6F1749,6F1799

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cherries(30)	15.000	0.10	0.02299
Peaches(114)	25.000	0.90	0.33725

MPI	TMRC	% ADI
0.9000 mg/day(60kg)	1.1305 mg/day(1.5kg)	125.61

****