

DP Barcode: D175063
 PC Code No.: 081901
 EFGWB Out: MAY 1 1992

To: Cynthia Giles-Parker
 Product Manager 22
 Registration Division

From: Akiva D. Abramovitch, Ph.D., Head
 Environmental Fate Review Section #3
 Environmental Fate & Ground Water Branch
 Environmental Fate and Effects Division (H7507C)

Thru: Henry Jacoby, Chief
 Environmental Fate & Ground Water Branch
 Environmental Fate and Effects Division (H7507C)

Attached, please find the EFGWB review of...

Reg./File #: 050534-00008
 Chemical Name: 2,4,5,6-tetrachloro 1,3-benzenedicarbonitrile (Chlorothalonil)
 Type Product: fungicide
 Product Name: Bravo
 Company Name: ISK Biotech
 Purpose: exemption from requirement for tolerance for metabolites; lifting
 of twelve-month crop rotation restriction

Action Code: EFGWB #(s): 92-0576 Total Review Time: 1.5 days

EFGWB Guideline/MRID/Status Summary Table: The review in this package contains...

161-1	162-4	164-4	166-1
161-2	163-1	164-5	166-2
161-3	163-2	165-1	166-3
161-4	163-3	165-2	167-1
162-1	164-1	165-3	167-2
162-2	164-2	165-4	201-1
162-3	164-3	165-5	202-1

Y = Acceptable (Study satisfied the Guideline)/Concur
 P = Partial (Study partially satisfied the Guideline, but additional information is still needed)
 S = Supplemental (Study provided useful information, but Guideline was not satisfied)
 N = Unacceptable (Study was rejected)/Non-Concur

bcp

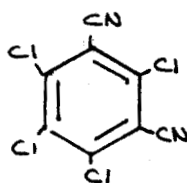
Chlorothalonil 92-0576

1

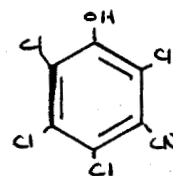
2029306

1. CHEMICAL:

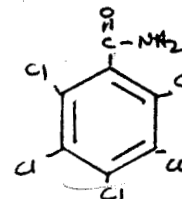
chemical name: 2,4,5,6-tetrachloro-1,3-benzenecarbonitrile
common name: Chlorothalonil
trade name: Bravo
structure:
CAS #: 1897-45-6
Shaughnessy #: 081901
characteristics:



Chlorothalonil



SDS-3701



SDS-46851

2. TEST MATERIAL:

n.a.

3. STUDY/ACTION TYPE:

request for exemption from inclusion of metabolites in tolerance; removal of twelve-month restriction on crop rotation

4. STUDY IDENTIFICATION:

n.a.

5. REVIEWED BY:

Typed Name: E. Brinson Conerly-Perks
Title: Chemist, Review Section 3
Organization: EFGWB/EFED/OPP

E.B. Conerly-Perks
4/28/92

6. APPROVED BY:

Typed Name: Akiva Abramovitch
Title: Head, Review Section 3
Organization: EFGWB/EFED/OPP

Akiva Abramovitch
APR 28 1992

7. CONCLUSIONS:

EFGWB agrees to withdraw the rotational crop restriction, based on TOX and Residue Branches' lack of concern for metabolite residues. Available data indicate that identifiable residues in rotational crops are metabolite, not parent. If some concern should arise regarding these metabolites at a later date, acceptable rotational crop data may have to be provided. At present EFGWB has no acceptable data upon which to base a suitable rotational interval.

There are no new environmental fate data in this submission.

8. RECOMMENDATIONS:

The applicant should be notified that the rotational crop restriction is withdrawn for the present use patterns.

9. BACKGROUND: See the attached memo.

Per the attached memo, TOX Branch has decided that metabolites SDS-3701 and SDS-46851 do not require regulation in all registered chlorothalonil uses. Residue Chemistry Branch has stated that they have no objections, TOX and EFGWB considerations permitting, to the exemption of these metabolites from tolerances in rotational crops.

27
DATE? A comprehensive review of submitted field crop accumulation data was completed 3/5/91 (q.v.). These were found to be unacceptable/unreviewable. To date, there are no acceptable data re accumulation of residues in field crops. The following is information which can be drawn from available data:

- 27
Why? Chemical
Probably Chlorothalonil
- a) Based on an acceptable confined study at exaggerated rates (MRID 410302-11), there was accumulation of residues. Approximately 1/3 were recognizable metabolites of Chlorothalonil (i.e. SDS-3701 and SDS-46851) and ca. 2/3 were incorporated in cellular structural material. The latter apparently derived from the "carbon pool" of end metabolites such as CO₂ and acetic acid. These levels would not have been detected at label application rates.
- b) Based on an unacceptable field study (MRID # unknown, reviewed 5/2/91), no uptake was observed. The study was not fully acceptable because the soil was not analyzed at planting time. A number of unreviewable field studies were mentioned in the comprehensive document of 3/5/91.

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES: n.a.
11. COMPLETION OF ONE-LINER: no added information n.a.
12. CBI APPENDIX: n.a. informational material attached



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

EXPEDITE

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Chlorothalonil Metabolites SDS-3701 and SDS-46851 -
Consideration of the toxicologic basis for inclusion in
the chlorothalonil tolerance expression

Caswell No. 215B
HED Project No. 2-0684

FROM: Elizabeth A. Doyle, Ph.D., Section Head
Review Section IV, Tox Branch II (H7509C)

TO: James Stone/Cynthia Giles-Parker, PM-22
Registration Division (H7505C)

THRU: Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (H7509C)

Registrant: ISK Biotech

Action Requested: 1) Review of toxicology studies for soil
metabolite SDS-46851, and 2) consideration of the toxicological
basis for inclusion of SDS-3701 and SDS-46851 in the tolerance
expression for chlorothalonil.

Background: The registrant has requested the removal of the
rotational crop restriction from the chlorothalonil label. In
support of this petition, the registrant has provided toxicology
data for a soil metabolite, SDS-46851, which has been found as a
residue in crops rotated to soil previously treated with
chlorothalonil. This data is provided in conjunction with a
petition for exemption from tolerance for this soil metabolite.

Currently, the tolerance expression for chlorothalonil contains
plant metabolite SDS-3701 which occurs in many treated crops. Tox
Branch, in conjunction with CBTS, has revisited the question of the
need for inclusion of this plant metabolite in the tolerance
expression based upon the database previously submitted by the
registrant.

Data Summary: The data in support of exemption of SDS-46851 from
tolerance are summarized below. Four new studies were submitted
with the current petition.

- 1) 28-Day Feeding Study - Mouse
MRID No. 420901-02
Doses: 0, 250, 500, 1000, 5000, 10,000 ppm in feed
No treatment related effects in males or females.
Core - Supplementary (Not a guideline study)
- 2) 90-Day Feeding Study - Mouse (82-1)
MRID No. 420901-03
Doses: 0, 250, 750, 2200, 7500 ppm
No treatment related effects in males or females.
Core - Supplementary (No clinical chemistry or ophthalmological examinations performed)
- 3) Metabolism - Rat (85-1)
MRID No. 420901-06
A single oral dose of 10 or 1000 mg/kg of ¹⁴C-SDS-46851 was given. Distribution and excretion of radiolabel was monitored for seven days. More than 90% of the radiolabel was excreted in urine and feces during the first 72 hours. No significant accumulation in tissue was reported.
Core - Supplementary (No identification of metabolites; only one treatment regimen was used)
- 4) Combined Chronic/Oncogenicity - Rat (Interim Report)
MRID No. 420901-04
Doses: 0, 80, 200, 500, 1000 mg/kg/day
No treatment related effects in males or females.
Core - Supplementary (Interim report only)

Although these studies do not meet guideline requirements, they provide sufficient information for consideration of this task. The registrant does not seek registration of SDS-46851.

Data previously reported for soil metabolite SDS-46851 included:

- no evidence of developmental toxicity in rats (NOEL > 2000 mg/kg/day) or rabbits (NOEL > 1000 mg/kg/day).
- a reproductive NOEL = 750 mg/kg/day and an LOEL = 2000 mg/kg/day based on reduced pup weights in rats.
- increased liver weights in rats and dogs given 750 and 50 mg/kg/day, respectively, for 90 days.
- no evidence of mutagenicity in assays from 84-2a, 84-2b or 84-4.

Data previously provided for plant metabolite SDS-3701 included:

- No evidence of carcinogenicity in mice or rats (NOEL > 20 mg/kg/day and 1500 mg/kg/day, respectively).
- No evidence of developmental (rat and rabbit) or reproductive toxicity (rats). (NOEL > 1000 mg/kg/day.)

- increased liver weights and decreased body weight gains in rats and mice (rats: NOEL = 3 mg/kg/day, LEL = 10 mg/kg/day; mouse: NOEL < 75 mg/kg/day).
- no evidence of mutagenicity in assays from 84-2a, 84-2b or 84-4.
- less than 30% of the metabolite is absorbed from the gut of rats.

The parent compound, chlorothalonil, is classified as a B2 carcinogen with a $Q^* = 1.1 \times 10^{-2}$ (mg/kg/day) based upon renal tumors in mice and rats. The RfD is 0.015 mg/kg/day based upon a chronic study in dogs in which renal tubular vacuolization was observed with an NOEL = 1.5 mg/kg/day and an LEL = 3.0 mg/kg/day.

Recommendation: Based upon the toxicologic data provided by the registrant, Tox Branch has no objections to 1) the exemption of SDS-46851 from tolerance in rotated crops, and 2) the deletion of SDS-3701 from the tolerance expression for chlorothalonil by direct application.