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

2/21/92
EXPEDITE

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

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

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2/21/92

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J.M. Lawrence for
2/21/92

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.

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- 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.)

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- 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.