7-2-80 PP-1G5 / TXR-355

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

000355

MEMORANDUM

OFFICE OF TOXIC SUBSTANCES

SUBJECT: 20954-10; PP#9F2195; Tolerance for residues of the insect growth regulator methoprene (isopropyl(E,E)-11-methoxy-3,7,11-trimethyl 1-2,4 dodecadienoate) in or on the raw agricultural commodity, mushrooms at 3.0 PPM.

FROM: Charles Frick e.f. 7/7/80
Toxicology Branch, HED (TS-769)

TO: Mr. Frank Gee (17)
Registration Division (TS-767)

THRU: William Burnam, Acting Chief
Toxicology Branch, HED (TS-769)

Petitioner: Zoecon Corp.
PaloAtto, Ca.

Comments and Recommendation:

It must be noted that an ADI for this compound has not been established.

For a permanent tolerance a second chronic feeding study (non-rodent) is required - preferable specie would be the dog.

The two teratology studies were conducted by Industrial Biotest, and at this point in time have not been validated by the Agency.

Permanent tolerances of Methoprene have been established on the following:

cattle, fat ---------- 0.3 ppm
Milk ---------- 0.05 ppm

CFR. 180.359
These tolerances were established on a conditional NEL of 1000 ppm in the 2-year rat feeding study.

When the IBT data validation problem is satisfactorily resolved and if the company agrees to fill the outstanding data gap (Dog study) within a reasonable period of time, Toxicology Branch would have no objection to the implementation of this action request.

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Formulation: Altosid 5E®

Methoprene - 71.625% active ingredient

[redacted] RCB memo by E. Leovey.

Toxicity Data Summary - The following has been extracted from a review of PP#6F1801, Oct. 12, 1976 by Dr. Reto Engler.

LD50 oral	> 10 g/kg
Teratology, Rat	negative at 500 mg/kg, slight indication of abnormalities at 1000 mg/kg
Teratology, Rabbit	negative at 500 mg/kg
Dominant Lethal, Rat	negative at 2000 mg/kg
90-Day Feeding, Rat	NEL 1000 ppm, increased organ weights at 5000 ppm
90-Day Feeding, Dog	NEL 500 ppm, increased liver ratios at 5000 ppm
3-Generation Reproduction, Rat	NEL 2500 ppm

2. Studies reviewed with this petition.

Long-term rat and mouse feeding studies were submitted with 2095-EUP-5 but were not reviewed at that time because they did not pertain to the EUP. These studies are reviewed below.

(a) 2-Year Rat Feeding/Oncogenicity Study:

(International Research & Development Co.; October 15, 1975)

Charles River CD rats were fed at levels of 0, 250, 1000, and 5000 ppm. 50 animals per sex per dose were used. Interim studies were performed at 3, 6, 12, 18, 24 months. At the end of the study survival was about 50%. Hematology, blood chemistry, and urinalysis were performed and were all unremarkable. Body weights, weight gains, and organ weights and ratios were also unremarkable. Gross and histopathology was performed as well. In some groups there was some liver pathology observed, consisting of slight portal lymphocytic infiltration, slight to very slight bile duct

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proliferation, and vacuolized hepatocytes. These findings were not consistent and dose related. No increased occurrence of tumors was observed in rats fed methoprene. The increased organ weights observed in the 90-day rat study at 5000 ppm were not observed in the 2-year study. Taking the effect observed in the subacute study into account we determine that a conservative NEL of 1000ppm can be assigned for effects observed in the rat.

(b) 18-Month Mouse Study:

(International Research & Development Co., March 14, 1975)

Charles River CD-1 mice were fed 0, 250, 1000, and 2500 ppm of methoprene. 50 animals per sex per level were used. Survival after 18 months was about 50%. The only parameters studies were weight gain, food consumption, gross and histopathology. No interim sacrifices or organ weight determinations were performed. The only effect noted was a dark brown granular pigment in the cytoplasm of liver parenchymal cells. This effect was pronounced at the 2500 ppm level, still obvious at the 1000 ppm level but was absent at the 250 ppm level. The effect thus seemed dose related and must be linked to the administration of the chemical. As indicated in the conclusions we refer this study to the pathologist of the Toxicology Branch for an opinion. Based on the liver pathology the NEL in this mouse study is 250 ppm. The tumor incidence in mice was not increased in this study. We request the petitioner to address the question of statistical analysis of the results of the mouse study.

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