CASWELL FILE

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

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

JUL 17 1985

SUBJECT: CGA-64250; Tilt® Fungicide; Tolerance in Bananas, 0.1 ppm

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

FROM: Alan C. Katz, M.S., D.A.B.T.
Toxicologist, Review Section IV
Toxicology Branch, HED (TS-769C)
Alan C Katz 7/16/85

THROUGH: Robert P. Zendzian, Ph.D.
Acting Head, Review Section IV
7/16/85
and
Theodore M. Farber, Ph.D., D.A.B.T.
Chief, Toxicology Branch
7/17/85

Registration No. 4E3026
Accession No. 072283
Caswell No.: 323EE (CGA-64250); 862B (Triazole alanine)

Action Requested:

Review petition for tolerance for the combined residues of the fungicide CGA-64250 (Tilt) and its metabolites in or on bananas at 0.1 ppm. No additional toxicologic data were included for review.

Recommendations:

Toxicology Branch recommends that the tolerance for CGA-64250 not be granted at this time. CGA-64250 causes liver tumors in male mice. The results of a 2-year dietary chronic toxicity/oncogenicity study with this compound in rats are considered inconclusive, pending submission of additional data from the sponsor. therefore, establishment of a tolerance is not currently toxicologically supportable. When the requested data are provided, oncogenicity will be evaluated by the Tox Branch ad hoc committee.

Background:

Compound: CGA-64250 Technical; Propiconazole; Trade names: Tilt, Banner; Chemical name: 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl] methyl]-1-H-1,2,4-triazole.

The attached one-liners provide a brief outline of accepted toxicology studies and overall conclusions.

Studies of the distribution and degradation of CGA-64250 in plants and animals (mice, rats, and goats) have been reviewed by the Residue Chemistry Branch (see memorandum from A. Smith to H. Jacoby, 5/15/84).

Acute studies with CGA-64250 may be summarized as follows:

Acute Study	Tox Category
Oral- rats, mice, Chinese hamsters, and rabbits	III
Inhalation- rats	III
Injection, ip- rats	II
Dermal Toxicity- rats	III
Dermal Irritation- rabbits	IV
Eye Irritation- rabbits	II
Dermal Sensitization- guinea pigs	Negative

No systemic toxicity was reported in a 21-day dermal study in rabbits at the highest dose tested (1 g/kg). However, no NOEL for skin lesions was observed. The lowest dose tested was 3 mg/kg.

A 90-day study was conducted in TIF:(RAIF)SPF rats with CGA-64250 technical at dietary concentrations of 0, 240, 1200 and 6000 ppm. A NOEL was apparent at the lowest dose tested. At 1200 ppm, body weight gain was reduced in females.

Beagle dogs were fed diet containing CGA-64250 at concentrations of 0, 50, 250 or 1250 ppm for 90 days. Treatment-related lesions involved lymphoid follicles in the mucous membranes of the pyloric region of the stomach, with an LEL of 250 ppm. No effect was apparent at 50 ppm. The in-life phase of a 1-year subchronic study in Beagle dogs with CGA-64250 at dietary levels of 0, 5, 50 and 250 ppm was scheduled to be completed October, 1984. The Toxicology Branch is awaiting the report on this study.

A 2-year feeding study in CD-1 mice was conducted with CGA-64250 at levels of 0, 100, 500 and 2500 ppm. A treatment-related increase in liver tumors was found at the high dose level (in males). No oncogenic effect was apparent at the mid dose. The NOEL for systemic toxicity was found to be 100 ppm. Based on the data from this study, the carcinogenic potency was calculated: $Q_1^* = 3 \times 10^{-2}$ (mg/kg/day)$^{-1}$.

In a 2-year feeding study in rats, no NOEL was established for several histological effects. Dermal fibromas in males and thyroid follicular tumors in females may be attributable to exposure to CGA-64250. Final conclusions on the results of this study will be made following submission and evaluation of pertinent historical control data.

CGA-64250 was not considered teratogenic in the rat at doses up to and including 300 mg/kg. Maternal toxicity (decreased body weight gain and food consumption) was found at 300 mg/kg, while fetotoxicity (ossification retardation) occurred at 100 and 300 mg/kg. The NOEL's for maternal toxicity

and fetotoxicity were 100 and 30 mg/kg, respectively. The compound was not teratogenic, fetotoxic or maternally toxic in the chinchilla rabbit at doses up to and including 180 mg/kg.

In a 2-generation study in Tif:RAlf[SPF] rats, CGA-64250 was administered at concentrations of 0, 400, 2000 or 5000 ppm in the diet. The compound caused perinatal death in all pregnant high dose F_0 females. Mating ratios and implantation rates were also reduced in this group. No other reproductive parameters appeared to be affected. Dose-related reductions in body weight gain and increased relative liver weights were evident in all CGA-64250-treated groups. At a dietary concentration of 2000 ppm, the test substance caused hypertrophy of centrilobular hepatocytes in F_1 adults. This study is considered "Supplementary". It provides data which may be useful in evaluating the results of a repeat 2-generation study which was initiated in March, 1983.

The battery of mutagenicity assays listed below has been performed on CGA-64250 technical, with negative results:

1. An Ames-type assay (with and without activation); 4 strains of S. typhimurium
2. A dominant lethal study in the Tif:MAG F (SPF) mouse
3. A nucleus anomaly test in the Chinese hamster
4. A BALB/3T3 cell transformation assay

The tests listed below were also performed; however, these were considered unacceptable, and additional information has been requested from the sponsor:

1. L5178Y/TK$^{+/-}$ mouse lymphoma test (in vitro)
2. S. cerevisiae D^7/mammalian-microsome test
3. Point mutation assay with mouse lymphoma cells (host-mediated)
4. Chromosome studies in mouse spermatogonia
5. Chromosome studies in mouse spermatocytes
6. Autoradiographic DNA repair test on human fibroblasts
7. Autoradiographic DNA repair test on rat hepatocytes
8. Sister chromatid exchange study (Chinese hamster bone marrow cells, in vivo)

The major metabolite of CGA-64250 in the fruiting parts of plants is triazole alanine (TA). TA has a low n-octanol/water partition coefficient (log P<-2), which suggests that it has no significant potential for bioaccumulation.

TA levels in untreated grain crops were found to be 0.01 to 0.03 mg/kg, irrespective of the kind or variety of cereal (barley, wheat, rye) or the country in which the cereal was cultivated (Germany, Norway, Sweden, France, Yugoslavia, U.S.A.). Since TA levels in these investigated samples could not have originated from applications of triazole fungicides, they are re-

garded as ubiquitous and occurring naturally. see pg 2 May 15 89

Because the formation of TA is not observed in animals, it is necessary to determine safety-related properties of this compound separately in order to assess the practical relevance of possible residues in edible crops.

In a study of the distribution, degradation and excretion of TA, male and female rats were given a single dose of 0.5 or 50 mg/kg of ^{14}C- triazole alanine. At both dose levels, analyses indicated that 95-105% of the dose was excreted within 24 hours, with 85-103% in the urine. No sex- or dose-related differences were found with respect to the extent of absorption or the rate or route of excretion. After 7 days, no residues were found in tissues of rats dosed with 0.5 mg/kg. Residues of no more than 22 ppb were found in liver, kidney and blood of animals dosed at the 50 mg/kg level. The major radioactive residue components in urine and feces were unchanged TA (69-86%) and a less polar derivative, N-acetyl triazole alanine (8-19%).

An acute oral toxicity study with TA in rats was considered invalid, since the study report did not sufficiently describe the materials or methods used. The following studies were regarded as supplementary, but may be upgraded if additional data are provided: acute oral toxicity study in fasted rats; acute oral toxicity study in unfasted rats; acute oral toxicity study in fasted mice; and acute intraperitoneal toxicity in rats.

A 2-week subacute toxicity study was conducted in male rats. TA was administered in the drinking water at levels of 0, 3000 or 10,000 ppm. No compound-related effects were apparent with respect to toxic signs, mortality, food consumption, body weight, organ weights or gross lesions at necropsy. In a follow-up, 4-week subacute oral toxicity study, male and female rats were given TA by gavage at doses of 0, 25, 100 and 400 mg/kg/day. No significant treatment-related effects were found.

A 3-month feeding study in male and female rats with TA was classified as "Supplementary." The sponsor must address deficiencies in the report before the Toxicology Branch can complete its evaluation of the study.

The following mutagenicity or cell transformation studies were conducted with TA:

1. Cell Transformation Test for Potential Carcinogenicity of R152056
2. Salmonella/Microsome Test for Point Mutagenic Effect
3. Micronucleus Test in CBC F1 Mice
4. Micronucleus Test for Mutagenic Effect on Mice
5. Pol A$^-$ Test on *E. coli* During Testing for Effects Harmful to DNA

The cell transformation test, as well as one of the two micronucleus tests, demonstrated apparent treatment-related mutagenic effects. In the Ames test, which used 5 strains of *S. typhimurium*, TA showed no mutagenic effect with or without S-9 activation. Also, in the *E. coli* pol A_1^- test,

TA with and without S-9 mix did not cause measurable DNA damage.

A 2-generation study with TA in the rat was initiated in 1983. The Toxicology Branch is awaiting submission of the final report for this study. The report on teratogenicity of TA in the rat was identical to that under review by Dr. George Ghali, Tox Branch Review Section IV, per Data Review Record, Record No. 113141.

Discussion:

CGA-64250 technical has a relatively low acute oral inhalation and dermal toxicity. Its action appears to be nonspecific. The compound has slight dermal irritation potential and is not a sensitizer, but causes a moderate level of eye irritation; no dermal toxicity was found at the highest dose tested (1 g/kg), except for local irritation.

Subchronic toxicity of CGA-64250 involved reduced weight gain in rats (NOEL, 240 ppm; LEL, 1200 ppm) and gastric lesions in dogs (NOEL, 50 ppm; LEL, 250 ppm). CGA-64250 caused liver tumors in mice in a 2-year feeding study; for systemic toxicity, the NOEL was 100 ppm and the LEL was 500 ppm. Based on data presented in a 2-year feeding study in rats, it is questionable whether CGA-64250 caused dermal fibromas in males and/or thyroid follicular tumors in females; historical control data will be used in making this determination.

The technical material is not teratogenic in the rat or rabbit. No conclusions have been made with respect to toxic effects on reproduction, pending review of a 2-generation study which was initiated in March, 1983.

In the absence of additional data for the 2-year feeding study in rats, it is considered inappropriate to set an ADI at this time. B. Litt, Tox Branch Statistics Team Leader, has determined that, based on the mouse liver tumor data, the carcinogenic potency estimator $Q_1^* = 3 \times 10^{-2}$ (see attached memorandum, B. Litt to H. Jacoby, 1/22/85).

The Toxicology Branch has requested that the sponsor provide a mouse metabolism study with CGA 64250 to identify metabolites resulting from a 100 ppm feeding level and a 2500 ppm feeding level. These results may elucidate the mechanism of oncogenicity at 2500 ppm.

Conclusions:

The tolerance requested for CGA-64250 is not toxicologically supportable, pending evaluation of additional data pertinent to the rat oncogenicity study.