CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D C. 20460

MAR 18 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Review of submitted studies on Tilt

To: Lois Rossi, PM-21
Registration Division, TS-767C

From: Marcia van Gemert, Ph.D.
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Thru: Theodore M. Farber, Ph.D.
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Chemical: CGA- 64 250, Tilt

Project No: 7-0227

Caswell No: 323EE

Record No: 185584

3/17/87

Action Requested: Review incoming data.

Comments:

A list of the studies submitted is enclosed and summarized below, along with the conclusions reached on each study. Concerning the metabolism studies, when taken as a whole, they appear to adequately cover the requirements for metabolism. It would have been important to do a repeat radioactive-dose study measuring radioactivity in tissues at various time periods to estimate tissue half-lives and potential bioaccumulation. However, the Toxicology guidelines concerning metabolism requirements are not sufficiently well stated to insist on this study at this time. Furthermore, judging from the information presented in this submission, bioaccumulation will probably not be a problem with this chemical.

1. Metabolism of CGA 64 250 in the rat. Study # 24/83, Sept. 1, 1983.
A single oral dose of 31.4 mg/kg ^{14}C-CGA 64 250 was administered by gavage to an unspecified number of rats. Urine and feces were collected for 3 days and analyzed. The major metabolic route taken by CGA 64 250 is by enzymatic attack of the propyl side chain and cleavage of the dioxolane ring. The phenyl ring is attacked by formation of a cyclohexadiene ring. Hydroxylation replacement of one of the chlorines by a hydroxyl group and

introduction of a methylthio group. The triazole ring can be oxidatively attacked to form hydroxy derivatives. Most of the alcoholic, phenolic, sulfuric acid and glucuronic acid conjugates are excreted in the urine.

Core classification: minimum

2. Distribution, degradation and excretion of CGA 64 250 in the rat. # 24/79, July 18, 1979.
2 animals/sex were given a single dose of 0.5 mg/kg or 25 mg/kg ^{14}C CGA 64 250. Urine, feces and expired CO_2 were collected at 24 hour intervals for 6 days post dosing, after which animals were killed and tissues collected for analysis. Administered ^{14}C appeared to be rapidly excreted in the urine. Very little radioactivity was recovered from expired CO_2. Most tissue residue levels were extremely low, except for liver and kidneys in males and females and ovaries in females. Urinary metabolite pattern of the 0-24 hour urines appeared similar for both sexes and both doses. There were 4-10 polar metabolites detected in urine with no detectable intact parent compound found (cis or trans).
Core Classification: supplementary

3. Characterization of urinary and fecal metabolites of rats after oral application of CGA 64 250. # 35/79, Aug. 31, 1979.
^{14}C-CGA 64 250 when given in a single gavage dose is extensively metabolized in the rat with no detectable parent compound in urine and about 5% found in feces after 3 days. About 80% of the urinary metabolites are acidic and fecal metabolites are somewhat less polar. Only 12 and 9% of urinary metabolites are susceptable to aryl sulfatase and b-glucuronidase respectively. There is evidence in urine and fecal metabolites that some metabolism is through cleavage of the dioxolane ring. However, two labels were used, one in the triazole and the other in the phenyl ring and very similar excretion patterns of these two would indicate that in most metabolites the bridge between the phenyl and the triazole ring remains intact.
Core Classification: minimum

4. Dermal absorption of ^{14}C propiconazole. # ABR-86064, 9/30/86.
Three groups of 4 male rats/group were treated with dermal application of ^{14}C propiconazole. One group was treated for 24 hours and immediately sacrificed, a second group was treated for 10 hours, the skin washed with soap and water rinse followed by 72 hours of depletion time after a soap and water rinse. Dose levels used were 0.1, 1.0 and 10.0 mg/rat. For the 24 hour exposed rats the percent absorbed was 57.1, 27.1 and 30.1% for the low, mid and high dose groups respectively. The rate of excretion of radioactivity was inversely related to the dose administered. For the 10 hour exposure (72 hour depletion) animals the dose absorbed was 42.4, 21.5 and 31.0% of the administered radioactive dose for the low, mid and high dose groups respectively. For the 24 hour exposure (72 hour depletion) animals the dose absorbed was 54.7, 29.8, and 29.8% of the dose administered for the low, mid and high dose groups respectively. Both groups of animals which had

depletion times excreted the bulk of the radioactivity within 24 and/or 48 hours, mainly in the urine. Results suggest that the radioactivity remaining in skin after 72 hours is somehow bound and is not available for further absorption.
Core Classification acceptable

5. Dermal absorption of ^{14}C-propiconazole in rats after a 10-hour exposure period. # ABR 86053, 8/4/86.
4 male rats/time point and 12/treatment level were given 0.1, 1.0 or 10.0 mg/rat. Treated rats were sacrificed at 2, 4 and 10 hours after skin application. The rate of absorption from skin was inversely proportional to the dose administered. The percent absorbed after 10 hours exposure was 54, 36 and 29% of the administered dose for the low, medium and high dose groups respectively. Most of the remaining radioactivity remained either on or in the skin, with total skin residues of 45.9, 78.8 and 60.2% for low, medium and high dose groups respectively.
Core classification: acceptable

6. Effect of repeated oral administration of CGA 64 250 on liver weight of male and female mice. # 12/86, Aug. 20, 1986.
Male and female mice were fed unlabeled CGA 64 250 for 21 days at doses of 5, 100, 2500 ppm CGA 64 250 followed by a single oral dose of ^{14}C CGA 64 250 at the corresponding dose level. Liver weights were recorded 4 days post ^{14}C dosing and were significantly increased in the high dose (2500 ppm) males and females. When presented as liver/body weight ratios, data for both males and females showed an increase in the high dose. A female animal treated with a single dose (equivalent to a daily dietary dose of 2500 ppm) only of ^{14}C-CGA 64 250 also showed an increase in absolute and relative liver weights.
Core Classification: supplementary

7. The major metabolic pathways of CGA 64 250 in the rat. #9/81, March 13, 1981.
This is an extension of the previously reviewed study where ^{14}C-CGA 64 250 was given in a single gavage dose and was extensively metabolized in the rat with no detectable parent compound found in urine and about 5% found in feces after 3 days. The major metabolic pathways in this study have been proposed for CGA 64 250 based on NMR and mass spectroscopy analyses. A major metabolic pathway is through cleavage of the dioxolane ring with subsequent dechlorination and conjugation.
Core Classification: minimum

8. The metabolism of [U-^{14}C] phenyl CGA 64 250 in mice after pretreatment with unlabeled CGA 64 250. # 12RB01,02,03,(PR 6/86) May 20, 1986.
Male and female mice and male rats were fed unlabeled Tilt for 21 days at doses of 5, 100, 2500 ppm CGA 64 250 followed by a single oral dose of ^{14}C CGA 64 250 at the corresponding dose level. Mice eliminate a major portion of the radioactivity in urine, with males excreting a greater percent than females.

Rats excreted equal amounts in both urine and feces. Four days post dosing with ^{14}C CGA 64 250 residues remained in liver, kidneys and carcass in mice and liver in rats. The predominant urinary metabolite in mice was the glucuronic acid conjugate of the metabolite CGA 91 305. The predominant metabolic pathway in mice involves the dioxolane ring cleavage.
Core classification; minimum

9. A teratology study in New Zealand White Rabbits. # 86043 (MIN 852172) Aug. 1, 1986.
Groups (19/group) of pregnant rabbits were administered CGA 64 250 at doses of 100, 250 and 400 mg/kg from gestation days 7 through 19. AT 250 and 400 mg/kg, the treated animals showed decreased food consumption and body weight gain during the treatment period. At 400 mg/kg, treated rabbits also showed increased incidence of abortion. There was, however, no evidence of developmental toxicity.
Based upon the data, the NOEL for maternal toxicity was estimated to be 100 mg/kg; LEL, 250 mg/kg. The NOEL for developmental toxicity was estimated to be 400 mg/kg (HDT).
Core Classification: supplementary. The report must contain the data on the animals which were sacrificed before the termination of the study, specifically those rabbits which had aborted or delivered early in the study.