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DATA EVALUATION REPORT

Study Type: Metabolism in rat Tox. Chem No. 323EE

Accession No.: 265794

Test Material: CGA 64 250 fungicide

Synonyms: Tilt, propiconazole

Study Number: 12RB01, 12RB02, 12RB03 (PR 6/86)

Sponsor: Ciba Geigy

Testing Facility: Ciba Geigy Agricultural Division, Basle Switzerland

Title of Report: The metabolism of [U-^{14}C]-phenyl CGA 65250 in mice after pretreatment with unlabelled CGA 64 250

Author: R. Bissig

Report Issued: May 20, 1986

Conclusions: Male and female mice and male rats were fed unlabeled Tilt for 21 days at doses of 5, 100, 2500 ppm CGA 54 250 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 642500 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

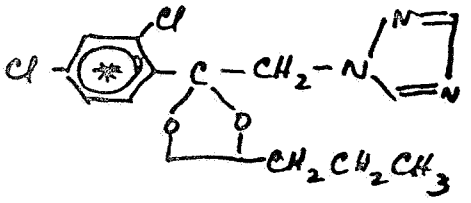
Quality Assurance Statement accompanied the report and was signed.

Information which may reveal manufacturing processes has been deleted

A. Materials:

1. Test Compound:

Description: Labelled compound: Specific Activity = 56.9uCi/mg
Batch: GAN-VI-43
Supplier: H. Mory, N. Wigger
Purity: 92%, increased to 97% via column chromatography
[redacted]
Structure:



Description: Unlabelled Compound:
Batch: OP 412127,
Purity: 91.1%
[redacted]
Dilution of labelled compound to a specific activity of 18.9 uCi/mg and 17.8 uCi/mg for males and females respectively.

2. Test Animals:

Species: Mice

Strain: CD-1

Age: 4 weeks

Weight:22-26 gms

Source: Charles River WIGA, GmbH, Switzerland, Germany

Species: Rat

Strain: Tif:RAI F (SPF)

Age: 7 weeks

Weight: 200 gms

Source: Animal Production Stein, Ciba Geigy

Study Design:

Animal assignments and study procedures:

Mice: 21 males (7/dose level) and 24 females (7/dose level at end of study). 2/sex were used as control. After dosing animals were kept in glass metabolism cages. Food containing the radioactive

CGA 64 250 and water were given ad libitum except the evening before ^{14}C- test compound administration. After ^{14}C dosing animals were allowed food and water ad libitum. Urine and feces were collected at 24 hour intervals. 4 days post ^{14}C-dosing animals were killed and blood, liver. kidneys, lungs and remaining carcass were analyzed. Body weights were taken at weekly intervals.

Rats: 3 male rats were used, one served as control. Food and water were given ad libitum except 19 hours pre ^{14}C dosing, when animals were fasted. Urine and feces were collected at 24 hour intervals. Animals were killed 4 days post ^{14}C dosing and blood, liver, kidneys, lungs and remaining carcass were taken for analysis. Body weights were taken at start and end of the experiment.

Test Procedure:

Test material was mixed in the diet and given for 21 days. Test doses were 5, 100 and 2500 ppm. ^{14}C CGA 64 2500 was dissolved in ethanol/ polyethylene glycol 200/water (7/9/4 v/v). Dosing solution was 0.1 and 0.4 ml by stomach tube for mice and rats respectively. Labelled ^{14}C CGA 642500 was equivalent to 5, 100 and 2500 ppm in the 24 hour food assuming a daily consumption of 5 gms for mice and 20 gms for rats consumed per day.

Measurement of radioactivity is on appended pages 1-4. Procedures for thin layer chromatography, liquid chromatography, high performance liquid chromatography, spectroscopic methods, enzymatic hydrolysis and calculations are on appended pages 4-12.

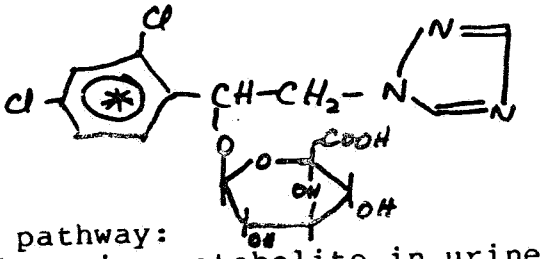
Results:

The 3 female mice given a bolus dose of 600 mg/kg ^{14}C-CGA 64 250 without pretreatment of unlabelled compound showed severe signs of toxicity and two died 48 to 72 hours post dosing.

Excretion:
Within 24 hours mice excreted 64% of the dose administered and rats excreted 94%. Major excretory route for mice with 45-81% excreted in urine and 22-43% excreted in feces by 96 hours was urine, while in rats, urine was 48% and feces 54% of the excreted radioactive dose. There is a slight difference in excretion pattern between sexes in mice.

Tissue residues:
Tissue residue data are on appended page 14. The highest residue levels appear to be in the liver and carcass for the male and female mice. Rat liver appeared to accumulate only about 10% (0.2245 ppm) of the residue levels found in mice (2.262 ppm for males and 2.956 ppm for females) and the carcass of the rat retained very little radioactivity. The residues in female mice were 1.3 to 2.2 times higher than males at all dose levels with respect to blood, liver, lungs and carcass (except for a 0.6 ratio in carcass in the 5 ppm treatment groups). Residues in the kidney were up to 5 times greater in males than in females.

Urinary metabolites:
Two dimensional TLC revealed 15-30 metabolites in 0-24 hour urines. There are sex and species differences in metabolites. Appended page 15 details the quantitative distribution of these metabolites. The most significant metabolite to show sex and species differences is metabolite U_2 which was 61-73% in male mice, 29-41% in female mice and 6% in male rats.
The U_{12} fraction was another example of sex and species as well as dosage difference in metabolic excretion products. At 5 and 100 ppm female mice and rats excreted more of the U_{12} metabolite whereas male mice and female mice at the 2500 ppm dose level excreted only 2-7% of this fraction. In an earlier study this metabolite was identified as a-hydroxy-carboxyacid (metC_U) See appended page 16 for structure.
According to the study text if mouse urines are incubated with b-glucuronidase then 75-85% of the U_2 fraction disappears giving rise to a more unpolar U_{18} fraction. In rat urine, however, the most polar fraction U_1 completely disappears after b-glucuronidase incubation and forms several unpolar fractions. The u_2 fraction is not significantly affected. The study authors conclude that there is some unique glucuronide conjugation inherent in the mouse.
The study text stated that incubation of the urines with aryl sulfatase did not significantly change the metabolite pattern.
The study text further stated that U_{18} fraction consisted of at least 2 compounds, one was the alcohol CGA 91 305, the structure of which can be found on appended page 16 and is the exacon of the major metabolite fraction U_2 in mice urines. The second major component of U_{18} was the analogous ketone CGA 91 304. (structure on appended page 16). The major urine metabolite isolated from the U_2 fraction was determined to be Met IU, the glucuronic acid conjugate of the metabolite CGA 91 305. The structure is elucidated below:



Metabolic pathway:
In mice the major metabolite in urine, regardless of sex, dose level and pretreatment, is the glucuronic acid conjugate of the metabolite CGA 91 305 with the structure above (Met IU).
The study text states that this implies that the major metabolic pathway in mice proceeds via elimination of the dioxolane ring leading via ketone formation (CGA 91 304) to the corresponding acid to yield IU. In males this represents 30% of the dose, whereas in females, this is 15% of the dose administered.

In rats the unpolar metabolite fractions U_{15} through U_{18} represent metabolites where the dioxolane ring had been cleaved. In summary mice cleave the dioxolane ring to a higher extent (70 and 40% for males and females) than do male rats (30%).

Discussion:
Male and female mice and rats were fed the unlabeled tilt for 21 days doses of 5, 100 or 2500 ppm CGA 64 2500 followed by a single oral dose of ^{14}C CGA 64 250 at the corresponding dose level.

Mice eliminate a major portion of 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.

TILT CGA-64250 Reviews

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p. 6-21

The next 110 page(s) is/are not included in this copy of the TILT reviews.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commerical/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X Detailed methods and results of a registrant submission.

___ Duplicate pages.

The information not included generally is considered confidential by product registrants. If you wish to obtain the information deleted, please contact the individual who prepared this response to your request.
