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DATA EVALUATION REPORT

Study Type: Metabolism in the rat

Tox. Chem No. 323EE

Accession No.: 265794

Test Material: CGA 64 250

Synonyms: Tilt, Propiconazole

Study Number: 24/83

Sponsor: Ciba Geigy

Testing Facility: Biochemistry Dept., Research and Development
Plant Protection, Agricultural Division, Ciba Geigy
Basle, Switzerland

Title of Report: The metabolism of CGA 64 250 in the rat

Author: W. Mucke

Report Issued: Sept. 1, 1983

Conclusions: 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, although the number of animals used was not specified, the identification of metabolic products appeared to be fairly exhaustive.

Schematics which may reveal the manufacturing process has been deleted

A. Materials:

1. Test Compound: Triazole ^{14}C-CGA 64 250

Specific Activity: 23.1 uCi/mg

[redacted]

Purity: > 98%

Dosing solution: Triazole labelled compound was dissolved in water/ethanol/polyethylene glycol 200 (50/30/20 v/v/v) to yield a solution of 5.5 mg/ml. 1 ml was given by gavage to each rat with an average dose of 31.4 mg/kg (29.6-32.9 mg/kg)

2. Test Animals:

Species: rats, male

Strain: TIF RAI f (SPF)

Age: not given

Weight: 167-186 gms

Source: Ciba Geigy farm, Stein Switzerland

Study Design:

Animal assignments and study procedures:

A single oral dose of 31.4 mg/kg ^{14}CGA 64 250 was administered to an unspecified number of rats. Urine and feces were collected daily for 3 days in metabolism cages and pooled for analysis.

Results:

Greater than 95% of the administered dose of radioactivity was excreted within 3 days. Appended page 12 tabulates excretion within 3 days. The total radioactivity excreted in urine was 52.3% and feces was 43.3% for a total of 95.6% of the administered dose.

Exhaustive metabolic work was done on both urine and fecal metabolites.

Urinary Metabolites:
Two dimensional TLC revealed 13 metabolites designated #5-17 and no parent compound, (limit of detection = 0.1%). These metabolites can be seen on appended page 13 corresponding to standards. HVE demonstrated that around 80% of these urinary metabolites are acidic. After treating fractions 17 and 15 with b-glucuronidase and aryl sulfatase they disappeared, giving rise to metabolites 1-5 (see appended page 13).
Six fractions of urinary metabolites were isolated which are

detailed on appended page 14. Individual isolation and purification of each of these fractions are summarized on appended pages 15-21.

Fecal metabolites:
The 0-24 hour fecal sample was analyzed and extracted with methanol/water (80/20 v/v). The extract according to the study text "containing 57% of the feces radioactivity was evaporated, the residue taken up in water (adjusted to pH 2) and extracted with ether. This feces extract E_1, representing 16.2% of the dose was chromatographed on silica gel using an ethyl acetate/methanol elution gradient, resulting in five major metabolite fractions, E_{10}, E_{131}, E_{16}, E_{17}, E_{19}."
Isolation and purification of these metabolic fractions are on appended pages 22-27. The entire proposed metabolic pathway is on appended pages 28 and 29 with the scheme of proposed metabolic origin of sulfur-containing metabolites on appended page 30.

Discussion:

The metabolic pathways followed by CGA 64 250 are very complex. However, the major metabolic pathway is by enzymatic attack of the propyl side chain and cleavage of the dioxolane ring.
The phenyl ring is attacked in several ways. Formation of a cyclohexadiene ring can occur, hydroxylation, replacement of one of the chlorines by a hydroxy group and introduction of a methylthio group can also occur. The triazole ring can be oxidatively attacked to form hydroxy derivatives. Most of the alcoholic, phenolic, sulfuric and glucuronic acid conjugates are excreted in the urine.

TILT CGA-64250 Reviews

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p. 4-33

The next 30 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.
