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DATA EVALUATION REPORT

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

Accession No.: 265794

Test Material: CGA 64 250

Synonyms: Tilt, Technical

Study Number: 35/79

Sponsor: Ciba Geigy

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

Title of Report: Characterization of urinary and fecal metabolites of rats after oral application of CGA 64 250

Author: M. Muecke

Report Issued: Aug. 31, 1979

Conclusions: ^{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

Quality Assurance Statement accompanied the report and was signed.

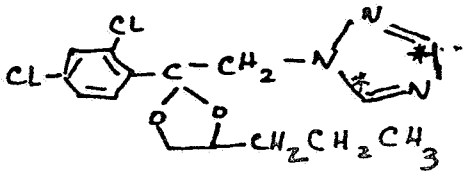
Information which may reveal manufacturing process has been deleted

A. Materials:

1. Test Compound: Two radiolabelled compounds were used.

A. Triazole [3,5-^{14}C] CGA 64 250 (triazole labelled)

Structure:



Specific Activity: 59.6 uCi/mg

[redacted]

Purity: > 98%

This material was diluted with unlabelled CGA 64 250 with the following characteristics:

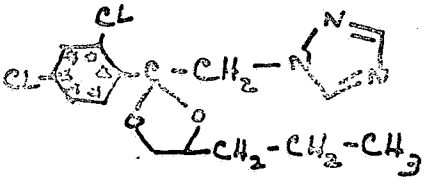
[redacted]

purity: 98.9%

to yield a specific activity of 23.1 uCi/mg

B. Phenyl [U-^{14}C]-CGA 64 250 (phenyl labelled)

Structure:



Specific Activity: 38.9 uCi/mg

[redacted]

radiochemical purity: > 98%

This material was diluted with the unlabelled CGA 64 250 (as above) to yield a specific activity of 21.9 uCi/mg.

2. Test Animals:
Species: rats, male
Strain: Tif: RAI f(spf)
Weight: 167-186 gms
Age: not given
Source: Ciba Geigy Farms, Stein, Switzerland

Dosing solution: Given by gavage, dissolved in water/ethanol/ polyethylene glycol 200 (50/30/20 v/v)
Triazole labelled CGA 64 250 - 5.5 mg/ml
phenyl labelled CGA 64 250- 5.78 mg/0.9 ml

Study Procedure and Animal Assignments:

Male rats, number unspecified in the study text, were kept in individual metabolism cages and fasted overnight before dosing. Doses used were also unspecified in the study text, however, in the table appended to the study the authors specify that 31.4 mg/kg of the triazole labelled material was used and 32.5 mg/kg of the phenyl labelled material was used. This table also specifies that 20 animals were given the triazole labelled material, and 3 animals were given the phenyl labelled compound. After dosing, the animals were given food and water ad libitum. Urine and feces were collected and pooled for an unspecified period of time, and analyzed for radioactivity.

Procedures for measurement of radioactivity, thin layer chromatography and high voltage electrophoresis are on appended pages 1-3.

Results:

Within 3 days > 95% of the administered triazole labelled dose was excreted in urine (52.3%) and feces (43.3%). Animals treated with the phenyl labelled compound showed a similar pattern of excretion. See appended page 5 for details.

Urinary metabolites:

TLC of 0-24 hour urines showed no parent compound (limit of detection, 0.2% of radioactivity). Two dimensional TLC of triazole labelled compound revealed 13 metabolites (numbered 5-17) all of which appeared in fractions from phenyl-labelled treated animals with the exception of fraction 12.

The study text stated in a somewhat confusing manner that "when the urines were incubated with b-glucuronidase or with b-glucuronidase/aryl sulfatase metabolite fraction 17 and metabolite fraction 17 and 15 disappeared, respectively. This indicates that fraction 17 consists of glucuronic acid and fraction 15 of sulfuric acid conjugates. Upon treatment with the above enzymes, the same cleavage products emerged designated 1 thru 4." (see appended page 6.)

The metabolites # 5 and 6 cochromatographed on TLC with reference compounds B and C on appended page 4, respectively. Metabolite #6 consists solely of C whereas fraction 5 is not homogeneous, with only one of its components being B.

According to results of high voltage electrophoresis, the majority of metabolites are acidic, with better than 80% of the urinary

radioactivity moving toward the anode at pH 6.9.

Appended page 6 gives percentages of urinary radioactivity for each metabolite fraction. Eight fractions contained over 5% of the total urinary radioactivity.

Fecal metabolites:

Following dosing the 0-24 hour fecal samples contained 36.5% triazole labelled and 44.2% phenyl labelled of the administered doses. Methanol extraction data are on appended page 7. The percentages of fecal metabolites extracted and distributed at various pH's were not substantially different between the triazole and phenyl labelled CGA 64 250.

TLC revealed at least 8 metabolites, which were less polar then urinary metabolites. About 35% of the total extracted radioactivity moved anionic in the HVE at pH 6.9. The remainder behaved neutral.

TLC in different systems revealed according to the study text, that about 9% of fecal radioactivity may be metabolite B and/or C and about 5% was unchanged parent compound.

Discussion:

CGA 64250 is extensively metabolized in the rat with no detectable parent compound appearing in urine and only about 5% appearing in feces. About 80% of 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 feces 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.

TILT CGA-64250 Reviews

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p. 5-11

The next 7 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.
