12/29/96

DATA EVALUATION REPORT

AZOXYSTROBIN

STUDY TYPE: METABOLISM - RAT (85-1)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
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DATA EVALUATION RECORD

STUDY TYPE: Metabolism - Rat
OPPTS 870.7485 [§85-1]

DP BARCODE: D218319 SUBMISSION CODE: S489692
P.C. CODE: 128810 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY):

unlabeled ICIA5504 (azoxystrobin) - 99% (MRID 43678150, 43678151, 43678152, 43678153, 43678154)
[$^{14}$C]-pyrimidinyl ICIA5504 - >98% (MRID 43678150)
[$^{14}$C]-pyrimidinyl ICIA5504 - >99% (MRID 43678151, 43678152, 43678153)
[$^{14}$C]-pyrimidinyl ICIA5504 - >95% (MRID 43678154)
[$^{14}$C]-phenylacrylate ICIA5504 - >95% (MRID 43678154, 34678150 [>98%])
[$^{14}$C]-cyanophenyl ICIA5504 - >95% (MRID 43678154, 43678150 [>98%])

SYNONYMS: azoxystrobin; methyl (E)-2-{2-cyanophenoxy)pyrimidin-4-yloxy]-phenyl}-3-methoxyacrylate; methyl (E)-2-{2-[6-(2-cyanophenoxy) pyrimidin-4-yloxy} phenyl}-3-methoxyacrylate

CITATION:

1. Lythgoe, R. and E. Howard (1993) ICIA5504: Whole body autoradiography in the rat following a single oral dose (1 mg/kg). ZENECA Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Report No. CTL/P/3785, January 25, 1993. MRID 43678150. Unpublished.

2. Lythgoe, R. and S. McAsey (1993) ICIA5504: Excretion and tissue retention of a single oral dose (1 mg/kg) in the rat. ZENECA Central Toxicology Laboratory. Report No. CTL/P/3883, February 25, 1993. MRID 43678151. Unpublished.

3. Lythgoe, R. and E. Howard (1993) ICIA5504: Excretion and tissue retention of a single oral dose (100 mg/kg) in the rat.ZENECA Central Toxicology Laboratory. Report No. CTL/P/3884, February 25, 1993. MRID 43678152. Unpublished.



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4. Lythgoe, R. and E. Howard (1993) ICIA5504: Excretion and tissue retention of a [$^{14}$C]-labeled single oral dose (1 mg/kg) following fourteen daily unlabeled doses in the rat.ZENECA Central Toxicology Laboratory. Report No. CTL/P/4039, February 25, 1993. MRID 43678153. Unpublished.

5. Lappin, G. and A. Gledhill (1994) ICIA5504: Biotransformation in the rat. ZENECA Central Toxicology Laboratory. Report No. CTL/P/4176, June 13, 1994. MRID 43678154. Unpublished.

SPONSOR: ICI Americas, Inc., Agricultural Products, Wilmington, DE (all studies)

EXECUTIVE SUMMARY: In a metabolism study (MRID 43678150, 43678151, 43678152, 43678153, 43678154), ICIA5504 (Azoxystrobin, 99% a.i. unlabeled or with pyrimidinyl, phenylacrylate, or cyanophenyl label) was administered to Alpk:APfSD rats (5-8/sex/group depending on the experiment) as single gavage doses of 1 or 100 mg/kg or 14-day repeated doses of 1 mg/kg. Biliary metabolites were assessed using rats with cannulated bile ducts given a single 100 mg/kg gavage dose of ICIA5504.

No animals died as a result of the treatment. The overall recovery of administered radioactivity in the single low-dose, 14-day repeated low-dose, and single high-dose groups were 91.75-103.99% indicating acceptable mass balance. Less than 0.5% of the administered dose was detected in the tissues and carcass up to seven days postdosing. Absorbed ICIA5504 following oral administration was widely distributed. However, a definitive quantitative assessment of absorption was difficult due to fecal sample extraction difficulties. The greatest amounts of absorbed ICIA5504 were detected in organs associated with excretory function, especially the liver and kidneys. There was no evidence of potential for bioaccumulation. Excretion via expired air was minimal. The primary route of excretion was via the feces (≈73-89%), although ≈9-18% was detected in the urine of the various dose groups. The fecal vs. urinary route of excretion did not vary considerably with dose, although for fecal excretion in the low-dose groups it was not possible to determine the relative contributions of parent compound and metabolites due to the previously noted extraction difficulties. For the single high-dose group, assessment of biliary excretion suggested approximately 70% absorption with approximately 32% of administered radioactivity remaining as parent compound in the gastrointestinal tract. However, in the biotransformation study, parent compound was not detected in the fecal extracts of the single low-dose and repeated low-dose groups nor were substantial quantities of metabolites detected. Sex-related differences in excretion were minor; slightly greater (≈3-7%) amounts of urinary radioactivity with commensurate reductions in fecal radioactivity were noted for female rats in all three treatment regimens. There were no apparent sex-related differences in distribution of administered radioactivity.

Absorbed ICIA5504 appeared to be extensively metabolized. Minor qualitative and quantitative differences in biliary metabolites were observed for males and females. With the exception of metabolite V (a glucuronide conjugate) which represented 29.3% (males) and 27.4% (females) of the administered dose, individual biliary metabolites represented less than 10% of the administered dose. A metabolic pathway, consistent with the data on metabolite identification and quantitation, was proposed showing hydrolysis and subsequent glucuronide conjugation as the major biotransformation process.

This metabolism study in the rat is classified supplementary and does not satisfy the guideline requirement for a metabolism study (85-1) in rats. The studies can be upgraded upon acceptable additional explanations of fecal excretion data and how they pertain to assessing absorption in the single low-dose and 14-day repeated low-dose groups.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

## I. MATERIALS AND METHODS

### A. MATERIALS

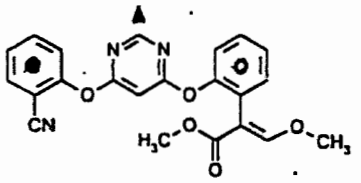
#### 1. Test compound

[$^{14}$C]-pyrimidinyl ICIA5504
Radiochemical purity: >99 % [determined by TLC]
Specific activity: 2.02GBq/mmol
Lot/Batch: Y06654/012 (Central Toxicol. Lab. ref. No.)

[$^{14}$C]-phenylacrylate ICIA5504
Radiochemical purity: >98 % [determined by TLC]
Specific activity: 1.895 GBq/mmol
Lot/Batch: Y06654/015 (Central Toxicol. Lab. ref. No.)

[$^{14}$C]-cyanophenyl ICIA5504
Radiochemical purity: >98 % [determined by TLC]
Specific activity: 2.307 GBq/mmol
Lot/Batch: Y06654/016 (Central Toxicol. Lab. ref. No.)

Non radioactive ICIA5504,
Purity: 99.0 % [TLC]
Lot/Batch No.: Y06654/009 (Central Toxicol. Lab. ref. No.)
Description: white powder
Contaminants: none noted
CAS No.: not available
Structure:



▲ Denotes position of pyrimidinyl ring label
o Denotes position of phenylacrylate ring label
● Denotes position of cyanophenyl ring label

2. Vehicle

polyethylene glycol (PEG 600)

3. Test animals

Species: rat
Strain: Alpk:APfSD
Age and weight at study initiation:
(1) 6-11 weeks; 200-245 g (2) 6-9 weeks; 195-224 g (3) 6-9 weeks; 168-210 g (4) 6-10 weeks; 190-228 g (5) 5-8 weeks; 210-364 g
Source: Barriered Animal Breeding Unit, Alderley Park
Housing: Housed in groups of the same sex (no. not specified) in standard rat cages or individually in metabolism cages during sample collection.
Diet: Pelleted PCD rat diet (Special Diets Services Ltd., Stepfield, Witham, Essex, UK) was fed ad libitum. Diet analysis affirmed compliance to required specifications. For biotransformation study (exp. no. 5), rats were also given an aqueous solution of 5% dextrose, 0.9% sodium chloride, and 0.05% potassium chloride for the duration of the study.
Water: water was provided ad libitum
Environmental conditions:
Temperature: 19°-23°C
Humidity: 32-77%
Air changes: not specified
Photoperiod: 12 hr light/12 hr dark
Acclimation period: 3-6 days (not specified for biotransformation study (exp. No. 5; MRID 43678154.)

4. Preparation of dosing solutions

(1) MRID 43678150. Three dosing solutions for autoradiography studies were prepared such that administration of 4 mL/kg would provide a dose of 1 mg ICIA5504/kg



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and 4.7 MBq/kg. Appropriate amounts of unlabeled ICIA5504 and the three radiolabeled forms ([$^{14}$C]-pyrimidinyl, [$^{14}$C]-phenylacrylate, and [$^{14}$C]-cyanophenyl) were prepared in 5 mL of PEG 600. The specific activities of the three solutions were 4.663, 4.699, and 4.665 MBq/mg of ICIA5504, respectively.

(2) MRID 43678151. Two dosing solutions for single low-dose tissue retention and excretion studies were prepared using unlabeled ICIA5504 (2.3 mg for solution 1 and 0.75 mg for solution 2), [$^{14}$C]-pyrimidinyl ICIA5504 and either 15 mL (solution 1) or 5 mL (solution 2) of PEG 600. Both solutions were formulated to achieve a concentration of 0.22 mg and 0.4 MBq/g of solution. The specific activity of the dosing solutions were 1.96 and 1.98 MBq/mg of ICIA5504, respectively.

(3) MRID 43678152. The dosing solution for single high-dose tissue retention and excretion studies was prepared by mixing [$^{14}$C]-pyrimidinyl and unlabeled ICIA5504 in a final volume of 15 mL PEG 600 to attain a concentration of 22.16 mg and 0.45 MBq/mg dosing solution. The specific activity of the solution was 20.4 kBq/mg ICIA5504.

(4) MRID 43678153. Two dosing solutions for tissue retention and excretion studies for a single low-dose following 14-day administration were prepared. Unlabeled 125.0 mg of ICIA5504 was dissolved in PEG 600 to provide a final volume of 250 mL. [$^{14}$C]-Pyrimidinyl (1.88 mg; 9.41 MBq) and unlabeled ICIA5504 (2.98 mg) was dissolved in PEG 600 to provide a final volume of 20 mL and concentration of 0.216 mg/g (0.42 MBq). The specific activity of the solution was 1.94 MBq/mg ICIA5504.

(5) MRID 43678154. Three dosing solutions with either the cyanophenyl, pyrimidinyl or phenylacrylate [$^{14}$C]-labels were prepared for the biotransformation study. For all of the solutions, unlabeled ICIA5504 and labeled compound were mixed with PEG 600 to achieve dosing solutions for which 4 mL would be equivalent to 100 mg ICIA5504/kg and 4 MBq/kg.



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B. STUDY DESIGN AND METHODS

1. Group arrangements

Animals were assigned randomly to the test groups in Table 1.

**TABLE 1. Dosing groups for pharmacokinetic studies for ICIA5504.**

| Test Group | Dose (mg/kg) | Number/sex | Remarks |
|---|---|---|---|
| Intravenous | | | not performed; |
| Low dose (MRID 43678151) | 1.0[a]<br>1.0[a] | 5M<br>5F | gavage administration (4 mL/kg); tissue retention/excretion studies; sacrificed at 7 days |
| Low dose (MRID 43678151) | 1.0[b]<br>1.0[b] | 1M<br>1F | gavage administration; expired air studies, sacrificed at 48 hrs |
| Low dose with pretreatment (MRID 43678153) | 1.0<br>1.0 | 8M<br>8F | gavage administration; 14 daily doses of unlabeled ICIA5504 followed by a single dose of labeled ICIA5504 on day 15; sacrificed at 22 days |
| High dose (MRID 43678152) | 100<br>100 | 5M<br>5F | gavage administration; sacrificed at 7 days |
| Biotransformation (MRID 43678154) | 100[c]<br>100[c] | 6M<br>6F | gavage administration (4 mL/kg); excreta, bile and cage washings collected; sacrificed at 48 hrs |
| Autoradiography (MRID 43678150) | 1.0[d]<br>1.0[d] | 6M<br>6F | sacrificed at 24 or 48 hrs |

[a]Dosing solution 1 [see I. A.4.(2)]
[b]Dosing solution 2 [see I. A.4.(2)]
[c]Dosing solutions [see I. A.4.(5)]
[d]Dosing solutions [see I. A.4.(1)]

2. Dosing and sample collection

The test article was administered by gavage. Dosing volumes were 4 mL/kg.



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a. Pharmacokinetic studies

For the autoradiography studies (MRID 43678150), rats 1, 2, 5, 6, 9, and 10 were terminated 24 hours after administration of [$^{14}$C]-ICIA5504, and immediately frozen in solid carbon dioxide and *n*-hexane. Rats 3, 4, 7, 8, 11, and 12 were terminated and frozen 48 hours after test article administration. The animals were then embedded on their sides in 2% carboxymethyl cellulose and sectioned at 30$\mu$m, freeze-dried, and mounted with Hyperfilm-$\beta$max X-ray film and exposed for 28 days.

For the excretion and tissue retention (single low-dose, single high-dose, and 14-day repeated dose) experiments (MRID 43678151, 43678152, 43678153), urine from 10 rats (low-dose), 12 rats (high-dose), or 8 rats (14-day repeated) was collected at 6, 12, 24, 36, and 48 hours and feces were collected at 12, 24, 36, 48 hrs, and at 24-hour intervals up to 7 days post-dosing. Cage wash was collected from the aforementioned at the same collection times. Expired air was collected from two additional rats (low-dose only) for 12-hr periods over 48 hours. Expired air was passed through two activated charcoal columns to trap volatile radioactivity and two Nilox columns (containing sodium hydroxide) to trap carbon dioxide. At termination (7 days postdosing), the following tissues were collected from all rats: blood (whole blood and plasma), brain, gonads, heart, large intestine, small intestine, kidneys, liver, lungs, spleen, abdominal fat samples, bone (femur), and muscle. Intestinal contents were also collected. For rats in the expired air experiments, only carcasses were saved. Tissue samples, excreta, and activated carbon trap contents were stored at -20°C (blood was stored at 4°C).

Fecal samples were homogenized with anhydrous magnesium sulfate and oxidized. Blood and soft tissue samples were solubilized in Soluene-350. The spleen was homogenized in water; liver and abdominal fat were homogenized prior to solubilization. Whole blood, spleen homogenate, bone, and homogenized fecal samples were oxidized in a Packard Tricarb sample oxidizer. The lumenal contents of the large and small intestines were removed by flushing with saline and combined with carboxymethyl cellulose and sodium salt prior to oxidation as previously described. Carcasses were homogenized and solubilized in Soluene-350.

Replicate samples of urine, cage wash, tissue samples, and sodium hydroxide from the carbon dioxide traps were mixed with Optiphase MP scintillation fluid and counted in a Packard Tricarb Model 2000CA scintillation counter for a maximum of 10 minutes each. Results were corrected for background and counting efficiency. DPM were calculated using appropriate quench correction.

b. Metabolite characterization studies

In the biotransformation study (MRID 43678154), excreta, bile, and cage wash were collected at 6, 12, 24, 36, and 48 hours and stored at -20°C. Zero-to-48-hr bile, fecal, and urine samples were each pooled. Samples for males and females were maintained separately. Urine and feces collected up to 168 hours postdosing in the low-dose, high-dose, and 14-day repeated dose experiments were used for quantification of metabolites. Some bile samples were enzymatically digested using cholylglycine hydrolase (30 units/mL), pH 5.6 at 37°C overnight.

Analytical techniques included, thin layer chromatography (TLC), column chromatography, and HPLC analysis. TLC used solvent systems 1-3, and column chromatography used solvent systems 4 and 5.

| | |
|---|---|
| (1) dichloromethane:diethyl ether | 4:1 v:v |
| (2) hexane:diethyl ether | 1:9 v:v |
| (3) hexane:ethyl acetate | 1:1 v:v |
| (4) chloroform:methanol | 9:1 v:v |
| (5) butanol:acetic acid:water | 12:3:5 v:v |

HPLC analysis utilized a Hichrome HIRPB reverse phase column, and mobile phases of water with 0.1% acetic acid (mobile phase A) and acetonitrile with 0.1% acetic acid (mobile phase B) with a gradient flow (80% A, 20% B for 5 minutes followed by 20% A to 80% B over 25 minutes). Flow rate was 1 mL/min with detection set at 254 nm. Small bore HPLC was also used for metabolite separation, and was conducted under the above conditions but using a smaller diameter column and flow rate of 250$\mu$l/minute. Preparative HPLC was used on untreated or enzyme-digested bile samples to obtain amounts of isolated metabolites sufficient for NMR analysis.

NMR and mass spectrophotometry (MS) were used for metabolite identification.



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3. Statistics

Although standard deviations and mean values for some data sets are provided, statistical analyses were not reported.

## II. RESULTS

### A. PHARMACOKINETIC STUDIES

1. Preliminary experiment

No preliminary experiments were conducted.

2. Absorption

Based upon low concentrations in tissues and organs, and urinary and fecal excretion data, relatively small amounts of the test material appeared to be absorbed following a single oral low dose (1 mg/kg). Mass balance data was sufficient and supports the contention of low absorption. However, in rats with cannulated bile ducts excretion of biliary metabolites accounted for 72.2 - 73.8% of the administered dose (100 mg/kg), thereby implying substantial absorption at this dose.

3. Tissue distribution

ICIA5504 appeared to be widely distributed following oral administration in rats but radioactivity in organs and tissues was minimal. Only those organs/tissues exhibiting the highest concentrations of radioactivity are shown in Table 2.



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**TABLE 2. Distribution of radioactivity in rat tissues/organs after administration of $C^{14}$-labeled ICIA5504.**

| Tissue/organ | Percent of radioactive dose administered | | | | | |
|---|---|---|---|---|---|---|
| | Single low dose | | Multiple low dose | | Single high dose | |
| | Male | Female | Male | Female | Male | Female |
| Liver | 0.06 ±<0.01 | 0.05 ±<0.01 | 0.08 ±0.01 | 0.04 ±<0.01 | 0.05 ±0.01 | 0.04 ±<0.01 |
| Kidneys | 0.03 ±<0.01 | 0.02 ±<0.01 | 0.04 ±0.01 | 0.02 ±<0.01 | 0.02 ±<0.01 | 0.01 ±<0.01 |
| Small intestine | 0.01 ±<0.01 | 0.01 ±<0.01 | <0.01 ±<0.01 | <0.01 ±<0.01 | <0.01 ±<0.01 | 0.01 ±<0.01 |
| Carcass | 0.23 ±0.02 | 0.23 ±0.06 | 0.50 ±0.08 | 0.31 ±0.05 | <0.26 | <0.27 |

Data extracted from Tables 3&4, MRID 43678151, 43678153, and 43678152.

a. Single low dose

As summarized in Table 2, less than 0.1% of the administered dose was recovered from the tissues and carcass residue represented only 0.23% of the administered dose. There was no ICIA5504-derived radioactivity detected in exhaled air. Total radioactivity in the tissues and carcass was less than 0.5%. The low tissue residue in conjunction with the low urinary and fecal excretion data suggest that absorption of the test article was relatively low, especially if fecal radioactivity was associated with parent compound.

b. Low dose with pretreatment

The relative distribution of ICIA5504-derived radioactivity was similar to that observed for the single low-dose and single high-dose groups. The liver and kidneys contained the most radioactivity but concentrations even in these organs was minimal. Total radioactivity in tissues, organs, and carcasses following fourteen-day repeated dosing (1 mg/kg/day) was only 0.62 and 0.39% for males and females, respectively.



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c. Single high dose

Similar to the single low-dose group, <0.1% of the administered dose was recovered in tissues/organs and carcass residue represented <0.27% of the administered dose. Total radioactivity in the tissue, organs and carcass was only ≈0.3%.

d. Intravenous dose

Experiments using intravenous dosing were not performed.

e. Single low-dose; Autoradiography

The distribution of orally administered radiolabeled test material (three different label positions as previously described) as determined by autoradiography showed that all three forms exhibited similar distributions with most radiolabel (at 48 hours after dosing) being associated with the intestinal contents, kidneys and liver.

4. Excretion

Excretory data for the various experiments are shown in Tables 3 and 4.



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**TABLE 3. Recovery of radioactivity in tissues and excreta of rats after oral administration of $C^{14}$-labeled ICIA5504.**

| Sample Analyzed | Percent of radioactive dose recovered | | | | | |
|---|---|---|---|---|---|---|
| | Single low dose | | Repeated low dose | | Single high dose | |
| | Male | Female | Male | Female | Male | Female |
| Expired air | NP | NP | NP | NP | NP | NP |
| Tissues | 0.11 ±<0.01 | 0.08 ±<0.01 | ≈0.12 | ≈0.08 | ≈0,07 | ≈0.05 |
| Carcass | 0.23 ±0.02 | 0.23 ±0.06 | 0.50 ±0.08 | 0.31 ±0.05 | <0.26 | <0.27 |
| Cage wash | 0.33 ± 0.13 | 0.93 ±0.58 | 0.50 ±0.5 | 0.10 ±0.1 | 0.38 ±0.13 | 1.15 ±0.78 |
| Urine | 10.19 ±1.53 | 17.89 ±3.50 | 12.50 ±3.4 | 17.00 ±2.7 | 8.54 ±1.03 | 11.54 ±1.42 |
| Feces | 83.24 ±1.52 | 72.62 ±5.40 | 89.10 ±5.9 | 86.5 ±1.7 | 89.37 ±3.99 | 84.53 ±1.98 |
| Total | 94.1 | 91.75 | 102.72 | 103.99 | ≈98.61 | ≈97.54 |

Data extracted from Tables 1-4, MRID 43678151, 43678152, and 43678153.
NP: not performed in the excretion/distribution studies.

a. Single low dose

As summarized in Table 3, urinary and fecal excretion were the major routes of excretion with most of the administered dose being eliminated in the feces. For the single low-dose (1 mg/kg) experiments, total excretion of radioactivity (urine, feces, and cage wash) was 93.76% and 91.44% for males and females, respectively over the 168-hour time period. Most (>85%) of the urinary and fecal excretion took place during the first 36 hours after dosing. Overall recovery of the administered radioactivity (94.1% and 91.75% in males and females, respectively) was an acceptable mass balance accounting.

b. Low dose with pretreatment

Administration of a single dose of radiolabeled test material following fourteen-day repeated dosing (1 mg/kg/day) resulted in excretion patterns similar to those observed after single dosing regimens (Table 3). Most of the radioactivity was excreted via the feces (86.5-89.1%) and the urine (12.5-17.0%) and most was



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excreted within 24 hours after administration of the radiolabeled test material. Total recovery of administered radioactivity was 102.72-103.99% indicating acceptable mass balance for this phase of the study.

c. Single high dose

Similar to the single high-dose, urinary and fecal excretion were the major routes of excretion with most of the administered dose being eliminated in the feces (84.53-89.37%). Most of the radioactivity eliminated via the urine and feces took place in the first 36-48 hours following dosing. Overall recovery of the administered radioactivity (>98% and 97% in males and females, respectively) was an acceptable mass balance accounting.

d. Intravenous dose

Studies utilizing intravenous dosing were not performed.

e. Single low-dose; Autoradiography

Excretion of a single oral low-dose of [$^{14}$C]-pyrimidinyl, [$^{14}$C]-phenylacrylate, or [$^{14}$C]-cyanophenyl ICIA5504 after 24 and 48 hours by rats used for autoradiographic analyses is shown in Table 4. Similar to the other experiments, the majority of the administered ICIA5504 was excreted in the feces and the urine, and total recovery of administered radioactivity at 48 hours was 80-98%. With the exception of trace amounts of radioactivity detected in expired air (<0.28% as carbon dioxide and 0.01% as expired volatile) of rats receiving the phenylacrylate and cyanophenyl labeled forms, there were no significant differences in the excretory patterns of the various radiolabeled forms.

**TABLE 4. Cumulative recovery of radioactivity in excreta of rats 24 and 48 hours after administration of [$^{14}$C]-pyrimidinyl, [$^{14}$C]-phenylacrylate, or [$^{14}$C]-cyanophenyl ICIA5504 (Azoxystrobin)[a].**

| | Cumulative percent of radioactive dose recovered | | | | | |
|---|---|---|---|---|---|---|
| | [$^{14}$C]-pyrimidinyl | | [$^{14}$C]-phenylacrylate | | [$^{14}$C]-cyanophenyl | |
| | Male | Female | Male | Female | Male | Female |
| Cage wash | | | | | | |
| 24-hr | 2.39 | 7.30 | 4.11 | 5.12 | 5.06 | 3.20 |
| 48-hr | 2.02 | 4.30 | 6.92 | 2.57 | 3.99 | 3.14 |
| Urine | | | | | | |
| 24-hr | 6.87 | 8.71 | 7.84 | 13.28 | 4.61 | 9.81 |
| 48-hr | 5.20 | 16.52 | 15.20 | 20.09 | 10.88 | 15.02 |
| Feces | | | | | | |
| 24-hr | 65.94 | 51.10 | 61.05 | 48.36 | 62.88 | 19.14 |
| 48-hr | 82.06 | 65.64 | 58.27 | 74.01 | 79.68 | 79.66 |
| Total | | | | | | |
| 24-hr | 75.20 | 67.11 | 72.99 | 66.77 | 72.56 | 32.16 |
| 48-hr | 89.28 | 86.46 | 80.39[b] | 96.67[b] | 94.55[b] | 97.82 |

[a]Time point data from single rats only; data extracted from Tables 1-4, pp. 26-29 of MRID 43678150.
[b]Total value does not include percent radioactivity exhaled as carbon dioxide (<0.28%) or exhaled volatile (0.01%).

f. Biliary excretion; Single high-dose

Based on biliary excretion data for rats given a single 100 mg/kg dose of either [$^{14}$C]-pyrimidinyl, [$^{14}$C]-phenylacrylate, or [$^{14}$C]-cyanophenyl ICIA5504 over 48 hours, 71.6% (males) and 74.2% (females) of the pyrimidinyl-derived radioactivity was excreted in the bile. For the cyanophenyl-derived radioactivity, 56.6% and 62.5% was excreted in the bile of males and females, respectively. For the phenylacrylate-derived radioactivity , 64.4% (males) and 63.6% (females) was excreted in the bile. Quantitatively, there were no significant differences in biliary excretion between males and females.

B. METABOLITE CHARACTERIZATION STUDIES

ICIA5504 underwent extensive metabolism. Urine and feces obtained from rats in the single and repeated dose experiments were used for metabolite analyses. Additionally, bile, urine and feces were collected for 48 hours from six male and six female rats given a single gavage dose of 100 mg [$^{14}$C]-ICIA5504/kg. A total of fifteen metabolites were detected in the excreta and subsequently identified (Tables 5-7). Seven additional metabolites were detected but not identified. None of the unidentified metabolites represented more than 4.9% of the administered dose. The quantitative data for the various metabolites in the feces and urine of rats from the different dose groups are summarized in Tables 5-7, and the quantitative data for metabolites detected in the bile of rats receiving a single 100 mg/kg dose of ICIA5504 are shown in Table 8. As shown in these tables, the mass balance for the metabolism identification study (MRID 43678154) indicated a substantial percentage of unaccounted radioactivity (45.6-73.6%) even though the excretion studies (MRID 43678151, 43678152, and 43678153) showed total recovery of 91.75-103.99% with 72.6-89.3% being in the feces. The unaccounted radioactivity was especially notable for the single low-dose and repeated low-dose groups. The study authors indicated that the variable efficiency in recovery could be explained by the fact that for metabolite identification, feces were extracted with acetonitrile which allowed partitioning of the parent compound when it was present in the feces (i.e., high-dose rats). For the single low dose and repeated low dose groups (where levels of the parent compound were minimal), most of the fecal radioactivity was associated with the polar metabolites that would not be present in the acetonitrile extract. The resulting radioactivity in the extract would, therefore, be very low. For the high-dose group, greater amounts of parent compound were left unabsorbed, thereby, resulting in greater amounts of parent compound available for partitioning into the acetonitrile extract.

The glucuronide conjugate (metabolite V) was the most prevalent biliary metabolite in both males and females. Metabolite I (parent compound) was not detected in the bile, implying that much of the radioactivity in the feces that was not associated with metabolites was probably due to the parent compound. As noted in MRID 43678154 (p.41), there were notable deficiencies in extraction of radioactivity from fecal samples.

**TABLE 5. Metabolite profile in excreta of rats administered a single low dose ( 1mg/kg) $C^{14}$-labeled ICIA5504[a].**

| Dose | Percent of Administered Dose Single Low Dose (1 mg/kg) | | | |
|---|---|---|---|---|
| Compound | Male | | Female | |
| | Feces | Urine | Feces | Urine |
| Metabolite I (parent) | ND | ND | 0.9 | ND |
| Metabolite II | 1.4 | 0.2 | 0.8 | 0.3 |
| Metabolite III | 2.7 | ND | 1.4 | ND |
| Metabolite IVa | 1.3 | 0.5 | 0.6 | 0.4 |
| Metabolite IVb | 0.7 | ND | ND | 3.0 |
| Metabolite V | 1.0 | ND | 1.4 | 0.9 |
| Metabolite VIa | see IVa | see IVa | see IVa | see IVa |
| Metabolite VIb | see IVb | ND | see IVb | see IVb |
| Metabolite VII | 0.7 | 0.7 | ND | ND |
| Metabolite VIII | 0.4 | ND | 0.7 | 1.1 |
| Metabolite IX | 1.1 | 0.1 | 0.6 | 1.6 |
| Metabolite X | 3.1 | ND | ND | 2.2 |
| Metabolite XI | see VII | see VII | ND | ND |
| Metabolite XII | ND | ND | ND | ND |
| Metabolite XIII | ND | ND | ND | 0.1 |
| Metabolite XIV | see VIII | ND | see VIII | see VIII |
| Metabolite XV | 0.4 | 0.8 | 0.3 | 0.8 |
| Unidentified 1 | ND | ND | 0.4 | ND |
| Unidentified 2 | 0.4 | 4.3 | 0.3 | 3.6 |
| Unidentified 3 | 3.4 | 1.8 | 2.3 | 1.9 |
| Unidentified 4 | ND | 0.5 | ND | 0.4 |
| Unidentified 5 | 0.2 | ND | ND | 0.4 |
| Unidentified 6 | ND | 0.7 | 4.1 | ND |
| Unidentified 7 | ND | ND | 0.3 | 0.2 |
| Total identified | 12.8 | 2.3 | 6.7 | 10.4 |



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TABLE 5. Continued

| Dose | Percent of Administered Dose Single Low Dose (1 mg/kg) | | | |
|---|---|---|---|---|
| Compound | Male | | Female | |
| | Feces | Urine | Feces | Urine |
| Total unidentified | 4.0 | 7.3 | 7.4 | 6.5 |
| Total accounted for | 16.8 | 9.6 | 14.1 | 16.9 |
| Lost/unaccounted for [b] | 73.6 | | 69.0 | |
| Total | 100 | | 100 | |

[a]Total accounted for = total identified + total unidentified
[b]100 - (Total accounted for)
Where metabolites are cross-referenced, the metabolite pairs were not fully resolved on the HPLC chromatogram and, therefore, the percent value is a composite representing both metabolites.
ND = Not detected
Data extracted from Table 12, pp. 101-102, MRID 43678154.



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**TABLE 6. Metabolite profile in excreta of rats administered multiple low doses (1 mg/kg) of $C^{14}$-labeled ICIA5504.**

| Dose | Percent of Administered Dose | | | |
|---|---|---|---|---|
| | Multiple Low Dose (1 mg/kg; 14 days) | | | |
| Compound | Male | | Female | |
| | Feces | Urine | Feces | Urine |
| Metabolite I (parent) | 2.1 | ND | 0.7 | ND |
| Metabolite II | 0.9 | 0.1 | 1.0 | 0.3 |
| Metabolite III | 3.7 | 0.1 | 2.9 | 0.5 |
| Metabolite IVa | ND | ND | 1.3 | 0.7 |
| Metabolite IVb | 1.4 | 0.7 | 2.2 | 2.9 |
| Metabolite V | 1.3 | ND | 0.8 | 0.7 |
| Metabolite VIa | ND | ND | see IVa | seeIVa |
| Metabolite VIb | see IVb | see IVb | see IVb | see IVb |
| Metabolite VII | ND | ND | ND | 0.6 |
| Metabolite VIII | 0.8 | 0.7 | ND | ND |
| Metabolite IX | 1.0 | ND | 2.0 | 1.1 |
| Metabolite X | 2.5 | ND | ND | ND |
| Metabolite XI | ND | ND | ND | see VII |
| Metabolite XII | ND | ND | ND | ND |
| Metabolite XIII | 0.4 | 0.1 | ND | 0.2 |
| Metabolite XIV | see VIII | see VIII | ND | ND |
| Metabolite XV | 0.5 | 1.1 | 0.3 | 0.8 |
| Unidentified 1 | 0.5 | ND | 0.4 | ND |
| Unidentified 2 | 0.3 | 4.9 | 0.4 | 3.8 |
| Unidentified 3 | 2.6 | 2.2 | 3.2 | 1.3 |
| Unidentified 4 | ND | ND | ND | 0.3 |
| Unidentified 5 | 0.4 | 0.5 | ND | 1.2 |
| Unidentified 6 | ND | 0.6 | 5.4 | 1.5 |
| Unidentified 7 | 0.4 | ND | ND | ND |



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TABLE 6. Continued

| Dose | Percent of Administered Dose | | | |
|---|---|---|---|---|
| | Multiple Low Dose (1 mg/kg; 14 days) | | | |
| Compound | Male | | Female | |
| | Feces | Urine | Feces | Urine |
| Total identified | 14.6 | 2.8 | 11.2 | 7.8 |
| Total unidentified | 4.2 | 8.2 | 9.4 | 8.1 |
| Total accounted for [a] | 18.8 | 11.0 | 20.6 | 15.9 |
| Lost/unaccounted for [b] | 70.2 | | 63.5 | |
| Total | 100 | | 100 | |

[a]Total accounted for = total identified + total unidentified
[b]100 - (Total accounted for)
Where metabolites are cross-referenced, the metabolite pairs were not fully resolved on the HPLC chromatogram and, therefore, the percent value is a composite representing both metabolites.
ND = Not detected
Data extracted from Table 13, pp. 103-104, MRID 43678154.



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**TABLE 7. Metabolite profile in excreta of rats administered a single low dose (1 mg/kg) of $C^{14}$-labeled ICIA5504.**

| Dose Compound | Percent of Administered Dose Single High Dose (100 mg/kg) | | | |
|---|---|---|---|---|
| | Male | | Female | |
| | Feces | Urine | Feces | Urine |
| Metabolite I (parent) | 32.6 | ND | 32.1 | ND |
| Metabolite II | ND | 0.1 | 2.1 | 0.4 |
| Metabolite III | 4.1 | ND | 2.6 | ND |
| Metabolite IVa | ND | ND | ND | 0.5 |
| Metabolite IVb | ND | ND | 2.1 | 0.5 |
| Metabolite V | 1.2 | 0.7 | | |
| Metabolite VIa | ND | ND | ND | see IVa |
| Metabolite VIb | ND | ND | see IVb | see IVb |
| Metabolite VII | ND | ND | ND | ND |
| Metabolite VIII | 0.5 | 0.4 | ND | 0.6 |
| Metabolite IX | ND | 0.2 | 1.1 | 1.0 |
| Metabolite X | ND | ND | 4.0 | ND |
| Metabolite XI | ND | ND | ND | ND |
| Metabolite XII | ND | ND | ND | ND |
| Metabolite XIII | ND | 0.2 | ND | 0.3 |
| Metabolite XIV | see VIII | see VIII | ND | see VIII |
| Metabolite XV | 0.3 | 0.6 | ND | 0.5 |
| Unidentified 1 | ND | 2.4 | ND | 1.6 |
| Unidentified 2 | ND | 0.8 | ND | 0.5 |
| Unidentified 3 | 1.5 | 1.4 | 1.9 | 0.8 |
| Unidentified 4 | ND | 0.3 | ND | 0.2 |
| Unidentified 5 | ND | 0.4 | ND | 0.4 |
| Unidentified 6 | 1.9 | 0.5 | ND | 1.2 |
| Unidentified 7 | ND | ND | ND | ND |
| Total identified | 38.7 | 2.2 | 44.0 | 3.8 |

TABLE 7. Continued

| Dose Compound | Percent of Administered Dose Single High Dose (100 mg/kg) | | | |
|---|---|---|---|---|
| | Male | | Female | |
| | Feces | Urine | Feces | Urine |
| Total unidentified | 3.4 | 5.8 | 1.9 | 4.7 |
| Total accounted for [b] | 42.1 | 8.0 | 45.9 | 8.5 |
| Lost/unaccounted for [b] | 49.9 | | 45.6 | |
| Total | 100 | | 100 | |

[a]Total accounted for = total identified + total unidentified
[b]100 - (Total accounted for)
Where metabolites are cross-referenced, the metabolite pairs were not fully resolved on the HPLC chromatogram and, therefore, the percent value is a composite representing both metabolites.
ND = Not detected
Data extracted from Table 11, pp. 99-100, MRID 43678154.

**TABLE 8. Quantitative profile of biliary metabolites from rats administered a single high dose (100 mg/kg) of $C^{14}$-labeled ICIA5504.**

| Dose | Percent of administered dose[a] | |
|---|---|---|
| | Single 100 mg/kg dose in bile duct cannulated rats | |
| Compound | Male | Female |
| Metabolite I (Parent compound) | ND | ND |
| Metabolite II | 6.5 | 6.8 |
| Metabolite III | ND | 1.7 |
| Metabolite IVa | 6.8 | 9.0 |
| Metabolite IVb | ND | 1.4 |
| Metabolite V | 29.3 | 27.4 |
| Metabolite VIa | See IVa | See IVa |
| Metabolite VIb | ND | See IVb |
| Metabolite VII | 7.0 | 1.6 |
| Metabolite VIII | 3.2 | 6.1 |
| Metabolite IX | 4.5 | 2.4 |
| Metabolite X | ND | 4.8 |
| Metabolite XI | See VII | See VII |
| Metabolite XII | | |
| Metabolite XIII | 2.8 | 0.9 |
| Metabolite XIV | See VIII | See VIII |
| Metabolite XV | 4.1 | 1.5 |
| Unidentified 1 | 4.4 | 2.1 |
| Unidentified 2 | 2.5 | 1.3 |
| Unidentified 3 | 1.1 | 1.1 |
| Unidentified 4 | ND | ND |
| Unidentified 5 | ND | 1.3 |
| Unidentified 6 | ND | 4.4 |
| Total biliary metabolites identified/detected | 72.2 | 73.8 |



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TABLE 8. Continued

| Dose | Percent of administered dose[a] | |
|---|---|---|
| | Single 100 mg/kg dose in bile duct cannulated rats | |
| Compound | Male | Female |
| Total urinary/cage wash radioactivity[a] | 8.92 | 12.69 |
| Total excreted: biliary + urinary + cage wash | 81.12 | 86.49 |
| Unaccounted/unextracted radioactivity | 18.88 | 13.51 |
| Total | 100 | 100 |

Where metabolites are cross-referenced; the metabolite pairs were not fully resolved on the HPLC chromatogram and, therefore, the percent value is a composite representing both metabolites.
ND = Not detected
[a]From Table 3 of this report
[b]Most of this represents radioactivity that could not be extracted from the feces (total fecal radioactivity [see Table 3]- total metabolite radioactivity)
Data extracted from Table 10, pp. 97-98, MRID 43678154.

## III. DISCUSSION

### A. DISCUSSION

A series of experiments was conducted to evaluate the absorption, distribution, excretion, and metabolism of ICIA5504 (Azoxystrobin) in male and female rats. Groups of male and female rats (5-8/sex/group depending on the experiment) were given single gavage doses of 1 or 100 mg/kg or 14-day repeated doses of 1 mg/kg. For assessment of biliary metabolites, a group of six male and six female rats with cannulated bile ducts were given a single 100 mg/kg gavage dose of ICIA5504. Assessment of inhalation as an excretory route was determined based upon experiments using one male and one female rats administered a single dose (1.0 mg/kg) of the test material. Distribution of the test material was also examined in an autoradiographic study in which six male and six female rats were given 1.0 mg ICIA5504/kg and sacrificed at 24 or 48 hours. Evaluation of absorption, distribution, and excretion following intravenous administration was not performed.



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No animals died as a result of the treatment. The overall recovery of administered radioactivity in the single low-dose, 14-day repeated low-dose, and single high-dose groups was 91.75-103.99% indicating acceptable mass balance. Less than 0.5% of the administered dose was detected in the tissues and carcass up to seven days postdosing. Based upon the results of the various experiments, absorption of ICIA5504 was difficult to accurately assess. For the single high-dose group, assessment of biliary excretion suggested approximately 70% absorption with approximately 32% of administered radioactivity remaining as parent compound in the gastrointestinal tract. However, in the biotransformation study, parent compound was not detected in the fecal extracts of the single low-dose and repeated low-dose groups nor were substantial quantities of metabolites detected. Mass balance assessments of data generated by the absorption/excretion studies indicated substantial fecal excretion of administered radioactivity and acceptable accounting of compound-related radioactivity. The study authors attributed the discrepancy (failure to quantify parent compound in the feces) to the extraction procedure used for the fecal samples. Absorbed ICIA5504 was widely distributed throughout the body with the greatest amounts detected in organs associated with excretory function, especially the liver and kidneys. Smaller amounts (<0.01%) were detected in the small intestine (excluding lumenal contents). The primary route of excretion was via the feces (≈73-89%), although ≈9-18% was detected in the urine of the various dose groups. The fecal vs. urinary route of excretion did not vary considerably with dose. Biliary metabolites represented 72.2% and 73.8% of the administered radioactivity in rats given a single 100 mg/kg dose; biliary cannulations were not performed on rats from any other dose groups. It is curious that summing of radioactivity associated with biliary metabolites (72.2-73.8% of the administered 100 mg/kg dose; Table 8) and parent compound (32%; Table 7) exceeds the total fecal radioactivity (85-89%; Table 3) noted for high-dose rats in the excretion studies. As previously noted there were extraction efficiency problems with the fecal samples. More definitive explanation needs to be provided by the study authors to more fully explain the apparent uncertainties (see study deficiencies). Sex-related differences in excretion were minor; slightly greater (≈3-7%) amounts of urinary radioactivity with commensurate reductions in fecal radioactivity were noted for female rats in all three treatment regimens. There were no apparent sex-related differences in distribution of administered radioactivity.

Absorbed ICIA5504 appeared to be extensively metabolized. Twenty-three metabolites were detected; sixteen metabolites were characterized and seven were unidentified. For



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identification of metabolites in the feces of rats from the absorption/excretion studies (i.e., rats without bile duct cannulae), fecal samples were extracted with acetonitrile to obtain the polar biliary metabolites. Minor qualitative and quantitative differences in biliary metabolites were observed for males and females. There were 14 metabolites in males and 20 in females. With the exception of metabolite V (a glucuronide conjugate) which represented 29.3% (males) and 27.4% (females) of the administered dose, individual biliary metabolites represented less than 10% of the administered dose.

A metabolic pathway was proposed that reflected the metabolite identification data. Specifically, the major metabolic pathway appears to be glucuronide conjugation of hydrolysis products.

B. STUDY DEFICIENCIES

Results of the biotransformation study indicated considerable deficiencies in radioactivity retrieval for the single low-dose and repeated low-dose groups. Specifically, no parent compound was detected in the fecal sample from these dose groups and only minimal metabolite-associated radioactivity was reported even though the mass balance data from the excretion studies indicated substantial radioactivity associated with the feces. Because biliary excretion was not assessed for the single low-dose and repeated low-dose groups, it is not possible to determine if the radioactivity in the feces was associated with unabsorbed parent compound or biliary metabolites. Approximately 42-46% of the administered radioactivity in the high-dose group was associated with metabolites and approximately 32% was associated with parent compound (Table 7). In the single low-dose and repeated low-dose groups, fecal metabolites represented 14.1-16.8% (Table 5) and 18.8-20.6% (Table 6), respectively of the administered dose but, at most, only 2% or less was associated with parent compound. Therefore, the overall fecal radioactivity in the biotransformation study (≤20.6%) is not consistent with the mass balance values of 72-89% from the excretion studies. These data are crucial in determining if the absorption and/or metabolism of ICIA5504 exhibits saturation and for assessing the kinetic nature of the absorption and excretion processes. If absorption is not saturated, it would be expected that minimal parent compound-associated radioactivity and notable metabolite-associated radioactivity would be present in the feces of the low-dose and repeated low-dose rats. However, neither is observed. The study authors contend that the absence of parent compound in the low-dose groups suggests dose-dependent absorption. However, the low levels of metabolite-associated radioactivity in the feces (14.1-20.6%,



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Tables 5 and 6), urinary radioactivity of 10-18% (Table 3) and minimal tissue burdens in these groups are not consistent with substantial absorption. In summary, the low levels of fecal radioactivity in the low-dose groups is neither consistent with dose-dependent absorption (i.e., greater absorption with greater dose) nor saturated absorption (i.e., greater absorption at the lower doses).

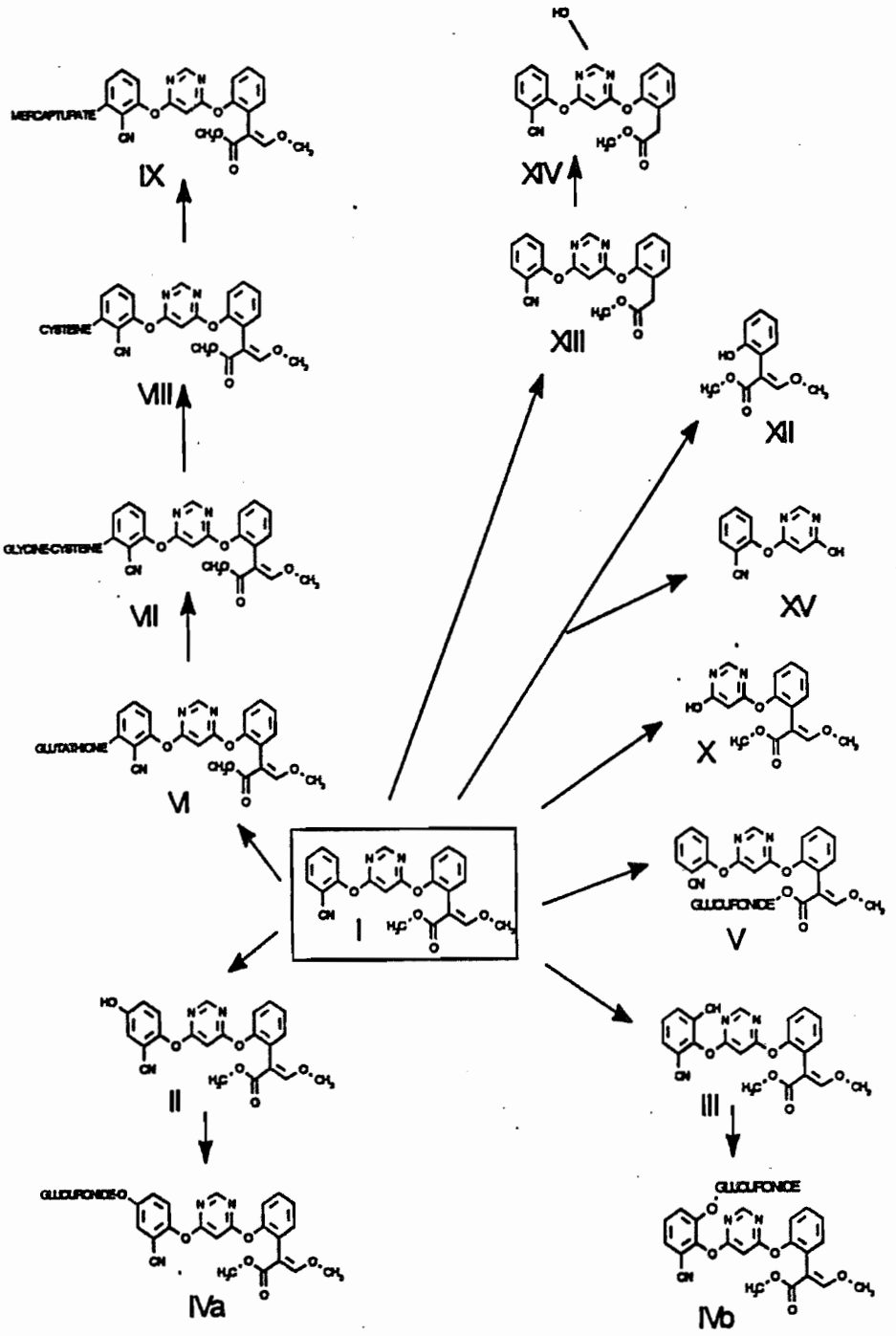
The study authors noted that the extraction procedures used for the feces in the biotransformation study favored extraction of polar metabolites and that absence of parent compound in the feces from rats in these groups indicated that "absorption was quantitative". This contention does not appear to adequately explain the inconsistencies noted above. The study authors also note that the feces from the bile duct cannulated rats contained only parent compound thereby indicating that absorption was dose-dependent. The biotransformation data do not support such a contention.

The experimental protocol and conduct of the studies are not necessarily flawed (with the possible exception of the extraction of radioactivity from the fecal samples), but more definitive and explanations of the results seem to be in order so that the aforementioned issues can be clarified.

Generally, based upon biliary metabolite data, urinary excretion and cage wash, absorption appears to be ≈81-82% after a single high dose. However, such an assessment cannot be made for the low-dose groups. Although urinary excretion and cage wash indicate ≈9-18% absorption in the single and repeated low-dose groups, it is impossible to determine total absorption without knowing what portion of the fecal radioactivity represents biliary metabolites (or parent compound that may have been absorbed and excreted unchanged) or unabsorbed parent compound.

THE FOLLOWING ATTACHMENTS ARE NOT AVAILABLE ELECTRONICALLY.
SEE THE FILE COPY

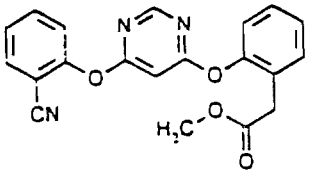
FIGURE 1. Proposed Biotransformation Pathway for ICIA5504 in the Rat.



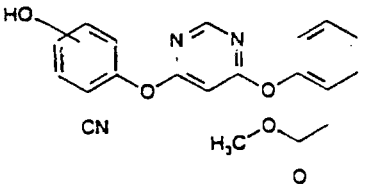

Metabolite numbers are given in Roman numerals.

Source: MRID no. 43678154, p. 83.

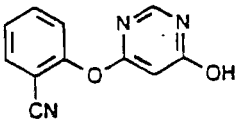
# METABOLITES OF ICIA5504 IDENTIFIED IN RAT EXCRETA



Metabolite XIII
Trivial name: Des-methoxy-methenyl-5504
Chemical name: Methyl {2[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl} acetate



Metabolite XIV
Trivial name: Hydroxy-des-methoxy-methenyl-5504
Chemical name: Methyl 2-[x-hydroxy-{2-[6-(2-cyanophenoxy) pyrimidin-4-yloxy]phenyl}]acetate. x - unknown locant



Metabolite XV
Trivial name: Cyanophenoxy-hydroxypyrimidinol
Chemical name: 6-(2-cyanophenoxy)pyrimidin-4-ol

Source: MRID no. 43678154, pp. 87-90.



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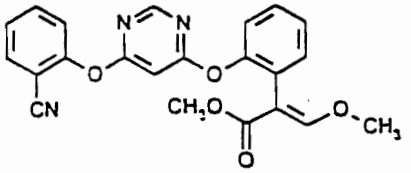
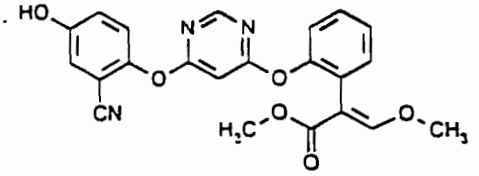
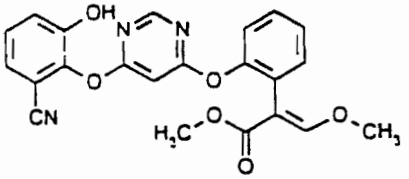
TABLE 1. Metabolites of ICIA5504 Identified in Rat Excreta



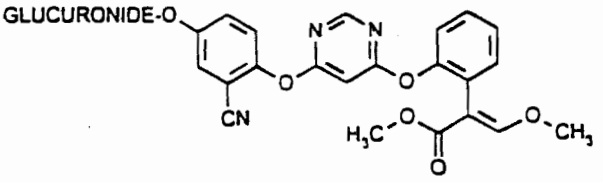
Metabolite I
Trivial name: ICIA5504
Chemical name: Methyl (E)-2-{2-[6-(2-cyanophenoxy)pyrimidine-4-yloxy] phenyl}-3-methoxyacrylate



Metabolite II
Trivial name: 8-hydroxy-5504
Chemical name: Methyl (E)-2-{2-[6-(2-cyano-4-hydroxyphenoxy)pyrimidin -4-yloxy]phenyl}-3-methoxyacrylate

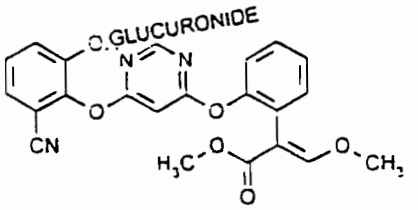


Metaboite III
Trivial name: 10-hydroxy-5504
Chemical name: Methyl (E)-2-{2-[6-(2-cyano-6-hydroxyphenoxy)pyrimidin -4-yloxy]phenyl}-3-methoxyacrylate

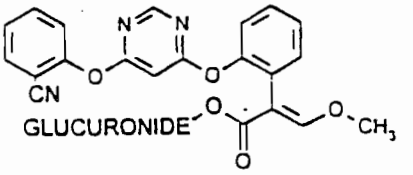



Metabolite IVa
Trivial name: 8-hydroxy-5504-glucuronide
Chemical name: Methyl (E)-2-{2-[6-(2-cyano-4-glucuronidyloxyphenoxy) pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate

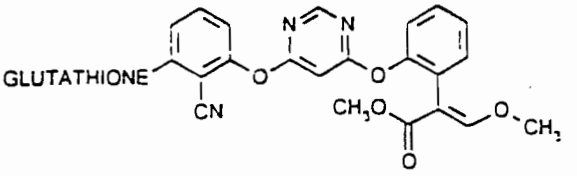
# METABOLITES OF ICIA5504 IDENTIFIED IN RAT EXCRETA



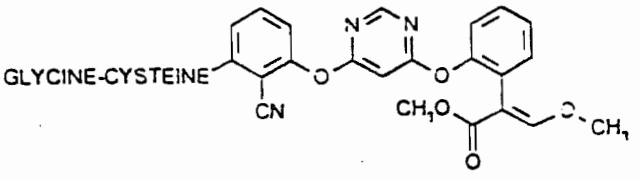

Metabolite IVb
Trivial name: 10-hydroxy-5504-glucuronide
Chemical name: Methyl (E)-2-{2-[6-(2-cyano-6-glucuronidyloxyphenoxy) pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate




Metabolite V
Trivial name: 5504-acid-glucuronide
Chemical name: Glucuronidyl (E)-2-{2-[6-(2-cyanophenoxy)pyrimidin -4-yloxy]phenyl}-3-methoxyacrylate

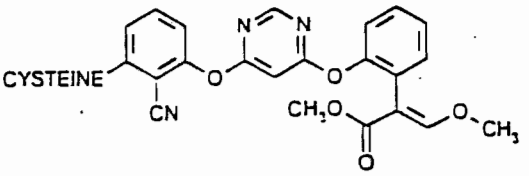



Metabolite VIa (VIb unknown isomer)
Trivial name: 7-Glutathione-5504
Chemical name: Methyl (E)-2-{2-[6-(2-cyano-3-glutathionylphenoxy) pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate

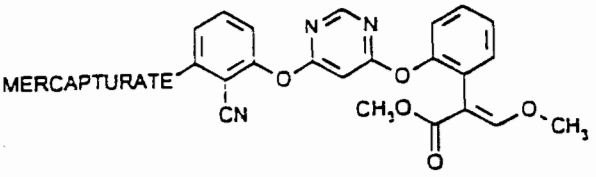



Metabolite VII
Trivial name: 7-Cysteinyl-glycine-5504
Chemical name: Methyl (E)-2-{2-[6-(2-cyano-3-(cysteine-glycinyl)phenoxy) pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate

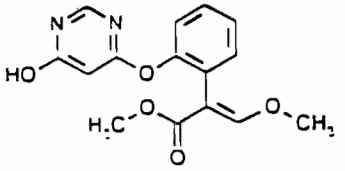
# METABOLITES OF ICIA5504 IDENTIFIED IN RAT EXCRETA



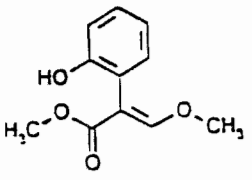

Metabolite VIII
Trivial name: 7-Cysteine-5504
Chemical name: Methyl (E)-2-{2-[6-(2-cyano-3-cysteinylphenoxy) pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate




Metabolite IX
Trivial name: 7-Mercapturate-5504
Chemical name: Methyl (E)-2-{2-[6-(2-cyano-3-(N-acetylcysteinyl)phenoxy) pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate




Metabolite X
Trivial name: Hydroxy-pyrimidinol-phenylacrylate
Chemical name: Methyl (E)-2-(6-hydroxypyrimidin-4-yloxy]phenyl)-3-methoxyacrylate




Metabolite XII
Trivial name: Hydroxy-phenylacrylate
Chemical name: Methyl (E)-2-(2-hydroxyphenyl)-3-methoxyacrylate



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