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4973  
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

010495

AUG 11 1993

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

SUBJECT: Imazalil: Metabolism in the Wistar Rat.

Barcode D171410  
S 407134  
HED No. 2-0527  
MRID 42012003  
PC Code 111901

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ACTION: Review the Metabolism Study in the Wistar  
Rat dosed with Imazalil

CONCLUSIONS AND RECOMMENDATIONS:

1. This study is classified as core: Supplementary. The study may be upgraded.
2. The study submission does not satisfy the 85-1 guidelines since several major metabolites were not characterized. However, submission of the characterizaion of these two urinary metabolites (# 3, 4) will allow for the upgrading of the study.
3. The study report shows that Imazalil is rapidly absorbed, distributed and almost completely metabolized. (1)



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4. From 83 to 93 % of the administered doses to both sexes were excreted in 24 hrs in about even proportion in the urine and feces of the treated animals.

5. Recovery of the test dose was almost complete by 96 hrs. T 1/2 values were not determined. At 96 hrs tissue residues containing <sup>14</sup>C amounted to about 1% of the test dose.

6. As many as 25 metabolites were formed by the rat metabolism of Imazalil with little to nil <sup>14</sup>CO<sub>2</sub> excreted and no conjugated forms found in the urine.

7. Residues were highest in the livers of animals given the test material after 96 hrs (about 110 ppb following repeated dosing at 1.25 mg/kg).

8. The study authors proposed that Imazalil is metabolized by epoxidation of the allyl moiety followed by epoxide hydrolysis, imidazole oxidation, O-dealkylation of the ether chain, imidazole scission and N-dealkylation, *and*

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FINAL

DATA EVALUATION REPORT

IMAZALIL

Study Type: Metabolism

Prepared for:

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Environmental Protection Agency  
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DATA EVALUATION REPORT

STUDY TYPE: Metabolism in rats

EPA IDENTIFICATION NUMBER:

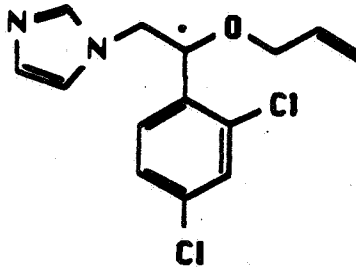
Caswell Number: 497AB

MRID Number: 420120-03

TEST MATERIAL: Imazalil

SYNONYMS: Fungaflor technical; CAS no. 7390-28-0; (+)-1-[2-(2,4-dichlorophenyl)-2-(2-propenyloxy)(2-<sup>14</sup>C)ethyl]-1H-imidazole; R 23979

REPORT NUMBER: R 23979/FK1116



\* denotes the position of the <sup>14</sup>C label

SPONSOR: Janssen Research Foundation, Beerse, Belgium

TESTING FACILITY: Department of Drug Metabolism and Pharmacokinetics, Janssen Research Foundation, Beerse, Belgium

TITLE OF REPORT: General Metabolism of Imazalil in the Rat.

STUDY AUTHORS: Mannens, G., Van Leemput, L., and Heykants, J.

REPORT ISSUED: June 13, 1991

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CONCLUSIONS: The absorption, distribution, metabolism, and excretion of imazalil were studied in groups of male and female Wistar rats administered a single intravenous (i.v.) dose of 1.25 mg/kg, a single oral gavage dose of 1.25 or 20 mg/kg [<sup>14</sup>C]-imazalil, or 14-day repeated oral doses of 1.25 mg/kg unlabeled imazalil followed by a single dose of 1.25 mg/kg [<sup>14</sup>C]-labeled imazalil on day 15.

[<sup>14</sup>C]-Imazalil was rapidly absorbed, distributed, almost completely metabolized, and eliminated in rats under all dosing regimens. Most of the radioactivity was recovered within 24 hours in the urine and feces (83.9-93.9% of the administered dose); recovery after 96 hours was essentially complete (86.60-98.33%). Female rats eliminated more of the test compound (as its metabolites) in the urine (55.10-59.96% of the administered dose) than in feces; the difference was smaller with males. The reason for this difference is unclear. The similar excretion and metabolite patterns following oral and i.v. dosing indicate that imazalil was efficiently absorbed. Biliary excretion is suggested by the high degree of fecal elimination in the i.v. dosage group. The oral absorption rate (and  $t_{1/2}$ ) could not be determined because the peak blood levels were not measured.

Seven days after dosing, the tissue residues of [<sup>14</sup>C]-imazalil and possible metabolites totaled ~1% of the administered dose in all dosing groups. The study authors did not determine the chemical identity of the residual label. The largest residues were found in the liver, with no significant sex- or route-related differences; tissue residues were proportional to the administered dose. These data indicate that imazalil and/or its metabolites do not bioaccumulate to any appreciable extent.

Whole urine and fecal extracts from males and females in each dosing group were subjected to reverse-phase high performance liquid chromatography (HPLC). The parent compound was not detectable in the urine and <1% was excreted in the feces, indicating that imazalil was almost completely transformed. Although the elimination half life is clearly <24 hours, it could not be calculated more accurately, because although 30-45% of the dose was eliminated in the feces within 24 hours, fecal elimination data were available only for the 0-24 hour pool. The most prevalent metabolites accounted for ~5%-13% of the administered dose in all groups; these compounds were not identified. Two metabolites present in both urine and feces at ~0.5% to ~5% in all groups were tentatively identified based on comparison with known standards. An additional fecal metabolite (0.4%-1.2% in all groups) and a minor metabolite (<1%) in urine were also tentatively identified. (These compounds are identified in Tables 3 and 4). No significant dose-, route-, or sex-related differences in metabolite patterns were observed. The patterns of metabolites in urine and feces were quite similar, but the less polar metabolites were more abundant in feces. Neither glucuronic acid nor sulphate conjugates were found, but they could not be completely ruled out due to apparent metabolite instability under the hydrolysis conditions. Based on the identified metabolites, two pathways of imazalil metabolism were proposed. In one pathway, imazalil was biotransformed by epoxidation and epoxide hydrolysis, imidazole oxidation, imidazole ring scission, N-dealkylation, and oxidative O-dealkylation. Oxidative O-dealkylation was the first step in the second metabolic pathway, followed by imidazole oxidation, imidazole ring scission,

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and N-dealkylation. Since most of the metabolites were not identified, additional important metabolic steps may not have been identified.

STUDY CLASSIFICATION: The study is classified as <sup>supplementary</sup> ~~acceptable~~. The study does not satisfy the registration requirements under Guideline Series 85-1 (and Addendum 7) for a metabolism study in rats. <sup>Basically</sup> Although there were minor deficiencies in the study, ~~that~~ they did not affect the overall study results and conclusions (see Reviewers' Discussion, Section E). However, ~~that the study is not acceptable~~

two major metabolites accounting for ~~the majority of the administered dose~~ <sup>or approaching 10% of the administered dose</sup> require characterization. These ~~are urinary metabolites #3 and #4.~~ <sup>are urinary metabolites #3 and #4.</sup> 4/14/93 ~~Hand~~ <sup>Hand</sup> 4/14/93 ~~Hand~~ <sup>Hand</sup>

## A. MATERIALS

1. Test Substance

The unlabeled test material (lot number V890-275) was described as a slightly yellow powder, with a purity of 98.7%. The structure of the test material was confirmed using mass spectroscopy (MS) and ultraviolet (UV), infrared (IR), and nuclear magnetic resonance (NMR) spectroscopy. Solutions of the unlabeled material were stored in the dark at room temperature and used within 1 week of preparation. The concentration was checked at the beginning and end of each week, and the test material formulation was found to be stable under the conditions of storage for at least 10 days (concentration range, 100-102.4% of the nominal value).

Previous studies by the testing laboratory had shown that imazalil labeled with [<sup>14</sup>C] at the 2-ethyl position was appropriate for metabolism studies. Batch number 761 of [<sup>14</sup>C]imazalil, with a specific activity of 91.2 µCi/mg and a radiochemical purity of 99.9%, was mixed with unlabeled imazalil to obtain the desired final specific activity and used for all radiolabeled dosing. The frequency of radiolabeled dosing solution preparation was not reported.

2. Test Animals

Wistar rats of unspecified age were obtained from the Janssen Animal Breeding Centre, Beerse, Belgium. Single or repeated oral gavage doses of imazalil were administered to groups of 5 males and 5 females. To determine the bioavailability of the test material, an additional group of 10 animals received an i.v. injection of 1.25 mg/kg body weight (Bwt.) imazalil. One reserve rat of each gender was added to the i.v., low-, and high-dose groups, and three of each gender were added to the repeated low-dose group. The male rats weighed 233-312 g and the female rats weighed 221-283 g at the time of radiolabeled dosing with imazalil.

## B. METHODS

1. Rats were acclimated individually in stainless steel metabolism cages for at least 3-5 days prior to dosing and maintained in the

cages for the duration of the study. The physical condition and general behavior of the animals were observed immediately before dosing and at the end of each feces collection period. Since previous experiments had shown that the test material was completely absorbed even when administered with food, tap water and food were available ad libitum at all times. The diet was not identified, and no analysis was conducted of the feed or water.

2. Oral dosing solutions were prepared in 0.42 mM sulfuric acid, and the i.v. dosing solution was prepared in 1.05 mM sulfuric acid, 55 mg/mL glucose hydrate. Groups of 10 rats (5/sex) were given a single dose by oral gavage of 1.25 mg/kg Bwt. (low-dose group) or 20 mg/kg Bwt. (high-dose group) [<sup>14</sup>C]-imazalil, or an oral gavage dose of 1.25 mg/kg/day of unlabeled imazalil for 14 days followed by a single gavage administration of 1.25 mg/kg [<sup>14</sup>C]-imazalil on day 15. Another group of 10 rats received a single i.v. injection of 1.25 mg/kg [<sup>14</sup>C]-imazalil via the tail vein. Each animal was weighed before dosing, and received 0.2 mL/100 g Bwt. i.v. or 1 mL/100 g Bwt. by gastric intubation of the appropriate dosing solution. Two rats (1 male, 1 female) were added to the i.v. and single oral dose groups, and 6 rats (3 males, 3 females) were added to the repeated dose group in case of animal mortality. The doses were chosen so that the low dose produced no effect and the high dose produced "some" toxic signs on chronic dosing. The physical condition of the animals was assessed immediately prior to dosing and at the end of each feces collection period.
3. Urine was collected at 4, 8, 24, 48, 72, and 96 hours after exposure to the labeled dose of imazalil. Feces were collected at 24, 48, 72, and 96 hours after exposure to the labeled dose. Samples of urine, cage washings, and methanol extracts of the feces were counted in a liquid scintillation counter, and the fecal residue was combusted and counted. In order to detect artifacts, blank urine and feces were also collected from untreated rats, fortified with known quantities of labeled imazalil, and analyzed as the other samples. Rats were decapitated 96 hours after receiving the radiolabeled imazalil. Whole blood was collected on heparin. Necropsies were conducted and major tissues were removed. The tissues removed included brain, heart, lung, liver, kidney, adrenal gland, spleen, stomach, large and small intestine, testes and uterus, and subsamples of muscle, peri-renal fat and bone. The contents of the stomach and intestines were obtained by rinsing the organs with 0.9% NaCl solution. Five samples of blood, and the adrenal gland, uterus and bone were dried by storage at 4°C and combusted. Fat was homogenized in solid carbon dioxide, mixed with cellulose powder, and combusted. Other tissues were homogenized in distilled water, and duplicate samples were dried and combusted. The carcass was lyophilized, homogenized, and combusted in quadruplicate. Expired air was not collected because a preliminary experiment found that <0.02% of the administered dose was exhaled in 24 hours. Statistical analyses were limited to simple expressions of variation (i.e., mean, median, or standard deviation).



4. For the characterization and identification of imazalil metabolites, the 0-24-, 24-48-, 48-72-, and 72-96-hour urines were pooled by dosing and sex groups. Pools of methanolic extracts of the 0-24- and 24-48-hour feces were similarly prepared. Where the amount of radioactivity in the urine or feces deviated from the mean by  $\geq 30\%$ , the excreta from that animal were excluded from the respective pools. One female each from the i.v., repeated oral-, and high-dose groups were excluded from the pools for this reason. Metabolites were tentatively identified by co-chromatography with known compounds on a C-18 reverse-phase HPLC column. To analyze conjugated metabolites, urine pools were treated with  $\beta$ -glucuronidase and/or aryl sulfatase at  $37^\circ\text{C}$  for 24 hours, and analyzed by reverse-phase HPLC.

In order to measure absorption, the amount of unchanged imazalil in the urine was measured by a sensitive gas chromatography (GC) method, and compared between the oral and i.v. dosing groups.

5. Protocol: The protocol for the metabolism study is presented in Appendix A (CBI "General Metabolism of Imazalil in the Rat," Materials and Methods pp. 9-17).

#### C. REPORTED RESULTS

1. Elimination and Recovery: Male rats in all dosage groups eliminated slightly more of the radioactive label in the urine (46.31-53.14%) than in the feces (41.74-47.55%). This difference was stronger in female rats of all groups, with urinary excretion accounting for 55.10- 59.96% of the label in the administered dose (Table 1). Similar elimination patterns were observed in animals of the same sex in different dosage groups. The test material was rapidly eliminated; 83.9-93.9% of the administered label was recovered in the urine and feces within 24 hours. Elimination was nearly complete 96 hours after dosing, with 0.85-1.2% of the administered label remaining in the tissues or blood. Almost all of the radioactivity in the orally administered doses was accounted for, with total recovery ranging from 96.63 to 99.84%. Total recovery in the intravenously-administered groups was lower (88.6% and 88.1% for males and females, respectively), but because the tissues were not analyzed it is not clear if this was due to lower overall recovery or higher accumulations in the tissues.
2. Distribution: A total of  $\approx 1\%$  of the administered dose was recovered in the tissues and carcass of all oral dosing groups (see Table 2 for the distribution). About half of the total body radioactivity was found in the liver (120 ppb maximum). Radioactivity levels in the lung, kidney, and adrenal gland were also higher than in the blood. No major sex-related differences were seen in residue levels. The increased administered dose in the high-dose group resulted in a proportionate increase in tissue levels (2320 ppb maximum in the liver), indicating dose-dependent tissue distribu-

tion. Results from the repeated-dose group did not indicate that the test material accumulated in any tissue.

### 3. Metabolism

Characterization and quantitation of urinary metabolites: Unchanged imazalil could not be detected in the urine of any test group (Table 3). The test compound was stable in urine, as shown by radio-HPLC analysis of urine fortified with [<sup>14</sup>C]-imazalil. Over 25 metabolites were detected by radio-HPLC of the 0-24-hour urine pools; metabolite patterns were quantitatively and qualitatively similar for both sexes and all dosage groups. Ten metabolites or metabolite fractions were chosen for mass balance determination on the basis of their abundance or their co-elution with reference compounds. The study authors considered fractions 3, 5, 6, and 7 to be mixtures, based on the shape of the corresponding chromatogram peaks.

About 60% of the radioactivity in the 0-24-hour urine, or about 30% of the administered dose, could be accounted for by the ten fractions. In most of the dosing groups, less than 0.1% of the dose was found in any metabolite fraction of the 24-48-hour urine. In both sexes of all dosing groups, metabolites 3 and 4 were the most abundant; female rats in the single low oral and i.v. groups had higher levels of both metabolites than the corresponding males. Based on their co-chromatographing with reference compounds, metabolite 8 was tentatively identified as R 61000 and metabolite 10 was tentatively identified as R 42243. A minor metabolite co-eluted with R 44085, but was not included in the mass balance calculations because it accounted for  $\leq 0.9\%$  of the dose in the 0-24-hour urine of male rats and was almost absent in the urine of female rats.

In order to detect glucuronic acid and sulfate conjugates, HPLC chromatograms of the 0-24-hour urine pools were compared before and after hydrolysis with  $\beta$ -glucuronidase and/or arylsulphatase. The study authors reported that no glucuronic acid or sulphate conjugates could be detected, but some metabolites appeared to be unstable after incubation for 24 hours at 37°C, making quantitation difficult. The study authors further stated that glucuronic acid conjugates of metabolites 8 and 10 "might" be present as less abundant metabolites, but presented no evidence for their statement.

Characterization and quantitation of fecal metabolites: Methanol-extractable material accounted for 62% of the radioactivity in the feces from male rats and 70% for female rats. No major dose-, route-, or sex-related differences in the metabolite patterns determined by HPLC were observed (Table 4). Over 25 metabolites were detected; less polar metabolites were more abundant in feces than in urine. Unchanged imazalil was found in feces from both sexes in all groups at concentrations ranging from 0.6-1.0% of the administered dose. Metabolites 8, 9, and 10 were the most abundant, accounting for a maximum of 3.4%, 3.0%, and 4.7% of the administered dose, respectively. Based on their co-chromatographing with refer-

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ence compounds, metabolites 8, 10, and 11 were tentatively identified as R 61000, R 42243, and R 14821, respectively. No attempt was made to analyze glucuronic acid or sulphate conjugates in the feces.

Based on the results of the metabolite characterization, the study authors proposed that imazalil is degraded by the metabolic pathway shown in Figure 1. Major metabolic steps include epoxidation of the allyl moiety followed by epoxide hydrolysis, imidazole oxidation, O-dealkylation of the ether chain, imidazole scission, and N-dealkylation. Since the metabolites were only tentatively identified and several major metabolites were not identified, the proposed pathway is likely to be incomplete.

#### D. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES

The study authors concluded that imazalil is rapidly and completely eliminated in the urine and feces, with an average of  $96.9 \pm 1.3\%$  of an oral dose of imazalil being excreted within 96 hours. At 96 hours after i.v. dosing, 88.6% and 89.0% of the radioactivity was eliminated by male and female rats, respectively. Both male and female rats excreted more of the radioactivity in the urine than in the feces, but the difference was larger for females. Residual tissue radioactivity totaled 1% of the dose 96 hours after dosing with [ $^{14}\text{C}$ ]-imazalil. The highest levels of radioactivity were found in the liver, accounting for half the residual radioactivity in the carcass. No sex-related differences in the tissue distribution pattern were found, but proportionately higher residues were found in all tissues of the high-dose group. There was no indication that the test material accumulated in tissues after multiple dosing.

Imazalil was extensively metabolized to at least 25 metabolites. No major sex-, dose-, or route-related differences in metabolites were observed. The profiles of urinary and fecal metabolites were also quite similar, but the less polar metabolites were more abundant in the feces, and an additional metabolite was identified in the feces. Unchanged imazalil was not detected in the urine, and accounted for <1% of the radioactivity in the feces. Urinary metabolites 8 and 10, and a minor metabolite, were tentatively identified by their cochromatographing with known compounds. Metabolites 8 and 10 were also found in the feces; fecal metabolite 11 was similarly identified.

To obtain an estimate of bioavailability, the study authors compared the amount of unchanged imazalil in the urine of orally- and i.v.-dosed rats. While recognizing that the excretion of the parent compound in the urine was too low for a quantitative determination, the study authors concluded that the extensive biotransformation and the low amount of imazalil excretion in the urine and feces suggested that bioavailability was high after oral dosing. The similarity in urinary and fecal metabolites, and the similarity in metabolites found after oral and i.v. dosing, also indicated that orally-administered imazalil was systemically available.

A quality assurance statement was signed and dated June 10, 1991.

E. CONCLUSIONS BASED ON REVIEWERS' DISCUSSION AND INTERPRETATION OF DATA

The studies adequately described the absorption, distribution, metabolism, and excretion of [<sup>14</sup>C]-imazalil in rats following low- and high-dose oral and repeated oral exposure, as well as single i.v. injection. The data indicate that labeled imazalil is well absorbed and eliminated. Urinary elimination is slightly predominant in males, and markedly predominant in females. The oral absorption rate could not be determined because the peak blood levels were not measured in the study. However, a preliminary experiment submitted with the metabolism study<sup>1</sup> found that peak plasma levels of imazalil and its metabolites were reached within half an hour of administration of 2.5 or 10 mg/kg imazalil by gavage. A 40 mg/kg dose resulted in a rapid rise in plasma levels, followed by a plateau for about 2 hours.

Biliary excretion is suggested, especially in males, since 42% of the i.v. dose was eliminated in the feces in males and 32% in females. Therefore, the fecal elimination of imazalil following oral exposure is probably due to the unabsorbed compound and biliary excretion. The specific extent of these two processes was not evaluated. However, the similarity in the profiles of urinary and fecal metabolites indicates that orally-administered imazalil was metabolized following absorption, rather than by intestinal microorganisms. The low tissue levels of radioactivity, as well as the rapid elimination, demonstrate that bioaccumulation and retention of imazalil and/or its metabolites is low in rats. Recovery of the radioactivity was acceptable (96.85-99.84%) for all oral dosing groups. Total recovery could not be calculated for the i.v. dosing group, because tissue radioactivity was not determined. Almost all of the parent compound was metabolized following oral or i.v. dosing, resulting in 25 metabolites. Appropriate data analysis methods were used.

The parent compound was not found in the urine, and 1% of the administered dose was found in the feces. Metabolite patterns were similar in the urine and feces, although less polar compounds were more abundant in the feces. There were no major sex-, dose-, or route-related differences in the metabolite patterns. Four metabolites were tentatively identified on the basis of co-chromatographing with known standards. Nothing was done to confirm the tentative assignments, and other metabolites were not identified. Of the identified metabolites, 2 major metabolites and 1 minor metabolite were found in both urine and feces, while 1 metabolite was found only in feces. The study authors concluded that the similarity in urinary and fecal metabolite profiles indicated that identical metabolic pathways were involved. However, the fact that metabolite 11 constitutes a separate pathway and is present

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<sup>1</sup>Michiels, M., R. Hendriks, R. Geerts, L. Michielsen, R. Woestenborghs, and J. Heykants. (1985) Comparative bioavailability of imazalil in the rat after subchronic administration of the drug admixed at 400 ppm in the food as imazalil technical or as an aerosil premix formulation. Janssen Research Products Report # R 23 979/52.

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only in the feces suggests that the second metabolic pathway may operate only in the liver.

No mention was made of any toxicological concerns of the metabolites. No conjugated metabolites were found, but technical problems prevented a definitive conclusion. No mention was made of the conditions under which urine and fecal samples were collected, but collecting the samples at room temperature would not have been problematic, since the preliminary experiment showed that the metabolites are not volatile.

TABLE 1. Mean Percent Recovery of Radioactivity 96 Hours  
After Administration of Imazalil to Rats

Dose Group	Sex <sup>b</sup>	Percent of Administered Dose <sup>a</sup>			
		Urine	Feces	Cage Washings	Total Recovery <sup>c</sup>
1.25 mg/kg (i.v.)	Male	46.31	41.74	0.55	88.60
	Female <sup>d</sup>	55.17	32.41	0.52	88.10
1.25 mg/kg (single oral)	Male	48.66	46.07	0.85	95.58
	Female	59.96	36.11	0.61	96.68
1.25 mg/kg <sup>e</sup> (repeated)	Male	50.91	47.55	0.37	98.83
	Female <sup>d</sup>	55.10	41.67	1.03	97.80
20 mg/kg (single oral)	Male	53.14	42.77	0.74	96.65
	Female <sup>d</sup>	56.86	37.71	1.25	95.82

<sup>a</sup>Expired air was not measured for radioactivity; a preliminary experiment found that <0.02% of the administered dose was found in the expired air in 24 hours.

<sup>b</sup>Five animals/sex.

<sup>c</sup>Calculated by our reviewers; differences between the values reported here and those in the study report are due to rounding errors and arithmetic errors by the study authors.

<sup>d</sup>The urine and feces from 1 animal in the group was excluded from the pools because it differed from the mean of the other 4 animals by >30%.

<sup>e</sup>Animals were given 1.25 mg/kg/day unlabeled imazalil for 14 days and a single dose of 1.25 mg/kg [<sup>14</sup>C]-imazalil on day 15.

Source: CBI Tables 8-15; CBI pp. 66-73

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TABLE 2. Distribution of Radioactivity in Tissues of Rats 96 Hours after Oral Administration of Imazalil

Tissue/Organ	Average Imazalil Residue in Tissues Expressed as ppb in Rats Dosed at:					
	1.25 mg/kg (single)		1.25 mg/kg (repeated)		20 mg/kg (single)	
	Males	Females	Males	Females	Males	Females
Brain	≤2 <sup>a</sup>	≤2	≤2	≤2	≤20	≤20
Heart	≤3	5.6±1	54±4	4.8±2	122±42	91±27
Lung	20.5±6	23.2±1	31.3±8	30.4±11	657±324	534±134
Liver	120±26	96.2±5	112.2±20	105.8±28	2320±570	2020±560
Kidney	45.2±10	29.7±2	359±7	29.9±4	582±150	507±87
Adrenal gland	25.9±12	32.7±10	17.4±4	22.6±3	968±508	817 <sup>b</sup>
Spleen	5.2±2	8.3±2	9.9±2	11.2±4	186±80	170±18
Stomach tissue	6.4±1	6.7±0.8	9.4±5	9.7±4	194±79	138±39
Stomach contents	≤0.4	≤0.3	≤0.4	≤0.4	≤5	≤5
Small intestine tissue	2.5 <sup>b</sup>	5.2±0.5	4.5±2	4.7±2	88±19	94±57
Small intestine contents	0.7 <sup>b</sup>	0.8±0.3	0.8±0.4	0.7±0.3	12±4	25±25
Large intestine tissue	4.5±1	5.7±2	7.0±2	9.0±5	189±56	141±39
Large intestine contents	0.1±0.4	0.9±0.2	1.7±2	1.1±0.4	25±8	15±5
Testes	≤2	--	≤2	--	44±9	--
Uterus	--	6.7±2	--	9.9±3	--	127±37
Muscle (subsampling)	≤2	≤2	≤2	≤2	46±18	≤20
Perirenal fat (subsampling)	2.3 <sup>b</sup>	1.8 <sup>b</sup>	1.7 <sup>b</sup>	1.8 <sup>b</sup>	41 <sup>b</sup>	≤30
Bone (subsampling)	3.8±2	2 <sup>b</sup>	2.5±0.5	4 <sup>b</sup>	127±69	≤30
Carcass	18.2±3	14.7±5	18.7±4	17.8±8	352±89	269±85
Blood (subsampling)	5.7±0.5	4.9±0.4	4.1±0.6	4.9±1	111±23	79±8

<sup>a</sup>Each value represents the mean ± standard deviation of 5 rats.

<sup>b</sup>Median value

-- = Not applicable.

Source: CBI Tables 2-7, CBI pp. 60-65.

TABLE 3. Mass Balance of Imazalil Metabolites in 0-24-Hour Urine

Metabolite Expressed as Percent of Administered Dose in Rats Dosed at:

Metabolite Fraction <sup>a</sup>	1.25 mg/kg (single intravenous)		1.25 mg/kg (single oral)		1.25 mg/kg (repeated oral)		20 mg/kg (single oral)	
	Males <sup>b</sup>	Females <sup>c</sup>	Males <sup>b</sup>	Females <sup>c</sup>	Males <sup>b</sup>	Females <sup>c</sup>	Males <sup>b</sup>	Females <sup>c</sup>
1	1.9±0.3	1.0±0.2	1.7±0.5	1.0±0.2	1.4±0.3	<0.4-1.2 <sup>d</sup>	1.3±0.1	0.9±0.2
2	1.9±0.3	3.3±0.4	1.5±0.2	3.1±0.5	1.7±0.2	2.6±0.5	1.6±0.4	1.7±0.5
3	7.0±1.5	10.7±1.4	6.5±2.9	11.3±1.1	7.4±1.4	9.0±1.3	8.5±1.4	8.1±1.9
4	5.1±1.1	7.0±1.1	5.7±1.5	7.7±0.8	7.0±1.3	5.7±1.3	4.8±1.6	4.6±1.3
5	1.7±1.3	1.8±0.5	2.8±0.7	2.9±0.4	3.2±1.0	3.4±1.0	2.1±0.6	1.8±0.3
6	1.3±0.3	2.3±0.9	1.4±0.3	1.7±0.6	1.2±0.6	1.6±0.8	3.1±1.1	3.3±1.5
7	2.9±1.1	1.4±0.1	2.0±0.4	1.8±0.2	2.2±0.9	1.6±0.4	2.9±0.7	1.5±0.5
8 <sup>e</sup>	1.9±0.8	3.8±0.8	2.6±1.5	4.4±0.9	1.7±1.0	3.3±1.6	2.7±1.7	3.5±2.4
9	1.6±0.6	2.2±0.4	2.1±0.8	2.6±0.3	1.5±0.6	2.1±1.0	1.1±0.6	<0.4-1.3 <sup>d</sup>
10 <sup>f</sup>	0.5±0.1	1.2±0.2	0.8±0.5	2.1±0.6	0.7±0.2	1.7±0.6	2.0±0.4	7.0±1.4
Total	25.7±1.8	34.7±3.3	27.1±6.2	38.5±3.3	28.1±4.0	31.8±2.3	30.1±3.0	33.1±6.4

<sup>a</sup>Except where otherwise stated, the metabolites were not identified.

<sup>b</sup>Each value represents the mean ± standard deviation of 5 rats.

<sup>c</sup>Each value represents the mean ± standard deviation of 4 rats.

<sup>d</sup>The amount of metabolite in one or more individual samples was below the detection limit; the lowest and highest values are reported.

<sup>e</sup>Tentatively identified as (±)-1-[2-(2,4-dichlorophenyl)-2-[(2,3-dihydroxypropyl)oxy]ethyl]-2,5-imidazolidinedione (R 61000).

<sup>f</sup>Tentatively identified as (±)-1-[2-(2,4-dichlorophenyl)-2-[(2,3-dihydroxypropyl)oxy]ethyl]-1H-imidazole (R 42243).

Source: CBI Tables 17-20, CBI pp. 75-78.



TABLE 4. Mass Balance of Methanol-Extractable Imazalil Metabolites in 0-24-Hour Feces

Metabolite Fraction <sup>a</sup>	Metabolite Expressed as Percent of Administered Dose in Rats Dosed at:							
	1.25 mg/kg (single intravenous)		1.25 mg/kg (single oral)		1.25 mg/kg (repeated oral)		20 mg/kg (single oral)	
	Males <sup>b</sup>	Females <sup>c</sup>	Males <sup>b</sup>	Females <sup>c</sup>	Males <sup>b</sup>	Females <sup>c</sup>	Males <sup>b</sup>	Females <sup>c</sup>
1	≤0.3	<0.3	<0.4	<0.3	<0.4	<0.4	<0.3	<0.4
2	<0.3-0.5 <sup>d</sup>	<0.3-0.9 <sup>d</sup>	<0.4	<0.3	<0.3-0.7 <sup>d</sup>	<0.2-0.5 <sup>d</sup>	<0.3-0.4 <sup>d</sup>	<0.4
3	1.8±0.4	1.7±1.2	1.9±1.1	1.1±0.2	1.6±0.6	1.0±0.6	1.5±0.5	0.7±0.4
4	0.9±0.3	1.4±1.1	1.2±0.8	0.6±0.1	1.3±0.9	1.7±1.0	0.7±0.3	0.3±0.5
5	1.3±0.6	1.1±0.2	1.1±0.7	0.8±0.2	1.3±0.6	1.4±0.9	1.1±0.3	0.6±0.3
6	1.8±0.6	2.2±0.4	1.5±0.2	2.0±0.3	2.1±0.7	1.6±1.0	2.3±0.6	2.4±1.3
7	0.7±0.4	0.8±0.5	1.1±0.5	0.4±0.1	0.9±0.3	0.8±0.5	1.0±0.3	<0.4-0.7 <sup>d</sup>
8 <sup>e</sup>	1.6±0.6	2.6±0.5	2.5±1.3	3.4±0.6	1.8±0.7	1.8±1.2	1.7±1.1	1.6±1.1
9	2.3±0.6	2.1±0.2	2.7±1.1	2.3±0.2	2.1±1.0	1.8±1.3	1.3±0.8	0.9±0.5
10 <sup>f</sup>	1.1±0.5	1.1±0.6	1.2±0.5	2.6±0.8	1.8±0.7	1.4±0.8	2.4±0.7	3.6±1.0
11 <sup>g</sup>	0.9±0.3	0.3±0.1	1.0±0.5	0.6±0.1	0.9±0.3	<0.2-0.6	1.4±0.4	0.6±0.2
Imazalil	0.6±0.1	1.0±1.1	0.8±0.2	0.7±0.1	0.7±0.2	<0.2-1.0	0.7±0.2	0.8±0.2
Total	13.6±1.7	14.6±3.4	14.9±4.4	14.6±1.8	14.7±1.5	12.9±6.6	14.2±1.9	11.9±2.9

<sup>a</sup>Except where otherwise noted, the metabolites were not identified.

<sup>b</sup>Each value represents the mean ± standard deviation of 5 rats.

<sup>c</sup>Each value represents the mean ± standard deviation of 4 rats.

<sup>d</sup>The amount of metabolite in one or more individual samples was below the detection limit; the lowest and highest values are reported.

<sup>e</sup>Tentatively identified as (±)-1-[2-(2,4-dichlorophenyl)-2-[(2,3-dihydroxypropyl)oxy]ethyl]-2,5-imidazolinedione (R 61000).

<sup>f</sup>Tentatively identified as (±)-1-[2-(2,4-dichlorophenyl)-2-[(2,3-dihydroxypropyl)oxy]ethyl]-1H-imidazole (R 42243).

<sup>g</sup>Tentatively identified as (±)-α-(2,4-dichlorophenyl)-1H-imidazole-1-ethanol (R 14821).

Source: CBI Tables 21-24, CBI pp. 79-82.

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