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DATA EVALUATION RECORD

1/23/91

Study Type: Metabolism - Pharmacokinetics.
Species: Rat
Guideline: 85-1

EPA Identification No.: MRID No. 415639-27
Document No. ABR-89119

Test Material: [Cyclohexyl-$^{14}$C]CGA-163935

Synonyms: 4-(cyclopropyl-α-hydroxy-methylene)-3,5-dioxo-cyclohexanecarboxylic acid, ethyl ester

Sponsor: CIBA-GEIGY Corporation. Agricultural Division, Greensboro, NC.

Study Number: CIBA-GEIGY Project No. 265988; Report No. ABR-89119

Testing Facility: CIBA-GEIGY Corporation, Greensboro, NC. and WIL Research Laboratories, Ashland, OH.

Title of Report: [Cyclohexyl- $^{14}$C]-CGA-163935. FIFRA Guideline Rat Metabolism Study: Metabolite Characterization and Identification.

Author: T.M. Capps (for metabolite identification). E.M. Craine (for preliminary, biological and analytical phases).

Report Issued: June 25, 1990 (Overall Report). October 4, 1989 (Preliminary Phase). April 4, 1990 (Biological and Analytical Phases).

Conclusions: The metabolism of [cyclohexyl-$^{14}$C]CGA-163935 was studied in male and female Crl:CD BR rats. The cyclohexyl-labeled compound was administered as a single intravenous (iv) dose of 0.91 mg/kg, as a single oral dose of 0.97 or 166 mg/kg, or as a single oral dose of 0.97 mg/kg following a 14-day pretreatment with unlabeled CGA-169935 at 1 mg/kg/day.

Recoveries of radioactivity in urine after oral dosing (94.5-97.3% of the dose) indicate extensive absorption of the compound from the GI tract. Total recovery of radioactivity 168 hours after treatment accounted for 97-99% of the dose in the orally dosed animals, and to 94.7-98.3% of the dose in the iv-treated rats. Among the orally dosed groups, approximately 94.5-97.3% of the dose was eliminated in urine and 1.0-2.4% of the dose was eliminated in feces. Most of the elimination occurred within the first 24 hours. No differences between the sexes or among dose groups were found. The low elimination of radioactivity in feces by the iv-dosed group (1.1-1.6% of the dose) suggests that there is very little or no biliary excretion of the compound and/or its metabolites in rats. At sacrifice, total radioactive residue in the carcass was less than 0.28% of the dose in all groups. A preliminary experiment indicated that by 72 hours

after dosing, elimination of radioactivity in expired air amounted to less than 0.06% of the dose for the low-dose rats and to less than 0.01% of the dose for the high-dose rats.

Only one metabolite, CGA-179500, was found in urine. Levels of CGA-179500 in urine accounted for 82.0-91.6% of the dose among the orally-dosed animals and for 74.1-75.3% of the dose among the iv-dosed animals. CGA-179500 is the carboxylic acid resulting from hydrolysis of the ester bond of parent CGA-163935.

Core Classification: Acceptable.

A. Materials

Test Compound:

[Cyclohexyl-1,2,6-$^{14}$C] CGA-163935 (for low doses)
Radiochemical purity: 98.2%
Specific activity: 30 µCi/mg
Lot: GAN-XVI-38

[Cyclohexyl-1,2,6-$^{14}$C] CGA-163935 (for high doses)
Radiochemical purity: 98.0%
Specific activity: 1 µCi/mg
Lot: CL-XVIII-31
Chemical Purity: 97.7%

Non radioactive CGA-163935
Chemical Purity: 96.6%
Code: S87-1209

Vehicle: absolute ethanol: polyethylene glycol (PEG 200): deionized water (30:40:30, v/v/v).

Test Animals: Species: rat
Strain: Crl:CD BR
Source: Charles River Breeding Laboratories, Portage, MI
Age (at time of dosing): 50-58 days (males); 34-67 days (females).
Weight (just before dosing): 233.1-319.4 (males); 181.7-243.8 (females)

B. Study Design

This study was designed to characterize the $^{14}$C elimination profile and to identify the significant metabolites of CGA-163935 in rats. The study was submitted in one volume, including data from the preliminary, biological, and analytical phases. A major objective of the preliminary study was to determine whether significant amounts of $^{14}$C would be eliminated in the expired air.

Group Arrangements

For the preliminary study, four groups of acclimated rats (2 rats/group) were treated with single oral doses of $^{14}$C CGA-163935 by gavage as follows: Groups 1 (males) and 2 (females) received 1.40 and 1.38 mg/kg, respectively; Groups 3 (males) and 4 (females) received 176.4 and 218.8 mg/kg, respectively. For the main study, four groups of acclimated rats (5 rats/sex/group) were dosed with single doses of $^{14}$C CGA-163935 as shown in Table 1. It should be noted that the rats were not randomized into the test groups of Table 1 from one single pool of rats, but came from three separate shipments of rats, with a wide scatter of ages among females. Each treatment group had a vehicle control consisting of one male and one female.

Table 1. Dosing groups for metabolism studies of CGA-163935

| Group No. | Test Group[1] | Route | $^{14}$C CGA-163935 (mg/kg) | Number/ sex | Remarks |
|---|---|---|---|---|---|
| 1 | Intravenous | IV | 0.91 | 5 | - |
| 2 | Low dose | Oral | 0.97 | 5 | - |
| 3 | High dose | Oral | 166 | 5 | - |
| 4 | Low dose with pretreatment[2] | Oral | 0.97 | 5 | Pretreatment with non-radioactive CGA-163935 once a day for 14 days, followed by a single oral dose of $^{14}$C CGA-163935. |

[1]Each treatment group had a vehicle control group consisting of one male and one female.
[2]The amounts of $^{14}$C CGA-163935 administered to individual rats were given for all groups. Individual rat data were not given for the pretreatment phase for Group 4; the dose was described as "low dose" (i.e. about 1 mg/kg/day).

Dosing and sample collection

All doses were administered as solutions in a mixture consisting (by volume) of polyethylene glycol 200 (40%), ethanol (30%), and deionized water (30%). Once prepared, the solutions were stored overnight under refrigerated conditions prior to dosing. Average $^{14}$C concentrations just prior and after dosing were used to calculate the actual dose administered; dose verification data were furnished by the author. The syringe/cannula was weighed before and after dosing to determine the actual amount of solution administered. The intravenous doses were administereed slowly over a period of about a minute through the tail vein. Approximately 1 g of solution/rat was administered to Groups 1-3 and about 1.1-1.4 g/rat to group 4. Concentration and stability of the non-radioactive CGA-163935 used in the pretreatment experiments were determined by HPLC analysis.

Radioactively dosed rats were placed in metabolism units which allowed separate collection of urine and feces, and in the case of the preliminary phase, of expired air components.

a. Pharmacokinetic Studies

In the preliminary experiment, urine, feces, and expired air were collected separately and radioassayed at various time points up to 72 hours after dosing, at which time the animals were sacrificed for analysis of residual radioactivity in blood, liver, kidney, and carcass. In the main experiment, urine and feces were collected at 4, 8, 12, and 24 hours post dosing, and thereafter over 24 hour periods for a total of 7 days. The animals were sacrificed at the end of the collection period for determination of residual radioactivity in tissues. Blood and the following tissues/organs were sampled and radioassayed: heart, lungs, spleen, both kidneys, liver, perirenal fat, gonads, uterus, muscle (leg),

bone, and brain. Liquids were assayed directly by liquid scintillation spectrometry (LSS), solids were combusted and assayed by LSS.

b. Metabolite characterization studies.

Metabolite characterization studies were performed with urine and feces samples collected during the first 24 hours post dosing.

Structural characterization of CGA-179500, the only metabolite detected other than parent, was done with urine of the high-dose males. The metabolite was found to co-chromatograph in high performance liquid chromatography (HPLC) and two-dimensional thin layer chromatography (2D-TLC) with authentic synthetic samples of the free-acid form of CGA-163935, 4-(cyclopropyl-α-hydroxy-methylene)-3,5-dioxo-cyclohexanecarboxylic acid. In addition, the metabolite was purified and its MS spectrum was found to correspond to that of synthetic standard of CGA-179500. Quantification of metabolites in raw urine of the various dose groups was done by HPLC; fractions were identified by co-chromatography with standard CGA-179500. 2D-TLC was used to confirm the presence of CGA-179500 in the urines. Quantification of metabolites in ethanol extracts of feces from the various dose groups was done by HPLC; fractions were identified by co-chromatography with standard CGA-179500 and CGA-163935 (the parent compopund). The presence of CGA-163935 (parent compopund) in feces was confirmed by MS spectrometry. In addition, the ethanol-insoluble residue from high-dose males was was sequentially extracted with acetonitrile/water followed by chloroform/methanol and studied by HPLC and 2D-TLC using standard CGA-179500.

Compliance

A signed Statement of No Data Confidentiality Claim was provided.

A signed Satement of compliance with EPA GLP was provided for the preliminary, the biological, and the analytical phases of the study. For the identification of metabolites phase it was stated that work performed after October 1989 complied with EPA-GLP (40 CFR 160). It was not stated explicitly whether metabolite identification work performed before October 1989 complied with the then existing EPA-GLP.

A signed Quality Assurance Statement was provided for each section (metabolite characterization, preliminary, biological, and analytical phases) of the study.

Results

a. Pharmacokinetic studies

Preliminary experiment

Results from the preliminary experiment indicated that by 72 hours post dosing less than 0.06% of the radioactive dose was eliminated in the expired air in the low-dose rats, and less than 0.01% of the radioactive dose was eliminated in the

expired air in the high-dose rats.

Tissue distribution and excretion

i. Single Intravenous Low Dose

Seven days following administration of a single intravenous dose of [cyclohexyl-1,2,6-$^{14}$C] CGA-163935 (0.91 mg/kg) to rats, approximately 94.74% of the dose was accounted for in males and 98.27% in females (Table 2). Elimination in the urine accounted for 90.43% of the dose in males and 94.22% in females; these values may be incremented by about 2.4-3.0% of the dose if radioactivity recovered in the cage wash (Table 2) is included. Most of the elimination in urine was complete within the first 24 hours after dosing. Elimination in the feces accounted for about 1.11% of the dose in males and 1.57% of the dose in females. At sacrifice, total radioactive residue in the carcass amounted to 0.2% of the dose in males and to 0.13% of the dose in females. Radioactive residues in lungs and kidneys amounted to 0.001 µg/g in rats of both sexes and to 0.001 and 0.002 µg/g in male and female fat, respectively (Table 3). Residues in the other tissues/organs examined were below 0.001-0.004 µg/g, the presumed (unspecified by the author) detection limits for residue levels in those tissues.

ii. Single Low Oral Dose

Seven days following administration of a single oral dose of [cyclohexyl-1,2,6-$^{14}$C] CGA-163935 (0.97 mg/kg) to rats, approximately 98.99% of the dose was accounted for in males and 97.18% of the dose was accounted for in females (Table 2). Elimination in the urine accounted for 94.53% of the dose in males and 95.27% in females; these values may be incremented by about 0.8-2.8% of the dose if radioactivity recovered in the cage wash (Table 2) is included. Most of the elimination in urine was complete within the first 24 hours after dosing. Elimination in the feces accounted for about 1.65% of the dose in males and 1.12% of the dose in females. At sacrifice, total radioactive residue in the carcass amounted to <0.28% of the dose in males and to <0.18% of the dose in females. Except for lungs in females and fat in males, which had residue levels of 0.001 µg/g (Table 3), residues in the other tissues/organs examined were below 0.001-0.004 µg/g, the presumed (unspecified by the author) detection limits for residue levels in those tissues.

iii. Single High Oral Dose

Seven days following administration of a single oral dose of [cyclohexyl-1,2,6-$^{14}$C] CGA-163935 (166 mg/kg) to rats, approximately 98.51% of the dose was accounted for in males and 98.89% of the dose was accounted for in females (Table 2). Elimination in the urine accounted for 95.28% of the dose in males and 97.28% in females; these values may be incremented by about 0.6-0.7% of the dose if radioactivity recovered in the cage wash (Table 2) is included. Most of the elimination in urine was complete within the first 24 hours after dosing. Elimination in the feces accounted for about 2.44% of the dose in males and 1.00% of the dose in females. At sacrifice, total radioactive residue in the carcass amounted to 0.06% of the dose in males and to <0.05% of the dose in females.

Except for kidneys (with residue levels of 0.016-0.018 µg/g) and fat (residue levels of 0.020-0.027 µg/g) in both sexes (Table 3), residues in the other tissues/organs examined were below 0.015-0.443 µg/g, the presumed (unspecified by the author) detection limits for residue levels in those tissues.

iv. Single Low Oral Dose with Preconditioning

Seven days following administration of a single oral dose of [cyclohexyl-1,2,6-$^{14}$C] CGA-163935 (0.97 mg/kg) to rats, preceded by single daily oral doses nonradioactive CGA-163935 (about 1 mg/kg) for 14 days, approximately 96.97% of the dose was accounted for in males and 97.50% of the dose was accounted for in females (Table 2). Elimination in the urine accounted for 95.02% of the dose in males and 95.71% in females; these values may be incremented by about 0.5-0.9% of the dose if radioactivity recovered in the cage wash (Table 2) is included. Most of the elimination in urine was complete within the first 24 hours after dosing. Elimination in the feces accounted for about 1.39% of the dose in males and 0.92% of the dose in females. At sacrifice, total radioactive residue in the carcass amounted to 0.1% of the dose in males and to <0.09% of the dose in females. Except for liver in males and fat in both sexes, which had residue levels of 0.001 µg/g (Table 3), residues in the other tissues/organs examined were below 0.001-0.004 µg/g, the presumed (unspecified by the author) detection limits for residue levels in those tissues.

**Table 2. Recovery[1] of radioactivity in tissues and excreta of rats 168 hours after a dosing with [cyclohexyl-1,2,6-$^{14}$C] CGA-163935.**

| | Percent of radioactive dose recovered with | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | I.V.[2] 0.91 mg/kg | | Oral 0.97 mg/kg | | Oral 166 mg/kg | | Oral Pretreatment plus 0.97 mg/kg | |
| Matrix | M | F | M | F | M | F | M | F |
| Urine | 90.43 | 94.22 | 94.53 | 95.27 | 95.28 | 97.28 | 95.02 | 95.71 |
| Feces | 1.11 | 1.57 | 1.65 | 1.12 | 2.44 | 1.00 | 1.39 | 0.92 |
| Cage wash | 3.00 | 2.35 | 2.81 | 0.79 | 0.73 | 0.61 | 0.46 | 0.87 |
| Carcass | 0.20 | 0.13 | <0.28 | <0.18 | 0.06 | <0.05 | 0.10 | <0.09 |
| Total: | 94.74 | 98.27 | 98.99 | 97.18 | 98.51 | 98.89 | 96.97 | 97.50 |

[1] Urine and feces data from Tables 7-10 of Analytical Part of Study Report. Cage wash data from Tables 37-40 (Appendix A) and carcass data from Tables 41-44 (Appendix A) of Analytical Part of Study Report.

[2] I.V. = intravenous. The four dosage groups depicted in the dosage columns of this table, correspond to Groups 1-4 of Table 1 of this DER.

Table 3. Average distribution of radioactivity in rat tissues/organs 168 hours after dosing with [cyclohexyl-1,2,6-$^{14}$C] CGA-163935[1].

| | Total residue (µg/g) after | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | I.V.[2] 0.91 mg/kg | | Oral 0.97 mg/kg | | Oral 166 mg/kg | | Oral Pretreatment plus 0.97 mg/kg | |
| Matrix | M | F | M | F | M | F | M | F |
| Heart | <0.001 | <0.001 | <0.001 | <0.001 | <0.013 | <0.015 | <0.001 | <0.001 |
| Lungs | 0.001 | 0.001 | <0.001 | 0.001 | <0.019 | <0.019 | <0.001 | <0.001 |
| Spleen | <0.002 | <0.002 | <0.002 | <0.003 | <0.088 | <0.097 | <0.002 | <0.001 |
| Kidneys | 0.001 | 0.001 | <0.002 | <0.002 | 0.016 | 0.018 | <0.001 | <0.001 |
| Liver | <0.001 | <0.001 | <0.001 | <0.001 | <0.026 | <0.026 | 0.001 | <0.001 |
| Testes | <0.001 | - | <0.001 | - | <0.013 | - | <0.001 | - |
| Ovaries | - | <0.004 | - | <0.004 | - | <0.094 | - | <0.004 |
| Uterus | - | <0.002 | - | <0.002 | - | <0.075 | - | <0.003 |
| Leg Muscle | <0.001 | <0.001 | <0.001 | <0.001 | <0.022 | <0.023 | <0.001 | <0.001 |
| Brain | <0.001 | <0.001 | <0.001 | <0.001 | <0.020 | <0.020 | <0.001 | <0.001 |
| Fat (sol) | 0.001 | 0.002 | 0.001 | <0.001 | 0.020 | 0.027 | 0.001 | 0.001 |
| Fat (insol) | <0.001 | <0.002 | <0.001 | <0.001 | <0.015 | <0.026 | <0.001 | <0.001 |
| Bone | <0.003 | <0.003 | <0.003 | <0.003 | <0.441 | <0.443 | <0.002 | <0.002 |
| Plasma | <0.001 | 0.001 | <0.001 | <0.001 | <0.034 | <0.033 | <0.001 | <0.001 |
| RBC | <0.001 | <0.001 | <0.001 | <0.001 | <0.033 | <0.032 | <0.001 | <0.001 |
| Whole carcass | 0.002 | <0.002 | <0.003 | <0.003 | 0.113 | <0.111 | 0.001 | <0.001 |

[1] Data from Tables 11 & 12 (Group 1), Tables 19 & 20 (Group 2), Tables 27 & 28 (Group 3) and Tables 35 & 36 (Group 4) of Appendix Aof the Analytical Part of the Study Report.

[2] I.V. = intravenous. The four dosage groups depicted in the dosage columns of this table, correspond to Groups 1-4 of Table 1 of this DER.

b. Metabolite characterization studies:

Metabolites in urine were studied using samples of urine collected during the first 24 hours after dosing and representing 87.28-95.49% (Table 4) of the dose. The results of HPLC analysis of these 24-hour urine samples are presented in Table 5.

Only one metabolite (CGA-179500, Table 5) was identified in urine of rats dosed with [cyclohexyl-1,2,6-$^{14}$C] CGA-163935. CGA-179500 was identified, by reference to a synthetic standard, as the carboxylic acid resulting from hydrolysis of the ester bond of parent CGA-163935. As shown in Table 5 for the orally dosed rats, CGA-179500 constituted at least 91.1-96816% of the urinary radioactivity, which accounted for 81.99-91.63% of the dose. There were no ma, or dose-dependent or pretreatment-dependent differences among orally dosed groups. Urinary excretion

of CGA-179500 by the intravenously-dosed rats was somewhat smaller, amounting to 74.01-75.29% of the dose. No parent CGA-163935 was reported in urine.

Except for the high-dose males, study of metabolites in feces was limited to analysis of ethanol extracts of feces collected up to 24 hours post-dosing, containing 0.56-2.01% of the dose (Table 4). The results of HPLC analysis of these 24-hour feces samples are presented in Table 5.

Two metabolites (CGA-179500 and parent CGA-163935, Table 5) were identified in feces. As shown in Table 5, CGA-179500 comprised 31.86-85.14% and CGA 163935 comprised 2.85-22.87% of the radioactivity in the ethanol-soluble fraction of feces. These percent values cannot be converted to percent of the dose, because the authors did not indicate what fraction of the feces is ethanol soluble. Only in the case of the high dose males was it stated that the ethanol-soluble and ethanol-insoluble fractions corresponded to 0.5% and 1.89% of the dose respectively (i.e. the ethanol-soluble fraction is approximately 20.9% of the radioactivity in feces). Subsequent solubilization of up to 75% of the ethanol-insoluble fraction, revealed that this solubilized fraction contained CGA-179500 as the only significant metabolite. **These results indicate that the major metabolite in feces, at least in the case of the high-dose males, is CGA-179500. It is noted that in feces, regardless of the relative amounts of parent and CGA-179500, total radioactivity in feces does not exceed 2.01% of the dose at 24 hours (Table 4) or up to 3-4% of the dose at 168 hours (Table 2, including some $^{14}C$ from the cage wash).**

**Table 4. Recovery[1] of radioactivity in urine and feces of rats 24 hours after dosing with [cyclohexyl-1,2,6-$^{14}C$] CGA-163935.**

| | Percent of radioactive dose recovered with | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | I.V.[2] 0.91 mg/kg | | Oral 0.97 mg/kg | | Oral 166 mg/kg | | Oral Pretreatment plus 0.97 mg/kg | |
| Matrix | M | F | M | F | M | F | M | F |
| Urine | 87.28 | 90.55 | 91.49 | 92.74 | 90.93 | 95.49 | 92.90 | 92.94 |
| Feces | 0.66 | 0.99 | 1.43 | 0.94 | 2.01 | 0.80 | 1.13 | 0.56 |
| Total: | 87.94 | 91.54 | 92.92 | 93.68 | 92.94 | 96.29 | 94.03 | 93.50 |

[1] Urine and feces data from Tables 7-10 of Analytical Part of Study Report.

[2] I.V. = intravenous. The four dosage groups depicted in the dosage columns of this table, correspond to Groups 1-4 of Table 1 of this DER.

Table 5. Quantitation of metabolites in raw urine and in ethanol extracts of feces from rats dosed with [cyclohexyl-1,2,6-$^{14}$C] CGA-163935.

| | Percent of urinary or fecal extract radioactivity | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | I.V.[1] 0.91 mg/kg | | Oral 0.97 mg/kg | | Oral 166 mg/kg | | Oral Pretreatment plus 0.97 mg/kg | |
| Compound | M | F | M | F | M | F | M | F |
| Urine: | | | | | | | | |
| CGA-179500 | 89.90[2] (75.29) | 86.13 (74.05) | 92.44 (81.99) | 93.47 (88.94) | 95.09 (85.02) | 96.16 (91.63) | 91.10 (82.49) | 94.07 (88.36) |
| Feces: | | | | | | | | |
| CGA-179500 | 71.84[3] | 49.76 | 53.13 | 45.67 | 85.14 | 71.86 | 45.93 | 31.86 |
| CGA-163935 | -[4] | - | 20.10 | 22.89 | 2.85 | 5.90 | 11.99 | 14.02 |

[1] I.V. = intravenous. The four dosage groups depicted in the dosage columns of this table, correspond to Groups 1-4 of Table 1 of this DER.

[2] Data obtained from Table II, Metabolite Identification Phase, of Study Report. Values in parentheses refer to amount of the compound expressed as percent of the administered dose. The value was obtained by the reviewer as follows: Value in parentheses = (% of urinary radioactivity as compound) x (% of dose excreted in urine) x (% recovery of HPLC) x $10^{-4}$.

[3] Except for the high-dose males, it was not possible to express values in feces as percent of the applied dose because the author did not state what fraction of the radioactivity in feces ethanol-extractable and because the ethanol-insoluble fraction was not analyzed. In the case of the high-dose males, the ethanol extract contained 20.92% of the radioactivity in feces (i.e. 0.5/2.39 X 100), thus the high-dose males would have excreted 0.37 and 0.01% of the dose as CGA 179500 and CGA 163935, respectively, in the ethanol-extractable fraction. In addition, 75% of the ethanol insoluble fraction was found to consist of CGA 179500. This percent would correspond, as estimated by the reviewer, to about 1.2% of the dose, assuming 79.08% of the radioactivity in feces is ethanol-insoluble and 2.0% of the dose is excreted in feces by the high-dose males.

[4] Considered non-applicable by the author.

Reviewer's comments/conclusions:

Although it was stated that work performed after October 1989 for the identification of metabolites complied with EPA-GLP (40 CFR 160), it was not stated explicitly whether metabolite identification work performed before October 1989 complied with the then existing EPA-GLP.

Recoveries of radioactivity in urine after oral dosing (94.5-97.3% of the dose) indicate extensive absorption of the compound from the GI tract. Total recovery of radioactivity 168 hours after treatment accounted for 97-99% of the dose in the orally dosed animals, and to 94.7-98.3% of the dose in the iv treated rats. Among the orally dosed groups, approximately 94.5-97.3% of the dose was eliminated in urine and 1.0-2.4% of the dose was eliminated in feces. Most of the elimination occurred within the first 24 hours. No differences between the sexes or among dose groups were found. The low elimination of radioactivity in feces by the iv-dosed group (1.1-1.6% of the dose) suggests that there is very little or no biliary excretion of the compound and/or its metabolites in rats. At sacrifice, total radioactive residue in the carcass was less than 0.28% of the dose in all groups. A preliminary experiment indicated that by 72 hours after dosing, elimination of radioactivity in expired air amounted to less than 0.06% of the dose for the low-dose rats and to less than 0.01% of the dose for the high-dose rats.

Only one metabolite, CGA-179500, was found in urine. CGA-179500 is the carboxylic acid resulting from hydrolysis of the ester bond of parent CGA-163935. Levels of CGA-179500 in urine accounted for 82.0-91.6% of the dose among the orally-dosed animals and for 74.1-75.3% of the dose among the iv-dosed animals.