EPA Reviewer: Ghazi Dannan, Ph.D. _____ , Date June 11, 1999
Registration Action Branch III (7509C)
EPA Secondary Reviewer: Virginia A. Dobozy, VMD, MPH _____, Date_____
Reregistration Branch I (7509C)
TXR: 0050329

# DATA EVALUATION RECORD

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

DP BARCODE: D243609 SUBMISSION CODE: S538189
P.C. CODE: 108800 TOX. CHEM. NO.:

TEST MATERIAL: (S)-2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)-acetamide radiolabelled in the phenyl [U-$^{14}$C] ring.

SYNONYMS: Metolachlor-S, or CGA-77102

CITATIONS: Muller, T. 1996. "Absorption, Distribution, and Excretion of [Phenyl-U-$^{14}$C] CGA-77102 in the Rat". Animal Metabolism, Product Safety Division, Novartis Crop Protection AG, Basle, Switzerland: PR 15/96 (Novartis No. 491-96) November 1, 1996, Laboratory Project: 30AM01. MRID No.: 44491401. Unpublished.

SPONSOR: Novartis Crop Protection, Inc., P.O.Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY:

[Phenyl-U-$^{14}$C] labeled CGA-77102 was administered by gavage to groups of Tif: RAI f (SPF) strain rats at a single low dose (0.5 mg/kg, Group B1), at a high dose (100 mg/kg, Group D1), or at a low dose following 14-daily oral high doses with the unlabeled test chemical (Group V1). The urine and feces were collected at specified times (from 5 animals/sex) to determine the extent of absorption and excretion; selected tissues were harvested after seven days. Blood samples from Groups B1 and D1 were taken periodically to determine the kinetics in plasma and blood cell (RBC); the expired air in Group D1 was also monitored for $^{14}CO_2$ for 72 hours. In a bile cannulation study in male rats (6/group), bile and excreta were collected at defined intervals up to 48 hours after the labeled test substance was administered at a single oral low (Group G1) or high (Group G2) dose. In all three dose groups (B1, D1, and V1), the seven day combined levels of radioactivity in urine were 31.1 - 36.5% for males and 40.8 - 45.5% for females; the fecal levels were 60.2 - 62.5% for males and 48.9 - 55.0% for females. Only 0.1% or less was eliminated in the expired air. The total recovery ranged from 96.5 ± 2.3% to 99.3 ± 0.9% which indicates an excellent efficiency of the study. The route or extent of excretion was slightly influenced by the sex of the animal but not by pretreatment with non-radiolabeled CGA-77102 or by the dose level. The degree of absorption, based on adding the cumulative urinary excretion to the total residues in tissues, was 35 - 39% in males and 43 - 49% in females of both dose groups.

However, based on the bile duct cannulation study, most of CGA-77102 was absorbed from the gastrointestinal tract since 85% of the dose was recovered in urine, bile fluid, and tissues during the 48 hours study period. Therefore, the biliary excretion and enterohepatic circulation play a significant role in the elimination process of CGA-77102.

Irrespective of the dose and sex, there seems to be a biphasic plasma profile with two concentration maxima ($C_{max}$); a fast rising first $C_{max}$ was reached at 0.25 - 1 hour post dosing which was succeeded by a second $C_{max}$ at 8 and at 12 - 24 hours following administration of the low and high dose, respectively. In the low dose group (B1), the first and second $C_{max}$ were nearly identical (~ 0.03 µg/ml); in the high dose group (D1), the first and second $C_{max}$ were, respectively, 4.6 and >3.9 µg/ml in males and 2.2 and 4.5 µg/ml in females. The time to half maximum plasma concentration ($t_{cmax/2}$) in males/females was 31/24 hours at the low dose and 44/32 hours at the high dose. Bioavailability, or the area under the plasma concentration curve ($AUC_{0-48hr}$), was nearly identical (~ 0.8 mg/kg.hr) among males and females of the low dose group. Also, both sexes in the high dose group had similar plasma $AUC_{0-48hr}$ (M/F: 143/125 mg/kg.hr) which increased almost proportionately with the 200-fold increase in the dose level. The residues in RBC increased steadily with time reaching peak levels (at 24 - 48 hours post-dosing) of 0.5-0.6 and 90 ppm (or µg/g) CGA-77102 equivalents for the low (B1) and high (D1) dose groups, respectively. The peak levels in RBC remained high and were nearly 20 fold higher than the respective plasma $C_{max}$ levels.

The kinetics of tissue distribution and depletion in both sexes were also followed for up to 144 hours following a single low or high oral dose (Groups F1 - F4). Peak residue levels were reached within 12 - 24 hours and ranged from 0.007 ppm (female muscle) to 0.123 ppm (male kidneys) at the low dose, and from 1.29 ppm (male brain) to 16.82 ppm (male liver) at the high dose, with the highest levels being among some of the well-perfused tissues (e.g., liver, kidneys, spleen, and lungs). The extent of residue depletion was variable among the tissue types but was minimally affected by the dose or the sex of the animal. The radiolabel was most persistent in some of the well-perfused organs (e.g., the heart, lungs, and spleen) in addition to the brain and bone where, after 144 hours, the levels were decreased to only 45 - 94% of their maximal concentrations. In Groups F1 - F4, peak residue concentration in the whole blood (0.2 and 42 - 47 µg/ml in the low and high dose groups, respectively) was reached at 24 hours and was maintained throughout the study. Overall, the high/low dose peak tissue levels (including blood) ranged from 132 to 282 which approximates the 200-fold increase in dosage.

Finally, it should be reemphasized that CGA-77102 has a high affinity for and a long half-life in blood (especially RBC) which might contribute to the retarded depletion of tissue residues.

CLASSIFICATION. Pending upgrading of the combined metabolism study (MRID 44491402), this study is classified as **ACCEPTABLE** (Guideline) and satisfies the requirement for a series 85-1 general metabolism study for Metolachlor-S (CGA-77102).

COMPLIANCE: Signed and dated statements were provided for GLP (Switzerland, March 1986

based on the OECD GLP of May 12, 1981), Quality Assurance, and Data Confidentiality.

## I. MATERIALS AND METHODS AND STUDY DESIGN

### A. MATERIALS:

1. Test Compound:

| | |
|---|---|
| Radiolabeled: | [Phenyl-U-$^{14}$C] CGA-77102 |
| Radiochemical purity: | >98 % |
| Batch No.: | GAN-XXXV-59-1 |
| Specific activity: | 51.35 µCi/mg (1.90 MBq/mg) |
| Non-radioalabeled: | CGA-77102 |
| Purity: | >99.0% |
| Batch No.: | AMS 757/101 |
| Description: | Extremely pale yellow clear liquid. |
| Contaminants: | No information. |
| CAS No.: | 87392-12-9 |

2. Vehicle: Ethanol/polyethylene glycol 200/water 3/2/3 (v/v)

3. Test animals:

| | |
|---|---|
| Species: | Rat |
| Strain: | Tif: RAI f (SPF) |
| Age: | 7 - 9 weeks |
| Weight at study initiation: | 200-250 g |
| Source: | Ciba-Geigy, Switzerland, Animal Production, Stein |
| Housing: | Individually beginning one day before dosing with the labeled material |
| Diet: | Certified standard diet (Nafag No. 890), ad libitum |
| Water: | Tap water (ad libitum) for all groups except for groups G1 and G2 which, following the bile cannulation surgery, were given water containing 5% glucose, 0.9% NaCl, and 0.05%KCl. |

B. STUDY DESIGN: The study consisted of seven parts as indicated in Table 1.

TABLE 1: Study Design

| Group | Description | Dose | Rats/sex | Dosing Schedule and Other Comments |
|---|---|---|---|---|
| B1 | Low Dose | ~0.5 mg/kg 5.2 µCi | 5 | Collection of blood (later separated into plasma + RBC), urine, and feces at defined time points; selected tissues after 7 days. |
| V1 | Pretreatment*; Low Dose | ~0.5 mg/kg 5.2 µCi | 5 | Collection of urine and feces at defined time points; selected tissues after 7 days. |
| D1 | High Dose | ~100 mg/kg 203.3 µCi | 5 | Collection of blood (later separated into plasma + RBC), urine, and feces at defined time points; selected tissues after 7 days. Monitoring expired $^{14}CO_2$ for 72 hours. |
| F1/F3 | Low Dose | ~0.5 mg/kg 5.4 µCi | 12 | Collection of selected tissues at 12, 24, 72, and 144 hours. |
| F2/F4 | High Dose | ~100 mg/kg 69.8 µCi | 12 | Collection of selected tissues at 12, 24, 72, and 144 hours. |
| G1 | Bile Duct Cannulation Low Dose | 0.5 mg/kg 6.3 µCi | 6 ♂ | Collection of bile, urine, and feces at defined intervals; gastro-intestinal tract and carcass after 48 hours. |
| G2 | Bile Duct Cannulation High Dose | 100 mg/kg 198.3 µCi | 6 ♂ | Collection of bile, urine, and feces at defined intervals; gastro-intestinal tract and carcass after 48 hours. |

* Animals in group V1 were administered 14 daily oral doses of 100 mg/kg of non-radiolabeled CGA-77102.

C. METHODS:

1. Preparation of dosing solutions and administration: (Refer to pages 22-23 of study report)

The dosing solutions were prepared by dissolving the radiolabeled test substance in the vehicle (above) at the two specified dose levels so that each animal received (by stomach tube) about 0.8 ml of the dosing formulation, except for animals of groups G1 and G2 which received 1.0 ml. During the pretreatment period, the animals of group V1 were administered the non-radiolabeled test substance in 0.7 - 0.8 ml of the administration solution. All dosing was by gavage after fasting overnight.

According to the report, the test substance in the administration solution was analyzed by TLC at the time of dosing and was found to be stable with CGA-77102 representing > 97% of the radioactivity. Two representative TLC radiochromatograms of the administration solution were provided (Figure 5 of report). For the repeated dosing group (V1), the radiolabeled test substance was found stable after 14 days at room temperature (radiochemical purity > 98%). No additional data were provided on the stability or dose verification.

2. Bile duct cannulation: (Refer to pages 23-24 of study report)

Using routine surgery, bile duct catheters were prepared, positioned subcutaneously, and securely exteriorized to the back of the animal to allow unrestrained movement in specially designed metabolism cages for collecting bile and excreta. Animals with bile flow rates of more than 0.5 $ml.h.^{-1}$ were selected for dosing. Tables 10 and 11 of the report show that during all bile collection periods, bile flow rates were around 1 to 1.5 $ml.h.^{-1}$ and that one animal in each of groups G1 and G2 died after 8 hours of dosing. All bile duct cannulated animals were killed after the last bile collection at 48 hours post dosing.

3. Specimen collection and storage: (Refer to pages 24-25 of study report)

Urine and bile samples were separately collected on dry ice while feces were collected at room temperature. Expired air (from the high dose group D1 only) was collected in ethanol-amine/ethylene glycol monomethyl ether (½, v/v) during 0-24, and 24-48 hours post dosing. (In Tables 24 and 25, pages 64 and 65 of the study report, expired air results were also reported for 48-72 hours.) For the blood kinetics study, blood from the tail vein was collected in capillary tubes from three animals of each sex of groups B1 and D1 and the plasma and red blood cells (RBC) were separated by centrifugation.

All animals were killed by an overdose of $CO_2$. Terminal blood was collected into heparinized tubes and, after saving aliquots of whole blood, the plasma and RBC were separated. Specimens and tissues were collected from individual animals at specified intervals as shown in *Attachment 1* which is reproduced from page 25 of the study report (MRID 44491401). Volumes and weights of all specimens were recorded prior to analysis. Until analyzed, urine, feces, bile, and tissues were kept frozen; blood was kept refrigerated, while $CO_2$-traps and the cage wash were kept at room temperature.

4. Radioactivity Measurement: (Refer to pages 26-27 of study report)

Radioactivity was measured by liquid scintillation counting (LSC) using a Packard Tri-Carb Counter. Measured aliquots of all liquid specimens were added directly to the scintillation cocktail. An aliquot (2 ml) of the solution containing the expired $CO_2$ was mixed with methanol (6 ml) and scintillation fluid (10 ml) prior to counting. Samples of feces, tissues, or carcass were homogenized, minced, or crushed as needed. Specimens of whole blood, blood cells, bone, lungs, GI tract, or homogenized feces or carcass were combusted in a special sample oxidizer prior to counting. Samples from the remaining soft tissues were digested (using 4 ml of Irgasolve solubilizer), neutralized with HCL (1N, 4 ml) then mixed with the Scintillation fluid (15 ml) prior to LSC. Background counts (dpm) were recorded with each experiment using the respective scintillation cocktail without any specimen.

5. Calculations and Statistics: The calculations performed on experimental data are summarized in the attached pages 28 and 29 of study report. No statistical tests were used to

assess the results and this is considered by RAB-III to be appropriate. The data were expressed as the mean ± the standard deviation.

## II. RESULTS AND DISCUSSION

One animal of group V1 (animal number or sex not specified) was reported to have died after dosing on the 13th day of pretreatment and, at autopsy, was reported to have a swollen gas-filled GI tract (page 31 of study report). However, according to Tables 2, 22, and 23, data were listed for all animals (animal numbers 95427-95431 for males and 95432-95436 for females) and there was no mentioning that an animal died before study termination. The reason for this discrepancy is not clear but the animal that died might have been replaced with a new one which was assigned the same number.

One female rat (no. 96045) in the high dose group F4 was found moribund after 24 hours and this rat was excluded from calculating the means of radioactivity in the tissues (Table 48, p. 88).

The bile duct cannulated rats of groups G1 and G2 lost weight which was attributed to the surgery and drug treatment. Four male bile-duct cannulated rats in the low dose G1 group showed chromodacryorrhoea beginning eight hours after dosing until the end of the experiment. One of these animals (no. 96954) died 18 hours after dosing. In the high dose G2 group, one bile-duct cannulated rat (no. 96059) was killed eight hours after dosing because the cannula was broken. All animals in this group were also reported to have piloerection, chromodacryorrhoea and reduced food intake after 18 hours of dosing until the end of the experiment.

### A. Absorption

The recovery of radioactivity in the excreta, tissues, and carcass of the various groups are summarized in Table 2. The degree of absorption, judged by the urinary excretion and the tissue residues, was independent of the dose level (Groups B1 vs. D1) or pretreatment with non-radiolabeled CGA-77102 (Group V1), but was slightly sex-dependent. The seven days combined urinary elimination and tissue residues in males and females were 35 - 39% and 43 - 49%, respectively. However, the bile duct cannulation study in male rats clearly shows that CGA-77102 was almost completely absorbed from the gastrointestinal tract as demonstrated by the 85% dose recovery in urine, bile fluid, and tissues during the 48 hours study period (Groups G1 and G2 in Table 2). The large amount of biliary excretion (Groups G1 and G2) indicates that most of what was excreted in the feces by the rats of Groups B1, V1, and D1 was not due to lack of absorption but rather was the result of biliary excretion into the intestinal tract.

Irrespective of the dose level (B1 vs. D1), sex of the animal, or repeated exposure (V1), all groups excreted more residue in the feces than in the urine; however, the relative preference for the fecal (over the urinary) route was more pronounced among the male groups (Table 2).

Table 2: Excretion After Oral Administration of [Phenyl-U-$^{14}$C] CGA-77102 (% of Dose)[a]

| Group | B1 | | V1 | | D1 | | G1 | G2 |
|---|---|---|---|---|---|---|---|---|
| Sex | Male | Female | Male | Female | Male | Female | Male | Male |
| Dose (mg/kg) | 0.5 | 0.5 | 0.5 | 0.5 | 100 | 100 | 0.5 | 100 |
| Urine | | | | | | | | |
| 0 - 24 h | 20.7 | 29.9 | 27.4 | 35.1 | 19.7 | 25.7 | 4.0 | 1.5 |
| 24 - 48h | 6.5 | 6.7 | 5.8 | 6.6 | 10.8 | 12.2 | 0.6 | 1.5 |
| 48 - 72h | 2.2 | 2.4 | 1.6 | 1.9 | 2.6 | 4.7 | n.a. | n.a. |
| 72 - 168h | 1.7 | 1.8 | 1.7 | 1.5 | 1.3 | 3.0 | n.a. | n.a. |
| subtotal | 31.1 | 40.8 | 36.5 | 45.2 | 34.4 | 45.5 | 4.6 | 3.0 |
| Bile 0 - 48h | Not Collected | | | | | | 79.8 | 79.8 |
| Feces | | | | | | | | |
| 0 - 24 h | 40.2 | 37.5 | 40.5 | 35.1 | 31.7 | 21.5 | 1.3 | 0.6 |
| 24 - 48h | 15.2 | 12.8 | 14.1 | 9.8 | 21.1 | 17.5 | 1.1 | 1.6 |
| 48 - 72h | 4.3 | 3.1 | 3.3 | 2.2 | 4.7 | 6.6 | n.a. | n.a. |
| 72 - 168h | 2.8 | 1.6 | 2.3 | 1.8 | 3.2 | 3.9 | n.a. | n.a. |
| subtotal | 62.5 | 55.0 | 60.2 | 48.9 | 60.7 | 49.5 | 2.4 | 2.2 |
| Expired Air | n.a. | n.a. | n.a. | n.a. | 0.1 | <0.1 | n.a. | n.a. |
| Cage Wash | 0.6 | 1.3 | 0.3 | 0.9 | 0.7 | 0.4 | 0.1 | 0.3 |
| *Total Excretion* | 94.2 | 97.1 | 96.9 | 94.9 | 95.9 | 95.5 | 87.0 | 85.3 |
| Tissue Residues | | | | | | | | |
| Tissues | 2.4 | 1.5 | 1.1 | 0.9 | 1.9 | 1.9 | 15.1[b] | 12.8[b] |
| Carcass | 1.1 | 0.7 | 0.9 | 0.7 | 1.2 | 1.1 | 1.1 | 1.7 |
| *Subtotal* | 3.5 | 2.2 | 2.0 | 1.6 | 3.1 | 3.0 | | |
| Total Recovery | 97.7 | 99.3 | 98.9 | 96.5 | 99.0 | 98.5 | 103.2 | 99.8 |

[a] Data are from Table on page 34 and from Tables 20 - 27 of the Study Report (MRID 44491401).

[b] This value is for gastrointestinal tract. Tissues were not collected for the bile duct cannulation groups.

As shown in Table 2, the combined tissue residues (including blood), at seven days post-dosing, ranged from 1.5 to 2.4% of the administered single low or high dose. In group V1, the combined tissue residue content was around 1% of the administered radiolabeled low dose after repeated pretreatment with the unlabeled chemical at the high dose. This could be due to the possible saturation of available tissue binding sites with the unlabeled compound. Around 1% of the administered label could be accounted for in the carcasses from all groups.

During the 48 hours period of expired air collection, the total amount of radiolabel in $CO_2$ represented ≤ 0.1% of the administered high dose to rats of both sexes.

Finally, with total recoveries of 96.5 - 103.2 %, the mass balance of the administered radiolabel was fully accounted for.

B. **Blood Kinetics**

The time-dependent distribution of the radiolabel in the blood can be monitored from two studies. In the first study (Groups B1 and D1), the blood kinetics were followed separately for the plasma and red blood cells (RBC) from 1/4-72 hours; the second study (Groups F1, F2, F3, and F4) examined the pharmacokinetics of residual radioactivity in selected tissues including whole blood from 12 to 144 hours post-dosing. The results of this second study will be discussed later under "Tissue Residue Distribution and Depletion." The following is a summary of the plasma and RBC kinetics findings.

Table 3 lists some of the plasma kinetics parameters where, irrespective of the dose and sex, there seems to be a biphasic plasma profile (also refer to Attached Figures 6 - 9 of the study report). The concentration of radioactivity in plasma rose rapidly to attain the first maximum within 0.25 - 1 hour post dosing. The second plasma maximum was attained after 8 hours and 12 - 24 hours following administration of the low and high dose, respectively. The report attributed this biphasic plasma pattern to possible enterohepatic circulation during the elimination process. This reviewer concurs.

Bioavailability, or the area under the plasma concentration curve ($AUC_{0\text{-}48hr}$), was nearly identical among males and females of the low dose group (Table 3). Also the high dose rats of both sexes had similar plasma $AUC_{0\text{-}48hr}$ and $AUC_{0\text{-}72hr}$, which, relative to the $AUC_{0\text{-}48hr}$ of the low dose group, increased almost proportionately with the 200 fold increase in the dose level.

Table 3: Means of Plasma Kinetics Findings*

| Group (Dose) | B1 (0.5 mg/kg) | | D1 (100 mg/kg) | |
|---|---|---|---|---|
| Sex | Male[1] | Female[1] | Male[1] | Female[1] |
| $C_{max}$ (ppm CGA-77102 equivalent or µg/mL) | 0.032/0.0275 | 0.033/0.031 | 4.6/>3.9[2] | 2.2/4.5 |
| $t_{cmax}$ (hours) | 0.25/8 | 0.5/8 | 0.5/12-24[2] | 1/12 |
| $t_{cmax/2}$ (hours) | 31 | 24 | 44 | 32 |
| $AUC_{0\text{-}48hr}$ (mg/kg.hr) | 0.79 | 0.83 | 142.7 | 125.1 |
| $AUC_{0\text{-}72hr}$ (mg/kg.hr) | n.a. | n.a. | 170.7 | 158.0 |

* Data are from Tables 13, 15, 17, and 19 of the Study Report (MRID 44491401).

[1] Two plasma concentration maxima were identified (1st/2nd) at both doses and for both sexes.

[2] The high dose males had identical plasma concentrations (3.9 ppm) at 12 and 24 hours which could be interpreted that the maximum (>3.9 ppm) was attained between 12 and 24 hours post-dosing.

In both B1 and D1 dose groups, the residues in blood cells increased steadily with time reaching peak levels of 0.5-0.6 and 90 ppm CGA-77102 equivalents for the low and high dose groups, respectively at 24 - 48 hours post-dosing (Table 4 and Attached Figures 6 - 9 of the study report). Within the same dose group and sex, the peak levels in RBC were nearly 20 fold higher than the respective plasma $C_{max}$ levels. The residues in RBC remained high throughout the remainder of the 72 hours testing period (Attached Figures 6 - 9).

Table 4: Mean Peak Radiolabel and Time to Peak Levels in RBC*

| Group (Dose) | B1 (0.5 mg/kg) | | D1 (100 mg/kg) | |
|---|---|---|---|---|
| Sex | Male | Female | Male | Female |
| Mean Peak Concentration (ppm or µg/mL) | ~ 0.5 | ~ 0.6 | ~ 90 | ~ 90 |
| Time to Peak Concentration (hours) | 48 | 24 | 48 | 48 |

* Data are from Tables 12, 14, 16, and 18 of the Study Report (MRID No.: 44491401)

The kinetics of radiolabeled residues in whole blood were followed at 12, 24, 72, and 144 hours after dosing of groups F1 - F4 (Table 5 below). In both sexes of the low and high dose groups, the peak whole blood level was attained at 24 hours post-dosing and this peak level was maintained throughout the study period of 144 hours. Also, while there were no sex related differences, the relative peak whole blood levels in the two dose groups were nearly equivalent to the 200-fold difference in the actual dose levels.

Table 5: Mean Peak Radiolabel and Time to Peak Levels in Whole Blood*

| Dose (mg/kg) | 0.5 | | 100 | |
|---|---|---|---|---|
| Group | F1 | F3 | F2 | F4 |
| Sex | Male | Female | Male | Female |
| Mean Peak Blood Concentration (ppm or µg/mL) | ~ 0.21 | ~ 0.20 | ~ 42 | ~ 47** |
| Time to Peak Concentration (hours) | 24 - 144 | 24 - 144 | 24 - 144 | 24 - 144** |

* Data are from Tables 34 - 49 of the Study Report (MRID No.: 44491401).

** While the peak concentration of 46.7 ppm was recorded at 24 hours, comparable levels of 38.4, and 44.4 ppm were also observed at the later time points of 72, and 144 hours, respectively.

## C. Kinetics of Tissue Residue Distribution and Depletion

The radiolabel distribution to other tissues and the time-dependent depletion were monitored in groups F1 - F4 at 12, 24, 72, and 144 hours after administration of a single dose of [Phenyl-U-$^{14}$C] CGA-77102 at 0.5 or 100 mg/kg. The data can be found in Tables 34 - 49 of the study report (MRID 44491401) and will be summarized here. As discussed above and shown in Table 5, maximum blood residue levels were reached at 24 hours and were maintained throughout the end of the study (144 hours). Peak residue levels in all other tissues were reached between 12 and 24 hours and ranged from 0.007 ppm (female muscle) to 0.123 ppm (male kidneys) at the low dose, and from 1.29 ppm (male brain) to 16.82 ppm (male liver) at the high dose. Some of the well-perfused tissues, such as the liver, kidneys, spleen, and lungs had the highest levels ranging in both sexes from 5.84 to 16.82 ppm at the high dose and from 0.03 to 0.12 ppm at the low dose. Other tissues, including the fat, ovaries, uterus, heart, and bone, also had relatively high levels. With minor exceptions (e.g., spleen, liver, and kidneys), both sexes within a dose group had comparable residue levels in the same tissue. Overall, the high/low dose tissue levels within the same sex ranged from 132 to 282 which approximates the 200-fold increase in dosage. However, fat (abdominal) from the high dose male rats had 417-fold increase in radiolabel relative to the same tissue of the low dose males.

The extent of residue depletion was variable among tissue types, but was only slightly or not influenced by the dose or the sex of the animal (Table 6 below). After 144 hours, depletion was most retarded in some of the well-perfused organs including the heart, lungs, and spleen in addition to the brain and bone where, in all of these organs, the levels were decreased to only 45 - 94% of their maximal concentrations. Also, it is noticeable that the test material is more persistent in tissues other than the fat and liver. Therefore, CGA-77102 is a relatively persistent chemical with an apparent half life in most of the well-perfused organs, brain, and RBC in excess of 144 hours.

After 144 hours, nearly 3 - 4 % of the administered dose to groups F1 - F4 was retained in all combined tissues (including whole blood), in addition to about 1% in the remaining carcass (Tables 37, 41, 45, and 49 of MRID 44491401) . (Somewhat lower (1.5 - 2.4%) combined tissue residue levels were reported after 7 days (168 hours) of administering a single dose in groups B1 and V1.) Finally, irrespective of the sex or the dose level in the F1 - F4 groups, nearly 2.5 - 2.8% of the administered dose remained in the blood, mostly in the RBC rather than in the plasma.

Table 6: Depletion of Maximal Tissue Residues at 144 Hours Post-Dosing*

| % of Maximal Concentration | | | | |
|---|---|---|---|---|
| Dose (mg/kg) | 0.5 | | 100 | |
| Group | F1 | F3 | F2 | F4 |
| Sex | Male | Female | Male | Female |
| Blood | ~ 100** | ~ 100** | ~ 100** | ~ 100** |
| Bone | 50 | 78 | 62 | 45 |
| Brain | 72 | 51 | 63 | 54 |
| Fat (abdominal) | 37 | 15 | 7 | 15 |
| Heart | 46 | 86 | 73 | 70 |
| Kidneys | 12 | 38 | 20 | 35 |
| Liver | 17 | 21 | 28 | 15 |
| Lungs | 56 | 58 | 64 | 62 |
| Muscle (skeletal) | 42 | 32 | 28 | 19 |
| Ovaries | - | 41 | - | 29 |
| Plasma | 6 | 9 | 10 | 8 |
| Spleen | 84 | 84 | 81 | 94 |
| Testes | 32 | - | 26 | - |
| Uterus | - | 22 | - | 23 |

* Data are from Table on page 35 based on Tables 50 - 53 of the Study Report (MRID 44491401).
** Levels in whole blood plateaued after reaching peak.

Pending upgrading of the combined metabolism study (MRID 44491402), this study is classified as Guideline **ACCEPTABLE** and does satisfy the requirement for a general metabolism study for Metolachlor-S. In this report, data on metabolite identification/quantification and proposed metabolism pathway were not provided. However, additional information may be found in the combined study (MRID 44491402) on comparing the metabolite patterns of CGA-77102 and CGA-24705 and in the earlier study (MRID 43164201) on racemic Metolachlor (CGA-24705) which was reviewed by T. McMahon (HED document no. 010990 dated May 23, 1994). The well-executed biliary cannulation study in this report demonstrated that absorption of CGA-77102 from the gastrointestinal tract was almost complete. Therefore, the absence of an intravenous study is not critical and, as such, is not considered a deficiency.

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

Reference to these attachments in the text states the purpose for including these attachments.

All attachments are from MRID No.: 44491401.

List of Attachments

Page 25 of 105: Type and time of specimen collection from all groups.

Pages 28 and 29: Calculations Performed on Experimental Data.

Figures 6 - 9: Plasma and blood cells levels after single oral administration of [phenyl-U-$^{14}$C] CGA-77102 to male and female rats at nominal doses of 0.5 or 100 mg/kg.