CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

SUMMARY OF TOXICOLOGY DATA
Metolachlor, S-Metolachlor, Metolachlor Oxanilic Acid, Metolachlor Ethanesulfonic Acid

Chemical Code #1996, 5133, 5806, 5807  Document Processing Number (DPN) 368, 52245
SB 950 # 87
10/7/86, 4/7/88, 11/20/89, 12/10/90, 8/29/97, 4/18/06, 12/18/15, 02/14/17

DATA GAP STATUS

Chronic toxicity, rat: No data gap, no adverse effect
Chronic toxicity, dog: No data gap, no adverse effect
Oncogenicity, rat: No data gap, possible adverse effect
Oncogenicity, mouse: No data gap, no adverse effect
Reproduction, rat: No data gap, no adverse effect
Developmental toxicity, rat: No data gap, no adverse effect
Developmental toxicity, rabbit: No data gap, no adverse effect
Gene mutation: No data gap, no adverse effect
Chromosome effects: No data gap, no adverse effect
DNA damage: No data gap, no adverse effect
Neurotoxicity: Data gap, no studies submitted

Toxicology one-liners are attached.

All record numbers for the above study types through Record number 296506 (Document No. 52245-0118, -0204) were examined. This includes all relevant studies indexed by DPR as of 02/14/17.

In the 1-liners below:
 indicates an acceptable study.
Bold face indicates a possible adverse effect.
## indicates a study on file but not yet reviewed.

File name: T170214
Revised by Name: N. Pasupuleti, 02/14/17
NOTE: The following symbols may be used in the Table of Contents which follows:
* = data adequately address FIFRA requirement
† = study(ies) flagged as “possible adverse effect”
N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

Table of Contents

METABOLISM AND PHARMACOKINETICS ................................................................. 5
Metolachlor ............................................................................................................ 6

ACUTE STUDIES ......................................................................................................... 6
  Acute oral toxicity, rat ............................................................................................. 6
  Acute dermal toxicity .............................................................................................. 6
  Acute inhalation toxicity, rat .................................................................................. 6
  Primary eye irritation, rabbit .................................................................................. 6
  Primary dermal irritation ....................................................................................... 7
  Dermal sensitization ............................................................................................. 7

SUBCHRONIC STUDIES ............................................................................................. 7
  Rat 4-Week Dietary Toxicity Study ....................................................................... 7
  Rat Subchronic Dietary Toxicity Study ................................................................. 7
  Dog Subchronic Dietary Toxicity Study ................................................................. 8
  Dog Six-Month Chronic Oral Toxicity Study ........................................................ 8
  Mouse 4-Week Dietary Toxicity Study .................................................................. 8
  Rabbit 21-Day Repeated Dosing Dermal Toxicity Study ........................................ 8

CHRONIC STUDIES .................................................................................................. 9
  Chronic, rat ............................................................................................................. 9
  Chronic, dog ........................................................................................................... 9
  Oncogenicity, rat .................................................................................................. 9
  Oncogenicity, mouse ............................................................................................ 9

GENOTOXICITY ....................................................................................................... 10
  Gene mutation ...................................................................................................... 10
  Chromosome damage ........................................................................................... 10
  DNA damage or miscellaneous effects .................................................................. 10

REPRODUCTIVE TOXICITY, RAT ......................................................................... 11

DEVELOPMENTAL TOXICITY ................................................................................. 11
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>11</td>
</tr>
<tr>
<td>Rabbit</td>
<td>12</td>
</tr>
<tr>
<td><strong>NEUROTOXICITY</strong></td>
<td>12</td>
</tr>
<tr>
<td>Acute neurotoxicity, rat</td>
<td>12</td>
</tr>
<tr>
<td>90-day neurotoxicity, rat</td>
<td>12</td>
</tr>
<tr>
<td>Developmental neurotoxicity, rat</td>
<td>12</td>
</tr>
<tr>
<td>Delayed neurotoxicity, hen</td>
<td>12</td>
</tr>
<tr>
<td><strong>IMMUNOTOXICITY</strong></td>
<td>12</td>
</tr>
<tr>
<td><strong>ENDOCRINE DISRUPTOR STUDIES</strong></td>
<td>12</td>
</tr>
<tr>
<td>(S)-Metalochlor</td>
<td>12</td>
</tr>
<tr>
<td><strong>ACUTE STUDIES</strong></td>
<td>12</td>
</tr>
<tr>
<td>Acute oral toxicity, rat</td>
<td>12</td>
</tr>
<tr>
<td>Acute dermal toxicity</td>
<td>13</td>
</tr>
<tr>
<td>Acute inhalation toxicity, rat</td>
<td>13</td>
</tr>
<tr>
<td>Primary eye irritation, rabbit</td>
<td>13</td>
</tr>
<tr>
<td>Primary dermal irritation</td>
<td>13</td>
</tr>
<tr>
<td>Dermal sensitization</td>
<td>13</td>
</tr>
<tr>
<td><strong>SUBCHRONIC STUDIES</strong></td>
<td>14</td>
</tr>
<tr>
<td>Rat Subchronic Dietary Toxicity Study</td>
<td>14</td>
</tr>
<tr>
<td>Dog Subchronic Dietary Toxicity Study</td>
<td>14</td>
</tr>
<tr>
<td><strong>CHRONIC STUDIES</strong></td>
<td>14</td>
</tr>
<tr>
<td>Chronic, rat</td>
<td>14</td>
</tr>
<tr>
<td>Chronic, dog</td>
<td>14</td>
</tr>
<tr>
<td>Oncogenicity, rat</td>
<td>15</td>
</tr>
<tr>
<td>Oncogenicity, mouse</td>
<td>15</td>
</tr>
<tr>
<td><strong>GENOTOXICITY</strong></td>
<td>15</td>
</tr>
<tr>
<td>Gene mutation</td>
<td>15</td>
</tr>
<tr>
<td>Chromosome damage</td>
<td>15</td>
</tr>
<tr>
<td>DNA damage or miscellaneous effects</td>
<td>15</td>
</tr>
<tr>
<td><strong>REPRODUCTIVE TOXICITY, RAT</strong></td>
<td>16</td>
</tr>
<tr>
<td><strong>DEVELOPMENTAL TOXICITY</strong></td>
<td>16</td>
</tr>
<tr>
<td>Rat</td>
<td>16</td>
</tr>
<tr>
<td>Rabbit</td>
<td>16</td>
</tr>
<tr>
<td><strong>NEUROTOXICITY</strong></td>
<td>16</td>
</tr>
</tbody>
</table>
Acute neurotoxicity, rat ................................................................. 16
90-day neurotoxicity, rat ............................................................... 16
Developmental neurotoxicity, rat .................................................. 16
Delayed neurotoxicity, hen ............................................................. 17

IMMUNOTOXICITY ................................................................. 17

ENDOCRINE DISRUPTOR STUDIES ........................................ 17

METABOLITES .................................................................. 17
Metolachlor Oxanilic Acid ............................................................... 17

ACUTE STUDIES .................................................................. 17
Acute oral toxicity, rat ................................................................. 17
Acute dermal toxicity .................................................................. 17
Acute inhalation toxicity, rat ....................................................... 17
Primary eye irritation, rabbit ....................................................... 17
Primary dermal irritation ............................................................. 18
Dermal sensitization ................................................................... 18

SUBCHRONIC STUDIES ......................................................... 18
Rat Subchronic Dietary Toxicity Study ......................................... 18
Dog Subchronic Oral Toxicity Study ............................................. 19
Rat Developmental Toxicity Study ................................................. 19

GENOTOXICITY ................................................................... 20
Mutagenicity ................................................................................ 20
Chromosomal Aberration ............................................................. 20
Metolachlor Ethanesulfonic Acid .................................................... 20

ACUTE STUDIES .................................................................. 20
Acute oral toxicity, rat ................................................................. 20
Acute dermal toxicity .................................................................. 21
Acute inhalation toxicity, rat ....................................................... 21
Primary eye irritation, rabbit ....................................................... 21
Primary dermal irritation ............................................................. 21
Dermal sensitization ................................................................... 22

SUBCHRONIC STUDIES ......................................................... 22
Rat Subchronic Dietary Toxicity Study ......................................... 22
Dog Subchronic Oral Toxicity Study ............................................. 22
Rat Developmental Toxicity Study ................................................. 23
Metolachlor and (S)-metolachlor have been grouped for the purposes of evaluating their toxicity profiles under the requirements of the Birth Defects Prevention Act (see memorandum of July 7, 1998). (S)-Metolachlor and CGA-77102 are synonymous. (S)-Metolachlor is also identified as acetamide in the CDPR database. Metolachlor and CGA-24705 are synonymous. (S)-Metolachlor is comprised of the same isomeric compounds as metolachlor, but with a different isomeric ratio. Please note that the other metolachlor moieties are metabolites.

**METABOLISM AND PHARMACOKINETICS**

**Metolachlor**

368-286; 138143; “Metabolism of [Phenyl-(U)-14C] Metolachlor in Rats (Preliminary & Definitive Phases)” (T. Cheng, Hazleton Wisconsin, Inc., Madison, WI, HWI 6117-208, 12/8/92). Single doses of [Phenyl-(U)-14C] CGA-24705 (98.2% - 99.1% radiochemical purity, S.A. = 1 uCi/mg (high dose) and 29.5 uCi/mg (low dose)) was administered to 5 Sprague Dawley rats/sex/group orally (1.5, 300 mg/kg) or intravenously (1.5 mg/kg). 5 rats/sex were pretreated with 14 daily nonradiolabeled doses followed by a single radiolabeled dose. By comparing the urinary excretion and tissue/carcass residue data from each oral dosing regimen to those from intravenous administration, 69.8% to 93.2% of the oral dose is absorbed from the GI tract by male and female rats. Less than 0.05% of the radioactivity was eliminated in expired air. Within 48 hrs postdose, 81.7% - 88.3% of the administered radioactivity were eliminated in urine and feces. At termination (day 7), 30.6% - 57.5% and 34.8% - 62.0% of the administered dose was recovered in urine and feces, respectively. A sex-related difference in excretion pattern for the low dose groups was revealed: urinary excretion was the primary elimination route for females and fecal elimination was the primary route for males. High dose group did not exhibit any sex-related differences in excretion pattern. No evidence of accumulation was noted after multiple oral dosing. Highest residual concentrations were detected in spleen (0.07 - 0.127 ppm), lungs, liver, kidney, and heart (0.028 - 0.106 ppm). Acceptable (Leung, 8/20/97).

368-286; 138143; “Characterization and Identification of Metabolites in Rats Treated with 14C-Metolachlor” (T.M. Capps, Hazleton Wisconsin, Madison, WI, ABR-94001, 3/11/94). Characterization of glucuronidase treated excreta samples from high dose rats demonstrated that males and females have similar metabolite patterns. Complicated and detailed isolation procedures followed by NMR and mass spectroscopy resulted in the identification of 26 new metabolites as well as 6 previously reported structures. All significant excreta metabolites were identified and accounted for 60.3% to 73.9% of the administered dose. Significant metabolites identified were CGA-46129 (12.3% - 26.3%), CGA-41638 (2.4% - 10.6%), CGA-133275 (1.2% - 7.4%), CGA-50026 (1.2% - 6.1%), F7/U12 (2% - 7.3%), F8/U13 (1.7% - 9.6%), F7/U12 (2% - 7.3%), F8/U13 (1.7% - 9.6%), and F14 in feces (0.4% - 4.6%) and U17 in urine (0.5% - 7.3%). Major degradative pathways of metolachlor involve cleavage of the methyl ether, oxidation of the resultant alcohol, conjugation of the chloroacetyl group with glutathione followed by
hydrolysis; and oxidation of the aryl methyl and/or ethyl groups to benzylic alcohols followed in some cases by cyclization. Supplemental (Leung, 8/21/97).

Metolachlor

ACUTE STUDIES

Acute oral toxicity, rat

368-0281; 138119; “Acute Oral Toxicity Study of Metolachlor Technical in Rats”; (S.M. Glaza; Hazleton Wisconsin, Inc., Madison, WI; Project ID. HWI 40100901; 5/23/94, amended, 12/2/94); Five Crl:CD (SD) BR rats/sex/group (unless otherwise noted) were dosed orally by gavage with 1000 (F only), 2000, 2500, 3000 (M only), or 4000 (M only) mg/kg of Metolachlor Technical (batch no. P.111072; purity: 97.3%). Mortality as a result of the treatment was as follows: 1000 (F: 0/5), 2000 (M: 0/5, F: 3/5), 2500 (M: 1/5, F: 4/5), 3000 (M: 2/5), 4000 (M: 3/5). Clinical signs included soft stools, red-stained faces, prostration, dyspnea, hunched posture, tremors, staggered gait, hypoaactivity, tonic convulsions, absence of righting reflex, hypersensitivity to touch, excessive salivation, and generalized erythema. In the necropsy examination, the pelvic region in the kidneys of one male each of the 3000 and 4000 mg/kg groups was enlarged. LD50 (95% confidence limits): (M) 3302 (2639 to 4131) mg/kg, (F) 2000 (1454 to 2750) mg/kg; Toxicity Category III; Study acceptable. (Moore, 4/19/06)

Acute dermal toxicity

368-0281; 138120; “Acute Dermal Toxicity Study of Metolachlor Technical in Rabbits”; (S.M. Glaza; Hazleton Wisconsin, Inc., Madison, WI; Project ID. HWI 40102428; 5/23/94); The skin of 5 New Zealand White rabbits/sex was exposed to 2000 mg/kg of Metolachlor Technical (batch no. P.111072; purity: 97.3%) for 24 hours under an occlusive wrap. No deaths resulted from the treatment. Clinical signs included hypoaactivity and staggered gait. These signs were no longer evident by day 4. No treatment-related lesions were noted in the necropsy examination. LD50 (M/F) > 2000 mg/kg; Toxicity Category III; Study acceptable. (Moore, 4/19/06)

Acute inhalation toxicity, rat

368-0281; 138121; “Acute Inhalation Toxicity Study in Rats”; (M.S. Holbert; Stillmeadow, Inc., Sugar Land, TX; Study No. 1043-94; 8/24/94); Five Sprague-Dawley rats/sex were exposed nose-only to 4.33 mg/l (analytical) of Metolachlor Technical (batch no. P.111072; purity: 97.3%) for 4 hours. The mean MMAD (GSD) was 4.00 (2.33) um. No deaths resulted from the exposure. Clinical signs included piloerection and decreased activity. No treatment-related lesions were noted in the necropsy examination. LC50 (M/F) > 4.33 mg/l; Toxicity Category IV; Study acceptable. (Moore, 4/19/06)

Primary eye irritation, rabbit

368-0281; 138122; “Primary Eye Irritation Study of Metolachlor Technical in Rabbits”; (S.M. Glaza; Hazleton Wisconsin, Inc., Madison, WI; Project ID. HWI 40102430; 5/23/94); The eyes of nine New Zealand White rabbits were treated by ocular instillation with 0.1 ml/eye of Metolachlor Technical (batch no. P.111072; purity: 97.3%). The eyes of three animals were washed within 30 seconds of treatment. For the eyes which were unwashed, corneal opacity, grade 1 (2/6), was noted at 1 hour post-dose, clearing the 24 hours. Iritis, grade 1 (2/6) was evident at 1 hour, clearing by 24 hours. Conjunctival redness, grade 1 (5/6), was noted at 24 hours, clearing by 72 hours. No chemosis nor discharge were evident at 24 hours. Blanching of the conjunctiva was noted at 1 hour post-dose for 2 of the animals. Toxicity Category III; Study acceptable. (Moore, 4/19/06)
Primary dermal irritation

368-0281; 138123; "Primary Dermal Irritation Study of Metolachlor Technical in Rabbits"; (S.M. Glaza; Hazleton Wisconsin, Inc., Madison, WI; Project ID. HWI 40102429; 5/23/94); The skin of 6 New Zealand White rabbits was exposed to 0.5 ml/site, one site/animal, of Metolachlor Technical (batch no. P.111072; purity: 97.3%) for 4 hours under a semi-occlusive wrap. Erythema, grades 2 (2/6) and 1 (4/6), was noted at 30 minutes post-exposure, diminishing to grade 1 (1/6) at 24 and 48 hours and clearing by 72 hours. Edema, grades 2 (2/6) and 1 (4/6), was evident at 30 minutes post-exposure, clearing by 24 hours. Toxicity Category IV; Study acceptable. (Moore, 4/19/06)

Dermal sensitization

368-0281; 138124; "Dermal Sensitization Study of Metolachlor Technical in Guinea Pigs - Closed Patch Technique"; (S.M. Glaza; Hazleton Wisconsin, Inc., Madison, WI; Project ID. HWI 40102431; 6/29/94); The skin of 5 Crl: (HA) BR guinea pigs/sex was treated with 0.4 ml/site in a Hill Top chamber, one site/animal, of Metolachlor Technical (batch no. P.111072; purity: 97.3%), undiluted, for 6 hours, once per week for 3 weeks in the induction phase. In the challenge phase, the induced animals were treated with 0.4 ml/site of the undiluted test material for 6 hours. A naive control group of 5 animals/sex was treated in the same manner. One animal in the treated group died on day 11. No signs of irritation were evident during the induction treatment period. In the challenge, 4 of the nine surviving animals in the treatment group demonstrated a positive irritation score (1 or 2) by 48 hours post-application. The naive control animals did not demonstrate an irritation response. The test material is a dermal sensitizer as evaluated in the Buehler assay. The positive control was functional. Study acceptable. (Moore, 4/19/06)

SUBCHRONIC STUDIES

Rat 4-Week Dietary Toxicity Study

209 (no record #) "Four-Week Pilot Study With Albino Rats," (IBT, 11/13/75). Metolachlor (purity unknown) was fed to "albino rats" (5/sex/group) at 0, 300, 1000, 10000, or 30000 ppm for 28 days. Diets were prepared fresh daily. Information presented for this study was two tables showing body weight and food consumption for the 28 days. At > 3000 ppm both food consumption and body weights decreased, however, it appeared 3,000 ppm was well tolerated. This test served as the basis for choice of dose range for the definitive study (035280), which was 0, 300, 1000 and 3000 ppm. No other data were provided. These data are supplementary. M. Silva, 10/6/89.

Rat Subchronic Dietary Toxicity Study

053 988462 "Three-Month Oral Toxicity Trial," (The Ongoing Research and Breeding Center, 3/1/74). Metolachlor Technical (93.8% pure, batch #: CGA 24 705) was fed, in diet for 13 weeks to Sprague-Dawley (A) rats at 0 (vehicle = alcohol; 30/sex) or Group I - 100 ppm (20/sex) from week 0 to 10 and 2000 ppm from week 10 to 13 (10/sex). Group II - 300 ppm (20/sex) for 13 weeks and Group III - 1000 ppm from week 0 to 13 (20/sex) and using additional animals, 1000 ppm from week 0 to 10 (10/sex) and 2000 ppm from week 10 to 13. At the end of week 13, controls (10/sex) and 2000 ppm (10/sex) animals were kept for recovery, then sacrificed at week 17. NOEL = 2000 ppm (no effects observed at any dose level). No adverse effect. This study is supplementary to 035280. M. Silva, 10/11/89.
Dog Subchronic Dietary Toxicity Study

060 988465 "Three-Month Oral Toxicity Test of CGA 24 705 in Dog," (The Oncins Research and Breeding Center, 3/1/74). Metolachlor technical (93.8% pure) was fed in diet for 15 weeks (plus a 4-week reversibility trial) to beagle dogs (4/sex/group) at 0 (vehicle = water), 50 (from week 1 to 9), 150, 500 and 1000 (from week 9 to 15). Dogs from the 0 and 1000 ppm groups were used for the reversibility trial. **No adverse effect indicated.** NOEL > 1000 ppm (no significant effects were observed at any dose level). This study is supplementary to 044404 and 071538. M. Silva, 11/2/89.

Dog Six-Month Chronic Oral Toxicity Study

161 044404 (with rebuttal and additional information in -196 055162): "Six-Month Chronic Oral Toxicity Study in Beagle Dogs," IRDC, 5/21/80. Metolachlor technical, 96.3% pure, in the feed at 1000, 300, 100, or 0 ppm to 6-8/sex/level for 6 months, with 4 week recovery of 2/sex at 1000 or 0 ppm. **NO ADVERSE EFFECT,** slight serum alkaline phosphatase and liver weight changes, NOEL=300 ppm; Unacceptable but upgradable only as subchronic in prior review (Choy, 10/10/86); **UNACCEPTABLE** and not upgradable for chronic data requirement in second review - no MTD or target organ toxicity. F. Martz, 1/7/88.

Mouse 4-Week Dietary Toxicity Study

209 (no record #) "28-Day Mouse Pilot Study With CGA-24705 (IBT #: 622-07857)." (IBT, 1975). Metolachlor (purity & grade unspecified) was fed to albino mice (unspecified strain) in diet for 28 days (5/sex/group) at 0 (vehicle unspecified), 100, 300, 1000, 3000, 10000, 30000 or 100000 ppm. All animals treated at 100000 ppm died in the first week of treatment, however no animals treated at lower doses experienced mortalities. Growth and food consumption was normal in animals treated at < 3000 ppm. Body weight loss was observed in animals fed > 10000 ppm. It was suggested to Ciba-Geigy by IBT that dietary levels for the chronic mouse study (oncogenicity study 988476-78) be 0, 300, 1000 and 3000 ppm. These data are supplementary and consist of summary data only. M. Silva, 11/1/89.

Rabbit 21-Day Repeated Dosing Dermal Toxicity Study

368-282, 298; 138125, 138558; "21- Day Dermal Toxicity Study in Rabbits" (F. Mastrocco, et. al., Pharmaceutical Div., Ciba-Geigy Corp., Summit, NJ, Report # 86141, 11/16/87). Metolachlor Technical (FL 841697, batch P.304015, 96.4% purity) was administered dermally to intact skin of rabbits at daily doses of 0, 10, 100, or 1000 mg/kg for 6 hours/day for 21 consecutive days. 5 New Zealand white rabbits/sex/dose were used. All animals survived the study without any treatment-related clinical signs or changes in body weight. Erythema (grade 1 or 2) and dry skin at application site were reported in all treated animals as early as days 4 and 6, respectively, and throughout the study. Fissuring of the skin was observed in 1/5 low dose and 2/5 mid dose females on days 11 and 12. Also, fissuring was noted in 2/5 mid dose males between days 8 and 18 and in all high dose animals between days 6 and 21. Necropsy revealed increased relative liver weights in high dose males and relative kidney weights in high dose females. Histopathology indicated increased incidence of hyperkeratosis in all treated males and in mid and high dose females. NOAEL(M/F) = 1000 mg/kg/day [No adverse effects]. Dermal NOEL (M/F) < 10 mg/kg/day (dermal effects); Systemic NOEL (M/F) = 100 mg/kg/day (increased relative liver and kidney weights). **Acceptable** (Leung, 8/29/97)
CHRONIC STUDIES

Chronic, rat
** 144-150, 209 035280-035286 "Two Year Chronic Toxicity and Oncogenicity Study With Metolachlor in Albino Rats," (Hazleton Raltech, Inc., 5/2/83). Metolachlor technical (95.4%) tested in the diet at 0, 30, 300 and 3000 ppm for 24 months; 60/sex/group; 10/sex/group at 0, and 3000 ppm for recovery study at 12-13 months. Systemic NOEL = 300 ppm (decrease in body weight in females at 3000 ppm; increased liver and testes weight in males and cholesterol (both sexes) at 3000 ppm. **Possible adverse effect.** Oncogenic NOEL = 300 ppm (increase in eosinophilic foci of hepatocellular alteration (both sexes) at 3000 ppm; increase in neoplastic liver nodules in males and females at 3000 ppm--24 months--statistically significant in females). This study was initially reviewed as unacceptable (Apostolou, 9/26/85 and Choy, 10/20/86) as a combined study but acceptable as an oncogenicity study only (M. Silva, 3/21/88). Upon submission of new information (368-209) and rebuttal discussion of 2/21/89 regarding the necessity of an ophthalmological exam, the study is now complete and **acceptable** as a combined (chronic & oncogenicity) study. M. Silva, 10/30/89.

** 210 071537 "Two-Year Chronic Oral Toxicity Study With CGA-24705 Technical in Albino Rats," (IBT, 2/9/79--EPA Supplemental). Metolachlor technical (Batch #: FL-750227; 99.9% and FL-752105; 96.5%) was fed in diet to Charles River CD rats at 0, 30, 300, 1000 and 3000 ppm for 24 months. **Possible adverse effect.** NOEL = 1000 ppm (decreased body weight, increased incidence of hepatocellular hypertrophy in males, hepatocellular carcinoma and cystic cholangioma in females). This study is supplementary to 035280. M. Silva, 11/7/89.

Chronic, dog
** 211, 298; 071538, 138560; "Chronic Toxicity Study in Dogs," (Hazelette, J.R., CIBA-GEIGY Corporation, Division of Toxicology/Pathology and Met Path Laboratories, Laboratory Study Number 862253, 1/23/89). Metolachlor technical (97% purity, Lot #: FL861768) was administered in feed at concentrations of 0 (vehicle = acetone), 100, 300 or 1000 ppm to Beagle dogs (4/sex/group). In addition, after 52 weeks of treatment, a 4 week recovery group (2/sex/group) was included. NOEL = 300 ppm (Significant increases were observed in mean alkaline phosphatase levels in females at 1000 ppm. Significant decreases in bodyweight gain and food consumption was observed in both sexes at 1000 ppm.) NOAEL = 1000 ppm (No significant effects were observed at any dose level.) **No adverse effect indicated.** Acceptable. (Kishiyama & Silva, 12/4/90).

Oncogenicity, rat
See Rat Chronic above.

Oncogenicity, mouse
** 151-154, 209 035287-90 "Carcinogenicity Study With Metolachlor in Albino Mice," (Hazleton Raltech, Inc., 8/31/82). Metolachlor technical (purity = 96.4%) was tested in diet at 0, 300, 1000 and 3000 ppm for 24 months (52/sex/group) with an additional 16/sex/group for samples at 8, 12 and 18 months. **No adverse effect.** NOEL = 1000 ppm (decrease in body weight, both sexes; increase in AST, ALT and alkaline phosphatase in males and increase in urine protein; decrease in spleen and seminal vesicle weight in males and uterus weight in females; possible increase in nodular hyperplasia in liver in males). There was no dose-related increase in neoplasms. Previously reviewed as unacceptable (Apostolou, 9/27/85 and Choy, 10/21/86), upon submission of the requested information (justification of dose selection), the study is now **acceptable.** M. Silva, 11/2/89.
054-055, 988476, 988478 "Carcinogenicity Study with CGA-24705 Technical (Metolachlor) in Albino Mice, Final Report." (IBT, 12/15/77) Metolachlor (99.9 and 96.5%) given in the diet at 0, 30, 1000 or 3000 ppm for 18 months (males) or 20 months (females); 50/sex/group; no consistent toxicological effects noted, MTD may not have been achieved; onco NOEL>3000 ppm; unacceptable; not upgradeable (no analysis of dosing material, no justification of dosing levels, food consumption not measured, body weights not recorded for first 4 months, no hematology data, incomplete histopathology). Gee, 4-22-85.

GENOTOXICITY

Gene mutation
051 988487 "Salmonella/Mammalian-Microsome Mutagenicity Test with CGA 24705 (Test for Mutagenic Properties in Bacteria) (Technical Metolachlor)." (Ciby-Geigy, 8/30/76) Metolachlor (purity unspecified); tested at 0, 10, 100, 1000 or 10,000 ug/0.1 ml on Salmonella strains TA 98, 100, 1537 and 1538 with S9; no indication of increased mutation frequency; unacceptable; possibly upgradeable (data on positive controls not included, test article purity not indicated, incubation time not indicated, inadequate description of preparation of the S9). Gee, 4-19-85.

** 166, 044413 "L5178Y/TK+- Mouse Lymphoma Mutagenicity Test, CGA 23705 (Metolachlor) Technical, Final Report." (Ciba-Geigy, 12/5/84) Metolachlor (95.5%) tested at 10.5 to 280 nl/ml with S9 activation and 9.5 to 190 nl/ml without S9 activation on mouse lymphoma cells L5178Y/TK++; 4 hours exposure. No adverse effect. Initially reviewed as unacceptable (W. Choy, 9/25/86) based on a single trial without S9 activation. Upon reconsideration, the study is upgraded to acceptable, based upon the repeat trial with activation. Gee, 4/6/88.

Chromosome damage
050, 988488 "Dominant Lethal Study on CGA 24705 Technical Mouse (Test for Cytotoxic/Mutagenic Effects on Male Germinal Cells) Also Addendum Included (Metolachlor)." Ciba-Geigy 9/8/76) Metolachlor (purity unspecified); tested at 0, 100 and 300 mg/kg on albino NMR1-derived mice in dominant-lethal assay; single dose by oral gavage; 20 males/group; 1 male/2 females for 1 week with 6 pairing periods; no evidence of adverse effect; unacceptable; not upgradeable (no evidence of toxicity at highest dose, purity of test article, analysis of dosing solution, no positive controls, only two dose levels, frequency of weighings and observations not clear, body weight data missing). Gee, 4-19-85.

**166, 209 044409 "Nucleus Anomaly Test in Somatic Interphase Nuclei of Chinese Hamster, Final Report," (Ciba-Geigy, 10/26/84). Metolachlor technical (95.9% pure) was administered orally by gavage at 0, 1250, 2500 and 5000 mg/kg (limit test) on two consecutive days to Chinese hamsters (3/sex/group) for micronucleus and polyploidy induction assays (1000 bone marrow cells/animal scored). Sampling time was 24 hours after the last dosing. No adverse effect. Previously reviewed as unacceptable (Choy, 9/26/86; Gee, 4/6/88--no justification for sampling time or for number of animals used), upon receipt of the requested information, the study has been upgraded to acceptable. M. Silva, 11/8/89.

DNA damage or miscellaneous effects
166 044411 "Autoradiographic DNA Repair Test on Human Fibroblasts, CGA 241705 (Metolachlor)Technical." (Ciba-Geigy, 11/20/86) Metolachlor (95.9%) tested in in vitro UDS assay at 0, 0.125, 0.625, 3.125 and 15.625 nl/ml on human fibroblasts; 5 hours exposure
without S9 activation; no adverse effect; unacceptable; not upgradeable (insufficient cytotoxicity, no activated trial). Choy, 9-26-86.

** 166 044412 "Autoradiographic DNA Repair Test on Rat Hepatocytes, CGA 24 705 (Metolachlor) Technical." (Ciba-Geigy, 11/20/86) Metolachlor (95.9%) tested in in vitro UDS assay at 0, 0.25, 1.25, 6.25 and 31.25 nl/ml on rat hepatocytes; 5 hours exposure; no adverse effect; acceptable. Choy, 9-26-86.

** 368-0385; 296467; “Evaluation of Metolachlor Technical in the In Vivo/In Vitro Rat Hepatocytes Unscheduled DNA Synthesis Assay” (Hazleton Biotechnologies Company, Kensington, Maryland; Study No. 20991; 08/10/88); Three Sprague Dawley rats/sex were dosed with 3, 30, 300 or 450 mg/kg of Metolachlor technical (FL# 841697). Hepatocytes were harvested from the rats at 2 and 15 hours for UDS and at 24 and 48 hours for S-phase DNA synthesis. For negative control, 3 rats/time points were dosed with vehicle and harvested at 15 hours (UDS) and 48 hours (S-phase). For positive controls, 3 rats/sex/dosing/timepoints were treated with 10 mg/kg or 20 mg/kg of dimethylnitrosamine (DMN) and harvested at 4 hours (UDS), 24 hours or 48 hours (S-phase). Upon recovery of the hepatocytes, a primary culture was established and the cells were exposed to $^3$H-thymidine (1 µCi/ml) for 18-19 hours. Fifty cells per coverslip from the triplicate coverslips were evaluated to calculate the mean net nuclear grain count. There was no treatment-related increase in unscheduled DNA synthesis in male and female rats. However, there was an increase in the percent of S-phase cells in hepatocytes isolated from female rats treated with the test item at the highest two doses. Hepatocytes isolated from male rats treated with the test item displayed a sporadic small increase in the S-phase cells. The positive controls were functional. No adverse effect indicated. Study acceptable. (Pasupuleti and Leung, 01/26/17)

REPRODUCTIVE TOXICITY, RAT

** 163-165, 209 044406-044408 "Two Generation Reproduction Study in Albino Rats With Metolachlor Technical," (ToxiGenics, 8/31/81). Metolachlor technical (95.4% pure) was tested in diet at 0, 30, 300 and 1000 ppm in a two generation, one litter/generation study (15 males/group & 30 females/group). No adverse effect. Reproductive NOEL = 300 ppm (decrease in food consumption in F1 females; decrease in F1 & F2 progeny body weights). Previously reviewed as unacceptable (Choy, 10/7/86) because dose level was not justified and it was believed that a MTD had not been reached, upon submission of requested information, the study has been upgraded to acceptable. M. Silva, 10/31/89.

049, 988486 "Three-Generation Reproduction Study with CGA-24705 Technical (Metolachlor) in Albino Rats, Final Report." (IBT, 12/15/77) Metolachlor (96.5%) tested in the diet for a 3-generation, 2 litters/generation study at 0, 30, 300 or 1000 ppm; 8 males/group, 16 females/group; reduced mating index at all dose levels; unacceptable; not upgradeable (inadequate number of animals per group; no justification of dose levels, dosing schedule differs from guidelines, inadequate histopathology, disease and mortality problems). Gee, 4-22-85.

DEVELOPMENTAL TOXICITY

Rat

050, 988480, 988481 "Reproduction Study CGA-24705 Technical (Metolachlor), Rat Segment II (Test for Teratogenic or Embryotoxic Effects." (Ciba-Geigy, 6/21/76) Metolachlor (purity unspecified) given by gavage at 0, 60, 180 or 360 mg/kg/day on days 6-15 of gestation; 25/group; maternal toxicity not noted at high dose; maternal, teratogenic and fetotoxic
NOELs>360 mg/kg; unacceptable; possibly upgradeable with justification of dosing levels, purity of test article, analysis of dosing solution, fetuses not sexed, corpora lutea not counted. Gee, 4-19-85.

** 162 044405 "Embryo/Fetal Toxicity and Teratogenic Potential Study of CGA-24705 (FL-841697) (Metolachlor) Administered Orally via Gavage to CRL:COBS CD (SD)br Presumed Pregnant Rats, Final Report." (Argus, 8/6/85) Metolachlor (96.4%) given by gavage at 0, 30, 100, 300 and 1000 mg/kg/day on 6-15 days of gestation; 20 to 24 pregnant animals/group; maternal toxicity noted at 1000 mg/kg/day (animal death and adverse clinical signs); maternal NOEL=300 mg/kg/day; developmental NOEL=300 mg/kg/day; no adverse effect; acceptable. Choy, 10-1-86.

Rabbit
**155 035291 "Teratogenic Potential of CGA-24705 (Metolachlor) in New Zealand White Rabbits (Segment II Evaluation)." (Argus, 7/25/80) Metolachlor (95.4%) given by gavage at 0, 36, 120 or 360 mg/kg/day on days 6-18 of gestation. Maternal NOEL = 36 mg/kg (decreased food consumption, miosis and decreased body weight gain at 120 and 360 mg/kg; blood in cage pan at 360 mg/kg). Developmental NOEL = 360 mg/kg (no consistent fetotoxic or teratogenic effect noted). This study was originally reviewed as unacceptable (analysis of dosing solution, pup brains not examined--Apostolou, 3/30/85). Upon receipt and evaluation of information requested by CDFA (196 055161), this study is now acceptable. F. Martz and M. Silva, 3/15/88.

NEUROTOXICITY
Acute neurotoxicity, rat
Study not submitted.

90-day neurotoxicity, rat
Study not submitted.

Developmental neurotoxicity, rat
Study not submitted nor required at this time.

Delayed neurotoxicity, hen
Study not submitted nor required at this time.

IMMUNOTOXICITY
Study not submitted.

ENDOCRINE DISRUPTOR STUDIES
Study not submitted nor required at this time.

(S)-Metolachlor

ACUTE STUDIES
Acute oral toxicity, rat
52245-027; 154022: Acute Oral Toxicity Study of CGA-77102 915EC-B in Rats; (S.M. Glaza; Corning Hazleton, Inc., Madison, WI; Project I.D. 60504750; 9/20/96); Five rats/sex/group
(unless otherwise indicated) were dosed orally, by gavage, with 500 (F only), 1000 (F only),
2000 or 5000 mg/kg of CGA-77102 915EC-B (A.I.: 83.3%). Two females died in the 1000 mg/kg
group. In the 2000 mg/kg group, one female died. One male and 4 females died in the 5000
mg/kg group. Clinical signs included staggered gait, tremors, hypoactivity, prostration,
mydriasis, excessive salivation, dyspnea, lacrimation, yellow stained anogenital area, and tonic
convulsions. Yellow milky fluid was noted in the stomach and the intestines of the decedents.
LD50 (95% confidence limits): (M) > 5000 mg/kg, (F) 2515 (1205 to 5249) mg/kg; Toxicity
Category III; Study acceptable. (Moore, 7/7/97)

Acute dermal toxicity
52245-028; 154023; Acute Dermal Toxicity Study of CGA-77102 915EC-B in Rabbits; (S.M.
Glaza; Corning Hazleton, Inc., Madison, WI; Project I.D. CHW 60504751; 8/15/96); The skin of 5
rabbits/sex was exposed to 2000 mg/kg of CGA-77102 915EC-B (A.I.: 83.3%) for 24 hours
under an occlusive wrap. No mortalities resulted from the exposure. Moderate to severe dermal
irritation was evident at the site of application. No treatment-related lesions were noted in the
necropsy. LD50 (M/F) > 2000 mg/kg; Toxicity Category III; Study acceptable. (Moore, 7/7/97)

Acute inhalation toxicity, rat
52245-029; 154024; Acute Inhalation Toxicity Study in Rats; (J. Bennick; Stillmeadow, Inc.,
Sugar Land, TX; Study No. 2982-96; 8/20/96); Five rats/sex were exposed to 2.61 mg/l
(analytical) of CGA-77102 915EC-B (A.I.: 83.9%) nose-only for 4 hours. The mean MMAD
(GSD) was 3.43 (2.05) um. No mortality resulted from the exposure. Clinical signs included
piloerection, decreased activity, nasal discharge, salivation, respiratory gurgle and anogenital
staining with urine and feces. The lungs were light red in color with white lumps diffuse
throughout the tissue. LC50 (M/F) > 2.61 mg/l; Toxicity Category IV; Study acceptable.
(Moore, 7/10/97)

Primary eye irritation, rabbit
52245-030; 154025; Primary Eye Irritation Study of CGA-77102 915EC-B in Rabbits; (S.M.
Glaza; Corning Hazleton, Inc., Madison, WI; Project I.D. CHW 60401688; 6/20/96); A dose of
0.1 ml of CGA-77102 915EC-B (A.I.: 83.3%) was instilled in the eyes of nine rabbits (6 eyes
unrinsed). Grade 1 corneal opacity was evident in the eyes of all animals at 24 hours, clearing
by 4 days. Likewise, grade 1 iritis was noted in the eyes of all animals at 24 hours, clearing by 7
days. Grade 2 redness was observed in the conjunctiva of all of the animals at 24 hours, all
positive scores clearing by 7 days. Chemosis, grades 3 (1/6), 2 (3/6) and 1 (2/6), was evident
at 24 hours, all positive scores clearing by 4 days. Discharge, grades 3 (1/6), 2 (2/6) and 1 (2/6)
at 24 hours, clear by 4 days. Toxicity Category III. Study acceptable. (Moore, 7/14/97)

Primary dermal irritation
52245-031; 154045; Primary Dermal Irritation Study of CGA-77102 915EC-B in Rabbits; (S.M.
Glaza; Corning Hazleton, Inc., Madison, WI; CHW 60401687; 6/26/96); The skin of six rabbits
was exposed for 4 hours under a semi-occlusive wrap to 0.5 ml/site of CGA-77102 915EC-B
(A.I.: 83.3%). Grade 1 erythema was noted for all of the animals at the end of the exposure.
Grade 1 erythema persisted in three of the animals through 72 hours. Erythema, grade 1, was
evident in two animals at 4 days and one animal at 7 days, clearing by 14 days. Grade 1 edema
was noted for two animals at the end of the exposure and one animal at 24 hours, clearing by 48
hours. Toxicity Category IV; Study acceptable. (Moore, 7/15/97)

Dermal sensitization
Study not submitted.
SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Study
034; 154051; A13-Week Oral Toxicity Study in Rats; (J.C.F. Chang; Pharmaceuticals Division, Ciba-Geigy Corporation, Summit, NJ; Study No. F-00191; 2/21/95); Ten rats/sex/group received CGA-77102 Technical (purity: 89.6%, 93.7% being the S-isomer) in the diet at doses of 0, 30, 300, 3000 or 10000 ppm) (M: 0, 1.81, 17.5, 180.3, 592.8 mg/kg/day, F: 0, 2.24, 23.0, 230.2, 730.5 mg/kg/day (calculated by reviewer)) for 13 weeks. An additional 5 animals/sex in the control and 10000 ppm groups were maintained for a recovery period of 4 weeks. No mortality resulted from the treatment. Body weight gain was reduced in a dose-related manner for both males and females (3000 and 10000 ppm, p<0.01). The apparent target organ was the liver. Mean relative liver/body weight ratio was significantly increased in all of the treatment groups for the males and the 3000 and 10000 ppm groups for the females (p<0.05 or p<0.01). The increase in the relative liver weight for the two lower dose male groups appeared to correspond to the increased incidence of glycogen vacuolation noted in these two groups alone. γ-Glutamyl transpeptidase activity was present in the serum of both sexes of the 10000 ppm group (p<0.01). The enzyme activity was not evident at the end of the recovery period. Intracytoplasmic inclusions were noted in the hepatocytes of 1 male in the 3000 ppm group and 7 males in the 10000 ppm group at the end of the 13 week treatment period. These lesions were not evident in the 10000 ppm recovery group. An anomalous dose-response decrease in SGPT activity was noted for both sexes (3000, 10000 ppm, p<0.01). A similar less pronounced effect was noted for SGOT. Reduced activity levels were noted for both enzyme activities in the high dose group even after the end of the recovery period. No adverse effect indicated. NOEL: 300 ppm ((M:17.5 mg/kg/day, F:23.0 mg/kg/day) (based upon reduced body weight gain for 3000 and 10000 ppm groups); NOAEL: 300 ppm; Study Acceptable. (Moore, 7/22/97)

Dog Subchronic Dietary Toxicity Study
033; 154049; 90-Day Dietary Toxicity Study in Dogs; (J.C.F. Chang; Ciba Environmental Health Center, Farmington, CT; Study No. F-00193; 6/14/95); CGA-77102 Technical (purity: 95.4%) was administered in the diet of four dogs/sex/group at doses of 0, 300, 500, or 1000 ppm for 16 weeks. An additional group was dosed with 2000 ppm of the test material for 2 weeks followed by an additional 14 weeks of dosing at 700 mg/day in capsules due to a problem in the palatability of the food (test material uptake: (M) 0, 9.0, 15.1, 31.1, and 62 mg/kg/day, (F) 0, 10.0, 17.2, 31.5, 74 mg/kg/day). No mortalities resulted from the exposure. Any effects upon body weight were apparently due to the palatability problem. No target organ was affected by the treatment. There was no dose-related response evident in the hematology, clinical chemistry or urinalysis data. Although an increase in the mean serum alkaline phosphatase activity was noted in the 2000 ppm/700 mg/kg/day group for both sexes (not statistically significant), no hepatic lesions were apparent histologically. Mean organ weights were not apparently affected by treatment. Histological examination of other tissues did not reveal any significant lesions. No adverse effect indicated. NOEL (M/F): 2000 ppm/700 mg/day (M: 62 mg/kg/day, F: 74 mg/kg/day). Study acceptable. (Moore, 7/25/97)

CHRONIC STUDIES

Chronic, rat
Study has not been submitted nor is required at this time.

Chronic, dog
Study has not been submitted nor is required at this time.
Oncogenicity, rat
Study has not been submitted nor is required at this time.

Oncogenicity, mouse
Study has not been submitted nor is required at this time.

GENOTOXICITY

Gene mutation
**038; 154056; "CGA-77102 Technical / Salmonella and Escherichia / Mammalian-Microsome Mutagenicity Test"; (Th. Hertner; Ciba-Geigy Ltd., Basle, Switzerland; Lab Study No. 941060; 6/9/95); CGA-77102 Technical (Batch No. V.4673/7; purity = 95.6%), dissolved in DMSO; S. typhimurium TA98, TA100, TA102, TA1535, TA1537, and E. coli WP2uvrA, with and without activation (Aroclor 1254-induced rat liver S9 fraction), by plate incorporation; dose ranges were 312.5-5000 ug/plate in original assay and 312.5-5000 or 78.13-1250 ug/plate in the confirmatory assay; 3 plates/strain/dose level; 48 hr incubation; no adverse effects; no increase in reversion rates; positive controls were functional; Acceptable. (Duncan, 8/6/97)

Chromosome damage
**037; 154055; "CGA-77102 Technical / Micronucleus Test, Mouse / (OECD Conform)"; (Th. Hertner; Ciba-Geigy Ltd., Basle, Switzerland; Lab Study No. 941061; 5/22/95); CGA-77102 Technical (Batch No. V.4673/7; purity = 95.6%), dosed as a mixture in arachis oil to groups of 5 Tif:MAGf(SPF) mice/sex/treatment; 0 (vehicle), 2000 mg/kg with termination after 16, 24, or 48 h; 500, 1000 mg/kg with termination at 24 h; 1000 polychromatic erythrocytes/animal were scored for micronuclei; no adverse effects were observed; no increase in micronucleated PCEs was observed; cyclophosphamide was functional in the assay. Acceptable. (Duncan, 8/6/97)

DNA damage or miscellaneous effects
**039; 154058; "CGA-77102 Technical / In Vivo/In Vitro Unscheduled DNA Synthesis in Rat Hepatocytes"; (Th. Hertner; Ciba-Geigy Ltd., Basle, Switzerland; Lab Study No. 941062; 6/8/95); CGA-77102 Technical (Batch No. V.4673/7; purity = 95.6%), dosed as mixtures in arachis oil to groups of Tif: RAIf(SPF) rats at 0 (vehicle), 500, or 1500 mg/kg; groups of 3
animals/sex/dose level were sacrificed at 2 h or 15 h after treatment; hepatocytes were labeled in vitro with 3H-Tdr; 50 cells on each of 2 slides/animal were counted; the effect of the test article on replicative DNA synthesis was evaluated in a separate assay at doses of 500, 1500 or 5000 mg/kg (males) and 500, 1500 or 3200 mg/kg (females) with isolation of hepatocytes 15 or 38 hrs after treatment; no adverse effects; no increase in net nuclear grain counts for UDS; cells in S-phase in females at 1500 mg/kg was increased at 15 and 38 hours; toxicity was observed at dose levels greater than 1500 mg/kg; positive control materials were functional; Acceptable. (Duncan, 8/7/97)

REPRODUCTIVE TOXICITY, RAT
Study has not been submitted.

DEVELOPMENTAL TOXICITY

Rat
**036; 154054; "CGA-77102 Technical / Rat Oral Teratogenicity " (S. Khalil; Ciba-Geigy Corp., Greensboro, NC; Lab Report No.941058;8/21/95); CGA-77102 Technical (Batch No. V.4673/7; purity = 95.6%), dosed as aqueous 0.5% carboxymethylcellulose suspensions to groups of 24 mated SD rats (Tif: RAIf(SPF)) at dose levels of 0 (vehicle), 5, 50, 500, or 1000 mg/kg/day on days 6-15 of gestation; no unscheduled deaths or failed pregnancies; reduced food consumption and body weight gain in high and mid-high dose dams during the dosing period; "pushing head through bedding" after dosing was observed in the top three dose groups; no treatment-related effects on pregnancy outcomes or the incidence of fetal abnormalities; no adverse effects; maternal NOEL = 50 mg/kg/day (decreased food consumption and weight gain); developmental NOEL = 1000 mg/kg/day (no effects observed); Acceptable. (Duncan, 8/5/97)

Rabbit
**035; 154053; "A Teratology Study of CGA-77102 Technical in New Zealand White Rabbits" (Pamela A. Gilles and Mary L. A. Giknis; Ciba-Geigy Corp., Pharmaceuticals Division, Summit, NJ; Lab Report No. F-00192; 4/27/95); CGA-77102 Technical (Batch No. FL-830813; purity = 89.6%), dosed as a suspension in aqueous 3% cornstarch/0.5% Tween 80 to groups of 19 artificially inseminated NZW rabbits at dose levels of 0 (vehicle), 20, 100, or 500 mg/kg/day on days 7-19 of gestation; food consumption and body weight in high-dose does decreased during the dosing period; one low-dose doe aborted her litter, one low-dose and one high-dose doe died after periods of anorexia (both had entirely or mostly resorbed litters); malformed fetuses were found in 1/16 mid-dose litters and 2/18 high-dose litters; in one high-dose litter, all five fetuses were malformed; no adverse effects; maternal NOEL = 100 mg/kg/day (decreased food consumption and weight gain); developmental NOEL = 500 mg/kg/day (no effects observed); Acceptable. (Duncan and Leung, 8/5/97)

NEUROTOXICITY

Acute neurotoxicity, rat
Study has not been submitted.

90-day neurotoxicity, rat
Study has not been submitted.

Developmental neurotoxicity, rat
Study has not been submitted nor is required at this time.
Delayed neurotoxicity, hen
Study has not been submitted nor is required.

IMMUNOTOXICITY
Study has not been submitted.

ENDOCRINE DISRUPTOR STUDIES
Study has not been submitted nor is required at this time.

METABOLITES

Metolachlor Oxanilic Acid

ACUTE STUDIES

Acute oral toxicity, rat
52245-122; 173975; “Acute Oral Toxicity in the Rat”; (H.R. Hartmann; CIBA-GEIGY Limited, Short-term Toxicology, 4332 Stein, Switzerland; Study ID. 911337; 12/12/91); Five Tif: RAI f rats/sex were dosed orally by gavage with 2000 mg/kg of CGA-51202 Technical (batch no. JD 7069/3, purity: 100%). The test material was suspended in 0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80. One male was euthanized for humane reasons on day 13. Clinical signs including piloerection, hunched posture, exophthalmos, dysnea, reduced locomotor activity and respiratory sounds were noted. The male that was euthanized had a distended abdomen which was first noted on day 9. In the necropsy examination, the deceased male had an inflated stomach. Otherwise, no treatment-related lesions were noted. LD50 (M/F) > 2000 mg/kg; Toxicity Category III; Study acceptable. (Moore, 5/6/03)

Acute dermal toxicity
52245-123; 173976; “Acute Dermal Toxicity in the Rat”; (H.R. Hartmann; CIBA-GEIGY Limited, Short-term Toxicology, 4332 Stein, Switzerland; Study ID. 911338; 12/12/91); The skin of five Tif: RAI f rats/sex was exposed to 1333 mg/kg of CGA-51202 Technical (batch no. JD 7069/3, purity: 100%) for 24 hours under a semi-occlusive wrap. The test material was moistened with 0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80. Due to the high liquid adsorption of the test material, the dosage was considered to be the highest level which could be reasonably achieved. No deaths resulted from the treatment. Clinical signs included piloerection and hunched posture which cleared by day 3. No lesions were evident in the necropsy examination. LD50 (M/F) > 1333 mg/kg; Toxicity Category II; Study acceptable. (Moore, 5/6/03)

Acute inhalation toxicity, rat
Study not submitted.

Primary eye irritation, rabbit
52245-124; 173977; “Acute Eye Irritation/Corrosion Study in the Rabbit”; (Ch. Hagemann; CIBA-GEIGY Limited, Short-term Toxicology, 4332 Stein, Switzerland; Study ID. 911339; 3/27/92); The eyes of 3 New Zealand White rabbits were treated by ocular instillation with 0.1 ml (38 mg)/eye of CGA-51202 Technical (batch no. JD 7069/3, purity: 100%). Corneal opacity, grades 3 (2/3) and 2 (1/3), was evident at 24 hours, persisting in all 3 animals with a score of 1 at 7 days, clearing in 2 animals by 14 days and the third by day 21. Iritis, grade 1 (3/3), was noted at 24 hours, persisting with a score of 1 in one animal at 7 days, clearing by 10 days.
Conjunctival redness, grade 3 (3/3), was evident at 24 hours, persisting with a score of 2 (3/3) at 7 days, clearing in all animals by day 21. Chemosis, grades 4 (1/3), 3 (1/3) and 2 (1/3), was noted at 24 hours, persisting with a score of 1 (2/3) at 7 days, clearing by 14 days. Toxicity Category I; Study acceptable. (Moore, 5/8/03)

Primary dermal irritation
52245-125; 173978; “Acute Dermal Irritation/Corrosion Study in the Rabbit”; (Ch. Hagemann; CIBA-GEIGY Limited, Short-term Toxicology, 4332 Stein, Switzerland; Study ID. 911340; 12/11/91); The skin of 3 New Zealand White rabbits was treated with 0.5 g/site, one site/animal, of CGA-51202 Technical (batch no. JD 7069/3, purity: 100%) for 4 hours under a semi-occlusive wrap. The test material was moistened with 0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80. Erythema, grade 1 (2/3), was noted at 1 hour post-exposure, clearing by 24 hours. No edema was evident throughout the 72 hour observation period. Toxicity Category IV; Study acceptable. (Moore, 5/8/03)

Dermal sensitization
52245-126; 173979; “Skin Sensitization Study in the Guinea Pig, Optimisation Test”; (Ch. Hagemann; CIBA-GEIGY Limited, Short-term Toxicology, 4332 Stein, Switzerland; Study ID. 911341; 5/18/92); In the induction phase, ten Pirbright White guinea pigs/sex/group received intradermal injections of 0.1 ml of either physiological saline or a 0.1% (w/w) solution of CGA-51202 Technical (batch no. JD 7069/3, purity: 100%) in physiological saline ten times over a 3 week period. During the 2nd and 3rd weeks, Bacto adjuvant (Freund’s complete adjuvant) was incorporated into the vehicle (vehicle:adjuvant, 1:1 (v/v)). After a two week interlude, all of the animals in both groups were challenged with a 0.1 ml intradermal injection of 0.1% (w/w) solution of the test material in physiological saline. After another week interlude, each animal received an epidermal challenge of a 10% (w/w) preparation of the test material in vaseline for 24 hours under an occlusive wrap. The control group did not demonstrate a positive response to either the intradermal injections or the epidermal applications of the test material. Five of the 20 animals in the treated group demonstrated a positive response to the intradermal challenge and 11 of the 20 animals a had positive response (a score of > 1 for erythema and/or edema) by 48 hours post-exposure in the epidermal challenge. The test material is a dermal sensitizer as demonstrated in the Optimization Test. The positive control was functional. Study acceptable. (Moore, 5/9/03)

SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Study
52245-127; 173980; “3-Month Oral Toxicity Study in Rats (Administration in Food)”; (M. Schneider; CIBA-GEIGY Limited, Short/Long-term Toxicology, 4332 Stein, Switzerland; Study ID. 911344; 7/23/92); Ten Tif: RAIf (SPF) rats/sex/group received 0, 300, 1000 or 15000 ppm of CGA-51202 Technical (batch no. JD 7069/3, purity: 100%) in the diet for 3 months ((M) 0, 18.65, 62.13, 1002 mg/kg/day, (F) 0, 20.63, 67.27, 1018 mg/kg/day). No deaths resulted from the treatment. There were no treatment-related effects upon mean body weights. Mean food consumption was reduced for the 15000 ppm males for the 1st week of the study, returning to the control level by the 2nd week. Although individual parameters for the hematology and clinical chemistry of the 15000 ppm group were statistically significantly different from those of the controls, there was no apparent dose-related response. There was no treatment-related effect upon the ophthalmology or urinalysis results. Although the mean absolute liver weight of the 15000 ppm males was less than that of the control (p<0.05), the relative weight was not
significantly affected. The mean relative adrenal weight for the 15000 ppm females was greater than that of the control (p<0.05). There was, however, no apparent histological effect upon the organ. Overall, the microscopic examination of the tissues did not reveal any histological lesions. **No adverse effect indicated. NOEL: (M/F) > 15000 ppm ((M): 1002 mg/kg/day, (F) 1018 mg/kg/day) (based upon the lack of a treatment-related effect on the 15000 ppm group); Study acceptable. (Moore, 5/13/03)**

**Dog Subchronic Oral Toxicity Study**

**52245-0204; 296506 “Oxanilic Acid Metabolite (CGA 51202): 90-Day Oral Toxicity Dogs”**

(Central Toxicity Laboratory, Cheshire, UK; Study PD1240, 03/16/2004). CGA 51202 (Batch No. KI 4352/6, purity, 100 % (w/w)) was administered orally by capsule to 4 beagle dogs/sex/dose at dose levels of 0 (diet only), 5, 50, 500 or 1000 mg/kg/day for 90 days. No mortalities occurred during the study interval. An increased incidence of salivation in males at 500 and 1000 mg/kg was observed and no other clinical signs were observed. Faint circular corneal opacity was observed in one male and one female at 1000 mg/kg during week 13. There were no treatment-related effects on bodyweights and food consumption. Hematological investigations revealed a treatment-related increase in mean platelet count in males at weeks 4 and 8 and for females at weeks 8 and 13 when compared to controls at 1000 mg/kg without any treatment-related changes in prothrombin and activated partial thromboplastin times. Mean monocyte counts were higher for females at 1000 mg/kg at week 13. Blood clinical chemistry investigations revealed a decrease in mean plasma urea in males and females at 1000 mg/kg at week 4 and 13, respectively. Plasma creatinine was higher in males at all doses at week 8 and 13. Plasma total protein and albumin were lower in males and females at 500 mg/kg and 1000 mg/kg. Plasma cholesterol was higher in females at 1000 mg/kg. Group mean plasma triglyceride was higher in treated males and group mean plasma total bilirubin was lower in females at 500 and 1000 mg/kg during weeks 4 and 8. Plasma alkaline phosphatase (ALP) was higher in females at 500 mg/kg (week 4 and 8) and in males at 500 (week 8) and 1000 mg/kg (all intervals). Group mean creatine kinase appeared to be lower in females (all doses, week 4) that was considered to be unrelated to treatment. Group mean plasma calcium was lower in males at 500 and 1000 mg/kg (week 8 and 13). Urinalysis revealed no treatment-related effects. The lower weight of left thyroid in males when compared to controls at 1000 mg/kg was considered to be unrelated to treatment as there was no effect on the weight of right thyroid in males. There were no treatment-related macroscopic and microscopic pathology findings. **No adverse effect indicated. NOAEL: (M) = 1000 mg/kg/day and (F) = 1000 mg/kg/day. Acceptable** (Pasupuleti and Leung, 01/31/17)

**Rat Developmental Toxicity Study**

**128; 173981; “CGA-51202 Technical: Rat Oral Teratogenicity”; (J.H. Marty; CIBA-GEIGY Limited, Reproduction Toxicology, 4332 Stein, Switzerland; Study ID. 911351; 11/3/92); Twenty four Tif: RAI f (SPF) mated females/group were treated orally by gavage with 0, 10, 100 or 1000 mg/kg/day of CGA-51202 Technical (batch no. JD 7069/3, purity: 100%) from day 6 through day 15 of gestation. One female in the 10 mg/kg group was euthanized in extremis on day 20. There were no treatment-related effects on mean body weight gain. Mean food consumption was reduced from day 6 through day 11 of gestation for the 1000 mg/kg group (p<0.05). There were no treatment-related effects on fetal development. **No adverse effect indicated. Maternal NOEL: 1000 mg/kg/day (based upon the lack of treatment-related effects in the 1000 mg/kg/day group); Developmental NOEL: 1000 mg/kg/day (based upon the lack of treatment-related effects in the 1000 mg/kg/day group); Study acceptable.** (Moore, 5/14/03)
GENOTOXICITY

Mutagenicity
** 130; 173983; “Salmonella and Escherichia/Liver-Microsome Test”; (Th. Hertner; CIBA-GEIGY Limited, Genetic Toxicology, Basle, Switzerland; Study ID. 911342; 3/20/92); S. typhimurium strains TA 98, TA 100, TA 1535, TA 1357, E. coli strain WP2 uvrA were treated for 48 hours at 37° C with CGA 51202 Technical (lot no. JD 7069/3; purity: 100%) at concentrations ranging from 312.5 to 5000 μg/plate with and w/o activation in two trials. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Positive controls were functional. **Study acceptable. **(Moore, 5/15/03)

** 134; 173987; “Gene Mutation Test with Chinese Hamster Cells V79”; (B. Ogorek; Genetic Toxicology, Novartis Crop Protection AG, CH-4002 Basle, Switzerland; Study No. 981112; 1/18/99); Chinese hamster V79 cells were treated with CGA 51202 Technical (lot no. JD 7069/3, purity: 100%) at concentrations ranging from 500 to 4000 μg/ml (1st trial) or 375 to 3000 µg/ml (2nd trial) for 5 hours (activation) or 21 hours (non-activation) at 37° C. Three trials were performed with duplicate samples for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. There was no treatment-related increase in the mutation frequency for either the non-activated and activated samples. **No adverse effect indicated; the positive controls were functional. **Study acceptable. **(Moore, 5/16/03)

Chromosomal Aberration
** 129; 173982; “Micronucleus Test, Mouse”; (Th. Hertner; CIBA-GEIGY Limited, Genetic Toxicology, Basle, Switzerland; Study ID. 911343; 8/28/92); In the first test, five Tif: MAGf (SPF) mice/sex/group/time point were treated orally by gavage with 600, 1200 or 2400 mg/kg/day CGA-51202 Technical (batch no. JD 7069/3, purity: 100%) and euthanized at 16, 24, and 48 hours after dosing; in addition, 5 animals/sex/group in the 0 (vehicle control) and positive control (cyclophosphamide, 64 mg/kg) groups were euthanized at 24 hours after dosing. Analysis of the dosing preparations revealed that the actual administered dose was only 80% of the target. A second test was performed in which 5 animals/sex/group/time point were dosed with 0 (vehicle control) or 2400 mg/kg of the test material and euthanized at 24 and 48 hours post-dose. An additional 5 animals/sex/group were treated with 600 or 1200 mg/kg of the test material or the positive control and euthanized 24 hours after dosing. Bone marrow samples from the femur were examined and the percentage of PCE with a micronucleus and the ratio of polychromatic (PCE) to normochromatic erythrocytes (NCE) were determined. No treatment-related increase in the number of polychromatic erythrocytes with a micronucleus was noted. **No adverse effect indicated. The positive control was functional. **Study acceptable. **(Moore, 5/14/03)

Metolachlor Ethanesulfonic Acid

ACUTE STUDIES

Acute oral toxicity, rat
52245-098; 174006; “Acute Oral Toxicity Study in the Rat (Limit Test)”; (S. Cantoreggi; Novartis Crop Protection AG, Toxicology, 4332 Stein, Switzerland; Study ID. 981038; 6/19/98); Five Hanlbnm:WIST rats/sex were dosed orally by gavage with 5000 mg/kg of CGA-354743 Technical (batch no. KI-5408/6, purity: 98%). The test material was suspended in distilled water. No deaths resulted from the treatment. No clinical signs related to the treatment were
noted. The animals exhibited reasonable body weight gain over the course of the observation period. No lesions were evident in the necropsy examination. LD50 (M/F) > 5000 mg/kg; Toxicity Category IV; Study acceptable. (Moore, 4/17/03)

52245-117; 174025; “Acute Oral Toxicity Study in the Rat (Limit Test)”; (G. Winkler; Short-term Toxicology, Novartis Crop Protection Inc., Toxicology, 4332 Stein, Switzerland; Study ID. 951132; 12/5/95); Five Tif: RAI F (SPF) rats/sex were dosed orally by gavage with 2000 mg/kg of CGA-354743 Technical (batch no. RV-2816/1, purity: 95%). The test material was suspended in 0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80. No deaths resulted from the treatment. Hunched posture and piloerection were noted on the day of treatment with piloerection persisting through day 2 post-dose. The animals exhibited reasonable body weight gain over the course of the observation period. No lesions were evident in the necropsy examination. LD50 (M/F) > 2000 mg/kg; Toxicity Category III; Study acceptable. (Moore, 5/1/03)

Acute dermal toxicity
52245-099; 174007; “Acute Dermal Toxicity Study in the Rat (Limit Test)”; (S. Cantoreggi; Novartis Crop Protection AG, Toxicology, 4332 Stein, Switzerland; Study ID. 981039; 6/19/98); The skin of five Hanlmb:WIST rats/sex was exposed to 2000 mg/kg of CGA-354743 Technical (batch no. KI-5408/6, purity: 98%) for 24 hours under a semi-occlusive wrap. The test material was moistened with distilled water. No deaths resulted from the treatment. No systemic clinical signs or dermal irritation related to the treatment were noted. No lesions were evident in the necropsy examination. LD50 (M/F) > 2000 mg/kg; Toxicity Category III; Study acceptable. (Moore, 4/17/03)

Acute inhalation toxicity, rat
Study not submitted.

Primary eye irritation, rabbit
52245-100; 174008; “Acute Eye Irritation/Corrosion in the Rabbit”; (S. Cantoreggi; Novartis Crop Protection AG, Toxicology, 4332 Stein, Switzerland; Study ID. 981041; 6/19/98); The eyes of 6 New Zealand White rabbits were treated by ocular instillation with 0.1 ml/eye (0.66 mg/eye) of CGA-354743 Technical (batch no. KI-5408/6, purity: 98%). Corneal opacity, grades 2 (2/6) and 1 (3/6), was evident at 1 hour after dosing, persisting with grade 1 (4/6) at 24 and 48 hours, grade 1 (2/6) at 72 hours and grade 1 (1/6) at 7 days, clearing by 10 days. Iritis, grade 1 (4/6), was noted at 24 hours, persisting with grade 1 (2/6) at 48 and 72 hours, clearing by 7 days. Conjunctival redness, grades 2 (5/6) and 1 (1/6), was evident at 24 hours, diminishing to grade 1 (1/6) at 7 days, clearing by 10 days. Chemosis, grade 1 (6/6), was noted at 24 hours, clearing by day 7. Toxicity Category II. Study acceptable. (Moore, 4/17/03)

Primary dermal irritation
52245-101; 174009; “Acute Dermal Irritation/Corrosion in the Rabbit”; (S. Cantoreggi; Novartis Crop Protection AG, Toxicology, 4332 Stein, Switzerland; Study ID. 981040; 5/1/98); The skin of 6 New Zealand White rabbits was treated with 0.5 g/site, one site/animal, of CGA-354743 Technical (batch no. KI-5408/6, purity: 98%) for 4 hours under an occlusive wrap. The test material was moistened with distilled water. Erythema, grade 1 (4/6), was evident at 1 hour post-exposure, diminishing to grade 1 (2/6) at 24 hours and grade 1 (1/6) at 48 hours, clearing by 72 hours. No edema was noted over the 72 hour observation period. Toxicity Category IV. Study acceptable. (Moore, 4/17/03)
Dermal sensitization

52245-102; 174010; “Skin Sensitization in the Guinea Pig (Buehler)”; (S. Cantoreggi; Novartis Crop Protection AG, Toxicology, 4332 Stein, Switzerland; Study ID. 981042; 2/3/99); The skin of 10 Himalayan Spotted (GOHI) guinea pigs/sex was treated with 0.35 ml/site of a 80% suspension of CGA-354743 Technical (batch no. KI-5408/6, purity: 98%) in distilled water for 6 hours, once per week, for 3 weeks in the induction phase. Twenty seven days after the first induction treatment, the skin of these treated animals were exposed for 6 hours with 0.35 ml/site of a 50% suspension of the test material. In addition, a naive control group of 10 animals was treated in the same manner. By the 3rd induction treatment, all of the animals exhibited irritation scores ranging from 1 to 3 at 24 hours post-exposure. In the challenge, two of the 20 treated animals exhibited irritation scores of 1 at 24 and/or 48 hours post-exposure. The naive control group did not exhibit any irritation response. The test material is a weak dermal sensitizer in the Buehler test. The positive control was functional. Study acceptable. (Moore, 4/18/03)

SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Study

52245-104; 174012; “3-Month Oral Toxicity Study in Rats (Administration in Food)”; (M. Bachmann; Novartis Crop Protection AG, Toxicology, 4332 Stein, Switzerland; Study ID. 971142; 1/26/99); Ten Sprague-Dawley-derived rats/sex/group were fed 360, 1200, 6000 or 20000 ppm of CGA-354743 technical (Metolachlor Ethanesulfonic Acid (metabolite of Metolachlor (CGA-24705), batch no. KI-5408/6, purity: 98%) or 5000 ppm of CGA-77102 technical (S-Metolachlor, batch no. P.501001, purity: 98.5%) in the diet for 13 weeks ((M): 26.6, 90.6, 461, 1638, and 454 mg/kg/day, (F): 30.1, 103, 560, 1786, and 597 mg/kg/day). A control group of 20 rats/sex were fed the untreated diet. No deaths resulted from the treatment. Although the mean body weights were not affected in a statistically significant manner, the mean body weight for the females treated with 5000 ppm of CGA-77102 was 90% that of the control group at the termination of the study. Food consumption was not affected by the treatment. There were no physiologically-relevant effects upon either the hematology or urinalysis parameters. In the clinical chemistry evaluation, the mean serum γ-glutamyl transpeptidase activities were increased for both the males and females treated with the 5000 ppm of CGA-77102 technical (<0.05). For the females treated with the 5000 ppm of CGA-77102 technical, the cholesterol level was increased and the total bilirubin concentration was decreased (p<0.05). The mean relative organ weights for the liver and thyroid gland of the females treated with 5000 ppm of CGA-77102 technical were greater than those of the controls (p<0.01). The mean relative spleen weight of the 20000 ppm females was greater than that of the control (p<0.01). In the microscopic examination, there was an incidence of hepatocellular hypertrophy in the liver of the females treated with 5000 ppm of CGA-77102 technical (0: 0/20 vs. 5000: 4/10). No adverse effect indicated. Subchronic NOEL: CGA-354743 technical, (M/F) 20000 ppm ((M): 1638 mg/kg/day, (F): 1786 mg/kg/day) (based upon the lack of a treatment-related effect upon the highest dose tested); CGA-77102 technical (M/F) < 5000 ppm ((M): <454 mg/kg/day, (F): <597 mg/kg/day) (based upon treatment-related effects on the liver of the only treatment group); Study acceptable. (Moore, 4/28/03)

Dog Subchronic Oral Toxicity Study

52245-103; 174011; “3-Month Subchronic, Comparative Oral Toxicity Study in Beagle Dogs”; (B. Altmann; Novartis Crop Protection AG, Toxicology, 4332 Stein, Switzerland; Study ID. 971089; 1/25/99); Four beagle dogs/sex/group were dosed orally with 0, 50, 200, 500 or 1000 mg/kg/day of CGA-354743 Technical (Metolachlor Ethanesulfonic Acid (metabolite of
Metolachlor (CGA-24705), batch nos. KI-5408/4 and KI-5408/5, purity: 99%) or 200 mg/kg/day of CGA-77102 technical (S-Metolachlor, batch no. P.501001, purity: 98.5%) in capsules for 13 weeks. There were no treatment-related effects upon mean body weights or food consumption for either of the test materials. In the hematology evaluation, the animals treated with 1000 mg/kg of CGA-354743 exhibited an increased percentage of eosinophils (males, 7 weeks, \(p<0.05\)), females, 13 weeks, \(p<0.05\)). For the females treated with 200 mg/kg of CGA-77102, the prothrombin time was greater than that of the controls (7 weeks, \(p<0.05\)). In the clinical chemistry evaluation, both sexes treated with CGA-354743 at 500 and 1000 mg/kg demonstrated increased total bilirubin levels by 13 weeks of treatment \(p<0.01\). The males in the 200 mg/kg group also had an increased serum level of total bilirubin as well \(p<0.05\). Mean albumin levels were decreased for the females treated with 500 or 1000 mg/kg of CGA-354743 (7 and 13 weeks \(p<0.05\) or 0.01) and for both sexes treated with 200 mg/kg of CGA-77102 \(p<0.05\) (males, 7 weeks, \(p<0.05\)), females, 7 and 13 weeks, \(p<0.05\)). The mean alkaline phosphatase activity levels were increased for the males treated with CGA-354743 at 1000 mg/kg by 7 weeks and persisted through 13 weeks \(p<0.01\). Treatment with CGA-77102 at 200 mg/kg resulted in elevated alkaline phosphatase activity levels for both sexes at 7 and 13 weeks \(p<0.05\). The mean γ-glutamyl transpeptidase activity levels were increased for the 1000 mg/kg males treated with CGA-354743 at 7 and 13 weeks, \(p<0.05\) or 0.01). Both sexes treated with 200 mg/kg of CGA-77102 demonstrated increased levels of activity for γ-glutamyl transpeptidase at 7 and 13 weeks \(p<0.05\). In the necropsy examination, the mean absolute liver weights were increased for both the 1000 mg/kg males treated with CGA-354743 and the 200 mg/kg males and females treated with CGA-77102 \(p<0.05\) or 0.01). The mean relative liver weights were increased for both the females treated with 1000 mg/kg of CGA-354743 or 200 mg/kg of CGA-77102 \(p<0.05\) or 0.01). The mean absolute and relative spleen weights for the males treated with 200 mg/kg of CGA-77102 was increased over those of the controls \(p<0.05\). Microscopic examination of the livers of males and females treated with 200 mg/kg of CGA-77102 revealed the presence of hepatocellular perilobular fatty change and bile duct hyperplasia (fatty change, males, 0: 0/4, 200: 4/4, females, 0: 0/4, 200: 2/4, bile duct hyperplasia, males, 0: 1/4, 200: 4/4, females, 0: 0/4, 200: 4/4). Cystic hyperplasia of the gall bladder was also noted for both sexes treated with 200 mg/kg of CGA-77102 (males, 0: 0/4, 200: 2/4, females, 0: 0/4, 200: 3/4). Target organ for both test materials: liver. No adverse effects indicated. Subchronic NOEL (CGA-354743) (M/F): 200 mg/kg/day (based upon treatment-related effects on the clinical chemistry (alkaline phosphatase, total bilirubin) of the 500 mg/kg treatment group); (CGA-77102) (M/F): < 200 mg/kg/day (based upon treatment-related effects on the clinical chemistry and liver histopathology of the 200 mg/kg treatment group); Study acceptable. (Moore, 4/22/03)

Rat Developmental Toxicity Study
** 105; 174013; “CGA-354743 Technical: Rat Oral Teratogenicity”; (M. Doubovetzky; Novartis Crop Protection AG, Toxicology, 4332 Stein, Switzerland; Study ID. 981009; 1/25/99); Twenty eight mated female Wistar B: Hanlbm:WIST rats/group were dosed orally by gavage with 0. 250, 500 or 1000 mg/kg/day of CGA-354743 technical (metolachlor ethanesulfonic acid (metabolite of metolachlor (CGA-24705)), batch no. KI-5408/6, purity: 98%) from day 6 through day 15 of gestation. The test material was diluted in aqueous 0.5% (w/w) sodium carboxymethylcellulose. No maternal deaths occurred during the study. There was no treatment-related effect upon maternal mean body weight gain or food consumption. There was no treatment-related effect upon fetal development. No adverse effects were evident. Maternal NOEL: 1000 mg/kg/day (based upon the lack of a treatment-related effect upon the dams in the highest dose tested). Developmental NOEL: 1000 mg/kg/day (based upon the lack of a treatment-related effect upon the fetuses in the highest dose tested). Study acceptable. (Moore, 4/29/03)
GENOTOXICITY

Mutagenicity
** 106; 174014; “Salmonella and Escherichia/Mammalian-Microsome Mutagenicity Study”; (B. Ogorek; CIBA-GEIGY Limited, Genetic Toxicology, Basle, Switzerland; Study ID. 951133; 1/15/96); S. typhimurium strains TA 98, TA 100, TA 102, TA 1535, TA 1357and E. coli strain WP2 uvrA were treated for 48 hours at 37°C with CGA-354743 technical (metolachlor ethanesulfonic acid (metabolite of metolachlor (CGA-24705); batch no. RV-2816/1; purity: 95%) at concentrations ranging from 312.5 to 5000 μg/plate with and w/o activation in two trials. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. No adverse effect indicated. Positive controls were functional. Study acceptable. (Moore, 4/29/03)

** 118; 174026; “Gene Mutation Test with Chinese Hamster Cells V79”; (B. Ogorek; Genetic Toxicology, Novartis Crop Protection AG, CH-4002 Basle, Switzerland; Study ID. 981018; 1/19/99); Chinese hamster V79 cells were treated with CGA-354743 Technical, Metolachlor Ethanesulfonic Acid (metabolite of Metolachlor (CGA-24705)), batch no. KI-5408/6, purity: 98%) at concentrations ranging from 185.2 to 5000.0 μg/ml for 5 hours (activation) or 21 hours (non-activation) at 37°C. Two trials were performed for the activated samples and three trials for the non-activated, with duplicate samples for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. Although a statistically significant increase in mutation frequency was noted for various treatment levels in both the activated and non-activated assays, there was no demonstration of a dose-related increase and the degree to which the mutation frequency was increased did not fulfill the 20-fold criteria which is used to stipulate a positive response. No adverse effect indicated. The positive control was functional. Study acceptable. (Moore, 5/2/03)

Chromosomal Aberration
** 107; 174015; “Micronucleus Test, Mouse”; (E. Deparade; Novartis Crop Protection AG, Toxicology, Genetic Toxicology, Basle, Switzerland; Study ID. 981016; 10/19/98); Five ICO:CD1 (CRL) mice/sex/group/time point were treated orally by gavage with a dose of 0 (vehicle control), or 5000 mg/kg of CGA-354743 Technical (Metolachlor Ethanesulfonic Acid (metabolite of Metolachlor (CGA-24705)), batch no. KI-5408/6, purity: 98%) and euthanized 16, 24 or 48 hours after dosing. An additional 5 animals/sex were treated with the positive control (cyclophosphamide, 64 mg/kg) or 1250 or 2500 mg/kg of the test material and euthanized 24 hours after dosing. Bone marrow samples from the femur were examined and the percentage of PCE with a micronucleus and the ratio of polychromatic (PCE) to normochromatic erythrocytes (NCE) were determined. No treatment-related increase in the number of polychromatic erythrocytes with a micronucleus was noted. No adverse effect indicated. The positive control was functional. Study acceptable. (Moore, 4/30/03)

DNA Damage
** 108; 174016; “Autoradiographic DNA Repair Test on Rat Hepatocytes (OECD Conform) In Vitro”; (B. Ogorek; Novartis Crop Protection AG, Toxicology, Genetic Toxicology, Basle, Switzerland; Study ID. 981017; 11/23/98); Primary rat hepatocyte cultures were exposed to CGA-354743 Technical, Metolachlor Ethanesulfonic Acid (metabolite of Metolachlor (CGA-24705)), batch no. KI-5408/6, purity: 98%) at concentrations ranging from 9.77 to 5000 μg/ml (Trial #1) and from 78.13 to 2500 ug/ml (Trial #2) for 16 to 18 hours at 37°C. Vehicle control (distilled water) and positive control (2-AAF: 10 μg/ml) cultures were included in the assay. There were 3 cultures per treatment level in the two trials. There was no treatment-related
increase in unscheduled DNA synthesis. No adverse effect indicated. The positive control was functional. Study acceptable. (Moore, 4/30/03)

**Rat Metabolism**

** 52245-109; 174017; “Determination of the Soil Metabolites CGA-354743, CGA-368208 and CGA-357704 in Excreta of Rats Administered [Phenyl-U-^{14}C] CGA-77102”; (K. Mewes; Novartis Crop Protection AG, CH-4002, Basle, Switzerland; Study ID. 030AM07; 5/6/98); Three Tif: RAI f (SPF) rats/sex were dosed orally by gavage with 0.5 or 100 mg/kg of [Phenyl-U-^{14}C] CGA-77102 (batch no. ILS-143.1, specific activity: 2000 kBq/mg, purity: 98.9%). Urine and feces were recovered periodically over a 72 hour period post-dose. Samples were pooled from the males and females in the respective dosing groups and analyzed for the respective metabolites of interest. Treatment levels did not affect the percentage of the administered dose which was recovered in the two routes of excretion. Approximately 30% and 55% was recovered in the urine and feces, respectively, of the males. For the females, approximately 42 and 48% was recovered in the urine and feces, respectively. For the particular metabolites of interest, no more than 0.28% of the administered dose for any of these metabolites (CGA 354743, 0.5 mg/kg) was recovered with the greater percentage in the feces. Study supplemental (non-guideline study). (Moore, 5/1/03)

110; 174018; “Disposition of [Phenyl-U-^{14}C] CGA-376994, A Sulfonic Acid Soil Metabolite of CGA-77102, in Bile-Duct Cannulated Rats after Oral Administration”; (S. Hassler; Novartis Crop Protection AG, CH-4002, Basle, Switzerland; Study ID. 030AM08; 7/1/99); Six bile duct-cannulated male Tif: RAI f (SPF) rats were dosed orally by gavage with 0.5 mg/kg of [Phenyl-U-^{14}C] CGA-376994 technical (batch no. ILS-125.4, specific activity: 43.8 uCi/mg, purity: 95.5%). Bile samples were recovered 7 times over the 48 hours after dosing. Urine and feces were collected at 24 and 48 hours post-dose. Only 17 to 18% of the radiolabel was absorbed into the systemic circulation (recovered from the bile, urine and carcass). The test material largely passed through the GI tract without being absorbed and was recovered in the feces, 77% by 48 hours post-dose. Study supplemental (non-guideline study). (Moore, 5/5/03)

111; 174019; “Disposition of [Phenyl-U-^{14}C] CGA-376994, A Sulfonic Acid Soil Metabolite of CGA-77102, in the Rat”; (T. Muller; Novartis Crop Protection AG, CH-4002, Basle, Switzerland; Study ID. 030AM06; 11/25/97); Four Tif: RAI f (SPF) rats/sex were dosed orally by gavage with 0.5 mg/kg of [Phenyl-U-^{14}C] CGA-376994 technical (batch no. ILS-125.4, specific activity: 43.8 uCi/mg, purity: 96.5%). Urine, feces and blood were collected periodically over the 72 hour period after dosing. A multitude of tissues were assayed for radiolabel after 72 hours. Ninety seven percent of the administered radiolabel was recovered in the feces within 24 hours of dosing. There was no sex-related difference in the excretion profile. Study supplemental (non-guideline study). (Moore, 5/5/03)