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MEMORANDUM

SUBJECT: Toxicology Chapter for Metolachlor/S-Metolachlor

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TO: Christina Jarvis, Risk Assessor
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Action Requested: Prepare toxicology chapter for Metolachlor/S-Metolachlor TRED

Recommendation: The toxicology chapter for Metolachlor/S-Metolachlor is attached. The chapter also includes reviews of a series of acute, subchronic, developmental (rat), mutagenicity and metabolism studies conducted with CGA 354743 (ethane sulfonic acid metabolite) and CGA 51202 (oxanilic acid degradate), metabolites of metolachlor/s-metolachlor found in water.

METOLACHLOR/S-METOLACHLOR

PC Codes: 108801, 108800

Toxicology Disciplinary Chapter for the Tolerance Reassessment Eligibility Decision (TRED) Document

Date completed:

November 29, 2001

Health Effects Division
Office of Pesticide Programs
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Arlington, VA 22202

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1.0 HAZARD CHARACTERIZATION

Metolachlor (CGA 24705) is a chloracetanalide herbicide, which is a racemic mixture of 50% each of the R-enantiomer (CGA 77101) and the S-enantiomer (CGA 77102, also referred to as alpha metolachlor). CGA 77102 is the isomer that is responsible for the herbicidal activity of metolachlor. S- metolachlor contains a higher ratio of CGA 77102:CGA 77101(88:12). Two sets of data were available; one for metolachlor and one for s-metolachlor.

Metolachlor

The metolachlor toxicology data base is complete. Metolachlor is moderately acutely toxic (toxicity category III) by oral, dermal and inhalation routes. It is not irritating to the skin or eyes but is a dermal sensitizer.

In the subchronic oral studies, the only evidence of toxicity was decreased body weight/body weight gain at 259 mg/kg/day in female rats and at 29 mg/kg/day in male and female dogs. The respective No Observed Adverse Effect Levels (NOAELs) for these studies were 23 mg/kg/day and 9 mg/kg/day, respectively. There was no evidence of systemic toxicity when 1000 mg/kg/day was applied topically to rabbits for 21 days. Dermal irritation was observed at 10 mg/kg/day and above.

Similar effects were seen after long-term administration of metolachlor. In the chronic dog study, the only adverse effect was decreased body weight gain in females at 33 mg/kg/day; the NOAEL was 10 mg/kg/day. In the mouse carcinogenicity study, possible treatment-related deaths in females and decreased body weight/body weight gain in both sexes were observed in female rats at 450 mg/kg/day; the NOAEL was 150 mg/kg/day. In the rat combined chronic toxicity/ carcinogenicity study, decreased body weight gain and food consumption were observed at 150 mg/kg/day; the NOAEL was 15 mg/kg/day. There was no evidence of carcinogenicity in mice; however, there were statistically significant increases in liver adenomas and combined adenomas/carcinomas in female rats. In male rats, there was a statistically significant trend but no pair-wise significance for liver tumors. There was no evidence of a mutagenic or cytogenetic effect *in vivo* or *in vitro*. Metolachlor has been classified as a Group C carcinogen with risk quantitated using a non-linear approach (Margin of Exposure).

The prenatal developmental studies in the rat and rabbit revealed no evidence of a qualitative or quantitative susceptibility in fetal animals. No significant developmental toxicity was found in rats or rabbits. In the rabbit prenatal developmental toxicity study, at 360 mg/kg/day, maternal animals had persistent anorexia and decreased body weight gain; the NOAEL was 120 mg/kg/day. There were no developmental effects at 360, the highest dose tested. In the rat prenatal developmental toxicity study, frank toxicity [death, clinical signs (clonic and/or tonic convulsions, excessive salivation, urine-stained abdominal fur and/or excessive salivation) and decreased body weight gain] was observed at the limit dose of 1000 mg/kg/day in maternal

animals; the NOAEL was 300 mg/kg/day. The developmental effects at 1000 mg/kg/day included slightly decreased number of implantations per dam, decreased number of live fetuses/dam, increased number of resorptions/dam and significant decrease in mean fetal body weight.

In the two-generation reproduction study in rats, there was no evidence of parental or reproductive toxicity at approximately 80 mg/kg/day, the highest dose tested. At this dose, there was a minor decrease in fetal body weight beginning at lactation day 4; the NOAEL was approximately 25 mg/kg/day. Since a similar body weight decrease was not seen on lactation day 0, the cause of the effect on later lactation days is most likely due to exposure of the pups to metolachlor in the diet and/or milk and therefore is not evidence of an increased quantitative susceptibility in post-natal animals.

Metolachlor is extensively absorbed and metabolized following oral administration. Elimination is via the urine and feces. Tissue residues were highest in red blood cells. A dermal absorption factor of 58% was selected based on a dermal absorption study in rats.

S-Metolachlor

The toxicology database for s-metolachlor is incomplete. Bridging toxicology data, including acute toxicity, subchronic toxicity in rat and dog, developmental toxicity in rat and rabbit, mutagenicity and metabolism studies are available. S-metolachlor is moderately acutely toxic (Toxicity Category III) by the oral and dermal route and relatively non-toxic (Toxicity category IV) by the inhalation route. It causes slight eye irritation and is non-irritating dermally but is a dermal sensitizer.

In one subchronic toxicity study in rodents with s-metolachlor, no effects were observed in male and female rats at the high dose of approximately 225 mg/kg/day. In another subchronic toxicity study in rats, decreased body weight/body weight gain, reduced food consumption and food efficiency and increased kidney weights in males were observed at 150 mg/kg/day; the NOAEL was 15 mg/kg/day. In the subchronic dog study, no effects were observed in dogs at the high dose of approximately 70 mg/kg/day.

There was no evidence of increased quantitative or qualitative fetal susceptibility in the prenatal developmental studies in rats and rabbits with either metolachlor or s-metolachlor. In general, significant developmental toxicity was not seen in rats or rabbits. In the rat, maternal toxicity [increased clinical signs of toxicity (pushing head through bedding) and decreased body weights/body weight gains, food consumption and food efficiency] was observed at 500 mg/kg/day; the NOAEL was 50 mg/kg/day. There were no developmental effects at 1000 mg/kg/day, the highest dose tested. In the rabbit, clinical signs of toxicity (little/none/soft stool) were observed at 100 mg/kg/day in maternal animals; the NOAEL for maternal toxicity was 20 mg/kg/day. No developmental effects were observed at 500 mg/kg/day, the highest dose

tested.There was no evidence of a mutagenic or cytogenic *in vitro* or *in vivo* studies with s-metolachlor.

S-metolachlor is extensively absorbed and metabolized following oral administration. Elimination is via the urine and feces. Tissue residues were highest in whole blood. Metabolism studies were inadequate for comparing the metabolic pathways of metolachlor and s-metolachlor. However, based on a comparison of the findings in other studies with both chemicals, it appears that s-metolachlor is of comparable toxicity to the racemic mixture (metolachlor).

A series of acute, subchronic, developmental (rat) and mutagenicity studies were conducted with CGA 354743 (ethane sulfonic acid metabolite of metolachlor and s-metolachlor) and CGA 51202 (oxanilic acid degradate), metabolites of metolachlor/s-metolachlor found in water. The currently available data appeared to indicate that the metabolites were less toxic than the parents metolachlor and s-metolachlor after repeated dosing based on subchronic studies in the rat and dog (CGA 354743 only) and developmental studies in the rat. No toxicity was observed in any of these studies with CGA 354743 or CGA 51202 at the limit dose of 1000 mg/kg/day or greater. Since toxicity was not demonstrated, the degree of difference between the metabolites and parents could not be established. Acute toxicity was essentially comparable, except both metabolites were moderate (CGA 354743) or severe (CGA 51202) eye irritants, whereas the parents were not.

One data gap exists as there is concern for toxicity by the inhalation route following applications on multiple days in a commercial setting. A 28-day inhalation study in rats with s-metolachlor should be conducted. The Registrant is recommended to follow the protocol provided in OPPTS Guideline 870.3465 (90-day inhalation study) but cease exposure at 28 days.

2.0 REQUIREMENTS

The requirements (CFR 158.340) for food use for Metolachlor are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1. Metolachlor

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	
870.3465	90-Day Inhalation	no	
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes[a]
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	no	-
870.6200b	90 Day Neuro. Screening Battery (rat)	no	-
870.6300	Develop. Neuro	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	yes
Special Studies for Ocular Effects Acute Oral (rat) Subchronic Oral (rat) Six-month Oral (dog)		no	

a Satisfied with combined chronic toxicity/carcinogenicity study

Bridging toxicology data for s-metolachlor included the following studies:

OPPTS Guideline Number	Study Type
870.1100	Acute oral toxicity
870.1200	Acute dermal toxicity
870.1300	Acute inhalation toxicity
870.2400	Acute eye irritation
870.2500	Acute dermal irritation
870.2600	Dermal sensitization
870.3100	90-day oral toxicity - rat
870.3150	90-day oral toxicity - rabbit
870.3700a	Prenatal developmental toxicity - rat
870.3700b	Prenatal developmental toxicity - rabbit
870.5100	Mutagenicity - gene mutation - bacterial
870.395	Mutagenicity - mammalian erythrocyte micronucleus test
870.5550	Mutagenicity - unscheduled DNA synthesis in mammalian cells in culture
870.7485	General metabolism

The HED Hazard Identification Assessment Review Committee concluded that s-metolachlor and metolachlor have comparable toxicity profiles. Studies with both chemicals were used interchangeably for toxicology endpoint selection.

3.0 DATA GAP(S)

A 28-day inhalation study in rats with s-metolachlor should be conducted. The Registrant is recommended to follow the protocol provided in OPPTS Guideline 870.3465 (90-day inhalation study) but cease exposure at 28 days.

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data bases for acute toxicity for both metolachlor and s-metolachlor are considered complete. Metolachlor is moderately acutely toxic (toxicity category III) by oral, dermal and inhalation routes. It is not irritating to the skin or eyes but is a dermal sensitizer. S-metolachlor is moderately acutely toxic (Toxicity Category III) by the oral and dermal route and relatively non-toxic (Toxicity category IV) by the inhalation route. It causes slight eye irritation and is non-irritating dermally but is a dermal sensitizer.

The acute toxicity data on metolachlor and s-metolachlor are summarized below in Tables 2 and 3, respectively.

Table 2. Acute Toxicity Data on Metolachlor* (PC code 108801)

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral - Rat	00015523	LD_{50} = 2780 mg/kg	III
81-2	Acute Dermal - Rabbit	00015526	LD_{50} = > 10 g/kg	III
81-3	Acute Inhalation - Rat	00015535	LC_{50} = > 1.75 mg/L	III
81-4	Primary Eye Irritation - Rabbit	00015528	non-irritating	IV
81-5	Primary Skin Irritation - Rabbit	00015530	non-irritating	IV
81-6	Dermal Sensitization - guinea pig	00015631	positive	
81-8	Acute Neurotoxicity - NA			

* Extracted from RED (April 1995)
NA - study not required

Table 3. Acute Toxicity Data on S-Metolachlor* (PC code: 108800)

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral - Rat	43928915	LD_{50} = 3267 mg/kg (♂); 2577 mg/kg/day (♀); 2672 mg/kg/day (combined)	III
81-2	Acute Dermal - Rabbit	43928916	LD_{50} = > 2000 mg/kg	III
81-3	Acute Inhalation - Rat	43928917	LC_{50} = > 2.91 mg/L	IV
81-4	Primary Eye Irritation - Rabbit	43928918	slight to moderate conjunctival irritation that cleared in 48 hours	III
81-5	Primary Skin Irritation - Rabbit	43928919	non-irritating	IV
81-6	Dermal Sensitization - guinea pig	43928920	positive	
81-8	Acute Neurotoxicity - NA			

* Extracted from HED document 012310
NA - study not required

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is not complete; a 28-day inhalation study with s-metolachlor is required. In the 90-day dietary study in rats with metolachlor, decreased body weight and body weight gain were observed in female rats at 259 mg/kg/day, the highest dose tested; the NOAEL was 23.4 mg/kg/day. No effects were observed in males. In one 90-day dietary study in rats with s-metolachlor, no effects were observed in males or females at 208 and 236 mg/kg/day, respectively. In another 90-day dietary study in rats with s-metolachlor, decreased body weight, reduced food consumption and food efficiency in both sexes and increased kidney weight in males at 150 mg/kg/day; the NOAEL was 15 mg/kg/day. In a 180-day dietary study in dogs with metolachlor, decreased body weight gain in both sexes was observed at 29 mg/kg/day; the NOAEL was approximately 9 mg/kg/day. A 90-day oral study with s-metolachlor in dogs was classified as acceptable/nonguideline. No effects were observed in males and females at 62 mg/kg/day and 74 mg/kg/day, respectively, the highest doses tested. When metolachlor was applied once daily to the skin of rabbits for 21 days, there was no evidence of systemic toxicity at 1000 mg/kg/day, the highest dose tested. However, dermal irritation was observed at all dose levels.

870.3100 90-Day Oral Toxicity - Metolachlor - Rat

In a 3-month dietary toxicity study (MRID 44775401), groups of male and female Sprague-Dawley rats (20/sex for controls, 10/sex/ treated group) were given CGA-24705 (a.i. 97.7 %, Lot/Batch P.111072) administered in feed at 0, 30, 300 or 3000 ppm (equivalent to 0, 2.00, 20.2 and 210 mg/kg/day for males and 0, 2.32, 23.4 and 259 mg/kg/day for females).

No treatment-related deaths or clinical signs occurred during the study. In addition, there were no treatment-related effects on ophthalmologic parameters, water consumption, urinalysis, food efficiency or pathology in either males or females. There was no evidence of any treatment-related effect in males.

Decreased body weights were observed in females given 300 ppm and 3000 ppm CGA-24705; however, decreases in the 300 ppm group were not considered toxicologically significant due to the small magnitude of the effect. Statistically significant decreased (22%) overall body weight gains were observed in 3000 ppm females. Decreases in the 30 and 300 ppm females was not considered toxicologically significant due to the lack of statistical significance and no dose-response effect. Statistically decreased food consumption was reported in 30, 300 and 3000 ppm females during Week 1 and in the 30 and 300 ppm group throughout the study. Overall mean food consumption was statistically decreased in 30, 300 and 3000 ppm females (-11%, -11% and -12%). The toxicological effect of treatment on food consumption is questionable as there was no dose-responsive effect and food efficiency was not affected.

Changes in a number of hematologic and clinical chemistry parameters were observed in female animals at all dose levels during the study; however, the toxicological significance is questionable due to the lack of a dose-response and the small magnitude of the effect.

Statistically significant changes in absolute and relative organ weights were limited to decreased liver weight in 30 and 300 ppm females (-11 % and -12%, respectively), increased liver/body weight in 3000 ppm females (+9), and increased kidney/body weight in 30, 300 and 3000 ppm females (+9%, +11% and +13%, respectively). These effects are not considered toxicologically significant due to the small magnitude and the lack of accompanying histopathology changes.

The LOAEL for female Sprague-Dawley rats was 3000 ppm (259 mg/kg/day) based on decreased body weight and body weight gain. The NOAEL for females was 300 ppm (23.4 mg/kg/day). The LOAEL for male Sprague-Dawley rats was not established. The NOAEL for males was 3000 ppm (210 mg/kg/day).

This study is classified as **Acceptable/Guideline [OPPTS 870.3100 (§82-1a)]** and satisfies the guideline requirements for a subchronic oral toxicity study in rodents.

870.3100 90-Day Oral Toxicity - S-Metolachlor - Rat

In a 3-month dietary toxicity study (MRID 44775402), groups of male and female Sprague-Dawley rats (20/sex for controls, 10/sex/ treated group) were given CGA-77102 (a.i. 98.5 %, Lot/Batch P.501001) administered in feed at 0, 30, 300 or 3000 ppm (equivalent to 0, 1.90, 20.4 and 208.0 mg/kg/day for males and 0, 2.13, 23.9 and 236.0 mg/kg/day for females).

No treatment-related deaths or clinical signs occurred during the study, however, one control female was sacrificed before schedule because of overall poor condition. No statistically significant changes in total body weight, body weight gain, food consumption or food efficiency were reported. There were no treatment-related changes in ophthalmologic or histopathology parameters.

Small, sporadic statistically significant changes in hematology parameters were observed during the study. These included increased MCHC in 30 ppm males (+2%), increased methemoglobin concentration (MetHb) in 3000 ppm males and females (both +13%), and decreased platelet count in 30 ppm females (-14%). Statistically significant changes in clinical chemistry parameters included decreased glucose (-14%), creatinine (-14%), chloride (-3%) and increased urea (+13%), globulin (+10%), and calcium (+5%) in 3000 ppm males, decreased bilirubin (-28%), AST (-29%), ALT (-36%) and A/G (-6%) in 3000 ppm females and AST in 300 ppm females (-24%). These changes are of no toxicological or biological concern.

Statistically significant changes in urinalysis parameters included increased mean volume (+48%), decreased relative density (-2%) and decreased ketones (-52%) in 300 ppm males, and decreased

relative density (-2%) in 30 ppm males. These changes also are of no toxicological or biological concern.

Statistically significant changes in absolute organ weight were limited to increased ovary weight in 30 ppm females (+13%). Increased relative organ weights included ovary/body in 300 ppm females (+14%), liver/ body in 3000 ppm males and females (+16% and +7%, respectively), kidney/body in 3000 ppm males (+14%), and spleen/body in 300 and 3000 ppm males (both +13%).

Under the conditions of this study, a LOAEL for male and female Sprague-Dawley rats cannot be defined. The NOAEL for male and female rats is 3000 ppm (equivalent to 208 mg/kg/day in males and 236 mg/kg/day in females).

This study is classified as **Unacceptable/Guideline [OPPTS 870.3100 (§82-1a)]** and does not satisfy the Subdivision F guideline requirements. The highest dose tested did not show a toxicological effect.

870.3100 90-Day Oral Toxicity - S-Metolachlor - Rat

In a subchronic oral study (MRID# 43928923), Sprague-Dawley rats (Strain: Crl: COBS® CD® (SD)BR from Source: Charles River Breeding Laboratories, Kingston, New York) received either 0, 30, 300, 3000, or 10000 ppm (0, 1.5, 15, 150 or 500 mg/kg/day) CGA-77102 Technical (Purity: 89.6% Dual content (93.7% S-Isomer); Batch No.: FL-830813 (SL-649)) in the diet for 13 weeks.

Treatment related systemic toxicity was noted at 3000 ppm and above as lower body weights and body weight gains in both sexes along with lower food consumption and reduced food efficiency. The 3000 and 10000 ppm males had increased absolute and relative kidney weights (statistically significantly different), this was a trend in the females also but only the relative organ weights were statistically significantly different. The 10000 ppm dose groups had increased gamma-GT activities and the males alone had increased eosinophilic intracytoplasmic inclusions bodies (of unknown etiology). **The Systemic Toxicity NOAEL was 300 ppm (15 mg/kg/day) and the LOAEL was 3000 ppm (150 mg/kg/day) based on lower body weights and body weight gains, reduced food consumption and reduced food efficiency in both sexes and increased kidney weights in males.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§82-1a) for a subchronic feeding study in rats.

870.3150 180-Day Oral Toxicity - Metolachlor - Dog

In a subchronic oral toxicity study (MRIDs 00032174 and 43244001), metolachlor (96.8% ai) was

administered in the diet to Beagle dogs (8/sex/group for control and high dose groups; 6/sex/group for low- and mid-dose groups) at dose levels of 0, 100, 300 or 1000 ppm (males: 0, 2.92, 9.71 and 29.61 mg/kg/day, respectively; females: 0, 2.97, 8.77 and 29.42 mg/kg/day, respectively) for six months.

There were no deaths or clinical signs of toxicity. Mean body weight gain was decreased during weeks 0-13 and 0-26 in the 1000 ppm group males (55-63% decrease) and females (44-50% decrease), although the changes were not statistically significant. Mean overall food consumption was not affected in the 1000 ppm group males but was slightly decreased (9%) in the 1000 ppm females. There was a significant decrease in the activated partial thromboplastin time (APTT) in the 300 and 1000 ppm group males and 300 ppm group females but the findings were not considered toxicologically significant because the decrease was slight and not dose-related. Alkaline phosphatase was signifcantly increased in the 300 ppm and 1000 ppm group males and females at week 26; however, the effect was not considered toxicologically significant due to the small magnitude of the increase and the lack of accompanying necropsy findings.

The LOAEL was 1000 ppm (males/females: 29.61/29.42 mg/kg/day) based on decreased body weight gain. The NOAEL was 300 ppm (males/females: 9.71/8.77 mg/kg/day).

The study is classified as **Acceptable/guideline** and **satisfies** the guideline requirements for a subchronic toxicity study in dogs (82-1; OPPTS 870.3150). The study was conducted for six months, whereas the guidelines require 90 days of dosing. However, toxicity parameters, with the exception of necropsy, were also evaluated at 90 days in the study.

870.3150 90-Day Oral Toxicity - S-Metolachlor - Dog

In a subchronic oral study (MRID# 43928922), male and female beagle dogs (Source: Marshall Farms, North Rose, NY.) received either 0, 300, 500, 1000, or 2000 ppm CGA-77102 Technical (95.4% purity; Lot Number FL-941255) in the diet or by capsule for 16 weeks. According to the investigators: "This study was initially designed to determine the toxicity of CGA-77102 via dietary exposure. However, during the first two weeks, very poor test diet consumption accompanied by weight loss were seen in both sexes given the top feeding level, 2000 ppm; the effect was worse in the females. Addition of corn oil or water to the test diet of the 2000-ppm females did not improve the palatability. Consequently, a decision was made to provide the test material orally to the high dose males and females via capsules; the daily dose (700 mg/dog) was calculated on the basis that all 350 grams of the test diet was consumed by each dog daily. Upon the initiation of capsule dosing, the 2000-ppm animals were switched to basal diet whereas the other dose groups continued to receive test diets. Because very little test diet was consumed by the 2000-ppm animals during the first two weeks, the whole duration of the study was extended by an additional three weeks to allow for a total of 14 weeks in capsule dosing and 16 weeks in test diet exposure. The overall study is best described as a 14/16 week oral/dietary study."

Other than the palatability problems noted above in the 2000 ppm dose group, no biologically relevant treatment related systemic toxicity was noted at any dose level tested. **The Systemic Toxicity NOAEL was equal to or greater than 2000 ppm, highest dose tested (62 mg/kg/day for males and 74 mg/kg/day for females) and the LOAEL was greater than 2000 ppm (62 mg/kg/day for males and 74 mg/kg/day for females).**

This study is classified as Acceptable-Nonguideline and dose not satisfy the guideline requirements (§82-1b) for a subchronic feeding study in non-rodents. This study needs to be repeated to fulfill this guideline requirement.

870.3200 21/28-Day Dermal Toxicity – Metolachlor - Rat

In a 21-day dermal toxicity study (MRID 41833101), metolachlor (96.4% a.i.) was applied topically once daily for 21 days to the intact skin of five New Zealand rabbits/sex/group at doses of 0, 10, 100 or 1000 mg/kg/day.

All animals survived the treatment. There were no treatment-related effects on clinical signs, body weight/body weight gain, food consumption, ophthalmoscopic examinations, hematology or necropsy examinations. Significant increases in total bilirubin were observed only in females treated at 100 mg/kg/day (68% increase) and 1000 mg/kg/day (72% increase). However, these increases were not considered toxicologically significant as there was no other evidence of organ effects at these doses and hyperbilirubinemia has not been reported in other toxicity studies with metolachlor. Absolute and relative liver weight were significantly increased in the 1000 mg/kg/day males and relative kidney weight was significantly increased in 1000 mg/kg/day females. These effects are not considered toxicologically significant as there were no accompanying laboratory or necropsy findings.

There was evidence of skin irritation in all treated groups. Very slight erythema and dry skin were observed in all animals of the 10 mg/kg/day group; one female at this dose had fissuring. With increasing doses, more animals were observed to have fissuring and wrinkling of the skin. On histopathology, hyperkeratosis, parakeratosis, congestion of the dermis, edema and subacute lymphocytic infiltration were reported in some or all of the treated animals.

The systemic LOAEL was not established. The NOAEL was 1000 mg/kg/day (HDT).

The dermal irritation LOAEL was 10 mg/kg/day (LDT) based on very slight erythema, dry skin and fissuring (one animal). The NOAEL was not established.

The study is classified as **acceptable/guideline** and **satisfies** the guideline requirements for a 21-day dermal toxicity study in rabbits (82-2; OPPTS 870.3200).

4.3 Prenatal Developmental Toxicity

Adequacy of data base for Prenatal Developmental Toxicity: The data bases for prenatal developmental toxicity for metolachlor and s-metolachlor are considered complete. The prenatal developmental studies in the rat and rabbit with both metolachlor and s-metolachlor revealed no evidence of a qualitative or quantitative susceptibility in fetal animals. No significant developmental toxicity was observed in most studies even at the highest dose tested.

870.3700a Prenatal Developmental Toxicity Study - Metolachlor - Rat

In a prenatal developmental toxicity study (MRID 00151941), CGA-24705 (metolachlor) (96.4% a.i.) in 0.5% (w/v) aqueous hydroxymethylcellulose was administered by gavage (10 ml/kg) to 25 presumed pregnant Crl:COBS®CD®(SD) BR rats from gestation days (GD) 6 through 15, inclusive, at dose levels of 0, 30, 100, 300 or 1000 mg/kg/day. The animals were sacrificed on GD 20 and the fetuses examined for evidence of developmental effects.

There were four treatment-related deaths [GD 7, 8 and 10 (2 rats)] in animals treated at 1000 mg/kg/day. Clinical signs of toxicity, including clonic and/or toxic convulsions, excessive salivation, urine-stained abdominal fur and/or excessive lacrimation, were observed in animals treated at 1000 mg/kg/day. There was also an increase in excessive salivation in the 300 mg/kg/day group. However, as this effect was most likely due to gastric irritation and there was no other evidence of treatment-related toxicity, the finding is not considered toxicologically significant. Body weight gain was significantly decreased in the 1000 mg/kg/day group during GD 6-16 (83% of control value; $p<0.05$), GD 6-20 (88% of control value; $p<0.05$) and GD 0-20 (88% of control value; $p<0.01$). Food consumption was not affected. In the 1000 mg/kg/day group, there was a slightly decreased number of implantations per dam (14.6 vs 15.8 in controls), decreased live fetuses/dam (13.8 vs 15.2 in controls) and increased number of resorptions/dam (0.8 vs 0.5 in controls). There was also a statistically significant decrease ($p<0.05$; 96% of control value) in mean fetal body weight.

The maternal toxicity LOAEL was 1000 mg/kg/day based on an increased incidence of death, clinical signs of toxicity (clonic and/or toxic convulsions, excessive salivation, urine-stained abdominal fur and/or excessive lacrimation) and decreased body weight gain. The NOAEL was 300 mg/kg/day.

The developmental toxicity LOAEL was conservatively established at 1000 mg/kg/day based on slightly decreased number of implantations per dam, decreased number of live fetuses/dam, increased number of resorptions/dam and significant decrease in mean fetal body weight. The NOAEL was 300 mg/kg/day.

The study is classified as **Acceptable/guideline** and **satisfies** the guideline requirements for a prenatal developmental toxicity study in rats (83-3a; OPPTS 870.3700).

870.3700a Prenatal Developmental Toxicity Study - S-Metolachlor - Rat

In a developmental (teratology) study (MRID# 43928925), rats (Strain: Tif: RAI f (SPF), hybrids of RII/1 x RII/2 from Animal Production, WST-455, CIBA-GEIGY Limited, 4332 Stein, Switzerland) received either 0, 5, 50, 500, or 1000 mg/kg/day CGA-77102 Technical (Batch No.: v. 4673/7 with a purity of 95.6%) suspension in 0.5% (w/w) aqueous solution of sodium carboxymethylcellulose by oral gavage from gestation days 6 through 15.

No treatment related mortality was noted. There was a dose related increase in clinical signs seen as all 500 and 1000 mg/kg/day animals and 9/24 of the 50 mg/kg/day animals exhibited as pushing head through bedding for about one hour. This was noted throughout the dosing period and may be an indication of neurotoxicity. The 500 and 1000 mg/kg/day dose groups had lower overall body weights at gestation days 15 and 21 and gained less weight than the control during the dosing period (gestation days 6-16) and for the calculated periods of gestation days 6-21 and 0-21, also for corrected body weight gains from gestation days 6-21. Also the 500 and 1000 mg/kg/day dose groups had reduced food consumption during the dosing period (gestation days 6-16, statistically significantly different), reduced food consumption following the dosing period and for the overall periods (gestation days 6-21 and 0-21). This is also reflected in reduced food efficiency for the same periods (6-16, 6-21, 6-21, and 0-21). **The maternal toxicity NOAEL was 50 mg/kg/day with a LOAEL of 500 mg/kg/day based on increased clinical signs of toxicity, decreased body weights and body weight gains and reduced food consumption and reduced food efficiency.**

No significant treatment related developmental toxicity was noted at the dose levels tests. **The developmental toxicity NOAEL was equal to or greater than 1000 mg/kg/day, the highest dose tested; a LOAEL was not reached.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§ 83-3a) for a teratology study in rats.

870.3700b Prenatal Developmental Toxicity Study - Metolachlor - Rabbit

In a prenatal developmental toxicity study (MRID 00041283), CGA-24705 (metolachlor) (95.4% a.i.) in 0.75% aqueous hydroxy methylcellulose was administered by gavage (10 ml/kg) to 16 pregnant New Zealand White rabbits/group from gestation days (GD) 6 through 18, inclusive, at dose levels of 0, 36, 120 or 360 mg/kg/day. The animals were sacrificed on GD 30 and the fetuses examined for evidence of developmental effects.

One doe at 36 mg/kg/day and another at 360 mg/kg/day died on GDs 24 and 29, respectively. The cause of death in both animals was attributed to persistent anorexia. Two rabbits aborted, one at 120 mg/kg/day (GD 25) and another at 360 mg/kg/day (GD 17). The high-dose animal had persistent anorexia. One rabbit in each group delivered prior to GD 30; the control, low- and high-dose animals on GD 29 and the mid-dose animal on GD 30. There was a treatment-related

increase in the incidence of persistent anorexia in the does treated at 360 mg/kg/day, which was defined as less than one-half of the daily food allotment consumed. However, food consumption data were not provided to support this finding. There was a treatment-related decrease in body weight gain in the 360 mg/kg/day group for GD 6-18 (-0.16 kg vs +0.04 kg in controls; $p<0.01$) and GD 6-30 (-0.01kg vs +0.03 kg in controls). There was no treatment-related increase in gross pathological findings in maternal animals at necropsy.

No treatment-related increase in external, visceral or skeletal developmental effects were observed.

The maternal toxicity LOAEL was 360 mg/kg/day based on an increased incidence of clinical observations (persistent anorexia) and decreased body weight gain. The NOAEL was 120 mg/kg/day. The developmental toxicity LOAEL was not established. The NOAEL was 360 mg/kg/day.

The study is classified as **Acceptable/guideline** and **satisfies** the guideline requirements for a prenatal developmental toxicity study in rabbits (83-3b; OPPTS 870.3700).

870.3700b Prenatal Developmental Toxicity Study - S-Metolachlor - Rabbit

In a developmental (teratology) study (MRID# 43928924), sexually mature virgin female New Zealand White, S.P.F. Rabbits (Strain: Har:PF/CF(NZW)BR) from H.A.R.E., Rabbits for Research, Hewitt, N.J. Received either 0, 20, 100, or 500 mg/kg/day CGA-77102 Technical (Lot No. FL-830813 with a purity of 89.6% (93.7% S isomer) suspension in 3% corn starch containing 0.5% Tween 80 by oral gavage from gestation days 7 through 19.

No treatment related mortality was noted. There was a dose related increase in The 500 mg/kg/day dose group had lower overall body weights at gestation days 19, 29 and corrected body weights at day 29 gained less weight than the control during the dosing period (gestation days 7-19) with a rebound weight gain following the dosing period (gestation days 19-29), an indicator of toxicity. This group also had lower overall weight gain for the calculated periods of gestation days 7-29, 0-29 and corrected body weight gains for 0-29. This was supported by reduced little/none/soft stool observations at the 100 and 500 mg/kg/day dose levels. food consumption during the dosing period (gestation days 7-19) and for the overall periods (gestation days 7-28 and 0-28) with a rebound in food consumption following dosing (gestation days 19-28) at the 500 mg/kg/day dose level. This is also reflected in reduced food efficiency for the same periods (719, 7-28, and 0-28) and increased food efficiency following dosing (19-28) at the 500 mg/kg/day dose level. **The maternal toxicity NOAEL was 20 mg/kg/day with a LOAEL of 100 mg/kg/day based on clinical signs of toxicity.**

No significant treatment related developmental toxicity was noted at the dose levels tests. **The developmental toxicity NOAEL was equal to or greater than 500 mg/kg/day (HDT); a LOAEL was not reached.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§83-3b) for a teratology study in rabbits.

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity of metolachlor is considered complete. No reproduction studies with s-metolachlor are available. In the two-generation reproduction study with metolachlor in rats, there was no evidence of parental or reproductive toxicity at approximately 80 mg/kg/day, the highest dose tested. At this dose, there was a minor decrease in fetal body weight beginning at lactation day 4; the NOAEL was approximately 25 mg/kg/day. Since a similar body weight decrease was not seen on lactation day 0, the cause of the effect on later lactation days was most likely due to exposure of the pups to metolachlor in the diet and/or milk and therefore is not evidence of an increased quantitative susceptibility in post-natal animals.

870.3800 Reproduction and Fertility Effects - Rat

In a two-generation reproduction study (MRID 00080897), metolachlor (95.4% a.i.) was administered in the diet to two consecutive generations of 15 male/30 female CD albino rats at dose levels of 0, 30, 300 or 1000 ppm (F_0 males: 0, 2.4, 23.5 and 75.8 mg/kg/day; F_0 females: 0, 2.5, 26.0 and 85.7 mg/kg/day; F_1males: 0, 2.3, 23.7 and 76.6 mg/kg/day; F_1 females: 0, 2.6, 25.7 and 84.5 mg/kg/day).

There were no deaths in the F_0 generation. Two females of the F_1 generation died during the pre-mating period, one in the 300 ppm group at 32 days and the other in the 1000 ppm group at 52 days. One female in the 300 ppm group was found dead on gestation day 19 and a control group female was sacrificed in a moribund condition on lactation day 1. Based on necropsy examinations, none of the deaths was treatment-related. There were no treatment-related clinical signs of toxicity in either generation. Body weight, body weight gain and food consumption were unaffected in the F_0 generation. In the F_1 generation, food consumption was significantly decreased in females of the 1000 ppm group at several timepoints; however, there was no effect on body weight/body weight gain. Therefore, this finding was not considered toxicologically significant. There were no treatment-related effects on organ weights or gross/microscopic necropsy examinations in either generation.

There was no evidence of a treatment-related effect on any of the reproductive parameters for either generation. Offspring body weight was significantly decreased in the F_1 litter on lactation days 14 and 21 (91- 96% of control value) and in the F_2 litter on lactation days 4, 7, 14 and 21 (92 - 95% of control value). Although the magnitude of the decrease is small, the finding is regarded as toxicologically significant.

The parental toxicity LOAEL was not established. The NOAEL was 1000 ppm (F_0 males/females: 75.8/85.7 mg/kg/day; F_1males/females: 76.6/84.5 mg/kg/day).

The reproductive toxicity LOAEL was not established. The NOAEL was 1000 ppm (F_0 males/females: 75.8/85.7 mg/kg/day; F_1males/females: 76.6/84.5 mg/kg/day).

The offspring LOAEL was conservatively established at 1000 ppm (F_0 males/females: 75.8/85.7 mg/kg/day; F_1males/females: 76.6/84.5 mg/kg/day) based on decreased body weight in F_1 and F_2 litters . The NOAEL is 300 ppm (F_0 males/females: 23.5/ 26.0 mg/kg/day; F_1males/females: 23.7/25.7 mg/kg/day).

The study is classified as **Acceptable/guideline** and **satisfies** the guideline requirements for a multi-generation reproduction study in rats (83-4; OPPTS 870.3800).

4.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity of metolachlor is considered complete; a combined chronic toxicity/carcinogenicity study in the rat satisfies the requirements for both the chronic toxicity and carcinogenicity studies.(See 4.6 Carcinogenicity.) No chronic toxicity studies with s-metolachlor are available. No significant chronic toxicity was found in either rats or dogs. In the rat, a decrease in body weight was observed at the highest dose tested. In the chronic dog study with Metolachlor, the only adverse effect was decreased body weight gain in females at 33 mg/kg/day; the NOAEL was 10 mg/kg/day.

870.4100a (870.4300) Chronic Toxicity – Rat

See Carcinogenicity section below.

870.4100b Chronic Toxicity - Dog

In a chronic toxicity study (MRIDs 40980701, 41164501, 42218601 and 42218602), metolachlor (97% a.i.) was administered in the diet to Beagle dogs (6/sex/group for control and high dose groups; 4/sex/group for low- and mid-dose groups) at dose levels of 0, 100, 300 or 1000 ppm (males: 0, 3.5, 9.7 and 32.7 mg/kg/day, respectively; females: 0, 3.6, 9.7 and 33.0 mg/kg/day, respectively) for one year. Two dogs of each sex in the control and high-dose group designated as recovery animals were treated for 52 weeks and were then allowed a 4-week recovery period. An additional 4 dogs/sex/group were treated at the same dose levels and sacrificed at 13 weeks.

There were no treatment-related deaths or clinical signs of toxicity. Mean body weight gain was decreased in the 1000 ppm group females, considering both all animals (5-17% decrease) and only those treated for 52 weeks (5-17% decrease). Alkaline phosphatase was significantly increased in the 1000 ppm females at weeks 12, 26 and 40; however, the increase was not considered toxicologically significant due to the small magnitude of the effect and the lack of accompanying necropsy findings.

The LOAEL was 1000 ppm for females (33.0 mg/kg/day) based on decreased body weight gain. The NOAEL was 300 ppm (9.7 mg/kg/day). The LOAEL for males was not

established. The NOAEL for males was 1000 ppm (32.7 mg/kg/day).

The study is classified as **Acceptable/guideline** and **satisfies** the guideline requirements for a chronic toxicity study in dogs (83-1; OPPTS 870.4100).

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity for metolachlor is considered complete. No carcinogenicity toxicity studies with s-metolachlor are available. There was no evidence of carcinogenicity in mice with metolachlor; however, there were statistically significant increases in liver adenomas and combined adenomas/carcinomas in female rats. In male rats, there was a statistically significant trend but no pair-wise significance for liver tumors. Metolachlor has been classified as a Group C carcinogen with risk quantitated using a non-linear approach (Margin of Exposure).

870.4200a Combined Chronic Toxicity/Carcinogenicity Study - Metolachlor - Rat

Executive Summary: In a chronic toxicity/carcinogenicity study (MRID 00129377), metolachlor (95.3%), was administered in the diet to 60 CD-Crl:CD albino rats/sex/group at dose levels of 0, 30, 300 or 3000 ppm (0, 1.5, 15 or 150 mg/kg/day) for two years. An additional 10 rats/sex/group were administered either 0 ppm or 3000 ppm in the diet for 12 months; 5 rats/sex/group were sacrificed after treatment and the remaining 5/sex/group were allowed to recover for four weeks and then sacrificed. Comparable mortality were observed in the treated and control animals. There were no treatment-related clinical signs of toxicity. Mean body weight gain was slightly decreased in the 3000 ppm females (6-17% decrease) throughout the study; the changes were not statistically significant. Mean food consumption was slightly decreased (4-9% decrease) in the 3000 ppm females; the decrease was not statistically significant. Absolute, relative and liver-to-brain weight were increased (7%, 13%, and 5%, respectively) in the 3000 ppm males. These increases were also observed in the 3000 ppm males after four-week recovery period. However, the toxicological significance of the finding is questionable as there were no accompanying clinical pathology or histologic changes.

For chronic toxicity, in males, the NOAEL was 3000 ppm (150 mg/kg/day), a LOAEL was not established. For females, the NOAEL was 300 ppm (15 mg/kg/day) and the LOAEL was 3000 ppm (150 mg/kg/day) based on slightly decreased body weight gain and food consumption.

The study is classified as **acceptable/guideline** and **satisfies** the guideline requirements for a chronic toxicity study in rats (83-1; OPPTS 870.4100).

870.4200b Carcinogenicity (feeding) - Mouse

Executive Summary: In a carcinogenicity study (MRID 00117597 [1]), metolachlor (reported to be 95% a.i.) was administered in the diet to 68 CD-1 mice/sex/group at doses of 0, 300, 1000 or 3000 ppm (0, 45, 150 or 450 mg/kg/day, based on 1ppm equals 0.150 mg/kg/day). Eight mice/sex/group were sacrificed at 12 and 18 months. High dose females had a significant increased mortality rate due to a number of deaths during the first few weeks of treatment (control: 24/52; high dose females: 34/52 at termination). Although the deaths were possibly attributable to a viral infection, the contribution of the test material can not be dismissed. Body weight was statistically significantly decreased (91-95% of control value) throughout the study in the 3000 ppm males and during the latter half of the study in the 3000 ppm females (93-95%). Body weight gain was consistently decreased in the 3000 ppm males (48-48%) and females (59-86%). Food consumption was comparable between treated and control group until week 90 of treatment, at which time the 3000 ppm males consumed 10% less than controls. The decrease was statistically significant at weeks 98, 102 and 104. There was no significant effect on female food consumption. There was no evidence of treatment-related effect on hematology or clinical chemistry parameters. Organ weight was not affected except for a dose-related decrease in absolute and relative weight of the seminal vesicles of males which was statistically significant at the high dose. However, there was no effect on testes weight and no accompanying histological changes in the seminal vesicles; therefore, the toxicological significance of the finding is questionable. There were no treatment-related microscopic changes. There were no treatment-related increases in tumor incidence in the study.

The NOAEL was 1000 ppm (150 mg/kg/day) and the LOAEL was 3000 ppm (450 mg/kg/day) based on possible treatment-related deaths in females and decreased body weight/body weight gain in males and females.

The study is classified as **acceptable/guideline** and **satisfies** the guideline requirements for a carcinogenicity toxicity study in mice (83-5; OPPTS 870.4200).

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The data bases for Mutagenicity for Metolachlor and S-Metolachlor are considered adequate based on 1991 mutagenicity guidelines. There was no evidence of a mutagenic or cytogenetic effect *in vivo* or *in vitro* with either Metolachlor or S-Metolachlor.

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[1] According to the Second Peer Review of Metolachlor (April 17, 1991), a mouse carcinogenicity study (MRIDs 00042725, 00084003) conducted by Industrial Biotest (validated by EPA)at doses of 0, 30, 1000 and 3000 ppm also showed no evidence of carcinogenic effects.

Metolachlor

Gene Mutation

Guideline 870.5100, gene mutation - bacterial reverse mutation MRID 00015397 acceptable/guideline	doses: 10, 100, 1000, 10000 ug/plate negative up to cytotoxic doses (1000 and 10,000 ug/plate)
Guideline 870.5300, gene mutation - mouse lymphoma MRID 00158929 acceptable/guideline	doses: 9.5-190 nl/ml without activation; 10.5-280 nl/ml with activation no effect on the incidence of mutation in presence or absence of metabolic activation

Cytogenetics

Guideline 870.5395, micronucleus assay in Chinese hamsters MRID 00158925 acceptable/guideline	doses: 0, 1250, 2500 or 5000 mg/kg no effect of treatment on incidence of micronuclei induction
Guideline 870.5450, dominant lethal assay in mice MRID 00015630 acceptable/guideline	doses: 100 or 300 mg/kg no effects on embryonic death, pre- and post-implantation or fertility in mated females

Other Genotoxicity

Guideline 870.5550, DNA damage/repair in rat hepatocytes MRID 00142828 acceptable/guideline	doses: 0.125, 0.625, 3.125 or 15.625 nl/ml no evidence of mutagenicity
Guideline 870.5550, DNA damage/repair in human fibroblasts MRID 00142827 acceptable/guideline	doses: 0.125, 0.625, 3.125 or 15.625 nl/ml no evidence of mutagenicity
Guideline 870.5550, unscheduled DNA synthesis (UDS) in rat hepatocytes MRID 43244003 acceptable/guideline	doses: 1250, 2500 or 4000 mg/kg for males; 500, 1000 or 1500 mg/kg for females negative for induction of UDS; however, significant increases in percentage of cells in S-phase were observed in females dosed at 500 mg/kg (but not at 1000 or 1500 mg/kg) and sacrificed at 15 hours

S- Metolachlor

Gene Mutation

Guideline 870.5100, gene mutation - Salmonella & Escherichia/Mammalian Microsome Mutagenicity MRID 43928927 acceptable/guideline	In independently performed microbial mutagenicity assays, *Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and TA102 and *Escherichia coli* WP2 *uvr*A were initially exposed to 312.5-5000.0 µg/plate CGA-77102 technical (95.6%) in the presence and absence of S9 activation. For the confirmatory trial, doses of 78.13-1250.0 µg/plate ±S9 were evaluated with *S. typhimurium* strains TA1535, TA1537, TA100 and TA102; concentrations of 312.5-5000.0 µg/plate ±S9 were examined with *S. typhimurium* TA 98 and *E.coli* WP2 *uvr*A. In general, doses ≥1250.0 µg/plate ±S9 were cytotoxic for *S. typhimurium* TA1535, TA1537, TA100 and TA102 and 5000.0 µg/plate ±S9 was slightly cytotoxic for *S. typhimurium* TA98 and *E. coli* WP2 uvrA. There was, however, no indication that CGA-77102 technical induced of a mutagenic effect in any tester strain either in the presence or the absence of S9 activation.

Cytogenetics

Guideline 870.5395, micronucleus test MRID 43928926 acceptable/guideline	Groups of five male and five female Tif:MAGf(SPF) mice received single oral gavage administrations of 500, 1000 or 2000 mg/kg CGA 77102 technical (95.6%). Toxic signs, similar to those seen in the preliminary range-finding studies (i.e., ataxia, tremors and/or hunched posture) were recorded for high-dose males and females throughout the 48-hour postexposure. No bone marrow cytotoxicity was seen at any dose or sacrifice time. The positive control induced the expected high yield of MPEs in males and females. There was, however, no evidence that CGA 77102 technical induced a clastogenic or aneugenic effect in either sex at any dose or sacrifice time.

Other Genotoxicity

Guideline 870.5550, Unscheduled DNA Synthesis MRID 43928928 acceptable/guideline	Groups consisting of three to four rats per sex received single oral gavage administrations of CGA-77102 Technical (95.6%) at doses of 500, 1500 or 5000 mg/kg (males) or 500, 1500 or 3200 mg/kg (females). Hepatocytes harvested at 15 and 38 hours were evaluated for viability and replicative DNA synthesis (RDS). For the UDS determination, additional groups (3/sex/dose) were exposed to 500 or 1500 mg/kg and the recovered hepatocytes were scored at 2 or 15 hours postexposure. Two of four females in the 3200-mg/kg group and 2 of 4 males in the 5000-mg/kg group died prior to the scheduled sacrifice at 38 hours. Severe cytotoxicity was seen in the hepatocytes recovered from 1 of 2 surviving males and both female survivors in the high-dose groups. Lower levels were neither toxic to the animals nor cytotoxic to the target cells. A clear dose-related increase in the percentage of cells in S-phase (RDS) was obtained from hepatocytes harvested 38 hours posttreatment of the male rats. The response ranged from a 5.3-fold increase at 1500 mg/kg to a 16.1-fold increase at the high dose (5000 mg/kg). In females, a marked increase in RDS was initially seen at 1500 mg/kg but the response declined over time with a 24.4-fold increase at 15 hours and a 12.2-fold increase at 38 hours. There was, however, no evidence that the CGA 77102 Technical at doses of 500 or 1500 mg/kg induced a genotoxic response at 2 or 15 hours posttreatment. We conclude, therefore, that the data indicate that CGA 77102 Technical was negative for genotoxicity but positive for cellular proliferation when tested up to overtly toxic and cytotoxic doses in this in vivo/in vitro rat hepatocyte RDS/UDS assay.

4.8 Neurotoxicity

Adequacy of data base for Neurotoxicity: Neurotoxicity screening studies for metolachlor and s-metolachlor are not available and are not recommended at this time. There was no evidence of neurotoxicity or neuropathology in any of the studies available in the database. The clonic and tonic convulsions and excessive salivation seen in maternal animals at the Limit Dose (1000 mg/kg/day) were considered to be agonal since these signs were seen only in dams that died at this dose.

4.9 Metabolism

Adequacy of data base for metabolism: The data bases for metabolism for both metolachlor and s-metolachlor are considered to be complete. Both metolachlor and s-metolachlor are extensively absorbed and metabolized following oral administration. Elimination is via the urine and feces. There are some minor sex differences in the elimination patterns. Tissue residues were highest in red blood cells for metolachlor; whole blood was highest for s-metolachlor.

Although the metabolic profiles of the two chemicals were qualitatively similar, there were quantitative differences. In one study (MRID 44491402), both sexes administered the racemic mixture (metolachlor) eliminated more of several urinary metabolic fractions than did rats of any group treated with the s-enantiomer. There were also quantitative differences in fecal metabolites. The DER for this study notes that specific fecal fractions (e.g., F_{10}, F_{12}, F_{13}) were 3-7 fold higher in the case of the s-enantiomer compared to the racemic formulation when the relative amount of s-enantiomer (assuming 100% pure) only doubled relative to its 50% concentration in the racemic mixture.

The HED Metabolism Assessment Review Committee concluded that, given the lack of certain data, such as proposed metabolic pathway for s-metolachlor and identification of metabolites for both chemicals, and uncertainties about findings in some studies, such as quantitative differences in metabolites, it was not possible to determine if the metabolism of the racemic mixture and s-metolachlor were comparable.

A dermal absorption study with metolachlor indicated that radioactivity remained in the skin after the 10-hour exposure and could be absorbed. After evaluating all the relevant metabolism and dermal absorption data, the HIARC selected a dermal absorption factor of 58% based on the combined values at the 10 hour measurement (33%) and the amount remaining on the skin (25%).

870.7485 Metabolism - Rat

Metolachlor

Executive Summary: In a metabolism study (MRID 00015425) urinary metabolites of CGA 24705 (N-(2-methoxy-1-methylethyl)-2-ethyl-6-methyl-chloroacetanilide) were identified following oral administration of 52 mg/kg, 28 mg/kg, and 33 mg/kg to male rats. Two metabolites, each comprising approximately 5% of chloroform extractable urinary radioactivity, were identified from oral administration of CGA 24705. These were the products CGA 37735 (2-ethyl-6-methyl-hydroxyacetanilide), in which N-dealkylation of R_1 (the N-(2-methoxy-1-methylethyl side chain) and side chain dechlorination and oxidation of R_2 (the N-chloroacetyl side chain) have occurred, and CGA 46129 (N-(1-carboxy-ethyl)-2-ethyl-6-methyl hydroxyacetanilide) in which the ether bond of R_1 has been split and oxidized to the corresponding carboxylic acid, while R_2 is similar to R_2 found in CGA 37735. In study #7/74, these 2 metabolites each represented approximately 5% of organic extractable urinary radioactivity, while in study #12/74, the percentage found as CGA 46129 was between 20-25% of urinary radioactivity, and CGA 37735 represented between 3-5% of organic extractable radioactivity.

The major metabolic pathway proposed from analysis of urinary as well as fecal metabolites is one of cleavage of the ether bond and subsequent oxidation to the carboxylic acid, as well as hydrolytic removal of the chlorine atom. Conjugation of CGA 24705 or metabolites with gluronic acid or sulfate does not appear to occur.

Aqueous extractable urinary radioactivity contained 58% of the total urinary radioactivity and was composed of 5 different radioactive fractions, which were not identified.

Current guideline recommendations as to dose levels and use of both sexes in metabolism studies were not followed. Thus, whether the metabolic pattern is altered with dose or repeated exposure cannot be evaluated from these data.

The study was classified as Supplementary (using classification system in place in 1991 when review was completed). The study does not satisfy the guideline requirements (85-1) for a metabolism study in rats. The actual percentage of CGA 46129 was not definitively quantitated, and aqueous extractable urinary radioactivity was not identified. Data from animals given a high dose and repeated low doses of CGA 24705 are also requested in order for this study to be considered core minimum data by the Agency.

Executive Summary: In a metabolism study (MRID 40114401), single low (1.5 mg/kg), single high (300 mg/kg) and repeated low (1.5 mg/kg/day for 15 days) oral doses of metolachlor were readily absorbed and eliminated by male and female rats. Urinary and fecal elimination of radioactivity associated with orally administered [^{14}C] metolachlor was essentially complete

within 48 to 72 hours after dosing. Low- and high-dose females eliminated ^{14}C more rapidly ($p<0.003$, half-lives of elimination, 16.6 and 15.6 hours, respectively) than low- and high-dose males and repeated-dose animals of both sexes (half-lives, 18.2 and 20.0 hours). Elimination by all animals followed first-order kinetics. Approximately one-half to two-thirds (48 to 64 percent) of the ^{14}C administered was recovered from the urine within 7 days; similar amounts were present in the feces. Low-dose males eliminated slightly more of the radioactive dose in the feces (55 percent) than the urine (48 percent). The opposite trend was seen in the low-dose females and repeated-dose rats of both sexes; these animals excreted approximately 58 to 64 percent of the ^{14}C dose in the urine and 42.5 to 46.5 percent in the feces within 7 days after dosing. High-dose animals excreted similar amounts (58 to 60 percent) of the radioactive dose in the urine and feces. Total recoveries of ^{14}C (urine, feces, and tissues) tended to be high and were between 105 and 122.5 percent.

Relatively low levels of radioactivity were present in the tissues of all animals at 7 days postdosing. Tissues of low- and repeated-dose rats contained approximately 1.6 to 2.5 percent of the ^{14}C dose; tissues of high-dose rats accounted for 3.2 (females) and 4.2 (males) percent. For all groups, most of the tissue radioactivity (1.1 to 3.0 percent of the dose) was associated with red blood cells (RBCs); RBCs also contained the highest concentrations of radiolabeled compound (0.6 to 0.9 ppm, low- and repeated-dose rats; 232 and 247 ppm, high-dose females and males, respectively), indicating that [^{14}C] metolachlor and/or its metabolites bind extensively to these cells. The next highest concentrations of radiolabel (0.03 to 0.13 ppm, low- and repeated-dose rats; 7.3 to 37 ppm, high-dose animals) were present in metabolically active tissues, including the heart, lung, kidney, liver and spleen. Brain, bone and muscle contained the smallest amounts of radioactivity (0.004 to 0.015 ppm, low- and repeated-dose rats; 1.7 to 3.5 ppm, high-dose rats). Tissue ^{14}C residues in high-dose males were approximately 250 to 500 times greater than those of low-dose males, indicating that the ratio of tissue concentrations (high dose:low dose) was much larger than the corresponding dose ratio of 200:1 (300 mg/kg: 1.5 mg/kg). In contrast, tissue ^{14}C levels of females were, in general, proportionate to dose. Tissues of low- and repeated-dose rats contained similar amounts of radioactivity. These data indicate that some ^{14}C was retained by all animals and that the greatest potential for accumulation of radioactivity was in male rats given a single high oral dose of [^{14}C] metolachlor.

The study was classified as Supplementary (using classification system in place in 1990 when review was completed). The study does not meet requirements set by EPA (Guideline 85-1) for the following reasons: (1) metabolites of metolachlor were not identified or quantified, (2) the intravenous dosing study performed was unacceptable and therefore could not be used to estimate absorption, (3) it was not clear whether the high dose used was high enough to produce transient signs of toxicity, and (4) the purity of the unlabeled metolachlor was not reported.

Executive Summary: In a rat metabolism study (MRID # 43164201),^{14}C-Metolachlor was administered orally in PEG-200 [HWI 6117-208] or corn oil [ABR-94001] to groups (5 sex/dose) of male and female Sprague-Dawley rats at a low oral dose (1.5 mg/kg), repeated low oral dose

(1.5 mg/kg x 14 days), and a single high dose (300 mg/kg). Control animals (1/sex) received blank formulation.
Comparison of oral and intravenous data showed that of the administered dose, between 69.6% and 93.2% was absorbed. Distribution data showed that the only significant sites of residual radioactivity at 7 days post-dose were residual carcass (0.9 - 2.2% of the administered dose) and red blood cells (0.95- 1.53 µg equivalents/gram in blood cells for all low dose male and female rats). Dosing regimen did not result in any apparent accumulation of residual radioactivity.
Excretion data showed that urine and feces were both significant routes for elimination of metolachlor derived radioactivity. In the low dose groups, the urine appeared more of a predominant route for excretion in female rats than in males, whereas fecal excretion was slightly higher in males. However, at the high oral dose, there were no apparent sex-related differences in the pattern of urinary excretion. Examination of urinary excretion data as presented in graphical format indicated that at the 300 mg/kg dose, excretion was delayed vs the low oral dose, suggesting saturation of elimination.

Metabolism of metolachlor in this study was complex, with up to 32 metabolites identified in urine and/or feces. The "major" urinary metabolite found in all dose groups was the metabolite designated CGA-46129. This metabolite was present as 5.6-13.1% of the total radioactive residue (TRR) in rat urine across all dose groups, and was highest in the intravenously dosed group. In the orally dosed rats, the percentage of this metabolite decreased from approximately 13% of TRR to between 5.6-9.2% of TRR. Other metabolites identified in urine which constituted near or at 5% of TRR were U10 (CGA-37735), U13, U17, U1, "polar 1", and "polar 2." The radioactivity constituting the 'polar 1' and 'polar 2' regions was further broken down to at least 12 components by TLC, but the identity of the metabolites in these regions was not demonstrated.

In feces, a similarly complex metabolite profile was obtained. The "major" metabolite observed in feces, F9, was identical to U7, or CGA-46129. Except for intravenously dosed rats, where the percentage of this metabolite in feces was equivalent in male and female rats (11.6 and 13.2% of TRR, respectively), the percentage of F9 in feces of orally dosed rats was always higher in males than in females. Other fecal metabolites identified at or near 5% of TRR in feces included F2 (CGA-41638), F3 (CGA-133275), F7, F8 and F8', F16, F14, and F17.

Based on these data, a scheme for metabolism of metolachlor was proposed.

The study is classified as Acceptable/guideline and satisfies the guideline requirements for a metabolism study in rats (85-1; OPPTS 870.7485)

S-Metolachlor

Executive Summary: In a rat metabolism study (MRID 44491402), the rat urinary and fecal metabolite patterns were compared following the administration of [Phenyl-U-^{14}C] CGA-77102 (S-Metolachlor) (Groups B1, D1, V1, G1, and G2) from the accompanying study (MRID

44491401) and after administration (3 rats/sex) of a single oral low dose (0.5 mg/kg, Group B2) of [Phenyl-U-^{14}C] CGA-24705 (R/S-Metolachlor, racemate). The pooled urine and feces (0-48 or 0-72 hours) from each group were subjected to clean-up or extraction prior to further analysis by 2-dimensional thin layer chromatography (2-D TLC). Bile fluid (genuine) from Groups G1 and G2 was also analyzed by 2D TLC. Selected bile and urine specimens were also examined for metabolite stability during the storage period lasting up to five months. Biliary metabolites seemed to be stable under the storage conditions. However, two out of three tested urine specimens showed large metabolite profile changes in at least eight of the 18 total fractions before and after storage. The study report did not explain how these results might impact the interpretation of the comparative metabolite profiles.

The 72 hour mean recovery of radioactivity in urine, feces, and carcass following administration of 0.5 mg/kg of [Phenyl-U-^{14}C] CGA-24705 was 43.1%, 47.0%, and 7.4% in males and 54.0%, 39.4%, and 4.1% in females, respectively. In contrast, both sexes excreted more of the label in the feces (M:F 59.7%:53.4%) than in the urine (M:F 29.4%:39.8%) during the same period following administration of the same dose of [Phenyl-U-^{14}C] CGA-77102 (the S-enantiomer) (MRID 44491401).

The urinary and fecal metabolite profiles, with 31 and 15 metabolite fractions, respectively, were qualitatively similar among all groups; however, there were large quantitative differences, based on the dosing formulation, on one hand, and the sex of the animal, on the other. Based on a percentage of the dose, several of the major urinary metabolite fractions (e.g., U1, U2, U3, U18, U24, and U30) were more abundant in the case of the racemic-Metolachlor (CGA-24705) than the S-Metolachlor (CGA-77102); in contrast, several fecal metabolite fractions (e.g., F9, F10, F12, and F13) were present at higher levels in the case of CGA-77102 than CGA-24705. On the other hand, there were sex-related differences regardless of the dosing formulation where, for instance, females had greater urinary concentrations than males of several metabolite fractions, including U3, U4, U8, U9, U18, U20, and U30; the males, however, excreted more of fractions U1 and U24 than the females. Also, several fecal fractions including F1, F3, F5, F6, F7, F8, and F13 were influenced by the sex regardless of the dose level (e.g. B1 vs. D1) or the stereochemical make-up of Metolachlor (B1 vs. B2). Other metabolite fractions were dependent on both the sex and the chemical formulation as, for instance, in the case of metabolite U2 which, relative to the opposite sex within the same group, was more abundant in the urine of the females of Group B2 (CGA-24705) and in the urine of the males of Group B1 (CGA-77102).

The bile fluid accounted for 79.8% of the administered low or high dose of CGA-77102 (Groups G1 and G2) where the 2D-TLC showed 14 biliary metabolite fractions (G1-G14) in the high dose Group and only six metabolites in the low dose Group. The two metabolite fractions G7 and G8 accounted, respectively, for 33.3% and 9.6% of the administered low dose and 31.3% and 14.6% of the administered high dose. Other major biliary metabolites were G3, G9, and G10 which accounted for about 5%, 5-7%, and 3-5%, respectively, of either dose group.

The results clearly show that the metabolite profile in excreta and bile fluid is very complex and that Metolachlor (racemate or S-enantiomer) is extensively metabolized. This was also shown earlier by another rat metabolism study on the absorption, distribution, excretion, and metabolite identification of racemic CGA-24705 (MRID 43164201, reviewed by T. McMahon, HED doc. no. 010990 dated May 23, 1994). No actual metabolites or pathways were identified in the current study and there were no data to support or refute the previous findings of four major degradation pathways with more than 30 metabolites. However, knowing the enantiomeric stereospecific reactions/metabolites is not likely to help in making comparative risk assessments between R/S-Metolachlor (CGA-24705) and S-Metolachlor (CGA-77102) since the contribution of each metabolite to the overall toxicity of Metolachlor is not well understood. Furthermore, other bridging animal studies with CGA-77102 should highlight possible toxicity differences from the well-studied CGA-24705 due to variations in the metabolite profiles.

The Registrant is requested to comment on or provide information on a number of issues including: 1) The stereoisomeric purity of CGA-24705 and CGA-77102. 2) The adequacy of the storage conditions and the validity of the metabolite profile results in light of the storage-related results variability. 3) Explain why, relative to the other dosing formulation, some metabolite fractions (e.g., F10, F12, and F13) were up to 7-fold higher in the case of the S-enantiomer (CGA-77102) while some urinary metabolite fractions (e.g., U1, U2, and U3) were up to 4-fold higher in the case of CGA-24705. 4) Provide rational for dose selection. 5) The Registrant might also have to comment on the possible formation and the level of methylethylaniline from either dosing formulation and the possible contribution of this metabolite to the carcinogenicity of Metolachlor. This issue was raised earlier by T. McMahon (HED document no. 010990 dated May 23, 1994) and might need to be followed up by HED's risk assessors who are in charge of S-Metolachlor.

The study is classified as **Guideline/unacceptable**. However, it may be Upgradable, pending the receipt of the Registrant's responses to the requested information and further assessment by HED.

Executive Summary: In a metabolism study (MRID 44491401) [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.

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).

870.7600 Dermal Absorption - Rat

In a dermal penetration study (MRID 41833102), ^{14}C-CGA 24705 (% a.i. unknown) suspended in deionized water was applied to a 10 cm^2 area of the backs of 4 male Crl:CD®BR rats/group at doses of 0.01, 0.1 or 1.0 mg/cm^2. Each dose group was exposed for either 2, 4, 10 or 24 hours and then the area was washed and the animals sacrificed. Another 4 animals/dose group were treated for either 10 or 24 hours, the skin was washed and they were placed in a metabolism cage for collection of urine and feces. Sacrifice was 72 hours later. The amount of radioactivity in the blood, urine, feces, carcass, skin and cage wash was determined for all animals.

CGA 24705 was rapidly absorbed with significant bioaccumulation. The total percentage of the applied dose which was found in the blood, urine, feces, carcass and cage wash (or absorbed) after 10 hours was 32.93, 20.26 and 6.98 at 0.01, 0.1 and 1.0 mg/cm^2, respectively. The percentage remaining on the skin was 24.66, 20.89 and 12.69 at the respective doses. The total percentage of the applied dose in the blood, urine, feces, carcass and cage wash (or absorbed) after 24 hours was 62.84, 26.85 and 16.15 at 0.01, 0.1 and 1.0 mg/cm^2, respectively. The percentage remaining on the skin was 11.09, 19.14 and 15.49 at the respective doses.

For rats with skin washings at 10 hours and sacrifice 72 hours after washing, the total percentage of the applied dose found in the blood, urine, feces, carcass and cage wash was 50, 38.61 and 15.46 at 0.01, 0.1 and 1.0 mg/cm^2, respectively. The percentage remaining on the skin was 5.30, 3.48 and 3.54 at the respective doses. For rats with skin washings at 24 hours and sacrifice 72 hours after washing, the percentage of the applied dose found in the blood, urine, feces, carcass and cage wash was 67.32, 43.46 and 30.49 at 0.01, 0.1 and 1.0 mg/cm^2, respectively. The percentage remaining on the skin was 3.39, 1.36 and 1.42 at the respective doses.

The study is classified as **Acceptable/guideline** and **satisfies** the guideline requirements for a dermal penetration study in rats (85-3; OPPTS 870.7600).

Comments about Dermal Absorption Factor: The percentage of the applied dose found in blood, urine, feces, carcass and cage was increased during the period between skin wash (10 hours) and sacrifice (72 hours). During the same period, the levels in the skin decreased by a similar amount. This observation suggested that metolachlor retained in skin was absorbed during the pre-sacrifice period. Therefore, the HIARC selected 58% dermal absorption value based on the combined values at 10 hours measurement (33%) and at the amount remaining on the skin (25%).

5.0 TOXICITY ENDPOINT SELECTION

5.1 See Section 9.2 for Endpoint Selection Table.

5.2 Dermal Absorption

Dermal Absorption Factor: 58% (10-hour value of 33% absorption plus 25% remaining on the skin)

The dermal absorption factor is required for long-term risk assessment since an oral dose was selected for this exposure periods. Risk assessments are not required for short- and intermediate-term dermal exposures.

5.3 Classification of Carcinogenic Potential

5.3.1 In the rat chronic toxicity/carcinogenicity study, there was a statistically significant increase in liver adenomas and combined adenomas/carcinomas in female rats. In male rats, there was a statistically significant trend but no pair-wise significance for liver tumors. There was no evidence of carcinogenicity in mice.

5.3.2 Classification of Carcinogenic Potential

Metolachlor was classifed by the HED Cancer Peer Review Committee (CPRC) as a Group C - possible human carcinogen (CPRC report dated November 16, 1994).

5.3.3 Quantification of Carcinogenic Potential

Margin of Exposure methodology should be used for estimation of human risk.

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

Based on currently available data, there is no quantitative / qualitative evidence of increased susceptibility of rat or rabbit fetuses to metolachlor or s-metolachlor exposures *in utero* in the prenatal developmental studies.

There is no quantitative / qualitative evidence of increased susceptibility in multi-generation reproduction study in rats. The offspring NOAEL of 25.9 mg/kg/day was lower than the parental systemic NOAEL of 85.1 mg/kg/day. The basis for setting the offspring NOAEL was decreased postnatal body weights at days 14 and 21 for F_{1a} litters and days 4, 7, 14 and 21 for F_{1b} litters. The

HIARC concluded that since a similar body weight decrease was not seen on lactation day 0, the cause of the effect on later lactation days could be due to exposure of the pups to metolachlor in the diet and/or milk. In addition, the body weight decreases were minor (91% of the control value on Day 14/21). Therefore, the HIARC concluded there is no quantitative increased postnatal susceptibility in offspring.

6.2 Recommendation for a Developmental Neurotoxicity Study

There are no neurotoxicity studies available. There was no evidence of neurotoxicity or neuropathology in any of the studies available in the database. The clonic and tonic convulsions and excessive salivation seen in maternal animals at the Limit Dose (1000 mg/kg/day) was considered to be agonal since these signs were see only in dams that died at this dose. Based on these results, a developmental neurotoxicity study is not required currently.

7.0 TOXICOLOGY STUDIES WITH METABOLITES

A series of acute, subchronic, developmental (rat) and mutagenicity studies were conducted with CGA 354743 (ethane sulfonic acid metabolite of metolachlor and s-metolachlor) and CGA 51202 (oxanilic acid degradate), metabolites of metolachlor/s-metolachlor found in water.

7.1 Acute Toxicity

The acute toxicity of the metabolites was essentially comparable to the parents, except both metabolites were moderate (CGA 354743) or severe (CGA 51202) eye irritants, whereas the parents were not.

Table 4: Acute Toxicity Data on CGA 354743

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral - Rat	44931704	LD_{50} = >5000mg/kg	IV
81-1	Acute Oral - Rat	44991101	LD_{50} = >2000mg/kg	III
81-2	Acute Dermal - Rabbit	44931705	LD_{50} = > 2000 mg/kg	III
81-3	Acute Inhalation - Rat	N/A		
81-4	Primary Eye Irritation - Rabbit	44931706	moderate irritant	II
81-5	Primary Skin Irritation - Rabbit	44931707	non-irritating	IV
81-6	Dermal Sensitization - guinea pig	44931708	weak dermal sensitizer	
81-8	Acute Neurotoxicity - NA			

NA - study not available

Table 5: Acute Toxicity Data on CGA 51202

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral - Rat	44929504	LD_{50} = >2000mg/kg	III
81-2	Acute Dermal - Rabbit	44929505	LD_{50} = > 1333 mg/kg	II
81-3	Acute Inhalation - Rat	N/A		
81-4	Primary Eye Irritation - Rabbit	44929506	severe irritant	II
81-5	Primary Skin Irritation - Rabbit	44929507	non-irritating	IV
81-6	Dermal Sensitization - guinea pig	44929508	positive	
81-8	Acute Neurotoxicity - NA			

NA - study not available

7.2 Subchronic Toxicity

In the rat subchronic studies, both CGA 354743 and CGA 51202 were non-toxic at ≥1000 mg/kg/day, the limit dose. At 5000 ppm (approximately 500 mg/kg/day), only dose tested, there

was evidence of decreased body weight gain and food efficiency, increased absolute and relative liver weights and an increased incidence of hepatic centrilobular hypertrophy, although the effects were mild. In the subchronic study in the dog with CGA 354743, no effects were observed at 1000 mg/kg/day.

870.3100 90-Day Oral Toxicity - Rat - CGA 354743

EXECUTIVE SUMMARY: In a 90-day subchronic oral toxicity limit study (MRID 44931710), groups of 10 male and 10 female Crl: CD BR rats were given CGA-354743 (Lot/Batch # KI-5408/6, 98% a.i.) administered in the diet at concentrations of 0, 360, 1200, 6000, or 20,000 ppm. These concentrations were equivalent to 0, 25.1, 86.2, 427.0 or 1545.0 mg/kg/day for males and 0, 28.4, 98.3, 519.0 and 1685.0 mg/kg/day for females. An additional 10 male and 10 female rats were given CGA-77102 (s-Metolachlor)(Lot/Batch # P.501001, 98.5% a.i.) administered in the diet at 5000 ppm (equivalent to 429 mg/kg/day for males and 563 mg/kg/day for females). The study was designed to assess the subchronic oral toxicity of CGA-354743 technical and to compare its toxic effects with those of its parent compound, CGA-77102 technical.

No deaths or clinical signs of toxicity occurred during this study. In addition, no statistically significant changes in body weight, body weight gain, food consumption, food efficiency, ophthalmologic examination, urinalysis, or histopathology was reported for animals fed CGA-354743. Limited and sporadic statistically significant changes in hematology, clinical chemistry, water intake and organ weight data were not dose-dependent, and were of questionable toxicological and biological importance.

Dietary exposure to CGA-77102 produced a statistically significant decreased body weight gain (-20%, $p \leq 0.01$) in males during week 1 only. Females exposed to CGA-77102 showed decreased body weight gain (-19%) by week 13, but these changes were not statistically significant. The food efficiency of rats fed CGA-77102 was decreased relative to their respective control animals. Male and female rats had increased absolute and relative liver weights. These results are consistent with a mild liver hypertrophy in females.

Based on the data presented in this study, the NOAEL is ≥20,000 ppm (1543 mg/kg/day and 1685 mg/kg/day for females) for CGA-354743. A LOAEL could not be established. At 5000 ppm (429 mg/kg/day in males and 563 mg/kg/day in females) CGA-77102 , there evidence of decreased body weight gain and food efficiency, increased absolute and relative liver weights and an increased incidence of hepatic centrilobular hypertrophy, although the effects were mild.

This subchronic oral toxicity study in rats is classified as **Acceptable/Guideline [OPPTS 870.3100 (§82-1a)]** and satisfies the guideline requirements.

870.3100 90-Day Oral Toxicity - Rat - CGA 51202

EXECUTIVE SUMMARY: In a subchronic oral feeding study, (MRID 44929509), CGA-51202 technical (100% a.i.; batch No. JD 7069/3) was fed to groups of 10 male and 10 female albino rats at dose levels of 0, 300, 1000, or 15,000 ppm for 3 months. The average achieved doses for the corresponding groups were 0, 18.7, 62.1, and 1000 mg/kg bodyweight for males, and 0, 20.6, 67.3, and 1020 mg/kg for females.

All animals survived to study termination and no treatment-related clinical signs were observed. There were no treatment-related effects on body weight, food consumption, ophthalmoscopic parameters, or urinalysis. Platelet counts were decreased 16% ($p<0.01$) in high-dose males. Total protein in high-dose males (5% decrease, $p<0.01$) and females (4% decrease, N.S.) was slightly decreased due to decreased globulin in males and decreased albumin and globulin fractions in females. These effects were not considered biologically significant. There were no treatment-related organ weight effects or macroscopic or microscopic lesions. **Under the conditions of this study, the NOAEL is 15,000 ppm in the diet (1000 mg/kg for males, 1020 mg/kg for females, limit dose) based on no biologically significant effects. A LOAEL was not identified.**

This subchronic toxicity study in rats (82-1) is classified as **Acceptable/Guideline.** It satisfies the guideline requirement for a subchronic dietary toxicity study in rodents.

870.3150 90-Day Oral Toxicity - Dog - CGA 354743

EXECUTIVE SUMMARY: In a 90-day subchronic oral toxicity study (MRID 44931709), CGA-354743 technical (Batch Nos. KI-5408/4 and KI-5408/5, 99% a.i.) was administered to 4 purebred beagle dogs/sex/dose by capsule at dose levels of 0, 50, 200, 500, and 1000 mg/kg/day for 13 weeks. An additional group of 4 males and 4 females received parent compound (CGA-77102 technical, Batch No. P.501001, 98.5% a.i.) at 200 mg/kg/day for 13 weeks.

There were no significant treatment related effects on mortality, body weight, food consumption, food conversion ratios, ophthalmological findings, hematology and urinalysis parameters, or gross and histopathological findings. Vomiting did occur at a higher incidence in females treated with 1000 mg/kg/day of CGA-354743. Clinical signs in animals treated with CGA-77102 included vomiting, salivation and hematuria. Mean alkaline phosphatase activity was slightly increased in males receiving 1000 mg/kg/day CGA-354743 at weeks 7 and 13 to levels which were less than double the pretest mean for this group. This finding correlated with slightly increased absolute liver weights, but there were no corresponding histopathological findings, or toxicologically significant increases in other biochemistry parameters. In females, mean ALP activities remained within the reference range for untreated animals and mean GGT activity exceeded the reference range only at week 13 and only for the 500 mg/kg/day CGA-354743 group. Absolute liver weights and liver weights relative to body weights were increased in females receiving 500 and 1000 mg/kg/day. In the absence of corresponding histopathological findings or biologically

significant increases in biochemistry parameters consistent with adverse hepatic effects, this finding is not considered toxicologically significant.

Mean ALP and GGT activities were significantly increased in both sexes at weeks 7 and 13 given CGA-77102. In addition, ALT activity of males was increased at weeks 7 and 13. Absolute and relative liver weights were significantly increased in males and females. There were small increases in the incidences and severity of bile duct hyperplasia, perilobular fatty change in the livers of both sexes, and cystic hyperplasia of the gallbladder occurred only in the parent compound group.

The results appear to indicate that CGA-354743 may have effects (vomiting, slight increases in ALT and liver weight) similar to those of its parent compound, CGA-77102; however, at the limit dose, 1000 mg/kg/day, the effects observed were so slight and of questionable toxicological significance in CGA-35743-treated dogs that a definitive comparison of the two compounds cannot be made.

Based on the data presented in this study, the LOAEL was not determined, and the NOAEL was greater than or equal to 1000 mg/kg/day.

This subchronic oral toxicity study in dogs is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a subchronic oral study [OPPTS: 870.3150 (§82-1b)] in dogs since the limit dose was tested.

7.3 Prenatal Developmental Toxicity

There was no evidence of maternal or developmental toxicity in the rat prenatal developmental study with CGA 354743 or CGA 51202 at the limit dose of 1000 mg/kg/day.

870.3700a Prenatal Developmental Toxicity Study - Rat - CGA 354743

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44931711), 28 presumed pregnant Wistar B: Hanlbm:WIST rats per group were administered CGA 354743 Technical (98%; Batch No. KI-5408/6) by gavage in 0.5% aqueous sodium carboxymethylcellulose in 0.1% aqueous polysorbate 80 at doses of 0, 250, 500, or 1000 mg/kg/day on gestation days (GD) 6-15, inclusive. Controls were treated with 0.5% sodium carboxymethylcellulose in 0.1% aqueous polysorbate 80 (vehicle). On GD 21, dams were sacrificed, subjected to gross necropsy, and all fetuses examined externally. Approximately one-half of each litter was processed for visceral examination and the remaining one-half was processed for skeletal examination.

All animals survived to terminal sacrifice. No clinical signs of toxicity were observed in any animal. Maternal body weights, body weight gains, and food consumption were similar between the treated and control groups throughout the study. Maternal necropsy was unremarkable.

Therefore, the maternal toxicity NOAEL is ≥1000 mg/kg/day and the maternal toxicity LOAEL was not identified.

No differences were observed between the treated and control groups for number of corpora lutea, number of implantation sites, live fetuses/dam, pre- and post-implantation losses, fetal body weights, or fetal sex ratios.

No treatment-related external, visceral, or skeletal malformations/variations were observed in any fetus from any group.

The high dose is equivalent to the limit dose for developmental toxicity studies.

Therefore, the developmental toxicity NOAEL is ≥1000 mg/kg/day and the developmental toxicity LOAEL was not identified.

This study is classified as **Acceptable/Guideline** and satisfies the requirements for a developmental toxicity study [870.3700 (§83-3a)] in rats.

870.3700a Prenatal Developmental Toxicity Study - Rat - CGA 51202

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44929510), 24 presumed pregnant Tif: RAI f (SPF) (hybrids of RII/1 × RII/2) rats per group were administered CGA 51202 Technical (100%; Batch No. JD 7069/3) by gavage in 0.5% aqueous sodium carboxy-methylcellulose solution at doses of 0, 10, 100, or 1000 mg/kg/day on gestation days (GD) 6-15, inclusive. Controls were treated with 0.5% sodium carboxymethylcellulose (vehicle). On GD 21, dams were sacrificed, subjected to gross necropsy, and all fetuses examined externally. Approximately one-half of each litter was processed for visceral examination and the remaining one-half was processed for skeletal examination.

One low-dose animal was sacrificed moribund on GD 20 with a urogenital infection. All other animals survived to terminal sacrifice. No clinical signs of toxicity were observed in any animal. Maternal body weights and body weight gains were similar between the treated and control groups throughout the study. Food consumption was not affected by treatment. Maternal necropsy was unremarkable.

Therefore, the maternal toxicity NOAEL is ≥1000 mg/kg/day and the maternal toxicity LOAEL was not identified.

No differences were observed between the treated and control groups for number of corpora lutea, number of implantation sites, live fetuses/dam, pre- and post-implantation losses, fetal body weights, or fetal sex ratios.

No treatment-related external, visceral, or skeletal malformations/variations were observed in any fetus from any group.

The high dose is equivalent to the limit dose for developmental toxicity studies.

Therefore, the developmental toxicity NOAEL is ≥1000 mg/kg/day and the developmental toxicity LOAEL was not identified.

This study is classified as **Acceptable/Guideline** and satisfies the requirements for a developmental toxicity study [870.3700 (§83-3a)] in rats.

7.4 Mutagenicity

There was no evidence of mutagenicity *in vitro* or *in vivo* with either CGA 354743 or CGA 51202.

Mutagenicity Studies with CGA 354743

Gene Mutation 870.5100	44931712 (1996) acceptable/guideline 312.5, 625.0, 1250.0, 2500.0 and 5000.0 µg/plate in the presence and absence of mammalian metabolic activation (S9-mix)	Strains TA98, TA100, TA102, TA1535 and TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* were exposed to CGA-354743 tech. in DMSO at concentrations of 312.5-5000.0 µg/plate in the presence and absence of mammalian metabolic activation (S9-mix). There was no evidence of induced mutant colonies over background.
Cytogenetics 870.5300	44991102 (1999) acceptable/guideline concentrations of 185.19, 555.56, 1666.67, 5000.00 µg/mL in the presence and absence of mammalian metabolic activation (S9-mix).	Chinese hamster V79 cells in culture were exposed to CGA-354743 tech. in bidistilled water at concentrations of 185.19 - 5000.00 µg/mL in the presence and absence of mammalian metabolic activation (S9-mix). There was suggestive (statistical) evidence of a possible induction of mutant colonies over background; however, the results are unlikely to be biologically significant because the absolute numbers of mutant colonies were low and within the testing laboratory's historical solvent control ranges.
870.5395 Micronucleus assay in mouse bone marrow cells	44931713 (1998) acceptable/guideline 1250, 2500 and 5000 mg/kg body weight	Five mice/sex/dose were treated once each via oral gavage with CGA-354743 tech. at doses of 1250 - 5000 mg/kg body weight. There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any dose or treatment time.
Other Effects 870.5503	44931714 (1998) acceptable/guideline concentrations of 9.77, 39.06, 156.25, 625.00, 2500.00, 5000.00 µg/mL	Primary rat hepatocyte cultures were exposed to CGA-354743 tech in bidistilled water at concentrations of 9.77 - 5000.00 µg/mL for 16 to 18 hours in an initial assay and to concentrations of 78.13 - 2500 µg/mL for 16 to 18 hours in a confirmatory assay. There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures (nuclear silver grain counts), was induced.

Mutagenicity Studies with CGA 51202

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Gene Mutation 870.5100 *Salmonella/Escherichia* bacterial reverse mutation assay	44929512 (1992) acceptable/guideline 312.5, 625, 1250, 2500, 5000 ug/plate	Strains TA98, TA100, TA1535 and TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* were exposed to CGA-51202 technical in DMSO at concentrations of 312.5 - 5000.0 µg/plate in the presence and absence of mammalian metabolic activation. There was no evidence of induced mutant colonies over background.
Cytogenetics 870.5395, Micronucleus assay in mouse bone marrow cells	MRID 44929511 (1992) 600, 1200 or 2400 mg/kg acceptable/guideline	Five mice/sex/dose were treated once via oral gavage with CGA-51202 technical at doses of 600-2400 mg/kg body weight. There was no biologically significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any dose or treatment time used in the study.
Gene Mutation 870.5300 mammalian cell gene mutation assay at the HPRT locus, Chinese hamster V79 cells	MRID 45001201 (1999) 500, 1000, 2000 or 4000 ug/ml in initial assay; 375, 750, 1500 or 3000 ug/m l in confirmatory assay, in the presence and absence of mammalian metabolic activation (S9-mix).	CGA 51202 tech. was tested up to cytotoxic concentrations. Statistically significant increases in mean mutant frequency were seen in the initial assay with S9-mix at 500 µg/mL (6.66 x 10^{-6}) and 1000 µg/mL (5.56 x 10^{-6}) compared to the solvent control value of 4.02 x 10^{-6} and without S9-mix at 500 µg/mL (15.35 x 10^{-6}) compared to the solvent control value of 12.90 x 10^{-6}. The increases were small and the actual mean mutant frequencies were within the range of historical solvent control values. No positive dose-response was seen and no statistically significant increases in mean mutant frequencies were seen in the confirmatory assay. The solvent and positive controls induced the appropriate response. **There was no evidence of a biologically significant induction of mutant colonies over background.**

7.5 Metabolism

870.7485 Metabolism - Rat

EXECUTIVE SUMMARY: In a metabolism study (MRID 44931715), groups of three male and three female rats were each given [phenyl-U-^{14}C] CGA 77102 (batch no. ILS-143.1; purity 98.9%) and non-radiolabeled CGA 77102 (batch no. AMS 757-101; purity 99.8%) to provide a total single oral dose of 0.5 or 100 mg/kg. Urinary and fecal excretion were monitored over 72 hours and major metabolites identified and quantified. The study focused on evaluating the presence of the metabolites CGA 354743, CGA 368208, and CGA 357704 in the excreta of rats.

There were no deaths or overt signs of toxicity attributed to the test material. Actual administered doses were 3-8% greater than nominal. Overall recovery of administered radioactivity was an acceptable 93.83-99.18%. Urinary excretion and carcass burden data implied that absorption was approximately 38-49% of the administered dose. Most (86.5-91.7%) of the radioactivity recovered at 72 hours post was associated with the urine and feces. The available data suggested that urinary excretion was slightly greater in female rats than male rats (42% for low- and high-dose females as compared to 30% and 32% of low- and high-dose males, respectively), and fecal elimination was expectedly less (approximately 13-15%) for females than for males. However, the small sample size (three rats per sex) precludes a definitive assessment of gender-specific differences in excretory pattern. Time-course data for absorption and excretion were not provided. Based upon the residual radioactivity in the carcasses, accumulation in the tissues was less than 10% of the administered dose at 72 hours after administration.

Both urinary and fecal metabolites were identified and quantified. For both routes of elimination, three major metabolites were identified but none represented more than 0.25% of the administered dose. Characterization of these metabolites and comparison to known reference standards revealed them to be CGA 357704, CGA 354743, and CGA 368208. In the feces, CGA 357704 and CGA 354743 represented a notably greater percent of the administered dose than in the urine. The amounts of CGA 368208 were similar in the feces and urine. Biliary excretion experiments were not performed and, therefore, no assessment can be made regarding biliary or gut microflora as the source of these biotransformation products in the feces.

This metabolism study in rats is **Acceptable/Non-guideline**. Although not satisfying the requirements for a Metabolism and Pharmacokinetics study [OPPTS 870.7485 (85-1)], the study was well designed and conducted, and provided supplemental data regarding the quantitation and identification of urinary and fecal metabolites in rats given a single oral dose of CGA 77102.

Executive Summary: In a metabolism study (MRIDs 44931716 and 44931717), groups of four male and female and six male Tif: RAI f (SPF) rats were given single oral doses of [Phenyl-U-^{14}C]-CGA-376944 (0.5 mg/kg nominal; Batch No. ILS-125.4 radiochemical purity >95.5%), for the metabolism and bile-duct cannulation studies, respectively.

There were no deaths or overt signs of toxicity that could be attributed to the test material. Weight loss in bile-duct cannulated rats was attributed to surgical trauma. Radioactivity inventory indicated an acceptable 96.46-99.01% recovery of the administered dose among the experimental groups. Based on urinary excretion, biliary excretion, and carcass burden, 17.35% of the administered radioactivity was absorbed following a single oral dose of 0.5 mg/kg of [Phenyl-U-^{14}C]-CGA-376944. Absorption was rapid but limited and most of the absorbed radioactivity (92.3%) was excreted within 24 hours; primarily in the bile. At 72 hours, measurable radioactivity was found only in the liver of non-cannulated rats. Carcass burdens accounted for <0.01% of the administered dose at necropsy.

Fecal elimination was the major route of excretion, accounting for most of the administered oral dose in non-cannulated rats (94.24-96.27%). Fecal excretion was rapid with 98.8-99.2% of the fecal excretion occurring within 24 hours post-dosing. Urinary excretion, accounted for only 2.1-4.4% of the dose in non-cannulated rats and 5.3% in bile-duct cannulated rats. Urinary excretion was rapid and nearly complete within 24 hours of dosing. Biliary excretion represented 11.5% of the administered dose at 48 hours. The majority of biliary excretion (99.2%) occurred within 24 hours after dosing. In bile-duct cannulated animals, an additional 76.8% of the administered dose was excreted in the feces. Based on these data, biliary excretion is a contributor to fecal elimination of the test material. This appears consistent with the occurrence of enterohepatic circulation via the hepatic portal system and bile-duct. Only a minor percentage of the dose (5.3%) appeared to enter the systemic circulation where it was rapidly excreted by the kidneys. No biologically relevant gender-related differences were detected in the oral dose groups.

Blood pharmacokinetic parameters could not be calculated due to low blood concentrations and rapid clearance of the administered dose. Blood levels of radioactivity peaked in both sexes within one hour post-dosing.

It is evident from the results of this study that the test material undergoes limited but rapid absorption and nearly complete excretion within 24 hours. The primary route of excretion is via the feces with biliary excretion products representing about 15.0% of the fecal excretion products. At the dose tested, [^{14}C]-CGA-376944 exhibits little potential for accumulation in the tissues. There were no significant gender-related differences in absorption and disposition of the test material. The unchanged test material accounted for >90% of the dose in both males and females. The unknown metabolites of urine and feces, separated by TLC accounted for 0.2-2.8% of the administered radioactivity and were not characterized further.

This combined metabolism study in rats is **Acceptable/Guideline** and satisfies the requirements for a Metabolism and Pharmacokinetics study [OPPTS 870.7485 (§85-1)].

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9.0APPENDICES
Tables for Use in Risk Assessment

9.1 Toxicity Profile Summary Tables

9.1.1 Acute Toxicity Table - See Section 4.1

9.1.2 Subchronic, Chronic and Other Toxicity Tables

CHEMICAL: Metolachlor
PC CODE: 108801

Toxicity Profile

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents	44775401 (1999) Acceptable/guideline 0, 30, 300, 3000 ppm (M/F: 0, 2.00/2.32, 20.2/23.4, 210/259 mg/kg/day)	NOAEL for males = 3000 ppm LOAEL for males not established NOAEL for females = 300 ppm LOAEL for females = 3000 ppm based on decreased body weight/body weight gain
870.3150 180-Day oral toxicity in nonrodents	00032174 (1980), 43244001 unacceptable/guideline 0, 100, 300, 1000 ppm (M/F: 0, 2.92/2.97, 9.71/8.77, 29.61/29.42)	NOAEL = 300 ppm LOAEL = 1000 ppm based on decreased body weight gain
870.3200 21/28-Day dermal toxicity	41833101 (1987) acceptable/guideline 0, 10, 100 or 1000 mg/kg/day	systemic NOAEL = 1000 mg/kg/day. systemic LOAEL was not established dermal irritation NOAEL was not established dermal irritation LOAEL = 10 mg/kg/day based on very slight erythema, dry skin and fissuring (one animal)
870.3700a Prenatal developmental in rodents	00151941 (1985) acceptable/guideline 0, 30, 100, 300 or 1000 mg/kg/day	**maternal toxicity NOAEL = 300 mg/kg/day.** **maternal toxicity LOAEL = 1000 mg/kg/day based on an increased incidence of death, clinical signs of toxicity (clonic and/or toxic convulsions, excessive salivation, urine-stained abdominal fur and/or excessive lacrimation) and decreased body weight gain.** **developmental toxicity NOAEL = 300 mg/kg/day developmental toxicity LOAEL = 1000 mg/kg/day based on slightly decreased number of implantations per dam, decreased number of live fetuses/dam, increased number of resorptions/dam and significant decrease in mean fetal body weight**
870.3700b Prenatal developmental in nonrodents	00041283 (1980) acceptable/guideline 0, 36, 120 or 360 mg/kg/day	maternal toxicity NOAEL = 120 mg/kg/day. maternal toxicity LOAEL = 360 mg/kg/day based on an increased incidence of clinical observations (persistent anorexia) and decreased body weight gain developmental toxicity NOAEL = 360 mg/kg/day developmental toxicity LOAEL was not established.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3800 Reproduction and fertility effects	00080897 (1981) acceptable/guideline 0, 30, 300 or 1000 ppm (F_0 males: 0, 2.4, 23.5 and 75.8 mg/kg/day; F_0 females: 0, 2.5, 26.0 and 85.7 mg/kg/day; F_1males: 0, 2.3, 23.7 and 76.6 mg/kg/day; F_1 females: 0, 2.6, 25.7 and 84.5 mg/kg/day).	Parental toxicity NOAEL = 1000 ppm (F_0 males/females: 75.8/85.7 mg/kg/day; F_1males/females: 76.6/84.5 mg/kg/day). Parental toxicity LOAEL was not established Reproduction toxicity NOAEL = 1000 ppm (F_0 males/females: 75.8/85.7 mg/kg/day; F_1males/females: 76.6/84.5 mg/kg/day). Reproduction toxicity LOAEL was not established Offspring NOAEL = 300 ppm (F_0 males/females: 23.5/ 26.0 mg/kg/day; F_1males/females: 23.7/25.7 mg/kg/day). Offspring LOAEL = 1000 ppm (F_0 males/females: 75.8/85.7 mg/kg/day; F_1males/females: 76.6/84.5 mg/kg/day) based on decreased body weight.
870.4100b Chronic toxicity dogs	40980701, 41164501, 42218601 and 42218602. (1989) acceptable/guideline 0, 100, 300 or 1000 ppm (males: 0, 3.5, 9.7 and 32.7 mg/kg/day, respectively; females: 0, 3.6, 9.7 and 33.0 mg/kg/day, respectively) for one year.	NOAEL = 300 ppm (9.7 mg/kg/day) for females LOAEL = 1000 ppm for females (33.0 mg/kg/day) based on decreased body weight gain LOAEL for males was not established; NOAEL = 1000 ppm (32.7 mg/kg/day).
870.4300 Chronic toxicity/ carcinogenicity rodents	00129377 (1983) acceptable/guideline 0, 30, 300 or 3000 ppm (0, 1.5, 15 or 150 mg/kg/day based on 1 ppm in food equals 0.05 mg/kg/day)	NOAEL = 300 ppm (15 mg/kg/day) for females LOAEL = 3000 ppm (150 mg/kg/day) for females based on slightly decreased body weight gain and food consumption. The LOAEL was not established for males. The NOAEL was 3000 ppm (150 mg/kg/day). **Administration of doses up to 3000 ppm was associated with statistically significant increases in liver adenomas and combined adenoma/carcinoma in female rats. In male rats, there was a stastically significant trend but not pair-wise significance for liver tumors.**
870.4300 Carcinogenicity mice	00117597 (1982) acceptable/guideline 0, 300, 1000 or 3000 ppm (0, 45, 150 or 450 mg/kg/day)	NOAEL = 100 ppm (150 mg/kg/day) LOAEL = 3000 ppm (450 mg/kg/day) based on possible treatment-related deaths in females and decreased body weight/body weight gain in males and females **no evidence of carcinogenicity**
Gene Mutation 870.5100 - bacterial reverse mutation	00015397 (1976) acceptable/guideline 10, 100, 1000 and 10,000 ug/plate	negative up to cytotoxic doses (1000 ug/plate)
Gene Mutation 870.5300 - mouse lymphoma	00158929 (1984) acceptabl/guideline 9.5-190 nl/ml without activation; 10.5-280 nl/ml with activation	no effect on the incidence of mutations in the presence or absence of metabolic activation

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Cytogenetics 870.5395 - micronucleus assay in Chinese hamsters	00158925 (1984) acceptable/guideline 0, 1250, 2500 or 5000 mg/kg	no effect of treatment on incidence of micronuclei induction
Cytogenetics 870.5450 - dominant lethal assay in mice	00015630 (1978) acceptable/guideline 100 or 300 mg/kg	no effect on embryonic death, pre- and post-implantation or fertility rates in mated females
Other Effects 870.5550 - DNA Damage/Repair in rat hepatocytes	00142828 (1984) acceptable/guideline 0.125, 0.625, 3.125 or 15.625 nl/ml	negative
Other Effects 870.5550 - DNA Damage/Repair in human fibroblasts	00142827 acceptable/guideline 0.125, 0.625, 3.125 or 15.625 nl/ml	negative
Other Effects 870.5550 - Unscheduled DNA synthesis in rat hepatocytes	43244003 (1994) acceptable/guideline 1250, 2500 or 4000 mg/kg to males; 500, 1000 or 1500 mg/kg to females	negative for induction of UDS; however, significant increases in percentage of cells in S-phase were observed in females dosed at 500 mg/kg (but not at 1000 or 1500 mg/kg) and sacrificed at 15 hours

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics	MRID 00015425 (1974) unacceptable 52, 28 or 33 mg/kg to male rats	Conclusions: Urinary metabolites of CGA 24705 (N-(2-methoxy-1-methylethyl)-2-ethyl-6-methyl-chloroacetanilide) were identified following oral administration of 52 mg/kg, 28 mg/kg, and 33 mg/kg to male rats. Two metabolites, each comprising approximately 5% of chloroform extractable urinary radioactivity, were identified from oral administration of CGA 24705. These were the products CGA 37735 (2-ethyl-6-methyl-hydroxyacetanilide), in which N-dealkylation of R_1 (the N-(2-methoxy-1-methylethyl side chain) and side chain dechlorination and oxidation of R_2 (the N-chloroacetyl side chain) have occurred, and CGA 46129 (N-(1-carboxy-ethyl)-2-ethyl-6-methyl hydroxyacetanilide) in which the ether bond of R_1 has been split and oxidized to the corresponding carboxylic acid, while R_2 is similar to R_2 found in CGA 37735. In study #7/74, these 2 metabolites each represented approximately 5% of organic extractable urinary radioactivity, while in study #12/74, the percentage found as CGA 46129 was between 20-25% of urinary radioactivity, and CGA 37735 represented between 3-5% of organic extractable radioactivity. The major metabolic pathway proposed from analysis of urinary as well as fecal metabolites is one of cleavage of the ether bond and subsequent oxidation to the carboxylic acid, as well as hydrolytic removal of the chlorine atom. Conjugation of CGA 24705 or metabolites with gluronic acid or sulfate does not appear to occur. Aqueous extractable urinary radioactivity contained 58% of the total urinary radioactivity and was composed of 5 different radioactive fractions, which were not identified. Current guideline recommendations as to dose levels and use of both sexes in metabolism studies were not followed. Thus, whether the metabolic pattern is altered with dose or repeated exposure cannot be evaluated from these data.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics	40114401 (1987) unacceptable Single low (1.5 mg/kg), single high (300 mg/kg) and repeated low (1.5 mg/kg/day for 15 days)	Conclusions: Single low (1.5 mg/kg), single high (300 mg/kg) and repeated low (1.5 mg/kg/day for 15 days) oral doses of metolachlor were readily absorbed and eliminated by male and female rats. Urinary and fecal elimination of radioactivity associated with orally administered [^{14}C] metolachlor was essentially complete within 48 to 72 hours after dosing. Low- and high-dose females eliminated ^{14}C more rapidly ($p<0.003$, half-lives of elimination, 16.6 and 15.6 hours, respectively) than low- and high-dose males and repeated-dose animals of both sexes (half-lives, 18.2 and 20.0 hours). Elimination by all animals followed first-order kinetics. Approximately one-half to two-thirds (48 to 64 percent) of the ^{14}C administered was recovered from the urine within 7 days; similar amounts were present in the feces. Low-dose males eliminated slightly more of the radioactive dose in the feces (55 percent) than the urine (48 percent). The opposite trend was seen in the low-dose females and repeated-dose rats of both sexes; these animals excreted approximately 58 to 64 percent of the ^{14}C dose in the urine and 42.5 to 46.5 percent in the feces within 7 days after dosing. High-dose animals excreted similar amounts (58 to 60 percent) of the radioactive dose in the urine and feces. Total recoveries of ^{14}C (urine, feces, and tissues) tended to be high and were between 105 and 122.5 percent. Relatively low levels of radioactivity were present in the tissues of all animals at 7 days postdosing. Tissues of low- and repeated-dose rats contained approximately 1.6 to 2.5 percent of the ^{14}C dose; tissues of high-dose rats accounted for 3.2 (females) and 4.2 (males) percent. For all groups, most of the tissue radioactivity (1.1 to 3.0 percent of the dose) was associated with red blood cells (RBCs); RBCs also contained the highest concentrations of radiolabeled compound (0.6 to 0.9 ppm, low- and repeated-dose rats; 232 and 247 ppm, high-dose females and males, respectively), indicating that [^{14}C] metolachlor and/or its metabolites bind extensively to these cells. The next highest concentrations of radiolabel (0.03 to 0.13 ppm, low- and repeated-dose rats; 7.3 to 37 ppm, high-dose animals) were present in metabolically active tissues, including the heart, lung, kidney, liver and spleen. Brain, bone and muscle contained the smallest amounts of radioactivity (0.004 to 0.015 ppm, low- and repeated-dose rats; 1.7 to 3.5 ppm, high-dose rats). Tissue ^{14}C residues in high-dose males were approximately 250 to 500 times greater than those of low-dose males, indicating that the ratio of tissue concentrations (high dose:low dose) was much larger than the corresponding dose ratio of 200:1 (300 mg/kg: 1.5 mg/kg). In contrast, tissue ^{14}C levels of females were, in general, proportionate to dose. Tissues of low- and repeated-dose rats contained similar amounts of radioactivity. These data indicate that some ^{14}C was retained by all animals and that the greatest potential for accumulation of radioactivity was in male rats given a single high oral dose of [^{14}C] metolachlor.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics	43164201 (1992) acceptable/guideline low oral dose (1.5 mg/kg x 14 days), and a single high dose (300 mg/kg)	In a rat metabolism study (MRID # 431642-01), ^{14}C-Metolachlor was administered orally in PEG-200 [HWI 6117-208] or corn oil [ABR-94001] to groups (5 sex/dose) of male and female Sprague-Dawley rats at a low oral dose (1.5 mg/kg), repeated low oral dose (1.5 mg/kg x 14 days), and a single high dose (300 mg/kg). Control animals (1/sex) received blank formulation. Comparison of oral and intravenous data showed that of the administered dose, between 69.6% and 93.2% was absorbed. Distribution data showed that the only significant sites of residual radioactivity at 7 days post-dose were residual carcass (0.9 - 2.2% of the administered dose) and red blood cells (0.95- 1.53 µg equivalents/gram in blood cells for all low dose male and female rats). Dosing regimen did not result in any apparent accumulation of residual radioactivity. Excretion data showed that urine and feces were both significant routes for elimination of metolachlor derived radioactivity. In the low dose groups, the urine appeared more of a predominant route for excretion in female rats than in males, whereas fecal excretion was slightly higher in males. However, at the high oral dose, there were no apparent sex-related differences in the pattern of urinary excretion. Examination of urinary excretion data as presented in graphical format indicated that at the 300 mg/kg dose, excretion was delayed vs the low oral dose, suggesting saturation of elimination. Metabolism of metolachlor in this study was complex, with up to 32 metabolites identified in urine and/or feces. The "major" urinary metabolite found in all dose groups was the metabolite designated CGA-46129. This metabolite was present as 5.6-13.1% of the total radioactive residue (TRR) in rat urine across all dose groups, and was highest in the intravenously dosed group. In the orally dosed rats, the percentage of this metabolite decreased from approximately 13% of TRR to between 5.6-9.2% of TRR. Other metabolites identified in urine which constituted near or at 5% of TRR were U10 (CGA-37735), U13, U17, U1, "polar 1", and "polar 2." The radioactivity constituting the 'polar 1' and 'polar 2' regions was further broken down to at least 12 components by TLC, but the identity of the metabolites in these regions was not demonstrated. In feces, a similarly complex metabolite profile was obtained. The "major" metabolite observed in feces, F9, was identical to U7, or CGA-46129. Except for intravenously dosed rats, where the percentage of this metabolite in feces was equivalent in male and female rats (11.6 and 13.2% of TRR, respectively), the percentage of F9 in feces of orally dosed rats was always higher in males than in females. Other fecal metabolites identified at or near 5% of TRR in feces included F2 (CGA-41638), F3 (CGA-133275), F7, F8 and F8', F16, F14, and F17. Based on these data, a scheme for metabolism of metolachlor was proposed.

CHEMICAL: s-Metolachlor
PC CODE: 108800

Toxicity Profile

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents	43928923 (1995) acceptable/guideline 0, 30, 300, 3000 or 10000 ppm (0, 1.5, 15, 150 or 500 mg/kg/day)	NOAEL = 300 ppm LOAEL = 3000 ppm based on lower body weights/body weight gains, reduced food consumption and food efficiency and increased kidney weights in males
870.3100 90-Day oral toxicity rodents	44775402 (1999) unacceptable/guideline 0, 30, 300, 3000 ppm (M/F: 0, 1.90/2.13, 20.4/23.9 and 208.0/236.0 mg/kg/day0	**NOAEL = 3000 ppm (equivalent to 208 mg/kg/day in males and 236 mg/kg/day in females** **LOAEL cannot be defined**
870.3150 90-Day oral toxicity in nonrodents	43928922 (1995) acceptable/nonguideline 0, 300, 500, 1000 or 2000 ppm (M/F: 0, 9/10, 15.1/17.2, 31.1/31.5 or 62/74 mg/kg/day)	NOAEL = 2000 ppm (M/F: 62/74 mg/kg/day) LOAEL = not established
870.3700a Prenatal developmental in rodents	43928925 (1995) acceptable/guideline 0, 5, 50, 500 or 1000 mg/kg/day	**Maternal** NOAEL = 50 mg/kg/day LOAEL = 500 mg/kg/day based on increased clinical signs of toxicity, decreased body weights/body weight gains, food consumption and food efficiency. **Developmental** NOAEL = 1000 mg/kg/day LOAEL = not established
870.3700b Prenatal developmental in nonrodents	43928924 (1995) acceptable/guideline 0, 20, 100 or 500 mg/kg/day	**Maternal** NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on clinical signs of toxicity **Developmental** NOAEL = 500 mg/kg/day LOAEL = not established
Gene Mutation 870.5100 Salmonella & Escherichia/Mammalian Microsome Mutagenicity Test	43928927 (1995) acceptable/guideline 78.13-1250.0 ug/plate	In independently performed microbial mutagenicity assays, *Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and TA102 and *Escherichia coli* WP2 *uvr*A were initially exposed to 312.5-5000.0 µg/plate CGA-77102 technical (95.6%) in the presence and absence of S9 activation. For the confirmatory trial, doses of 78.13-1250.0 µg/plate ±S9 were evaluated with *S. typhimurium* strains TA1535, TA1537, TA100 and TA102; concentrations of 312.5-5000.0 µg/plate ±S9 were examined with *S. typhimurium* TA 98 and *E.coli* WP2 *uvr*A. In general, doses ≥1250.0 µg/plate ±S9 were cytotoxic for *S. typhimurium* TA1535, TA1537, TA100 and TA102 and 5000.0 µg/plate ±S9 was slightly cytotoxic for *S. typhimurium* TA98 and *E. coli* WP2 uvrA. There was, however, no indication that CGA-77102 technical induced of a mutagenic effect in any tester strain either in the presence or the absence of S9 activation.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Cytogenetics 870.5395 Micronucleus test	43928926 (1995) acceptable/guideline 500, 1000 or 2000 mg/kg	Groups of five male and five female Tif:MAGf(SPF) mice received single oral gavage administrations of 500, 1000 or 2000 mg/kg CGA 77102 technical (95.6%). Toxic signs, similar to those seen in the preliminary range-finding studies (i.e., ataxia, tremors and/or hunched posture) were recorded for high-dose males and females throughout the 48-hour postexposure. No bone marrow cytotoxicity was seen at any dose or sacrifice time. The positive control induced the expected high yield of MPEs in males and females. There was, however, no evidence that CGA 77102 technical induced a clastogenic or aneugenic effect in either sex at any dose or sacrifice time.
Other Effects 870.5550 Unscheduled DNA synthesis	43928928 (1995) acceptable/guideline 500, 1500, 3200 (females), 5000 (males) mg/kg	Groups consisting of three to four rats per sex received single oral gavage administrations of CGA-77102 Technical (95.6%) at doses of 500, 1500 or 5000 mg/kg (males) or 500, 1500 or 3200 mg/kg (females). Hepatocytes harvested at 15 and 38 hours were evaluated for viability and replicative DNA synthesis (RDS). For the UDS determination, additional groups (3/sex/dose) were exposed to 500 or 1500 mg/kg and the recovered hepatocytes were scored at 2 or 15 hours postexposure. Two of four females in the 3200-mg/kg group and 2 of 4 males in the 5000-mg/kg group died prior to the scheduled sacrifice at 38 hours. Severe cytotoxicity was seen in the hepatocytes recovered from 1 of 2 surviving males and both female survivors in the high-dose groups. Lower levels were neither toxic to the animals nor cytotoxic to the target cells. A clear dose-related increase in the percentage of cells in S-phase (RDS) was obtained from hepatocytes harvested 38 hours posttreatment of the male rats. The response ranged from a 5.3-fold increase at 1500 mg/kg to a 16.1-fold increase at the high dose (5000 mg/kg). In females, a marked increase in RDS was initially seen at 1500 mg/kg but the response declined over time with a 24.4-fold increase at 15 hours and a 12.2-fold increase at 38 hours. There was, however, no evidence that the CGA 77102 Technical at doses of 500 or 1500 mg/kg induced a genotoxic response at 2 or 15 hours posttreatment. We conclude, therefore, that the data indicate that CGA 77102 Technical was negative for genotoxicity but positive for cellular proliferation when tested up to overtly toxic and cytotoxic doses in this in vivo/in vitro rat hepatocyte RDS/UDS assay.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics	44491401 (1996) acceptable/guideline single dose of 0.5 (group B1) or 100 mg/kg (group D1) radiolabeled CGA-77102; 100 mg/kg/day non-radiolabeled CGA 77102 for 14 days followed by 0.5 mg/kg radiolabeled CGA-77102 (Group V1); single dose of 0.5 or 100 mg/kg radiolabeled CGA-77102 for bile-cannulation study	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%. 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.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
		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. 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.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics	44491402 (1996) unacceptable/guideline single dose of 0.5 (group B1) or 100 mg/kg (group D1) radiolabeled CGA-77102; 100 mg/kg/day non-radiolabeled CGA 77102 for 14 days followed by 0.5 mg/kg radiolabeled CGA-77102 (Group V1); single dose of 0.5 or 100 mg/kg radiolabeled CGA-77102 for bile-cannulation study (from MRID 44491401) single oral low dose (0.5 mg/kg, Group B2) of [Phenyl-U-^{14}C] CGA-24705 (R/S-Metolachlor, racemate)	The 72 hour mean recovery of radioactivity in urine, feces, and carcass following administration of 0.5 mg/kg of [Phenyl-U-^{14}C] CGA-24705 was 43.1%, 47.0%, and 7.4% in males and 54.0%, 39.4%, and 4.1% in females, respectively. In contrast, both sexes excreted more of the label in the feces (M:F 59.7%:53.4%) than in the urine (M:F 29.4%:39.8%) during the same period following administration of the same dose of [Phenyl-U-^{14}C] CGA-77102 (the S-enantiomer) (MRID 44491401). The urinary and fecal metabolite profiles, with 31 and 15 metabolite fractions, respectively, were qualitatively similar among all groups; however, there were large quantitative differences, based on the dosing formulation, on one hand, and the sex of the animal, on the other. Based on a percentage of the dose, several of the major urinary metabolite fractions (e.g., U1, U2, U3, U18, U24, and U30) were more abundant in the case of the racemic-Metolachlor (CGA-24705) than the S-Metolachlor (CGA-77102); in contrast, several fecal metabolite fractions (e.g., F9, F10, F12, and F13) were present at higher levels in the case of CGA-77102 than CGA-24705. On the other hand, there were sex-related differences regardless of the dosing formulation where, for instance, females had greater urinary concentrations than males of several metabolite fractions, including U3, U4, U8, U9, U18, U20, and U30; the males, however, excreted more of fractions U1 and U24 than the females. Also, several fecal fractions including F1, F3, F5, F6, F7, F8, and F13 were influenced by the sex regardless of the dose level (e.g. B1 vs. D1) or the stereochemical make-up of Metolachlor (B1 vs. B2). Other metabolite fractions were dependent on both the sex and the chemical formulation as, for instance, in the case of metabolite U2 which, relative to the opposite sex within the same group, was more abundant in the urine of the females of Group B2 (CGA-24705) and in the urine of the males of Group B1 (CGA-77102). The bile fluid accounted for 79.8% of the administered low or high dose of CGA-77102 (Groups G1 and G2) where the 2D-TLC showed 14 biliary metabolite fractions (G1-G14) in the high dose Group and only six metabolites in the low dose Group. The two metabolite fractions G7 and G8 accounted, respectively, for 33.3% and 9.6% of the administered low dose and 31.3% and 14.6% of the administered high dose. Other major biliary metabolites were G3, G9, and G10 which accounted for about 5%, 5-7%, and 3-5%, respectively, of either dose group.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
		The results clearly show that the metabolite profile in excreta and bile fluid is very complex and that Metolachlor (racemate or S-enantiomer) is extensively metabolized. This was also shown earlier by another rat metabolism study on the absorption, distribution, excretion, and metabolite identification of racemic CGA-24705 (MRID 43164201, reviewed by T. McMahon, HED doc. no. 010990 dated May 23, 1994). No actual metabolites or pathways were identified in the current study and there were no data to support or refute the previous findings of four major degradation pathways with more than 30 metabolites. However, knowing the enantiomeric stereospecific reactions/metabolites is not likely to help in making comparative risk assessments between R/S-Metolachlor (CGA-24705) and S-Metolachlor (CGA-77102) since the contribution of each metabolite to the overall toxicity of Metolachlor is not well understood. Furthermore, other bridging animal studies with CGA-77102 should highlight possible toxicity differences from the well-studied CGA-24705 due to variations in the metabolite profiles. The Registrant is requested to comment on or provide information on a number of issues including: 1) The stereoisomeric purity of CGA-24705 and CGA-77102. 2) The adequacy of the storage conditions and the validity of the metabolite profile results in light of the storage-related results variability. 3) Explain why, relative to the other dosing formulation, some metabolite fractions (e.g., F10, F12, and F13) were up to 7-fold higher in the case of the S-enantiomer (CGA-77102) while some urinary metabolite fractions (e.g., U1, U2, and U3) were up to 4-fold higher in the case of CGA-24705. 4) Provide rational for dose selection. 5) The Registrant might also have to comment on the possible formation and the level of methylethylaniline from either dosing formulation and the possible contribution of this metabolite to the carcinogenicity of Metolachlor. This issue was raised earlier by T. McMahon (HED document no. 010990 dated May 23, 1994) and might need to be followed up by HED's risk assessors who are in charge of S-Metolachlor.

9.2 Summary of Toxicological Dose and Endpoints for Metolachlor/S-Metolachlor for Use in Human Risk Assessment[1]

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 300 UF = 100	death, clinical signs of toxicity (clonic and/or tonic convulsions, excessive salivation, urine-stained abdominal fur and/or excessive salivation) and decreased body weight gain	prenatal developmental toxicity study in rats with metolachlor
	Acute RfD = 3.0 mg/kg		
Chronic Dietary	NOAEL = 9.7 UF = 100	decreased body weight gain in females	chronic study in dogs with metolachlor
	Chronic RfD = 0.1 mg/kg/day		
Incidental Oral, Short-Term	NOAEL= 50	increased incidence of clinical signs, decreased body weight/body weight gain, food consumption and food efficiency	prenatal developmental toxicity study in rats with s-metolachlor
Incidental Oral, Intermediate-Term	NOAEL= 8.8	decreased body weight gain	subchronic (6 month) toxicity study in dogs with metolachlor
Dermal, Short-& Intermediate Term	Hazard was not identified for quantification of risk. No systemic toxicity was seen at the Limit Dose following dermal applications and no there is no concern for developmental toxicity in rat or rabbits.		
Dermal, Intermediate-Term	NOAEL= 1000	risk assessment not required since there was no systemic toxicity at the limit dose	21-day dermal toxicity study in rabbits with metolachlor
Dermal, Long-Term[a]	Oral NOAEL= 9.7	decreased body weight gain in females	chronic toxicity study in dogs with metolachlor
Inhalation, Short-Term[b]	Oral NOAEL= 50	increased incidence of clinical signs, decreased body weight/body weight gain, food consumption and food efficiency	prenatal developmental toxicity study in rats with s-metolachlor
Inhalation, Intermediate-Term[b]	Oral NOAEL=8.8	decreased body weight gain	subchronic (6 month) toxicity study in dogs with metolachlor
Inhalation, Long-Term[b]	Oral NOAEL= 9.7	decreased body weight gain in females	chronic toxicity study in dogs with metolachlor

a Since an oral NOAEL was selected, a dermal absorption factor of 58% should be used in route-to-route extrapolation.
b Since an oral NOAEL was selected, an inhalation factor of 100% should be used in route-to-route extrapolation.