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Toxicology of Major Environmental Degradates of Acetochlor & Alachlor

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Toxicology Excellence for Risk Assessment

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Outline

- Background
  - Similarities and/or differences in structures
- Database for the acetanilide degradates
  - Potential endpoints evaluated
  - Toxicokinetic differences between parents and degradates
  - Differences in potency between parents and degradates
  - Species comparison
- Uncertainty factors

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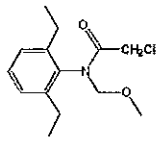
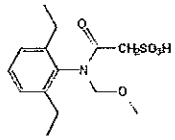
2

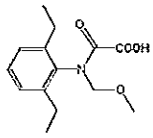
Chemical Structures



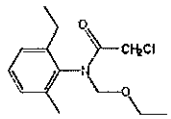
Alachlor



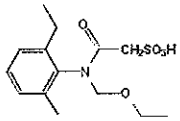
Alachlor t-ESA



Alachlor t-OXA



Acetochlor



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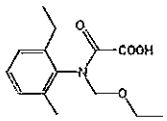

Acetochlor t-OXA

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Available Toxicity Data on t-ESA & t-OXA Degradates

Acute Toxicity
Genotox Battery
ADME[1]
Rat teratology[2]
28-day rat
90-day rat
Mechanistic studies

No reproductive or chronic studies available

1 - all except alachlor t-OXA
2 - acetochlor t-OXA & alachlor t-ESA

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Potential Endpoints Evaluated

- Decreased BW
- Thyroid toxicity
- Reproductive/developmental toxicity
- Hematology and clinical chemistry changes
- Other effects

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5

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Decreased BW

- Preliminary Conclusion:
  - ↓BW not solely due to ↓palatability & is treatment-related adverse effect
- Acetochlor & alachlor
  - ↓BW, BW gain
    - accompanied by ↓ food consumption & food utilization
- Degradates (Dietary & DW studies)
  - ↓BW, adjusted BW, BW gain
  - ↓food consumption
    - Secondary to ↓palatability or general systemic toxicity
    - Palatability issues were more pronounced in DW studies and affected water consumption
  - ↓food utilization

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6

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Thyroid Endpoints

- Preliminary Conclusions:
  - The acetochlor degradates, for which data were available, do not produce the biological effects expected of a thyroid disruption MOA as observed with the parent chemicals
  - Acetochlor ESA and OXA show at most weak effects related to the thyroid, but the toxicological significance is unclear
- Acetochlor and alachlor
  - Affected thyroid hormone homeostasis
    - Induction of hepatic UDPGT, ↑Liver weight, ↓ serum T4, ↑ TSH, ↑thyroid weights
- Degradates:
  - Liver & thyroid weights measured for all degradates
  - Thyroid hormone levels for acetochlor ESA & OXA (28-day) only
  - Minor and inconsistent changes in liver and thyroid weights and thyroid hormone levels.

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7

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Reproductive and Developmental Toxicity (1)

- Preliminary Conclusions:
  - Acetochlor ESA & alachlor OXA did not cause developmental effects even at maternally-toxic doses.
  - There are no indications that the degradates caused reproductive toxicity based on examination of reproductive organs in subchronic studies
- Acetochlor & Alachlor
  - The parents did not show evidence of reproductive toxicity in rats, except that one of 3 reproductive studies for acetochlor showed evidence of reproductive toxicity
  - Both parents caused developmental toxicity only at maternally-toxic doses
  - Both parent chemicals are not developmental toxicants in rabbits
  - Neither chemical was teratogenic

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Reproductive and Developmental Toxicity (2)

- Degradates
  - No reproductive toxicity studies are available
  - No effects on M or F reproductive organs in short-term and subchronic studies
  - Developmental toxicity studies available for acetochlor ESA and alachlor OXA
    - Showed no developmental toxicity even at maternally-toxic doses.
    - No evidence of teratogenicity

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9

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Hematological & Clinical Chemistry Changes

- Preliminary conclusion:
  - Degradates do not appear to cause consistent treatment-related adverse affects on hematological and/or clinical chemistry parameters up to highest doses tested
- Acetochlor
  - Caused only mild alterations in hematology and clinical chemistry (↓ prothrombin time, packed cell volume (or Hct), Hb, MCV, and MCH (28-day)
- Alachlor
  - Not reported to cause any effects in the rat
  - Caused hemosiderosis and anemia in dogs in a 1-year study (USEPA 2007)
- Degradates
  - Some changes observed in hematology and/or clinical chemistry (28- and 90-day)
    - Minor, inconsistent, but sometimes stat. sig.
    - Were without alteration in morphology or histopathology

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10

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Comparative Toxicokinetics (1)

- Preliminary Conclusions:
  - The degradates are not in vivo metabolites
  - There are significant differences between parent chemicals and degradates
  - The degradates are much more polar while the parent chemicals are not soluble
  - Parents & degradates are structurally similar, but they have functional group differences
  - Parents have specific tissue binding properties that the degradates lack (e.g., RBC binding, nasal turbinates, etc)
- Acetochlor & Alachlor
  - near complete absorption after oral dosing
  - undergo extensive metabolism (~95%)

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11

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Comparative Toxicokinetics (2)

- Degradates
  - Poorly absorbed
    - acetochlor ESA (10-12%)
    - acetochlor OXA (34-39%)
    - alachlor ESA (2-19%)
  - Limited metabolism
    - Excreted largely unchanged (77-83%)
  - Rapidly eliminated compared to parent chemicals
  - Lack the reactive chlorine atom of the parents

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12

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Comparative Toxicity

- Preliminary conclusions:
  - There are no clear target organs for the degradates
  - Both parents and degradates induce BW changes as a sensitive endpoint in rats
  - Parents are significantly more potent than the degradates

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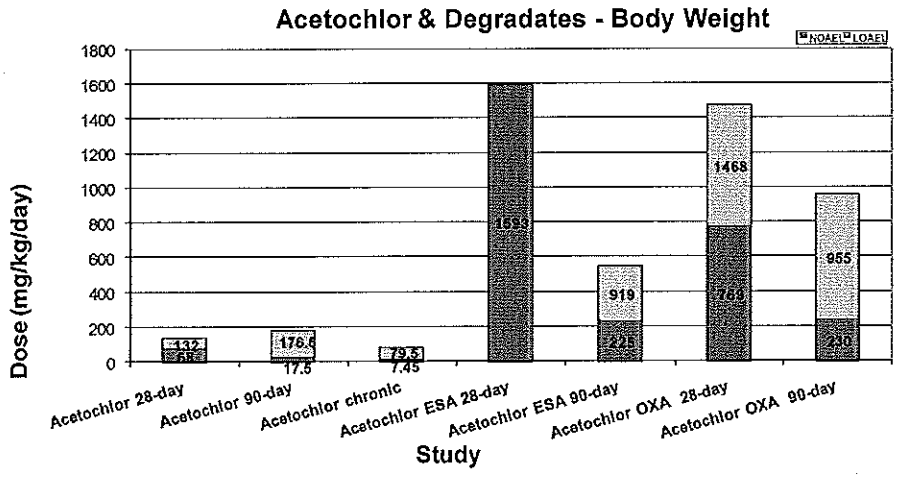
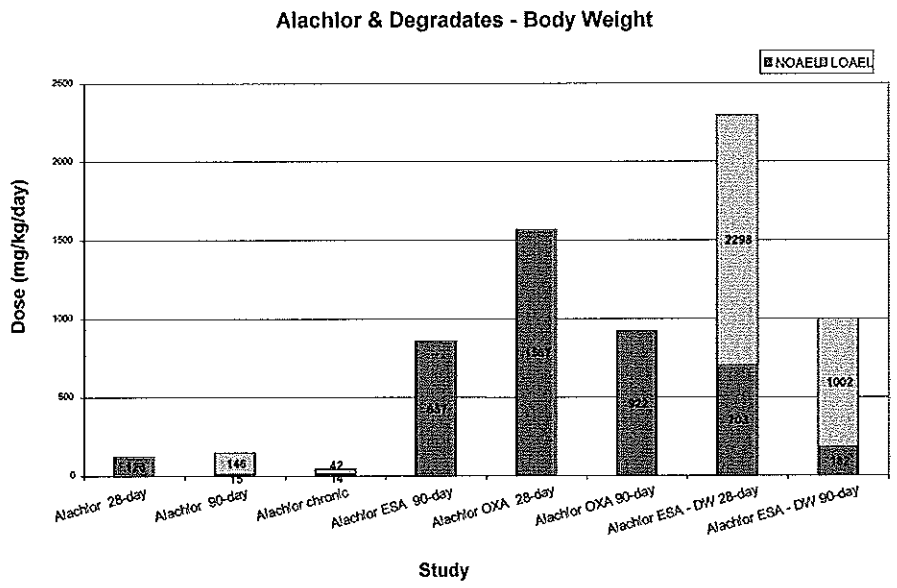
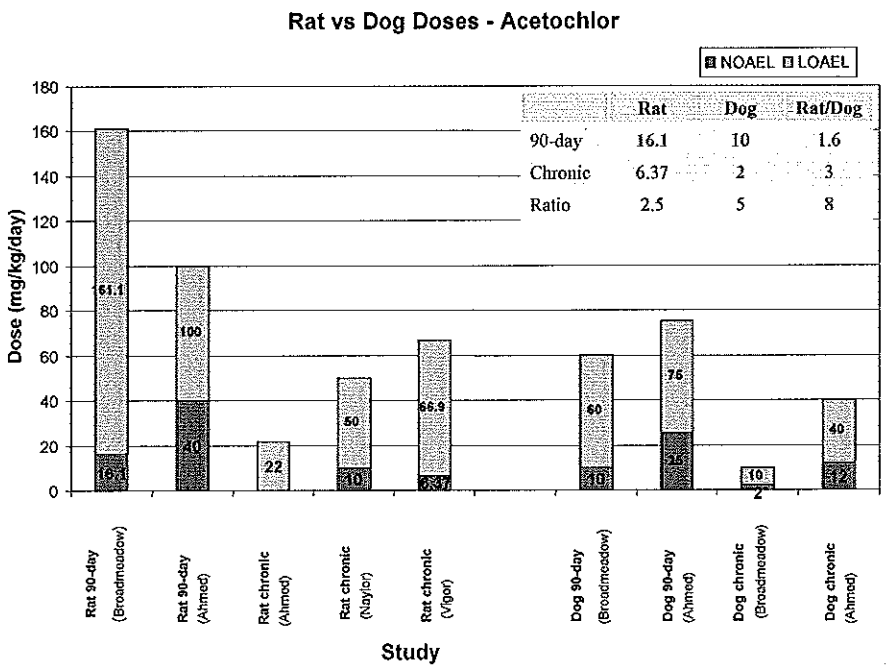
13



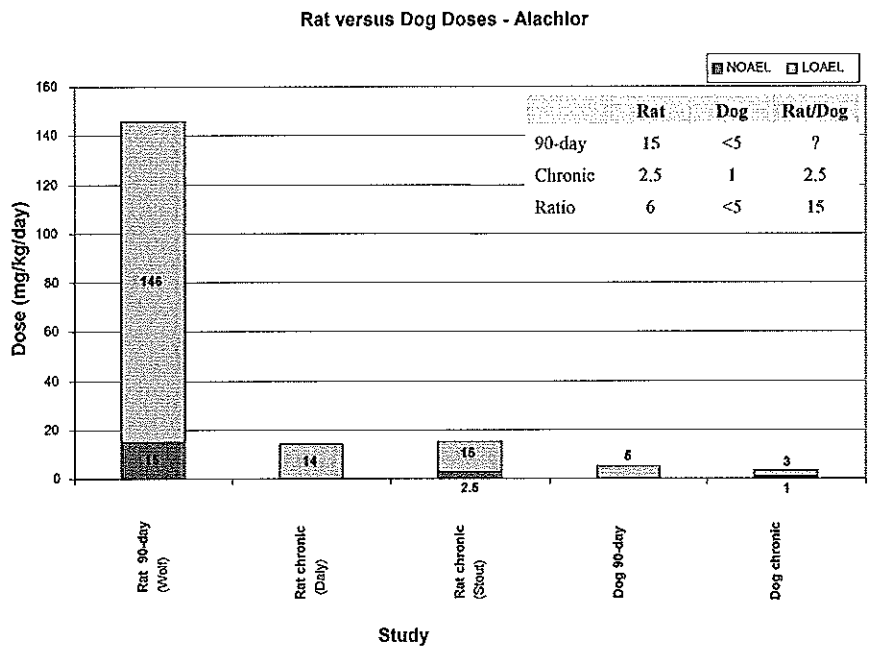
14


Alachlor & Degradates - Body Weight
NOAEL LOAEL
Dose (mg/kg/day)
2500
2000
1500
1000
500
0
146
15
42
14
1002
Alachlor 28-day
Alachlor 90-day
Alachlor chronic
Alachlor ESA 90-day
Alachlor OXA 28-day
Alachlor OXA 90-day
Alachlor ESA - DW 28-day
Alachlor ESA - DW 90-day
Study

15


Rat vs Dog Doses - Acetochlor
NOAEL LOAEL
Rat Dog Rat/Dog
90-day 16.1 10 1.6
Chronic 6.37 2 3
Ratio 2.5 5 8
Dose (mg/kg/day)
180
160
140
120
100
80
60
40
20
0
61.1
100
22
50
66.9
60
75
10
40
Rat 90-day (Broadmeadow)
Rat 90-day (Ahmed)
Rat chronic (Ahmed)
Rat chronic (Naylor)
Rat chronic (Vigor)
Dog 90-day (Broadmeadow)
Dog 90-day (Ahmed)
Dog chronic (Broadmeadow)
Dog chronic (Ahmed)
Study

16



17

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Uncertainty Factors

- UF_A & UF_H
  - No adequate kinetic and dynamic data to address chemical-specific adjustment factors (CSAF) for these areas of uncertainty
- UF_L
  - NOAELs and/or BMDLs available
- UF_S
  - Evidence of increased potency with duration
- UF_D
  - Lacking systemic toxicity in second species
  - Lacking developmental toxicity in second species
  - Lacking multi-generation study

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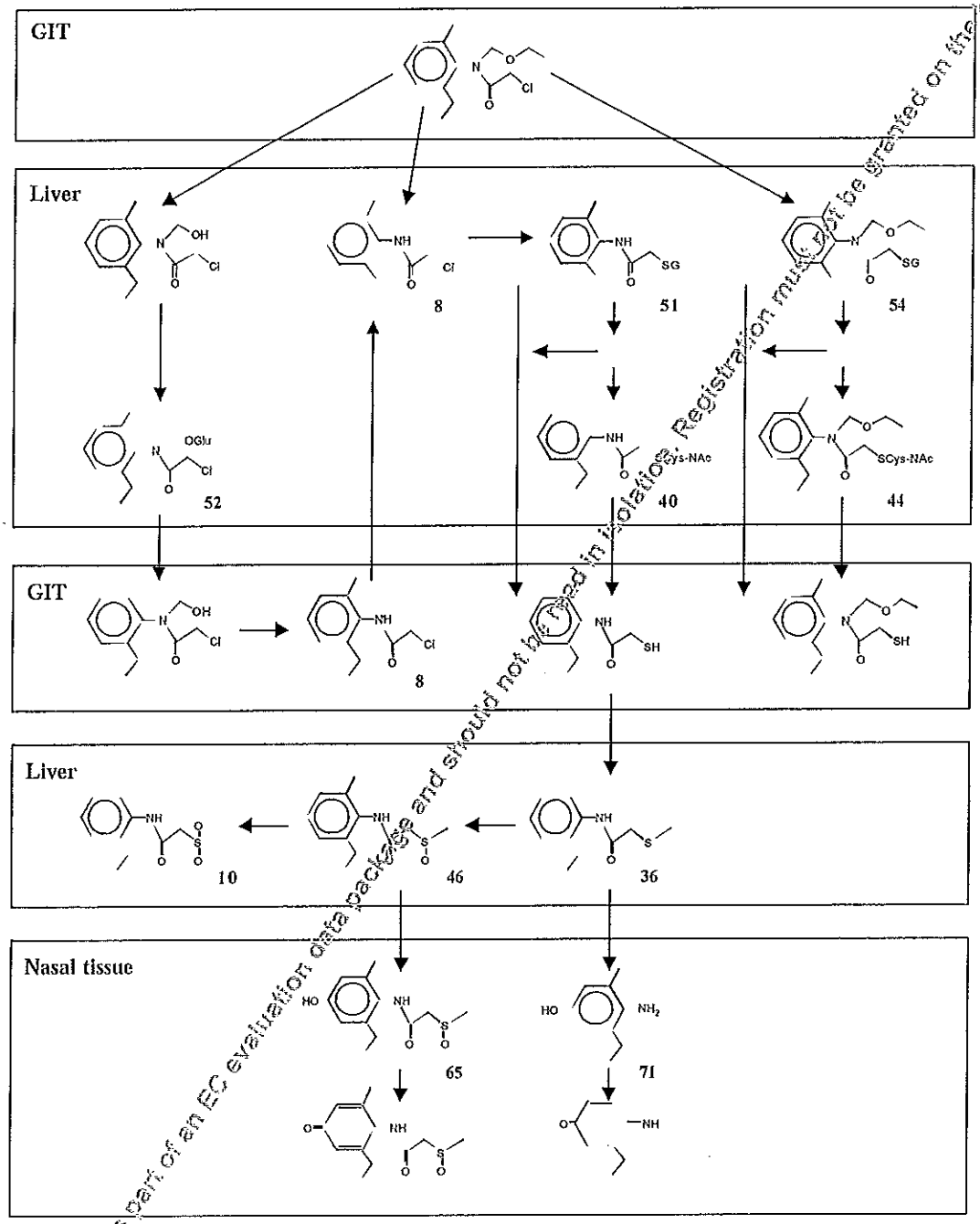
18

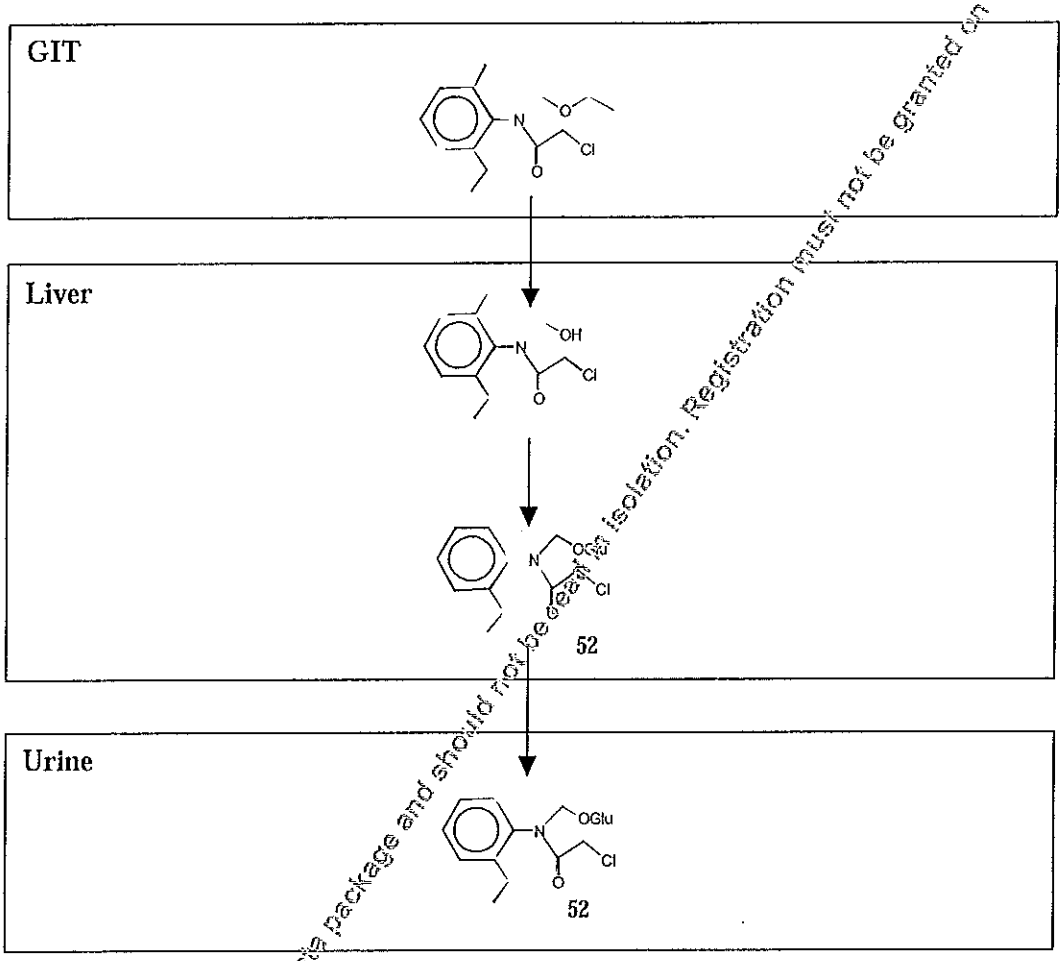
Figure 6.1-1: Major metabolic pathways of acetochlor in the rat



WARNING: This document forms part of an EC evaluation data package and should not be used in isolation. Registration must not be granted on the basis of this document.

The metabolism of acetochlor differed between rat and mouse. While in rats, acetochlor eliminated by urine metabolites derived from glutathione conjugates, the mouse eliminated glucuronide conjugates.

Figure 6.1-2: Major metabolic pathways in the mouse



After a single parenteral injection and percutaneous application of ^{14}C-acetochlor to rhesus monkeys, the metabolites found in urine were evaluated. The HPLC analysis of the concentrated urine samples revealed the same metabolic pattern for the four test groups (iv, im, sc and percutaneous), which consisted of two major radioactive fractions (36-60% radioactivity). These radioactive peaks were identified to be the mercapturic acid conjugates of acetochlor; a *tert*-amide mercapturic acid (44) and the N-dealkylated metabolite of acetochlor or *sec*-amide mercapturic acid (40). From the time-course analysis of urine samples collected from the monkeys treated dermally, it appears that the *tert*-amide mercapturic acid is excreted initially followed by the *sec*-amide mercapturic acid.

The metabolism data obtained in this study demonstrate that the glutathione conjugation pathway leading to the formation of mercapturic acid conjugates is by far the predominant route of metabolism of acetochlor in the Rhesus monkey.

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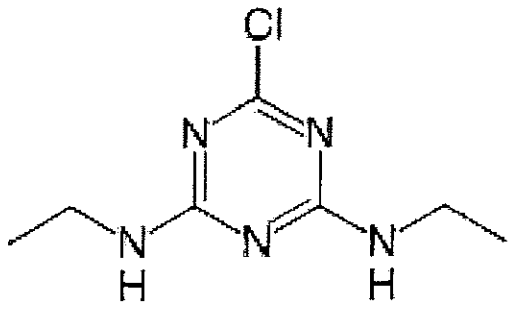
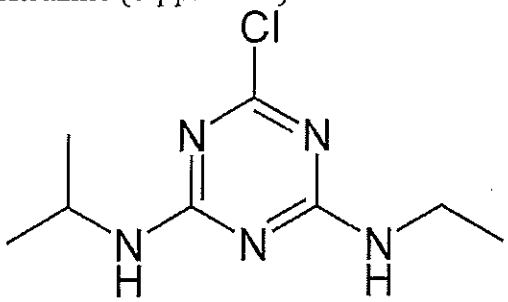
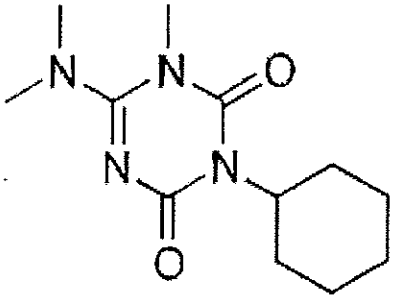
Simizine (4 ppb MCL)

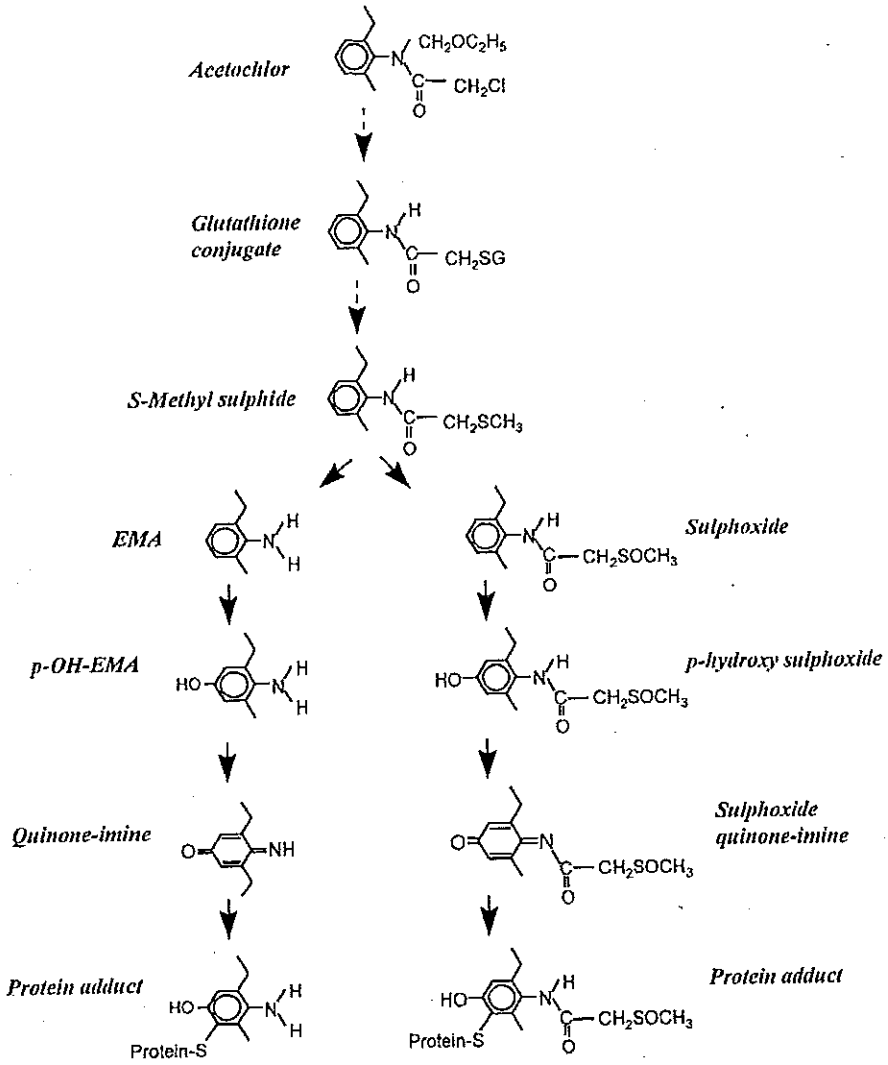


Atrazine (3 ppb MCL)



Hexazinone (400 ppb HA, lifetime)





Scheme A **Scheme B**

Attachment 3

SCIENTIFIC SUPPORT DOCUMENTATION

FOR

CYCLE 8

REVISIONS OF NR 140.10

GROUNDWATER ENFORCEMENT STANDARD

&

PREVENTIVE ACTION LIMIT

RECOMMENDATIONS

Prepared by:

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Henry Anderson, MD, Chief Medical Officer

Wisconsin Department of Health and Family Services
Division of Public Health

March 2005
(revised August 2005)

CONTENTS

ABBREVIATIONS iii

INTRODUCTION iv

ALACHLOR-ESA 1

BUTYLATE 8

DACTHAL 12

MOLYBDENUM 16

NAPHTHALENE 20

ABBREVIATIONS

AA	= Atomic absorption spectrophotometry
cm	= centimeter
DHFS	= Wisconsin Department of Health and Family Services
DNR	= Wisconsin Department of Natural Resources
EPA	= Environmental Protection Agency
ES	= Enforcement Standard
g	= gram
HSDB	= Hazardous Substances Data Bank (a computerized database distributed by the National Library of Medicine)
ICP	= inductively-coupled plasma absorption emission spectrophotometry
IRIS	= Integrated Risk Information System (a computerized database distributed by the USEPA)
kg	= kilogram
L	= Liter
LC_{50}	= Lethal Concentration for 50% of Exposed Animals (inhalation exposure)
LD_{50}	= Lethal Dose for 50% of Exposed Animals (oral exposure)
LOAEL	= Lowest Observed Adverse Effect Level
LOEL	= Lowest Observed Effect Level
MCL	= Maximum Contaminant Level
MCLG	= Maximum Contaminant Level Goal
mg	= milligram
MRID	= Master Record Identification (number)
NOAEL	= No Observed Adverse Effect Level
NOEL	= No Observed Effect Level
PAL	= Preventive Action Level
ppb	= parts per billion
ppm	= parts per million
RfD	= Reference Dose
RSC	= Relative Source Contribution
UF	= Uncertainty Factor
USEPA	= United States Environmental Protection Agency
µg	= microgram (0.000001 gram)

INTRODUCTION

This document contains recommendations for the establishment of groundwater enforcement standards (ES) and preventive action limits (PAL) for five substances (Table 1).

The recommendations found in this document contain background information on the chemistry, uses, possible routes of human exposure and occurrence in Wisconsin groundwater of each chemical proposed for regulation. In addition, DHFS has included a brief literature review of the important health effects, acute and chronic toxicity, and environmental fate of each substance. Based upon its review, DHFS has calculated enforcement standards and preventive action limits utilizing the procedures stipulated in Ch. 160 Stats.:

TABLE 1. Recommended Enforcement Standards and Preventive Action Limits

Compound	Enforcement Standard (ppb)	Preventive Action Limit (ppb)
Alachlor-ESA	20	4
Butylate	400	80
Dacthal	70	14
Molybdenum	40	8
Naphthalene	100	10

Chapter 160, Stats. directs the Department of Natural Resources (DNR) to identify and rank substances which may contaminate Wisconsin groundwater. The Department of Health and Family Services (DHFS) then develops recommendations for ES and PALs for these substances. Since 1986, Public Health Groundwater Quality Standards for 120 substances have been adopted under Chapter NR 140, the Wisconsin Administrative Code for Groundwater Quality.

STRUCTURE OF THE STANDARDS DOCUMENTS

Introduction: A brief description of the uses of the chemical, if any.

Chemical Profile: A list of the important properties of the substance, including chemical structure, molecular weight, specific gravity and synonyms.

Occurrence: Description of quantities estimated to enter the environment through industrial production and/or waste generation. Includes results of groundwater testing by state and federal agencies.

Human Exposure Routes: Description of observed and potential routes of human exposure, including the estimated contribution of drinking water to total exposure.

Toxicity

> **Acute.** LD_{50}s or LC_{50}s in rats and mice. The LD_{50} is the oral dose which causes lethality in half the exposed animals, while the LC_{50} is a corresponding air concentration from inhalation studies.
>
> **Subchronic.** Results of animal studies of durations from 90 days to 1 year.
>
> **Chronic.** Results of animal or human studies lasting longer than 1 year.
>
> **Carcinogenicity.** Results of animal or human studies on the ability of the chemical to cause cancer..
>
> **Mutagenicity.** Results of any short-term mutagenicity assays, such as the Ames test or the mouse lymphoma forward mutation assay, on the chemical.
>
> **Reproductive and Developmental Effects.** Reports of any effects of the chemical on reproduction or development.
>
> **Interactive Effects.** Results of experiments in which the chemical was administered in combination with other chemicals, or a discussion of concerns related to simultaneous exposure to other chemicals.

Environmental Fate: Description of the stability of the chemical in air, soil, surface water or groundwater, including the chemical's tendency to move from soil to groundwater.

Analytical Laboratory Methods: A brief description of the methods used to detect the chemical, including the current limit of detection.

USEPA Regulatory Position: Availability of toxicity values published by the US EPA.

> **Maximum Contaminant Level (MCL).** The maximum allowable concentration of a chemical allowed in drinking water under the Safe Drinking Water Act. The MCL takes into account cost of remediation and analytical capabilities in addition to potential health effects.

Maximum Contaminant Level Goal (MCLG). The maximum allowable concentration of a chemical allowed in drinking water if only health effects are considered.

Lifetime Health Advisory (LHA). An EPA standard used for health-based guidance for substances for which MCLs and MCLGs have not been promulgated.

For noncarcinogens, the following parameters may be reported.

No Observed Adverse Effect Level (NOAEL). The highest dose of a chemical which produced no adverse effects in experimental animals or humans.

No Observed Effect Level (NOEL). The highest dose of a chemical at which no exposure-related effects were observed.

Lowest Observed Adverse Effect Level (LOAEL). The lowest dose which produced adverse effects in experimental animals or humans.

Lowest Observed Effect Level (LOEL). The lowest dose of a chemical at which no exposure-related effects were observed.

Uncertainty Factor (UF). Divisor applied to a NOAEL or LOAEL to obtain an acceptable human dose for daily exposure.

Reference Dose (RfD). The RfD is an estimate of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. RfDs are derived on the basis of a NOAEL, LOAEL or benchmark dose, with uncertainty factors applied to reflect limitations of the data used.

Drinking Water Equivalent Level (DWEL). Drinking water concentration derived on the basis of an RfD. Calculations use assumptions of a 70-kg adult human body weight, consumption of 2 liters of water a day and 100% exposure to the chemical occurring via drinking water.

For carcinogens, the following parameters may be reported.

Cancer Potency Factor. U.S. EPA concludes that a chemical is carcinogenic if animals form tumors in a dose-related manner upon exposure. Data on doses and numbers of tumors are entered into a complex computer program and an estimate of the slope of the line is called the cancer potency factor.
10^{-6} Risk Level. The concentration in water calculated to produce an excess cancer risk of 1 in 1,000,000 assuming lifetime exposure to a 70 kg person drinking 2 L/day of water.

Other Toxicology Information: Any other information pertinent to development of groundwater standards.

Recommendations and Conclusions: The following discussion briefly summarizes the procedure by which DHFS is directed to develop recommendations for enforcement standards and preventive action limits:

- If a single federal number exists for a substance, the federal number shall be the enforcement standard;
- If more than one federal number exists for a substance, the most recently established federal number representing the most current data shall be the enforcement standard.
- If no federal number exists for a substance, but there is a state drinking water standard, the state drinking water standard shall be the enforcement standard.
- If neither a federal number nor a state drinking water standard exists for a substance, [DHFS] shall develop a recommended enforcement standard using the methodology under s. 160.13."

In this process, DHFS is directed to use a 'federal number' if one exists. In Ch. 160.01(3), the term "federal number" is defined as "a numerical expression of the concentration of a substance in water, established as:

(a) A drinking water standard or maximum contaminant level, by the federal environmental protection agency;
(b) A suggested no-adverse-response level, by the federal environmental protection agency; or
(c) For oncogenic substances, a concentration based on a risk level determination by the federal environmental protection agency or a concentration based on a probability of risk model determined by the national academy of sciences."

For those substances for which neither a federal number nor a state standard exists, DHFS is directed to determine the acceptable daily intake (ADI) for the substance and to convert that value into a numerical drinking water concentration by applying a daily water consumption rate of 1 L/day and a body weight of 10 kg (s. 160.13(2)(c)).

For non-carcinogens, if DHFS finds no serious flaws in the methodology used to derive the RfD, which constitutes a suggested no-observed-effect level from EPA (based on EPA's NOAEL or LOAEL and UF), DHFS is directed to use this value as a basis for setting the enforcement standard. If no RfD exists, or the RfD is determined by DHFS to be based on data that do not accurately reflect current scientific knowledge on the chemical, DHFS is directed to make an independent determination as to a NOEL or LOEL and a UF. In such cases, DHFS uses the assumptions that 1 L (0.9 qt) of this water is consumed by a 10 kg (22 lb) child, and that all (100%) of the chemical consumed by the child comes from drinking water. From this information, a drinking water concentration is calculated using the following formula:

$$\frac{\text{NOEL or LOEL (mg/kg/day)} \times 10\text{ kg} \times 100\%}{\text{UF} \times 1\text{ L}} = \text{ES}$$

For carcinogens, DHFS determines the concentration of the chemical at which lifetime consumption of the chemical would be assumed to cause one excess cancer case among 10,000 to 1,000,000 exposed persons as compared to unexposed persons. The concentration in water associated with a 1 in 10,000 to 1 in 1,000,000 (the "cancer risk") is determined by assuming a 70-year lifetime exposure, a 70-kg (154 lb.) human, 2 L (1.8 qt) water consumption per day and that 100% of exposure to that chemical comes from drinking water. The calculations are as follows:

$$\frac{70\text{ kg} \times \text{cancer risk}}{\text{Cancer potency factor} \times 2\text{ L/day}} = \text{ES}$$

Significant figures: All enforcement standards and preventive action limits have been rounded to contain no more than two significant figures.

USEPA CANCER CLASSIFICATIONS

The USEPA has classified environmental chemicals according to their suspected carcinogenicity. The classifications are as follows:

Group A--Human Carcinogen

Sufficient evidence in epidemiologic studies to support causal association between exposure and cancer.

Group B--Probable Human Carcinogen

Limited evidence in epidemiologic studies (Group B1) and/or sufficient evidence in animal studies (Group B2).

Group C--Possible Human Carcinogen

Limited or equivocal evidence from animal studies and inadequate or no data in humans.

Group D--Not Classified

Inadequate or no human and animal evidence of carcinogenicity.

Group E--No Evidence of Carcinogenicity for Humans

No evidence of carcinogenicity in at least two adequate animal tests in different species or in adequate epidemiologic and animal studies.

UNCERTAINTY FACTORS

As described in Ch. 160 Stats., an uncertainty factor is applied to a NOEL or LOEL to obtain a dose level or concentration assumed safe for long-term exposure to human populations. UFs are applied to account for sources of variability which might otherwise cause the observed concentration to be insufficiently protective. Among the most common sources of variability and uncertainty that are addressed by the use of UFs are biological variability among species, biological variability within a species, the lack of an experimental NOEL for a substance, the lack of a chronic health study for a substance, and the lack of data needed to adequately assess effects that could be anticipated based on knowledge of related chemicals or chemical structure, such as carcinogenicity or developmental toxicity.

Typically, uncertainty factors ranging from 10 to 10,000 are used. Low uncertainty factors are common in cases where there is an experimental NOEL based on a chronic health study, especially when the NOEL is derived from experience with human exposure. Higher uncertainty factors are more common when only limited or incomplete chronic or subchronic toxicity data are available, or when experimental data on endpoints of particular concern are unavailable.

METABOLITES

The Department of Health and Family Services recognizes that many substances degrade in the environment to metabolites which may also contaminate groundwater. In the absence of adequate toxicological information, we believe that these breakdown products should be considered to have biological effects similar to those of the parent compound. Under this assumption, these breakdown products, or metabolites, can be regulated using existing groundwater standards which were developed based on the toxicological profile of the parent compound.

We recommend that when a metabolite is detected in the groundwater, and a groundwater standard exists for the parent compound but not for the metabolite, the existing groundwater standard should be used to regulate the sum of any parent and metabolite detected. If the metabolite weighs significantly more or less than the parent compound, a molecular weight conversion should be conducted since the toxicity assumption is based on molecular equivalency.

DNR HEARINGS PROCESS

DNR staff review the DHFS recommended standards and hold public hearings for comment on the appropriateness of the proposed numerical standards. After completing the review process, public comments will be incorporated into the technical support document and any changes made will be written into the final text. The DNR Board, after reviewing the recommended groundwater standards document (including responses to public comments), will vote to accept or reject the original or modified risk assessments. Standards accepted by the DNR Board are sent to the Wisconsin State Legislature for their review and approval. Upon acceptance, these standards become law and are printed in the Wisconsin Administrative Code.

ETHANE SULFONIC ACID METABOLITE OF ALACHLOR (ALACHLOR-ESA)

Introduction

Alachlor-ESA is a metabolite of the herbicide alachlor. Alachlor is a broadleaf preemergent acetanilide herbicide used widely on corn and soybeans in Wisconsin.

Chemical Profile

Chemical Name:	Alachlor, ethane sulfonic acid metabolite
Molecular Formula:	$C_{13}H_{20}SNO_5$
Molecular Weight:	302.37
Synonyms:	MON 5775
	2',6'-diethyl-N-methoxymethyl-2-sulfoacetanilide, sodium salt
	2-[2,6-diethylphenyl (methoxymethyl) amino]-2-oxoethane sulfonic acid, sodium salt

Occurrence

Alachlor-ESA has been detected in groundwater and surface waters in Wisconsin and elsewhere in the Midwest. In a 1994 study of acetochlor and related herbicides in 12 Midwestern states, alachlor-ESA was found in each of 104 surface water samples at median concentrations of 0.80 µg/L (pre-application) and 5.2 µg/L (post-application).[1] Alachlor-ESA was detected in 65.8% of groundwater samples at a median concentration of 0.28 µg/L.

Human Exposure

In a 1994 Wisconsin survey of private wells considered at risk for contamination, alachlor-ESA was detected in 206 of 293 samples. Observed concentrations ranged from 1.1 to 26.7 µg/L (average = 4.9 µg/L).[2] Alachlor was detected in only 12 of these 293 samples.

In 2000, the Wisconsin Department of Agriculture, Trade and Consumer Protection (DATCP) conducted a survey of chloroacetanilide herbicides and their degradates in monitoring wells, private drinking water wells and municipal wells considered at risk for herbicide contamination.[3] The survey yielded the following results:

Well Type	*Wells Sampled*	*Wells with Detects*	*Percent w/Detects*	*Average Detect (µg/L)*	*Highest Detect (µg/L)*
Monitoring Wells	27	22	81	4.7	33
Private DW Wells	22	20	91	3.5	9.0
Municipal Wells	23	11	48	1.9	4.4

In a separate Wisconsin survey, 336 private water supplies selected in a random, stratified fashion were sampled for atrazine, alachlor and other herbicides as well as their degradates. Alachlor-ESA was detected in 27.8% of surveyed wells, and was detected in a higher percentage of wells than any other contaminant. The mean observed concentration of alachlor-ESA was 1.0 µg/L, with the highest concentration observed at 14.8 µg/L.[4]

Toxicity

Acute

An acute oral LD_{50} of greater than 6000 mg/kg was observed for alachlor-ESA in rats.[5]

Subchronic

Two oral subchronic rat studies have been conducted on the toxicity of alachor-ESA.

In a 91-day study, alachlor-ESA was administered to male and female Fischer F-344 rats (10 per sex per dose level) in drinking water at doses of 0, 20, 182 or 1002 mg/kg/day.[6,7] Effects observed in the study included changes in physical appearance of test animals, decreased body weight, ophthalmic effects and alterations in clinical chemistry and hematological measures.

- *Physical appearance*. Increased incidence was reported versus controls for the following endpoints at all dose levels: decreased activity, rapid/shallow breathing, few feces, feces small in size, dehydration, urine staining, emaciation, hunched posture, rough coat, unkempt appearance, dark material/stain on pads of forelimb, around eyes, mouth and nose, clear and red ocular discharge, and hair loss around eyes.

- *Decreased body weight*. Female rats in the lowest dose group showed a statistically significant decrease in body weight relative to controls on days 22 through 85 of the study, although food and water intakes were similar. Similarly, body weights in the high-dose group were significantly lower on days 8 through 91. Body weights for mid-dose females were lower as well. Two-sample t tests conducted by the Wisconsin Department of Health and Social Services (now DHFS) showed significant differences between the body weights of controls and animals in each of the three dose groups ($p = 0.016$, 0.044 & <0.001, respectively).[8]

- *Ophthalmic changes*. Both dacryoadenitis (inflammation of the lacrimal gland) and chorioretinopathy (lesions on the retina and/or chorion) were observed with increased frequency in exposed animals versus controls. In laboratory studies assessing the toxicity of alachlor, ocular lesions and molting of retinal pigmentation (described as *uveal degeneration syndrome*) have been seen in Long-Evans rats.[5] Because the Fischer 344 rat has an unpigmented eye, the full range of alachlor-related ocular effects could not be assessed in this experiment.

- *Clinical chemistry indices*. Low-dose females had a statistically significant decrease in levels of aspartate aminotransferase relative to controls ($p<0.01$). Low- and mid-dose females also had significantly lower levels of potassium ($p<0.05$) and calcium ($p<0.01$). Effects were not consistent at higher dose levels.

- *Hematological effects*. Male rats in the middle dose group had a statistically significant decrease in erythrocyte counts ($p.< 0.05$). This finding was more pronounced ($p < 0.01$) in test animals at the highest dose. Hematocrit values and hemoglobin levels, both of which were significantly lower at the high dose vs. controls ($p < 0.05$), were moderately lower than controls at the mid-dose, consistent with a dose-response relationship. Bilibubin, a by-product of the breakdown of hemoglobin, was increased at statistically-significant levels in both mid-dose and high-dose animals.

In a more recent 90-day study, alachlor-ESA was administered to three groups of Crl:CD(SD)IGS BR rats in the diet at dosage levels of 3000, 6000 and 12,000 ppm (209, 422 and 857 mg/kg/day, respectively).[9] Observed effects included changes in sensory observations, testis weight, serum chemistry and hematological effects.

- *Sensory observations*. Unresponsiveness to touch response was measured in control and test animals. The mean number of times animals had no reaction to the touch response was increased in males in the high-dose group ($p<0.05$). No dose-related change was observed in other sensory observations such as tail pinch response, startle response and approach response.

- *Organ weights*. Relative testis weight was found to be increased in low-dose males ($p<0.05$). No corresponding increase was seen in mid-dose and high-dose males, and no increase in absolute testis weight was observed.

- *Serum chemistry*. Mean triglyceride levels were significantly lower in high-dose males when compared to controls ($p<0.05$). There were no significant changes in triglyceride levels among the low-dose and mid-dose groups.

- *Hematological effects*. Mean absolute and relative reticulocyte counts were elevated in both mid-dose and high-dose males ($p<0.05$). These values were also elevated in low-dose males, but the increase at this dose level was not statistically significant.

Chronic

No data on the chronic toxicity of alachlor-ESA are available.

Carcinogenicity

No data from long-term carcinogenicity studies are available for alachlor-ESA.

In oral feeding studies, alachlor has been shown to cause tumors in nasal epithelium, stomach and thyroid. Among the primary metabolites of alachlor of concern for nasal tumors is 2-chloro-*N*-(2,6-diethylphenyl)acetamide (CDEPA), which can be metabolized to 2,6-diethylaniline (DEA). DEA can be oxidized to form a diethylbenzoquinone imine (DEBQI), which binds to cellular protein, leading to cell death. Ensuing regenerative cell proliferation has been hypothesized by EPA to lead to neoplasia through fixation of spontaneous mutations.[5] The mechanism by which rats and humans form the DEBQI metabolite is similar.[10]

Alachlor-ESA has been demonstrated to show less affinity for accumulation in nasal turbinates than alachlor.[11] A 91-day study failed to show nasal cell proliferation following administration of alachlor-ESA at a dose level of 157 mg/kg/day.[12] A separate 91-day study showed no apparent fundic mucosal atrophy upon exposure to alachlor-ESA, an effect which precedes cell proliferation and stomach tumors upon alachlor exposure.[13] Cell proliferation in the stomach resulting from alachlor-ESA exposure was described by the investigators as minimal.

Mutagenicity

Chromosomal effects of alachlor-ESA were evaluated in the mouse micronucleus test. Single oral doses of 500, 1000 or 2000 mg/kg alachlor-ESA were administered to five male CD-1 mice

by gavage.[5,7] Animals were sacrificed at 24 or 48 hours after administration. Bone marrow cells were harvested and examined for the presence of micronucleated polychromatic erythrocytes. No treatment-related increase was observed in the frequency of polychromatic erythrocytes with micronuclei. A range of other tests have failed to demonstrate any substantive mutagenic potential for alachlor-ESA.[14,15]

Reproductive and Developmental Toxicity

Single doses of alachlor-ESA in doses of 0, 150, 400 and 1000 mg/kg/day in corn oil were administered by gavage to bred female rats (25 at each dose level) on gestational days 6 through 15.[5,7] Animals were euthanized on gestational day 20 and examined for uterine and ovarian abnormalities. Fetuses were sexed, weighed and examined for gross developmental abnormalities. Rales were observed in some dams at the highest dose, and body weight of mid-dose pups was decreased relative to controls ($p < 0.05$). No treatment-related changes were observed between test and control animals in food consumption or organ weight among dams or fetuses, and no increase in external, visceral or skeletal variations or malformations were seen in fetuses.

Interactive Effects

No data on interactive effects of alachlor-ESA are available.

Environmental Fate

Atmospheric

The vapor pressure of alachlor-ESA has not been determined. Given its chemical similarity to alachlor (vapor pressure = 2.2×10^{-5} mm Hg), the volatility of alachlor-ESA is likely to be relatively low.

Terrestrial

In a study of the behavior of alachlor and metolachlor and their metabolites in soil following a single application, alachlor-ESA was found to penetrate more deeply in soil than its parent compound. In the upper 15 cm of soil, alachlor-ESA concentrations reached peak levels at 9 to 10 weeks after application at 60% of parent concentration. Conversely, alachlor-ESA concentrations were more than 10 times greater than alachlor at depths of 60 to 75 cm after six weeks.[16]

Aquatic

Alachlor-ESA was found to be very mobile in studies conducted with Sable silty clay loam soils and Sarpy sandy loam soils mixed and equilibrated with calcium chloride.[5] Alachlor-ESA is highly persistent in surface water, with long-term declines in surface water concentration attributed more directly to dilution than degradation.[17]

Analytical Methods

Alachlor-ESA can be quantified in water samples by high-performance liquid chromatography / mass spectrometry. This method yields detection limits as low as 0.10 μg/L.[18]

U.S. EPA Regulatory Position

	Alachlor-ESA	Alachlor
EPA MCL & MCLG:	None	2 µg/L (MCL), 0 µg/L (MCLG)
EPA Reference Dose:	None	0.01 mg/kg/day
EPA Reference Concentration:	None	None
EPA Lifetime Health Advisory:	None	None
EPA Carcinogenicity Classification:	No classification	B2, probable human carcinogen*[19]

* Reflects cancer classification at the time of regulation.

EPA Reregistration Eligibility Decision[5]

In its 1998 RED for alachlor, the hematological effects observed at the middle and high doses in the 91-day subchronic oral study for alachlor-ESA were acknowledged to be of statistical significance, but were described as "minor, mostly not dose related and...not considered to be biologically relevant, especially in the absence of any organ or tissue pathology". In addressing the development of a reference dose for alachlor-ESA, two alternative methods with default assumptions were offered: (1) the use of the RfD for alachlor of 0.01 mg/kg/day, which is based on observations of hemolytic anemia and hemosiderosis at various organ sites in a one-year study in dogs, and (2) a value based on the agency's NOEL and an uncertainty factor of 1000 to account for "interspecies extrapolation, intraspecies variability and a lack of a complete database".

In the RED, alachlor is described as "likely to be a human carcinogen at high doses but not likely at low doses". No quantitative benchmark is provided to distinguish between 'high doses' and 'low doses'. Alachlor-ESA is described in the RED as "unlikely to be carcinogenic".

Recommendations and Conclusions for Alachlor-ESA

Ch. 160 Stats. defines a "no-observable-effect-level" (NOEL) as "that level of intake of a substance which, when administered to a group of humans or experimental animals, does not produce any of the effects observed or measured at any higher level of intake and produces no significant difference between the test groups and an unexposed control group of humans or animals maintained under identical conditions". In reviewing the available data on alachlor-ESA, the two subchronic studies represent the best available data on which to identify a NOEL. The results from these studies show a marked difference in observed toxicity, which may be due to differences in the route of exposure. Test compound was administered in drinking water in the 1993 study, was administered with food in the 2003 study. Given that the route of exposure in the older study matches that of concern for a groundwater enforcement standard, and the sharp difference in observed toxicity between the two studies, it is appropriate to give deference to the 1993 study as a better representation of the toxicity of alachlor-ESA in drinking water than the more recent subchronic. Therefore, based on Ch. 160 Stats. and our analysis of data from studies of the subchronic toxicity of alachlor-ESA, the hematological findings in the study by Siglin *et al* at the dose of 182 mg/kg/day constitute the lowest level at which effects are observed, thereby establishing a no-observed-effect-level (NOEL) of 20 mg/kg/day.

In establishing an uncertainty factor, DHFS is directed in Ch. 160 Stats. to consider a range of factors, including the quality and quantity of available data, potential interactions with environmental chemicals and known chronic or subchronic effects of exposure to similar or related compounds. In the case of alachlor-ESA, the lack of data on chronic or carcinogenic

effects and the frequency with which alachlor-ESA is found in drinking water with alachlor, metolachlor and acetochlor and other degradates of these chloroacetanilide herbicides, require special consideration.

Based on these considerations, an uncertainty factor of 10,000* (10 for interspecies variability, 10 for intraspecies variability, 10 for use of a subchronic study and 10 for data gaps, including lack of a carcinogenicity study for the metabolite of a potentially carcinogenic parent compound) is applied.

$$\frac{(20\ \text{mg/kg/day})\ (10\ \text{kg})}{(1\ \text{L/day})\ (10{,}000)} = 0.02\ \text{mg/L}\ (20\ \mu\text{g/L})$$

In accordance with Chapter 160 of Wis. Stats., the Department of Health and Family Services recommends adoption of a groundwater enforcement standard and preventive action limit for alachlor-ESA as follows:

Recommended enforcement standard:	20 µg/L**
Recommended preventive action limit factor:	20%
Recommended preventive action limit:	4 µg/L

*Uncertainty factors of 10,000 have been previously used in developing groundwater enforcement standards for methyl-tert-butyl ether and n-hexane; they have also been used by EPA in establishing the MCLs for lindane and styrene that were adopted as Wisconsin groundwater enforcement standards.
**Corresponds to an acceptable daily intake value of 20 µg/day.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: March 1, 2006

MEMORANDUM

SUBJECT: **ACETOCHLOR**. Revised HED Chapter of the Tolerance Reassessment Eligibility Decision (TRED) Document. PC Code:121601, DP Barcode: D292336

Regulatory Action: Tolerance Reassessment
Risk Assessment Type: Single Chemical /Aggregate

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THROUGH: Louis Scarano, Ph.D., Chief
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Health Effects Division (7509C)

TO: Felicia Fort, Chemical Review Manager
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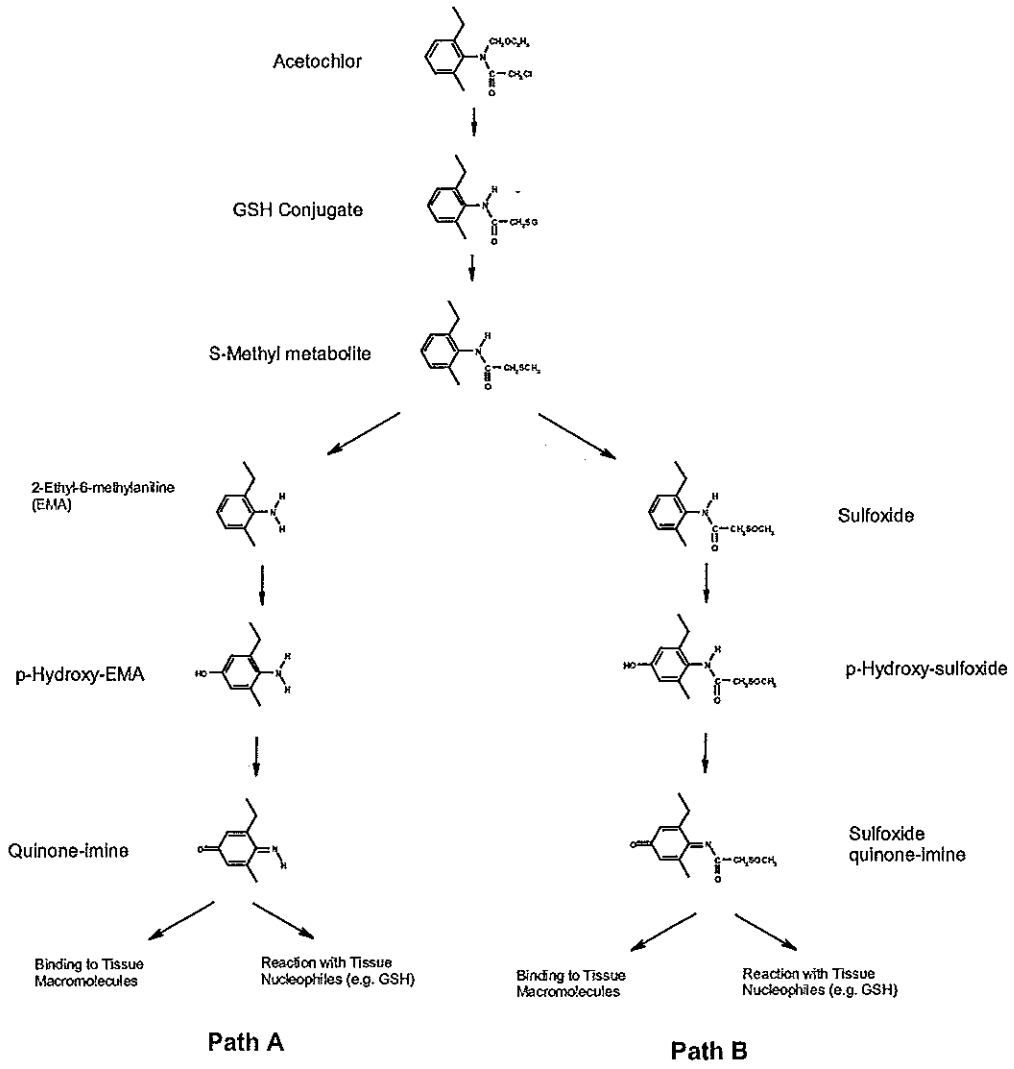
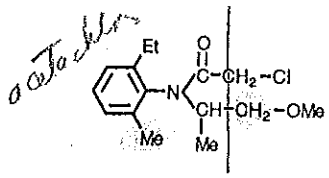


Figure 3.1. Summary of acetochlor biotransformatiom, leading to either methylethylquinone imine (MEQI) or methylethylquinone imine sulfoxide in the rat

Metolachlor

Uses Metolachlor is a chloroacetanilide herbicide used for the pre-emergence and pre-plant control of annual grass and broad-leaved weeds in maize, soyabeans, peanuts, sugarcane, cotton, potatoes, vegetables and woody ornamentals.

Mode of action The precise phytotoxic action of metolachlor is not well defined. Metolachlor has been shown to affect a broad spectrum of plant growth functions such as seed germination, shoot development, cell division, lipid and protein synthesis.

Common name	Metolachlor
Chemical name (IUPAC)	2-Chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(2-methoxy-1-methylethyl)acetamide
CASRN	51218–45–2
Molecular formula	$C_{15}H_{22}ClNO_2$
Molecular weight	283.8
Chemical structure	
Water solubility	488 mg l^{-1} (in water, 25 °C)
K_{oc}	121–309
Vapour pressure	4.2×10^{-3} Pa (25 °C)
Log K_{ow}	2.9 (25 °C)
pK_a	Non-ionised

Metabolic pathways

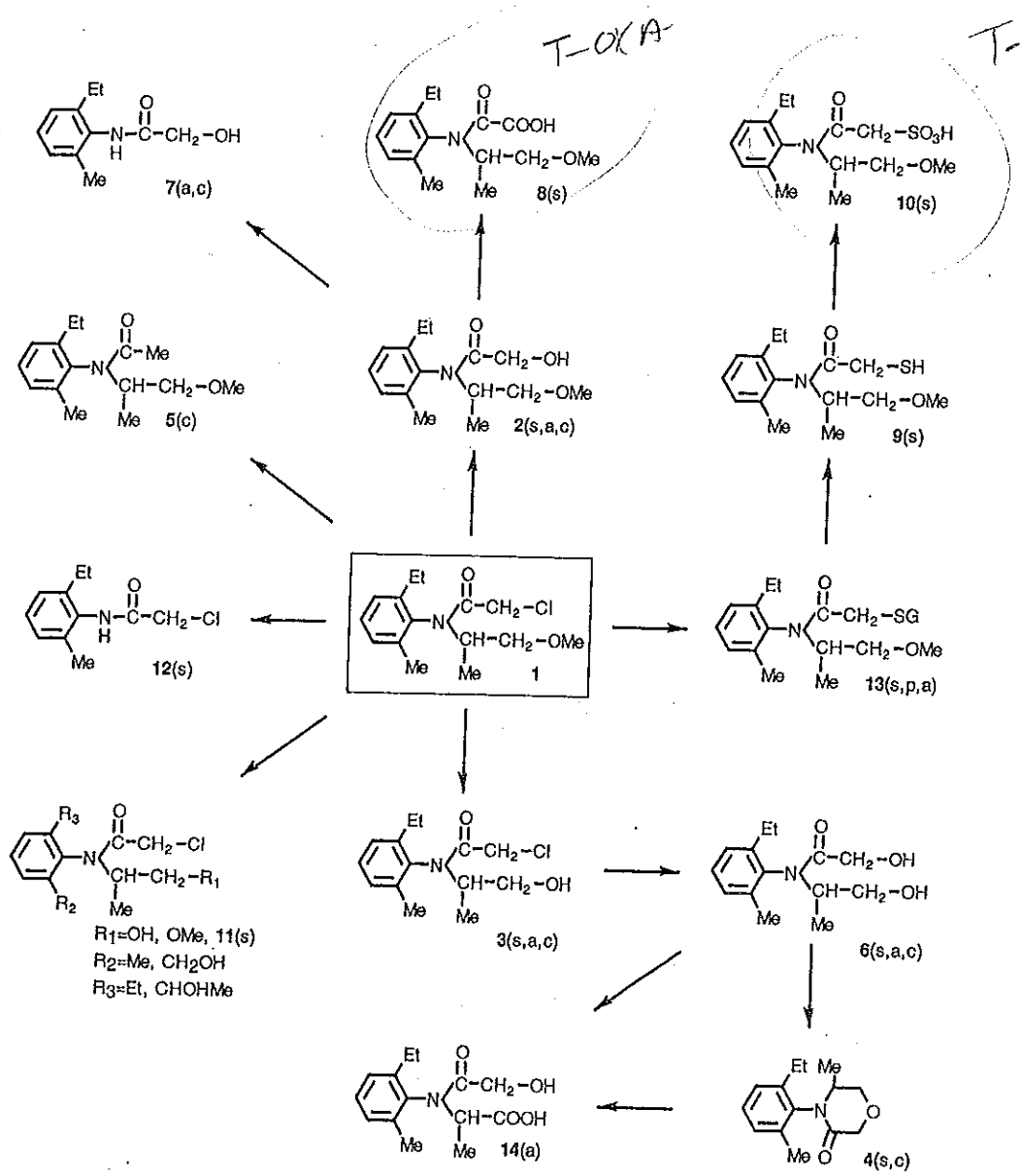
Metolachlor degrades extensively in soil, plants and animals by a combination of complex metabolic reactions. The major metabolic pathway involves the nucleophilic displacement of the chlorine and the glutathione conjugate of metolachlor was the major plant metabolite recovered. It was further degraded to multiple secondary catabolic products such as malonylcysteine, cysteine and thiolactic acid conjugates, and sulfoxide derivatives. Approximately 25 metabolites were identified as oxidation, hydroxylation, *O*-demethylation and *N*-dealkylation products. A simplified metabolic pathway is presented in Scheme 1 to illustrate the primary degradation/metabolic reactions of metolachlor. Not all identified products are included.

Chemical degradation

Metolachlor (**1**) was stable to hydrolytic degradation with a half-life (DT_{50}) >200 days at 20 °C in pH 1–9 solutions and 97 days at pH 13 (LeBaron *at al.*, 1988). It degraded under strong alkaline conditions (0.1 N NaOH solution) by a nucleophilic displacement/dechlorination reaction to yield *N*-(2-ethyl-6-methylphenyl)-2-hydroxy-*N*-(methoxyprop-2-yl)acetamide (**2**). Under acidic conditions (0.1 N HCl), it underwent *O*-demethylation to yield 2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(hydroxyprop-2-yl)acetamide (**3**) which then rapidly converted into the corresponding morpholinone product [**4**, 4-(2-ethyl-6-methylphenyl)-5-methyl-3-morpholinone]. In natural lake water, metolachlor was found to be stable with <4% degradation after 100 days at 20 °C (Kochany and Maguire, 1994). The calculated DT_{50} for metolachlor under UV light (313 nm) in pH 4–9 buffer solutions was 53–88 min. The DT_{50} of metolachlor in lake water, when exposed to natural sunlight during the summer season, was equivalent to *ca.* 11 days of continuous irradiation. Four sunlight induced photodegradation products were identified: product **2** from a dechlorination reaction; product **5** [*N*-(2-ethyl-6-methylphenyl)-*N*-(methoxyprop-2-yl)acetamide] from the dehydrochlorination reaction; product **4** from the internal cyclisation of 2-hydroxy-*N*-(2-ethyl-6-methylphenyl)-*N*-(hydroxyprop-2-yl)acetamide (**6**) and product **7** [2-hydroxy-*N*-(2-ethyl-6-methylphenyl)acetamide] from the *N*-dealkylation of product **2**. Product **4** was the major product recovered when metolachlor in water containing soil mineral and organic matters was exposed to UV light (254 nm) (Mathew and Khan, 1996).

Degradation in soils

The degradation of metolachlor in soil is mediated by soil microorganisms. The DT_{50} of metolachlor in several US test soils at 15–25 °C and



Scheme 1 Primary metabolic pathways of metolachlor (chemical, c; soils, s; plants, p; animals, a).

12–15% moisture content ranged from 21–50 days (Walker and Brown, 1985). LeBaron *et al.* (1988) described the detection of alcohol **2** under aerobic sterile conditions, whereas the primary degradation pathway of metolachlor in non-sterilised test soil was oxidation of the chloroacetyl moiety to yield **8** [*N*-(2-ethyl-6-methylphenyl)-*N*-(methoxyprop-2-yl)-oxalamide]. Marucchini *et al.* (1996) described **2** as the only metabolite detected in the laboratory lysimeter study. When the soil and leachates collected from the field lysimeters were analysed, neither metolachlor

nor its soil metabolites were detected. The recent identification of the ethanesulfonic acid metabolite **10** of metolachlor illustrates the potential significance of the glutathione conjugation pathway in the soil environment (Aga *et al.*, 1996).

Numerous degradation products were observed when metolachlor was incubated with various soil fungal cultures and isolates. Krause *et al.* (1985) and Saxena *et al.* (1987) reported that soil *Actinomycete* and *Bacillus* cultures degraded metolachlor *via* multiple metabolic pathways which included mainly benzylic hydroxylation (yielding multiple hydroxylated products **11**), and *N*-dealkylation [**12**, *N*-(2-ethyl-6-methylphenyl)-chloroacetamide]. Liu *et al.* (1989) reported compounds **4**, **6** and **9** were recovered after metolachlor was incubated with primary effluent of municipal sewage. The chemical nature of these metolachlor soil microbial culture degradation products are described in more detail by Chesters *et al.* (1989).

Muller and Buser (1995) and Ueji *et al.* (1995) noted the stereo-selective metabolism of metolachlor diasteromers in sewage sludge and soil. The herbicidally active (1'*S*) enantiomer was found to degrade faster when racemic material was applied to soil.

Metabolism in plants

LeBaron *et al.* (1988) described the primary metabolic fate of metolachlor in maize, soyabeans, lettuce, potato and sorghum. It involved the glutathione mediated nucleophilic displacement of the chlorine to yield the glutathione conjugate **13** followed by extensive biotransformation to the various malonylcysteine, cysteine, and thiolactic acid conjugates, and sulfoxide derivatives (pathway not shown in Scheme 1). *O*-Demethylation of the methoxypropyl moiety **3** followed by carbohydrate conjugation was also observed. This *O*-demethylation reaction was also observed during the *in vitro* metabolism of metolachlor by sorghum shoot microsomes (Moreland *et al.*, 1990).

Metabolism in animals

LeBaron *et al.* (1988) summarised the fate of metolachlor in animals. Rapid absorption, extensive metabolism and elimination of metolachlor occurred in rat, goat and chicken following oral dosing. Minimal transfer and retention of metolachlor-derived residues to milk, eggs, organs and tissues was observed.

The metabolite distribution profile in rat excreta was complex and approximately 20 metabolites were detected. The principal metabolic pathways could be simplified to include: *O*-demethylation to **3**, dechlorination of **3** to yield **6** and the oxidation of **6** to **14** [*N*-(2-ethyl-6-methylphenyl)-*N*-(hydroxyacetyl)-DL-alanine] and the *N*-dealkylation of **2** to **7**.

Other minor metabolic pathways included the hydroxylation of the aryl methyl and ethyl moieties (11).

The metabolism of metolachlor in bluegill sunfish included *O*-demethylation (3), hydroxylation of the aryl alkyl-moiety (11) followed by glucuronide conjugation, and the glutathione-mediated dechlorination of 3 (Cruz *et al.*, 1993).

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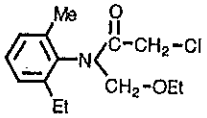
Acetochlor

Uses Acetochlor is a selective systemic chloroacetanilide herbicide for the pre-emergence and early post-emergence control of annual grasses and selected broad-leaved weeds in maize. Acetochlor is generally applied by surface application after planting, or as a pre-plant surface or incorporated treatment.

Mode of action Acetochlor residues are taken up from soil primarily through the shoots and later through the root. The mode of phytotoxic action of acetochlor is not well defined. Numerous physiological processes such as protein and lipid synthesis are affected by treatment with acetochlor.

Common name	Acetochlor
Chemical name (IUPAC)	2-Chloro-2′-ethyl-6′-methyl-*N*-ethoxymethylacetanilide
CASRN	34256–02–1
Molecular formula	$C_{14}H_{20}ClNO_2$
Molecular weight	269.8
Chemical structure	
Water solubility	233 mg l^{-1} (25 °C)
K_{oc}	130–140
Vapour pressure	4.5×10^{-9} Pa (25 °C)
Log K_{ow}	2.48 (25 °C)
pK_a	Non-ionised

Metabolic pathways

Acetochlor is metabolised in both plants and animals to a diverse array of metabolites. More than 30 metabolic products have been identified. The metabolism of acetochlor is similar to that of other acetanilide herbicides such as alachlor. Metabolism proceeds through common pathways, involving the initial displacement of chlorine by nucleophiles such as glutathione followed by formation of multiple secondary sulfur-containing catabolism products; hydrolytic/oxidative displacement of chlorine; *N*-dealkylation; hydroxylation of the arylethyl moiety and carbohydrate conjugation. The major metabolic pathways of acetochlor in soil, plants and animals are presented in Schemes 1 and 2. Not all identified metabolites are included in these schemes.

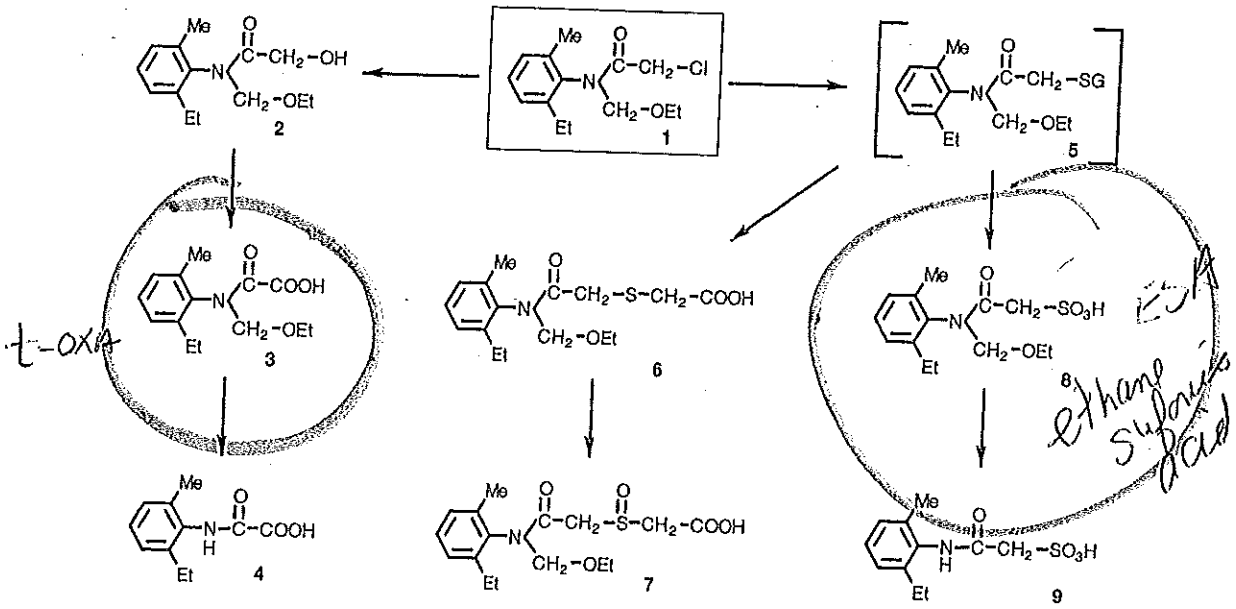
Chemical degradation

Acetochlor (**1**) was stable to hydrolysis for 30 days at 25 °C in sterile aqueous buffers at pH 3, 6 and 9 (Campbell and Hamilton, 1980). Acetochlor did not degrade in sterile water when irradiated under simulated sunlight for up to 34 days (Letendre and Klemm, 1982). Hydrolysis and photochemical degradation in water are not expected to be significant dissipation pathways for acetochlor in the environment.

Degradation in soils

Acetochlor degraded rapidly in soil under aerobic incubation conditions with half-life (DT_{50}) values ranging from 8 to 12 days (Campbell and Hamilton, 1980). Acetochlor was metabolised in soil mainly by two primary pathways. The first pathway involved the hydrolytic/oxidative displacement of chlorine to form the alcohol **2** and the oxidation of the alcohol **2** to oxanilic acid **3**. *N*-Dealkylation of **3** yielded oxanilic acid **4**. The second pathway involved the displacement of chlorine by glutathione and the further secondary catabolism of the glutathione conjugate **5** to the various sulfinylacetic and sulfonic acid products (**6**–**9**). Compounds **3**, **7**, **8** and **9** are major soil degradation products since each accounted for >10% of the applied radioactivity. Approximately 25% of the radioactivity was converted into CO_2, indicative of the ready mineralisation potential of acetochlor and its soil degradates.

Under anaerobic incubation conditions, the DT_{50} values were estimated to range from 17 to 21 days (Campbell and Hamilton, 1989). The principal degradation products were CO_2 and thioacetic acid. The thioacetic acid **6** was also observed under anaerobic conditions. The proposed degradation pathway of acetochlor in soil is presented in Scheme 1.

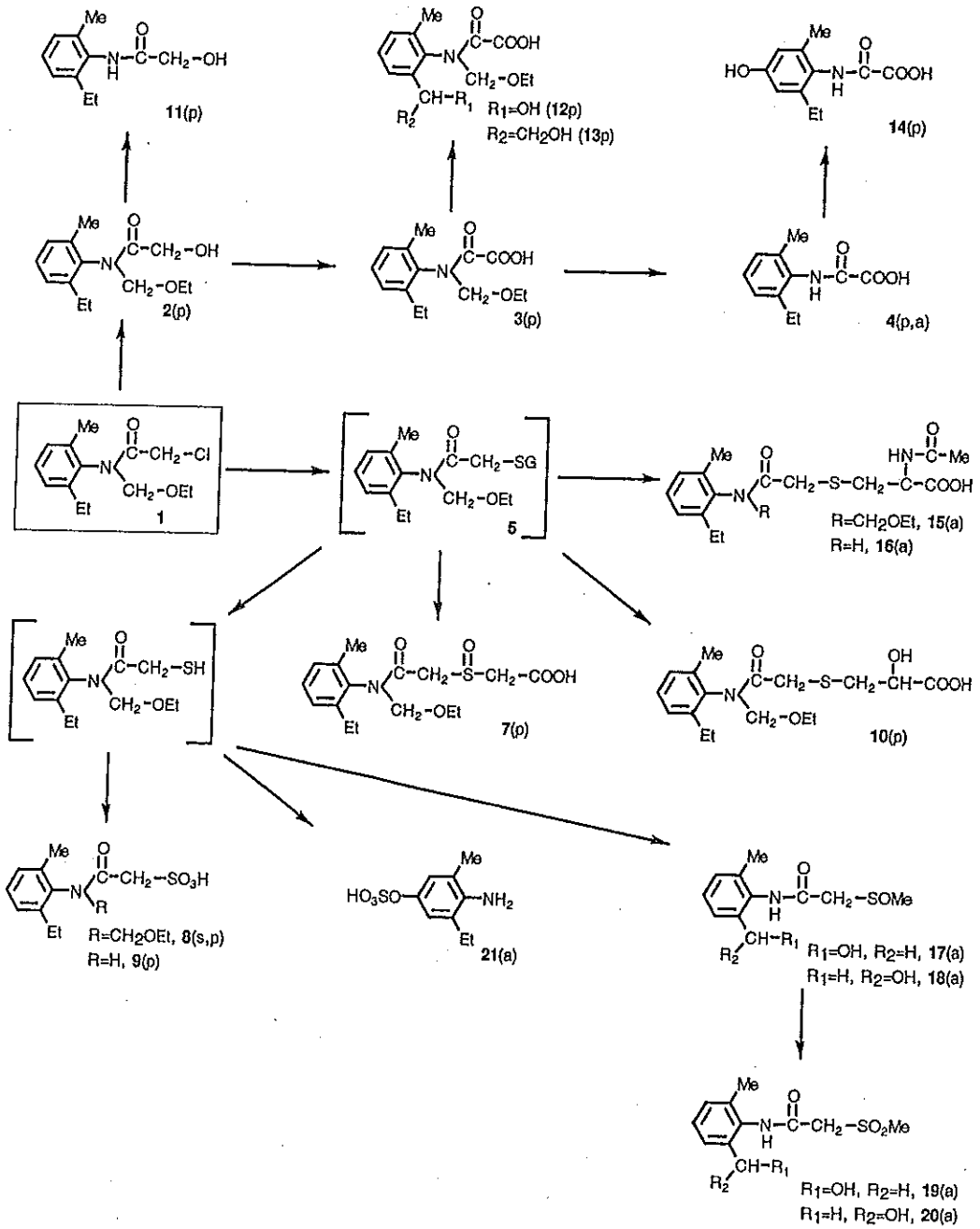


Scheme 1 Degradation pathway of acetochlor in soil.

Metabolism in plants

The plant metabolism of acetochlor was investigated in maize, soyabeans, peanuts, sorghum and rotational crops (Breaux and Erickson, 1982; Leyes and Hoobler, 1984; O'Neal and Johnson, 1992). Unmetabolised acetochlor was not detected in the plant matrix. Acetochlor was degraded to a diverse array of metabolites by a combination of multiple metabolic reactions. Primary metabolic reactions included: hydrolytic/oxidative displacement of chlorine; *N*-dealkylation; and glutathione displacement of the chlorine followed by formation of the various sulfur-containing secondary catabolism products. Major metabolites (compounds constituting more than 5% of the total radioactive residue in a matrix) in maize were sulfinyl-lactic acid **10** and the carbohydrate conjugate of the *N*-dealkylated alcohol **11**. Plant metabolites of acetochlor could be classified by the absence or presence of hydroxylation at the arylethyl moiety. Major metabolites in soyabeans were oxanilic acid **3** and its 1- and 2-hydroxylated products **12**, **13**; sulfinyl acetic acid **7**, and sulfonic acid **8**. Major metabolites in sorghum were oxanilic acid **3**, the carbohydrate conjugate of **13**, sulfonic acid **8**, sulfinyl-lactic acid **10** and the carbohydrate conjugate of **11**. Major metabolites in peanuts were **10** and **11**. Aryl hydroxylation of **4** to yield **14** was observed as a minor metabolic pathway in sorghum and peanuts.

The complexity of acetochlor plant metabolism requires the development of a residue method which is capable of measuring all acetochlor-derived residues. The residue method converts acetochlor metabolites



Scheme 2 Metabolic pathway of acetochlor in plants (p) and animals (a).

into analytes, 2-ethyl-6-methylaniline (EMA) and 2-(1-hydroxyethyl)-6-methylaniline (HEMA), by base hydrolysis. The magnitude of the total acetochlor equivalent residues is expressed as the sum of EMA and HEMA analytes.

Metabolism in animals

Acetochlor was rapidly and extensively metabolised in rats and readily eliminated in the urine and faeces (Carr *et al.*, 1983; Oppenhuizen and Yalamanchili, 1985). Fourteen metabolites were identified in the urine, and seven metabolites were identified in the faeces. The primary metabolic pathways included: (1) the displacement of chlorine by glutathione and the further degradation of the glutathione conjugate **5** by the mercapturic acid pathway; (2) hydroxylation of the arylethyl moiety and (3) *N*-dealkylation. Significant rat metabolites included compounds **15–20**. One additional pathway, observed only in animals, involved the hydrolysis of the amide bond, *para*-hydroxylation and subsequent conjugation to the sulfate conjugate **21**. The observed metabolic pathway in hens and goats is consistent with that observed in crops (Leyes, 1982; Cheng, 1990; Letendre *et al.*, 1987). Negligible levels of acetochlor residues were observed in milk, eggs and edible tissues.

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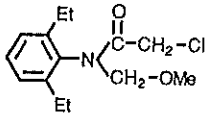
Alachlor

Uses Alachlor is a selective systemic chloroacetanilide herbicide for the pre-emergence control of annual grasses and selected broad-leaved weeds in maize, soyabeans, peanuts and other crops. Alachlor is applied to the soil surface prior to or after planting, or by shallow incorporation. Alachlor may also be applied early post-emergence to certain crops at the ground-cracking stage of seed emergence.

Mode of action Alachlor residues are taken up from soil primarily through the shoots and later through the root. The mode of action of alachlor is not well defined. Alachlor inhibits root elongation by affecting processes such as protein and lipid synthesis.

Common name	Alachlor
Chemical name (IUPAC)	2-Chloro-2′,6′-diethyl-*N*-methoxymethylacetanilide
CASRN	15972–60–8
Molecular formula	$C_{14}H_{20}ClNO_2$
Molecular weight	269.8
Chemical structure	
Water solubility	188 mg l^{-1} (pH 5, 20 °C), 170 mg l^{-1} (pH 7, 20 °C)
K_{oc}	122
Vapour pressure	2.9×10^{-3} Pa (25 °C)
Log K_{ow}	3.09 (25 °C)
pK_a	Non-ionised

Metabolic pathways

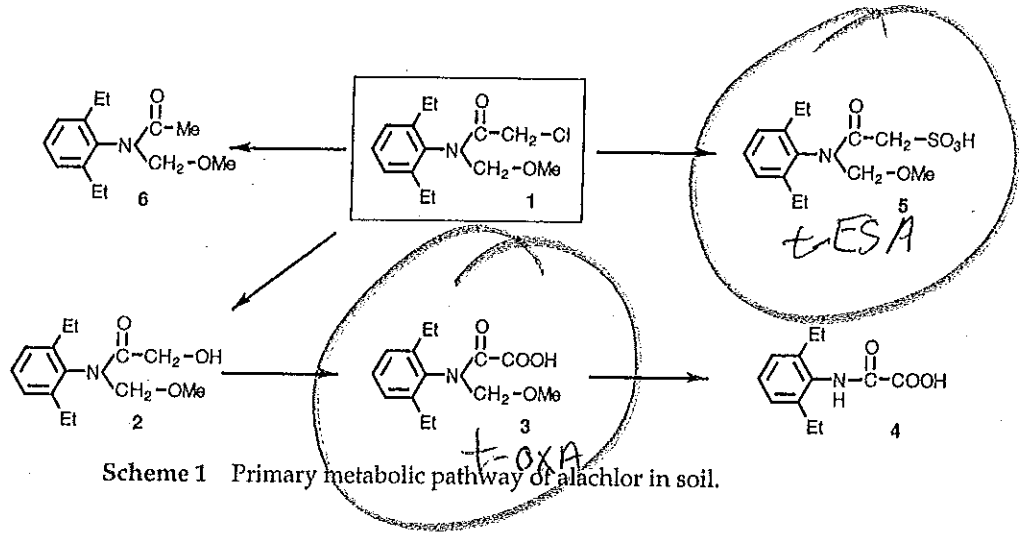
Alachlor is metabolised in soil, plants and animals by common degradation pathways. Numerous degradation products are generated as the result of the following major metabolic reactions: (1) displacement of chlorine by nucleophiles such as glutathione followed by the formation of multiple sulfur-containing secondary catabolic degradation products; (2) hydrolytic/oxidative replacement of chlorine; (3) *N*-dealkylation; (4) hydroxylation of the aryl ethyl moiety and (5) carbohydrate conjugation. The primary soil degradation pathway of alachlor is summarised in Scheme 1. The major plant and animal metabolic pathways are presented in Scheme 2. Not all identified metabolites are included in these schemes.

Chemical degradation

Minimal degradation of alachlor (1) in sterile pH 3, 6, and 9 buffer solutions at 25 °C under dark conditions was observed (Suba and Pearson, 1979). Alachlor was also found to be stable to photolysis in sterile water. When an aqueous solution of alachlor was exposed to natural sunlight for 30 days, its photolytic half-life (DT_{50}) was estimated to be *ca.* 239 days (Kesterson *et al.*, 1990). No hydrolytic or photolytic degradation products accounting for >1% of the applied radioactivity were detected. Hydrolysis and photochemical degradation in water are not expected to be significant dissipation pathways for alachlor in the environment.

Degradation in soils

Alachlor was rapidly degraded in soil by microorganisms under aerobic conditions with DT_{50} values ranging from 6 to 16 days, and DT_{90} values ranging from 31 to 68 days (Suba and Pearson, 1979). There were two major pathways. The first degradation pathway involved the hydrolytic/oxidative replacement of chlorine and *N*-dealkylation to form alcohol **2** and oxanilic acids **3** and **4**. The second degradation pathway involved the displacement of chlorine by glutathione and further degradation/oxidation of the glutathione conjugate to yield sulfonic acid **5**. Under anaerobic incubation conditions, degradation of alachlor was accelerated. The principal degradation product was compound **6** (acetanilide) formed by the reductive dehalogenation of alachlor. In sandy loam and clay loam sediment/water systems, alachlor degraded with DT_{50} values of 18 and 37 days, respectively, and DT_{90} values of 58 and 123 days, respectively. The principal degradation reaction was reductive dechlorination to yield compound **6**. Hydrolytic/oxidative dechlorination occurred gradually and compound **2** was observed after 100 days in the clay loam system. Compounds **3**, **4** and **5** were tentatively identified in both sediment systems (Phillips and Hall, 1995).



Scheme 1 Primary metabolic pathway of alachlor in soil.

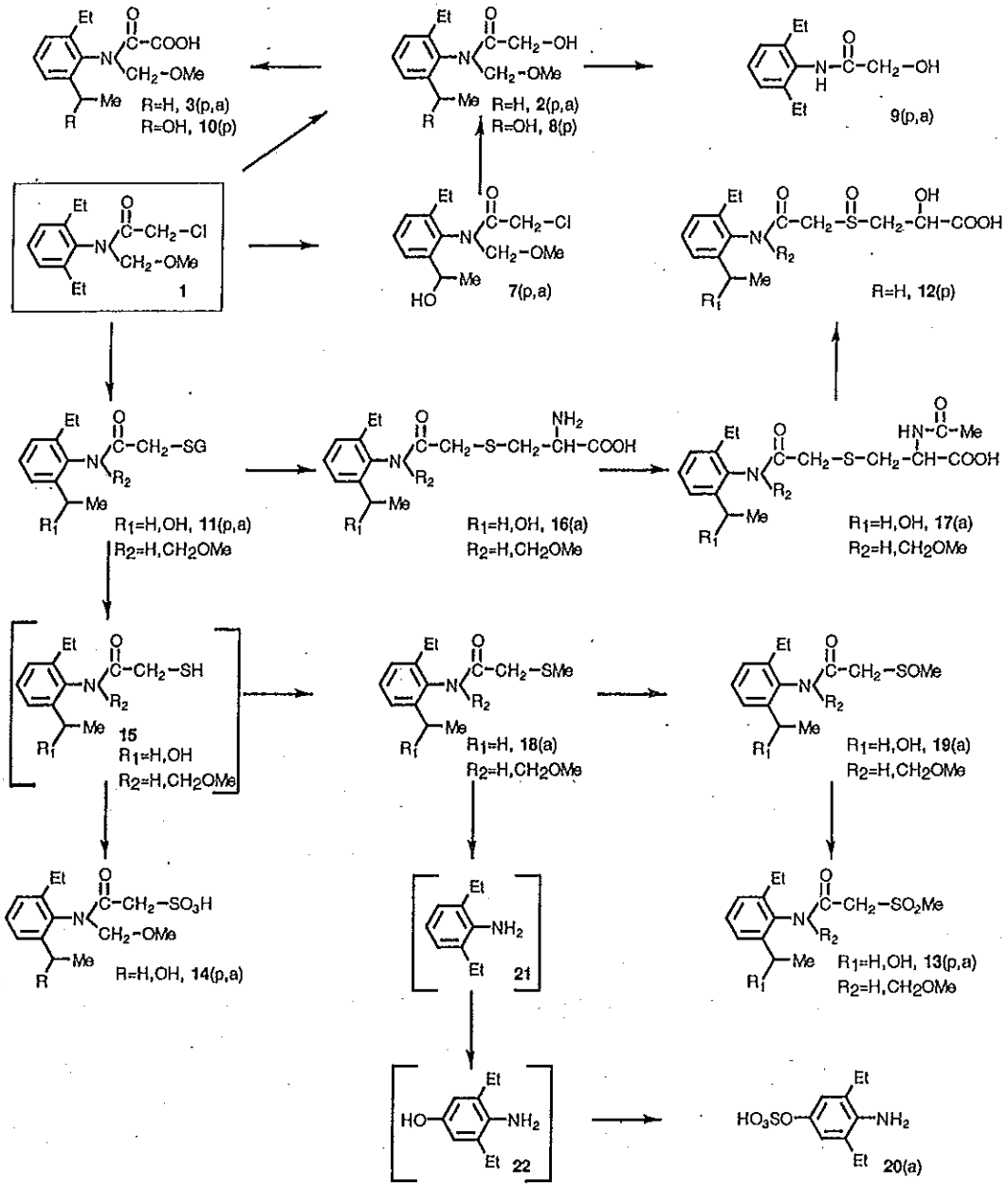
Metabolism in plants

The plant metabolism of alachlor was investigated in maize, soyabeans and rotational crops (radishes, lettuce and wheat) in accordance with the intended use pattern (Nadeau, 1982a,b; Hackett *et al.*, 1992). Unmetabolised alachlor was not detected in any plant matrix. Alachlor degraded extensively to a diverse array of metabolites similar to those described for the soil metabolism. Major metabolic reactions included: (1) hydrolytic/oxidative replacement of the chlorine atom; (2) *N*-dealkylation; (3) hydroxylation of the arylethyl moiety and (4) glutathione displacement of the chlorine atom followed by the formation of multiple sulfur-containing catabolic degradation products. These metabolic reactions can be grouped into two primary pathways.

The first pathway involved the hydrolytic/oxidative displacement of the chlorine atom of alachlor and its 1-hydroxylated metabolite **7** to yield dechlorination products **2** and **8**. *N*-Dealkylation of **2** yielded **9**. Further oxidation of **2** and **8** yielded the corresponding oxanilic acids **3** and **10**. Both the free alcohol metabolites (**2** and **8**) and their carbohydrate conjugates were detected. The second pathway involved the nucleophilic displacement of the chlorine atom of alachlor and its hydroxylated product **7** by glutathione to form glutathione conjugate **11**, followed by extensive catabolism to yield multiple secondary sulfur-containing compounds. Major metabolites (metabolites constituting more than 5% of the total radioactive residue in the crop matrix) in maize were sulfinyl-lactic acid **12** and the carbohydrate conjugates of **2** and its corresponding *N*-dealkylated product **9**. The major soyabean plant metabolites were methyl sulfone **13**, alcohol **8**, oxanilic acid **10**, sulfonic acid **14** and their carbohydrate conjugates. The formation of the methyl sulfone and sulfonic acid was likely from the thiol intermediate **15** derived from degradation of the glutathione conjugate.

Plant metabolism data showed that there are two major classes of

alachlor metabolites, distinguishable by their 2,6-diethylaniline (DEA)- or 2-ethyl-6-(1-hydroxyethyl)aniline (HEEA)-based structure. The current crop residue method involves the conversion of alachlor metabolites by base hydrolysis to DEA and HEEA, and the magnitude of alachlor residues in crop samples is determined as the sum of DEA and HEEA analytes.



Scheme 2 Primary metabolic pathway of alachlor in plants (p) and animals (a).

Metabolism in animals

The metabolism of alachlor has been studied in rats, mice and monkeys. Alachlor was metabolised extensively and eliminated rapidly in animal urine and faeces. The elimination half-lives in rats and monkeys were *ca.* 14 and 6 hours, respectively. Minimal transfer into or concentration of ^{14}C-residues in animal organs and tissues was observed.

The overall metabolite distribution profiles between rats and mice are consistent (Moran and Grabiak, 1983; Howe *et al.*, 1986a,b; Chott and Howe, 1986). Approximately 30 metabolites were identified in the rat excreta. Metabolism in the monkey was less extensive (Howe *et al.*, 1985, 1986c; Wilson *et al.*, 1995). The primary metabolic pathway observed in rats, mice and monkeys was the displacement of chlorine by glutathione to form the glutathione conjugate **11**. Degradation of **11** yielded numerous secondary sulfur metabolites including cysteine conjugate **16**, mercapturate **17**, methyl sulfide **18**, methyl sulfoxide **19** and methyl sulfone **13**. A combination of the following reactions: oxidative dechlorination, hydroxylation of the arylethyl moiety, and *N*-dealkylation yielded alcohols **2** and **8**, oxanilic acids **3** and **10**, and dealkylated alcohol **9**.

A common metabolic pathway between plant and animal systems is proposed. One additional pathway, observed only in animals, involved the hydrolysis of the amide bond, *para*-hydroxylation and subsequent conjugation of the *para*-hydroxy-moiety to the sulfate conjugate **20**. Based on *in vitro* metabolism studies of alachlor by rat and monkey liver and nasal turbinate tissues (Li *et al.*, 1992), the formation of **20** was proposed to occur by metabolism of methyl sulfide **18** through intermediates **21** (DEA) and **22** (hydroxy-DEA). The observed metabolic pathway in hens and goats is consistent with that observed in plants (Nadeau *et al.*, 1992). Negligible levels of alachlor residues were observed in milk, eggs and edible tissues.

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[Page 509-511]

TITLE 40--PROTECTION OF ENVIRONMENT

CHAPTER I--ENVIRONMENTAL PROTECTION AGENCY (CONTINUED)

PART 180_TOLERANCES AND EXEMPTIONS FROM TOLERANCES FOR PESTICIDE CHEMICALS IN

Subpart C_Specific Tolerances

Sec. 180.368 Metolachlor; tolerances for residues.

(a) General. (1) Tolerances are established for the combined residues (free and bound) of the herbicide metolachlor [2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide] and its metabolites, determined as the derivatives, 2-[(2-ethyl-6-methylphenyl)amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound, in or on the raw agricultural commodities.

Commodity	Parts per million
Almond, hulls	0.3
Animal feed, nongrass, group 18	3.0
Barley, grain	0.1
Barley, straw	0.5
Buckwheat, grain	0.1
Cabbage	1.0
Cattle, fat	0.02
Cattle, kidney	0.2
Cattle, liver	0.05
Cattle, meat	0.02
Cattle, meat byproducts, except kidney and liver	0.02
Celery	0.1
Corn, forage and fodder	8.0
Corn, grain	0.1
Corn, sweet, kernel plus cob with husks removed	0.1
Cotton, undelinted seed	0.1
Egg	0.02
Fruit, stone, group 12	0.1
Goat, fat	0.02
Goat, kidney	0.2
Goat, liver	0.05
Goat, meat	0.02
Goat, meat byproducts, except kidney and liver	0.02
Horse, fat	0.02
Horse, kidney	0.2
Horse, liver	0.05
Horse, meat	0.02
Horse, meat byproducts, except kidney and liver	0.02
Milk	0.02
Millet, fodder	0.5

[[Page 510]]

Millet, forage	0.5
Millet, grain	0.1
Milo, fodder	0.5
Milo, forage	0.5
Milo, grain	0.1
Nut, tree, group 14	0.1
Oat, forage	0.5
Oat, grain	0.1
Oat, straw	0.5
Peanut	0.5
Peanut, forage and hay	30.0
Pepper, bell	0.1
Potato	0.2
Poultry, fat	0.02
Poultry, liver	0.05
Poultry, meat	0.02
Poultry, meat byproducts, except liver	0.02
Rice, forage	0.5
Rice, straw	0.5
Rice, grain	0.1
Rye, forage	0.5
Rye, grain	0.1
Rye, straw	0.5
Safflower, seed	0.1
Sheep, fat	0.02
Sheep, kidney	0.2
Sheep, liver	0.05
Sheep, meat	0.02
Sheep, meat byproducts, except kidney and liver	0.02
Sorghum, forage and fodder	2.0
Sorghum, grain, grain	0.3
Soybean	0.2
Soybean, forage and hay	8.0
Vegetable, foliage of legume, except soybean, subgroup 7A	15.0
Vegetable, seed and pod, except soybean	0.3
Wheat, forage	0.5
Wheat, grain	0.1
Wheat, straw	0.5

(2) Tolerances are established for combined residues of the herbicide S-metolachlor acetamid, 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)-, (S) and its metabolites, determined as the derivatives, 2-(2-ethyl-6-methylphenyl)amino-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound S-metolachlor in or on the following raw agricultural commodities:

Commodity	Parts per million
Asparagus	0.10
Beet, sugar, molasses	2.0
Beet, sugar, roots	0.5
Beet, sugar, tops	15.0
Grass, forage	10.0
Grass, hay	0.2
Spinach	0.5
Sunflower, seed	0.5
Sunflower, meal	1.0

(3) Tolerances are established for the combined residues (free and bound) of the herbicide S-metolachlor [S-2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide], its R-enantiomer, and its metabolites, determined as the derivatives, 2-[2-ethyl-6-methylphenyl)amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound, in or on the following raw agricultural commodities:

Commodity	Parts per million
Brassica, head and stem, subgroup 5A	0.6
Cattle, fat	0.04
Cattle, kidney	0.2
Cattle, liver	0.1
Cattle, meat	0.04
Cattle, meat byproducts, except kidney and liver	0.04
Corn, field, stover	6.0
Corn, pop, stover	6.0
Corn, sweet, stover	6.0
Corn, field, forage	6.0
Corn, sweet, forage	6.0
Corn, sweet, kernel plus cob with husks removed	0.1
Corn, field, grain	0.1
Corn, pop, grain	0.1
Cotton, gin byproducts	4.0
Cotton, undelinted seed	0.1
Egg	0.04
Garlic, bulb	0.1
Goat, fat	0.04
Goat, kidney	0.2
Goat, liver	0.1
Goat, meat	0.04
Goat, meat byproducts, except kidney and liver	0.04
Horse, fat	0.04
Horse, kidney	0.2
Horse, liver	0.1
Horse, meat	0.04
Horse, meat byproducts, except kidney and liver	0.04
Leaf petioles subgroup 4B	0.1
Milk	0.02
Onion, bulb	0.1
Onion, green	2.0
Pea and bean, dried shelled, except soybean, subgroup 6C	0.1
Peanut	0.2
Peanut, hay	20.0
Peanut, meal	0.4
Poultry, fat	0.04
Poultry, meat	0.04
Poultry, meat byproducts	0.04
Pumpkin	0.1
Safflower, seed	0.1
Shallot, bulb	0.1
Sheep, fat	0.04
Sheep, kidney	0.2
Sheep, liver	0.1
Sheep, meat	0.04
Sheep, meat byproducts, except kidney and liver	0.04
Sorghum, grain, forage	1.0
Sorghum, grain, stover	4.0

Sorghum, grain, grain	0.3
Soybean, forage	5.0
Soybean, hay	8.0
Soybean, seed	0.2
Squash, winter	0.1
Tomato, paste	0.3

[[Page 511]]

Vegetable, foliage of legume, except soybean, subgroup 7A	15.0
Vegetable, fruiting, group 8, except tabasco pepper	0.1
Vegetable, legume, edible podded, subgroup 6A	0.5
Vegetable, root, except sugar beet, subgroup 1B	0.3
Vegetable, tuberous and corm, subgroup 1C	0.2

(b) Section 18 emergency exemptions. [Reserved]

(c) Tolerances with regional registrations. (1) Tolerances with regional registration as defined in Sec. 180.1(n) are established for the combined residues (free and bound) of the herbicide metolachlor [2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide] and its metabolites, determined as the derivatives, 2-[(2-ethyl-6-methylphenyl)amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound, in or on the following raw agricultural commodities:

Commodity	Parts per million
Onion, bulb	1.0
Pepper, chili	0.5
Pepper, cubanelle	0.1
Pepper, tabasco	.5

(2) Tolerances with regional registration as defined in Sec. 180.1(n) are established for the combined residues (free and bound) of the herbicide S-metolachlor [S-2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide], its R-enantiomer, and its metabolites, determined as the derivatives, 2-[2-ethyl-6-methylphenyl)amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound, in or on the following raw agricultural commodities:

Commodity	Parts per million
Pepper, tabasco	0.5

(d) Indirect or inadvertent residues. Tolerances are established for the indirect or inadvertent combined residues (free and bound) of the herbicide S-metolachlor [S-2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide], its R-enantiomer, and its metabolites, determined as the derivatives, 2-[2-ethyl-6-methylphenyl)amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound, in or on the following raw agricultural commodities:

Commodity	Parts per million
Animal feed, nongrass, group 18	1.0
Barley, grain	0.1
Barley, hay	1.0
Barley, straw	0.5
Buckwheat, grain	0.1
Oat, forage	0.5
Oat, grain	0.1
Oat, hay	1.0
Oat, straw	0.5
Rice, grain	0.1
Rice, straw	0.5
Rye, forage	0.5
Rye, grain	0.1
Rye, straw	0.5
Wheat, forage	0.5
Wheat, grain	0.1
Wheat, hay	1.0
Wheat, straw	0.5

[44 FR 10385, Feb. 20, 1979]

Editorial Note: For Federal Register citations affecting Sec. 180.368, see the List of CFR Sections Affected, which appears in the Finding Aids section of the printed volume and on GPO Access.

[Code of Federal Regulations]
[Title 40, Volume 23]
[Revised as of July 1, 2008]
From the U.S. Government Printing Office via GPO Access
[CITE: 40CFR180.470]

[Page 558]

TITLE 40--PROTECTION OF ENVIRONMENT

CHAPTER I--ENVIRONMENTAL PROTECTION AGENCY (CONTINUED)

PART 180_TOLERANCES AND EXEMPTIONS FROM TOLERANCES FOR PESTICIDE CHEMICALS IN

Subpart C_Specific Tolerances

Sec. 180.470 Acetochlor; tolerances for residues.

(a) General. Tolerances are established for residues of acetochlor; 2-chloro-2'-methyl-6-ethyl-N-ethoxymethylacetanilide, and its metabolites containing the ethyl methyl aniline (EMA) moiety and the hydroxyethyl methyl aniline (HEMA) moiety, to be analyzed as acetochlor and expressed as acetochlor equivalents, in or on the following raw agricultural commodities.

Commodity	Parts per million
Corn, field, forage	3.0
Corn, field, grain	0.05
Corn, field, stover	1.5
Corn, pop, grain	0.05
Corn, pop, stover	1.5
Corn, sweet, forage	1.5
Corn, sweet, kernels plus cob with husks removed	0.05
Corn, sweet, stover	1.0
Sorghum, grain, forage	1.6
Sorghum, grain, grain	0.05
Sorghum, grain, stover	1.7

(b) Section 18 emergency exemptions. [Reserved]

(c) Tolerances with regional registrations. [Reserved]

(d) Indirect or inadvertent residues. Tolerances are established for indirect or inadvertent residues of acetochlor; 2-chloro-2'-methyl-6-ethyl-N-ethoxymethylacetanilide, and its metabolites containing the ethyl methyl aniline (EMA) moiety and the hydroxyethyl methyl aniline (HEMA) moiety, to be analyzed as acetochlor and expressed as acetochlor equivalents, in or on the following raw agricultural commodities when present therein as a result of application of acetochlor to the growing crops in paragraph (a) of this section:

Commodity	Parts per million
Animal feed, nongrass, group 18, forage	1.3
Animal feed, nongrass, group 18, hay	3.5
Beet, sugar, root	0.05
Beet, sugar, tops	0.05
Grain, cereal, forage, fodder and straw, group 16, except	0.5

corn, grain sorghum, rice and wheat, forage.....	
Grain, cereal, forage, fodder and straw, group 16, except corn, grain sorghum, rice and wheat, hay.....	2.0
Grain, cereal, forage, fodder and straw, group 16, except corn, grain sorghum, rice and wheat, stover.....	0.1
Grain, cereal, forage, fodder and straw, group 16, except corn, grain sorghum, rice and wheat, straw.....	0.3
Grain, cereal, group 15, except corn, grain sorghum, rice, and wheat, grain.....	0.05
Pea and bean, dried shelled, except soybean, subgroup 6C...	0.05
Potato.....	0.05
Soybean, forage.....	0.7
Soybean, hay.....	1.0
Soybean, seed.....	0.1
Sunflower, seed.....	0.05
Wheat, forage.....	0.5
Wheat, grain.....	0.02
Wheat, hay.....	2.0
Wheat, straw.....	0.1

[72 FR 27468, May 16, 2007]

[Code of Federal Regulations]
[Title 40, Volume 23]
[Revised as of July 1, 2008]
From the U.S. Government Printing Office via GPO Access
[CITE: 40CFR180.249]

[Page 478-479]

TITLE 40--PROTECTION OF ENVIRONMENT

CHAPTER I--ENVIRONMENTAL PROTECTION AGENCY (CONTINUED)

PART 180_TOLERANCES AND EXEMPTIONS FROM TOLERANCES FOR PESTICIDE CHEMICALS IN

Subpart C_Specific Tolerances

Sec. 180.249 Alachlor; tolerances for residues.

(a) General. Tolerances are established for combined residues of alachlor (2-chloro-2',6'-diethyl-N-(methoxymethyl)acetanilide) and its metabolites which can be converted to 2,6-diethylaniline (DEA) or 2-ethyl-6-(1-hydroxyethyl)aniline (1-HEEA) upon basic hydrolysis, calculated as alachlor in or on the following raw agricultural commodities.

Commodity	Parts per million
Beans, dry	0.1
Beans, succulent lima	0.1
Cattle, fat	0.02
Cattle, meat byproducts	0.02
Cattle, meat	0.02
Corn, field, forage	2.0
Corn, field, grain	0.2

[[Page 479]]

Corn, field, pop	0.2
Corn, field, stover	2.0
Corn, pop, stover	2.0
Corn, sweet (K+CWHR)	0.05
Corn, sweet, stover	2.0
Cotton, gin byproducts	0.7
Cotton, undelinted seed	0.03
Cowpea, forage	5.0
Cowpea, hay	5.0
Egg	0.02
Goat, fat	0.02
Goat, meat byproducts	0.02
Goat, meat	0.02
Hog, fat	0.02
Hog meat byproducts	0.02
Hog, meat	0.02
Horse, fat	0.02
Horse, meat byproducts	0.02
Horse, meat	0.02
Milk	0.02
Peanut	0.5
Poultry, fat	0.02

Poultry, meat byproducts	0.02
Poultry, meat	0.02
Sheep, fat	0.02
Sheep, meat byproducts	0.02
Sheep, meat	0.02
Sorghum grain, forage	2.0
Sorghum, grain, grain	0.1
Sorghum, grain, stover	1.0
Soybeans, seed	1.0
Sunflower, meal	3.4
Sunflower, seed	2.5

(b) Section 18 emergency exemptions. [Reserved]

(c) Tolerances with regional registrations. [Reserved]

(d) Indirect or inadvertent residues. Tolerances are established for indirect or inadvertent residues of alachlor (2-chloro-2',6'-diethyl-N-(methoxymethyl)acetanilide) and its metabolites which can be converted to 2,6-diethylaniline (DEA) or 2-ethyl-6-(1-hydroxyethyl)aniline (1-HEEA) upon basic hydrolysis, calculated as alachlor, in or on the following raw agricultural commodities when present therein as a result of the application of alachlor to the growing crops in paragraph (a) of this section:

Commodity	Parts per million
Animal feed, nongrass, group 18, forage	1.4
Animal feed, nongrass, group 18, hay	1.2
Grain, cereal, forage, and straw, group 16 except corn, sorghum, rice, straw	0.8
Grain, cereal, forage, fodder and straw, group 16 except corn, sorghum, rice, forage	0.6
Grain, cereal, forage, fodder, and straw, group 16 except for corn, sorghum, rice, hay	0.8
Grain, cereal, group 15 except corn, sorghum, rice	0.05

[72 FR 54584, Sept. 26, 2007]

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

May 23, 2002

MEMORANDUM

SUBJECT: Metolachlor. **Revised** HED Science Assessment for Tolerance Reassessment Eligibility Decision. PC Code 108801. DP Barcode D282964.

FROM: Christina Jarvis, Risk Assessor
Reregistration Branch II
Health Effects Division (7509C)

THROUGH: Alan Nielsen, Branch Senior Scientist
Reregistration Branch II
Health Effects Division (7509C)

TO: Anne Overstreet, Chemical Review Manager
Reregistration Branch III
Special Review and Reregistration Division (7508W)

Attached is the **revised** tolerance reassessment eligibility decision document for metolachlor and s-metolachlor, prepared by the Health Effects Division (HED). This assessment has been revised to take into consideration comments made by Syngenta Crop Protection during the 30-day registrant comment period. HED notes that no changes to the toxicological endpoint selection have been made in this revised assessment, nor have any of Syngenta's comments resulted in a significant change to the risk picture for metolachlor and s-metolachlor. New estimated environmental concentrations of metolachlor/s-metolachlor in drinking water have **not** resulted in a significant change to the aggregate risk assessment.

This assessment includes the hazard characterization from Virginia Dobozy, residential exposure assessment from Richard Griffin, dietary exposure and residue chemistry assessments from Sherrie Kinard, product chemistry from Ken Dockter, drinking water assessment from Mark Corbin, and aggregate exposure assessment and risk characterization from Christina Jarvis. The disciplinary science chapters and other supporting documents referenced in this document

Appendix A Table 1: Toxicity Profile for Metolachlor (PC Code 108801)

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 acceptable/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 statistically 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 based on 1 ppm in food equals 0.150 mg/kg/day)	NOAEL = 1000 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)

technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA), Public Law 104–113, section 12(d) (15 U.S.C. 272 note). Since tolerances and exemptions that are established on the basis of a petition under section 408(d) of the FFDCA, such as the exemption in this final rule, do not require the issuance of a proposed rule, the requirements of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*) do not apply. In addition, the Agency has determined that this action will not have a substantial direct effect on States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government, as specified in Executive Order 13132, entitled *Federalism*(64 FR 43255, August 10, 1999). Executive Order 13132 requires EPA to develop an accountable process to ensure "meaningful and timely input by State and local officials in the development of regulatory policies that have federalism implications." "Policies that have federalism implications " is defined in the Executive order to include regulations that have "substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government." This final rule directly regulates growers, food processors, food handlers and food retailers, not States. This action does not alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of section 408(n)(4) of the FFDCA. For these same reasons, the Agency has determined that this rule does not have any "tribal implications" as described in Executive Order 13175, entitled *Consultation and Coordination with Indian Tribal Governments* (65 FR 67249, November 6, 2000). Executive Order 13175, requires EPA to develop an accountable process to ensure "meaningful and timely input by tribal officials in the development of regulatory policies that have tribal implications." "Policies that have tribal implications" is defined in the Executive order to include regulations that have "substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and the Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes." This rule will not have substantial direct effects on tribal governments, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes, as specified in Executive Order 13175. Thus, Executive Order 13175 does not apply to this rule.

XIII. Congressional Review Act

The Congressional Review Act, 5 U.S.C. 801 *et seq.*, as added by the Small Business Regulatory Enforcement Fairness Act of 1996, generally provides that before a rule may take effect, the agency promulgating the rule must submit a rule report, which includes a copy of the rule, to each House of the Congress and to the Comptroller General of the United States. EPA will submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of this final rule in the**Federal Register**. This final rule is not a "major rule" as defined by 5 U.S.C. 804(2).

List of Subjects in 40 CFR Part 180

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: August 23, 2005.

Lois Rossi,

Director, Registration Division, Office of Pesticide Programs.

■ Therefore, 40 CFR chapter I is amended as follows:

PART 180—[AMENDED]

■ 1. The authority citation for part 180 continues to read as follows:

Authority: 21 U.S.C. 321(q), 346a and 371.

■ 2. In § 180.910, the table is amended by adding alphabetically the following inert ingredients to read as follows:

§ 180.910 Inert ingredients used pre- and post-harvest; exemptions from the requirement of a tolerance.

* * * * *

Inert Ingredients	Limits	Uses
* *	*	* *
Lactic acid, 2-ethylhexyl ester (CAS Reg. No. 6283–86–9).	.....	Solvent
Lactic acid, 2-ethylhexyl ester, (2S)-(CAS Reg. No. 186817–80–1).	.....	Solvent
* *	*	* *

■ 3. In § 180.930, the table is amended by adding alphabetically the following inert ingredients to read as follows:

§ 180.930 Inert ingredients applied to animals; exemptions from the requirement of a tolerance.

* * * * *

Inert Ingredients	Limits	Uses
* *	*	* *
Lactic acid, 2-ethylhexyl ester (CAS Reg. No. 6283–86–9).	.....	Solvent
Lactic acid, 2-ethylhexyl ester, (2S)-(CAS Reg. No. 186817–80–1).	.....	Solvent
* *	*	* *

[FR Doc. 05–17360 Filed 8–30–05; 8:45 am]

BILLING CODE 6560–50–S

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[OPP–2004–0326; FRL–7716–1]

S-metolachlor; Pesticide Tolerance

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This regulation establishes tolerances for combined residues (free and bound) of S-metolachlor in or on certain commodities as set forth in Unit II. of the **SUPPLEMENTARY INFORMATION.** The Interregional Research Project Number 4 (IR–4), 681 U.S. Highway #1 South, North Brunswick, NJ 08902–3390, requested these tolerances under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act of 1996 (FQPA), on behalf of the registrant, Syngenta Crop Protection, Swing Road, Greensboro, NC 276419.

DATES: This regulation is effective August 31, 2005. Objections and

requests for hearings must be received on or before October 31, 2005.

ADDRESSES: To submit a written objection or hearing request follow the detailed instructions as provided in Unit VI. of the **SUPPLEMENTARY INFORMATION.** EPA has established a docket for this action under docket identification (ID) number OPP–2004–0326. All documents in the docket are listed in the EDOCKET index at *http://www.epa.gov/edocket.* Although listed in the index, some information is not publicly available, i.e., Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available either electronically in EDOCKET or in hard copy at the Public Information and Records Integrity Branch (PIRIB), Rm. 119, Crystal Mall #2, 1801 S. Bell St., Arlington, VA. This docket facility is open from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The docket telephone number is (703) 305–5805.

FOR FURTHER INFORMATION CONTACT: Sidney Jackson, Registration Division (7505C), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001; telephone number: (703) 305–7610; e-mail address: *jackson.sidney@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. Potentially affected entities may include, but are not limited to:

- Crop production (NAICS 111), e.g., agricultural workers; greenhouse, nursery, and floriculture workers; farmers.
- Animal production (NAICS 112), e.g., cattle ranchers and farmers, dairy cattle farmers, livestock farmers.
- Food manufacturing (NAICS 311), e.g., agricultural workers; farmers; greenhouse, nursery, and floriculture workers; ranchers; pesticide applicators.
- Pesticide manufacturing (NAICS 32532), e.g., agricultural workers; commercial applicators; farmers; greenhouse, nursery, and floriculture workers; residential users.

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. The North American Industrial Classification System (NAICS) codes have been provided to assist you and others in determining whether this action might apply to certain entities. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT.**

B. How Can I Access Electronic Copies of this Document and Other Related Information?

In addition to using EDOCKET *(http://www.epa.gov/edocket/),* you may access this **Federal Register** document electronically through the EPA Internet under the "**Federal Register**" listings at *http://www.epa.gov/fedrgstr/.* A frequently updated electronic version of 40 CFR part 180 is available at E-CFR Beta Site Two at *http://www.gpoaccess.gov/ecfr/.* To access the OPPTS Harmonized Guidelines referenced in this document, go directly to the guidelines at *http://www.epa.gpo/opptsfrs/home/guidelin.htm/.*

II. Background and Statutory Findings

In the **Federal Register** of August 13, 2004 (69 FR 50196) (FRL–7371–7), EPA issued a notice pursuant to section 408(d)(3) of FFDCA, 21 U.S.C. 346a(d)(3), announcing the filing of a pesticide petition (3E6787) by IR-4 on behalf of Syngenta Crop Protection, Swing Road, Greensboro, NC 27419. The petition requested that 40 CFR 180.368 be amended by establishing tolerances for combined residues (free and bound) of the herbicide S-metolachlor [S-2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(2-methoxy-1-methylethyl)acetamide], its R-enantiomer, and its metabolites, determined as the derivatives, 2-(2-ethyl-6-methylphenyl)amino-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound, S-metolachlor. It should be noted that the above chemical nomenclature for S-metolachlor differs slightly from that previously listed under 40 CFR 180.368(a)(2). The Agency is establishing these tolerances for residues of S-metolachlor under a new paragraph, 180.368 (a)(3), using this nomenclature because it is more technically accurate in terms of the nature of the residues and the components determined by the analytical method. The Agency has determined that the tolerance expression as listed in paragraph (a)(2) should be changed and will be proposing that change in an upcoming rule. Further chemical definition of S-metolachlor can be found in Unit III. A. of this document. In petition, PP 3E6787, IR-4 requested tolerances for S-metolachlor in or on the following raw agricultural commodities (RACs):

1. Brassica, head and stem, subgroup 5A at 0.5 parts per million (ppm).
2. Cattle, fat at 0.04 ppm; cattle, kidney at 0.20 ppm; cattle, meat at 0.04 ppm; cattle, meat byproducts, except kidney at 0.04 ppm.
3. Corn, field, grain at 0.10 ppm; corn, field, stover at 6.0 ppm; corn, field, forage at 6.0 ppm; corn, sweet, forage at 6.0 ppm; corn, sweet, stover at 6.0 ppm; corn, pop, stover at 6.0 ppm; corn, pop, grain at 6.0 ppm; corn, sweet, kernel plus cob with husk removed at 0.1 ppm.
4. Cotton, gin byproducts at 4.0 ppm; cotton, undelinted seed at 0.1 ppm.
5. Egg at 0.04 ppm.
6. Garlic, bulb at 0.1 ppm.
7. Goat, fat 0.04 ppm; goat, kidney at 0.20 ppm; goat, meat at 0.04 ppm; goat, meat byproducts, except kidney at 0.04 ppm.
8. Horse, fat 0.04 ppm; horse, kidney at 0.20 ppm; horse, meat at 0.04 ppm; horse, meat byproducts, except kidney at 0.04 ppm.
9. Leafy petioles subgroup 4B at 0.10 ppm.
10. Milk at 0.02 ppm.
11. Onion, dry bulb at 0.1 ppm; onion, green at 2.0 ppm.
12. Pea and bean, dried shelled, except soybean, subgroup 6C at 0.1 ppm.
13. Peanut 0.2 ppm; peanut, hay at 20 ppm; peanut, meal at 0.40 ppm.
14. Poultry, fat at 0.04 ppm; poultry, meat at 0.04 ppm; poultry, meat byproducts, except liver at 0.04 ppm.
15. Safflower, seed at 0.1 ppm.
16. Shallot at 0.1 ppm.
17. Sheep, fat at 0.04 ppm; sheep, kidney at 0.20 ppm; sheep, meat at 0.04 ppm; sheep, meat byproducts, except kidney at 0.04 ppm.
18. Sorghum grain, stover at 4.0 ppm; sorghum grain, forage at 1.0 ppm; sorghum grain, grain at 0.3 ppm.
19. Soybean, seed at 0.2 ppm; soybean, forage at 5.0 ppm; soybean, hay at 8.0 ppm.
20. Vegetable, foliage of legume, except soybean, subgroup 7A at 15 ppm.
21. Vegetable, fruiting, group 8 at 0.5 ppm.
22. Vegetable, legume, edible podded, subgroup 6A at 0.5 ppm.
23. Vegetable, root, except sugar beet, subgroup 1B at 0.3 ppm.
24. Vegetable, tuberous and corm, subgroup 1C at 0.2 ppm.

Several of the proposed tolerances were subsequently amended as follows:

Tolerances for vegetable, fruiting, group 8 (except tabasco pepper) at 0.1 ppm; tomato, paste at 0.3 ppm; a separate regional tolerance for pepper, tabasco at 0.5 ppm; brassica, head and stem increased from 0.5 to 0.6 ppm; corn, pop, grain decreased from 6.0 to 0.1 and barley straw from 0.1 to 0.5 ppm. Furthermore, the proposed tolerance of cattle, goat, horse and sheep meat byproducts, except kidney at 0.04 ppm was subsequently amended to establish tolerances for meat byproducts, except kidney and liver of cattle, goat, horse and sheep at 0.04 ppm and separate tolerances for liver of cattle, goat, horse and sheep at 0.1 ppm. The tolerance for poultry, meat byproducts, except liver at 0.04 ppm was also amended to poultry, meat byproducts at 0.04 ppm.

Additionally, IR-4 proposed to amend 40 CFR 180.368(a)(2) by removing tolerances established for the combined residues (free and bound) of the herbicide S-metolachlor [S-2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(2-methoxy-1-methylethyl)acetamide], and its metabolites, determined as the derivatives, 2-(2-ethyl-6-methylphenyl)amino-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound, in or on the following RAC's: Carrot, roots at 0.20 ppm; Horseradish at 0.20 ppm; onion, green at 0.20; rhubarb at 0.10 ppm; swiss chard at 0.10 ppm; and tomato at 0.1 ppm. The Agency concurs with this proposal based on the fact that these uses are covered by crop group and/or crop subgroup tolerances promulgated under section (a)(3) of this ruling.

Additionally, IR-4 proposed to amend 40 CFR 180.368(d) by establishing tolerances for indirect or inadvertent combined residues (free and bound) of the herbicide S-metolachlor [S-2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(2-methoxy-1-methylethyl)acetamide] its R-enantiomer,, and its metabolites, determined as the derivatives, 2-(2-ethyl-6-methylphenyl)amino-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound, S-metolachlor in or on the following RAC's:

1. Animal feed, nongrass, group 18 at 1.0 ppm
2. Barley, grain at 0.1 ppm; barley straw at 0.1 ppm
3. Buckwheat, grain at 0.1 ppm
4. Oat, forage at 0.5 ppm; oat, grain at 0.1 ppm; oat straw at 0.5 ppm
5. Peanut, meal at 0.4 ppm
6. Rice, grain at 0.1 ppm; rice, straw at 0.5 ppm
7. Rye, forage at 0.5 ppm; rye, grain at 0.1 ppm; rye straw at 0.5 ppm
8. Wheat, forage at 0.5 ppm; wheat grain at 0.1 ppm; wheat straw at 0.5 ppm

These tolerances for the various grains (barley, buckwheat, oats, rice, rye, wheat) and nongrass animal feeds are being established to cover residues of S-metolachlor in these crops when planted as rotational crops following treatment of a primary crop. The Agency concludes that these tolerances should be assigned to § 180.368(d) for indirect and inadvertent residues, and that adequate data are available to set the rotational crop tolerance for the nongrass animal feeds at 1.0 ppm. In addition, the Agency has concluded that tolerances should be established on the hays of barley, oats, and wheat at 1.0 ppm in paragraph (d). The peanut meal tolerance will be established under paragraph (a)(3) and is not necessary as proposed in (d).

The notice proposing these tolerances included a summary of the petition prepared by Syngenta Crop Protection, Incorporated, the registrant. There were no comments received in response to the notice of filing.

Section 408(b)(2)(A)(i) of FFDCA allows EPA to establish a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if EPA determines that the tolerance is "safe." Section 408(b)(2)(A)(ii) of FFDCA defines "safe" to mean that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." This includes exposure through drinking water and in residential settings, but does not include occupational exposure. Section 408(b)(2)(C) of FFDCA requires EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in establishing a tolerance and to "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue. . . ."

EPA performs a number of analyses to determine the risks from aggregate exposure to pesticide residues. For further discussion of the regulatory requirements of section 408 of FFDCA and a complete description of the risk assessment process, see the final rule on Bifenthrin Pesticide Tolerances November 26, 1997 (62 FR 62961) (FRL-5754-7).

III. Aggregate Risk Assessment and Determination of Safety

Consistent with section 408(b)(2)(D) of FFDCA, EPA has reviewed the available scientific data and other relevant information in support of this action. EPA has sufficient data to assess the hazards of and to make a determination on aggregate exposure, consistent with section 408(b)(2) of FFDCA, for a tolerance for combined residues (free and bound) of S-metolachlor on commodities and at tolerance levels presented in Unit II. of this document. EPA's assessment of exposures and risks associated with establishing the tolerance follows.

A. Toxicological Profile

Metolachlor is a chloroacetanilide herbicide that was first registered as a pesticide in 1976. Metolachlor (known as racemic metolachlor) is a mixture consisting of 50% each of the R-enantiomer (CGA 77101) and the S-enantiomer (CGA 77102). The S-enantiomer is the herbicidally active isomer.S-metolachlor is also a racemic mixture comprised of 88% S-enantiomer and 12% R-enantiomer. The Agency has determined that S-metolachlor has either comparable or decreased toxicity as compared to racemic metolachlor.

EPA has evaluated the available toxicity data and considered its validity, completeness, and reliability as well as the relationship of the results of the studies to human risk. EPA has also considered available information concerning the variability of the sensitivities of major identifiable subgroups of consumers, including infants and children. The nature of the toxic effects caused by S-metolachlor as well as the no-observed-adverse-effect-level (NOAEL) and the lowest-observed-adverse-effect-level (LOAEL) from the toxicity studies reviewed are discussed in Unit III.A. of the **Federal Register** of April 2, 2003 (68 FR 15945) (FRL-7299-8).

B. Toxicological Endpoints

The dose at which the NOAEL from the toxicology study identified as appropriate for use in risk assessment is used to estimate the toxicological level of concern (LOC). However, the LOAEL of concern is sometimes used for risk assessment if no NOAEL was achieved in the toxicology study selected. An uncertainty factor (UF) is applied to reflect uncertainties inherent in the extrapolation from laboratory animal data to humans and in the variations in sensitivity among members of the human population as well as other unknowns. An UF of 100 is routinely used, 10X to account for interspecies differences and 10X for intraspecies differences.

Three other types of safety or UFs may be used: "Traditional UF;" the "special FQPA safety factor;" and the "default FQPA safety factor." By the term "traditional UF," EPA is referring to those additional uncertainty factors used prior to FQPA passage to account for database deficiencies. These traditional uncertainty factors have been incorporated by the FQPA into the additional safety factor for the protection of infants and children. The term "special FQPA safety factor" refers to those safety factors that are deemed necessary for the protection of infants and children primarily as a result of the FQPA. The "default FQPA safety factor" is the additional 10X safety factor that is mandated by the statute unless it is decided that there are reliable data to choose a different additional factor (potentially a traditional UF or a special FQPA safety factor).

For dietary risk assessment (other than cancer) the Agency uses the UF to calculate an acute or chronic reference dose (aRfD or cRfD) where the RfD is equal to the NOAEL divided by an UF of 100 to account for interspecies and intraspecies differences and any traditional uncertainty factors deemed appropriate (RfD = NOAEL/UF). Where a special FQPA safety factor or the default FQPA safety factor is used, this additional factor is applied to the RfD by dividing the RfD by such additional factor. The acute or chronic Population Adjusted Dose (aPAD or cPAD) is a modification of the RfD to accommodate this type of safety factor.

For non-dietary risk assessments (other than cancer) the UF is used to determine the LOC. For example, when 100 is the appropriate UF (10X to account for interspecies differences and 10X for intraspecies differences) the LOC is 100. To estimate risk, a ratio of the NOAEL to exposures (margin of exposure (MOE) = NOAEL/exposure) is calculated and compared to the LOC.

The linear default risk methodology (Q*) is the primary method currently used by the Agency to quantify carcinogenic risk. The Q* approach assumes that any amount of exposure will lead to some degree of cancer risk. A Q* is calculated and used to estimate risk which represents a probability of occurrence of additional cancer cases (e.g., risk). An example of how such a probability risk is expressed would be to describe the risk as one in one hundred thousand (1×10^{-5}), one in a million (1×10^{-6}), or one in ten million (1×10^{-7}). Under certain specific circumstances, MOE calculations will be used for the carcinogenic risk assessment. In this non-linear approach, a "point of departure" is identified below which carcinogenic effects are not expected. The point of departure is typically a NOAEL based on an endpoint related to cancer effects though it may be a different value derived from the dose response curve. To estimate risk, a ratio of the point of departure to exposure (MOE_{cancer}= point of departure/exposures) is calculated. A summary of the toxicological endpoints for S-metolachlor used for human risk assessment is discussed in Unit III.B. of the final rule published in the Federal Register of April 2, 2003 (68 FR 15945) (FRL–7299–8). Should you desire additional information in this regard, please refer to that document.

C. Exposure Assessment

1. *Dietary exposure from food and feed uses.* Tolerances have been established (40 CFR 180.368(a)(2)) for the combined residues of S-metolachlor, in or on a variety of RAC's. S-metolachlor is a selective, chloroacetanilide herbicide that is applied as a preplant, preplant-incorporated (PPI), pre-emergence, or post-emergence application, primarily for the control of grass weeds. S-metolachlor is registered to Syngenta Crop Protection, Inc., for use on a wide variety of crops including: Corn, cotton, grasses grown for seed, legume vegetables, peanuts, potatoes, safflower, sorghum, sunflower, and tomatoes and complement the metolachlor (racemic mixture) product line with S-metolachlor products that contain a higher percentage of active pesticidal ingredient.

Permanent tolerances for the combined S-metolachlor residues have been established in/on plant commodities ranging from 0.1 ppm in/on a variety of plant commodities to 15 ppm in/on sugar beet tops 40 CFR 180.368(a))(2). Permanent tolerances are also established for combined residues of racemic metolachlor in 180.368(a)(1) and (c) at levels of 0.02 to 30 ppm.

The Agency has recently reviewed plant metabolism data on S-metolachlor from field tests on soybeans and corn, *in vitro* tests on corn seedlings, and greenhouse tests on seedlings of corn, sorghum, soybeans and peanuts. These data support the petitioners assertion that the metabolism of S-metolachlor in plants is similar to the racemic mixture, metolachlor. The Agency has also recently reviewed animal metabolism data on S-metolachlor. Data from a goat metabolism study indicated that the residues of concern for S-metolachlor in animals are the same as for metolachlor. For both metolachlor and S-metolachlor the residues of concern in plants and animals include the parent compound and its metabolites, determined as the derivatives CGA-37913 and CGA-49751. In the case of S-metolachlor tolerances, the residues of the R-enantiomer should be included in the expression.

Risk assessments were conducted by EPA to assess dietary exposures from S-metolachlor in food as follows:

i. *Acute exposure.* Acute dietary risk assessments are performed for a food-use pesticide, if a toxicological study has indicated the possibility of an effect of concern occurring as a result of a 1 day or single exposure. In conducting the acute dietary risk assessment EPA used the Lifeline™ Model, Version 2.0, which incorporates food consumption data as reported by respondents in the United State Department of Agriculture (USDA) 1994–1996 and 1998 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII), and accumulated exposure to the chemical for each commodity. A conservative Tier 1 acute dietary exposure assessment was conducted for all labeled metolachlor and all labeled and proposed S-metolachlor food uses using 100% crop treated (CT) and tolerance level residues.

ii. *Chronic exposure.* In conducting the chronic dietary risk assessment EPA used the Lifeline™ Model, Version 2.0, which incorporates food consumption data as reported by respondents in the USDA 1994–1996 and 1998 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII), and accumulated exposure to the chemical for each commodity. The following assumptions were made for the chronic exposure assessments: A conservative Tier 1 chronic dietary exposure assessment was conducted for all labeled metolachlor and all labeled and proposed S-metolachlor food uses using 100% CT and tolerance level residues.

Both the acute and chronic analyses assume tolerance-level residues on all crops with established, pending, or proposed tolerances for metolachlor and/or S-metolachlor (collectively referred to as metolachlor in this document). In cases where separate tolerance listings occur for both metolachlor and S-metolachlor on the same commodity, the higher value of the two is used in the analyses. The analyses also assume that 100% of the crops included in the assessment were treated with metolachlor. These assumptions result in overestimates of exposure and are, therefore, highly conservative with respect to dietary risk assessment.

iii. *Cancer.* Metolachlor has been classified as a Group C, possible human carcinogen based on liver tumors in rats at the highest dose tested (HDT). The

chronic NOAEL, 15 milligram/kilogram/day (mg/kg/day), that was established based on tumors in the rat seen at the HDT of 150 mg/kg/day) is comparable to the NOAEL of 9.7 mg/kg/day selected for establishing the chronic reference dose for metolachlor. The Agency concludes that the chronic dietary PAD is protective for cancer dietary risk. Therefore, a separate cancer dietary risk assessment was not conducted.

2. *Dietary exposure from drinking water.* The environmental fate database is complete for S-metolachlor. Parent metolachlor/S-metolachlor appear to be moderately persistent to persistent, and range from mobile to highly mobile in different soils. Metolachlor and S-metolachlor are expected to have similar degradation pathways and rates in soil and water environments.

Drinking water assessment was conducted based on monitoring data from several sources, as well as on Tier 1 First Index Reservoir Screening Tool (FIRST) and Screening Concentration In Groundwater (SCI-GROW) and Tier II modeling (PRZM/EXAMS) for selected vulnerable sites. This assessment is a worst-case scenario and demonstrates high end numbers. It is important to note that the analytical methods used to obtain the monitoring data are not able to distinguish between metolachlor and S-metolachlor; therefore, the estimated environmental concentrations (EECs) presented in this risk assessment are representative of both racemic metolachlor and S-metolachlor.

EECs for metolachlor and S-metolachlor were calculated for both the parent compound and the ethanesulfonic acid (ESA) and oxanilic acid (OA) degradates. The PRZM/EXAMS model was used to estimate the EECs for the surface water concentrations of the parent compound and the FIRST model was used to estimate the EECs for the surface water concentrations of the ESA and OA degradates. Groundwater concentrations were modeled using the SCI-GROW. Although it was determined by the Agency that the ESA and OA metabolites appear to be less toxic than parent metolachlor, they are included in the risk assessment since they were found in greater abundance than the parent in water monitoring studies.

The EECs were estimated for the crops with the highest maximum seasonal application rates, turf (S-metolachlor only) and corn (racemic metolachlor and S-metolachlor) with a maximum seasonal application rate of 4.0 lbs ai per acre (lbs ai/acre).

i. *Surface water modeling of parent metolachlor/S-metolachlor.* Based on PRZM/EXAMS modeling the maximum peak and annual average concentrations of metolachlor/S-metolachlor in surface water were 199 µg/l and 9.2 µg/l, respectively. Based on an evaluation of U.S. Geological Survey (USGS) National Water Quality Assessment (NAWQA) surface water monitoring data, the estimate of the maximum drinking water concentration from surface water sources of parent metolachlor/S-metolachlor is 77.6 µg/l, and the EEC is 4.3 µg/l for the maximum annual time-weighted mean concentration for parent metolachlor/S-metolachlor. These data suggest that the PRZM/EXAMS estimates for metolachlor/S-metolachlor are slightly overestimating the potential impact of metolachlor/S-metolachlor use on surface water.

ii. *Surface water modeling of degradates.* Based on FIRST modeling results, the estimate of the drinking water concentration from surface water sources of metolachlor ESA (ground application with no spray drift) is not likely to exceed 31.9 µg/L for the annual peak concentration and 22.8 µg/L for the annual average exposure for use on turf/corn at a maximum annual application rate of 4.0 lbs ai per acre. Based on FIRST modeling results, the estimate of the drinking water concentration from surface water sources of metolachlor OA (ground application with no spray drift) is not likely to exceed 91.4 µg/L for the annual peak concentration and 65.1 µg/L for the annual average exposure for use on turf/corn at a maximum annual application rate of 4.0 lbs ai per acre.

iii. *Groundwater modeling of parent metolachlor/S-metolachlor.* Metolachlor/S-metolachlor appears to be mobile in different soil types. Metolachlor/S-metolachlor and its degradates have been detected in ground water demonstrating that it is likely to impact ground water resources. In order to augment existing monitoring data, the (SCI GROW) screening model was used to estimate ground water concentrations. The model estimates the upper bound ground water concentrations of pesticides likely to occur when the pesticide is used at the maximum allowable rate in areas with ground water vulnerable to contamination. The estimated concentration of metolachlor/S-metolachlor in drinking water from shallow ground water sources is 5.5 µg/l for application on corn at a seasonal maximum rate of 4.0 lbs ai. per acre. This concentration is appropriate for both the peak and annual average exposures.

From the available ground water monitoring data , the highest annual maximum concentration from the (NAWQA) ground water monitoring data for acute exposure to metolachlor/S-metolachlor is 32.8 µg/l. Data collected in Iowa as part of the NAWQA program indicate that metolachlor/S-metolachlor has been detected in ground water at concentrations as high as 15.4 µg/l. However, these data are not used quantitatively in the risk assessment because the next highest concentration detected is 1.7 µg/l suggesting that the maximum concentration may be an outlier. Additionally, recent data collected by the Suffolk County, New York Department of Health Services, Bureau of Groundwater Resources indicate that both metolachlor/S-metolachlor (analytical methods did not determine the enantiomeric ratio) and its degradates have been detected in ground water. In data collected between 1997 and 2001, metolachlor/S-metolachlor was detected in 60 well samples with a maximum concentration of 83 µg/l. No information was available on frequency of detection and since only summary statistics were provided, these data are not used quantitatively in this assessment. Nonetheless, even use of the 83 µg/l value as the exposure level in drinking water would not raise the aggregate risk estimate, as discussed in Unit III.E. of this document the level of concern.

iv. *Groundwater modeling of degradates.* The EEC for metolachlor ESA from use on turf/corn is not expected to exceed 65.8 µg/l for peak and annual average exposures. The EEC for metolachlor OA from use on turf/corn is not expected to exceed 31.7 µg/l for peak and annual average exposures. These values exceed the maximum values detected in the Iowa NAWQA study (63.7 µg/l for metolachlor ESA and 4.4 µg/l for metolachlor OA and also exceed those detected in the two PGW studies (metolachlor ESA was detected at a maximum concentration of 24 µg/l, while metolachlor OA was detected at a maximum concentration of 15.6 µg/l).

Recent data collected by the Suffolk County, New York Department of Health Services, Bureau of Groundwater Resources indicate that both metolachlor/S-metolachlor (analytical methods did not determine the enantiomeric ratio) and its degradates have been detected in ground water. In data collected between 1997 and 2001, metolachlor ESA was detected in 296 wells with a maximum concentration of 39.7 µg/l, while metolachlor OA was detected in 228 wells with a maximum concentration of 49.6 µg/l. No information was available on frequency of detection and only summary statistics were provided on these data. Therefore,

these data are not used quantitatively in this assessment. However, these data suggest that the screening level SCI-GROW estimates for metolachlor ESA and OA are slightly overestimating the potential impact of metolachlor/S-metolachlor use on ground water.

A summary of metolachlor EEC's in surface water and ground water is presented in Table 1.

TABLE 1.—METOLACHLOR EEC'S

	Surface Water (peak)	Surface Water (average)	Ground Water
Parent	199	9.2	5.5
Metolachlor ESA	31.9	22.8	65.8
Metolachlor OA	91.4	65.1	31.7
Total EECs (ppb)	322.3	97.1	103.0

3. *From non-dietary exposure.* The term "residential exposure" is used in this document to refer to non-occupational, non-dietary exposure (e.g., for lawn and garden pest control, indoor pest control, termiticides, and flea and tick control on pets).

S-metolachlor is registered (as an emulsifiable concentrate formulation) for use on lawn, turf (including sod farms), golf courses, sports fields, and ornamental gardens and marketed to commercial applicators. Current product labels include the statement, "Not intended for homeowner purchase or use." Therefore, a residential handler assessment was not conducted.

Based on the use pattern of residential products, duration of post application exposure is expected to be short term. A short-term dermal endpoint was not selected, since no systemic toxicity was seen at the limit dose of 1,000 mg/kg/day; therefore, a dermal risk assessment was not conducted.

Post-application inhalation exposure is also expected to be minimal since S-metolachlor is only applied in an outdoor setting and the label specifies that residents should not re-enter treated areas until after sprays have dried. Based on these assumptions, a postapplication inhalation exposure was not calculated.

However, the following post-application incidental oral scenarios following application to lawns and turf have been identified:

i. Short-term oral exposure to toddlers and children following hand-to-mouth exposure

ii. Short-term oral exposure to toddlers and children following object-to-mouth exposure

iii. Short-term oral exposure to toddlers and children following soil ingestion. The term "incidental" is used to distinguish the inadvertent oral exposure of small children from exposure that may be expected from treated foods or residues in drinking water.

The exposure estimates for the three post-application scenarios (object-to-mouth, hand-to-mouth, and incidental soil ingestion) were combined to represent the possible (if not likely) high-end oral exposure resulting from lawn (or similar) use. Table 2 summarizes the results of the residential post-application assessment.

TABLE 2.—SUMMARY OF SHORT-TERM RESIDENTIAL POST-APPLICATION EXPOSURE

Exposure Scenario[a]	S-metolachlor[b]	Oral Dose (mg/kg/day)
Object-to-mouth	S-metolachlor	0.0092
Hand-to-mouth	S-metolachlor	0.037
Soil ingestion	S-metolachlor	0.00012
Combined exposure	S-metolachlor	0.046

[a]Exposure scenario represents oral exposure of children, with an assumed body weight of 15 kg.
[b]S-metolachlor application rate is 2.47 lb ai/acre.

4. *Cumulative effects from substances with a common mechanism of toxicity.* Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." EPA has examined the common mechanism potential for S-metolachlor and has concluded that S-metolachlor should not be included with the chloroacetanilide pesticides designated as a "Common Mechanism Group." The Agency's position is that only some chloroacetanailides, namely acetochlor, alachlor and butachlor should be considered as a "Common Mechanism Group" due to their ability to cause nasal turbinate tumors.

For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's web site at *http://www.epa.gov/pesticides/cumulative/.*

D. Safety Factor for Infants and Children

1. *In general.* Section 408 of FFDCA provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the data base on

toxicity and exposure unless EPA determines based on reliable data that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA risk assessments either directly through use of a MOE analysis or through using UF (safety) in calculating a dose level that poses no appreciable risk to humans. In applying this provision, EPA either retains the default value of 10X when reliable data do not support the choice of a different factor, or, if reliable data are available, EPA uses a different additional safety factor value based on the use of traditional UFs and/or special FQPA safety factors, as appropriate.

2. *Prenatal and postnatal sensitivity.* There is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure in the available toxicity data.

3. *Conclusion.* There is a sufficient toxicity data base and exposure data are complete or are estimated based on data that reasonably accounts for potential exposures. The FQPA Safety Factor for the protection of infants and children has been reduced to 1X because:

i. The toxicology data base is complete for the FQPA assessment.

ii. There is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to metolachlor in the available toxicity data.

iii. A developmental neurotoxicity study is not required for S-metolachlor.

iv. The dietary (food and drinking water) and non-dietary exposure (residential) assessments will not underestimate the potential exposures for infants and children from the use of S-metolachlor.

E. Aggregate Risks and Determination of Safety

To estimate total aggregate exposure to a pesticide from food, drinking water, and residential uses, the Agency calculates DWLOCs which are used as a point of comparison against EECs. DWLOC values are not regulatory standards for drinking water. DWLOCs are theoretical upper limits on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food and residential uses. In calculating a DWLOC, the Agency determines how much of the acceptable exposure (i.e., the PAD) is available for exposure through drinking water e.g., allowable chronic water exposure (mg/kg/day) = cPAD - (average food + residential exposure). This allowable exposure through drinking water is used to calculate a DWLOC.

A DWLOC will vary depending on the toxic endpoint, drinking water consumption, and body weights. Default body weights and consumption values as used by the EPA's Office of Water are used to calculate DWLOCs: 2 liter (L)/70 kg (adult male), 2L/60 kg (adult female), and 1L/10 kg (child). Default body weights and drinking water consumption values vary on an individual basis. This variation will be taken into account in more refined screening-level and quantitative drinking water exposure assessments. Different populations will have different DWLOCs. Generally, a DWLOC is calculated for each type of risk assessment used: Acute, short-term, intermediate-term, chronic, and cancer.

When EECs for surface water and ground water are less than the calculated DWLOCs, EPA concludes with reasonable certainty that exposures to the pesticide in drinking water (when considered along with other sources of exposure for which EPA has reliable data) would not result in unacceptable levels of aggregate human health risk at this time. Because EPA considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of comparison in drinking water may vary as those uses change. If new uses are added in the future, EPA will reassess the potential impacts of residues of the pesticide in drinking water as a part of the aggregate risk assessment process.

1. *Acute risk.* The acute aggregate risk assessment addresses potential exposure from combined residues of metolachlor/S-metolachlor on food and total residues of metolachlor/S-metolachlor plus ESA and OA degradates in drinking water (surface water and ground water). Using the exposure assumptions discussed in this unit for acute exposure, the acute dietary exposure from food to metolachlor/S-metolachlor will occupy <1% of the aPAD for the U.S. population and all population subgroups. In addition, there is potential for acute dietary exposure to metolachlor/S-metolachlor and the ESA and OA degradates in drinking water. After calculating DWLOCs and comparing them to the EECs for surface water and ground water, EPA does not expect the aggregate exposure to exceed 100% of the aPAD, as shown in the following Table 3:

TABLE 3.—AGGREGATE RISK ASSESSMENT FOR ACUTE EXPOSURE TO METOLACHLOR/S-METOLACHLOR

Population Subgroup	aPAD (mg/kg)	%aPAD (Food)	Surface Water EEC (ppb)	Ground Water EEC (ppb)	Acute DWLOC (ppb)
U.S. population	3.0	<1	322	103	105,000
Infants (<1year)	3.0	<1	322	103	30,000
Children (1–2 years)	3.0	<1	322	103	30,000
Females (13–49 years)	3.0	<1	322	103	90,000

2. *Chronic risk.* The chronic aggregate risk assessment addresses potential exposure from combined residues of metolachlor/S-metolachlor on food and total residues of metolachlor/S-metolachlor plus ESA and OA degradates in drinking water (surface water and ground water). There are no residential uses that result in chronic residential exposure to S-metolachlor. EPA has concluded that chronic exposure to metolachlor/S-metolachlor from food will utilize 1% of the cPAD for the U.S. population, 4% of the cPAD for children 1 to 2 years, the subpopulations at greatest exposure and 1% of the cPAD for females 13 to 49 years. In addition, there is potential for chronic dietary exposure to metolachlor/S-metolachlor and ESA and OA degradates in drinking water. After calculating DWLOCs and comparing them to the EECs for surface water and ground water, EPA does not expect the aggregate exposure to exceed 100% of the cPAD, as shown in the following Table 4:

TABLE 4.–AGGREGATE RISK ASSESSMENT FOR CHRONIC (NON-CANCER) EXPOSURE TO METOLACHLOR/S-METOLACHLOR

Population subgroup	cPAD mg/kg/day	%cPAD (Food)	Surface Water EEC (ppb)	Ground Water EEC (ppb)	Chronic DWLOC (ppb)
U.S. population	0.1	1	97	103	3,500
Infants (<1 year)	0.1	2	97	103	1,000
Children (1 to 2 years)	0.1	4	97	103	1,000
Females (13 to 49 years)	0.1	1	97	103	3,000

3. *Short-term risk.* Short-term aggregate exposure takes into account residential exposure plus chronic exposure to food and water (considered to be a background exposure level).

S-metolachlor is currently registered for use that could result in short-term residential exposure and the Agency has determined that it is appropriate to aggregate chronic food and water and short-term residential exposures for metolachlor/S-metolachlor.

Using the exposure assumptions described in this unit for short-term exposures, EPA has concluded that food and residential exposures aggregated result in an aggregate MOE of 1,000 for children 1 to 2 years. This aggregate MOE does not exceed the Agency's level of concern for aggregate exposure to food and residential uses. In addition, short-term DWLOCs were calculated and compared to the EECs for chronic exposure of metolachlor/S-metolachlor and ESA and OA degradates in ground water and surface water. After calculating DWLOCs and comparing them to the EECs for surface water and ground water, EPA does not expect short-term aggregate exposure to exceed the Agency's level of concern, as shown in the following Table 5:

TABLE 5.—AGGREGATE RISK ASSESSMENT FOR SHORT-TERM EXPOSURE TO METOLACHLOR/S-METOLACHLOR

Population Subgroup	Aggregate MOE (Food + Residential)	Aggregate Level of Concern (LOC)	Surface Water EEC (ppb)	Ground Water EEC (ppb)	Short-Term DWLOC (ppb)
Children (1–2 years)	1,000	100	97	103	4,500

4. *Intermediate-term risk.* An intermediate-term aggregate risk assessment considers potential exposure from food, drinking water, and non-occupational (residential) pathways of exposure. However, for metolachlor/S-metolachlor, no intermediate-term non-occupational exposure scenarios (greater than 30 days exposure) are expected to occur. Therefore, intermediate-term DWLOC values were not calculated and an intermediate-term aggregate risk assessment was not performed.

5. *Aggregate cancer risk for U.S. population.* An aggregate cancer risk assessment considers potential carcinogenic exposure from food, drinking water, and non-occupational (residential) pathways of exposure. However, the NOAEL (15 mg/kg/day), that was established based on tumors in the rat (seen at the HDT of 150 mg/kg/day) is comparable to the NOAEL of 9.7 mg/kg/day selected for establishing the cRfD dose for metolachlor. Therefore, the chronic risk assessment is protective for cancer as well as other chronic risks.

6. *Determination of safety.* Based on these risk assessments, EPA concludes that there is a reasonable certainty that no harm will result to the general population, and to infants and children from aggregate exposure to metolachlor/S-metolachlor residues.

IV. Other Considerations

A. Analytical Enforcement Methodology

The Pesticide Analytical Manual (PAM) Vol. II, lists a GC/NPD method (Method I) for determining residues in/on plants and a GC/MSD method (Method II) for determining residues in livestock commodities. These methods determine residues of metolachlor and its metabolites as either CGA–37913 or CGA–49751 following acid hydrolysis. Residue data from the most recent field trials and processing studies were obtained using an adequate GC/NPD method (AG–612), which is a modification of Method I. Adequate data are available on the recovery of metolachlor through Multi-residue Method Testing Protocols. The FDA PESTDATA database indicates that metolachlor is completely recovered through Method 302, PAM Vol. I (3rd ed., revised 10/97).

B. International Residue Limits

No maximum residue limits for either metolachlor or S-metolachlor have been established or proposed by Codex, Canada, or Mexico for any agricultural commodity; therefore, no compatibility issues exist with respect to U.S. tolerances.

V. Conclusion

Therefore, the tolerances are established at 180.368 for combined residues (free and bound) of the herbicide S-metolachlor [S-2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(2-methoxy-1-methylethyl)acetamide], its R-enantiomer, and its metabolites, determined as the derivatives, 2-[2-ethyl-6-methylphenyl)amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound S-metolachlor, in or on vegetable brassica, head and stem, subgroup 5A at 0.6 ppm; cattle, fat at 0.04 ppm; cattle, kidney at 0.20 ppm; cattle liver at 0.1 ppm; cattle, meat at 0.04 ppm; cattle, meat byproducts, except kidney and liver at 0.04 ppm; corn, field, grain at 0.10 ppm; corn, field, stover at 6.0 ppm; corn, field, forage at 6.0 ppm; corn, sweet, forage at 6.0 ppm; corn, sweet, stover at 6.0 ppm; corn, pop, stover at 6.0 ppm; corn, pop, grain at 0.1 ppm; corn, sweet, kernel plus cob with husk removed at 0.1 ppm; cotton, gin byproducts at 4.0 ppm; cotton, undelinted seed at 0.1 ppm; egg at 0.04 ppm; garlic, bulb at 0.1 ppm;

goat, fat 0.04 ppm; goat, kidney at 0.20 ppm; goat, liver at 0.1 ppm; goat, meat at 0.04 ppm; goat, meat byproducts, except kidney and liver at 0.04 ppm; horse, fat 0.04 ppm; horse, kidney at 0.20 ppm; horse liver at 0.1 ppm; horse, meat at 0.04 ppm; horse, meat by-products, except kidney and liver at 0.04 ppm; vegetable leaf petioles subgroup 4B at 0.10 ppm; milk at 0.02 ppm; onion, dry bulb at 0.1 ppm; onion, green at 2.0 ppm; vegetable legumes, pea and bean, dried shelled, except soybean, subgroup 6C at 0.1 ppm; peanut at 0.2 ppm; peanut, hay at 20 ppm; peanut, meal at 0.40 ppm; poultry, fat at 0.04 ppm; poultry, meat a 0.04 ppm; poultry, meat by-products, at 0.04 ppm; safflower, seed at 0.1 ppm; shallot, bulb at 0.1 ppm; sheep, fat at 0.04 ppm; sheep, kidney at 0.20 ppm; sheep, liver at 0.1 ppm; sheep, meat at 0.04 ppm; sheep, meat by-products, except kidney and liver at 0.04 ppm; sorghum grain, stover at 4.0 ppm; sorghum grain, forage at 1.0 ppm; sorghum grain, grain at 0.3 ppm; soybean, seed at 0.2 ppm; soybean, forage at 5.0 ppm; soybean, hay at 8.0 ppm; tomato, paste at 0.3 ppm; vegetable, foliage of legume, except soybean, subgroup 7A at 15 ppm; vegetable, fruiting, group 8, except tabasco pepper, at 0.1 ppm; vegetable, legume, edible podded, subgroup 6A at 0.5 ppm; vegetable, root, except sugar beet, subgroup 1B at 0.3 ppm; and vegetable, tuberous and corm, subgroup 1C at 0.2 ppm; pepper tabasco at 0.5 ppm; nongrass, animal feed (forage, fodder, straw, hay), group 18 at 1.0 ppm; barley, grain at 0.1 ppm; barley straw at 0.5 ppm; barley hay at 1.0 ppm; buckwheat, grain at 0.1 ppm; oat, forage at 0.5 ppm; oat, grain at 0.1 ppm; oat, straw at 0.5 ppm; rice, grain at 0.1 ppm; rice, straw at 0.5 ppm; rye, forage at 0.5 ppm; rye, grain at 0.1 ppm; rye, straw at 0.5 ppm; wheat, forage at 0.5 ppm; wheat, grain at 0.1 ppm; wheat, straw at 0.5 ppm and wheat, hay at 1.0 ppm.

VI. Objections and Hearing Requests

Under section 408(g) of FFDCA, as amended by FQPA, any person may file an objection to any aspect of this regulation and may also request a hearing on those objections. The EPA procedural regulations which govern the submission of objections and requests for hearings appear in 40 CFR part 178. Although the procedures in those regulations require some modification to reflect the amendments made to FFDCA by FQPA, EPA will continue to use those procedures, with appropriate adjustments, until the necessary modifications can be made. The new section 408(g) of FFDCA provides essentially the same process for persons to "object" to a regulation for an exemption from the requirement of a tolerance issued by EPA under new section 408(d) of FFDCA, as was provided in the old sections 408 and 409 of FFDCA. However, the period for filing objections is now 60 days, rather than 30 days.

A. What Do I Need to Do to File an Objection or Request a Hearing?

You must file your objection or request a hearing on this regulation in accordance with the instructions provided in this unit and in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number OPP–2004–0326 in the subject line on the first page of your submission. All requests must be in writing, and must be mailed or delivered to the Hearing Clerk on or before October 31, 2005.

1. *Filing the request.* Your objection must specify the specific provisions in the regulation that you object to, and the grounds for the objections (40 CFR 178.25). If a hearing is requested, the objections must include a statement of the factual issues(s) on which a hearing is requested, the requestor's contentions on such issues, and a summary of any evidence relied upon by the objector (40 CFR 178.27). Information submitted in connection with an objection or hearing request may be claimed confidential by marking any part or all of that information as CBI. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. A copy of the information that does not contain CBI must be submitted for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice.

Mail your written request to: Office of the Hearing Clerk (1900L), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001. You may also deliver your request to the Office of the Hearing Clerk in Suite 350, 1099 14th St., NW., Washington, DC 20005. The Office of the Hearing Clerk is open from 8 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Office of the Hearing Clerk is (202) 564–6255.

2. *Copies for the Docket.* In addition to filing an objection or hearing request with the Hearing Clerk as described in Unit VI.A., you should also send a copy of your request to the PIRIB for its inclusion in the official record that is described in ADDRESSES. Mail your copies, identified by docket ID number OPP–2004–0326, to: Public Information and Records Integrity Branch, Information Resources and Services Division (7502C), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001. In person or by courier, bring a copy to the location of the PIRIB described in ADDRESSES. You may also send an electronic copy of your request via e-mail to: *opp-docket@epa.gov.* Please use an ASCII file format and avoid the use of special characters and any form of encryption. Copies of electronic objections and hearing requests will also be accepted on disks in WordPerfect 6.1/8.0 or ASCII file format. Do not include any CBI in your electronic copy. You may also submit an electronic copy of your request at many Federal Depository Libraries.

B. When Will the Agency Grant a Request for a Hearing?

A request for a hearing will be granted if the Administrator determines that the material submitted shows the following: There is a genuine and substantial issue of fact; there is a reasonable possibility that available evidence identified by the requestor would, if established resolve one or more of such issues in favor of the requestor, taking into account uncontested claims or facts to the contrary; and resolution of the factual issues(s) in the manner sought by the requestor would be adequate to justify the action requested (40 CFR 178.32).

VII. Statutory and Executive Order Reviews

This final rule establishes a tolerance under section 408(d) of FFDCA in response to a petition submitted to the Agency. The Office of Management and Budget (OMB) has exempted these types of actions from review under Executive Order 12866, entitled *Regulatory Planning and Review* (58 FR 51735, October 4, 1993). Because this rule has been exempted from review under Executive Order 12866 due to its lack of significance, this rule is not subject to Executive Order 13211, *Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use* (66 FR 28355, May 22, 2001). This final rule does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA), 44 U.S.C. 3501 *et seq.*, or impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act of 1995 (UMRA) (Public Law 104–4). Nor does it require any special considerations under Executive Order 12898, entitled *Federal Actions to Address Environmental Justice in Minority Populations and Low-Income*

Populations (59 FR 7629, February 16, 1994); or OMB review or any Agency action under Executive Order 13045, entitled *Protection of Children from Environmental Health Risks and Safety Risks* (62 FR 19885, April 23, 1997). This action does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA), Public Law 104–113, section 12(d) (15 U.S.C. 272 note). Since tolerances and exemptions that are established on the basis of a petition under section 408(d) of FFDCA, such as the tolerance in this final rule, do not require the issuance of a proposed rule, the requirements of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*) do not apply. In addition, the Agency has determined that this action will not have a substantial direct effect on States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government, as specified in Executive Order 13132, entitled *Federalism* (64 FR 43255, August 10, 1999). Executive Order 13132 requires EPA to develop an accountable process to ensure "meaningful and timely input by State and local officials in the development of regulatory policies that have federalism implications." "Policies that have federalism implications" is defined in the Executive Order to include regulations that have "substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government." This final rule directly regulates growers, food processors, food handlers and food retailers, not States. This action does not alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of section 408(n)(4) of FFDCA. For these same reasons, the Agency has determined that this rule does not have any "tribal implications" as described in Executive Order 13175, entitled *Consultation and Coordination with Indian Tribal Governments* (65 FR 67249, November 6, 2000). Executive Order 13175, requires EPA to develop an accountable process to ensure "meaningful and timely input by tribal officials in the development of regulatory policies that have tribal implications." "Policies that have tribal implications" is defined in the Executive Order to include regulations that have "substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and the Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes." This rule will not have substantial direct effects on tribal governments, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes, as specified in Executive Order 13175. Thus, Executive Order 13175 does not apply to this rule.

VIII. Congressional Review Act

The Congressional Review Act, 5 U.S.C. 801 *et seq.*, as added by the Small Business Regulatory Enforcement Fairness Act of 1996, generally provides that before a rule may take effect, the agency promulgating the rule must submit a rule report, which includes a copy of the rule, to each House of the Congress and to the Comptroller General of the United States. EPA will submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of this final rule in the **Federal Register**. This final rule is not a "major rule" as defined by 5 U.S.C. 804(2).

List of Subjects in 40 CFR Part 180

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: August 23, 2005.

Lois Rossi,

Director, Registration Division, Office of Pesticide Programs.

■ Therefore, 40 CFR chapter I is amended as follows:

PART 180—[AMENDED]

■ 1. The authority citation for part 180 continues to read as follows:

Authority: 21 U.S.C. 321(q), 346a and 371.

■ 2. Section 180.368 is amended:

i. In paragraph (a)(2), in the table, by removing the commodities carrot, roots; horseradish; onion, green; rhubarb; swiss chard; and tomato;

ii. By adding paragraph (a)(3);

iii. By adding paragraph (c)(2); and

iv. In paragraph (d) by adding text.

The amendments read as follows:

§ 180.368 Metolachlor; tolerances for residues.

(a) * * *

(3) Tolerances are established for the combined residues (free and bound) of the herbicide *S*-metolachlor [S-2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(2-methoxy-1-methylethyl)acetamide], its R-enantiomer, and its metabolites, determined as the derivatives, 2-[2-ethyl-6-methylphenyl)amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound, in or on the following raw agricultural commodities:

Commodity	Parts per million
* * *	* *
Cattle, fat	0.04
Cattle, kidney	0.2
Cattle, liver	0.1
Cattle, meat	0.04
Cattle, meat by-products, except kidney and liver	0.04
Corn, field, stover	6.0
Corn, pop, stover	6.0
Corn, sweet, stover	6.0
Corn, field, forage	6.0
Corn, sweet, forage	6.0
Corn, sweet, kernel plus cob with husks removed	0.1
Corn, field, grain	0.1
Corn, pop, grain	0.1
Cotton, gin byproducts	4.0
Cotton, undelinted seed	0.1
Egg	0.04
Garlic, bulb	0.1
Goat, fat	0.04
Goat, kidney	0.2
Goat, liver	0.1
Goat, meat	0.04
Goat, meat byproducts, except kidney and liver	0.04
* * *	* *
Horse, fat	0.04
Horse, kidney	0.2
Horse, liver	0.1
Horse, meat	0.04
Horse, meat by-products, except, kidney and liver	0.04
* * *	* *
Milk	0.02
Onion, dry bulb	0.1
Onion, green	2.0
Peanut	0.2
Peanut, hay	20.0
Peanut, meal	0.4
Poultry, fat	0.04
Poultry, meat	0.04
Poultry, meat by-products	0.04
* * *	* *
Safflower, seed	0.1
Shallot, bulb	0.1
Sheep, fat	0.04

Commodity	Parts per million
Sheep, kidney	0.2
Sheep, liver	0.1
Sheep, meat	0.04
Sheep, meat by-products, except kidney and liver	0.04
Sorghum, grain, forage	1.0
Sorghum, grain, stover	4.0
Sorghum, grain, grain	0.3
Soybean, forage	5.0
Soybean, hay	8.0
Soybean, seed	0.2
* * *	* *
Tomato, paste	0.3
Vegetable, brassica, head and stem, subgroup 5A	0.6
Vegetable, foliage of legume, except soybean, subgroup 7A	15.0
Vegetable, fruiting group 8, (except tabasco pepper)	0.1
Vegetable, leaf petioles, subgroup 4B	0.1
Vegetable, legume, edible podded, subgroup 6A	0.5
Vegetable, legume, pea and bean, dried shelled, (except soybean) subgroup 6C	0.1
Vegetable, root, (except sugar beet) subgroup 1B	0.3
Vegetables, tuberous and corm, subgroup 1C	0.2

* * * * *

(c) * * *

(2) Tolerances with regional registration as defined in § 180.1(n) are established for the combined residues (free and bound) of the herbicide S-metolachlor [S-2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(2-methoxy-1-methylethyl)acetamide], its R-enantiomer, and its metabolites, determined as the derivatives, 2-[2-ethyl-6-methylphenyl)amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound, in or on the following raw agricultural commodities:

Commodity	Parts per million
Pepper, tabasco	0.5

(d) *Indirect or inadvertent residues.* Tolerances are established for the indirect or inadvertent combined residues (free and bound) of the herbicide S-metolachlor [S-2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(2-methoxy-1-methylethyl)acetamide], its R-enantiomer, and its metabolites, determined as the derivatives, 2-[2-ethyl-6-methylphenyl)amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound, in or on the following raw agricultural commodities:

Commodity	Parts per million
Barley, grain	0.1
Barley, hay	1.0
Barley, straw	0.5
Buckwheat, grain	0.1
Nongrass, animal feed (forage, fodder, straw, hay) group 18	1.0
Oat, forage	0.5
Oat, grain	0.1
Oat, hay	1.0
Oat, straw	0.5
Rice, grain	0.1
Rice, straw	0.5
Rye, forage	0.5
Rye, grain	0.1
Rye, straw	0.5
Wheat, forage	0.5
Wheat, grain	0.1
Wheat, hay	1.0
Wheat, straw	0.5

[FR Doc. 05–17367 Filed 8–30–05; 8:45 am]

BILLING CODE 6560–50–S

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 261

[FRL–7961–3]

Hazardous Waste Management System; Identification and Listing of Hazardous Waste; Final Amendment

AGENCY: Environmental Protection Agency.

ACTION: Final rule.

SUMMARY: The Environmental Protection Agency (EPA, also the Agency or we in this preamble) today is granting a petition to modify an exclusion (or delisting) from the lists of hazardous waste previously granted to BMW Manufacturing Co., LLC (BMW) in Greer, South Carolina. This action responds to a petition for amendment submitted by BMW to eliminate the total concentration limits in its wastewater treatment sludge covered by its current conditional exclusion.

EPA received public comments on the November 26, 2004, Proposed Rule (69 FR 68851) and took into account all public comments before granting this final rule. The Agency re-evaluated the specific information initially provided by the petitioner in its original request and delistings granted to other automobile manufactures for their F019 waste. This final decision eliminates the total concentration limits for barium, cadmium, chromium, lead, nickel, and cyanide from its conditionally excluded wastewater treatment sludge from the requirements of the hazardous waste regulations under the Resource Conservation and Recovery Act (RCRA). The waste will still be subject to local, State, and Federal regulations for nonhazardous solid wastes.

DATES: Effective August 31, 2005.

ADDRESSES: The RCRA regulatory docket for this final rule is located at the EPA Library, U.S. Environmental Protection Agency, Region 4, Sam Nunn Atlanta Federal Center, 61 Forsyth Street, SW., Atlanta, Georgia 30303, and is available for viewing from 9:00 a.m. to 4:00 p.m., Monday through Friday, excluding Federal holidays. The public may copy material from any regulatory docket at no cost for the first 100 pages, and at a cost of $0.15 per page for additional copies. For copying at the South Carolina Department of Health and Environmental Control, please see below.

FOR FURTHER INFORMATION CONTACT: For general and technical information concerning this final rule, please contact Kris Lippert, RCRA Enforcement and Compliance Branch (Mail Code 4WD–RCRA), U.S. Environmental Protection Agency, Region 4, Sam Nunn Atlanta Federal Center, 61 Forsyth Street, SW., Atlanta, Georgia 30303, (404) 562-8605, or call, toll free (800) 241–1754, and leave a message, with your name and phone number, for Ms. Lippert to return your call. Questions may also be e-mailed to Ms. Lippert at *lippert.kristin@epa.gov.* You may also contact Cindy Carter, Appalachia III District, South Carolina Department of Health and Environmental Control (SCDHEC), 975C North Church Street, Spartanburg, South Carolina. If you wish to copy documents at SCDHEC, please contact Ms. Carter for copying procedures and costs.

SUPPLEMENTARY INFORMATION: The information in this section is organized as follows:

I. Overview Information
A. What Action Is EPA Finalizing?
B. Why Is EPA Approving This Petition for Amendment?
C. What Are the Terms of This Exclusion?
D. When Is the Final Amendment Effective?
E. How Does This Action Affect States?

Image

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460
Office of Prevention, Pesticides
and
Toxic Substances

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

November 29, 2001

TXR#: 0050314

MEMORANDUM

SUBJECT: Toxicology Chapter for Metolachlor/S-Metolachlor

PC Code: 108801/108800
DP Barcode: D274326
Submission: S595674

FROM: Virginia A. Dobozy, V.M.D., M.P.H., Veterinary Medical Officer 12/4/01
Reregistration Branch I, Health Effects Division (7509C)

THRU: Whang Phang, Ph.D., Branch Senior Scientist 12/4/01
Reregistration Branch I, Health Effects Division (7509C)

TO: Christina Jarvis, Risk Assessor
Reregistration Branch II, Health Effects Division (7509C)

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.

Table 4: Acute Toxicity Data on CGA 354743 ESA

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 - OXA

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

ESA OXA

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 ESA

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 OYA

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 ESA

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 ESA

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 GXA

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 carboxymethylcellulose 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.

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