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

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Alachlor, The Partially Revised HED Chapter of the Reregistration Eligibility Decision Document (RED), Case 0063, Chemical 090501

FROM: Kathryn Boyle, Chemist Kathryn Boyle 5/18/98
Reregistration Branch I
Health Effects Division (7509C)

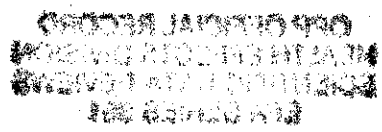
THRU: Whang Phang, Branch Senior Scientist Whang Phang 5/18/98
Reregistration Branch I
Health Effects Division (7509C)

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

The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Special Review and Reregistration Division (SRRD) of OPP has requested that HED evaluate the information submitted by Monsanto in their Response to the HED Science Chapter. The partially revised Human Health Assessment for the Reregistration Eligibility Document for alachlor is attached. SRRD should be receiving the revised product and residue chemistry sections directly from Susan Hummel. SRRD should be receiving the revised toxicology sections directly from Steve Dapson.

This partial response addresses the changes to the drinking water assessment, the aggregate assessment, and the occupational assessment. All major issues concerning these assessments have been addressed in red-line/strike-out in this document. Additionally, the determination for removing the 10X factor has been included in the dose-reponse section.

The revised water numbers were provided to HED by Sid Abel (EFED). The occupational sections of this assessment were reviewed by the Exposure Science Advisory Committee (SAC). Their comments have been incorporated.



Data Required:

Residue Chemistry (to be handled in Sue Hummel assessment)

GLN 860.1900 Field rotational crop studies - root crop and leafy crop Alternatively, the labels may be changed to prohibit rotation to any crop not specified on the label.

Required field residue data or label revisions - see section on Magnitude of the Residue in Plants

Note that Monsanto has indicated that it does not plan to support post-emergent uses of the EC formulation on field corn. However, all label changes have not yet been finalized. Since uses in excess of 4 lb ai/acre/season on sweet corn are also not being supported, label changes to distinguish between field corn and sweet corn are necessary.

Product Chemistry (to be handled in Sue Hummel assessment)

GLN 830.7050 UV/visible absorption (This is a new requirement.)

Occupational/Residential

Impregnation of dry bulk fertilizer with alachlor - both dermal (GLN 875.2400) and inhalation data (GLN 875.2500)

cc: Jack Housenger (SRRD)
Betty Shackelford (SRRD)
files
cc: memo only
Susan Hummel
Steve Dapson

ALACHLOR

PARTIALLY REVISED HED CHAPTER

Introduction

This document superceedes the previous HED chapters signed March 5, 1995, and August 15, 1997. Review of Monsanto's response to the most recent HED chapter as well as additional data on concentrations of alachlor in surface water indicated the need for changes. These changes are marked in this document in either red-line/strike-out, or with notations as revised text/tables.

In this document, which is for use in EPA's development of the alachlor Reregistration Eligibility Decision Document (RED), Health Effects Division (HED) presents the results of its risk assessment/characterization of the potential human health effects of dietary, and occupational exposure to alachlor. Alachlor is a restricted-use pesticide; therefore, there are no residential uses of alachlor. Included is a discussion of the available product chemistry data, toxicological studies, residue chemistry data, and surface and ground water sampling that have been submitted and reviewed.

Monsanto has submitted draft labels reducing the annual application rate of alachlor products to 4 lbs of alachlor per acre per year on corn. In anticipation of this change, the 6 lb ai/acre rate has been taken out of the occupational section of this document. If the label changes do not occur, then the risk assessment using the 6 lb ai/acre in the 8/15/97 chapter must be used. It should be emphasized that the results of the risk assessment presented in this Assessment could change as a result of additional information or new data submissions. Changes to the risk assessment could also result if further changes in labeled uses are made to achieve risk reduction.

Alachlor has been the subject of previous Agency regulatory action. The Agency issued a Notice of Initiation of Special Review of Registrations of Pesticide Products Containing Alachlor (PD1) on January 9, 1985 (50FR 1115). The Special Review of alachlor was initiated because of carcinogenic concerns. In response to this Notice, the Agency received new data on worker, dietary, and ground and surface water exposure. A Notice of Preliminary Determination (PD2/3) concerning alachlor was published October 8, 1986 (51FR 36166). In its December 31, 1987, Notice of Intent to Cancel Registrations; Conclusion of Special Review (PD4) (52FR 49480), the Agency required that alachlor be classified for restricted use by certified applicators or persons under their direct supervision; that aerial application of alachlor be allowed only if mechanical and not human flaggers are used; and that persons applying alachlor to 300 or more acres per year use mechanical transfer (pumping) systems for mixing and loading alachlor.

Other Agency documents include the Registration Standard Guidance Document for Alachlor (issued November 1984), and the Alachlor Product and Residue Chemistry Reregistration Standard Update (completed on 7/2/91). Additionally, on June 26, 1996, the Pesticides and Ground Water State Management Plan Regulation; Proposed Rule was published in the Federal Register (61FR 33260). Alachlor was selected as one of the five pesticides for regulation under SMPs based on ground water contamination potentials, hazards, pesticide use patterns as well as the frequency of detection in ground and surface water.

The Food Quality Protection Act (FQPA) was signed on August 3, 1996. FQPA amended both FIFRA (Federal Insecticide, Fungicide, and Rodenticide Act) and FFDCA (Federal Food, Drug and Cosmetic Act). FQPA requires the Agency to consider aggregate exposure in its decision-making process for dietary (food source and drinking water), residential , and other non-occupational exposures. The alachlor risk assessment presented in this document is a single chemical/multi-pathway assessment. Note that under FQPA occupational exposure is prohibited from being aggregated with any other exposures for the purpose of tolerance setting.

FQPA requires that the Agency consider the cumulative effects of alachlor and other chemicals that have a common mechanism of toxicity. This requires that the Agency first determine that a common mechanism of toxicity exists for a group of chemicals, decides on the appropriate methodology for combining exposures, and then, after reviewing use information/patterns, determines which of the exposures/scenarios for which chemicals are to be added together, i.e. aggregate exposure does occur.) Alachlor is structurally similar to four other pesticides: acetochlor, butachlor, propachlor, and metolachlor. However, the Agency has not yet completed its assessment of whether or not these chemicals actually have a common mechanism of toxicity. Additionally, the single chemical/multi-pathway assessments of <u>each</u> of the other chemicals must be completed before the Agency could perform the multi-chemical/multi-pathway assessment.

Executive Summary

Chronic Dietary (Food): When using anticipated residues and percent crop treated data, all population subgroups are well below ~~the RfD~~ 100 for alachlor. Chronic dietary risk from alachlor from all food uses recommended through reregistration is not of concern.

Chronic Dietary (Water): All % RfDs are well below ~~the RfD~~ 100 for alachlor. Chronic dietary risk from alachlor from consumption of water containing residues of alachlor <u>per se</u> is not of concern.

Aggregate Chronic (Food and Water): All % RfDs for aggregate chronic dietary risk are well below ~~the RfD~~ 100 for alachlor. Chronic dietary risk from alachlor from food containing residues of alachlor and from consumption of water containing residues of alachlor <u>per se</u> and/or residues of alachlor ESA is not of concern.

Dietary Carcinogenic (Food): MOEs were estimated for adult males and females, ranging from 50,000 to 2,000,000.

Dietary Carcinogenic (Water): MOEs were estimated for adult males and females, ranging from 7,500 (at the MCL) to 35,000,000.

Aggregate Dietary Carcinogenic (Food and Water): MOEs were estimated for adult males and females, ranging from 29,000 to 1,400,000.

Short-Term Exposure - Occupational M/L/As: It was possible to achieve MOEs greater than 100 for all scenarios for which data existed in PHED.

Intermediate-Term Exposure - Occupational M/L/As: It was possible to achieve MOEs greater than 100 for all scenarios for which data existed in PHED, except for scenario (3a) mixing/loading dry flowables for aerial application.

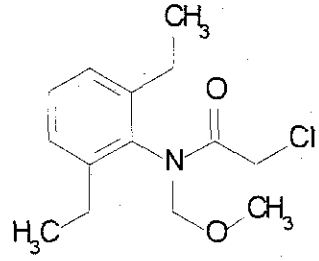
Post-Application: HED believes that, based on the current uses of alachlor, post-application exposure will be negligible and therefore is not requiring post-application exposure studies at this time.

I. SCIENCE ASSESSMENT

A. PHYSICAL AND CHEMICAL PROPERTIES ASSESSMENT

1. DESCRIPTION OF CHEMICAL

Alachlor (2-chloro-N-(2,6-diethylphenyl)-N-(methoxymethyl)acetamide) or (2-chloro-2',6'-diethyl-N-(methoxymethyl)acetanilide) is an herbicide registered for use on the following crops: succulent and dry beans; field, pop, and sweet corn; peanuts; grain sorghum; and soybeans. According to the labels alachlor is typically applied on these crops as a broadcast or band application made preplant incorporated/surface, preemergence, or postemergence.



Empirical Formula:	$C_{14}H_{20}NO_2Cl$
Molecular Weight:	269.77
CAS Registry No.:	15972-60-8
Shaughnessy No.:	090501

2. IDENTIFICATION OF ACTIVE INGREDIENT

Technical alachlor is a colorless to white crystalline solid with a melting point of 39.5-41.5 °C and a specific gravity of 1.133 g/mL at 25 °C. At 25 °C alachlor is soluble in water at 242 ppm. Alachlor is soluble in ether, acetone, benzene, alcohol, and ethyl acetate, and is slightly soluble in hexane.

3. MANUFACTURING-USE PRODUCTS

A search of the Reference Files System (REFS) conducted 7/7/97 identified two registered alachlor manufacturing-use products (MPs), the Monsanto Agricultural Company 94% stabilized technical (T; EPA Reg. No. 524-316) and 60% formulation intermediate (FI; EPA Reg. No. 524-315). Current Agency reviews identify the FI as a 65% formulation in accordance with the product name and nominal concentration of the active ingredient presented on the Confidential Statement of Formula CSF. The Monsanto FI will be referenced throughout this document as the 65% FI (EPA Reg. No. 524-315). The two Monsanto MPs are the only products subject to a reregistration eligibility decision.

The current status of the product chemistry data requirements for the Monsanto alachlor products are presented in the Tables 1 and 2.

TABLE 1: Product Chemistry Data Summary - 94% T (EPA Reg. No. 524-316)

Guideline Number	Requirement	Are Data Requirements Fulfilled? [a]	MRID Number
830.1550	Product Identity and Disclosure of Ingredients	Y	00146114, CSF [b]
830.1600 830.1620 830.1650	Starting Materials and Manufacturing Process	Y	00146114, 40396301
830.1670	Discussion of Formation of Impurities	Y	00146114, 00152206, Letter [c]
830.1700	Preliminary Analysis	Y	00146114, 00152206

830.1750	Certification of Ingredient Limits	Y	00146114, CSF [b]
830.1800	Analytical Methods to Verify the Certified Limits	Y	00146114, 00147476, 00152206, 40396301, Letter [d]
830.6302	Color	Y	00146114
830.6303	Physical State	Y	00146114
830.6304	Odor	Y	00146114
830.6313	Stability	Y	00146114
830.6314	Oxidation/Reduction	Y	00146114
830.6315	Flammability	Y	00146114
830.6316	Explodability	Y	00146114
830.6317	Storage Stability	Y	00146114
830.6319	Miscibility	N/A	
830.6320	Corrosion Characteristics	Y	00146114
830.7000	pH	Y	00146114
830.7050	UV/Visible Absorption	N[f]	
830.7100	Viscosity	N/A	
830.7200	Melting Point/Melting Range	Y	00146114
830.7220	Boiling Point/Boiling Range	N/A	
830.7300	Density/Relative Density/Bulk Density	Y	00146114
830.7550	Dissociation Constant in Water	N/A	
830.7550	Octanol/Water Partition Coefficient	Y	00146114, 00152209,
830.7560			00152210, 40396301
830.7570			
830.7840	Solubility	Y	00146114, 00152209,
830.7860			40396301, Letter [e]
830.7950	Vapor Pressure	Y	00146114, 00152209

[a] Y = Yes; N = No; N/A = Not Applicable.

[b] CSF dated 11/18/92; CB No. 11015, D185214, dated 5/14/93, by F. Toghrol.

[c] Letter dated 12/18/92 from Monsanto; CB No. 11100, D186162, dated 6/3/93, by S. Hummel

[d] Letter dated 11/14/90 from Monsanto.

[e] Letter dated 6/1/90 from Monsanto; CB No. 6767, dated 9/6/90, by N. Dodd.

[f] This is a new guideline requirement.

TABLE 2: Product Chemistry Data Summary - 65% FI (EPA Reg. No. 524-315)

Guideline Number	Requirement	Are Data Requirements Fulfilled? [a]	MRID Number
830.1550	Product Identity and Disclosure of Ingredients	Y	00146114, CSF [b]
830.1600	Starting Materials and Manufacturing Process	Y	00146114, 40396301,
830.1620			42194001
830.1650			

830.1670	Discussion of Formation of Impurities	Y	00146114, 00152206, Letter [c], 42194001
830.1700	Preliminary Analysis	Y	00146114, 00152206
830.1750	Certification of Ingredient Limits	Y	00146114, CSF [b]
830.1800	Analytical Methods to Verify the Certified Limits	Y	00146114, 00147476, 00152206, 40396301, Letter [d]
830.6302	Color	Y	00146114, 42194001
830.6303	Physical State	Y	00146114
830.6304	Odor	Y	00146114, 42194001
830.6313	Stability	Y	00146114
830.6314	Oxidation/Reduction	Y	42194001
830.6315	Flammability	Y	42194001
830.6316	Explodability	Y	42194001
830.6317	Storage Stability	Y	42194001
830.6319	Miscibility	N/A	
830.6320	Corrosion Characteristics	Y	42194001
830.7000	pH	Y	00146114, 42194001
830.7050	UV/Visible Absorption	N[f]	
830.7100	Viscosity	N/A	
830.7200	Melting Point/Melting Range	Y	00146114
830.7220	Boiling Point/Boiling Range	N/A	
830.7300	Density/Relative Density/Bulk Density	Y	00146114, 42194001
830.7550	Dissociation Constant in Water	N/A	
830.7550 830.7560 830.7570	Octanol/Water Partition Coefficient	Y	00146114, 00152209, 00152210, 40396301
830.7840 830.7860	Solubility	Y	00146114, 00152209, 40396301, Letter [e]
830.7950	Vapor Pressure	Y	00146114, 00152209

[a] Y = Yes; N = No; N/A = Not Applicable.

[b] CSF dated 11/18/92; CB No. 11015, D185214, dated 5/14/93, F. Toghrol.

[c] Letter dated 12/18/92 from Monsanto; CB No. 11100, D186162, dated 6/3/93, by S. Hummel

[d] Letter dated 11/14/90 from Monsanto.

[e] Letter dated 6/1/90 from Monsanto; CB No. 6767, dated 9/6/90, by N. Dodd.

[f] This is a new guideline requirement

4. CONCLUSIONS

WATCH

All pertinent data requirements are satisfied for the two Monsanto MPs, except for a new data requirement concerning UV/visible absorption (OPPTS 830.7050). Provided that the

registrant certifies that the suppliers of starting materials and the manufacturing process for the alachlor technical product have not changed since the last comprehensive product chemistry review or submits a complete updated product chemistry data package, HED has no objections to the reregistration of alachlor with respect to product chemistry data requirements.

B. HUMAN HEALTH ASSESSMENT

1. HAZARD IDENTIFICATION

Toxicology data are used by HED to assess the hazards to humans and domestic animals. The data are derived from a variety of acute, subchronic, and chronic toxicity tests; developmental/reproductive tests; and tests to assess mutagenicity and pesticide metabolism. Reregistration eligibility decisions require that HED have sufficient information to select the appropriate end-points for performing a human health risk assessment. This requires a toxicological database that is not only complete, but of acceptable quality.

The toxicity database for alachlor is adequate and will support reregistration eligibility.

a. GLN 81/Acute Toxicity

Acute toxicity studies with alachlor indicate low toxicity. Table 3 summarizes the available information on the acute toxicity of alachlor.

TABLE 3: Acute Toxicity of Alachlor

GLN No.	Study Type (%a.i.)	MRID No.	Results	Toxicity Category
§81-1	Acute Oral (92.8%)	00139383	LD50 = 930 mg/kg	III
§81-2	Acute Dermal (90.0%)	00139384	LD50 = 13.3 g/kg	IV
§81-3	Acute Inhalation (95.3%)	00109561	LC50 > 1.04 mg/L (4 hours)	III
§81-4	Primary Eye Irritation (92.8%)	00139385	No significant irritation	IV
§81-5	Primary Skin Irritation (92.8%)	00139386	No significant irritation	IV

§81-6	Dermal Sensitization (94.5%)	00161728	Sensitizer	N/A

The oral LD_{50} for alachlor in a rat study was 930 (810-1050) mg/kg (MRID No. 00139383). Clinical signs observed after oral dosing included ataxia, muscle tremors, hyperactivity, lethargy, dyspnea, and convulsions. The LC_{50} for rat inhalation was 1.04 mg/L for 4 hours. Clinical signs were related to eye and nasal irritation (MRID No. 00109561).

Alachlor has been shown to be a skin sensitizer in guinea pigs (MRID No. 00161728). Alachlor was also a skin sensitizer in a repeated insult patch test in humans (MRID No. 00023611, 00023612).

b. GLN 82/Subchronic Toxicity

In an **IBT** (Industrial Biotest Study) subchronic toxicity study (MRID No. 00023658), male and female Charles River albino rats from Charles River Breeding Laboratories, Inc., North Wilmington, MA received 0, 20, 200, or 2000 ppm CP50144 technical alachlor which is 0, 1.5, 15, or 146 mg/kg/day for the control, low, mid and high dose groups, respectively by standard conversion factors for 90 days. Systemic toxicity was noted in the high dose animals as decreased body weights and body weight gains, decreased food consumption and efficiency, increased absolute and relative spleen weights, increased relative liver weights, increased relative to body weight kidney weights, and decreased relative gonad weights (testis and ovaries). The systemic toxicity NOEL (No Observed Effect Level) is 15 mg/kg/day and the systemic toxicity LOEL (Lowest Observed Effect Level) is 146 mg/kg/day based on decreased body weights, body weight gains, reduced food consumption, increased spleen, liver and kidney weights, and decreased gonad weights. This study is classified as unacceptable since it is an invalidated IBT study. Guideline requirements are not satisfied. However, this study was not repeated since an adequate chronic toxicity study was performed by the registrant.

In a subchronic feeding study, Beagle dogs were administered doses of 0, 5, 25, 50, or 75 mg/kg/day of alachlor (93.3% a.i.; Lot No. MTLT 1128X) in capsules for six months. Systemic toxicity was noted as an increase in liver weights at the lowest dose tested (LDT; 5 mg/kg/day) and above in males, and at 25 mg/kg/day and above in females. An increase in the incidence of gross pathological observations (discoloration of the liver and biliary hyperplasia) in the liver were noted at 25 mg/kg/day and above in both sexes. Dose related body weight gain decrement, reduction in total serum protein levels, glubulin levels, increase in Serum AP, LDH and occasionally SGPT activities in both sexes was noted at 25 mg/kg/day and above and increased incidence of emaciation and mortality were noted at 50 mg/kg/day and above. The systemic toxicity NOEL could not be determined, but would be less than 5 mg/kg/day (LDT). The systemic toxicity LOEL is equal to or less than 5 mg/kg/day based on increased liver weight

(MRID No. 00087479).

In a 21-day dermal toxicity study, alachlor (EC MCB/C9; Lot# MDLL0407B, 45.3% a.i. and Lot# MDLL0429B, 45.2% a.i.) was administered to New Zealand white rabbits at dose levels of 0, 50, 300, or 1000 mg/kg. Repeated exposure resulted in skin damage ranging from dermal irritation to corrosion. The observations occurred in a dose-related manner. Systemic toxicity was noted as an increase in polymorphonuclear leukocytes which may have resulted from the presence of the chronic inflammatory reaction in the dermis. There was also a significant ($p < 0.01$) decrease in body weight in both sexes at the high dose. There was also regenerative anemia, with an elevated white blood cell count, and platelet counts, and a decreased albumin/globulin ratio. Also, there was evidence of liver glycogen depletion at the high dose. Three animals in the mid dose and 6 animals in the high dose died or were sacrificed *in extremis*. The cause of death may be related to bacterial pneumonia due to bacteria entering through damaged skin.

The systemic toxicity NOEL is 50 mg/kg/day. The systemic toxicity LOEL is 300 mg/kg/day based on hematological and clinical chemistry changes. The dermal toxicity NOEL could not be determined, but would be less than 50 mg/kg/day. The dermal toxicity LOEL is equal to or less than 50 mg/kg/day due to skin damage (MRID No. 00147328).

c. GLN 83/Chronic Toxicity and Carcinogenicity Studies

In a 1 year study in beagle dogs, alachlor technical (94.1% a.i.; Lot# MULT 0417B) was given by capsule at doses of 0 (control), 1.0, 3.0, or 10 mg/kg/day. Systemic toxicity was noted at the 3 mg/kg/day dose as hemosiderosis in the kidney of one male dog and in the spleen of another male dog; and at the high dose as hemosiderosis and hemolytic anemia in the liver of males (3/6). The systemic toxicity NOEL is 1 mg/kg/day. The systemic toxicity LOEL is 3 mg/kg/day based upon signs of hemosiderosis and hemolytic anemia (MRID No. 00148923).

In a two-year feeding study, Long-Evans rats received doses of 0, 100, 300, or 1000 ppm (approximately 0 (control), 14, 42, or 126 mg/kg/day) technical alachlor in the diet for approximately 117 weeks in males (812 to 813 days) and 106 weeks in females (741 to 744 days). It should be noted that the test substance used for the first 11 months of the study was stabilized with 0.5% epichlorohydrin (Lot # XHI-167, 92.6% a.i.), while the test substance used for the remaining 16 months of the study was stabilized with epoxidized soybean oil (Lot # MHK-6, 92.19% a.i.). Epichlorohydrin is carcinogenic for male Wistar rats and Sprague-Dawley rats: when given in drinking water it causes forestomach tumors (squamous cell papillomas and carcinomas) in male Wistar rats (Konishi et al. Gann 71:922-923, 1980); by inhalation it causes squamous carcinomas of the nasal cavity (Laskin, et al. J. Natl. Cancer Inst. 65:751-755, 1980). The effect of epichlorohydrin on tumor formation in this study is not known.

Systemic toxicity was noted at 14 mg/kg/day and above as ocular lesions in the form of uveal

degeneration syndrome, and as increased thyroid weights in both sexes; and as increased liver weight in the high dose groups. These observations were correlated with degenerative liver changes at all dose levels. There were decreased body weights in the mid and high dose males and the high dose females during the second year of the study. Statistical evaluation of mortality indicated an increasing trend for male and female rats with increasing doses. Male rats had an increased incidence of nasal respiratory epithelium adenomas, and adenomas and/or adenocarcinomas combined at 42 and 126 mg/kg/day ($p < 0.01$ and significant trends). Also, there was increased incidence in malignant mixed gastric tumors and gastric adenocarcinomas and/or malignant mixed gastric tumors combined at 126 mg/kg ($p < 0.01$ and significant trends). There were increased incidences in thyroid follicular cell adenomas and adenomas and/or carcinomas combined at 126 mg/kg ($p < 0.01$ and significant trends). There were increased incidences in the 126 mg/kg/day dose group for stomach osteosarcomas, and thyroid follicular cell carcinomas (both at $p < 0.05$). There were increased incidences of brain oligodendrogliomas of the hypothalamus, stomach osteosarcomas, and thyroid follicular cell carcinomas (all at $p < 0.01$) and significant trends. For female rats there was increased incidence of nasal turbinate adenomas, and adenomas and/or adenocarcinomas combined at 42 ($p < 0.05$) and 126 ($p < 0.01$) mg/kg/day and significant trends for these tumor types. There was also an increased incidence of malignant mixed gastric tumors, and gastric adenocarcinomas and/or malignant mixed gastric tumors combined ($p < 0.01$) at 126 mg/kg/day, as well as significant trends for these tumor types. Also, increased incidence at 14 and 126 mg/kg/day of mammary gland adenofibromas, adenofibromas and/or fibroadenomas combined, and adenofibromas, fibroadenomas, and papillary adenocarcinomas combined ($p < 0.05$). There were significant increasing trends in liver adenomas, stomach osteosarcomas, and thyroid follicular cell adenomas and/or adenocarcinomas combined (all at $p < 0.01$). Of all the tumors listed above, only the increasing trend observed in brain oligodendrogliomas of the hypothalamus, and the significant trend in brain ependymomas and ependymomas and/or malignant ependymomas combined in male rats and the significant pair-wise comparisons for mammary gland adenofibromas, adenofibromas and/or fibroadenomas combined, and adenofibromas, fibroadenomas, and papillary adenocarcinomas combined and liver adenomas in female rats were considered to have occurred at excessively toxic doses. The systemic toxicity NOEL could not be determined but would be less than 14 mg/kg/day. The systemic toxicity LOEL is equal to or less than 14 mg/kg/day based on ocular lesions (uveal degeneration syndrome) and hepatic toxicity (MRID No. 00091050).

In a second long-term study, Long-Evans rats were fed doses of 0, 0.5, 2.5 or 15 mg/kg/day technical alachlor (94.13%; Lot# MULT 0417B; stabilized with 1.28% epoxidized soybean oil) for 110 weeks (25 to 26 months). Systemic toxicity was noted at 15 mg/kg/day (HDT) as molting of the retinal pigmentation (uveal degeneration syndrome), increased mortality rate (significant increasing trend) in females (no effect in males) and abnormal disseminated foci in male livers. Male rats had increased incidence of nasal respiratory epithelium adenomas at 15 mg/kg/day ($p < 0.01$ with significant trend). Female rats had an increased incidence of adrenal benign pheochromocytomas and nasal respiratory epithelium adenomas at the 15 mg/kg/day dose level ($p < 0.05$ and $p < 0.01$, respectively and significant trend). There was also increased incidence of thymus malignant lymphosarcomas at the 15 mg/kg/day dose level ($p < 0.05$). The

systemic toxicity NOEL is 2.5 mg/kg/day and the systemic toxicity LOEL is 15 mg/kg/day, based on molting of retinal pigmentation and increased mortality in females, with abnormal disseminated foci of the liver in males (MRID No. 00139021).

In a special two-year study, technical alachlor (94.13% a.i.; Lot# MULT-0417B; stabilized with 1.28% epoxidized soybean oil) was administered in the diet at 126 mg/kg/day to Long-Evans rats for two years to assess ocular effects of the compound (uveal degeneration syndrome). It was observed that females were more sensitive than males, and that once the uveal degeneration syndrome was observed, it was irreversible (a group with 5 to 6 months exposure). The nasal, thyroid and gastric tumors observed in earlier investigations were observed. The nasal tumors were first noted in the 5 to 6 month treatment group (MRID No. 00141060).

In a carcinogenicity study, technical (alachlor; Lot# XHI-167, 92.6% a.i.; Lot# MHK-6, 92.19% a.i.) stabilized with epichlorohydrin at the start of the study (for 11 months) and then with a lot stabilized with epoxidozed soybean oil was given to CD-1 albino mice in the diet for 18 months at doses of 0 (control), 26, 78 or 260 mg/kg/day. Systemic toxicity was noted in the mid and high dose groups as increased liver weights, increased kidney weight in the mid and high dose males, and in the high dose females as reduced survival (statistical evaluation of mortality showed no significant incremental changes with increasing doses of alachlor in male mice while female mice showed a significant increasing trend in mortality with increasing doses of alachlor) and body weight gains (10%), males were not similarly affected. Thyroid follicular atrophy was noted in the mid and high dose males and the high dose females. There was an increase in water consumption in the high dose groups. Males had a significant increasing trend in bronchioalveolar adenomas at $p < 0.05$. There were no significant differences in the pair-wise comparisons of the male dosed groups with the controls. Female mice had significant increasing trends, in addition to significant differences in the pair-wise comparisons of the 260 mg/kg/day dose group with the controls, for bronchioalveolar adenomas and adenomas and/or carcinomas combined, all at $p < 0.01$ (MRID No. 00075709).

In a second carcinogenicity study, CD-1 albino mice (60 animals/sex/dose) from Charles River Laboratory (Portage MI) received 0 (control), 100, 400 or 1600 ppm (male: 0, 16.64, 65.42, or 262.40 mg/kg/day; and female: 0, 23.73, 90.34, or 399.22 mg/kg/day respectively, calculated directly from food consumption data) of alachlor (94.64% a.i.; Lot# MUS-9107-3181-T) in the diet for 18 months. Ten animals/ sex/ dose were sacrificed at 12 months. Systemic toxicity was noted in high dose males as lower body weight gains for the period ending on day 91; high dose males and females with lower body weight gains for the period ending on day 372 and high dose females with lower body weight gains to the end of the study. There were no decreases in food consumption, rather there were increases in high dose females. No treatment related effects on food efficiency were noted in the treated males; however, the high dose females had a dose related decrease in food efficiency at 12 and 18 months. Gross pathological observations included (at 18 months) a mass/nodule of the liver as noted in 6/41, 7/40, 10/41, and 10/41 in males and 1/40, 0/42, 1/36, and 3/40 in females for the control, low, mid and high dose groups, respectively; a mass/nodule of the lung in 3/41, 9/40, 10/41, and 12/41

in males and 1/40, 2/42, 9/36, and 6/40 in females for the control, low, mid and high dose groups, respectively. There was a statistically significant increase in absolute liver weights of the low and high dose females and liver weights relative to brain weights in high dose females at 12 months. Also, there was an increase in relative liver weights in high dose females at 18 months. The high dose males showed a statistically significant increase in absolute and relative liver weights at 18 months. There was a statistically significant decrease in kidney weights relative to body weights in high dose females at 12 months and a decrease in absolute kidney weight in high dose females at 18 months. The males at 18 months had a significant increase in absolute kidney weights in all dose groups, increased kidney weights relative to body weights in the low and high dose groups and increased kidney weights relative to brain weight in the mid and high dose groups. Non-neoplastic observations included slight increases in tubular epithelium hyperplasia/regeneration in the kidney(s) of high dose males, an increase in centrilobular hepatocellular hypertrophy in mid and high dose males along with an increase in high dose females of fibrous osteodystrophy of the sternum. Neoplastic observations included an increase in bronchoalveolar adenomas in all treated groups in males (7, 18, 27, and 22%, for the control, low, mid and high dose groups, respectively) and females (5, 14, 10, and 17% for the control, low, mid and high dose groups, respectively), statistical significance was achieved in mid dose males. The combined incidence of bronchoalveolar adenomas/carcinomas was increased in all treated groups in males (7, 18, 32, and 22% for the control, low, mid and high dose groups, respectively). Only the mid dose males was statistically significantly different from the controls. These data indicate that alachlor has carcinogenic activity, inducing the formation of bronchoalveolar adenomas (mostly) and/or carcinomas in the lung of male and female CD-1 mice. The systemic toxicity NOEL for males is 16.64 mg/kg/day and the systemic toxicity LOEL for males is 65.42 mg/kg/day based on an increase in centrilobular hepatocellular hypertrophy in mid and high dose males. The systemic toxicity NOEL for females is 90.34 mg/kg/day and the systemic toxicity LOEL for females is 399.22 mg/kg/day based on body weight gain decrements and an increase in fibrous osteodystrophy of the sternum. (MRID No. 43507601).

d. <u>GLN 83-3/Developmental Toxicity</u>

In a developmental toxicity (teratology) study, Charles River rats were given 0(control), 50, 150 or 400 mg/kg/day of alachlor (92.19% a.i.; Lot# MHK-6) by gavage on gestation days 6 through 19, inclusive. Maternal systemic toxicity was noted at the high dose as maternal deaths and increased incidence of soft stools, red matter around the nose and mouth and anogenital staining and reduced body weight gains. Developmental toxicity was noted at the high dose as a slight increase in the mean number of early and late resorptions with related increased post-implantation loss and a slight reduction in the mean number of viable fetuses. The maternal toxicity NOEL is 150 mg/kg/day and the maternal toxicity LOEL is 400 mg/kg/day based on increased mortality, increased incidence of clinical signs and reduced body weight gains. The developmental toxicity NOEL is 150 mg/kg/day. The developmental toxicity LOEL is 400 mg/kg/day based on increased resorptions and decreased litter size (MRID No. 00043645).

In a developmental toxicity study, New Zealand white rabbits received doses of 0 (control), 50, 100 or 150 mg/kg/day alachlor (94.7% a.i., Lot# 51486-C) by gavage on days 7 through 19, inclusive. Maternal systemic toxicity was noted at the high dose as decreased body weight gain during the dosing period followed by a rebound in body weight gain during the period following dosing. No developmental toxicity was noted in the parameters measured. The maternal toxicity NOEL is 100 mg/kg/day. The maternal toxicity LOEL is 150 mg/kg/day based upon a reduction in body weight gains. The developmental toxicity NOEL is equal to or greater than 150 mg/kg/day (highest dose tested) and the developmental toxicity LOEL is greater than 150 mg/kg/day (MRID No. 40579402).

e. GLN 83-4/Reproduction

In a three-generation reproduction study, Sprague Dawley CD rats received either 0 (control), 3, 10, or 30 mg/kg/day technical alachlor (92.6% a.i.; Lot# XHI-167) in the diet. Parental/ Offspring systemic toxicity was noted at the high dose in the form of discoloration of the kidney and reduced kidney weights (especially in F_2 parents and F_{3b} pups). Histopathology revealed chronic nephritis in the high dose males. The high dose females of each parental generation and the F_{3b} females had lower ovary weights (this decrease was maximal (17%) and significant in the F_o generation, and was also associated with 17% decrease in the ovaries to body weight ratio). No microscopic changes were reported in the ovaries and no effect was noted on reproductive parameters. The parental/offspring systemic toxicity NOEL is 10 mg/kg/day. The parental/offspring systemic toxicity LOEL is 30 mg/kg/day based on kidney effects. Since there were no effects on reproductive parameters, the reproductive toxicity NOEL is equal to or greater than 30 mg/kg/day (HDT). The reproductive toxicity LOEL is greater than 30 mg/kg/day. (MRID No. 00075062).

f. GLN 84/Mutagenicity

(i). Alachlor

A reverse mutation assay in five strains of Salmonella typhimurium (TA1535, TA100, TA1537, TA1538, and TA98) using 10 to 5000 μg/plate with and without S9 metabolic activation was negative (MRID No. 00109563).

An E. coli WP2 hcr reverse mutation assay using 10 to 5000 μg/plate with and without S9 metabolic activation was negative (MRID No. 00109563).

A rec assay with Bacillus subtilis (H17 and M45) using 20 to 2000 μg/disk was negative (MRID No. 00109563).

Alachlor was positive in an *in vivo/in vitro* UDS (unscheduled DNA synthesis) assay at 1000 mg/kg, a dose approximating the LD_{50} in rats. Doses tested were 50, 200, and 1000 mg/kg with evaluations a 2 and 12 hours (MRID No. 00141061).

An assay of structural chromosomal aberrations (e.g., *in vivo* cytogenetics in rat bone marrow) was negative. Single doses of 0, 100, 300, or 1000 mg/kg with sacrifice times of 6, 12, 24, and 48 hours (MRID No. 00141062).

A CHO (Chinese hamster ovaries) HGPRT mammalian cell forward mutation test was negative. Dose levels tested were 15 to 150 μg/ml without S9 metabolic activation and 15 to 330 μg/ml with S9 metabolic activation (MRID No. 00148921).

Alachlor was negative in an Ames Salmonella typhimurium mammalian microsome plate incorporation assay, conducted in the absence of S9 and with S9 prepared from uninduced rat, mouse, or monkey nasal turbinates, at concentrations ranging from 50 to 5000 μg/plate. Tester strains TA98, TA100, TA1535, and TA1537 were used (MRID No. 42651301).

Alachlor was positive for inducing unscheduled DNA synthesis (UDS) in hepatocytes recovered from male Fischer-344 rats at 12 hours after oral gavage administration of 1000 mg/kg. Positive net nuclear grains counts were obtained were obtained with 2/5 animals, and increases of >5 net grains were observed with 3/5 animals. Similarly, >10% of the cells were in repair in 3/5 animals. Similarly, a comparison of the individual data from treated animals and the vehicle control group showed that hepatocytes recovered from 3 of 5 animals were positive for UDS, cells from one animal showed a borderline positive response, and liver cells from the remaining animal was negative. These data are suggestive of a genotoxic response. (It is noted that the dose at which a positive response was observed **approximates the LD_{50}** of alachlor in rats.) There was no indication of UDS activity at 12 hours after oral gavage administration of lower doses (50, 200, or 500 mg/kg) or at 2 hours following gavage with 1000 mg/kg (MRID No. 42651302).

Alachlor was negative in a micronucleus assay in Long-Evans rats conducted with a single intraperitoneal injection of 150, 300, or 600 mg/kg and 24-, 48-, and 72-hour sacrifice times. Two males and one female receiving the high dose died, and clinical signs of toxicity were observed in males at all doses and in mid- and high-dose females. A separate experiment in the same study with radiolabeled alachlor provided evidence that the test material reached the target organ - bone marrow - when administered intraperitoneally. (MRID No. 42651303).

In a mouse micronucleus assay (MRID No. 44032103), groups of 10-15 male CD-1 mice received single oral gavage administrations of 250, 500 or 1000 mg/kg alachlor (>99%). The test material was delivered to the animals in corn oil. Animals were sacrificed at 24 and 48 hours postadministration; bone marrow cells were harvested and 2000 polychromatic erythrocytes per male were examined for the incidence of micronucleated polychromatic erythrocytes (MPEs).Death and other clinical signs (i.e., piloerection and/or decreased defecation) were observed at the highest dose tested. Cytotoxicity for the target organ was not observed at any dose. The positive control induced the expected high yield of MPEs in the treated males. There was, however, no evidence that alachlor induced a clastogenic or aneugenic effect at any dose or sacrifice time. The study is classified as Acceptable. The study contained major guideline deficiencies (i.e, use of a single sex, only 5 males/dose/sampling time and no 72-hour

posttreatment sacrifice). However, these requirements were waived for the following reasons:

- Previous studies have shown that alachlor is not active in the mouse bone marrow micronucleus assay.
- Adequate justification for the use of males only was provided.
- Variations within and among treatment groups were minimal; hence, the findings with the smaller than recommended sample size are considered valid.
- The uniformly negative response in conjunction with the absence of an effect on cell cycling suggest that sampling cells 72 hours after compound administration would not have altered the outcome of the study.

Based on these considerations, it was concluded that the study satisfies the requirements for 84-2 for in vivo cytogenetic mutagenicity data.

(ii) Metabolites of Alachlor

Urine from alachlor treated rats tested in an Ames Salmonella assay using strains TA98, TA100, TA1535, and TA1537 in the presence and absence of arochlor 1254-induced mammalian activation system and/or ß-glucuronidase/sulfatase and dose levels of 0.005 to 0.5 ml/plate. There was a weak mutagenic response in strain TA98 in the presence of ß-glucuronidase. A weak mutagenic response was also observed in strain TA1537 in the presence of both ß-glucuronidase and metabolic activation (MRID No. 00155389, 00155392).

Bile from alachlor treated Long-Evans rats tested in an Ames Salmonella assay using strains TA98, TA100, TA1535, and TA1537 in the presence and absence of arochlor 1254-induced liver homogenate (S-9) or ß-glucuronidase at dose levels of 0.01 to 0.20 ml/plate was negative under all conditions (MRID No. 00155389, 00155393).

Ames Salmonella assays with **synthesized** metabolites of alachlor using strains TA98, TA100, TA1535, and TA1537 at dose levels of 0.004 to 10.00 mg/plate both with and without S9 metabolic activation showed that of five metabolites tested (t-hydroxysulfone [CP101394; rat, mouse, goat, hen, rotation crops metabolite], *sec*- amide p-hydroxy methylsulfone [CP51214; rat metabolite], t-sulfinyllacetic acid [CP108267; corn metabolite], t-oxanilic acid [CP108064; soil, water, soybean metabolite], and t-sulfonic acid [CP108065; corn, soil, soybeans, water metabolite]), only the t-hydroxysulfone metabolite was observed to be mutagenic (strain TA100 at 3 and 10 mg/plate in the presence and absence of metabolic activation). (MRID No. 00151394, 00151395, 00151396, 00151397, 00151398, 001513999)

Ames Salmonella assays with **synthesized** metabolites of Alachlor (CP97230 and CP101384 [s-hydroxysulfone]) using strains TA98, and TA100 at dose levels of 0.01 to 10.00 mg/plate both with and without S9 metabolic activation only the s-hydroxysulfone metabolite was observed to be weakly mutagenic (strain TA100 at 1, 3 and 10 mg/plate in the presence and absence of metabolic activation) although the responses were less than a 2-fold increase used to

indicate a positive response (MRID No. 00155389, 00155391).

Two alachlor metabolites, 2'6'-Diethyl-2-methyl thioacetanilide (DMTA) and 2'6'-Diethylaniline (DEA), were tested (MRID No. 42651301) in an Ames *Salmonella typhimurium* mammalian microsome plate incorporation assay in the absence of S9 and with S9 prepared from uninduced rat, mouse, or monkey nasal turbinates. Tester strains TA98, TA100, TA1535, and TA1537 were used. DMTA was positive in strain TA1535 in three independent *Salmonella typhimurium* mammalian microsome plate incorporation assays, conducted with S9 prepared from mouse nasal turbinates. In addition, there was a tendency for increased numbers of revertants of TA1535 to occur following exposure to higher dose levels (1500 and/or 5000 μg/plate) of DMTA. This was also observed in one of two assays conducted with rat nasal turbinate S9. Although only marginal increases were observed, the increases were reproducible and statistically significant. There was no response in tester strains TA98, TA100 or TA1537 with the nonactivated test material or in the presence of S9 prepared from mouse, rat or monkey nasal turbinates. However, it should be noted that DMTA is not a stable product of Alachlor metabolism.

DEA was positive in strains TA1535 and TA100 in at least two independent *Salmonella typhimurium*/mammalian microsome plate incorporation assays, conducted with S9 prepared from mouse nasal turbinates. The nonactivated test material and the test material activated with rat nasal turbinate S9 were also positive in strain TA100. Although only marginal increases were observed, they were reproducible and statistically significant. There was no consistent response in tester strains TA98 and TA1537.

g. Metabolism

Metabolism studies in Sprague Dawley rats found that an oral dose of 7 or 700 mg/kg of alachlor was mainly eliminated in urine and feces, and that 89% of dose was eliminated in 10 days (minimal alachlor was found in the expired CO_2). The elimination was considered to be biphasic; the initial rapid phase had a half life of 0.2 to 10.6 hours, which then slowed to a half life of 5 to 16 days. Fourteen metabolites were identified in urine and 13 in feces. Three of the metabolites were common to both urine and feces. The eliminated metabolites were conjugates of mercapturic acid, glucuronic acid, and sulfate (MRID No. 000132045).

From a metabolism study in Rhesus monkeys, five urinary metabolites were identified after intravenous injection. One of these metabolites, (also found in rat and mouse urine, N-[2-ethyl-6-(1-hydroxyethyl)-phenyl]-N-(methoxymethyl)-2(methylsulfonyl)acetamide), tested positive in the Ames test with Salmonella typhimurium, with and without activation. This metabolite was an HEEA metabolite not previously identified in the monkey.

Of the metabolites found in the above two metabolism studies, only two urinary metabolites were common to both the rat and monkey (secondary and tertiary mercapturic acid conjugates). Side chain hydroxylation and sulfate conjugation metabolites were not found in monkey urine as

they were in rats (MRID No. 40000901).

The definitive rat metabolism study was conducted on male and female Long Evans rats (MRID 42651306, 42852107, 42651308, 42852108). Both oral dosing studies using corn oil as the vehicle and intravenous administration studies using propylene glycol as the vehicle were performed. Together these studies satisfy GLN 85-1.

Oral administration of alachlor was studied using female Long-Evans Crl:CD(LE)BR rats six to nine weeks of age in five dose groups. Groups 1, 2, and 3 each consisted of 33 rats. Each group received single oral doses of radiolabeled alachlor (uniformly labeled in the phenyl ring with 14-C, and enriched with 13-C at the C-2 carbon) at target doses of 7 (Group 1), 70 (Group 2), or 700 (Group 3) mg/kg. Group 4 consisted of 21 rats which received 15 consecutive daily doses of radiolabeled alachlor at 700 mg/kg/day. Group 5 consisted of 6 rats which received a single oral dose of radiolabeled alachlor at 700 mg/kg for the purpose of obtaining plasma samples at 2, 4, and 6 hours post-dosing.

Long Evans rats (5/sex/dose) were used to study the disposition and metabolism of alachlor following intravenous administration at 7 (Group 6) or 70 (Group 7) mg/kg.

In the oral studies absorption at the 7 or 70 mg/kg dose levels was essentially complete, with a slight decrease in absorption at the 700 mg/kg dose level. Repeated oral dosing at 700 mg/kg had no significant effect on absorption. Residual radioactivity did not exceed 5% of the administered dose at any of the dose levels in this study. On a ug/g basis, the residual radioactivity in the non-glandular stomach was higher than in the glandular stomach except at 4 hours post-dose at the 700 mg/kg dose level. Decreasing the dose decreased the percentage of the dose in the non-glandular stomach but not in the glandular stomach. Nasal turbinates showed a secondary peak of radioactivity at 8 hours post-dose at the 700 or 70 mg/kg dose levels in contrast to other tissues. Excretion of alachlor derived radioactivity was approximately equivalent between urine and feces, with between 30-47% excreted in urine and 41-45% excreted in feces at single oral doses of 7, 70, or 700 mg/kg. Intravenous dosing at 7 or 70 mg/kg resulted in a similar excretion profile. Repeated oral dosing at 700 mg/kg resulted in a slight increase in fecal excretion of radioactivity. In urine, the *sec-* amide hydroxymethyl sulfone metabolite (metabolite **F5**) of alachlor was the predominant urinary metabolite after oral and intravenous administration, ranging from 2.1-7.4% of the dose. Repeated oral dosing resulted in the appearance of several additional metabolites, but it is not known whether these additional metabolites are unique to repeated oral administration of Alachlor. In feces, the *tert-* amide mercapturic acid and the disulfide appeared to be the major metabolites after single oral doses of Alachlor. Increasing the dose appeared to increase the percentage of these 2 metabolites in feces (MRID No. 42651308 and 42852108).

In this study, (MRID No. 42651305, 42852106) male and female CD-1 mice (10/sex) received a single oral dose of radiolabeled alachlor in corn oil (890 mg/kg for male mice, 819 mg/kg for female mice). Urine and feces were collected daily for up to 7 days post-dose for analysis of excreted radioactivity and for identification of metabolites. In urine, 18.4 $\pm$3.9% and

23.6±4.1% of the dose was excreted in male and female mice, respectively. In feces, 66.5±6.9% and 53.6±3.6% of the dose was excreted in male and female mice, respectively. Total recovery of radioactivity was 85.5±3.7% for male mice, and 79.4±2.7% for female mice. (The low recoveries may be due to the fact that the mice were housed in pairs in units larger than those normally used for a mouse.) Analysis of blood at seven days post-dose showed 0.095±0.016% of the dose in males, and 0.075±0.017% of the dose in females. Half life for urinary elimination was reported as 0.88±0.11 days in males, and 1.18±0.16 days in females. Half-life for fecal elimination was reported as 0.90±0.06 days in males, and 1.11±0.05 days in females. The data in this study show that in contrast to the rat, feces is the major route of excretion for alachlor derived radioactivity in CD-1 mice. The high percentage of fecal excretion could be the result of poor absorption of test chemical or extensive biliary excretion in the mouse.

Pooled urine and fecal samples representing the 0-48 hour collection time for urine and the 0-96 hour collection time for feces, were analyzed for metabolites of alachlor in male and female CD-1 mice. In feces, at least 10 metabolites were isolated. These are summarized below:

	% of Dose	
Metabolite	Male Feces	Female Feces
Alachlor	1.8	2.2
tert- amide mercapturic acid	4.1	3.3
disulfide conjugate	0.6	1.0
sec- amide mercapturic acid	0.7	0.6
tert-amide thioacetic acid	1.2	0.9
tert- amide hydroxy sulfone	0.6	0.5
tert- amide dihydroxysulfone	0.0	0.0
benzyl glucuronide	2.1	1.0
tert- amide cysteine conjugate + NCH2o-glucuronide	5.0	3.7

Urinary metabolites characterized in this study included the following:

	% of Dose	
Metabolite	Male Urine	Female Urine
tert- amide cysteine conjugate	0.1	0.3
NCH2O glucuronic acid	1.9	3.2
cysteine sulfoxide (proposed)	0.2	0.3
sec- amide dihydroxysulfone	0.1	0.2
sec- amide hydroxy sulfoxide	0.1	0.2
sec- amide hydroxy sulfone	0.1	0.2
para-amino sulfate	0.1	0.2

While metabolism of alachlor utilizes the same metabolic pathways in mice as in rats, there are quantitative differences between mice and rats in the metabolite profile present. Mouse feces was found to contain greater amounts of mercapturic acid conjugate and lesser amount of disulfide conjugate than in rat feces. The number of urinary metabolites observed in mouse urine was greater than in rat urine. Mouse urine was found to contain greater amounts of glucuronic acid conjugates and cysteine conjugates than the rat, but a lesser amount of phenolic (hydroxylated) metabolites.

h. Dermal Penetration

The requirement for a dermal absorption study in the rat was waived, since data from three Rhesus monkey studies were combined to determine the dermal absorption factor.

Three pharmacokinetic studies on Rhesus monkeys were performed: an intravenous route of administration study (Acc# 256624, Part C), dermal application of alachlor emulsifiable concentrate (EC) (Acc# 256624, Parts D and F), and a dermal application of alachlor micro-encapsulate formulation (Mcap) (Acc# 256624, Part E). In all three studies, the levels of radioactivity were monitored in the blood for seven days and urine and feces for 9 to 14 days.

The purpose of the intravenous study was to determine the pharmacokinetics of alachlor distribution and elimination. Two monkeys/sex/dose were given single doses of 0.24 or 2.4 mg/kg/day. Alachlor was rapidly distributed in the blood (whole, plasma, and red blood cells) within the first 15 minutes and rapidly eliminated in urine primarily within the first 24 hours. Approximately 93.3 percent of the low dose and 99.6 percent of the high dose were eliminated in excreta during the 10-day study period. The majority of this elimination was via the urine (82.1% low dose, and 91.4%, high dose).

In both the EC and the Mcap dermal studies, the formulations were tested undiluted and diluted (1:29 for EC and 1:17 for Mcap) with water, 2 monkeys/sex/formulation or dilution/EC or Mcap. The dosages (EC: 32 ug/cm^2 and 300 ug/cm^2; and Mcap 10.8 ug/cm^2 and 217 ug/cm^2) were applied to a 40 cm^2 skin area and were left on the skin for 12 hours before removal.

For the EC the rate of alachlor absorption was slow and reached a peak in the blood after 24 hours. The total dermal absorption in the low dose animals (32ug/cm^2), estimated from excretion of radiolabel and retention of label in tissues, was 6-7% in males and 12-13% in females, uncorrected. However, calculation of the actual amount of test material absorbed through the skin was complicated by the fact that recovery of radiolabelled test material in this test group was poor, ranging from 21 to 77% of the nominal amount applied. Data were submitted demonstrating that up to 40% of the applied dose could apparently evaporate from skin (under conditions simulated *in vitro*) and that application error could result in application of up to 20% less than the nominal value. In the face of these uncertainties, values for excretion and absorption

were calculated based upon the amount of radiolabel that was recovered. Using these correction factors, absorption was 10-24 % (low dose) in males and 16-20% (low dose) in females.

For the EC, recovery of radiolabel was better in the high dose animals (300 ug/cm^2), and application of a correction factor had little effect. Absorption was 4-9% in males and 10-11% in females.

It is also possible to estimate a percent dermal absorption by using a ratio of the corrected percent radiolabel excreted in urine after dermal application / the average percent radiolabel excreted in urine after intravenous administration, which is 87%. Using this ratio, the dermal absorption estimates for the low dose EC group were 9.2-24.8% for males and 16-21.8% for females. For the high dose EC group, the dermal absorption estimates were 4.7-8.9% for the males and 10.7-11.4% for the females. Thus, similar estimates of dermal absorption were obtained by either method of calculation.

For the Mcap, the total dermal absorption for the low dose (10.8 ug/cm^2) ranged from 3-23% in males and 6-7% in females. For the high dose (217 ug/cm^2) the total dermal absorption ranged from 2-4% in males and 3-4% in females. Percent dermal absorptions were also estimated using the ratio specified in the discussion of the EC group. Using this ratio, the dermal absorption estimates for the low dose Mcap group were 3.2-23.4% for males and 6.7-7.1% for females. For the high dose Mcap group, the dermal absorption estimates were 2-3.8% in males, and 2.2-3.9% in females. Again, similar estimates of dermal absorption were obtained by either method of calculation.

I. Special Studies

Monsanto has voluntarily submitted these special studies on alachlor which were performed to better understand the mechanisms involved in the toxic responses induced by alachlor, including tumor formation. The following special studies can be categorized in the following groups: in vivo metabolism studies, in vitro metabolism studies, whole body autoradiography (WBA) studies, mutagenicity studies, and cell proliferation/cytotoxicity studies. Some of the submitted data used for cancer peer review consisted of studies conducted with butachlor, a structural analog of alachlor. These special studies do not satisfy any guideline requirements.

In-Vivo Metabolism Studies

Effect of Multiple Oral Dosing on the Metabolism, Distribution, and Elimination of Alachlor in the Long-Evans Rat; MRID No. 42651310, 42852109.

A Study of the Metabolism and Excretion of Alachlor in Rats Chronically Exposed to Alachlor; Routes and Rates of Elimination. MRID No. 42651307 Characterization of Metabolites in the Urine and Feces. MRID No. 42931101

Metabolism of Alachlor Methyl Sulfide in Long-Evans Rats.
MRID No. 42651309.

In-Vitro Metabolism Studies with Alachlor and Alachlor Metabolites

A Study of the In Vitro Liver Slice Metabolism of Alachlor in the Male Rat, Mouse, and Monkey. MRID No. 42651311.

A Study of the In Vitro Metabolism of Alachlor Using Enzyme Preparations From Selected Rat Tissues. Part I. Preparation of Tissue Homogenates. MRID No. 42651312.

In Vitro Metabolism of Alachlor by Rat Liver, Kidney, Lung, Nasal, and Stomach Homogenates. MRID No. 42852110

In Vitro Metabolism of Alachlor by Rat and Mouse Liver and Nasal Enzymes. MRID No. 42852111

Metabolism of Alachlor Methyl Sulfide in Long-Evans Rats. MRID No. 42651309

In Vitro Metabolism Study of Alachlor, Alachlor Secondary Methyl Sulfide, and 2,6-Diethylaniline by Rat and Monkey Nasal Turbinate Part II. MRID No. 42651314.

In Vitro Metabolism of Alachlor, Alachlor Secondary Sulfide, Alachlor Sec-Amide, and 2,6-Diethylaniline by Rat and Human Nasal Turbinates and Liver. MRID No. 43482301.

Effects of Alachlor on Tissue Levels of Glutathione in the Rat. MRID No. 42651318.

Effect of Alachlor on Glutathione Levels of Cultured Adult Rat Hepatocytes. MRID No. 43641603. (Note: This study was not conducted according to 40 CFR Part 160, but is a report based on university thesis research conducted at Searle, a Monsanto subsidiary.)

Studies on Alachlor Using Whole Body Autoradiography (WBA)

Whole Body Autoradiography Studies on 14-C Alachlor in Rats, Mice, and Monkeys. MRID No. 42852103.

A Comparative Study of the Distribution and Localization of Alachlor, Metolachlor, and MON 4601 in Rats Using WBA. MRID No. 428521-04.

A Study of the Distribution and Localization of Alachlor-Methylsulfide in Rats Using WBA. MRID No. 42651304.

A Study of the Distribution and Localization of Diethylaniline (DEA) in Rats and Mice Using WBA. MRID No. 43507401.

A Study of the Distribution and Localization of Dimethylaniline (DMA) in Rats and Mice Using WBA. MRID No. 43706001.

Comparison of the Distribution and Excretion of Radiolabeled Alachlor in the Sprague-Dawley, Fisher 344 and Long-Evans Rat and Golden Syrian Hamster. MRID No. 42852105.

Mutagenicity Studies with Alachlor

Determination of CP-50144-Derived Radioactivity in Rat. MRID No. 43369201.

Study of the Effects of Alachlor on Cellular Stress Response Genes in Rat Nasal Turbinate Tissue. MRID No. 43590002.

Cell Proliferation / Cytotoxicity Studies

Characterization of Covalent Adducts Formed with Nasal Tissue Protein Following Dietary Administration of 14-C Alachlor to Female Long-Evans Rats. MRID No. 43641604.

A Study of the Effect of Alachlor and Selected Metabolites on Cytotoxicity Markers in Nasal Tissue of the Long-Evans Rat. MRID No. 43641602.

Gastric Tumor Initiation/Promotion Study of Butachlor in Sprague-Dawley Rats (Monsanto Company, The Agricultural Group, Environmental Health Laboratory for Monsanto Company, Monsanto Study#: ML-92-365, Monsanto EHL Study#: EHL 92142, August 18, 1994, MRID No. 43729502).

A Study of the Mechanism of Butachlor Induced Carcinogenicity in Female Sprague-Dawley Rats (Monsanto Company, The Agricultural Group, Environmental Health Laboratory for Monsanto Company, Monsanto Study#: EHL-92049, Monsanto Study#: ML-92-146, February 9, 1995, MRID No. 43750801).

A Study on the Effect of Butachlor on Cell Proliferation in Selected Tissues of the Mouse (Monsanto Company, The Agricultural Group, Environmental Health Laboratory for Monsanto Company, Monsanto Study#: EHL-93064, Monsanto Study#: ML-93-153, August 11, 1994, MRID No. 43729503).

Effects of Butachlor on Cell Proliferation and Mucosal Thickness in the Gastric Tissue of Female Rhesus Monkeys (American Health Foundation and White Sands Research Center and Environmental Health Laboratory for Monsanto Company, Monsanto Study#: EHL-93064, Monsanto Study#: WS-93-164 and WS-93-165, MRID No. 43729501).

Gastric Tumor Promotion Study of Alachlor in Long-Evans Rats. Monsanto Company, The Agricultural Group, Environmental Health Laboratory for Monsanto Company, Monsanto Study No. ML-93-137, Monsanto EHL Study# EHL 93049, February 3, 1995. MRID No. 43590001.

The data from these studies were used to draw the following conclusions:

I. Nasal Tumors

Based upon the available data for alachlor, the following hypothesis has been proposed for the production of tumors in the nasal mucosa: Alachlor is metabolized in the rat to the glutathione (mercapturic acid) conjugate, which is excreted through the bile into the gut. In the gut, enteric bacteria metabolize the conjugate to the thiol conjugate, with subsequent S-methylation of the thiol. This product, the methyl sulfide, is re-absorbed into the systemic circulation where conversion to the secondary sulfide occurs. Hydrolysis of the secondary sulfide by arylamidase produces the diethylaniline metabolite of alachlor. Oxidation of the diethylaniline metabolite produces the putative toxic metabolite, diethylbenzoquinone imime (DEBQI). This metabolite binds to cellular protein, resulting in eventual cell death. Ensuing regenerative cell proliferation can then lead to neoplasia through "fixation" of spontaneous mutations.

The registrant presented data in support of their conclusion that the nasal tumors observed following alachlor administration are unique to the rat based on differences in disposition of alachlor in the rat versus other species. In vivo studies in Long-Evans rats (MRID No. 42651306, 42651308, 42852107, 42852108) and CD-1 mice (MRID No. 42651305, 42852106) showed that a greater percentage of a given dose of alachlor was eliminated in feces of mice vs rats. In addition, it was shown that mouse urine contained a greater percentage of glucuronide conjugates and cysteine conjugates of alachlor, while rat urine contains a greater amount of phenolic (hydroxylated) metabolites. In addition, rat feces was found to contain greater percentages of mercapturic acid conjugates and sulfone metabolites than mouse feces. These data are supportive of the proposed metabolic pathway for production of the putative toxic intermediate of alachlor in the rat. In addition to the comparative metabolism of alachlor in rats versus mice, the in vivo metabolism of the methyl sulfide metabolite of alachlor in female Long-Evans rats demonstrated the production of 4-amino-3,5-diethylphenylsulfate, a stable end-product indicative of the formation of the quinone imine precursor (MRID No. 42651309).

In vitro studies conducted by the registrant demonstrated the presence of the reactions necessary for production of the DEBQI intermediate. These include glutathione conjugation of alachlor, hydrolysis of the secondary sulfide by arylamidase, and hydroxylation of 2,6-diethylaniline. Further in vitro studies demonstrated significant species differences in the rates

of these reactions. Comparative in vitro metabolism of alachlor by several tissues in the Long-Evans rat (MRID No. 42852110) showed the presence of arylamidase activity in liver and nasal tissue resulting in formation of the 2,6-diethylaniline metabolite. Oxidation of the 2,6-diethylaniline metabolite to 4-amino-3,5-diethylphenol was shown to be approximately 50 times greater in nasal microsomes than in liver microsomes. Rat and mouse liver and nasal tissues were compared for their ability to metabolize alachlor to the proposed DEBQI intermediate (MRID No. 42852111). The velocity of the nasal aryl amidase reaction in rat nasal tissue towards the sec-amide metabolite of alachlor was observed to be 14-20 times higher in rat than in mouse. The velocity of the nasal arylhydroxylase towards diethylaniline in rat nasal tissue was found to be approximately 2-fold higher than in mouse. This study demonstrated that certain key enzymes responsible for production of the proposed toxic intermediate of alachlor are more active in rat nasal mucosa vs mouse nasal mucosa. Liver and nasal cytosolic or microsomal fractions were used from rat and monkey to study metabolism of alachlor to the GSH conjugate, the hydrolysis of alachlor secondary sulfide by arylamidase, and the hydroxylation of 2,6-diethylaniline (MRID# 42651314). Velocity of rat liver GST was 3.9 times greater than monkey GST towards alachlor. Velocity of rat nasal GST was 114.3 times greater than monkey GST towards alachlor. Velocity of secondary sulfide hydrolysis was equivalent in rat and monkey liver preparations, but was 4 times greater in rat nasal tissue vs monkey nasal tissue. Velocity of DEA hydroxylation in rat liver was 3 times greater than in monkey liver, and 7.6 times greater in rat nasal tissue than in monkey nasal tissue. Thus, the enzymes thought to be responsible for production of the toxic intermediate of alachlor are more active in rat nasal tissue vs monkey nasal tissue.

In MRID No. 43482301, cytosolic and microsomal fractions from rat and human liver and nasal tissue were studied to determine the differential species capability to conjugate alachlor with glutathione, to hydrolyze the secondary methyl sulfide (secondary sulfide), and to hyroxylate the 2,6-diethylaniline metabolite of alachlor. Velocity of glutathione conjugation in rat liver and nasal tissue was 4.0 and 32.5 times greater than in human liver and nasal tissue, respectively. Velocity of hydrolysis of the secondary sulfide was 5.8 times greater in rat nasal tissue vs human. Velocity of DEA hydroxylation was 7.5 times greater in rat liver vs human, and 129.8 times greater in rat nasal tissue vs human.

Whole body autoradiographic studies conducted in rats, mice, and monkeys provided further support for the species specificity of the mechanism of alachlor-induced nasal tumors. In MRID# 42852103, whole body autoradiography (WBA) studies in rats, mice, and monkeys following single oral doses of 7, 70, and 700 mg/kg were conducted. A similar picture of tissue distribution was observed in all species with the exception of blood, in which significant amounts were observed only in the rat at 5 days post-dose, and the nasal turbinates, in which significant accumulation was observed in the rat, less in the mouse, and none in the monkey. Comparative WBA studies on the localization of alachlor, metolachlor, and MON 4601 were conducted in male and female rats after target doses of 7 and 700 mg/kg (MRID No. 42852104). Nasal turbinate localization appeared less for alachlor than for metolachlor and MON 4601 at one day post-dose at the 7 and 700 mg/kg dose. The data in this study indicated a faster clearance of alachlor from the intestinal tract vs metolachlor and MON 4601, and also indicate that metolachlor and MON

4601 undergo biliary excretion and enterohepatic circulation. Whole body autoradiography studies of the localization of the methylsulfide metabolite in rats after oral administration at 0.7 and 7.0 mg/kg (MRID# 42651304) and localization of the diethylaniline metabolite of alachlor in rats after oral administration of 7 and 70 mg/kg (MRID# 43507401) showed that for the methyl sulfide metabolite, localization in the nasal turbinate was evident up to 5 days post-dose, while for the diethylaniline metabolite, nasal turbinate localization was evident in the rat but not the mouse. Comparative distribution of alachlor using WBA after oral doses of 7 and 70 mg/kg was examined in Sprague-Dawley, Long-Evans, and Fisher 344 rats as well as in Syrian hamsters (MRID# 42852105). Nasal localization was evident in all three strains but was most apparent in the Long-Evans rat. Nasal localization was not evident in the hamster.

Collectively, these WBA studies support the conclusion that the distribution of alachlor derived radioactivity to the nasal turbinates as well as that of alachlor metabolites thought to be involved in nasal tumor formation is greater in the rat than in the mouse or monkey. When considered in conjunction with in vitro studies on the activities of enzymes responsible for formation of the DEBQI intermediate, it is evident that not only does alachlor derived radioactivity localize to the rat nasal turbinate tissue to a greater degree than in mice or monkeys, but that the activities of the enzymes involved in the conversion of the secondary sulfide to the DEBQI intermediate are significantly higher in the rat than in the mouse, monkey, or human.

The mechanism of alachlor-induced nasal tumors is considered by the registrant as a non-genotoxic mechanism. This argument is largely based upon the mutagenicity database, in which it is argued that alachlor has no significant genotoxic activity in mammalian systems. Studies examining the effect of alachlor administration on tissue glutathione levels following in vivo administration of oral and intraperitoneal doses of alachlor to Long-Evans rats as well as the effect of alachlor on glutathione levels in cultured hepatocytes have been conducted (MRID#'s 42651318 and 43641603). These studies showed depletion of hepatic glutathione followed by recovery after a single i.p. dose of 350 mg/kg or single oral doses of 126 and 350 mg/kg. Alachlor was hepatotoxic at concentrations above 400μM, and significant glutathione depletion was also observed at concentrations above 300μM alachlor. While no significant depletion of nasal glutathione levels were observed, the DNA damaging effect of alachlor might be related to depletion of glutathione and subsequent tissue toxicity, and not to a direct mode of action. It is noted that significant hepatoxicity in the form of elevated serum ALT, AST, and LDH as well as centrilobular cytoplasmic eosinophilia, centrilobular inflammation, and centrilobular hepatocellular degeneration/necrosis was observed at a dose of alachlor (1000 mg/kg) which also caused a weak UDS response. These data are consistent with a non-genotoxic mode of action for alachlor. With regard to the nasal tissue, two studies addressed the mechanism of nasal turbinate induced tumors. In the first study (MRID No. 43641604), female Long-Evans rats were fed 14-C alachlor in the diet at a targeted dose level of 126 mg/kg/day for a total of 13 days. On days 1, 3, 7, and 13, 3 rats were sacrificed and the covalent binding of alachlor derived radioactivity to nasal protein was determined. The results of this study showed a direct correlation between the total level of alachlor binding to rat nasal proteins and length of treatment. The major adduct was identified as the 3,5-diethylbenzo-quinone-4-imime (DEBQI)-cysteine adduct. Formation of DEBQI in the rat

nasal tissue is believed to be required for induction of nasal tumors. In the second study (MRID No. 43641602), the in vitro cytotoxicity of alachlor, DEA, secondary sulfide, and secondary amide were assessed in preparations of rat nasal turbinate as evidenced by leakage of the enzyme acid phosphatase in to the culture medium. Concentrations of alachlor and metabolites used were either 1 or 5mM. Alachlor at both 1 and 5 mM was shown to increase acid phosphatase levels in the culture medium. Neither the secondary sulfide or secondary amide caused an increase in acid phosphatase levels at 1 mM (5mM concentration not possible due to solubility limitations). DEA was observed to increase acid phosphatase levels at 5 mM in nasal tissue. The cytotoxicity observed with alachlor in nasal tissue is consistent with the cell proliferation response observed in nasal tissue after administration of alachlor, but the entity responsible for the cytotoxic response is not known with certainty.

ii. Gastric Tumors

In response to scientific and regulatory questions raised in Japan, an extensive research program was undertaken to understand the mechanism by which chloroacetanilides induce stomach tumors in rats. The majority of this work was conducted with butachlor in Sprague-Dawley rats. Since butachlor is a close structural analog of alachlor, and the two compounds produce the same glandular stomach tumors, extrapolation of the mechanistic information to alachlor is scientifically justified. To further support this, some bridging data have been developed with alachlor and were previously reported to the Agency. The purpose of these provided data are to: (a) report the results and conclusions of the mechanistic studies conducted with butachlor; (b) integrate these results with those from the alachlor work to show that the same mechanisms are operative for both herbicides.

In a gastric tumor initiation/promotion study (MRID# 43729502) the results showed that butachlor had no initiating potential of its own when used at dose levels which produced gastric tumors in the chronic toxicity study in rats. Butachlor was found to enhance the formation of gastric neoplasms when combined with an initiating agent. This occurs primarily in females and at the dose which induces neoplasms in the chronic rat study. In a study of the mechanism of butachlor induced carcinogenicity in female Sprague-Dawley rats (MRID No. 43750801) the investigators concluded that these data delineated the mechanistic processes involved in the production of the gastric, nasal and thyroid tumors for butachlor. It was suggested that the data provided support for the involvement of non-genotoxic mechanisms that would be threshold sensitive to humans. They also stated that these studies further support the view that the rat tumors induced by butachlor are not relevant to man and that butachlor does not pose a human health risk (not formally reviewed by the Agency). In a study on the effect of butachlor on cell proliferation in selected tissues of the mouse (MRID No. 43729503) the investigators found no consistent increase in cell proliferation in either the fundic or pyloric regions. There was a slight increase in the fundic neck region but not in the base region and there was no evidence of toxicity in the mucosa. In another study on the effects of butachlor on cell proliferation and mucosal thickness in the gastric tissue of female Rhesus monkeys (MRID No. 43729501), according to the investigators there were no relevant changes in cell proliferation in any area of the stomach and

no changes in the mucosal thickness in any of the monkeys up to and including 400 mg/kg. The results of this study differ from those studies in the rat, where increases in proliferative activity and reductions in mucosal thickness were observed. The doses used in the monkey are reported to exceed the MTD in the rat by 2 to 4 times.

The registrant conducted an initiation-promotion study with Alachlor (MRID No. 43590001) as a follow-up to a stomach tumor initiation/promotion study with butachlor. In this study, 100 male and 100 female Long-Evans rats obtained from Charles River Breeding Laboratory, Portage, MI, 6 weeks of age and weighing 168-219 g for males and 139-176 g for females were administered by oral gavage a single dose of 150 mg/kg of the known gastric tumor initiator N-methyl-N'-nitro-N-nitroso-guanidine (MNNG) to 4 groups of 20 animals per sex. One of these groups was not further treated. Another group received dietary administration of 8000 ppm catechol, and two groups received either 15 or 126 mg/kg/day of Alachlor in the diet for 1 year while another group (not MNNG treated) received a single oral dose of DMSO (5 ml/kg) followed by dietary administration of alachlor at a level of 126 mg/kg/day (there was another group of 15 animals per sex obtained near the end of the study to serve as "control" animals for serum gastrin levels, gastric fluid amount, pH, and HCl concentration). The investigators determined, at the end of the study, stomach pH, gastric acid secretion over a 4 hour period in 5-6 of the control and DMSO/Alachlor treated animals. They also obtained blood from 9-10 control and DMSO/Alachlor treated animals for serum gastrin determinations. The stomachs of all animals were examined grossly and microscopically.

Alachlor was found to promote the development of glandular stomach tumors in females and to a lesser extent in males. No effect of treatment was noted in the MNNG alone treated animals (1 tumor). Alachlor alone produced no tumors in males and 4 tumors in females. MNNG/Alachlor treated animals produced tumors in 75% of treated females and 30% of treated males at 126 mg/kg/day. These tumors were neoplasms of the glandular stomach, mostly in the fundus region. In the 15 mg/kg/day Alachlor + MNNG no tumors were observed in the females. However several tumors were found in males at both doses and in females at the 126 mg/kg/day dose following MNNG. The investigators interpreted this as due to MNNG rather than alachlor, since they occurred at equivalent frequency in the males at both doses, the lower of which had no promotional activity. In a previous butachlor initiation/promotion study, the group treated with MNNG only induced adenomas and adenocarcinomas in the pyloric region. Alachlor administration was noted to produce atrophy of the fundic mucosa in almost every animal at 126 mg/kg/day both with and without the initiator, MNNG. No atrophy was noted in any animal at 15 mg/kg/day alachlor for 1 year. High dose alachlor animals of both sexes had reduced amount of fluid in the stomachs. Stomach pH was numerically increased, and gastric hydrochloric acid secretion was decreased and serum gastrin levels were elevated in high dose animals. The investigators believe that these data provide evidence that alachlor produces glandular stomach tumors in rats through the same non-genotoxic, threshold sensitive mechanism as butachlor and that this mechanism may be operative in humans under certain specific pathological states.

Alachlor has been shown to produce glandular stomach tumors in Long-Evans rats at doses

considered in excess of an adequate dose for carcinogenicity testing. Butachlor also induced these gastric neoplasms in Sprague-Dawley rats following chronic high dose exposure. In this butachlor bioassay, the occurrence of gastric tumors was restricted solely to the highest dose tested (give dose), a level of exposure which was considered greatly in excess of an adequate dose for carcinogenicity testing. In a butachlor chronic bioassay with F-344 rats, the highest dose was considered adequate for carcinogenicity testing, and no gastric tumors were found. This and other information indicate that chloroacetanilides produce stomach tumors in rats via a threshold-type mechanism.

The Health Effects Division Carcinogenicity Peer Review Committee evaluated the data submitted in support of the threshold-type mechanism for induction of gastric tumors by alachlor and concurred with the explanation put forth by the registrant.

iii. Thyroid Tumors

Mechanistic data in support of the thyroid tumors consisted of two studies. In the first, dose levels of 0 and 126 mg/kg/day were used to measure indices of thyroid function (T3, T4, and TSH levels). While the results of this study showed no significant effect of alachlor on T3, T4, or TSH levels, the results pertaining to TSH levels were considered invalid based on the use of human antibodies in the TSH assay.

In the second study (MRID No. 42957201), Long-Evans rats were dosed with Alachlor for up to 120 days at dose levels of 0 and 126 mg/kg/day. Separate groups were exposed to control diet or alachlor in the diet for 7, 14, 28, 60, or 120 days, with a separate group exposed to alachlor for 60 days in the diet and then control diet for 60 days. The results of this study showed increased liver weights at all time points, increased activity of uridine 5'-di-phosphoglucuronyl transferase (UDPGT), and increased thyroid weights from day 14 throughout the remainder of the study. TSH levels were statistically significantly increased from day 14 on, although the increase at day 120 was not significant. T3 levels were increased over control at 7, 14, 60, and 120 days; T4 levels were decreased at 7 and 28 days and increased at 14 days, returning towards normal at following time points. The dose group which received alachlor for 60 days and then 60 days with control diet showed relatively unaffected T3, T4 and TSH levels. Thyroid follicular hypertrophy/hyperplasia was also noted in the treated animals mainly in the 28 and 60 day groups, with 1 animal in the 120 day group progressing to nodular hyperplasia.

The results of the above studies suggest that thyroid tumors (which only occur in the male rat), result from induction of hepatic UDPGT, with a consequent decrease in circulating T3 and T4 and a subsequent increase in TSH (although 1 study showed increased T3 levels). This action is known to result in a hyperplastic response of the thyroid. The mechanism of thyroid tumorigenesis observed with alachlor is consistent with the mechanism of thyroid tumorigenesis observed with other chemicals causing a disruption of thyroid hormone balance.

j. Human Studies

(I). Human Bio-monitoring

A biomonitoring study of a pesticide, involves following a group of workers during a defined field use of the pesticide. Urine is collected before and after exposure and analyzed for metabolites of the pesticide. From this data one determines the quantity of pesticide absorbed during the defined field exposure. Thus, a biomonitoring study consists of two parts (1) a qualitative and quantitative identification of the metabolites of the pesticide, usually by following radiolabel in a mammalian species, and (2) the field study in human subjects.

In all three studies the internal dosage of alachlor was estimated by analysis of the urinary excretion of alachlor metabolites which contained the DEA and HEEA moieties.

The first biomonitoring study (Acc# 256623/4) was conducted using two formulations of alachlor, the EC (emulsifiable concentrate) and the Mcap (microencapsulated). The study was designed to determine the dosages of alachlor in workers, and to compare the dosages of the two formulations. The study was conducted in Indiana during May 1984. Both the EC and Mcap were applied by shallow incorporation to corn fields at an application rate of 4 lbs a.i./acre. Each formulation was applied by four different individuals. Applicators 1, 3, 5, and 7 applied EC and applicators 2, 4, 6, and 8 applied Mcap. Additionally a control subject was present at the field during the application.

The subjects were Monsanto employees who wore goggles and elbow length rubber gloves during mixing/loading and leather boots, trouser, longsleeve shirts and caps throughout the entire operation. The clothing was in agreement with the protective clothing requirements stated on the labels. Each applicator emptied eight 2.5 gallon containers of EC or Mcap into 200 gallon tanks. Water was added from nurse tanks with constant agitation. Immediately following mixing, the worker entered a closed cab and applied the alachlor to 20 acres.

The urine was collected in borosilicate glass bottles with teflon caps for 120 hours (5 days) after the alachlor application was completed. The samples were analyzed for metabolites of alachlor containing the DEA and HEEA moieties using GC/MS. Urine samples with non-detectable levels of alachlor metabolites were computed as containing 1.25 ppb (one-half the LOD, limit of detection, of 2.5 ppb). The practice of using one-half of the LOD is a standard analytical procedure for dealing with the analytical LODs for chemical residues.

The highest internal dosage for mixing, loading and applying (of the four replicates) for EC formulation was estimated to be 0.0066 ug/kg/lb ai. The internal dosage for the Mcap was estimated to be 0.027 ug/kg/lb ai.

Another biomonitoring study was conducted in May and July 1985 in Missouri. In this study the Mcap and WDG (a water dispersable granular formulation), were evaluated. This study was conducted in a manner similar to that of the May 1984 bio-monitoring study: Monsanto employees wearing clothing in accordance with the label, 4 lbs ai/acre, and 20 acres. Open

loading was used, with each subject handling 80 lbs ai. Control urine samples were collected prior to study initiation. Urine was collected for 5 days. The urine samples were also analyzed for alachlor metabolites containing the DEA and HEEA moities, but by HPLC (high performance liquid chromatography).

No measurable levels of the alachlor metabolites containing the HEEA moiety were detected in any urine samples for all study subjects. Measurable levels of DEA metabolites were detected for most of the subjects, primarily within the first 48 hours. The internal dosage of the Mcap was estimated to be 0.0038 ug/kg/ai. The internal dosage of the WDG was estimated to be 0.0059 ug/kg/lb ai.

A third bio-monitoring study was also performed in May and July 1985. This study was also conducted in the same manner as that of the Mcap and WDG 1985 bio-monitoring study. However, a closed loading system was used to transfer the EC.

The internal dosage of the EC was estimated to be 0.0034 ug/kg/lb ai.

For all three studies there were concerns due to the small number of replicates as well as the use of protective clothing and the use of the closed cab. Only 20 acres were treated instead of the 100 to 120 acres that could be expected to be treated and incorporated. Additionally, the scenario is only representative of 4 lb ai/acre. The small number of replicates cannot indicate the range of dosage that would be expected. Due to the protected nature of the applicators (clothing and cab) it was assumed that the dosage estimate is from the lower end of the range. A literature search of ground boom application studies indicated that exposure to the applicators ranged over three orders of magnitude. In the alachlor PD4 two orders of magnitude was chosen by HED to define the exposure range since mixing and loading is included in the dosage estimates with the estimate from the Monsanto bio-monitoring studies considered to be the low end of the range.

As part of the re-registration process, the first biomonitoring study (May 1984, Indiana) was re-reviewed (Zendzian). The review indicated that there is probably a formulation related difference for application of the EC versus the Mcap. For the 4 lb ai/acre scenario, the internal estimated dosages were:

EC = 0.0032 ug/kg/lb ai

Mcap = 0.0126 ug/kg/lb ai

It was noted that the same internal exposure estimates would be appropriate for mixer/loaders, mixer/loader/applicators, or applicators.

(ii) Epidemiology Study of Ocular Health Among Alachlor Manufacturing Workers

Long-Evans rats were noted to develop severe ocular lesions at the highest test doses

during a chronic feeding study (MRID No. 00139021) with alachlor. Another study in Long-Evans rats was also conducted to characterize the progression of the previously observed eye lesions (MRID No. 00141060). It was observed that females were more sensitive than males, and that once the uveal degereration syndrome was observed, it was irreversible.

To determine if workers might be at risk, it was decided to conduct an ophthalmologic study which would focus on an human eye lesion that could be considered equivalent to the initiating eye lesion found in Long-Evans rats. Differences between Long-Evans rat and human eyes were considered to be minor ; thus, an equivalence for the purpose of evaluating a potential effect of alachlor exposure among workers could be assumed. The uveal tract consists of the iris, ciliary body, and choroid. Long-Evans rats, like humans, have pigmented eyes and each uveal component has melanin-containing cells. The human equivalent of the initiating lesions, uveal pigment disruption and dispersion, is the clinically described Pigment Dispersion Syndrome (PDS). PDS consists of the loss of pigment from the mid-posterior iris with deposition of the pigment on the cornea, trabecular meshwork, lens, and iris.

The study site was the Muscatine, Iowa plant, which began operation in 1961. At Muscatine, herbicide production began in 1964, with the production of alachlor beginning in 1968. To determine whether there were ocular effects among exposed workers, a group of 135 highly exposed alachlor production workers were examined for the presence of PDS. There was a control group of 84 unexposed co-workers and relatives. All participants were examined by the same ophthalmologist at the University of Iowa. The ophthalmologist was unaware of the exposure status of the individual participants.

Components of the eye exam included slit-lamp biomicroscopy of the anterior chamber and a dilated exam of the lens and fundus with scleral depression as well as the routine functional exam. Intraocular pressure was measured prior to dilation. Only one study participant had eye defects meeting the study criteria of PDS. This person was in the control group. For eye abnormalities other than PDS, prevalence rates were similar for exposed and unexposed study participants.

Thus, no evidence of increased risk of ocular disease was found when workers were compared to controls. Only one subject, who was from the control group, had the same defect as reported in the study of Long-Evans rats. (MRID No. 43267501)

iii. Epidemiologic Study of Workers

Monsanto performed an epidemiologic study of workers at an alachlor manufacturing plant in Muscatine, Iowa. The product has been manufactured in this plant since 1969. (MRID #43878501).

The population studied included 1199 workers employed for 1 year or more between 1961 and December 1993. Both mortality and cancer incidence were assessed in this cohort. Mortality

follow-up was by company records, social security number, national death index, credit agency, and state motor vehicle records. Follow-up for vital status was very successful, covering over 99% of the cohort. Death certificates were obtained for all 17 decedents.

Assessment of cancer incidence was conducted using the statewide cancer registry in Iowa which was initiated in 1969. Linking with the registry was by social security number, full name, and birth date. Inexact matches were verified by consulting with employee records and the State Health Registry. Workers who left Iowa (< 1/3 the cohort) did not have cancer incidence assessed but were assumed to be similar to those who remained in state.

Quantitative data were insufficient to estimate actual exposure at the plant. Qualitative estimates (high, medium, and low) were made by industrial hygienists based primarily on work history and the potential for dermal exposure. Alachlor's low vapor pressure and airborne measurements taken at the plant (averaging less than 10 ppb) suggest this route of exposure is not significant. The potential for contaminated water occurred between 1968 and 1975. In 1975 low levels of alachlor had been detected in the plant's drinking water. However, when the alachlor first appeared in the drinking water is not known. Exposure characterization took into account the contaminated drinking water. Analysis both included and excluded this possibility due to the uncertainty associated with it. Twenty-six non-whites were excluded from the analysis due to inadequate sample size for statistical analysis. However, it was noted that no cancers occurred in this group where 0.1 cases would have been expected. Appropriate discussion of follow-up and statistical techniques are presented.

The study did not find any evidence of statistically increased incidence or mortality from cancer either overall or by individual cancer site with one exception. No deaths or incidence of cancer was reported for the stomach, thyroid, or nasal cavities, as was reported in laboratory rats. The one statistically significant finding was based on two cases of chronic myeloid leukemia where only 0.1 cases would have been expected. The 95 percent confidence interval for the standardized incidence ratio was quite wide, 1.9 to 58.1. Given that this ratio is based on only two cases (one of which had worked at the plant less than 5 years) and the number of statistical tests performed, this result should probably be considered a chance finding without other supporting evidence.

By completion of this study only 24 cancers and 8 cancer deaths had been reported in the entire cohort. The overall cancer mortality ratio (number of observed/expected cases) was 0.9 with a 95% confidence interval of 0.4 to 1.7. The overall cancer incidence ratio was 1.4 based on 24 observed and 17.1 expected cases (95% confidence interval 0.9 to 2.1). For those workers categorized as having high exposure to alachlor (68% of the cohort), the cancer incidence ratio was 1.2 (95% confidence interval 0.7 to 2.0). HED concludes that while no appreciable hazard has been identified to date, one cannot rule out adverse effects in this cohort until these individuals have been followed-up over the course of a lifetime.

k. <u>ESA Metabolite of Alachlor</u>

The ethane sulfonic acid (ESA) metabolite of alachlor is variously referred to as MON 5775, 2',6'-diethyl-N-methoxymethyl-2-sulfoacetanilide, sodium salt or 2-[2,6-diethylphenyl (methoxymethyl) amino]-2-oxoethane sulfonic acid, sodium salt. The formation of the ESA metabolite of alachlor involves the displacement of a chlorine atom by a sulfonic acid moiety. The metabolic route leading to the ESA metabolite is postulated to involve initial glutathione displacement of the chlorine atom, followed by successive degradation of the sulfur conjugated moiety through organic acid and methylsulfone intermediates, to ultimately form the sulfonic acid group as a terminal oxidative degradate. Alachlor ESA has always been isolated from natural matrices and synthetic preparations as a salt. The sodium salt has always been utilized for toxicology studies.

Alachlor ESA was originally identified as a metabolite of alachlor in soil (MRID No. 00134327). The ESA metabolite was determined to be 15 - 25% of the total applied radioactivity, making it the first or second most prevalent degradate. Alachlor ESA has also been quantified in field soil dissipation studies following alachlor applications (MRID No. 42528002, 43774701). Low concentrations were detected but alachlor ESA was not found to persist or leach below 18 inches.

The ESA metabolite has been identified as a minor alachlor degradate in a laboratory aqueous sediment metabolism study (MRID No. 43774702). It has also been detected in water samples from Indiana (MRID No. 42479901) and Wisconsin (no MRID, submitted under FIFRA 6(a)(2)). In the Indiana well water samples, alachlor ESA concentrations ranged from < 1.0 - 23.0 μg/L, and in Wisconsin they ranged from < 1.0 - 26.7 μg/L.

(I) Acute Toxicity

In an acute oral toxicity study in rats, the acute oral LD_{50} of ESA is greater than 6000 mg/kg. This is toxicity category IV (MRID No. 42701501).

(ii) Subchronic Toxicity

In a special 91-day drinking water study, male and female Fischer CDF® F-344 Crl BR VAF/Plus® rats from Charles River Laboratories, Inc. Raleigh, NC received either 0, 200, 2000, or 10000 ppm (male: 0 (control), 16, 157, or 896 mg/kg/day; female: 0 (control), 23, 207, or 1108 mg/kg/day) ESA. Systemic toxicity was observed in high dose male and female rats, with increased incidences of decreased activity with rapid/shallow breathing, few feces and feces small in size, dehydration, urine staining, emaciation, hunched posture, rough coat, unkempt appearance, and dark material/stain on pads of forelimb, around eyes, mouth and nose, clear and red ocular discharge, and hair loss around eyes. Slight decreased body weight gains (10%) was also noted in high dose male rats (decreased body weight gains were noted in all treated females; however, no dose response was noted). Several statistically significant hematological effects

(decreased hemoglobin, hematocrit, red cells, increased MCH and MCHC) and clinical chemistry alterations (decreased AST, ALT, urea nitrogen, albumin, glucose, increased bilirubin and phosphorous) were observed at the mid and high dose in males and/or females, but were minor, mostly not dose related and were not considered biologically relevant, especially in the **absence** of any organ or tissue pathology at this dose. Eye lesions noted in this study were determined not to be related to treatment or to those lesions seen with the parent compound, alachlor. The clinical observations reported related to the eye are due to ocular abnormalities specific to the F-344 rat. The systemic toxicity NOEL was 2000 ppm (157 mg/kg/day in males and 207 mg/kg/day in females). The systemic toxicity LOEL was 10,000 ppm (896 mg/kg/day in males and 1108 mg/kg/day in females) based on increased incidence of clinical signs of toxicity in males and females, and decreased body weight gains in males (MRID No. 42863701).

(iii) Developmental Toxicity

In a prenatal developmental toxicity (teratology) study, female Sprague-Dawley Crl:CD®BR rats from Charles River Breeding Laboratories, Inc., Portage, Michigan received 0 (control), 150, 400, or 1000 (limit dose) mg/kg/day ESA (90.0% a.i.; Lot No.: NPD-9203-3974-T) in corn oil by oral gavage from days 6 through 15 of gestation, inclusive. Actual doses were 0, 135, 360, or 900 mg/kg/day based on 90.0% a.i. No maternal toxicity was noted in any measured parameter at the dose levels tested. The maternal toxicity NOEL is equal to or greater than 900 mg/kg/day and the maternal toxicity LOEL is greater than 900 mg/kg/day. No developmental toxicity was noted in any measured parameter at the dose levels tested. Therefore, the developmental toxicity NOEL is equal to or greater than 900 mg/kg/day, and the developmental toxicity LOEL is greater than 900 mg/kg/day (MRID No. 43908101).

(iv) Mutagenicity

In an Ames Salmonella mutagenicity assay, alachlor's ethanesulfonic acid, or ESA metabolite, did not cause increases in the reversion of four S. typhimurium strains (TA98, TA100, TA1535, and TA1537) in either the presence or absence of S9 activation at dose levels of 0.01 to 10.00 mg/plate under the conditions of two independent assays (MRID No. 00151398).

In a mouse micronucleus assay, groups of five male CD-1 mice received single oral gavage administrations of 500, 1000 or 2000 mg/kg ESA (90.7%). The test material was delivered to the animals in deionized water. Animals were sacrificed at 24 and 48 hours postadministration; bone marrow cells were harvested and 2000 erythrocytes per male were examined for the incidence of micronucleated polychromatic erythrocytes (MPEs). No overt toxicity for the treated animals or cytotoxicity for the target organ was observed up to the currently recommended limit dose (2000 mg/kg). The positive control induced the expected high yield of MPEs in the treated males. There was, however, no evidence that the test material induced a clastogenic or aneugenic effect at any dose or sacrifice time (MRID No. 43889403).

(v) Metabolism

In a special metabolism study, two groups of male and female Long-Evans rats (two/sex/group) were administered alachlor ESA at a dose of 70 mg/kg by gavage. Group 1 rats were sacrificed 24 hours after treatment and Group 2 rats at 5 days after treatment. Disposition of alachlor ethane sulfonate was determined by collection of excreta and by whole-body autoradiography. Metabolism was assessed by HPLC analysis of processed urine and feces samples. The major route of excretion for alachlor ESA at 70 mg/kg was the feces, with between 71-82% of the administered dose excreted by this route. Excretion was rapid with the majority of radioactivity excreted by 24 hours post-dose. HPLC analysis of urine and feces showed alachlor ESA to be the major component in both urine and feces, with three other components isolated but not identified, each comprising less than 2% of the dose. Autoradiographic data on alachlor ESA derived radioactivity at 14 hours postdose showed the major areas of localization were stomach contents, cecum, intestinal contents and urinary bladder. The data indicate that alachlor's ESA metabolite is poorly absorbed, rapidly excreted, and undergoes minor metabolism. This study provides information on the disposition of alachlor ethane sulfonate in Long-Evans rats (MRID No. 43889404).

(vi) Special Studies

In a special study, the proliferating cell nuclear antigen technique (PCNA) was utilized to determine the effect of treatment with 2000 ppm Alachlor (157 mg/kg/day for 91 days) on cell proliferation in the olfactory region at the second palatial ridge (Level III), where alachlor-induced tumors are found. Mean nasal cell proliferation values (number of labelled cells per mm of mucosal length) showed no statistically significant increases in cell proliferation in either the olfactory septum or turbinates of male Fischer 344 rats administered MON 5775 in drinking water for 91 days. This study provides limited information on the nasal proliferative response from administration of MON 5775 to male Fischer 344 rats (MRID No. 43889401).

In a special study, glandular stomach tissue from female Fischer 344 rats treated with alachlor ESA in drinking water at a dose of 10,000 ppm for 91 days was evaluated using the proliferating cell nuclear antigen for evidence of a proliferative response or changes in mucosal thickness. A significant increase in the percentage of labelled cells in the fundic neck region was observed in treated rats, but there were no significant changes in labelling of the fundic base nor in mucosal thickness (MRID No. 43889402).

(vii). Conclusions

TABLE 4: Comparison of Alachlor and Alachlor ESA

Test	Alachlor	Alachlor ESA
Acute oral LD_{50}	930 mg/kg Toxicity category III	> 6000 mg/kg Toxicity category IV
Subchronic Toxicity (1)	90 day invalidated feeding study	91-day drinking water study NOEL = 157 mg/kg/day LOEL = 896 mg/kg/day
Developmental Toxicity	maternal NOEL = 150 mg/kg/day LOEL = 400 mg/kg/day developmental NOEL = 150 mg/kg/day LOEL = 400 mg/kg/day	maternal NOEL => 900 mg/kg/day LOEL > 900 mg/kg/day developmental NOEL => 900 mg/kg/day LOEL > 900 mg/kg/day
Mutagenicity	weakly mutagenic - tested positive in 2 UDS studies. Other alachlor metabolites also found to be weakly mutagenic	no mutagenic activity in two studies
Metabolism (2)	Absorption was essentially complete with alachlor being present in the blood at 24 hours and 5 days post dose. Alachlor excreted approximately equally between urine and feces.	ESA is the major component in both urine and feces. ESA is poorly absorbed, rapidly excreted (71-82% in the feces within 24 hours), and undergoes minor metabolism.

(1) The subchronic data available for comparison of alachlor with the ESA metabolite of alachlor are not by the same route of administration (in the diet for alachlor *per se* and in the drinking water for the ESA metabolite of alachlor). Also, the study with alachlor *per se* is an IBT study which was not validated nor repeated; therefore the data may be suspect. It is important to note that the subchronic and chronic toxicity studies with alachlor were conducted with different strains of rats ("Charles River Albino rats" vs Long-Evans rats) than the 91 day drinking water study (Fisher 344 rats); however, the available metabolism data do not show any major differences in the handling of the compounds in the Long-Evans versus the Fisher rats.

(2) The available *in vivo* metabolism data indicate that in comparison to alachlor, the ESA metabolite is poorly absorbed and metabolized to only a minor degree. The products of alachlor ESA metabolism were not identified. The available autoradiography data indicate that in comparison to alachlor, the ESA metabolite does not show any significant localization to the nasal cavity, thyroid and glandular stomach (gastric mucosa). The available cell proliferation data

indicate that in comparison to alachlor, ESA does not induce cell proliferation.

Overall, the data provided indicate that alachlor's ESA metabolite has less toxic potential than the parent alachlor.

(viii). Ad Hoc HED Metabolism Committee Meeting

An ad hoc HED Metabolism Committee meeting held 1/18/95 discussed the available toxicity data for the alachlor ethane sulfonic acid (ESA) metabolite.

The ad hoc HED Metabolism Committee concluded the following:

(a) Since alachlor ESA is sulfonated, and highly polar, there is likely to be little absorption via the oral or dermal routes, and even if absorbed, it is expected to be readily excreted.

(b) Information has been provided by the Registrant which indicates toxicity of the parent is based in part on formation of the quinone imine. [HED agrees with the hypothesis.]

© Formation of the potentially carcinogenic quinone-imine from Alachlor ESA is unlikely if the metabolite occurs solely in the sulfonated form in the body, or if minimal cleavage to the unsulfonated form occurs.

(d) Because of the reasons cited above, alachlor ESA is unlikely to be carcinogenic in a 2-year bioassay.

(e) Alachlor ESA should, however, continue to be included in non-cancer dietary exposure estimates (for comparison to the RfD).

(f) Alachlor ESA was non-mutagenic.

2. DOSE RESPONSE ASSESSMENT

a. Reference Dose (RfD)

A Reference Dose (RfD) represents the quantity of a substance which if absorbed on a daily basis over a lifetime, is not expected to pose significant risk of adverse health effects.
The RfD for alachlor was first assessed on February 21, 1986. This RfD was subsequently verified by the Agency RfD Work Group on March 11, 1986, and again on March 27, 1991.

At that time the RfD was based on a NOEL of 1 mg/kg/day in a one year chronic dog study (MRID No. 00148923). The LOEL was 3 mg/kg/day based on hemosiderosis and hemolytic anemia. An uncertainty factor (UF) of 100 was used to account for interspecies extrapolation and intraspecies variability. The RfD was calculated to be 0.01 mg/kg/day.

This value was entered into IRIS (Integrated Risk Information System). The IRIS entry indicates that the principal study is of good quality and is given a high confidence rating. Additionally, there are generally good toxicological studies available on alachlor which provide high confidence in the database. High confidence in the RfD follows.

The HED RfD Committee met on 8/19/93 (actual memo was signed 1/31/94) to discuss and reevaluate the RfD for alachlor. At this meeting, it was recommended that the RfD of 0.01 mg/kg/day remain unchanged

b. Cancer Peer Review

The carcinogenicity of alachlor was first evaluated on March 25, 1986, by HED's Peer Review Committee. The information available at the time included two chronic rat studies, a special 2-year rat study for ocular lesions, and an 18 month mouse study, as well as historical control data on the mouse, several in vitro and in vivo mutagenic assays, and metabolism data.

The Committee concluded that the data available for alachlor was sufficient for a classification of B2, probable human carcinogen.

> Alachlor met all but one of the criteria specified for the B2 classification, any of which alone can be sufficient for such a classification. That is, alachlor produced an increased incidence in malignant, or combined malignant and benign, nasal turbinate tumors and (other tumor types) in Long-Evans rats in three different experiments at more than one dose level via dietary administration. Alachlor also produced a statistically significant increase in lung tumors in female CD1 mice at 2 dose levels. In another experiment with Long-Evans rats, nasal turbinate tumors occurred after only 5-6 months of exposure. The tumor incidence was as high as 50% and tumor site was unusual; i.e., not an increase of a normal high background tumor type. Additionally, a metabolite of alachlor was mutagenic in the Ames test at 6 dose levels.

On November 19, 1986, the SAP (Science Advisory Panel) upheld the B2 classification concluding that alachlor was a B2 carcinogen since it produced "an usual type of neoplasm (nasal turbinate tumors) in the rat, coupled with the finding that two metabolites of alachlor are mutagenic."

The Committee reconsidered the classification on April 15, 1987, in light of the conclusions of the SAP and the registrant's rebuttal that alachlor should be classified as a C, possible human carcinogen. Upon reconsideration of the available data and review of the registrant's arguments and

the SAP's decision, the Committee determined that alachlor's classification as a B2, probable human carcinogen was appropriate; thus, corroborating the March 25, 1986, decision.

A low dose extrapolation model was applied to the animal data to calculate the cancer potency factor. The Q1* was calculated to be 0.08 (mg/kg/day)-1. This information was verified and then entered into the Agency's Integrated Risk Information System (IRIS).

As part of HED's peer review process, alachlor was considered by HED's Carcinogenicity Peer Review Committee (CPRC) on September 27, and October 3, 1995 and January 3, 1996. The registrant, Monsanto, voluntarily provided new data to the Agency consisting of a new mouse carcinogenicity study, additional mutagenicity studies, mechanistic data, special metabolism, pharmacokinetic, and cell proliferation studies in support of a request for re-classification of the carcinogenic potential of alachlor. These new data were reviewed by the Agency with respect to the proposed mechanism(s) for induction of nasal, gastric, and thyroid tumors.

Upon evaluation of all of the submitted data regarding the carcinogenicity potential of alachlor and consideration of the full weight-of-the-evidence, the Health Effects Division Carcinogenicity Peer Review Committee could not reach a consensus as to the classification of alachlor as a carcinogen. Therefore the CPRC recommended to defer the carcinogenicity classification of alachlor and reconsider the classification at a later date, using the new Cancer Assessment Guidelines when such guidelines are in effect. In addition, the CPRC recommended not to utilize the linear low dose approach, but to utilize the Margin of Exposure (MOE) methodology for the estimation of human risk. The CPRC concluded that the data in support of the mechanism for the nasal turbinates is indicative of a rat specific response. Although the rat and human were recognized to possess the same enzyme(s) involved in production of the putative toxic species from alachlor, it was also recognized that the activity of these enzymes was substantially greater in the rat compared to the human. Thus, the model of rat nasal tumorigenesis may not be relevant for human cancer assessment. Thyroid tumors have been proposed to be the result of induction of hepatic glucuronyl transferase with subsequent decrease in circulating T3 and T4, a subsequent increase in TSH, and eventual hyperplastic response of the thyroid. The mechanistic data for thyroid tumor formation meet the criteria established by the Agency and the use of the MOE approach for human cancer assessment is consistent with Agency policy. The CPRC stated that the stomach tumor formation was a direct contact effect, non-genotoxic mechanism which parallels human pathological conditions. These tumors result from an indirect response to change in pH. The use of the MOE approach for human cancer assessment was consistent with Agency policy.

On October 30, 1996 the SAP met to consider the weight-of-evidence for alachlor. The SAP was asked to comment on mode of action data, provided by the registrant, for the tumor types in the rat associated with administration of alachlor.

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on February 05, 1997 to discuss and evaluate the weight-of-the-evidence on alachlor with particular

reference to its carcinogenic potential and to consider the comments from the FIFRA Scientific Advisory Panel (SAP).

The SAP and CPRC conclusions on the tumors induced by alachlor in the rat are summarized as follows:

Thyroid tumors: Both the SAP and the CPRC agreed that the Agency requirements for demonstrating a hormonal mode of action were met by the registrant and that the tumors were observed only at an excessive dose.

Stomach: The SAP stated: "Evidence was presented that the carcinomas resulting from alachlor were examined to prove that they were carcinoids, not adenocarcinomas or gastric sarcomas, which are unrelated to the proposed gastrin-induced effect". The CPRC felt that the evidence alluded to was based on the butachlor study and that the tumors in the alachlor study could be assumed to be carcinoids, by inference only. Although the tumor increases were significant only at the highest dose (excessive), it was noted that there was also 1 tumor (vs 0 in controls) at the mid-dose (which was considered to be adequate, not excessive) and this is a rare tumor type.

Nasal tumors: The SAP considered these possibly relevant to humans but only at exposures in excess of anticipated human exposures for pesticide use. The CPRC considered these tumors relevant to humans (with a quantitative difference). There also was 1 tumor at the mid-dose (not excessive) and this too is a rare tumor type.

In accordance with the EPA proposed Guidelines for Carcinogen Risk Assessment (April 23, 1996), alachlor was characterized as "likely" to be a human carcinogen at high doses, but "not likely" at low doses, by all routes of exposure. This conclusion was based on increased incidences of malignant and combined benign/malignant multiple tumor types in both sexes of the Long Evans rat, which occurred mainly at higher doses. Based on a consideration of modes of action for these tumors, the CPRC agreed that a non-linear margin of exposure (MOE) approach should be used for the purpose of risk assessment. The consensus of the CPRC was that MOEs for both the malignant mixed gastric tumors and the nasal adenomas be presented for a risk management decision.

The CPRC recognizes that while the response occurs only at higher doses and quantitative differences exist in sensitivity between rats and humans, a similar mechanism for nasal tumor production is present in humans, and therefore its relevance to humans cannot be dismissed. The SAP agrees with this position. The rarity of the nasal tumor type and SAR support also adds to the CPRC's concern. The presence of stomach tumors, which are also considered a rare tumor type, and the lack of a consistent histopathologic response, leads to the conclusion that some hazard potential may exist in humans after intense exposures. Clarification of the similarity or dissimilarity of the relevance of the rat stomach tumors could shed light on this uncertainty. The CPRC agrees that the rat stomach tumors are relevant to humans at this time. The CPRC agrees

with the SAP in that thyroid tumor induction may be relevant to humans, but that the tumors in rats were seen at an excessive dose.

Since these are considered rare tumor types, for purposes of risk assessment, the MOE for the nasal tumors should be determined with 0.5 mg/kg/day as the "point of departure" as no tumor response was seen at this dose level. Also, the MOE for the stomach tumors should be determined with 14 mg/kg/day as the "point of departure" as no tumor response was seen at this dose level. Both tumor types were present at the next highest tested dose level (females at 2.5 mg/kg/day in the 1983 rat study for nasal tumors; females at 42 mg/kg/day in the 1981 rat study for stomach tumors). While not statistically significant at these next higher dose levels, the Committee considered tumor presence biologically significant due to their rarity in rats.

(This entire section c. is new)

c. Report of the FQPA (Food Quality Protection Act) Safety Factor Committee

The Health Effects Division (HED) FQPA Safety Factor Committee met on March 30, 1998 to evaluate the hazard and exposure data for alachlor and recommend application of the FQPA Safety Factor (as required by FQPA), to ensure the protection of infants and children from exposure to this chemical. The Committee recommended that the 10x Safety Factor for enhanced sensitivity to infants and children (as required by FQPA) should be removed. This decision was based on the following:

1. HAZARD ASSESSMENT

(a). Determination of Susceptibility

There is no evidence of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to alachlor. In the prenatal developmental toxicity studies in rats and rabbits and the multi-generation reproduction study, effects in the offspring were not observed at levels which resulted in evidence of parental toxicity (*Memorandum:* S. Dapson to E. Zager, dated March 25, 1998).

(b). Adequacy of Database

There are **no data gaps** for the assessment of the effects of alachlor following *in utero* and/or postnatal exposure. Based on the toxicity profile for alachlor, a developmental neurotoxicity study in rats is not required.

ii. EXPOSURE ASSESSMENT

(a). Dietary Exposure Considerations

Alachlor tolerances are expressed in terms of "alachlor and its metabolites." The current enforcement method measures alachlor and its metabolites containing the DEA and HEEA moieties. There are several other classes of alachlor metabolites that are not included in the tolerance expression.

Alachlor is a herbicide, generally used pre- or early postemergence. Residues are systemic. Rotational crop tolerances are needed indicating that residues remain in the soil for at least a year after use. No maximum residue limits (MRLs) for alachlor have been established by Codex for any agricultural commodity. Therefore, no questions of compatibility exist with respect to U.S. tolerances.

The anticipated residues were provided for alachlor carcinogenic dietary exposure assessment. Anticipated residues for alachlor were based on the average residues found in field trials where alachlor was used at the maximum typical application rate and weighted for the percent of use at each application timing (i.e., preemergence vs. postemergence). Adequate information on percent of crop treated is available for all crops. Up to 35% of corn and lima beans are treated, and up to 15 % of soybeans. Lesser amounts of other crops are treated (e.g., <5% of peanuts). These percentages are down from 10 years ago (when 62% of peanuts were treated).

Monitoring data available from FDA are too limited to use for dietary exposure assessment since the analyses did not include the alachlor metabolites of concern.

Since the dietary exposure assessment is based on field trial data, the anticipated residues are likely to overestimate the dietary exposure because application rates and timing assumed in the dietary exposure analysis are conservative, and residues are likely to degrade after the farm gate where field trial samples are obtained.

Crops contributing most highly to the dietary exposure for both adults and children were legumes (beans and soybeans) and milk, followed by corn.

(b). Drinking Water Exposure Considerations

Estimates of alachlor concentrations in ground water are based on the National Alachlor Well Water Survey (NAWWS). These samples represent approximately 6 million wells from which approximately 20 million people draw their drinking water. Reported values are for alachlor per se. No degradates of alachlor were analyzed for in the NAWWS. NAWWS data are considered to be of high quality, and because of the statistical design of the survey, are also considered to be the best available data concerning alachlor residues per se in ground water.

Estimates of alachlor concentrations in surface water are also based on available monitoring data from several studies. No degradates of alachlor were analyzed in these studies.

Alachlor concentrations per se are reported as time weighted mean concentrations (TWMC) which reflect "amortization" of periods of high and low concentrations. Therefore, annual TWMCs (calculated using at least one year of sampling data) are the most appropriate values to use for estimation of chronic exposure to alachlor in drinking water.

The alachlor degradates are expected to be of lower toxicity than that of the parent. Considering that less than 3% of the RfD is occupied by water using high quality survey data for the parent, even if all of the degradates were present, it is not likely that the exposure estimates would more than double.

(c). Residential Exposure Considerations

Alachlor is a restricted use pesticide; and therefore, can only be used by certified applicators and cannot be purchased or used by the general public. HED has not identified any alachlor products that are intended for residential use.

iii. RISK CHARACTERIZATION

(a). Determination of the Factor

The Committee recommended that the **10x factor** for enhanced sensitivity to infants and children (as required by FQPA) should be **removed.**

(b). Rationale for Selection of the FQPA Factor

- There was no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to alachlor. In the prenatal developmental toxicity studies in rats and rabbits and the multi-generation reproduction study, effects in the offspring were not observed at levels which resulted in evidence of parental toxicity.
- The toxicology data base is complete. The toxicity profile does not indicate the need for a developmental neurotoxicity study.
- The use of generally high quality data together with conservative models in the exposure assessment provided adequate protection fo infants and children.
- Alachlor is not currently registered for any residential uses.

d. World Health Organization

Alachlor has not been reviewed by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR).

e. Toxicological Endpoints of Concern for Use in Human Risk Assessment

The toxicological effects of a pesticide can vary with different exposure durations. HED considers the entire toxicity data base, and based on the effects seen for different durations and routes of exposure, determines which risk assessments should be done to assure that the public is adequately protected from any pesticide exposure scenario. Both short and long durations of exposure are always considered. Typically, risk assessments include "acute", "short-term", "intermediate term", and "chronic" risks. These assessments are defined as follows:

Acute risk results from a one day or single event consumption of food and water, and reflects toxicity which could be expressed following oral exposure to the pesticide residues. High-end exposure to food and water residues are assumed.

Short-term risk results from exposure to the pesticide for a period of 1-7 days, and therefore overlaps with the acute risk assessment. Historically, this risk assessment was intended to address primarily dermal and inhalation exposure which could result, for example, from occupational pesticide applications. Since enaction of FQPA, this assessment has been expanded. The assessment will be performed when there are primary dermal and inhalation exposures that result from residential or occupational exposures lasting from 1-7 days. However, the analysis for residential exposures will now address both dietary and non-dietary sources of exposure, and will typically consider exposure from food, water, and residential uses when reliable data are available. In a short term assessment, risks from average food and water exposure, and high-end residential exposure, are aggregated. High-end exposures from all three sources are not typically added because of the very low probability of this occurring in most cases, and because the other assumptions built into the assessment assure adequate protection of public health.

Intermediate-term risk results from exposure for 7 days to several months. This assessment is handled in a manner similar to the short-term risk assessment.

Chronic risk assessment describes risk which could result from several months to a lifetime of exposure. For this assessment, risks are aggregated considering average exposure from all sources for representative population subgroups including infants and children.

HED's Toxicity Endpoint Selection Committee has met three times to select the appropriate endpoints for use in the alachlor risk assessment. The results of the latest meeting on May 14, 1996, are presented below.

Acute Dietary Assessment:

As part of the dose-response assessment, the Agency's toxicologists review the available database to determine the endpoints of concern. For alachlor, there is no concern for an acute dietary assessment since the available data do not indicate any evidence of significant toxicity from

a one day or single event exposure by the oral route. Therefore, this assessment for a one day high-end dietary exposure is not required.

Short Term (1 to 7 days) Occupational Exposure Assessment:

This assessment is required. The NOEL to be used for calculating the MOE (Margin of Exposure) is 150 mg/kg/day from a developmental study (MRID No. 00043645). (The LOEL was 400 mg/kg/day based on maternal hair loss, soft stools, anogenital staining, increased mortality, increased post-implantation loss and a reduced number of live fetuses.) Since the selected NOEL is from a gavage study, the exposure will need to be adjusted by the dermal absorption factor. Since the selected NOEL is from a developmental study, the appropriate population subgroup is females 13+.

For all occupational scenarios, HED has no concerns for an MOE in excess of 100 for non-cancer effects when the NOEL used in calculating the MOE is from an animal study.

Intermediate (1 week to several months) Occupational Exposure Assessment:

This assessment is required. The NOEL to be used for calculating the MOE is 50 mg/kg/day from a 21-day dermal toxicity study (MRID No. 00147328). (The LOEL was 300 mg/kg/day based on mortality, and hematological and clinical chemistry.) Since the selected NOEL is from a dermal study, the dermal exposure will not need to be adjusted by the dermal absorption factor. The selected NOEL is from a dermal study; therefore, it could be considered inappropriate to use the total dose (combined dermal and inhalation exposure) in the MOE calculation. However, in the case of alachlor, the inhalation component is insignificant when compared to the dermal, so the combined total is essentially a dermal exposure.

For all occupational scenarios, HED has no concerns for an MOE in excess of 100 for non-cancer effects when the NOEL used in calculating the MOE is from an animal study.

Chronic (several months to lifetime) Occupational Exposure Assessment:

As part of the hazard assessment process an endpoint of concern was determined for the chronic occupational assessment. However, during the exposure assessment process, the exposures which would result from the use of alachlor were determined to be of an intermittent nature. The frequency and duration of these exposures do not exhibit a chronic exposure pattern. The exposures do not occur often enough to be considered a chronic exposure, i.e. a continuous exposure that occurs for at least several months. Therefore, performing a chronic occupational assessment is not appropriate.

If a chronic scenario can be identified, then this assessment is required,. The NOEL to be used for calculating the MOE is 1 mg/kg/day from a 1-year dog study (MRID No. 00148923). (The LOEL is 3 mg/kg/day based upon signs of hemosiderosis and hemolytic anemia.) Since the

selected NOEL is from an oral (capsules) study, the exposure will need to be adjusted by the dermal exposure factor.

For all occupational scenarios, HED has no concerns for an MOE in excess of 100 for non-cancer effects when the NOEL used in calculating the MOE is from an animal study.

Residential

Alachlor is a restricted use pesticide; therefore, alachlor can be used only by certified applicators and cannot be purchased or used by the general public. HED has not identified any alachlor products that are intended for home use, or uses in/around schools, parks, or other public areas. Therefore, residential assessments are not appropriate.

Inhalation

For alachlor, inhalation exposure is not considered to be a concern based on the LC_{50} of > 1.04 mg/L, since this is acute toxicity category IV. Therefore, a separate risk assessment for inhalation exposure will not be performed.

Percent Dermal Absorption:

A dermal absorption factor of 24% as determined from the three rhesus monkey studies (Acc# 256624 Parts C, D, E, and F) will be used to adjust dermal exposures when compared to a NOEL from an oral study.

Chronic Dietary:

The RfD is the traditionally selected endpoint for chronic dietary risk. As previously discussed, the RfD for alachlor was determined to be 0.01 mg/kg/day. The aggregate dietary assessment will consider both food and water. As previously stated, there is no chronic residential assessment to aggregate with the chronic dietary assessment.

Carcinogenic:

CPRC recommended not to use the linear low dose approach, but to utilize the MOE methodology for estimation of human risk. The MOE methodology is consistent with a threshold mechanism which requires continuous exposure. Thus, the likelihood of a positive carcinogenic response depends on the duration of the exposure as well as the magnitude of the exposure.

It is not appropriate to calculate a carcinogenic MOE for the occupational scenario, as there are no chronic exposure scenarios for the application of alachlor. Calculation of a carcinogenic MOE for agricultural workers based on intermittent exposure is not appropriate. However, this carcinogenic assessment is required for the dietary and/or drinking water scenario. It is likely that

individuals will consume alachlor residues throughout their lifetime in the food and water consumed.

The MOE for the nasal tumor should be determined with 0.5 mg/kg/day as the "point of departure" as no tumor response was seen at this dose level. The MOE for the stomach tumors should be determined with 14 mg/kg/day as the "point of departure" as no tumor response was seen at this dose level

3. DIETARY EXPOSURE AND RISK ASSESSMENT/CHARACTERIZATION

a. DIETARY EXPOSURE from FOOD SOURCES

The residue chemistry database includes information on the pesticide residues found in plants and animals, the levels of the detected pesticide residues, and a description of the analytical methods used. Residue chemistry data are used by HED to determine the residues of concern and to establish tolerances in food and feed. Tolerances are pesticide residue levels that should not be exceeded in or on a raw agricultural commodity in the channels of interstate commerce when the pesticide is applied according to label directions. Tolerances for residues of alachlor in/on raw plant commodities, and in animal commodities are currently expressed in terms of the combined residues of alachlor and its metabolites (calculated as alachlor) (40 CFR §180.249). These tolerances are set at 0.02-3.0 ppm. No food/feed additive tolerances have been established for alachlor residues of concern.

The residue chemistry database for alachlor is adequate and will support reregistration eligibility, provided the necessary label changes are made.

(I). GLN 860.1200: Directions for Use:

A REFS search conducted 7/7/97 indicated that there are 11 alachlor end-use product labels registered to American Cyanamid Company and Monsanto Company. The following alachlor formulations are registered.

Company/EPA Reg. No.	Label Date	Formulation	Product Name
American Cyanamid Company			
241-311	5/89	3 lb/gal EC	Ala-Scept Herbicide
241-329	2/90	3 lb/gal EC	Ala-Scept® Herbicide
Monsanto Company			
524-296	6/96	15% G	Lasso II Granular Herbicide
524-314	10/96	4 lb/gal EC	Lasso® Herbicide
524-329	3/97	2.5 lb/gal FlC	Lariat®
524-341	12/93	2.6 lb/gal EC	Bronco® Herbicide
524-344	10/96	4 lb/gal Mcap	Micro-Tech®
524-403	4/96	65% DF/Mcap	Partner® WDG Herbicide

524-418	12/96	2.5 lb/gal FlC	Bullet® Herbicide
524-422	5/97	2.67 lb/gal EC	Freedom® Herbicide

DF	Dry flowable
EC	Emulsifiable concentrate
G	Granular
FlC	Flowable concentrate
Mcap	Microencapsulated
WDG	Water Dispersable Granules

There was also a Special Local Need (SLN) registration for use on sorghum reported in REFS on 7/9/97: SLN No. OK93000600 (Parent Reg. No. 524-296).

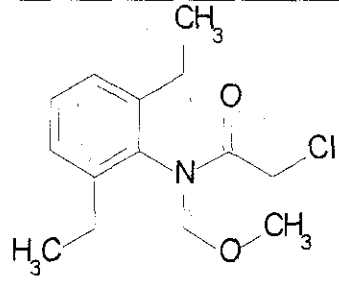
(ii). GLN 860.1300: Nature of the Residue - Plants

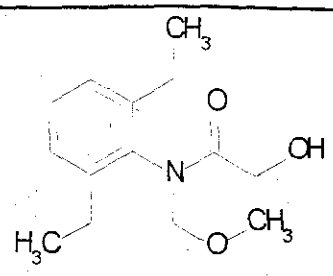
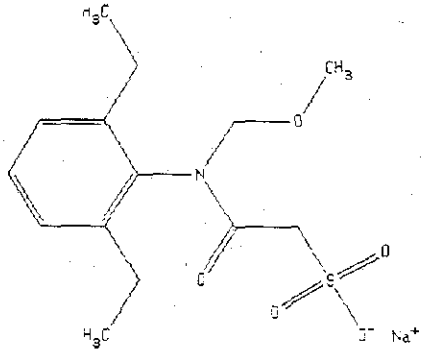
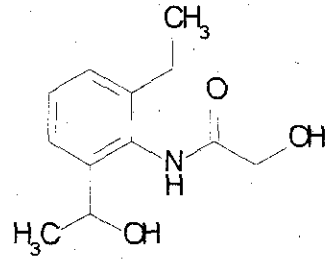
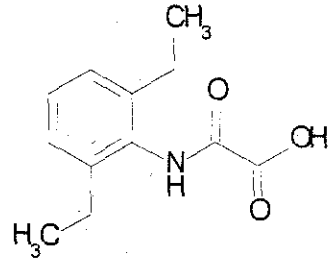
The qualitative nature of the residue in plants is adequately understood. Studies with corn and soybeans indicate that alachlor is readily absorbed from soils and translocated throughout the plant. Very little alachlor is translocated from the foliage. Metabolism involves the displacement of chlorine by oxygen or sulfur nucleophiles, hydroxylation at the 1- position of the ethyl group, and conjugation of the metabolites endogeneous cellular component. The terminal residues to be regulated are those metabolites which can be hydrolyzed under basic conditions to 2,6-diethylaniline (DEA) and 2-ethyl-6-(1-hydroxyethyl)aniline (1-HEEA). (MRID No. 00026221, 00081314, 00131424).

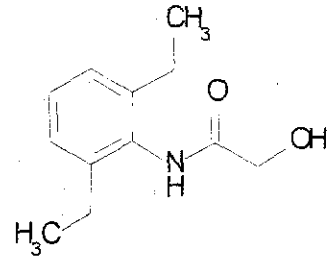
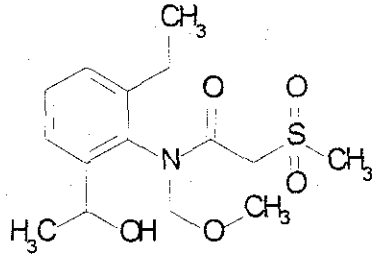
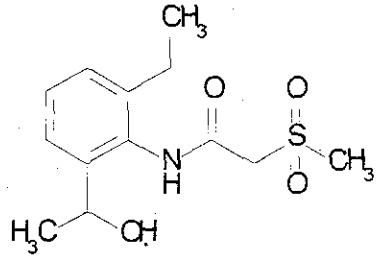
ESA was identified as one of many alachlor degradates present in these crops. Since ESA is converted to diethylaniline (DEA) by the alachlor crop residue methodology, it has been quantified in the crop residue analyses conducted for alachlor and is therefore included in the existing crop tolerances listed at 40 CFR § 180.249.

The chemical structures of representative metabolites are presented in Figure A.

Figure A. The Chemical Structures of Representative Metabolites of Concern of Alachlor.

Common Name Chemical Name	Chemical Structure
alachlor 2-chloro-2',6'-diethyl-N-(methoxy-methyl)acetanilide	

Common Name Chemical Name	Chemical Structure
alcohol metabolite (A-23) N-[(2,6-diethyl)phenyl]-N-methoxymethyl-2-hydroxyacetamide	
ESA metabolite MON 5775, 2',6'-diethyl-N-methoxymethyl-2-sulfoacetanilide, sodium salt or 2-[2,6-diethylphenyl (methoxymethyl) amino]-2-oxoethane sulfonic acid, sodium salt.	 Alachlor ESA
A-11 N-{[2-ethyl-6-(1-hydroxyethyl)]phenyl}-2-hydroxyacetamide	
A-18 N-[(2,6-diethyl)phenyl]oxanilic acid	

Common Name Chemical Name	Chemical Structure
A-20/AP-7 N-[(2,6-diethyl)phenyl]-2-hydroxyacetamide	
sulfone metabolite (S-24) N-{[2-ethyl-6-(1-hydroxyethyl)phenyl}-N-methoxymethyl-2-(methyl-sulfone)acetamide	
S-16 N-{[2-ethyl-6-(1-hydroxyethyl)]phenyl}-2-(methyl-sulfone)acetamide	

(iii). GLN 860.1300: Nature of the Residue - Livestock

The qualitative nature of the residue in animals is adequately understood. Studies involving lactating goats and laying hens fed an alachlor alcohol or sulfone metabolite indicate that metabolism of alachlor in hens and ruminants is similar. After displacement of chlorine, metabolites undergo loss of the methoxymethyl group, hydroxylation of the ethyl side-chain(s) usually at the 1- position, and formation of glucuronide conjugates. (MRID No. 00137777, 00137778, 00147472, 00147473, 40393901, 40394001, 42594901, 42594902, 42594903, 42594904)

It should be noted that alachlor's ESA metabolite has not been identified as a mammalian metabolite of alachlor. (MRID No.s 00132045, 42852107, 42931101, 42852106, 00154238, 40000901). The initial chlorine displacement step involving glutathione catalyzed by glutathione

transferase has been firmly established in these mammals. Methylsulfone and sulfur-conjugated organic acids have been shown to arise from further metabolic conversion of the glutathione adduct in rats and monkeys. Although the initial metabolism of alachlor in mammals is oxidative conversion of the sulfur atom, the metabolic product is not alachlor ESA.

Livestock metabolism studies which included alachlor ESA as one of the dosed components were performed (MRID No. 00147472, 00147473). Results from these experiments demonstrated that alachlor ESA was excreted by the animals unchanged, largely via the feces (goats). It did not accumulate in edible tissues.

The residues to be regulated are those metabolites which can be hydrolyzed under basic conditions to 2,6-diethylaniline (DEA) and 2-ethyl-6-(1-hydroxyethyl)aniline (1-HEEA). See Figure A.

(iv). GLN 860.1340: Residue Analytical Methods

Three GLC methods, Methods I(a), I(b), and II, are currently available in the Pesticide Analytical Manual (PAM) Vol. II for the enforcement of tolerances for alachlor residues of concern; however, these methods do not recover 1-HEEA-yielding metabolites. An HPLC method, which determines DEA- and 1-HEEA-yielding metabolites has been validated by the Agency and is considered acceptable for enforcement purposes for plant commodities. The method uses HPLC with oxidative coulometric electrochemical detection of both DEA- and 1-HEEA-producing residues, and was recommended for inclusion in PAM Vol. II as Method III; the limit of detection is 0.01 ppm for each metabolite class. (MRIDs 00023663, 00093160, 00148285, 00149999, 00152197, 00154237, 00154332, 00155732, 00159793, 00159796, 00162939, 40039901, 40040301, 40040401, 40271801, 40271802, 40529201, 40558001, 40820601, 41916001, 42086001, 42192501, 42286701, 42286702, 42308701, 42349101, 43140001, and PP#9F0740)

(v). GLN 860.1360: Multiresidue Methods

The FDA Pestrak database (PAM Vol. I, Appendix II, dated 11/90) indicates that alachlor, per se, is completely recovered through Multiresidue Protocols D and E. In addition, multiresidue protocol testing of five alachlor metabolites has been submitted and forwarded to FDA (MRID No. 41949601).

(vi). GLN 860.1380: Storage Stability Data:

Adequate storage stability data are available for corn, peanuts, soybeans and their processed commodities, for sorghum, and for animal commodities. Residues of alachlor metabolites are stable during frozen storage (< -18 °C) in/on corn forage and fodder, sorghum grain, forage, and fodder, and soybeans for up to 1394 days. Residues of alachlor metabolites are

stable during frozen storage in/on sunflower seeds for up to 280 days and in the processed commodities of sunflowers for up to 91 days. These storage stability data can be translated to all crops for which alachlor is currently registered. (MRID No. 00149406, 00150090, 00152198, 00152868, 00154237, 40491101, 40628301, 40946901, and 42239501)

(vii). GLN 860.1500: Crop Field Trials

The conclusions regarding the reregistration eligibility of alachlor are based on the use patterns registered by the basic producer, Monsanto Corporation.

Some of the data used in support of existing or proposed tolerances were generated at Craven Laboratories. The Agency determined that it would not rely on Craven data for regulatory decisions, and identified the data that would not to be replaced. (Memo, 1/28/92 M. Metzger) However, replacement of the Craven generated magnitude of the residue data were not required for soybeans, provided postemergence and sequential uses on soybeans were removed from all alachlor labels. At this time all Craven data for corn and peanuts have been replaced or the label modified to remove the use.

Data for magnitude of the residue in sorghum grain, forage, and fodder have been evaluated and deemed adequate. Data are available to support the G formulation of alachlor on sweet corn applied preplant incorporated and preemergence at up to 4 lb ai/A. Data are available to support the use of the Mcap/G formulation on sweet corn: preemergence and preplant incorporated and postemergence at 4 lb ai/A. Data have been submitted to support use of the Mcap formulation on corn at 4 lb ai/A preemergence followed by 2 lb/A early postemergence (before the corn is 5" high). Data have been submitted to support use of the EC or Mcap fomulation of alachlor on corn at up to 6 lb ai/A applied preemergence or preplant incorporated. (Note that labels must be consistent with the use patterns for which data were submitted.)

Additional field residue data (or the uses can be removed from the labels) are required for beans (dry and succulent), to support pre-emergence uses; for field corn grain, forage, and stover, to support sequential uses of the EC formulation; for sweet corn (K+CWHR) and sweet corn forage and stover to support postemergence and sequential uses of the EC formulation and uses in excess of 4 lb ai/A/season; and for peanuts to support postemergence and sequential uses. Monsanto has elected to delete the postemergent uses on field corn from the EC labels rather than generate additional residue data at this time. (Letter Monsanto May 20, 1996)

The proposed tolerances for soybeans and soybean aspirated grain fractions must be revised; higher tolerances are required. Tolerance petitions for bean vines and hay, corn forage and fodder, peanuts, peanut hulls, and sorghum forage are pending. (MRID No. 00022988, 00023664, 00023665, 00024526, 00025262, 00026995, 00028556, 00028557, 00028558, 00035389, 00035390, 00035391, 00035395, 00035399, 00068044, 00068045, 00081311, 00147475, 00148285, 00152197, 00152199, 00155732, 00159793, 00159796, 00159936, 41083801, 40039901, 40040301, 40189701, 40271801, 40341201, 40502101, 40511201,

40511301, 40511901, 40662601, 40820601, 41083801, 41862901, 41916301, 42309001, 42313301, 42348901, 42348902, 42349101, 42741601, 42741601, 42929901, 42971701)

Feeding restrictions have been established for peanut vines and hay, and soybean forage and hay; therefore, the established tolerances for these commodities should be revoked.

(viii). GLN 860.1520: Processed Food/Feed:

No food or feed additive tolerances for alachlor are needed on any processed product of any commodity for which alachlor is currently registered. However, all data submitted for magnitude of the residue in processed food/feed have been evaluated and deemed adequate.(MRID No. 00148285, 00152197, 00154239, 00154240, 00162937, 00162939, 40040401, 40271802, 40788201, 40947101, 41856301, 41862901, 41916301, 42302001, and PP#0F2313)

Reduction of residue data were submitted for dry beans and peanuts as required by a Special Review DCI. Residues were determined in canned beans, peanut butter, dry and oil roasted peanuts following commercial processing. A processing factor of 0.2x was determined for canning beans. Processing factors of 0.70x, 0.75x, and 0.83x were determined for peanut butter, dry roasted peanuts, and oil roasted peanuts, respectively. These factors will be used for the determination of anticipated residues for alachlor.

Limited monitoring studies were submitted for peanut butter and infant soy formula. Three major brands of peanut butter were collected in major cities across the US in 1989 in 2 studies. Of the 192 samples collected, 89% had detectable residues of alachlor metabolites. The average residue found was 0.029 ppm alachlor equivalents (with no correction for percent crop treated). In another study, several samples of 2 major brands of soy formula were collected in 9 major cities across the US. No detectable residues of alachlor DEA or HEEA metabolites were found (LOD=0.01 ppm) in any of the 1398 samples. (MRID No. 40330301, 40820601, 40820701, 42158601, 42276701, 42309001).

(ix). GLN 860.1480: Meat, Milk, Poultry and Eggs:

Data for magnitude of the residue in meat, milk, poultry, and eggs have been evaluated previously; however, the adequacy of the data could not be assessed because at that time the qualitative nature of the residue in animals was not adequately understood. These data were generated from feeding studies in which dairy cattle and poultry were dosed with of a mixture of DEA- and 1-HEEA-yielding metabolites (60% DEA-yielding and 40% 1-HEEA-yielding metabolites) at approximately 4, 12, and 40 ppm. Tissues, milk, and eggs were analyzed for residues of DEA- and 1-HEEA-yielding metabolites and residues were expressed as alachlor equivalents. The maximum residues of DEA-yielding metabolites were 0.9 ppb in milk, 1.0 ppb in fat, 6.2 ppb in kidney, 3.6 ppb in liver, and 0.8 ppb in muscle, and the maximum residues of 1-HEEA-yielding metabolites were 1.6 ppb in milk, 1.5 ppb in fat, 5.4 ppb in kidney, 6.8 ppb in liver, and 1.1 ppb in muscle of dairy cattle fed at approximately 12 ppm (1.7x the maximum

expected dietary burden). The maximum residues of DEA-yielding metabolites were 1.0 ppb in eggs, <0.5 ppb (nondetectable) in fat, 1.0 ppb in kidney, 1.1 ppb in liver, and <0.5 ppb in muscle, and the maximum residues of 1-HEEA-yielding metabolites were 7.8 ppb in eggs, <0.5 ppb in fat, <1.0 ppb (nondetectable) in kidney, <1.0 ppb in liver, and 0.5 ppb in muscle of poultry fed at 4 ppm (approximately 2x the maximum expected dietary burden) (MRID No. 00149406, 00150090, 00152198, and 00152868).

These results support the established tolerances of 0.02 ppm for eggs; milk; and the fat, meat, and meat byproducts of cattle, goats, hogs, horses, poultry and sheep. The maximum expected dietary burdens of alachlor residues for cattle and poultry are calculated below; soybean forage and hay, and peanut vines and hay were not included in this calculation since feeding restrictions have been established for these commodities and tolerance revocations have been recommended.

TABLE 5: Calculated Dietary Burdens

Commodity	Percent in Diet	Percent Dry Matter	Tolerance[1]	ppm (in diet)
Cattle:				
Field corn grain	30	0.88	0.2	0.07
Bean vines	25	0.35	5	3.6
Soybean hulls	25	0.90	5	1.4
Soybean grain dust	20	0.85	10	2.4
Dietary Burden				Total = 7.5
Poultry:				
Soybeans	50	--	1	0.5
Soybean meal	20	--	1	0.2
Soybean grain dust	20	--	10	1.0
Corn Grain	10	--	0.2	0.02
Dietary Burden				Total = 1.8

1. In cases where tolerance proposals are required or pending, appropriate tolerance levels from the Tolerance Reassessment Summary were used.

(x). GLN 860.1400: Water, Fish, and Irrigated Crops

Alachlor is not registered for direct use of water and aquatic food and feed crops; therefore, no residue chemistry data are required under this guideline topic.

(xi). GLN 860.1460: Food Handling

Alachlor is not registered for use in food-handling establishments; therefore, no residue chemistry data are required under this guideline topic.

NAWWS to estimate the proportions of private, rural domestic wells with detectable concentrations of alachlor. NAWWS was a complex, statistically designed survey of alachlor occurrences which was targeted to counties where alachlor was used in 1986. These samples represent approximately 6 million wells from which approximately 20 million people draw their drinking water.

Water samples were collected from 1,430 wells beginning in July 1988, and continuing through May 1989. The samples were analyzed by GC/MS (gas chromatography using a mass selective detector) in SIM (selected ion monitoring) mode. The limit of detection (LOD) for alachlor was 0.03 ppb.

Reported values are for alachlor per se. No degradates of alachlor were analyzed for in the NAWWS. All "Non-detects" (values reported as ND) were averaged in (with the detected residues) using ½ of the LOD, or 0.015 ppb. This is a standard procedure for dealing with the analytical limits of detection for chemical residues.

NAWWS data (Table 6) are considered to be of high quality, and because of the statistical design of the survey are also considered to be the best available data concerning alachlor per se residues in ground water and the population exposed to those residues.

TABLE 6:

Alachlor Residue Level in Ground Water	Estimated Population Exposed	Percentage Population Exposed
0.015 ppb (NDs are ½ the LOD)	19,603,040	99.5 %
< 0.2 ppb	63,249	0.32
>=0.2 ppb	35,647	0.18
> 2 ppb	3,000	0.015

TOTAL: 19,704,936

The approximate proportion of the population in the alachlor use area exposed to the various levels of alachlor in ground water is estimated above, using the data from the NAWWS. Approximately 19,704,936 people received ground water from wells included in the survey area.

(ii). Surface Water

The Agency's Office of Water has provided data indicating that approximately 29 million people rely on surface water for their drinking water in the 11 major corn-producing states.

(xii). GLNs 860.1850: Confined Accumulation in Rotational Crops:

All data for confined rotational crops have been evaluated and deemed adequate (MRID No. 42395301 and 42395302). Alachlor residues were found to accumulate in all three rotational crops tested. Radishes, lettuce, and wheat were planted 31, 91, 120, or 365 days following the second of two applications of uniformly ring-labeled [^{14}C]-alachlor to sandy loan soil at 4 and 2 lb ai/acre (total 6 lb ai/A). Alachlor per se was not detected in the plants. The major classes of alachlor metabolites found were those containing the DEA and 1-HEEA moities.

(xiii). GLNs 860.1900: Field Accumulation in Rotational Crops:

Limited field rotational crop studies have been submitted (MRID No. 43442001). Soybeans and wheat were planted at various plant-back intervals following preemergence application at 4 lb ai/A (1x) and postemergence application at 2 lb ai/A (1x) of a representative 4 lb/gal Mcap formulation to corn. The data indicate that residues of alachlor and its metabolites containing the DEA and HEEA moieties exceed 0.01 ppm (the LOQ) in/on many raw agricultural commodities of soybeans and wheat. Because quantifiable alachlor residues are present in/on rotational crops, rotational crop tolerances need to be established, or the labels may be changed to prohibit rotation to any crop not specified on the label.

Soybeans and wheat can represent legume vegetables and cereal grains. Therefore, data pertaining to field rotational crop studies are still required for a root crop and a leafy crop. Monsanto plans to support cereal grains (except rice), non-grass animal feeds, cotton, and sunflowers as rotational crops. Rotational crop tolerances for cotton and sunflowers should be proposed.

b. DIETARY EXPOSURE from DRINKING WATER

Alachlor is regulated under the SDWA (Safe Drinking Water Act). The MCL (Maximum Contaminant Level) for alachlor is 2 ppb. An MCL is the maximum permissible level of a contaminant in drinking water which is delivered to any user of a public water supply system. Water systems are required to test for regulated chemicals on a quarterly basis. Cost and the availability of treatment technologies are also considered in promulgating an MCL.

The available information is inadequate to assess exposure to alachlor and its metabolites on a national level. A national statistically representative database on detections of alachlor *per se* and/or metabolites does not exist. However, sufficient information is available on regional detections of alachlor which can be used to extrapolate the following conclusions/generalizations.

(I). Ground Water

Estimates of alachlor concentrations in well or ground water were prepared by the Environmental Fate and Effects Division (EFED; memo 11/1/94 Elizabeth Behl). These values are based on the National Alachlor Well Water Survey (NAWWS). Monsanto conducted

Estimates of alachlor concentrations in surface water were prepared by the Environmental Fate and Effects Division (EFED: memo 5/24/96 R. D. Jones; memo 1/25/93 H. Nelson; Surface Water Assessment of Alachlor 5/28/96).

Alachlor can contaminate surface water at application via spray drift or for several weeks postapplication due to run-off. Alachlor surface water concentrations tend to peak in May to early June during the first runoff events following application with rapid decline to approximately pre-application levels by July or August. Concentration of alachlor in surface water depends on numerous factors including the quantity of alachlor used on the drainage area upstream, the infiltration characteristics of the drainage area soils, and the timing, numbers and intensities of post-application runoff events.

No degradates of alachlor were analyzed in these studies. Alachlor per se concentrations are reported as time weighted mean concentrations (TWMCs) which reflect "amortization" of periods of high concentration and of low concentration. Annual TWMCs (calculated using at least a year's worth of sampling data) are the most appropriate values to use for estimation of chronic exposure to alachlor in drinking water because TWMCs compensate for times of high and low contamination which occur during the year.

Lauer et. al. (1986) Study

In this study samples of the raw and finished water of 24 community water systems (CWSs) in Missouri (3), Ohio (4), Illinois (6), Iowa (3), North Carolina (3), Indiana (6), and Michigan (2) were analyzed. Samples were collected daily from April 1985 to January or February 1986. Daily samples collected on 7 consecutive days were time composited for analysis. The LOD was 0.2 ppb. All "Non-detects" (values reported as ND) were averaged in (with the detected residues) using the LOD. Concentrations of alachlor on raw and the corresponding finished (treated) waters were almost identical at all locations. This is not unexpected since conventional water treatment facilities do not significantly reduce the amount of alachlor in the finished water. The TWMC for the samples from this study was 0.25 ppb.

Smith et. al. (1987) Study

In this study sampling was conducted of the finished water of 30 community water systems (CWSs) in Wisconsin (1), Ohio (8), Illinois (5), Iowa (3), Virginia (2), Missouri (3), Kansas (6), Indiana (1), and Tennessee (1). The CWSs selected represented various combinations of low to high alachlor use areas and low to high susceptibility to run off. Source types included small creeks, rivers, large man-made impoundments, and small to large lakes. Additionally, the CWSs sampled were different from those of the Lauer study. Samples were collected daily from April 1986 to August or September 1986. Daily samples collected on seven consecutive days were time composited for analyses. The LOD was 0.2 ppb. All "Non-detects" (values reported as ND) were averaged in (with the detected residues) using the LOD. The TWMC for the samples from this study was 0.36 ppb.

Moyer and Cross (1986-1988)

Samples were collected from a 30 station subnetwork of the 208 station Illinois Ambient Water Quality Monitoring Network. Twenty-six of the 30 reportedly received drainage from agricultural water sheds. The other four stations drained non-agricultural areas; and therefore, served as controls. Cross sectional composite samples were collected at each location twice in the spring, twice in the summer, and once in the winter from October 1985 to October 1988. The LOD was 0.02 ppb. All "Non-detects" (values reported as ND) were averaged in (with the detected residues) using the LOD. The TWMC for the samples from this study was 0.18 ppb.

USGS Reservoir Study (1992-1993)

In 1992 and 1993, USGS sampled 76 midwestern reservoirs. Each reservoir was sampled 4 times each year. The samples were analyzed for both alachlor and alachlor ESA. The LOD for alachlor was 0.05 ppb. The LOD for alachlor ESA was 0.03 ppb. The TWMC for the 2 year period (90th percentile) for ESA was 3.00 ppb and for alachlor was 0.22 ppb.

This section has been revised

Acetochlor Registration Partnership Data (1995-1996)

This is the most recent as well as the most extensive data on alachlor concentrations in surface waters available to the Office of Pesticide Programs. Samples were collected at 179 sites in 12 states (Delaware, Illinois, Indiana, Iowa, Kansas, Maryland, Minnesota, Missouri, Nebraska, Ohio, Pennsylvania, and Wisconsin) once every two weeks from April through September for both 1995 and 1996. All of the data was collected at drinking water treatment facilities and is therefore finished (treated) water. Two to three additional samples were collected at each site, one or two in the fall and the other in the winter. Unfiltered samples were analyzed for alachlor using GC/MS. The LOD for the study was 0.02 ppb.

The TWMC for the 2 year period was 0.1 ppb, [90th percentile (upper 10th percentile) the value equaled exceeded at 10% of the sites].

(iii). Exposure Estimates

Adult Female

The exposure estimate for an adult female (13+ years) is calculated by the following equation:

Exposure = (chemical concentration in μg/L in consumed water) X (10^{-3} mg/μg) ÷ (60 kg body weight) X (2L water consumed/day)

The 2 Liters of water is a default assumption used by the Office of Water. The 60 kilograms is the Agency's default female body weight.

Adult Male

The exposure estimate for an adult male is calculated by the following equation:

Exposure = (chemical concentration in μg/L in consumed water) X (10^{-3} mg/μg) ÷ (70 kg body weight) X (2L water consumed/day)

The 2 Liters of water is a default assumption used by the Office of Water. The 70 kilograms is the Agency's default male body weight.

Child (1 - 6 years)

The exposure estimate for a child (1- 6 years) is calculated by the following equation:

Exposure = (chemical concentration in μg/L in consumed water) X (10^{-3} mg/μg) ÷ (10 kg body weight) X (1L water consumed/day)

The 1 Liter of water is a default assumption used by the Office of Water. The 10 kilograms is an assumption per memo of D. Edwards.

The other assumption used is assuming that water from the same source containing the same contaminant level is consumed throughout a 70 year lifetime. Most of the US population moves at some time during their life and does not live in the same area, drinking from the same water source for a 70 year lifetime. It could be considered as either an over-estimation or an under-estimation of risk depending on the contaminant levels in the other sources of drinking water.

Information on detections of the ESA metabolite of alachlor was available for only one study - the USGS Reservoir Study. Thus, for all other studies the exposure values should be considered as under-estimated. The alachlor ESA metabolite has been detected in midwestern reservoirs and streams at concentrations and frequencies that greatly exceed that of alachlor detections.

TABLE 7A: Drinking Water Exposure Estimates - Adult Male

STUDY	Concentration (ppb)	Exposure (mg/kg/day)
MCL	2	0.0000571
Surface Water		
Smith et. al. (1987)	0.36	0.0000102
Lauer et. al. (1986)	0.25	0.0000071
Moyer & Cross, (1986-1988)	0.18	0.0000051
USGS - Alachlor	0.22	0.0000062

USGS - Alachlor ESA	3.00	0.0000857
Acetochlor Data, (1995-1996)	0.1	0.0000028
Ground Water		
NAWWS	0.2	0.0000057
NAWWS (99.5% population)	0.015	0.0000004

TABLE 7B: Drinking Water Exposure Estimates - Adult Female

STUDY	Concentration (ppb)	Exposure (mg/kg/day)
MCL	2	0.0000666
Surface Water		
Smith et. al. (1987)	0.36	0.000012
Lauer et. al. (1986)	0.25	0.0000083
Moyer & Cross, (1986-1988)	0.18	0.000006
USGS - Alachlor	0.22	0.0000073
USGS - Alachlor ESA	3.00	0.0001
Acetochlor Data, (1995-1996) .	0.1	0.0000033
Ground Water		
NAWWS	0.2	0.0000066
NAWWS (99.5% population)	0.015	0.0000005

TABLE 7C: Drinking Water Exposure Estimates - Child (1-6 years)

STUDY	Concentration (ppb)	Exposure (mg/kg/day)
MCL	2	0.0002
Surface Water		
Smith et. al. (1987)	0.36	0.000036
Lauer et. al. (1986)	0.25	0.000025
Moyer & Cross, (1986-1988)	0.18	0.000018
USGS - Alachlor	0.22	0.000022
USGS - Alachlor ESA	3.00	0.0003

Acetochlor Data, (1995-1996)	0.1	0.00001
Ground Water		
NAWWS	0.2	0.00002
NAWWS (99.5% population)	0.015	0.0000015

c. Dietary Risk Assessment and Characterization

As previously stated, an acute dietary risk assessment is not required. The RfD of 0.01 mg/kg/day will be used for calculating chronic dietary risk. For calculating carcinogenic dietary risk two NOELs (14 mg/kg/day for stomach tumors and 5 mg/kg/day for nasal tumors) will be used.

The tolerances used in this analysis are listed in Table 20: Tolerance Reassessment. The registrant has expressed interest in supporting rotational crop tolerances for cotton and sunflowers. For this reason these uses were included in the assessment at the tolerance levels that were recently revoked. Until residue data supporting the establishment of rotational crop tolerances are submitted to the Agency it remains unclear how appropriate these tolerances levels are for risk assessment, but it is unlikely that expected residues from crop rotation would be higher than the previously existing tolerances reflecting direct agricultural use.

The consumption information used in this analysis is derived from USDA's 1977-78 Nationwide Food Consumption Survey (NFCS). Over 30,000 respondents were surveyed over three days as to what foods they ate, with each individual's consumption information being associated with their body weight, sex, age, ethnicity and other sociodemographic information. Individual consumption estimates were weighted to be nationally representative. From these data single day and 3 day average consumption estimates were derived for the U.S. population and select population subgroups. Three day average information is used in the DRES chronic exposure analyses.

HED acknowledges that the data from this survey are nearly 20 years old. However, at this time, the data are the best information available to the Agency. USDA did conduct another NFCS in 1987-1988. However, the representativeness of these consumption data were called into question per a GAO Report due to the low response rate of certain groups. Therefore, the data are not used for routine risk assessment purposes. Another survey was conducted in 1989-1991. These data are currently undergoing translation, which involves taking the consumed foods such as apple pie; breaking this into raw agricultural commodities such as sugar, apples, and flour; and then using standard recipes to reaggregate the amounts of sugar, apples and flour with all of the other foods consumed.

(I). High End Chronic Dietary (Food Source) Risk

The DRES chronic exposure analysis assumes tolerance level residues and one hundred percent crop treated to calculate the Theoretical Maximum Residue Contribution (TMRC) for the overall U.S. population and 22 population subgroups. Selected subgroups are reported in Table 8.

Table 8:

Subgroup	Exposure(mg/kg/day)	%Reference Dose
U.S. population	0.000756	8
Non-nursing Infants (< 1 year)	0.003258	33
Children (1-6)	0.001744	17
Children (7-12)	0.001221	12

All other population subgroups were less than 10 % of the RfD.

(ii). Refined Chronic Dietary (Food Source) Risk

The Dietary Exposure Assessment was refined using anticipated residues (ARs) and percent crop treated (%CT) to give a refined, i.e. more realistic, dietary assessment.

Calculation of Anticipated Residues

Existing FDA monitoring data were not used in calculating alachlor ARs because the data were considered to be of limited usefulness for dietary risk assessment. FDA found no detectable residues of alachlor, per se, in 53600 samples, but the analyses did not include any of the alachlor metabolites of concern.

These anticipated residues were based on the average residue found in field trials where alachlor was used at the maximum application rate. Additionally a weighting factor was used for the percent of use at each application timing (i.e., preemergence vs. postemergence). For example, 90% of corn is typically treated preemergence at 4 lb ai/A or less with less than 10% treated postemergence (including sequential applications). Results of processing studies were also used to adjust the residue levels found in the raw commodity to account for changes in residue levels due to processing (both commercial and other types of processing). The typical application rates and timing used for the anticipated residue analysis is provided in Table 9 for each crop.

Table 9: Anticipated Residues, Plant Commodities: Calculations and Summary

Average Residues from Alachlor Uses			
	Avg. Residue	Proc. Factor	Avg. Residue
Corn- 90% of use was preemergence at 4 lb ai/A, 10% of use was postemergence at 4 lb ai/A or sequential applications (4+2 lb ai/A)			
Corn grain	0.011		0.011

Average Residues from Alachlor Uses			
	Avg. Residue	Proc. Factor	Avg. Residue
Corn meal		0.91[1]	0.010
Corn oil (refined)		0.12[1]	0.0014
Corn starch		0.19[2]	0.0022
Corn forage[7]	0.21		0.21
Corn silage[7]	0.22		0.22
Corn stover[7]	0.12		0.12
Sweet Corn K+CWHR			
preemergence 4 lb ai/A	0.007		0.007
Peanuts-35% of use was preemergence, 75% of use was cracking			
Peanut hulls[7]	0.38		0.38
Peanut nutmeat	0.15		0.15
Peanut meal[7]		1.37[1]	0.21
Peanut oil (refined)		0.06[1]	0.009
Peanut butter		0.70[3]	0.11
Peanuts, dry roasted		0.75[3]	0.11
Peanuts, oil roasted		0.83[3]	0.12
Sorghum preemergence 4 lb ai/A			
Sorghum grain	0.02		0.02
Sorghum forage[7]	0.29		0.29
Sorghum fodder[7]	0.29		0.29
Sorghum stover[7]	0.2		0.20
Soybeans preemergence 4 lb ai/A			
Soybean grain and soybean full fat and low fat flour	0.105		0.11
Soybean grain dust[7]		6.00[4]	0.63
Soybean hulls[7]		1.22[4]	0.13
Soybean toasted meal (feed)[7]		0.88[4]	0.092
Soybean defatted meal (food)		1.30[4]	0.137
Soybean oil (refined)		0.17[4]	0.018
Soybean protein concentrate		0.32[4]	0.034
Soybean protein isolate		0.21[4]	0.022
Soybean defatted flour			0.090[5]
Soybean forage[7]	1.36		1.36
Soybean hay[7]	2.61		2.61
Dry Beans preplant incorporated 3 lb ai/A			

Average Residues from Alachlor Uses			
	Avg. Residue	Proc. Factor	Avg. Residue
Dry beans	0.048	0.20[6]	0.010
Dry lima beans	0.040	0.20[6]	0.008
Bean forage[7]	0.340		0.34
Bean vines[7]	0.396		0.40
Bean hay[7]	0.866		0.87

[1] MRID 00162939
[2] MRID 40788201
[3] MRID 40820601
[4] MRID 00154239, 00154240, 40947101, 41862901 41916301
[5] 4/7 defatted meal + 3/7 protein concentrates and isolates
[6] MRID 40820701
[7] Livestock feed only

Anticipated residues for milk, poultry and eggs were calculated in the manner demonstrated in Section, "Meat, Milk, Poultry, and Eggs". However, instead of using tolerances as the level of alachlor present in the feed items, anticipated residues as calculated in Table 9 were used in the calculation. Estimated dietary burdens based on average residues in livestock feeds for cattle, poultry, and swine were determined to be 0.49, 0.20, and 0.27 ppm, respectively. The anticipated residues in livestock commodities was then corrected for the expected recovery in each livestock tissue. (The percent theoretical recoveries are found in the C. Olinger memo of 6/1/93) Anticipated residue estimates for livestock commodities are listed Table 10.

Table 10: Anticipated Residues in Livestock Commodities.

Alachlor Feeding Study Results			Estimated Residues			
	Feeding level (ppm)	Residue (ppb)	Dietary Burden (ppm)	Residue Measured by Method (ppb)	% Residue of Concern Measured by Method	Total Residue of Concern (ppb)
BEEF						
muscle	4.20	1.20	0.53	0.15	38%	0.40
fat	4.20	1.90	0.53	0.24	70%	0.34
liver	4.20	7.80	0.53	0.98	58%	1.70
kidney	4.20	8.70	0.53	1.10	68%	1.61
milk	4.20	1.50	0.69	0.25	40%	0.62
POULTRY						

muscle	12.00	1.00	0.09	0.01	34%	0.02
fat	12.00	1.30	0.09	0.01	75%	0.01
liver	4.00	2.10	0.09	0.05	51%	0.09
eggs	4.00	6.90	0.09	0.16	60%	0.26
SWINE						
muscle	4.00	1.30	0.19	0.06	38%	0.16
fat	4.00	2.60	0.19	0.12	70%	0.18
liver	4.00	4.10	0.19	0.19	58%	0.34
kidney	12.00	7.40	0.19	0.12	68%	0.17

Since the dietary exposure assessment is based on field trial data, the anticipated residues are likely to overestimate the dietary exposure because the application rates and timing assumed in the dietary exposure analysis were at the highest rate on the label, which is not necessarily the typical rate used by the applicator. Additionally, residues are likely to degrade from the time that samples are obtained at the farm gate during transportation before consumption. For the livestock commodities, the following assumptions were used: (1) all alachlor metabolite residues found in the livestock animal metabolism studies are residues of concern and (2) the percentage recovery of the analytical method in livestock commodities is based on the percentage of metabolites recovered in metabolism studies. Alachlor metabolites not identified specifically in the metabolism studies may respond to the analytical method, so the analytical recovery may be higher than estimated.

Percent Crop Treated Data

Percent crop treated (%CT) information was supplied by OPP's Biological and Economic Analysis Division (BEAD) for a three year period 1993 - 1995. These data are based on a variety of proprietary and non-proprietary sources, as well as information from USDA and state statistics. When a range of percent of crop treated estimates were supplied, the upper end (in bold) was used. One hundred percent CT (default assumption) was used if no information was provided for a crop.

TABLE 11:
Percent of Various U.S. Crops Treated Annually with Alachlor

Commodities	Percent Crop Treated	Major Region or State
Beans, Dry	< 10	Nationwide
Beans, Succulent	10 - **35**	CA and ID
Corn, Sweet	30 - **35**	Nationwide

Commodities	Percent Crop Treated	Major Region or State
Corn, Field	20 - **25**	Nationwide
Ornamentals	<5	Southeast
Peanuts	<5	Southeast
Sorghum	10 - **15**	Nationwide
Soybeans	5 - **10**	Nationwide
Sunflowers	<1 - **1**	SD and NE

Refined dietary exposures and percent RfDs for selected subgroups are reported in Table 12.

Table 12:

Subgroup	Exposure(mg/kg/day)	%Reference Dose
U.S. population	0.000011	0.1
Non-nursing Infants	0.000050	0.5
Children (1-6 years)	0.000029	0.3
Male (20+ years)	0.000007	0.07
Female (13+ years), nursing	0.000010	0.1
Children (7-12 years)	0.000019	0.2

All other population subgroups were less than 0.2% of the RfD.

Thus, when using anticipated residues and percent crop treated data, all population subgroups are well below the RfD for alachlor. Chronic dietary risk from alachlor from all food uses recommended through reregistration is not of concern.

(iii) Chronic Drinking Water Risk

Percent RfDs for consumption of drinking water containing residues of alachlor per se were estimated using the RfD for alachlor of 0.01 mg/kg/day. All RfDs were rounded to one significant figure.

TABLE 13A: Drinking Water Percent RfDs for Alachlor per se - Adult Male

STUDY	Concentration (ppb)	Exposure (mg/kg/day)	% RfD
MCL	2	0.0000571	0.6

Surface Water			
Smith et. al. (1987)	0.36	0.0000102	0.1
Lauer et. al. (1986)	0.25	0.0000071	0.07
Moyer & Cross, (1986-1988)	0.18	0.0000051	0.05
USGS - Alachlor	0.22	0.0000062	0.06
Acetochlor Data, (1995-1996)	0.1	0.0000028	0.03
Ground Water			
NAWWS	0.2	0.0000057	0.06
NAWWS (99.5% population)	0.015	0.0000004	0.004

TABLE 13B: Drinking Water Percent RfDs for Alachlor per se - Adult Female

STUDY	Concentration (ppb)	Exposure (mg/kg/day)	% RfD
MCL	2	0.0000666	0.7
Surface Water			
Smith et. al. (1987)	0.36	0.000012	0.1
Lauer et. al. (1986)	0.25	0.0000083	0.08
Moyer & Cross, (1986-1988)	0.18	0.000006	0.06
USGS - Alachlor	0.22	0.0000073	0.07
Acetochlor Data, (1995-1996)	0.1	0.0000033	0.03
Ground Water			
NAWWS	0.2	0.0000066	0.07
NAWWS (99.5% population)	0.015	0.0000005	0.005

TABLE 13C: Drinking Water Percent RfDs for Alachlor per se - Child (1 - 6 years)

STUDY	Concentration (ppb)	Exposure (mg/kg/day)	% RfD
MCL	2	0.0002	2
Surface Water			
Smith et. al. (1987)	0.36	0.000036	0.4
Lauer et. al. (1986)	0.25	0.000025	0.3

Moyer & Cross, (1986-1988)	0.18	0.000018	0.2
USGS - Alachlor	0.22	0.000022	0.2
Acetochlor Data, (1995-1996)	0.1	0.00001	0.1
Ground Water			
NAWWS	0.2	0.00002	0.2
NAWWS (99.5% population)	0.015	0.0000015	0.02

All % RfDs are well below the RfD for alachlor. Chronic dietary risk from alachlor from consumption of water containing residues of alachlor per se is not of concern.

No RfD for alachlor ESA has been determined; the toxicological data base is incomplete. Therefore, a default assumption would be to use the parent alachlor RfD for the metabolite. Using the exposures estimated in Tables 7A, 7B, and 7C and the alachlor RfD of 0.01 mg/kg/day, percent RfDs were estimated to be of 0.9%, 1%, and 3% for adult male, adult female and child (1-6 years), respectively . Another assumption would be to calculate a value for use in a chronic dietary risk assessment using the NOEL from the 91-day alachlor ESA drinking water study. Using the NOEL of 157 mg/kg/day and an uncertainty factor of 1000 (to account for interspecies extrapolation, intraspecies variability and lack of a complete database) a value of 0.16 mg/kg/day was calculated. This gives percent RfDs of 0.05%, 0.06%, and 0.2% for adult male, adult female and child (1-6 years), respectively . Note that both of these approaches indicate little concern for consumption of ESA in the drinking water.

(iv). Aggregate Chronic Dietary (Food Source and Drinking Water) Risk

Percent RfDs for aggregate chronic dietary risk were calculated for adult males, adult females, and children (1 - 6 years). All RfDs were rounded to one significant figure.

Adult Male - Alachlor

Using the refined adult male food source exposure from Table 12 and NAWWS (Midwest ground water) exposure from Table 13A:

Exposure = 0.000007 mg/kg/day +0.0000057 mg/kg/day = 0.0000127 mg/kg/day

% RfD = 0.0000127 / 0.01 (100)= 0.1 %

Using the refined adult male food source exposure from Table 12 and USGS reservoir (Midwest surface water) from Table 13A:

Exposure = 0.000007 mg/kg/day + 0.0000062 mg/kg/day = 0.0000132 mg/kg/day

%RfD =0.0000132 / 0.01 (100) = 0.1 %

Using the refined adult male food source exposure from Table 12 and acetochlor (12 state area surface water) from Table 13A:

Exposure = 0.000007 mg/kg/day +0.0000028 mg/kg/day = 0.0000098 mg/kg/day

% RfD = 0.0000098 / 0.01 (100) = 0.1 %

Adult Male - Alachlor and Alachlor ESA

Using the refined adult male food source exposure from Table 12 and USGS reservoir (Midwest surface water) exposure from Table 13A/Table 7A:

Exposure = 0.000007 mg/kg/day + 0.0000062 mg/kg/day + 0.0000857 mg/kg/day = 0.0000989 mg/kg/day

% RfD = 0.0000989 / 0.01 (100) = 1 %

Adult Female Alachlor

Using the refined adult female food source exposure from Table 12 and NAWWS (Midwest ground water) exposure from Table 13B:

Exposure = 0.000010 mg/kg/day + 0.0000066 mg/kg/day = 0.0000166 mg/kg/day

% RfD = 0.0000166 / 0.01 (100) = 0.2 %

Using the refined adult female food source exposure from Table 12 and USGS reservoir (Midwest surface water) from Table 13B:

Exposure = 0.000010 mg/kg/day + 0.0000073 mg/kg/day = 0.0000173 mg/kg/day

% RfD = 0.0000173 / 0.01 (100) = 0.1%

Using the refined adult female food source exposure from Table 12 and acetochlor (12 state area surface water) from Table 13B:

Exposure = 0.000010 mg/kg/day + 0.0000033 mg/kg/day = 0.0000133 mg/kg/day

% RfD = 0.0000133 / 0.01 = 0.1%

Adult Female - Alachlor and Alachlor ESA

Using the refined adult female food source exposure from Table 12 and USGS reservoir (Midwest surface water) from Table 13B/Table 7B:

Exposure = 0.000010 mg/kg/day + 0.0000073 mg/kg/day +0.0001 mg/kg/day = 0.0001173 mg/kg/day

% RfD = 0.0001173 / 0.01 (100) = 1 %

Child (1-6 years) - Alachlor

Using the refined child (1-6 years) food source exposure from Table 12 and NAWWS (Midwest ground water) exposure from Table 13C:

Exposure = 0.000029 mg/kg/day + 0.00002 mg/kg/day = 0.000049 mg/kg/day

% RfD = 0.000049 / 0.01 (100) = 0.5 %

Using the refined child (1-6 years) food source exposure from Table 12 and USGS reservoir (Midwest surface water) from Table 13C:

Exposure = 0.000029 mg/kg/day + 0.000022 mg/kg/day = 0.000051 mg/kg/day

% RfD = 0.000051 / 0.01 (100) = 0.5 %

Using the refined child (1-6 years) food source exposure from Table 12 and acetochlor (12 state area surface water) from Table 13C:

Exposure = 0.000029 mg/kg/day + 0.00001 mg/kg/day = 0.000039 mg/kg/day

% RfD = 0.000039 / 0.01 (100) = 0.4 %

Child (1 - 6 years) - Alachlor and Alachlor ESA

Using the refined child (1-6 years) food source exposure from Table 12 and USGS reservoir (Midwest surface water) from Table 13C/Table 7C:

Exposure = 0.000029 mg/kg/day + 0.000022 mg/kg/day + 0.0003 mg/kg/day = 0.000351 mg/kg/day

% RfD = 0.000351 / 0.01 (100) = 4 %

All % RfDs for aggregate chronic dietary risk are well below the RfD for alachlor. Chronic dietary risk from alachlor from food containing residues of alachlor and from

consumption of water containing residues of alachlor per se and/or residues of alachlor ESA is not of concern.

(v). Dietary Carcinogenic (Food Sources) Risk

As stated previously, CPRC recommended using a Margin of Exposure (MOE) approach for estimation of human risk, rather than the linear low dose approach. The CPRC recommended the use of 0.5 mg/kg/day for nasal tumors and 14 mg/kg/day for stomach tumors. MOEs were estimated for adult females and adult males using the chronic exposures in Table 12

Carcinogenic MOE = NOEL/ exposure

At this time HED is not making any recommendations on the level of MOEs to be considered acceptable for dietary risk. However, given the magnitude of the calculated MOEs, dietary cancer risk from the recommended uses of alachlor does not seem to be of concern. Note that all MOEs in Table 14 have been rounded to two significant figures.

Table 14: Carcinogenic MOEs

Population Group	Exposure	MOE
Nasal Tumors (0.5 mg/kg/day)		
Adult Male	0.000007	71,000
Adult Female	0.000010	50,000
Stomach Tumors (14 mg/kg/day)		
Adult Male	0.000007	2,000,000
Adult Female	0.000010	1,400,000

(vi). Carcinogenic Drinking Water Risk

MOEs were calculated for adult males and females only. An MOE for alachlor ESA was not calculated per the recommendation of the HED Metabolism Committee. All MOEs were rounded to two significant figures.

Table has been revised

TABLE 15A: Drinking Water Carcinogenic MOEs - (Adult Male)

STUDY	Concentration (ppb)	Exposure (mg/kg/day)	MOE[1]	MOE[2]
MCL	2	0.0000571	8,800	250,000
Surface Water				

USGS - Alachlor	0.22	0.0000062	45,000	2,300,000
Acetochlor Data (1995-1996)	0.1	0.0000028	180,000	6,400,000
Ground Water				
NAWWS	0.2	0.0000057	88,000	2,500,000
NAWWS (99.5% population)	0.015	0.0000004	1,200,000	35,000,000

1 MOE for nasal tumors (0.5 mg/kg/day)
2 MOE for stomach tumors (14 mg/kg/day)

Table has been revised
TABLE 15B: Drinking Water Carcinogenic MOEs - (Adult Female)

STUDY	Concentration (ppb)	Exposure (mg/kg/day)	MOE[1]	MOE[2]
MCL	2	0.0000666	7,500	210,000
Surface Water				
USGS - Alachlor	0.22	0.0000073	68,000	1,900,000
Acetochlor Data	0.1	0.0000033	150,000	5,400,000
Ground Water				
NAWWS	0.2	0.0000066	76,000	21,000,000
NAWWS (99.5% population)	0.015	0.0000005	1,000,000	28,000,000

1 MOE for nasal tumors
2 MOE for stomach tumors

(vii). Total Carcinogenic Dietary Risk (Food and Water)

MOEs for total carcinogenic dietary risk were calculated for adult males and females. All MOEs were rounded to two significant figures.

Adult Male

Using the refined adult male food source exposure from Table 12 and NAWWS (Midwest ground water) exposure from Table 13A:

Exposure = 0.000007 mg/kg/day +0.0000057 mg/kg/day = 0.0000127 mg/kg/day

MOE (nasal) = 0.5 / 0.0000127 = 390,000

MOE (stomach) = 14 / 0.0000127 = 1,100,000

Using the refined adult male food source exposure from Table 12 and USGS reservoir (Midwest surface water) from Table 13A:

Exposure = 0.000007 mg/kg/day + 0.0000062 mg/kg/day = 0.0000132 mg/kg/day

MOE (nasal) = 0.5 / 0.0000132 = 38,000

MOE (stomach) = 14 / 0.0000132 = 1,100,000

Using the refined adult male food source exposure from Table 12 and acetochlor (12 state area surface water) from Table 13A:

Exposure = 0.000007 mg/kg/day +0.0000028 mg/kg/day = 0.0000098 mg/kg/day

MOE (nasal) = 0.5 / 0.0000098 = 51,000

MOE (stomach) = 14 / 0.0000098 = 1,400,000

Adult Female

Using the refined adult female food source exposure from Table 12 and NAWWS (Midwest ground water) exposure from Table 13B:

Exposure = 0.000010 mg/kg/day + 0.0000066 mg/kg/day = 0.0000166 mg/kg/day

MOE (nasal) = 0.5 / 0.0000166 = 30,000

MOE (stomach) = 14 / 0.0000166 = 840,000

Using the refined adult female food source exposure from Table 12 and USGS reservoir (Midwest surface water) from Table 13B:

Exposure = 0.000010 mg/kg/day + 0.0000073 mg/kg/day = 0.0000173 mg/kg/day

MOE (nasal) = 0.5 / 0.0000173 = 29,000

MOE (stomach) = 14 / 0.0000173 = 810,000

Using the refined adult female food source exposure from Table 12 and acetochlor (12 state area surface water) from Table 13B:

Exposure = 0.000010 mg/kg/day + 0.0000033 mg/kg/day = 0.0000133 mg/kg/day

MOE (nasal) = 0.5 / 0.0000133 = 38,000

MOE (stomach) = 14 / 0.0000133 = 1,100,000

At this time HED is not making any recommendations on the level of MOEs to be considered acceptable for aggregate (food and water) dietary risk. However, given the magnitude of the calculated MOEs (ranging from 29,000 to 1,400,000), total carcinogenic dietary risk from the recommended uses of alachlor does not seem to be of concern.

d. Dietary Risk Characterization

The dietary (food source) exposure estimates for both chronic and carcinogenic dietary scenarios were performed using data on alachlor per se and its metabolites of concern HEEA and DEA containing moities). These exposures may be slightly overestimated since application of alachlor during the field trials was at the highest label rate. However, application at the label rate is legal and can occur. Therefore, HED has confidence in these estimates as approaching a more realistic estimate of alachlor residues, including metabolites, that can occur in the food supply.

However, for the drinking water assessments the detections for surface water and groundwater, with the exception of the USGS reservoir data, are for alachlor per se. Sufficient analytical information on alachlor metabolites of which alachlor ESA is only one metabolite were not available. The information available to HED indicates that alachlor ESA is detected more often and in larger concentrations than alachlor. Note that the Agency's Pesticide in Ground Water Database contains information on a detection of hydroxyalachlor in Iowa at 0.910 ppb. Little is known about the persistence and mobility or the human health effects of metabolites of alachlor other than alachlor ESA. Therefore, drinking water exposures that reflect only exposure to alachlor per se, or alachlor and its ESA metabolite could be considered as underestimated. The corresponding %RfDs would also be underestimated. The corresponding carcinogenic MOEs would be overestimated.

In combining the food source and the drinking water exposure estimates, HED is combining a slightly over-estimated dietary exposure estimate and a possibly underestimated drinking water exposure estimate. Even though the %RfDs are extremely low and the carcinogenic MOEs range from 29,000 to 1,400,000 ~~generally exceed 100,000 to 1,000,000~~, due to the lack of available information on detections in ground water and surface water of all metabolites of alachlor (of which alachlor ESA is only one metabolite) and on toxicity information of these metabolites, HED has concerns for the exposure to drinking water containing alachlor and alachlor metabolites.

4. OCCUPATIONAL RISK ASSESSMENT/CHARACTERIZATION

This entire section has been revised. Use to replace no-redlining in this section

a. Introduction

HED has not identified any alachlor products that are intended for home use. Therefore, only an occupational assessment is required.

An occupational exposure assessment is required for an active ingredient if (1) certain toxicological criteria are triggered and (2) there is potential exposure to handlers (mixers, loaders, applicators; M/L/As) during use or to persons entering treated sites after application is complete. In the case of alachlor the identification of short-term and intermediate-term endpoints triggers the toxicological criteria and exposure to M/L/As has been identified.

As previously stated, there are no chronic exposure scenarios for the application of alachlor; therefore, a chronic exposure scenario is not calculated. Also, calculation of a carcinogenic MOE for agricultural workers based on intermittent exposure is not appropriate.

(I) Use Patterns

Alachlor [2-chloro-2'-6'-diethyl-N-(methoxymethyl) acetanilide] is a broad spectrum herbicide used on terrestrial food and feed crops and on terrestrial non-food targets. The timing for applications is just prior to, at, or shortly after planting (i.e., preplant, pre-emergent, at planting for corn and soybeans, post-transplant for ornamentals, post-emergent, and at ground-crack for peanuts only).

Agricultural use sites include corn, soybeans, peanuts, grain sorghum (milo), and beans (i.e. dry, lima, red kidney, and mung). Non-food and ornamental uses include applications to ornamental woody shrubs and vines (i.e., junipers and yew). Alachlor is formulated as a liquid (active ingredient 25.2 to 45.1 percent), as a dry flowable (active ingredient 65 percent), as a microencapsulate (active ingredient 41.5 percent) and as a granular (15 percent active ingredient). The maximum application rates range from 4.0 lb ai/acre for corn to 3.0 lb ai/acre for soybean. Several of the application methods involve soil incorporation techniques. Dry bulk fertilizers are impregnated with alachlor at commercial fertilizer or farm chemical dealerships using specially designed, closed systems. In these systems, alachlor and the fertilizers are mixed and blended in a system such as a closed rotary drum container, or similar system. Nozzles situated inside the rotary drum are used to apply the alachlor onto the fertilizer. The fertilizer impregnated with alachlor is then applied using spin-type spreaders, or positive displacement equipment.

(ii) Incident Data

Alachlor is considered a mild irritant according to EPA's "Recognition and Management of Pesticide Poisoning" (Fourth Edition, 1989). No serious cases (deaths or hospitalized cases) have been reported in national surveys of deaths (in the 1960s or 1970s, the last surveys completed) or hospitalization (1971 through 1982). California reported just 3 physician-treated cases in the 12 year period, 1982 through 1993. Two of these three cases involved skin or eye effects and one case was considered a possible systemic poisoning. Thirteen unconfirmed cases have been screened by the Office of Pesticide Program's Incident Data system, most of which reportedly experienced minor dermal effects. No changes in labeling are recommended based on this incident data. (communication Blondell)

(iii) Previous Agency Regulatory Action/ Special Review

At the time of the Special Review of alachlor the Agency used the best available data to estimate worker exposure. Risk estimates for the PD1 were based on patch data supplied by the registrant which measured exposure to the EC, Mcap, and G formulations. However, in response to the PD1, the registrant submitted additional data, namely the previously discussed 1984 and 1985 human biomonitoring data. The Agency reviewed these data (see Section B.1.j.). Numerous limitations were identified related to the biomonitoring data, such as: (1) the small number of replicates (4 persons per study) which cannot indicate the range (the expected variability) of exposure to alachlor; (2) study subjects were Monsanto employees; (3) mixer/loaders wore protective goggles, rubber gloves, and rubber overshoes; (4) applicators used enclosed cab tractors exclusively; (5) only 20 acres were treated with alachlor-containing formulations instead of the 80 to 120 acres that could be expected to be treated; (6) some products were soil incorporated; (7) biological monitoring and passive dosimetry were conducted concurrently on the same individual which may reduce the amount of pesticide reflected in biomonitoring results; (memo J. Reinert).

At the time of the PD4, the biomonitoring data were the best data available, so the Agency used the biomonitoring data to estimate exposure. In fact, the PD4 stated that the Agency believed that biomonitoring data from well-designed and executed studies, if supported by adequate pharmacokinetic studies, provide a better measure of exposure than patch data. At the time of the PD4, the Agency used monkey data showing the rate and ratio of excreted alachlor metabolites to interpret the results of the biomonitoring data.

Using the previously submitted patch data from the registrant, and data available in the literature documenting exposure variability, the Agency estimated a range of exposures of two orders of magnitude, with the biomonitoring data representing the low end of the range for exposure to alachlor during mixing/loading and groundboom application. In 1987 the Agency believed the range of exposures defined by the biomonitoring data, the patch data, and the open literature values more accurately reflected applicator exposure estimates than the estimates that were used in the PD1.

In this risk assessment for the purpose of the re-registration of alachlor, HED has used data from PHED as well as the registrant-generated biomonitoring data. As noted previously limitations were identified. Of particular significance were (1) the small number of replicates (4 persons per study), and (7) biological monitoring and passive dosimetry were conducted concurrently on the same individual. The small number of replicates lowers the confidence level in the results; however, the higher of the two values (0.0000126 mg/kg/lb ai.) was used in the assessment. The concurrent monitoring is in all probablity a small percent of the total amount of alachlor that could be absorbed given the small surface areas of the patches. These data do not meet the Agency's guideline requirements (875.2600), for biological monitoring.

During the 10 year interval since the PD4, the Pesticide Handlers Exposure Database (PHED; currently Version 1.1) was developed. PHED was developed by Health Canada, the American Crop Protection Association, and EPA, and initially released for public use in 1992. PHED is a comprehensive generic/surrogate exposure database containing a large number of

measured values of dermal and inhalation exposure for pesticide workers (e.g., mixers, loaders, and applicators) involved in the handling or application of pesticides in the field. Use of surrogate or generic data is appropriate since it is generally believed that the formulations and the method of application, not the chemical properties of the pesticide control the amount of dermal and inhalation exposure. Thus, PHED allows exposure and risk assessments to be conducted with a much larger number of observations than available from a single exposure study. The current version of PHED (Version 1.1) contains larger numbers of exposure replicates and a broader spectrum of mixer/loader and applicator scenarios reflecting use of a variety of personal protective equipment. Note that Table 16 rates the data (for number of replicates and quality control parameters) used to estimate exposure for mixing liquids and groundboom application (baseline) as high confidence with the number of replicates varying up to 122.

Generally, biomonitoring data are preferable to passive-dosimetry data. The use of a dermal absorption factor is not necessary for biomonitoring data. Biomonitoring data can give a more accurate estimate of absorbed dose. But, biomonitoring does not determine the source of the exposure (inhalation/dermal; hands/head), and thus, cannot be used to identify what measures, to mitigate exposures, are likely to be the most effective.

Therefore, for the alachlor Reregistration Eligibility Decision Document, HED is using PHED Version 1.1 to assess pesticide handlers exposure to alachlor. However, the results of the biomonitoring study will be used for comparison purposes.

b. Occupational Exposure

(I) Occupational Exposure Scenarios

HED has determined that there are potential exposures to mixers, loaders, applicators, or other handlers during usual use-patterns associated with alachlor. Based on the use patterns, nine major exposure scenarios were identified for alachlor:
(1a) mixing/loading liquids for aerial and chemigation application;
(1b) mixing/loading liquids for groundboom application;
(2) mixing/loading granulars for drop type tractor drawn application;
(3a) mixing/loading dry flowables for aerial application;
(3b) mixing/loading dry flowables for groundboom application;
(4) aerial application of liquids (fixed-wing);
(5) aerial application of liquids (helicopter);
(6) groundboom application of liquids;
(7) granular drop type tractor drawn application;
(8) mixing/loading and application to dry bulk fertilizer; and,
(9) flaggers.

A summary and description of the caveats and parameters specific to each exposure scenario is shown in Table 16.

(ii) Occupational Exposure Tables

Table 17-A shows the baseline daily exposure for occupational workers exposed to alachlor. Table 17-B shows the exposure for workers protected by additional PPE. Table 17-C shows the exposure for workers protected by engineering controls (i.e. mechanical systems). Table 17-D shows the exposure for workers using the values from the registrant-submitted biomonitoring studies. Note that the explanation of calculations are in the footnotes.

Table 16: Exposure Scenario Descriptions for Uses of Alachlor

Exposure Scenario (Number)	Data Source	Daily Acres Treated[a]	Comments[b]
Mixer/Loader Exposure			
Mixing/Loading Liquid (1a and b)	PHED V1.1	80 acres groundboom, and 350 acres aerial	**Baseline:** "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 53 replicates; Dermal = 25 to 122 replicates; Inhalation = 85 replicates. High confidence in dermal data; high confidence in inhalation data. **PPE:** "Best Available" grades: Hands and dermal acceptable grades. Hands = 59 replicates; Dermal = 25 to 122 replicates. High confidence in dermal and inhalation data. **Engineering Controls:** "Best Available" grades: Dermal and inhalation acceptable grades. Hands = 31 replicates, Dermal = 16 to 22 replicates; Inhalation = 27 replicates. High confidence in dermal and inhalation data. PHED data used for baseline and engineering controls, no Protection Factor (PF) were necessary. Fifty percent PF was used for coveralls (PPE).
Mixing/Loading Granulars (2)	PHED V1.1	80 acres	**Baseline:** "Best Available" grades: Hands all grades, dermal and inhalation acceptable grades. Dermal = 29 to 36 replicates; inhalation = 58 replicates; and hands = 10 replicates. Low confidence in dermal data, high confidence in inhalation data. PHED data used for baseline, no PFs were necessary.
Mixing/Loading Dry Flowables (3a and 3b)	PHED V1.1	80 acres	**Baseline:** "Best Available" grades: Hands grades A,B, C; dermal and inhalation acceptable grades. Dermal = 16 to 26 replicates; inhalation = 23 replicates; and, hands = 7 replicates. Low confidence in dermal data, high confidence in inhalation data. **PPE:** "Best Available" grades: Hands, dermal and inhalation acceptable grades. Hands = 21 replicates; Dermal = 16 to 26 replicates, inhalation = 23 replicates. High confidence in dermal and inhalation data. PHED data used for baseline, no PFs were necessary. Fifty percent PF was used for coveralls (PPE).
Applicator Exposure			
Aerial equipment--fixed wing enclosed cab (liquids) (4)	PHED V1.1	350 acres	**Engineering Controls:** "Best Available" grades: Hands acceptable grades, dermal and inhalation grades A,B,C. Hands = 34 replicates; Dermal = 24 to 48 replicates; Inhalation = 23 replicates. Medium confidence in dermal and inhalation data. PHED data used for engineering controls, no PFs were necessary.

Exposure Scenario (Number)	Data Source	Daily Acres Treated[a]	Comments[b]
Aerial equipment--helicopter enclosed cab (liquids) (5)	PHED V1.1	350 acres	**Engineering Controls:** "Best Available" grades: dermal grades A,B,C; inhalation grades "acceptable". Hands = 2 replicates, Dermal = 3 replicates; Inhalation = 3 replicates. Low confidence in dermal and inhalation data. PHED data used for engineering controls, no PFs were necessary.
Groundboom Application (liquids) (6)	PHED V1.1	80 acres	**Baseline:** "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 29 replicates; Dermal = 32 to 42 replicates; Inhalation = 22 replicates. High confidence in dermal and inhalation data. **PPE:** "Best Available" grades: Hands grades ABC and dermal acceptable grades. Hands = 21 replicates Dermal = 32 to 42 replicates Medium confidence in dermal data; high confidence in inhalation data. **Engineering Controls:** "Best Available" grades: Hands, and dermal = ABC grades; Inhalation = acceptable grades. Hands = 16 replicates Dermal = 20 to 31 replicates; Inhalation = 16 replicates. Medium confidence in dermal data; high confidence in inhalation. PHED data used for baseline and engineering controls, no PFs were necessary. Fifty percent PF was added for coveralls for PPE.
Granular Drop Type Tractor Drawn Spreader Application (7)	PHED V1.1	80 acres	**Baseline:** "Best Available" grades: Hand, dermal and inhalation acceptable grades. Dermal = 4 to 5 replicates; hands = 5 replicates; inhalation = 5 replicates. Low confidence in dermal and inhalation data. PHED data was used for baseline, no PFs were necessary.
Mixer/Loader/Applicator			
Mixing/Loading and Application for Dry Bulk Fertilizer (8)	No data	No data	No data
Flaggers			
Flaggers for Aerial Applications (9)	PHED V1.1	350 acres	**Baseline:** "Best Available" grades: Hand, dermal and inhalation acceptable grades. Dermal = 16 to 18; hands = 16; inhalation = 18. High confidence in dermal, hand and inhalation data. PHED data was used for baseline, no PFs were necessary.

a Daily acres treated are from HED estimates of acreage that could be treated in a single day for each exposure scenario of concern.

b These grades are based on Quality Assurance/Quality Control data provided as part of the exposure studies. A replicate refers to data acquired during one complete work cycle. "Best Available" grades are defined by HED SOP for meeting Subdivision U Guidelines. Best available grades are assigned as follows: matrices with grades A and B data and a minimum of 15 replicates; if not available, then grades A, B, and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality and number of replicates. Data confidence are assigned as follows: High confidence = grades A and B and 15 or more replicates per body part

Medium confidence = grades A, B, and C and 15 or more replicates per body part
Low confidence = grades A, B, C, D, and E or any combination of grades with less than 15 replicates

Table 17-A: Alachlor Exposure Estimates to be Used in Short-Term and Intermediate-Term Risk Assessments - Baseline PHED Values

Exposure Scenario (Scenario #)	Baseline Dermal Unit Exposure (mg/lb ai)[a]	Baseline Inhalation Unit Exposure (mg/lb ai)[b]	Crop and Application Rate (lb ai/acre)[c]	Daily Acres Treated[d]	Daily Dermal Exposure (mg/day)[e]	Daily Inhalation Exposure (mg/day)[e]	Baseline Daily Total Exposure (mg/day)[e]	Daily Absorbed Dermal Exposure (mg/day)[g]	Baseline Daily Absorbed Total Exposure (mg/day)[h]
Mixer/Loader Exposure									
Mixing/Loading Liquids for Aerial Application and Chemigation (1a)	2.9	0.0012	Corn 4.0	350	4,060	1.68	4,061.7	974	976
			Soybeans 3.0		3,045	1.26	3,046.3	731	732
Mixing/Loading Liquids for Groundboom Application (1b)			Corn 4.0	80	928	0.384	928.4	223	223
			Soybeans 3.0		696	0.288	696.3	167	167
Mixing/Loading Granulars for Drop Type Tractor Drawn Spreaders (2)	0.0076	0.0017	Corn 4.0	80	2.4	0.544	2.9	0.58	1.1
			Soybeans 3.0		1.8	0.408	2.2	0.43	0.83
Mixing/Loading Dry Flowables for Aerial Application (3a)	0.07	0.00077	Corn 4.0	350	98	1.08	99.08	24	25
			Soybeans 3.0		73.5	0.81	74.31	18	18
Mixing/Loading Dry Flowables for Groundboom Application (3b)			Corn 4.0	80	22.4	0.25	22.65	5.4	5.6
			Soybeans 3.0		16.8	0.19	16.99	4.0	4.2
Applicator Exposure									
Aerial Application of Liquids - Fixed-Wing Aircraft - Enclosed Cockpit (4)	See Engineering Controls	See Engineering Controls	Corn 4.0	350	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls
			Soybeans 3.0						
Aerial Application of Liquids - Helicopter Aircraft - Enclosed Cockpit (5)	See Engineering Controls	See Engineering Controls	Corn 4.0	350	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls
			Soybeans 3.0						
Groundboom Application of Liquids - (6)	0.015	0.0007	Corn 4.0	80	4.8	0.224	5.02	1.2	1.4
			Soybeans 3.0		3.6	0.168	3.77	0.86	1.0
Granular Drop Type Tractor Drawn Spreader Application (7)	0.01	0.00022	Corn 4.0	80	3.2	0.07	3.3	0.77	0.84
			Soybeans 3.0		2.4	0.053	2.5	0.58	0.63
Mixer/Loader/Applicator Exposure									
Mixing/Loading and Application of Impregnated Dry Bulk Fertilizer (8)	See text								
Flaggers									

Exposure Scenario (Scenario #)	Baseline Dermal Unit Exposure (mg/lb ai)[a]	Baseline Inhalation Unit Exposure (mg/lb ai)[b]	Crop and Application Rate (lb ai/acre)[c]	Daily Acres Treated[d]	Daily Dermal Exposure (mg/day)[e]	Daily Inhalation Exposure (mg/day)[e]	Baseline Daily Total Exposure (mg/day)[f]	Daily Absorbed Dermal Exposure (mg/day)[g]	Baseline Daily Absorbed Total Exposure (mg/day)[h]
Flaggers for Aerial Applications (9)	0.01	0.00028	Corn 4.0	350	14.0	0.39	14.39	3.4	3.8
			Soybeans 3.0		10.5	0.29	10.79	2.5	2.8

a Baseline dermal unit exposure represents long pants, long sleeve shirts, no gloves, open mixing/loading, open cabs or cockpits. Note that data on open cockpit aerial applications are not available.
b Baseline inhalation exposure represents no respirator.
c Application rate comes from maximum values found in the alachlor labels EPA Reg Nos. 524-344, 524-403, 524-418, 524-422 and 524-314.
d Daily acres treated are from HED estimates of acreage that could be treated in a single day for each exposure scenario of concern.
e Daily exposure (mg/day) = Exposure (mg/lb ai) * Appl. rate (lb ai/A) * Acres Treated.
f Total daily exposure (mg/day) = daily dermal exposure (mg/day) + daily inhalation exposure (mg/day). Note that this exposure number is used for the intermediate-term scenario only since the NOEL for calculation of MOE is from a dermal study and the use of the dermal absorption factor is not necessary.
g Daily absorbed dermal exposure (mg/day) = daily dermal exposure (mg/day) * dermal absorption factor (0.24)
h Total absorbed daily exposure (mg/day) = daily absorbed dermal exposure (mg/day) + daily inhalation exposure (mg/day) Note that this exposure is used for the short-term scenario only since the NOEL for calculating the MOE is from an oral study and it was necessary to use the dermal absorption factor.

Table 17-B: Alachlor Exposure Estimates to be used in Short-Term and Intermediate-Term Risk Assessments - PHED Personal Protective Equipment (PPE) Values

Exposure Scenario (Scenario #)	PPE Dermal Unit Exposure (mg/lb ai)[a]	Baseline Inhalation Unit Exposure (mg/lb ai)[b]	Crop and Application Rate (lb ai/acre)[c]	Daily Acres Treated[d]	Daily Dermal Exposure (mg/day)[e]	Daily Inhalation Exposure (mg/day)[f]	PPE Daily Total Exposure (mg/day)[g]	Daily Absorbed Dermal Exposure (mg/day)[h]	PPE Daily Absorbed Total Exposure (mg/day)[i]
Mixer/Loader Exposure									
Mixing/Loading Liquids for Aerial Application and Chemigation (1a)	0.043	0.0012	Corn 4.0	350	60.2	1.7	61.9	14.4	16.1
			Soybeans 3.0		45.2	1.3	46.5	10.8	12.1
Mixing/Loading Liquids for Groundboom Application (1b)	0.043	0.0012	Corn 4.0	80	13.8	0.38	14.2	3.3	3.7
			Soybeans 3.0		9.6	0.29	9.9	2.3	2.6
Mixing/Loading Granulars for Drop Type Tractor Drawn Spreaders (2)	n/a	n/a	Corn 4.0	80	n/a	n/a	n/a	n/a	n/a
			Soybeans 3.0		n/a	n/a	n/a	n/a	n/a
Mixing/Loading Dry Flowables for Aerial Application (3a)	0.04	0.00077	Corn 4.0	350	56	1.1	57.1	13.4	14.5
			Soybeans 3.0		42	0.81	42.8	10.1	10.9
Mixing/Loading Dry Flowables for Groundboom Application (3b)	n/a	n/a	Corn 4.0	80	n/a	n/a	n/a	n/a	n/a
			Soybeans 3.0		n/a	n/a	n/a	n/a	n/a
Applicator Exposure									
Aerial Application of Liquids - Fixed-Wing Aircraft - Enclosed Cockpit (4)	See Engineering Controls	See Engineering Controls	Corn 4.0	350	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls
			Soybeans 3.0						
Aerial Application of Liquids - Helicopter Aircraft - Enclosed Cockpit (5)	See Engineering Controls	See Engineering Controls	Corn 4.0	350	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls
			Soybeans 3.0						
Groundboom Application of Liquids - (6)	n/a	n/a	Corn 4.0	80	n/a	n/a	n/a	n/a	n/a
			Soybeans 3.0		n/a	n/a	n/a	n/a	n/a
Granular Drop Type Tractor Drawn Spreader Application (7)	n/a	n/a	Corn 4.0	80	n/a	n/a	n/a	n/a	n/a
			Soybeans 3.0		n/a	n/a	n/a	n/a	n/a
Mixer/Loader/Applicator Exposure									
Mixing/Loading and Application of Impregnated Dry Bulk Fertilizer (8)	See text								

Exposure Scenario (Scenario #)	PPE Dermal Unit Exposure (mg/lb ai)[a]	Baseline Inhalation Unit Exposure (mg/lb ai)[b]	Crop and Application Rate (lb ai/acre)[c]	Daily Acres Treated[d]	Daily Dermal Exposure (mg/day)[e]	Daily Inhalation Exposure (mg/day)[e]	PPE Daily Total Exposure (mg/day)[f]	Daily Absorbed Dermal Exposure (mg/day)[g]	PPE Daily Absorbed Total Exposure (mg/day)[h]
Flaggers									
Flaggers for Aerial Applications (9)	n/a	n/a	Corn 4.0	350 acres	n/a	n/a	n/a	n/a	n/a
			Soybeans 3.0		n/a	n/a	n/a	n/a	n/a

n/a No longer necessary to carry scenario through analysis as exposure in baseline scenario is sufficiently low to calculate an MOE that will exceed 100

a Scenario 1a and 1b single layer clothing and chemical resistant gloves, open mixing/loading
Scenario 3a: open mixing/loading, double layer of clothing and chemical resistant gloves.
b Baseline inhalation exposure represents no respirator.
c Application rate comes from maximum values found in the alachlor labels EPA Reg Nos. 524-344, 524-403, 524-418, 524-422 and 524-314.
d Daily acres treated are from HED estimates of acreage that could be treated in a single day for each exposure scenario of concern.
e Daily exposure (mg/day) = Exposure (mg/lb ai) * Appl. rate (lb ai/A) * Acres Treated.
f Total daily exposure (mg/day) = daily dermal exposure (mg/day) + daily inhalation exposure (mg/day). Note that this exposure number is used for the intermediate-term scenario only since the NOEL for calculating the MOE is from a dermal study and the use of the dermal absorption factor is not necessary.
g Daily absorbed dermal exposure (mg/day) = daily dermal exposure (mg/day) * dermal absorption factor (0.24)
h Total absorbed daily exposure (mg/day) = daily absorbed dermal exposure (mg/day) + daily inhalation exposure (mg/day) Note that this exposure is used for the short-term scenario only since the NOEL for calculating the MOE is from an oral study and it was necessary to use the dermal absorption factor.

Table 17-C; Alachlor Exposure Estimates to be Used in Short-Term and Intermediate-Term Risk Assessments - Engineering Control (Eng C) PHED Values

Exposure Scenario (Scenario #)	Eng C Dermal Unit Exposure (mg/lb ai)[a]	Baseline Inhalation Unit Exposure (mg/lb ai)[b]	Crop and Application Rate (lb ai/acre)[c]	Daily Acres Treated[d]	Eng C Daily Dermal Exposure (mg/day)[e]	Daily Inhalation Exposure (mg/day)[e]	Eng C Daily Total Exposure (mg/day)[f]	Eng C Daily Absorbed Exposure (mg/day)[g]	Eng C Daily Absorbed Total Exposure (mg/day)[h]
Mixer/Loader Exposure									
Mixing/Loading Liquids for Aerial Application and Chemigation (1a)	0.009	0.00008	Corn 4.0	350	9.8	0.11	9.9	2.4	2.5
			Soybeans 3.0		7.4	0.08	7.5	1.8	1.9
Mixing/Loading Liquids for Groundboom Application (1b)			Corn 4.0	80	2.2	0.026	2.2	0.54	0.57
			Soybeans 3.0		1.7	0.02	1.7	0.4	0.42
Mixing/Loading Granulars for Drop Type Tractor Drawn Spreaders (2)	n/a	n/a	Corn 4.0	80	n/a	n/a	n/a	n/a	n/a
			Soybeans 3.0		n/a	n/a	n/a	n/a	n/a
Mixing/Loading Dry Flowables for Aerial Application (3a)	No data	No data	Corn 4.0	350	No data	No data	No data	No data	No data
			Soybeans 3.0		No data	No data	No data	No data	No data
Mixing/Loading Dry Flowables for Groundboom Application (3b)	n/a	n/a	Corn 4.0	80	n/a	n/a	n/a	n/a	n/a
			Soybeans 3.0		n/a	n/a	n/a	n/a	n/a
Applicator Exposure									
Aerial Application of Liquids - Fixed-Wing Aircraft - Enclosed Cockpit (4)	0.005	0.000068	Corn 4.0	350	7	0.095	7.1	1.7	1.8
			Soybeans 3.0		5.3	0.07	5.3	1.3	1.4
Aerial Application of Liquids - Helicopter Aircraft - Enclosed Cockpit (5)	0.0021	0.0000018	Corn 4.0	350	3.0	0.003	3.0	0.7	0.7
			Soybeans 3.0		2.2	0.002	2.2	0.53	0.53
Groundboom Application of Liquids - (6)	n/a	n/a	Corn 4.0	80	n/a	n/a	n/a	n/a	n/a
			Soybeans 3.0		n/a	n/a	n/a	n/a	n/a

Exposure Scenario (Scenario #)	Eng C Dermal Unit Exposure (mg/lb ai)[a]	Baseline Inhalation Unit Exposure (mg/lb ai)[b]	Crop and Application Rate (lb ai/acre)[c]	Daily Acres Treated[d]	Eng C Daily Dermal Exposure (mg/day)[e]	Daily Inhalation Exposure (mg/day)[e]	Eng C Daily Total Exposure (mg/day)[f]	Eng C Daily Absorbed Exposure (mg/day)[g]	Eng C Daily Absorbed Total Exposure (mg/day)[h]
Granular Drop Type Tractor Drawn Spreader Application (7)	n/a	n/a	Corn 4.0	80	n/a	n/a	n/a	n/a	n/a
			Soybeans 3.0		n/a	n/a	n/a		
Mixer/Loader/Applicator Exposure									
Mixing/Loading and Application of Impregnated Dry Bulk Fertilizer (8)	See text								
Flaggers									
Flaggers for Aerial Applications (9)	n/a	n/a	Corn 4.0	350 acres	n/a	n/a	n/a	n/a	n/a
			Soybeans 3.0		n/a	n/a	n/a	n/a	n/a

n/a No longer necessary to carry scenario through analysis as exposure in baseline scenario or with addition of PPE is sufficiently low to calculate an MOE that will exceed 100

a Engineering controls dermal unit exposure represents long pants, long sleeve shirts, closed mixing/loading, closed cab tractor.
Scenarios 1a: chemical resistant gloves.
Scenarios 4 and 5: closed cockpit single layer clothing, and no gloves.

b Baseline inhalation exposure represents no respirator.

c Application rate comes from maximum values found in the alachlor labels EPA Reg Nos. 524-344, 524-403, 524-418, 524-422 and 524-314.

d Daily acres treated are from HED estimates of acreage that could be treated in a single day for each exposure scenario of concern.

e Daily exposure (mg/day) = Exposure (mg/lb ai) * Appl. rate (lb ai/A) * Acres Treated.

f Total daily exposure (mg/day) = daily dermal exposure (mg/day) + daily inhalation exposure (mg/day). Note that this exposure number is used for the intermediate-term scenario only since the NOEL for calculating the MOE is from a dermal study and the use of the dermal absorption factor is not necessary.

g Daily absorbed dermal exposure (mg/day) = daily dermal exposure (mg/day) * dermal absorption factor (0.24)

h Total absorbed daily exposure (mg/day) = daily absorbed dermal exposure (mg/day) + daily inhalation exposure (mg/day) Note that this exposure is used for the short-term scenario only since the NOEL for calculating the MOE is from an oral study and it was necessary to use the dermal absorption factor.

NEW!!

Table 17-D: Alachlor Exposure Estimates to be Used in Short-Term and Intermediate-Term Risk Assessments - Values from Registrant-Submitt
Biomonitoring Studies

Exposure Scenario (Scenario #)	Biomonitoring Internal Estimated Exposure (mg/kg/lb ai)[a]	Adjusted Biomonitoring Internal Estimated Exposure (mg/kg/lb ai)[b]	Crop and Application Rate (lb ai/acre)[c]	Daily Acres Treated[d]	Biomonitoring Internal Dose (mg/kg/day)[e]
Mixer/Loader Exposure					
Mixing/Loading Liquids for Aerial Application and Chemigation (1a)	0.0000126	n/a	Corn 4.0	350	0.01764
Mixing/Loading Liquids for Groundboom Application (1b)			Corn 4.0	80	0.004032
Mixing/Loading Granulars for Drop Type Tractor Drawn Spreaders (2)	n/a	0.0000000647	Corn 4.0	80	0.0000207
Mixing/Loading Dry Flowables for Aerial Application (3a)	n/a	0.000000316	Corn 4.0	350	0.0004424
Mixing/Loading Dry Flowables for Groundboom Application (3b)	n/a	0.00000032	Corn 4.0	80	0.0001024
Applicator Exposure					
Aerial Application of Liquids - Fixed-Wing Aircraft - Enclosed Cockpit (4)	This scenario not performed for biomonitoring data				
Aerial Application of Liquids - Helicopter Aircraft - Enclosed Cockpit (5)	This scenario not performed for biomonitoring data				
Groundboom Application of Liquids - (6)	0.0000126	n/a	Corn 4.0	80	0.004032
Granular Drop Type Tractor Drawn Spreader Application (7)	n/a	0.00000767	Corn 4.0	80	0.002454
Mixer/Loader/Applicator Exposure					
Mixing/Loading and Application of Impregnated Dry Bulk Fertilizer (8)	This scenario not performed for biomonitoring data				
Flaggers					
Flaggers for Aerial Applications (9)	This scenario not performed for biomonitoring data				

n/a = not applicable

a Biomonitoring internal estimated exposure represents Monsanto employees who wore long pants, long sleeve shirts, elbow length rubber gloves, caps, goggles, open mixing/loading, no respirator, closed cab tractor.
b The biomonitoring studies were conducted with liquidformulations. Therefore, these internal estimated exposures are not appropriate for use with granular or dry flowable formulations. In an attempt to estimate the internal estimated exposurea ratio of PHED exposure values that have been converted to baseline absorbed total doses were used in a ratio of other formulation/liquid formulation. The alachlor baseline absorbed total doses are from Table 18.

Scenario 2: (0.0000126 mg/kg/lb ai)(0.019/3.7) = 0.0000000647 mg/kg/lb ai
Scenario 3a: (0.0000126 mg/kg/lb ai)(0.41/16.3) = 0.000000316 mg/kg/lb ai
Scenario 3b: (0.0000126 mg/kg/lb ai)(0.094/3.7) = 0.00000032 mg/kg/lb ai
Scenario 7: (0.0000126 mg/kg/lb ai)(0.014/0.023) = 0.00000767 mg/kg/lb ai

c Application rate comes from the application rate of 4 lbs ai used in the Monsanto study.
d Daily acres treated are from HED estimates of acreage that could be treated in a single day for each exposure scenario of concern.
e Biomonitoring internal dose (mg/kg/day) = Biomonitoring internal estimated exposure (mg/kg/lb ai) * Appl. rate (4 lb ai/A) * Acres Treated/day.

(iii) Post Application Exposure

The potential for post-application worker exposure is negligible, provided the Restricted Entry Interval is observed. This is due to the timing of applications. Alachlor is applied to the soil and/or soil incorporated preplant, pre-emergent, at planting for corn and soybeans, post-transplant for ornamentals, early post-emergent on corn, and at ground-crack for peanuts. This is well before the plants are mature, which mitigates the potential for post-application exposure. Exposure to alachlor during harvesting, even with sweet corn harvesting or seed corn detasseling, is not likely to occur as alachlor is applied primarily preplant and pre-emergent. Therefore, HED does not require that any post-application exposure or residue dissipation monitoring data be generated to support the reregistration of alachlor.

c. Occupational Risk

(i) Short Term Risk

For the short-term risk assessment, a NOEL of 150 mg/kg/day was used to calculate the MOE. HED used a 60 kg body weight, the Agency's default female body weight since the selected endpoint is from a developmental study. Since the NOEL is from an oral study, the dermal absorption factor of 24 percent was used.

(ii) Intermediate Term Risk

For the intermediate-term risk assessment, a NOEL of 50 mg/kg/day was used to calculate the MOE. HED used a 70 kg body weight, the Agency's default male body weight. Since the NOEL is from a 21 day dermal toxicity study, use of the dermal absorption factor is not appropriate.

Estimates of short-term and intermediate-term occupational risk to alachlor are summarized in Tables 18 and 19. All MOEs have been rounded to 1 or 2 significant figures.

Table 18: Short-Term Risk from Alachlor

Exposure Scenario (Scenario #)	Crop/ Rate[a]	Baseline Absorbed Total Dose (mg/kg/day)[b]	Baseline MOE[c]	PPE Absorbed Dose[b] (mg/kg/day)	PPE MOE[c]	Eng. C Absorbed Dose[b] (mg/kg/day)	Eng. C MOE[c]	Biomonitoring Internal Dose (mg/kg/day)[d]	Biomonitoring MOE[c]
Mixer/Loader Exposure									
Mixing/Loading Liquids for Aerial Application and Chemigation (1a)	Corn 4.0	16.3	9	0.27	560	N/A	N/A	0.01764	8500
	Soybean 3.0	12.2	12	0.20	750	N/A	N/A	N/A	N/A
Mixing/Loading Liquids for Groundboom Application (1b)	Corn 4.0	3.7	41	0.061	2,500	N/A	N/A	0.004032	37,000
	Soybean 3.0	2.8	54	0.046	3,300	N/A	N/A	N/A	N/A
Mixing/Loading Granulars for Drop Type Tractor Drawn Spreader Application (2)	Corn 4.0	0.019	7,900	N/A	N/A	N/A	N/A	0.00002070	720,000
	Soybean 3.0	0.014	11,000	N/A	N/A	N/A	N/A	N/A	N/A
Mixing/Loading Dry Flowables for Aerial Application (3a)	Corn 4.0	0.41	370	N/A	N/A	N/A	N/A	0.0004424	34,000
	Soybean 3.0	0.31	480	N/A	N/A	N/A	N/A	N/A	N/A
Mixing/Loading Dry Flowables for Groundboom Application (3b)	Corn 4.0	0.094	1,600	N/A	N/A	N/A	N/A	0.0001024	150,000
	Soybean 3.0	0.07	2,100	N/A	N/A	N/A	N/A	N/A	
Applicator Exposure									
Aerial Application of Liquids - Fixed-Wing Aircraft - Enclosed Cockpit (4)	Corn 4.0	See Eng. Controls	See Eng. Controls	See Eng. Controls	See Eng. Controls	0.030	5000	N/A	N/A
	Soybean 3.0	See Eng. Controls	See Eng. Controls	See Eng. Controls	See Eng. Controls	0.022	6800	N/A	N/A
Aerial Application of Liquids - Helicopter - Enclosed Cockpit (5)	Corn 4.0	See Eng. Controls	See Eng. Controls	See Eng. Controls	See Eng. Controls	0.012	13000	N/A	N/A
	Soybean 3.0	See Eng. Controls	See Eng. Controls	See Eng. Controls	See Eng. Controls	0.009	17000	N/A	N/A
Groundboom Application of Liquids (6)	Corn 4.0	0.023	6,500	N/A	N/A	N/A	N/A	0.004032	35,000
	Soybean 3.0	0.017	8,800	N/A	N/A	N/A	N/A	N/A	N/A
Granular Drop Type Tractor Drawn Spreader Application (7)	Corn 4.0	0.014	11,000	N/A	N/A	N/A	N/A	0.002454	61,000
	Soybean 3.0	0.01	15,000	N/A	N/A	N/A	N/A	N/A	N/A
Mixer/Loader/Applicator									

Exposure Scenario (Scenario #)	Crop/ Rate[a]	Baseline Absorbed Total Dose (mg/kg/day)[b]	Baseline MOE[c]	PPE Absorbed Dose[b] (mg/kg/day)	PPE MOE[c]	Eng. C Absorbed Dose[b] (mg/kg/day)	Eng. C MOE[c]	Biomonitoring Internal Dose (mg/kg/day)[d]	Biomonitoring MOE[c]
Mixing/Loading and Application for Dry Bulk Fertilizer (8)	See text								
Flaggers									
Flaggers for Aerial Applications (9)	Corn 4.0	0.063	2,400	N/A	N/A	N/A	N/A	N/A	N/A
	Soybean 3.0	0.047	3200						

PPE personal protective equipment (See Table 17-B)
Eng. C engineering controls (See Table 17-C)
a Rates are from Alachlor labels EPA Reg Nos. 524-344, 524-403, 524-418, 524-422 and 524-314.
b Absorbed Total Dose ((daily dermal exposure * dermal absorption rate 0.24) + (daily inhalation exposure)) / 60 kg.
c MOE = NOEL (150 mg/kg/day) / absorbed total dose.
d Biomonitoring (See Table 17-D) Estimated only for 4 lb ai.

Table 19: Intermediate-Term Risk from Alachlor

Exposure Scenario (Scenario #)	Crop/ Rate[a]	Baseline Total Dose (mg/kg/day)[b]	Baseline Total Dermal MOE[c]	PPE Daily Total Dose[b] (mg/kg/day)	PPE Total MOE[c]	Eng. C Daily Total Dose[b] (mg/kg/day)	Eng. C Total MOE[c]	Biomonitoring Internal Dose (mg/kg/day)[d]	Biomonitoring MOE[c]
Mixer/Loader Exposure									
Mixing/Loading Liquids for Aerial Application and Chemigation (1a)	Corn 4.0	58.0	0.9	0.54	93	0.18	280	0.01764	2800
	Soybean 3.0	43.5	1	0.39	130	N/A	N/A	N/A	N/A
Mixing/Loading Liquids for Groundboom Application (1b)	Corn 4.0	13.3	4	0.2	250	N/A	N/A	0.004032	12,000
	Soybean 3.0	9.9	5	0.17	300	N/A	N/A	N/A	N/A
Mixing/Loading Granulars for Drop Type Tractor Drawn Application (2)	Corn 4.0	0.04	1,300	N/A	N/A	N/A	N/A	0.0000207	2,400,000
	Soybean 3.0	0.03	1,700					N/A	N/A
Mixing/Loading Dry Flowables for Aerial Application (3a)	Corn 4.0	1.42	35	0.82	61	No data	No data	0.0004424	110,000
	Soybean 3.0	1.05	47	0.61	82			N/A	N/A
Mixing/Loading Dry Flowables for Groundboom Application (3b)	Corn 4.0	0.32	160	N/A	N/A	N/A	N/A	0.0001024	490,000
	Soybean 3.0	0.24	210					N/A	N/A
Applicator Exposure									
Aerial Application of Liquids - Fixed-Wing Aircraft - Enclosed Cockpit (4)	Corn 4.0	See Engineering Controls		See Engineering Controls	See Engineering Controls	0.10	500	N/A	N/A
	Soybean 3.0					0.08	630	N/A	N/A
Aerial Application of Liquids - Helicopter - Enclosed Cockpit (5)	Corn 4.0	See Engineering Controls		See Engineering Controls	See Engineering Controls	0.042	1,200	N/A	N/A
	Soybean 3.0					0.031	1,600	N/A	N/A
Groundboom Application of Liquids (6)	Corn 4.0	0.072	690	N/A	N/A	N/A	N/A	0.004032	12,000
	Soybean 3.0	0.054	930	N/A	N/A	N/A	N/A	N/A	N/A
Granular Drop Type Tractor Drawn Spreader Application (7)	Corn 4.0	0.047	1,100	N/A	N/A	N/A	N/A	0.002454	20,000
	Soybean 3.0	0.036	1,400					N/A	N/A
Mixer/Loader/Applicator									

Exposure Scenario (Scenario #)	Crop/ Rate[a]	Baseline Total Dose (mg/kg/day)[b]	Baseline Total Dermal MOE[c]	PPE Daily Total Dose[b] (mg/kg/day)	PPE Total MOE[c]	Eng. C Daily Total Dose[b] (mg/kg/day)	Eng. C Total MOE[c]	Biomonitoring Internal Dose (mg/kg/day)[d]	Biomonitoring MOE[c]
Mixing/Loading and Application for Dry Bulk Fertilizer (8)	See text								
Flaggers									
Flaggers for Aerial Applications (9)	Corn 4.0	0.206	240	N/A	N/A	N/A	N/A	N/A	N/A
	Soybean 3.0	0.154	330						

N/A - not applicable

a From Alachlor labels EPA Reg Nos. 524-344, 524-403, 524-418, 524-422 and 524-314.
b Total dose = (daily dermal exposure) + (daily inhalation exposure) / 70 kg.
c MOE = NOEL (50 mg/kg/day) / total dose (mg/kg/day).
d Biomonitoring (See Table 17-D) Estimated only for 4 lb ai.

d. Occupational Risk Characterization

(I) Short-Term Exposure

Using the registrant-submitted biomonitoring data, all short-term MOEs are much greater than 100.

Using PHED data for short-term risk the MOEs are more than 100 at **baseline** for scenarios:
(2) mixing/loading granulars for drop type tractor drawn spreader application,
(3a) mixing/loading dry flowables for aerial application,
(3b) mixing/loading dry flowables for groundboom application,
(6) liquid groundboom application,
(7) granular drop type tractor drawn spreader application, and
(9) flaggers

Using PHED data with additional PPE and the corresponding decreases in exposure, the MOEs are more than 100 for short-term risk for scenarios:
(1a) mixing/loading liquids for aerial application and chemigation, and
(1b) mixing/loading liquids for groundboom application.

Using PHED data with engineering controls and the corresponding decreases in exposure, the calculated MOEs are more than 100 for short-term risk for scenarios:
(4) liquid aerial application (fixed-wing), and
(5) liquid aerial application (helicopter).

Thus it was possible to achieve MOEs greater than 100 for all scenarios for which data existed in PHED.

(ii) Intermediate-Term Exposure

Using the registrant-submitted biomonitoring data, all intermediate MOEs are much greater than 100.

Using PHED for intermediate term risk the MOEs are more than 100 at **baseline** for risk for scenarios:
(2) mixing/loading granulars groundboom application,
(3b) mixing/loading dry flowables for groundboom application,
(6) liquid groundboom application, and
(9) flaggers.

Using PHED with additional PPE and the corresponding decreases in exposure the MOEs are more than 100 for intermediate-term risk for scenarios:
(1a) mixing/loading liquids for aerial application (for rate of 3.0 lb ai/acre), and
(1b) mixing/loading liquids for groundboom application.

Using PHED with engineering controls and the corresponding decreases in exposure the calculated MOEs are more than 100 for intermediate-term risk for scenarios:
(1a) mixing/loading liquids for aerial application (for the rates of 4.0 lb ai/acre),
(4) aerial application of liquids (fixed-wing aircraft), and
(5) aerial application of liquids (helicopter).

However, despite available PPE mitigation measures, it was not possible to achieve an MOE of greater than 100 for scenario (3a) mixing/loading dry flowables for aerial application. Therefore, further discussion with the registrant is necessary to evaluate mitigation options for mixing/loading dry flowables for aerial application. The possibility of packaging dry flowable formulation containing alachlor in water-soluble packets may not be practical given the amount of formulation handled in one day for this scenario of use.

Another option to consider may be to limit the amount of alachlor handled by mixer/loaders per day. However, there are concerns with this approach mostly regarding how to track who is handling the alachlor formulations, and for how long. Additionally, HED notes that differences in protective clothing were required to mitigate the same scenario (1a) for the short-term (use of PPE) than for the intermediate-term scenario (use of engineering controls for 4 lbs ai, use of PPE for 3 lbs ai.). The MOEs using PPE for the intermediate term scenario were 93 (4 lbs ai/acre) and 130 (3 lbs ai/acre). The use of a closed mixing system was required to mitigate the 4 lbs a.i./acre, (MOE = 280).

While these approaches demonstrate that achieving MOEs greater than 100 is possible, it will be difficult to write enforceable label requirements to insure that workers with an anticipated short-term exposure are allowed to wear single-layer clothing (baseline), but that workers with an anticipated intermediate-term exposure would wear double layer clothing (PPE). Thus, mitigation will need to address the intermediate-term scenario using the NOEL of 50 mg/kg/day.

Another possible solution would be to continue with the Special Review agreement, that persons applying alachlor to 300 or more acres per year use mechanical transfer (pumping) systems for mixing and loading alachlor. Since, this system is currently in use, this would seem to be a practicable approach.

e. Dry Bulk Fertilizer Scenario

Using information provided by Monsanto, HED estimated MOEs for mixer/loaders using a liquid alachlor product to impregnate dry bulk fertilizer, and for applicators applying the treated fertilizer. (Memo - Boyle, 9/12/97) This assessment was based on information provided to HED by Monsanto in a fax dated August 11, 1997, in which the processes involved in treating fertilizer with

alachlor and applying the treated fertilizer were described and in MRID 444923-02 titled Monsanto Response to the Draft Health Effects Division Science Chapter.

Dry bulk fertilizer impregnated with alachlor is typically prepared by local agricultural dealers, and is then transported to the fields and applied. According to the information provided by Monsanto there is a division of labor, in that most "dealers, even small dealer operations, usually have different individuals running the mixing equipment and applying the mix to fields. This is because of the different skill requirements and for the sake of productivity." Thus, HED performed separate assessments for mixer/loaders, and applicators. If an individual were to mix/load/apply, then the risk would increase correspondingly.

There is also a Granu-Blend system, which is a system for applying granular alachlor at the same time as application of the fertilizer, and is thus similar to the mixer/loader and applicator scenarios for granular materials discussed in other sections of this alachlor RED chapter.

Mixer/Loaders

HED's preliminary review of exposure to workers impregnating dry bulk fertilizer with liquid formulations of alachlor expressed concern over an absence of data and the potential for significant exposure.

According to the labels the blending must be performed by commercial fertilizer or chemical dealerships properly equipped for the procedure. The amount of fertilizer and alachlor handled depends on the number of acres to be treated. According to alachlor labels, from 200 to 450 lbs. of impregnated fertilizer may be applied per acre, preplant to corn, grain sorghum, and soybeans. The maximum application rate for alachlor is 4 lbs ai/acre per new labels submitted to the Agency, December 30, 1997.

The Agency's Biological and Economic Analysis Division provided (April 28, 1998, memo George Keitt) provided the following information obtained through the University of Illinois Extension Service: The herbicide is metered from a mini-bulk tank (several hundred gallons) to a mixing drum via a closed system. The herbicide is sprayed onto the fertilizer, which is stirred by an auger that lifts it to the top of the drum. After impregnation, the treated fertilizer is gravity-fed through a hopper onto a conveyor belt leading to an auger truck, which carries it to the field. At the field, the auger truck feeds the treated fertilizer onto the applicator vehicle, which dispenses it from either a rotary spinner or a boom with numerous outlets. The transfer of the treated fertilizer in each instance is nearly dust-free, as it has been moistened by the herbicide. Because all processes are mechanized, there is minimal contact of either the mixer at the treatment site or the loader at the transfer sites. Applicator exposure is minimized by the use of a closed cab.

The information supplied by Monsanto indicates that impregnation of fertilizer in a mixing tower is typically a closed system operation. Monsanto provided a diagram of a mixing/loading tower which specifies that up to 120 tons of fertilizer can be processed per hour. If the tower were assumed to process for 8 hours per day, then this would be 960 tons of fertilizer processed per 8 hour day. At 4 lbs, or 3 lbs active ingredient per 200 lbs fertilizer, each ton of fertilizer would require 40 lbs,

or 30 lbs of alachlor active ingredient. Thus, the total amount of active ingredient for 960 tons for 4 lbs ai handled is (960)(40) = 38400 lbs, for 3 lbs ai handled is (960)(30) = 28800 lbs. The new information submitted by Monsanto and confirmed by the BEAD memo has specified that the typical or average fertilizer use rate is approximately 400 lbs/acre. At 4 lbs active ingredient per 400 lbs fertilizer, each ton of fertilizer would require 20 lbs of alachlor active ingredient. Thus, the total amount (based on 400lbs fertilizer per acre) for 4 lbs ai handled is (960)(20) = 19200 lbs.

Using the above information, HED has estimated risk for mixers/loaders impregnating the dry bulk fertilizer assuming use of engineering controls (metered delivery from a mini-bulk tank). Only the dermal values will be used in this assessment since, technical alachlor is classified as toxicity category III, and for liquids, the unit inhalation exposure value is insignificant (differing by several orders of magnitude) when compared to the unit dermal exposure value.

Daily exposure (mg/day) is estimated using the following equation:

unit exposure (mg/lb ai) x lbs ai handled per day

Daily dose (mg/kg/day) is calculated by dividing the daily exposure (mg/day) by the body weight (bw) of the worker. For the short-term scenario, HED used a 60 kg body weight, the Agency's default adult female body weight since the selected endpoint is from a developmental study. Since the selected endpoint is from an oral study, the exposure must be adjusted to account for dermal exposure. The dermal absorption factor is 24 percent (0.24).

Thus, for the short-term scenario, absorbed daily dose = daily exposure (mg/day) / 60 kg x 0.24.

For the intermediate-term scenario, HED used a 70 kg body weight, the Agency's default adult male body weight. Since the selected endpoint is from a dermal toxicitystudy, the use of the dermal absorption factor is not appropriate.

Thus, for the intermediate-term scenario, daily dose = daily exposure (mg/day) / 70 kg.

Risk, in terms of margins of exposure (MOE), is calculated by using the following equation:

NOEL (mg/kg/day) / daily dose (mg/kg/day) = MOE.

All MOEs are rounded to one or two significant digits. For the short-term scenario, the NOEL is 150 mg/kg/day. For the intermediate-term scenario, the NOEL is 50 mg/kg/day. HED has no concerns for an MOE greater than or equal to 100.

The PHED V1.1 unit dermal exposure for a closed mixing/loading mechanical transfer system (single layer clothing - with gloves) is 0.009 mg/lbs ai - high confidence.

Table 20-A: Short-Term with Engineering Controls (Closed Transfer System)

Unit Exposure (mg/lbs ai)	Application Rate (lbs ai/day)	Daily Exposure (mg/day)	Daily Dose (mg/kg/day)	MOE
0.009	38400	346	1.38	110
0.009	28800	259	1.04	140
0.009	19200	173	0.69	220

Table 20-B: Intermediate-Term with Engineering Controls (Closed Transfer System)

Unit Exposure (mg/lbs ai)	Application Rate (lbs ai/day)	Daily Exposure (mg/day)	Daily Dose (mg/kg/day)	MOE
0.009	38400	346	4.9	10
0.009	28800	259	3.7	14
0.009	19200	173	2.5	20

HED made assumptions in performing this assessment and acknowledges that many of the assumptions were deliberately intended toward performing an upper-end assessment. One of the most conservative of these assumptions was that the mixing tower would run at full capacity for 8 hours a day, thus generating 960 tons of alachlor impregnated fertilizer. At 200 lbs per acre this corresponds to 9600 acres per day. At 400 lbs per acre this corresponds to 4800 acres per day. It could require "many" trucks to spread 9600 acres or 4800 acres in one day. The impregnated fertilizer market is likely to be a custom operation, in that (1) the blending occurs on an as needed/as ordered basis, and (2) only the amount ordered is prepared .

All intermediate-term MOEs are less than 100; however, HED acknowledges that the estimation of these MOEs did contain the conservative estimate of the mixing tower working 8 hours per day/ The short-term MOEs are greater than 100 considering mitigation with a closed transfer system. It should be remembered that only the dermal exposure - no inhalation - was considered.

HED also has concerns that the data in PHED may not adequately represent this scenario. This is not a typical usage under agricultural field conditions. The amount of alachlor necessary to impregnate the tons of fertilizer that can be processed in a day is far too large to be handled by opening individual bottlesor containers (as data collected for PHED), and probably involves transfer from huge containers such as tanker trucks or railroad tank cars.

It is recognized that extrapolating a unit exposure in the range of 19200 to 38400 lb ai/day from the available data in PHED is likely to result in an over-estimate. HED does not have any bulk transfer/loading data. This type of exposure data may be necessary for refining this assessment, and a possible option for Monsanto would be to supply data per GLN 875.2400 (dermal exposure) and GLN 875.2500 (inhalation exposure) for mixer/loaders.

Applicators - Baseline - Open Cab

HED has no data for spreader trucks applying treated fertilizer, and therefore selected from PHED "solid broadcast spreader application - open cab". The dermal unit exposure value (baseline - single layer clothing, no gloves, open cab) for a granular drop-type spreader applicator is 0.01 mg/lb ai, and the inhalation unit exposure value (baseline - open cab) is 0.0012 mg/lbs ai (PHED V1.1, **low confidence dermal and inhalation**). Inhalation and dermal unit exposures will be combined for the applicator scenario since the values are within two orders of magnitude.

MOEs for both the short-term and intermediate-term scenarios have been estimated. However, HED believes that the intermediate-term scenario is the most appropriate, since available information indicates that for pre-plant herbicide and fertilizer applications that a "window" of approximately 28 days is available once the weather and field conditions are right and the equipment can enter the fields.

For the short-term scenario, the total daily absorbed exposure (mg/day) is estimated using the following equation:

[dermal unit exposure (mg/lb ai) x application rate (lbs ai/acre) x number of acres treated x dermal absorption factor] + [inhalation unit exposure (mg/lb ai) x application rate (lbs ai/acre) x number of acres treated]

Given:

dermal unit exposure value = 0.01 mg/lbs ai,
inhalation unit exposure value = 0.0012 mg/lbs ai,
maximum application rate is 4 lbs ai per acre,
max number of acres treated is 800
typical number of acres treated is 500
dermal absorption factor is 0.24

Therefore:

Max total daily absorbed exposure = (0.01)(4)(800)(.24) + (0.0012)(4)(800)
= 11.52 mg/day.
Typical total daily absorbed exposure = (0.01)(4)(500)(.24) + (0.0012)(4)(500)
= 7.2 mg/day

Total daily absorbed dose (mg/kg/day) is calculated by dividing the total daily absorbed exposure (mg/day) by 60 kg, the Agency's default adult female body weight.

Max total daily dose = 11.52 mg/day / 60 kg = 0.192 mg/kg/day

Typical total daily dose = 7.2 mg/day / 60 kg = 0.12 mg/kg/day

Risk is estimated by using the following equation:

MOE = NOEL (mg/kg/day) / max total daily dose (mg/kg/day) = 150/ 0.192 = 780

MOE = NOEL (mg/kg/day) / typical total daily dose (mg/kg/day) = 150/ 0.12 = 1300

For the short-term scenario, the MOE for applicators applying fertilizer impregnated with alachlor at the maximum application rate of 4 lbs ai to 800 acres per day is 780, to 500 acres per day is 1300. If lower application rates such as 3 lb ai/acre were to be used in the calculation, the MOEs would be even higher.

For the intermediate-term scenario, the total daily exposure (mg/day) is calculated using the following equation:

[dermal unit exposure (mg/lb ai) x application rate (lbs ai/acre) x number of acres treated] + [inhalation unit exposure (mg/lb ai) x application rate (lbs ai/acre) x number of acres treated]

Given:

dermal unit exposure value = 0.01 mg/lbs ai,
inhalation unit exposure value = 0.0012 mg/lbs ai,
maximum application rate is 4 lbs ai per acre,
max number of acres treated is 800
typical number of acres treated is 500

Therefore:

Max total daily exposure = (0.01)(4)(800) + (0.0012)(4)(800) = 35.84 mg/day.

Typical total daily exposure = (0.01)(4)(500) + (0.0012)(4)(500) = 22.4 mg/day

Total daily dose (mg/kg/day) is calculated by dividing the daily exposure (mg/day) by 70 kg, the Agency's default male body weight.

Max total daily dose = 35.84 (mg/day)/ 70 kg = 0.512 mg/kg/day

Typical total daily dose = 22.4 (mg/day)/ 70 kg = 0.32 mg/kg/day

Risk is estimated by using the following equation:

MOE = NOEL (mg/kg/day) / max total daily dose (mg/kg/day) = 50 / 0.512 = 98

MOE = NOEL (mg/kg/day) / typical total daily dose (mg/kg/day) = 50/0.32 = 160

For the intermediate-term scenario, the MOE for applicators applying fertilizer impregnated with alachlor equals 98 at the 4 lbs ai rate for 800 acres and 160 at the 4 lbs ai rate for 500 acres.

HED made assumptions in performing this assessment and acknowledges that many of the assumptions used in estimating the risk range were deliberately intended toward performing an upper-end assessment. Additionally, HED had only low confidence data due to the number of replicates (5) in PHED.

Applicators - Use of Engineering Controls

HED has no data for spreader trucks applying treated fertilizer, and therefore selected from PHED "solid broadcast spreader application - closed cab". The dermal unit exposure value (closed cab) is 0.002 mg/lb ai, and the inhalation unit exposure value (closed cab) is 0.00022 mg/lbs ai (PHED V1.1, **low confidence dermal; high confidence hands and inhalation; no PFs were used**). Inhalation and dermal unit exposures will be combined for the applicator scenario since the values are within two orders of magnitude.

MOEs for both the short-term and intermediate-term scenarios have been estimated.

For the short-term scenario, the total daily absorbed exposure (mg/day) is estimated using the following equation:

[dermal unit exposure (mg/lb ai) x application rate (lbs ai/acre) x number of acres treated x dermal absorption factor] + [inhalation unit exposure (mg/lb ai) x application rate (lbs ai/acre) x number of acres treated]

Given:

dermal unit exposure value = 0.002 mg/lbs ai,
inhalation unit exposure value = 0.00022 mg/lbs ai,
maximum application rate is 4 lbs ai per acre,
max number of acres treated is 800
typical number of acres treated is 500
dermal absorption factor is 0.24

Therefore:

Max total daily absorbed exposure = (0.002)(4)(800)(.24) + (0.00022)(4)(800)
= 2.24 mg/day.
Typical total daily absorbed exposure = (0.002)(4)(500)(.24) + (0.00022)(4)(500)
= 1.4 mg/day

Total daily absorbed dose (mg/kg/day) is calculated by dividing the total daily absorbed exposure (mg/day) by 60 kg, the Agency's default adult female body weight.

Max total daily dose = 2.24 (mg/day)/ 60 kg = 0.037 mg/kg/day

Typical total daily dose = 1.4 (mg/day)/ 60 kg = 0.0233 mg/kg/day

Risk is estimated by using the following equation:

MOE = NOEL (mg/kg/day) / max total daily dose (mg/kg/day) = 150/ 0.037 = 4000

MOE = NOEL (mg/kg/day) / typical total daily dose (mg/kg/day)
= 150/0.0233 = 6400

For the short-term scenario, the MOE for applicators applying fertilizer impregnated with alachlor at the maximum application rate of 4 lbs ai to 800 acres per day is 4000, to 500 acres is 6400. If lower application rates such as 3 lbs ai were to be used in the calculation, the MOEs would be even higher.

For the intermediate-term scenario, the total daily exposure (mg/day) is calculated using the following equation:

[dermal unit exposure (mg/lb ai) x application rate (lbs ai/acre) x number of acres treated] + [inhalation unit exposure (mg/lb ai) x application rate (lbs ai/acre) x number of acres treated]

Given:

dermal unit exposure value = 0.002 mg/lbs ai,
inhalation unit exposure value = 0.00022 mg/lbs ai,
maximum application rate is 4 lbs ai per acre,
max number of acres treated is 800
typical number of acres treated is 500

Therefore:

Max total daily exposure = (0.002)(4)(800) + (0.00022)(4)(800) = 7.1 mg/day.

Typical total daily exposure = (0.002)(4)(500) + (0.00022)(4)(500) = 4.44 mg/day

Total daily dose (mg/kg/day) is calculated by dividing the daily exposure (mg/day) by 70 kg, the Agency's default male body weight.

Max total daily dose = 7.1 (mg/day)/ 70 kg = 0.101 mg/kg/day

Typical total daily dose = 4.44 (mg/day)/ 70 kg = 0.063 mg/kg/day

Risk is estimated by using the following equation:

MOE = NOEL (mg/kg/day) / max total daily dose (mg/kg/day) = 50/0.101 = 490

MOE = NOEL (mg/kg/day) / typical total daily dose (mg/kg/day) = 50/0.063 = 790

For the intermediate-term scenario, the MOE for applicators applying fertilizer impregnated with alachlor using a closed cab equals at the 4 lbs ai rate to 800 acres is 490, to 500 acres is 790.

All MOEs both short-term and intermediate-term are greater than HED's level of concern of 100. Therefore, HED has no concerns for applicators in closed cabs applying alachlor impregnated fertilizer.

f. Additional Occupational Exposure Studies

(I) Handler Studies

Optimally, worker exposure assessments are based on adequate data of acceptable quality. Handler exposure studies are sometimes required for reregistration in situations in which no data or no acceptable data exist. Exposure study data are desirable for alachlor for the process of impregnating dry bulk fertilizer. While the HED has used PHED data is its assessment, The PHED data used is not directly related to a process such impregnating dry bulk fertilizer. It appears that this is a closed system; however, exposure may be significant based on the large volumes of alachlor involved. PHED does not contain any data for transferring from mini-bulk containers. Therefore, additional confirmatory data are required. The confirmatory data should address the dry bulk fertilizer impregnation process. This should address both dermal and inhalation data at both outdoor and indoor (at least partially enclosed) sites.

(ii) Post-Application Studies

HED believes that, based on the current uses of alachlor, post-application exposure will be low and therefore is not requiring post-application exposure studies at this time.

C. FQPA CONSIDERATIONS

1. Cumulative Effects

Alachlor is a member of the acetanilide class of herbicides. It is structurally similar to acetochlor, butachlor, metolachlor, and propachlor.

Section 408(b)(2)(D)(v) of FQPA 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." The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, but also policies and methodologies for conducting cumulative risk assessments. For most pesticides, the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a

common mechanism of toxicity with any other substances. However, at this time the Agency does not have the methodology to resolve the scientific issues concerning common mechanism of toxicity in a meaningful way. The Agency has begun a pilot process to study this issue further through the examination of particular classes of pesticides. Hopefully, the results of this pilot process will enable the Agency to develop and apply policies for evaluating the cumulative effects of chemicals having a common mechanism of toxicity. At present, however, the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments. Exceptions include pesticides that are toxicologically and structurally dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case the metabolite must be assessed as part of a common mechanism assessment).

In making individual tolerance decisions, the Agency will determine whether:

1) it has sufficient information to determine that a pesticide does not appear to share a common mechanism of toxicity with other substances;

2) it is unable to conclude that a pesticide does not share a common mechanism of toxicity with other substances; or

3) it is able to conclude that a pesticide does share a common mechanism of activity with other substances.

Due to the structural similarities with acetochlor, metolachlor, butachlor, and propachlor, alachlor may fall into the second category. However, at this time the Agency has not yet made a final decision concerning a possible common mechanism of toxicity for these five chemicals to scientifically apply that information to the tolerance decision. The process has begun, but is not yet completed. Therefore, for the purposes of this decision document, the tolerance decision will be reached based upon the best available and useful information for alachlor only. The risk assessment has been performed for alachlor only assuming that no common mechanism of toxicity exists. However, these decisions will be reexamined after methodologies and procedures for integrating information concerning common mechanism of toxicity into risk assessments are developed by the Agency.

Monsanto must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether alachlor shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for alachlor need to be modified or revoked.

2. Endocrine Disruptor Effects

The Agency is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." The Agency

is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1996) to implement this program. At that time, EPA may require even further testing of alachlor for endocrine disruptor effects.

3. Use of Anticipated Residues

Section 408(b)(2)(E) requires that if a tolerance relies on anticipated or actual residue levels, that the Agency make a determination every five years as to the reliability of the data, i.e. that the current residue levels are not above the levels relied on.

For alachlor, anticipated residues were based on the average residue found in field trials where alachlor was used at the maximum application rate. Results of processing studies were also used to adjust the residue levels found in the raw commodity to account for changes in residue levels due to processing (both commercial and other types of processing). For anticipated residues for milk, poultry and eggs, instead of using tolerances as the level of alachlor present in the feed items, anticipated residues as calculated for food /feed crops were used in the calculation.

To provide for the periodic evaluation of these anticipated residues, the Agency will require under Section 408(b)(2)(E) residue data to be submitted every 5 years as long as the tolerances remain in force.

4. Use of Percent Crop-Treated Data

Section 408(b)(2)(F) requires that if a tolerance relies on percent crop-treated data, that the Agency make a determination as to the reliability of the data.

Percent crop-treated estimates are derived from federal and private market survey data. Typically, a range is assumed for the exposure assessment. By using this upper end estimate of percent crop treated, the Agency is reasonably certain that exposure is not understated for any significant population sub-group. Additionally, the DRES (Dietary Risk Evaluation System) modeling used in estimating chronic dietary risk uses regional consumption information to estimate exposure for four population sub-groups that are geographically based regions of the United States. None of these sub-groups exceeded the Agency's level of concern.

To provide for the periodic evaluation of these estimates of percent crop treated, the Agency will require under Section 408(b)(2)(F) percent crop treated data to be submitted every 5 years as long as the tolerances remain in force.

5. FQPA 10X Factor

The Health Effects Division (HED) FQPA Safety Factor Committee met on March 30, 1998 to evaluate the hazard and exposure data for alachlor and recommend application of the FQPA Safety Factor (as required by FQPA), to ensure the protection of infants and children from

exposure to this chemical. The Committee recommended that the 10x Safety Factor for enhanced sensitivity to infants and children (as required by FQPA) should be removed.

6. Determination of Safety

Determination of safety includes consideration of special sensitivity to children, potential cumulative effects with pesticides that have a common mode of toxicity and aggregate risks resulting from exposure to dietary residues, residues in drinking water, and residential sources.

The database for developmental and reproductive toxicity of alachlor is considered to be complete at this time. There is no unique or special sensitivity for pre- or post-natal exposure. Based on these two factors, the Agency has concluded that the results of these data did not raise concerns regarding the use of 100 as the uncertainty factor.

The Agency has determined that consideration of a common mode of toxicity with other chemicals such as acetochlor, butachlor, metolachlor, and propachlor is not appropriate at this time. Tolerance reassessments have occurred in the RED as a result of new data on the concentrations of alachlor residues present in food. However, tolerance reassessments as required under FQPA cannot occur until a determination of common mode is made and the cumulative risk assessments is performed.

There are no residential uses of alachlor. Aggregate risk from exposure to alachlor in food and water, do not result in aggregate risk that exceed HED's level of concern.

D. HED RECOMMENDATIONS FOR RISK MITIGATION

1. TOLERANCE REASSESSMENT SUMMARY

The tolerances listed in 40 CFR §180.249 are for the combined residues of alachlor and its metabolites (calculated as alachlor).

On June 22, 1993, the HED Metabolism Committee determined that all alachlor metabolites which can be converted to 2,6-diethylaniline (DEA) and 2-ethyl-6-(1-hydroxyethyl)aniline (1-HEEA) upon basic hydrolysis are to be regulated and will be included in the tolerance expression. Therefore, the tolerance expression in 40 CFR §180.249 should be modified as follows: "Tolerances are established for the combined residues of the herbicide alachlor (2-chloro-2',6'-diethyl-*N*-(methoxymethyl) acetanilide) and its metabolites which can be converted to 2,6-diethylaniline or 2-ethyl-6-(1-hydroxyethyl)aniline upon basic hydrolysis, (calculated as alachlor), in or on the following raw agricultural commodities: ...".

Thus, for some commodities tolerance increases will be necessary. The more recent residue chemistry data reflect analysis for two classes of alachlor metabolites (DEA and HEEA); whereas some of the older data used to establish the existing tolerances reflect analysis for DEA metabolites only.

Sufficient data are available to ascertain the adequacy of the established tolerances listed in 40 CFR §180.249 for sorghum grain and fodder; eggs; milk; and fat, meat, and meat byproducts of cattle, goats, hogs, horses, poultry, and sheep; see Table 21 for modifications in commodity definitions.

Additional field residue data are required for the following commodities: beans, succulent and dry; corn, field, grain, forage, and stover; corn, pop, grain, and stover (translated from field corn grain); corn, sweet (K + CWHR); and sweet corn, forage and stover; alternatively, all preemergence uses on beans, succulent and dry; all post emergence uses of the EC formulation on field corn; all post emergence uses and sequential uses of the EC formulation and all uses in excess of 4 lb ai/A on sweet corn and soybeans may be removed from all alachlor labels. Tolerances for these commodities have been reassessed based on available data.

Tolerances have been proposed for the following commodities: bean forage and fodder at 5.0 ppm (PP#3F4179); corn forage and fodder at 2.0 ppm (PP#0F2348); peanuts, peanut hulls, and peanut meal at 1, 8 and 1 ppm, respectively (PP#0F2313/FAP#1H5612); sorghum forage at 2 ppm (PP#8F3671); and soybean grain, soybean hulls, and soybean grain dust at 0.2, 1, and 2 ppm, respectively (PP#9F3776/FAP#2H5629). Higher tolerances must be proposed for soybean grain and soybean aspirated grain fractions; and a lower tolerance (than the proposed 1 ppm) must be proposed for peanuts; see Table 21.

Field rotational crop studies are still required for a root crop and a leafy vegetable; rotational crop tolerances are needed. Monsanto is initiating studies to support cereal grains (except rice), non-grass animal feeds, cotton, and sunflowers as rotational crops.

Table 21: Tolerance Reassessment Summary.

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	*Correct Commodity Definition*/Comment
Beans, dry	0.1	0.1	
Beans, forage	0.2	5.0 [(2)]	*Cowpeas, forage*
Beans, hay	0.2	5.0 [(2)]	*Cowpeas, hay*
Beans, lima (green)	0.1	0.1	*Beans, succulent lima*
Cattle, fat	0.02	0.02	
Cattle, mbyp	0.02	0.02	
Cattle, meat	0.02	0.02	

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	*Correct Commodity Definition*/Comment
Corn, fodder	0.2	2.0[1]	*Corn, field, stover* *Corn, pop, stover* *Corn, sweet, stover* Postemergence uses must be removed from all EC labels, or use limited to 4 lb. ai/A/season
Corn, forage	0.2	2.0[1]	*Corn, field, forage* *Corn, sweet, forage* Postemergence uses must be removed from all EC labels, or use limited to 4 lb. ai/A/season
Corn, fresh (inc. sweet K+CWHR)	0.05	0.05	*Corn, sweet (K+CWHR)* Post-emergence and sequential uses must be removed from all labels and use must be limited to 4 lb ai/A.
Corn, grain	0.2	0.2	*Corn, field, grain* *Corn, field, pop* Postemergence uses must be removed from all EC labels, or use limited to 4 lb. ai/A/season
Eggs	0.02	0.02	
Goats, fat	0.02	0.02	
Goats, mbyp	0.02	0.02	
Goats, meat	0.02	0.02	
Hogs, fat	0.02	0.02	
Hogs, mbyp	0.02	0.02	
Hogs, meat	0.02	0.02	
Horses, fat	0.02	0.02	
Horses, mbyp	0.02	0.02	

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	*Correct Commodity Definition*/Comment
Horses, meat	0.02	0.02	
Milk	0.02	0.02	
Peanuts	0.05	0.5[3]	PP# 0F2313 to be amended
Peanuts, forage	3.0	Revoke	Feeding restrictions exist; not considered a major livestock feed.
Peanuts, hay	3.0	Revoke	Feeding restrictions exist.
Peanuts, hulls	1.5	Revoke	Based on Table II, peanut hulls are not considered to be a major livestock feed. Note that PP#0F2313 had proposed a tolerance of 8 ppm.
Poultry, fat	0.02	0.02	
Poultry, mbyp	0.02	0.02	
Poultry, meat	0.02	0.02	
Sheep, fat	0.02	0.02	
Sheep, mbyp	0.02	0.02	
Sheep, meat	0.02	0.02	
Sorghum, fodder	1.0	1.0	*Sorghum, grain, stover*
Sorghum, forage	2.0	2.0	*Sorghum, grain, forage*
Sorghum, grain (milo)	0.1	0.1	*Sorghum, grain, grain*
Soybeans	0.2	1[3]	PP#9F3776
Soybeans, forage	0.75	Revoke	All alachlor products with uses on soybeans have feeding restrictions or are in the process of being cancelled.

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	*Correct Commodity Definition*/Comment
Soybeans, hay	0.2	Revoke	All alachlor products with uses on soybeans have feeding restrictions or are in the process of being cancelled.
Proposed Tolerances:			
Peanut meal (FAP#1H5612)	none	petition should be withdrawn	The proposed food and feed tolerance of 1 ppm is not needed.
Soybean grain dust (PP#9F3776)	none	10	*Soybeans, aspirated grain fractions*
Soybean hulls (FAP#2H5629)	none	petition should be withdrawn	No food or feed additive tolerances are needed for any soybean product.

(1) PP#0F2348 Data are available to support the G formulation of alachlor on sweet corn applied preplant incorporated and preemergence at up to 4 lb ai/A. Data are available to support the use of the Mcap/G formulation on sweet corn: preemergence and preplant incorporated and postemergence at 4 lb ai/A.

(2) PP#3F4179 The available data indicate that the combined residues of alachlor and its DEA and HEEA metabolites in bean forage/vines will exceed the established tolerance of 0.2 ppm following preplant incorporated treatment at 3 lb ai/A. The maximum combined residues in/on lima bean forage/vines were 1.1 ppm; in/on dry bean and lima bean forage were 0.68 ppm; in/on dry bean and lima bean straw were 1.9 ppm; in/on dry bean forage were 2.0 ppm; in/on dry bean vines were 1.1 ppm; and in/on dry bean straw were 4.1 ppm. The available data will support a single preplant incorporated application to dry beans and lima beans at 3 lb a.i./A. The proposed tolerances are appropriate for a single preplant incorporation of alachlor at 3 lb a.i./A. However, preemergence uses must be removed from the label or a full set of residue data must be submitted reflecting pre-emergence uses on dry beans and lima beans at the maximum rate on the label.

(3) At the time that the existing tolerances were established, residue data reflected analysis for alachlor per se and those alachlor metabolites that contained the DEA moiety. Newer residue data reflects analysis for alachlor per se and two classes of alachlor metabolites, those containing

the HEEA moiety and those containing the DEA moiety. The tolerance increases are necessary to account for the increase(s) in detected residues.

2. CODEX HARMONIZATION

No maximum residue limits (MRLs) for alachlor have been established by Codex for any agricultural commodity. Therefore, no questions of compatibility exist with respect to U.S. tolerances.

3. REGULATORY POSITION AND LABELING RATIONALE - RESERVED

4. LABEL REQUIREMENTS

When end-use product DCIs are developed (e.g., at issuance of the RED), RD should require that all end-use product labels (e.g. MAI labels, SLNs, and products subject to the generic data exemption) be amended such that they are consistent with the basic producer labels.

Preemergence uses on dry beans and succulent lima beans must be removed from all alachlor labels or supporting residue data provided to support preemergence uses on dry beans and succulent lima beans which remain on some product labels (red kidney beans in IL and WI, mung beans in OK).

Postemergence and sequential uses on soybeans must be removed from all alachlor labels or supporting non-Craven data submitted.

Label revisions are needed, limiting use to one preplant application per season for all bean commodities or supporting data for preemergence applications are needed.

Additional residue data on field corn are required to support sequential uses for the EC formulation. Monsanto has elected to delete the postemergent uses on field corn from the EC labels rather than generate additional residue data at this time. (Letter Monsanto May 20, 1996)

Postemergence and sequential uses on sweet corn must be removed from all alachlor labels or supporting data submitted.

Postemergence and sequential uses of the EC formulation on sweet corn and all uses of alachlor on sweet corn in excess of 4 lb a.i./A must be removed from all alachlor labels or supporting data provided.

Label restrictions prohibiting rotation to crops not specified on the label are required if field rotational crop studies (root crop and leafy crop) are not submitted.

13544

R060800

Chemical:	**Alachlor**
PC Code:	**090501**
HED File Code	**12000 Exposure Reviews**
Memo Date:	**05/18/98 12:00:00 AM**
File ID:	**DPD185214; DPD186162**
Accession Number:	***412-04-0047***

HED Records Reference Center
04/05/2004