2-3-94

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: HED Risk Assessment for Use of Acetochlor on Field Corn.
DP No. 196166.

FROM: Stephanie H. Willett, Chemical Manager SHW 2/2/94
Registration Section
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THRU: Albin Kocialski, PhD, Section Head
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Health Effects Division (7509C)

ABK 2/3/94

TO: Robert Taylor/Vickie Walters, PM Team 25
Fungicide-Herbicide Branch
Registration Division (7505C)

As requested, HED has completed a risk assessment for use of acetochlor on field corn. Based on the data available at this time, exposure to acetochlor via the diet is estimated to result in a theoretical maximum exposure accounting for not more than 0.6% of the RfD. The upper bound carcinogenic risk from the corn and rotational crop tolerances was calculated to be 2.2×10^{-6}. The assumptions used may overestimate the dietary risk. The excess cancer risk to workers ranges from 1.8×10^{-6} to 4.2×10^{-5}. This assessment assumes that acetochlor will be used at the maximum use rates. A complete HED data summary and discussion of this risk assessment is provided in the attached document.

A summary of some pertinent TOX and dietary exposure data for acetochlor and alternative corn herbicides is also being provided, as requested in the 1/13/94 memo from Allen Jennings to Stephen Johnson.

If additional input is needed, please advise.

Revised 2/1/94

SUMMARY TABLE: HED TOX AND DIETARY EXPOSURE DATA ON ACETOCHLOR AND ALTERNATIVE PESTICIDES

CHEMICAL	CARCINOGENICITY EVALUATION		CHRONIC DIETARY EXPOSURE		COMMENTS
	HED/SAP	Q_1^*	RfD (mg/kg/d)	% RfD Used[4] (General Pop)	
Acetochlor	B2/B2	0.017	0.02	0.6	
2,4-D[1]	D/D	N/A	0.003	710	Data Gaps-Once, Chronic, Dev.
Alachlor	B2/B2	0.08	0.01	6.2	
Atrazine	Cq[2]/C	0.22	0.035	2.8	
Butylate	E	N/A	0.05	0.1	
Cyanazine	Cq	0.84, 1.0[3]	0.002	8.6	
Dicamba	E	N/A	0.03	0.06	Data Gaps-Repro., Dev.
Dimethanid (SAN 582)	C	N/A	0.05	0.01	
EPTC	E	N/A	0.025	4.0	Data Gap-Dev.
Flumetsulam	E	N/A	1.0	0.003	
Metolachlor	Cq[2]/C	0.009	0.1	1.5	
Nicosulfuron (Accent)	E	N/A	1.25	0.003	
Primisulfuron (Beacon)	D	N/A	0.006	9.5	

1 Cancer Peer Review scheduled for February 1994.
2 HED evaluation was used for comparison in the following table.
3 As determined by HED and CRAVE, respectively.
4 Includes all registered uses.

Revised 2/1/94

COMPARISON TABLE: ACETOCHLOR AND ALTERNATIVE PESTICIDES RANKED "BEST TO WORST"

Ranked According to Carcinogenicity Evaluation[1]	Ranked According to Q_1^* [2]	Ranked According to RfD[3]	Ranked According to % RfD Utilized[4]
E EPTC	Metolachlor	Nicosulfuron	Flumetsulam
Butylate	**Acetochlor**	Flumetsulam	Nicosulfuron
Dicamba	Alachlor	Metolachlor	Dimethanid
Flumetsulam	Atrazine	Butylate	Dicamba
Nicosulfuron	Cyanazine	Dimethanid	Butylate
D 2,4-D		Atrazine	**Acetochlor**
Primisulfuron		Dicamba	Metolachlor
C Dimethanid		EPTC	Atrazine
Cq Metolachlor		**Acetochlor**	EPTC
Atrazine		Alachlor	Alachlor
Cyanazine		Primisulfuron	Cyanazine
B2 **Acetochlor**		2,4-D	Primisulfuron
Alachlor		Cyanazine	2,4-D

1 Ranking is from conclusive evidence for being noncarcinogenic to humans (E), to nonclassifiable as a human carcinogen (D), to most positive evidence for human carcinogenicity (C, Cq, B2); chemicals which appear together are comparable.

2 Ranking is from lowest Q_1^* value to highest. This information is not as relevant as the carcinogenicity evaluation in column 1.

3 Ranking is from highest RfD value to lowest.

4 Ranking is from lowest % RfD utilized to highest % RfD utilized. Please note that none of these chemicals are RfD exceeders, with the exception of 2,4-D.

HED DATA SUMMARY AND HUMAN HEALTH RISK ASSESSMENT RESULTING FROM USE OF ACETOCHLOR ON CORN

I. BACKGROUND

Monsanto and ICI/Zeneca are cooperatively, as the Acetochlor Registration Partnership, pursuing the registration of the active ingredient acetochlor (ID No. 66748-R) and an EC formulation (66478-E). From 1983 until April of 1993, both companies were independently pursuing the registration of acetochlor. The proposed use is for field corn, silage corn and popcorn to control or suppress growth of several types of weeds (broadleaf, grass and sedge). Both Monsanto and ICI previously requested, and were issued EUPs and temporary tolerances for this use.

The Health Effects Division has evaluated the majority of the acetochlor study data. A summary of the findings and an assessment of human risk resulting from the proposed use of acetochlor are provided in this document.

II. USE PATTERN

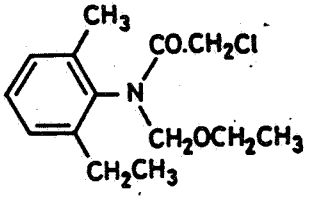
Acetochlor EC may be applied preemergence to the surface or incorporated into the top 1-2 inch layer of soil, or by chemigation before emergence of corn. It may be used alone or tank mixed with other pesticides. The application rate ranges from 1.6 to 3 lb ai/A, depending on the soil type.

Acetochlor EC will be a restricted use pesticide. The label says to wear a disposable suit, coveralls or long-sleeved shirt and pants, mid-forearm chemical resistant glove, waterproof boots and goggles or full-face shield when handling or mixing concentrate. The signal word for humans and domestic animals is "warning".

III. PRODUCT CHEMISTRY

Common Name: Acetochlor

Chemical Name: 2-chloro-2'-methyl-6'ethyl-N-ethoxymethyl-acetanilide



Physical/Chemical Properties (TGAI): blue to purple colored oil; density 1.14 g/cm^3; negligible vapor pressure; water solubility, 223 mg/l

The manufacture and formulation of technical grade acetochlor has been adequately described.

IV. TOXICOLOGY DATA SUMMARY

A. Acute Toxicity

Acceptable acute oral, dermal and inhalation study data were submitted for technical grade acetochlor and typical end use products. Toxcitity categories of 2, 3, or 4 were assigned to the TGAI and end use products. Both the TGAI and the end use products were sensitizers. Based on these studies, the appropriate signal word is "warning". The minimum personal protective equipment (PPE) and work clothing for handling activities have been adequately specified on the proposed label.

B. Subchronic Toxicity

In a study submitted by Monsanto (1980), groups of Sprague-Dawley rats (30/sex/dose) were fed diets containing acetochlor at levels of 0, 800, 2000 or 6000 ppm (0, 40, 100, and 300 mg/kg/day) for 3 months. A statistically and biologically meaningful decrease in the food consumption and body weight was observed in the mid- and high-dose males and females. The differences in these parameters between the control and low-dose group was statistically significant (3-8% decreases), but were not considered to be as biologically meaningful in either sex. Therefore, based on decreased food consumption and body weight, the NOEL and LEL for systemic toxicity were set at 800 and 2000 ppm (40 and 100 mg/kg/day), respectively. This study was core graded minimum.

In ICI's subchronic rat study (1986), groups of Sprague-Dawley CD rats (10/sex/dose) were administered acetochlor in the diet at levels of 0, 20, 200 or 2000 ppm (0, 1.6, 16.1, and 161.1 mg/kg/day in males; 0, 1.9, 18.7 and 191.9 mg/kg/day in females) for 13 weeks. Systemic toxicity was observed at 2000 ppm. These effects, although somewhat marginal, included hematological effects in both male and female rats; increased organ-to-body weight ratios for the liver, kidney, and brain; decreased plasma acetyl- and butyryl-cholinesterase activity (males only); and increased plasma urea and cholesterol. No significant effects related to test article administration were observed at other doses. Based on the effects observed at the high-dose, the LEL for systemic toxicity was established at 2000 ppm. The NOEL for systemic toxicity was

established at 200 ppm. This study was core graded supplementary.

Groups of beagle dogs (6/sex/dose) were administered acetochlor in capsules at levels of 0, 25, 25/50/75, or 50/100/150/200 mg/kg/day for 119 days (Monsanto, 1980). Control animals received a sham capsule for the duration of the study. The low-dose group received 25 mg/kg/day for the duration of the study. The mid-dose group received 25 mg/kg/day during the first week, 50 mg/kg/day during the second week, and 75 mg/kg/day during the remainder of the study. The high-dose group received 50 mg/kg/day during the first week, 100 mg/kg/day during the second week, and 150 mg/kg/day for the remainder of the study. Capsules were given once daily, approximately one hour after feed was withdrawn. Under the conditions of this study, administration of acetochlor produced severe toxic effects at the high-dose (death or morbidity, decreased body weight, abnormal urinalysis, and histopathological findings), toxic effects at the mid-dose (death or morbidity and histopathological findings), and mild toxic effects an the low-dose (abnormally elevated SCPT and increased liver to body weight ratio). Therefore the LEL for systemic toxicity was set at 25 mg/kg/day. A NOEL for systemic toxicity was not established. This study was core graded minimum.

Groups of beagle dogs (4/sex/dose) were administered acetochlor by gelatin capsule at levels of 0, 2, 10 or 60 mg/kg/day for 13 weeks (ICI, 1986). At 60 mg/kg/day, systemic toxicity was evident in both male and female dogs and consisted of diarrhea and mucous in the feces, and significant decreases in body weight gain in males (32%) and females (40%). Additional effects observed were significant decreases in hemoglobin, hematocrit, and RBC values in females; a significant increase in alanine aminotransferase in both sexes (51-59%; a decrease in blood glucose; and a significant increase in the liver-body-weight ratio for both sexes. No treatment related effects were noted at the low- and mid-dose levels. Based on the effects observed at the high-dose, the LEL for systemic toxicity was set at 60 mg/kg/day, and the NOEL was 10 mg/kg/day. This study was core graded supplementary.

ICI conducted a 21 day dermal study on rats (1989). Male and female SPF Wistar rats (5/sex) were given dermal doses of 0.1, 1.0 10 or 100 mg/kg/day of acetochlor (89.4%) in olive oil on 5 days/week. Minimal to mild skin irritation was observed in males and females after 21 days. Signs of systemic toxicity were not apparent at any dose level. Higher doses were apparently not possible due to the severe dermal toxicity of acetochlor at higher doses. Based on this study, the systemic NOEL was determined to be > 100 mg/kg/day. The study was core graded minimum.

Monsanto conducted a 21 day dermal study using rabbits in 1981. Levels of acetochlor (94.5%) administered to NZW rabbits were 0, 100, 400 or 1200 mg/kg/day. The NOEL for systemic effects was 400 mg/kg. The LOEL for systemic effects (mortality and

decreased body weight) was 1200 mg/kg (HDT). The LOEL for dermal irritation was 100 mg/kg (LDT). A NOEL for dermal irritation was not established. This study was classified as core minimum.

C. Chronic Toxicity

1. Chronic Dog Studies

In a study conducted by ICI (1988), groups of 20-week old purebred beagles (5/sex/dose) were administered acetochlor daily by gelatin capsule for 52 weeks at levels of 0, 2, 10 or 50 mg/kg/day. Systemic toxicity was evident at 10 and 50 mg/kg/day in both male and female dogs. Symptoms included excessive salivation and abnormal shaking of the head. At 50 mg/kg/day, significant increases in alanine aminotransferase, gamma-glutamyl transpeptidase, and ornithine carbamyl transferase were observed in male and female dogs over the course of treatment. At 10 mg/kg/day, histopathological changes were observed only in the kidneys, epididymides, and testes of males. Kidney changes consisted of interstitial nephritis and chronic vasculitis. Hypospermia of the epididymides and seminiferous tubule degeneration were reported at 10 mg/kg/day. Testicular toxicity, evident at both 10 and 50 mg/kg/day, consisted of decreased relative testes weight, atrophy, and degeneration of seminiferous tubules and hypospermia. Renal toxicity was evident at 50 mg/kg/day after 24 weeks of treatment as evidenced by increased water intake, urinary volume, and significantly increased blood urea and creatinine values. This was accompanied by renal histopathology consisting of hyperplasia in the collecting duct, transitional cell hyperplasia, cortical atrophy with fibrosis and scaring accompanied by chronic vasculitis, interstitial nephritis, dilatation of Bowman's space, and deposition of lipofuscin pigment in cortical tubules. Significant neurological effects were also evident at 50 mg/kg/day and consisted of abnormal head movements; stiffness and rigidity of the hindlimbs; ataxia, tremor; depressed righting, hopping and flexor reflexes; and exaggerated tonic neck reflex. These neurologic symptoms were accompanied by histopathological findings in the vermis cerebellum. Two male and 1 female were killed between weeks 39 and 51 due to severe neurological effects. Based on the results of this study, the LEL for systemic toxicity was established at 10 mg/kg/day based on salivation, increased alanine aminotransferase and ornithine carbamyl transferase accompanied by significant increases in triglyceride levels, and decreased blood glucose levels, histopathological changes in the kidney and testes of males. The NOEL for systemic toxicity was determined to be 2 mg/kg/day. The study was acceptable.

In a similar study conducted by Monsanto (1981), purebred beagle dogs (6/sex/dose) were administered acetochlor at levels of 0, 4, 12 or 40 mg/kg/day for 12 months (Monsanto, 1981). Under the conditions of this study, the NOEL for systemic toxicity was 12

mg/kg/day. The LEL for systemic effects is 40 mg/kg/day based on decreased body weight gains in males, decreased terminal body weights in females, testicular atrophy (6/6) with accompanying decreased absolute and relative (to body weight) testicular weights, increased absolute and relative adrenal weights in females, increased relative liver weights in males and females, and increased SGOT and SGPT levels. This study was core graded minimum.

2. Mouse Feeding/Carcinogenicity Studies

In a study conducted by Monsanto in 1983, groups of Swiss albino CD-1 mice (50/sex/dose with a 12 month interim sacrifice of 10/sex/dose) were fed diets containing acetochlor at levels of 0, 500, 1500 or 5000 ppm (equivalent to 0, 75, 225 and 750 mg/kg/day) for 2 years. Dose-related changes included the following: 1) increased mortality in both high-dose males and females; 2) decreased mean body weights in both high-dose males and females; 3) decreased red blood cell count, hematocrit, and hemoglobin in high-dose females at terminal sacrifice; 4) increased white blood cell count in high-dose males at terminal sacrifice; 5) increased platelet count in mid- and high-dose females at terminal sacrifice; 6) increased mean liver weight and liver-to-body-weight ratios at study termination in all dose groups of males and in high-dose females, as well as increased liver-to-body weight ratios in all dosed males and females a 12 months; increased absolute and relative kidney weights in all dose groups of males at termination; increased absolute and relative adrenal weights in all groups of males and in high dose females at study termination; and 7) increased interstitial nephritis in high-dose males and females. Based on increased liver and kidney weights, the LEL for systemic toxicity was determined to be 75 mg/kg/day, which was the lowest dose tested. A NOEL for systemic toxicity was not established. This study was core graded minimum.

In ICI' s study (1989), groups of CD-1 mice (50/sex/dose with a 52 week interim sacrifice of 10/sex/dose) were fed diets containing acetochlor at levels of 0, 10, 100, or 1000 ppm (equal to 0, 1.1, 11 and 116 mg/kg/day in males; 0, 1.4, 13 and 135 mg/kg/day in females) for 78 weeks. In males, a dose- related increase in absolute and relative kidney weight (compared to body weight) was observed and accompanied by significant but not dose-dependent increases in renal tubular basophilia at all dietary levels. Similar effects were observed in the older CD-1 mouse study conducted by Monsanto, but were inconsistent and not dose-dependent. OPP considered the renal tubular basophilia observed at all dose levels to most likely be the result of normal aging. In females, the only compound-related finding was a significant increase in anterior polar vacuoles in the lens of the eye at the high-dose level. Based on these results, the NOEL and LEL for systemic toxicity in females was determined to be 13 and 135 mg/kg/day. This study was core graded minimum.

(See section IV-G for discussion of carcinogenic potential.)

3. Rat Chronic Feeding/Carcinogenicity Studies

In one of two studies conducted by Monsanato (1983), groups of Sprague-Dawley rats (60/sex/dose with an interim sacrifice at 12 months of 10/sex/dose) were fed diets containing acetochlor at levels of 0, 500, 1500 and 5000 ppm (equal to 0, 22, 69 and 250 mg/kg/day in males; 0, 30, 93 and 343 mg/kg/day in females) for 2 years. There was increased mortality in high-dose females. There was a significant dose-related decrease in mean body weights in males and females of the mid- and high-dose groups, and a significant decrease in food consumption in high-dose males and females. A decrease in the mean body weight of low-dose males also reached a significant level at the end of the study (week 103-115). Histopathologic examination of the tissues indicated increased incidence of polyarteritis of the testis and arteries of high-dose males, and liver necrosis and alveolar histiocytosis in high-dose females. Based on body weight, the LEL for systemic toxicity was determined to be 22 mg/kg/day, which was the lowest dose tested. A NOEL for systemic toxicity was not determined. This study received a core grade of minimum.

In the second Monsanto study (1986), groups of Sprague-Dawley rats (60/sex/dose with an interim sacrifice of 10/sex/dose) were fed diets containing acetochlor at levels of 0, 2, 10 and 50 mg/kg/day for 2 years (equal to 0, 40, 200 or 1000 ppm). Body weight and body weight gain decreased in high-dose males from day 8 to the end of the study (statistically significant from days 455-678). High-dose females also had a slight, but not statistically significant decrease in body weight and body weight gain. Statistically significant increases in gamma glutamyl transpeptidase were observed in high-dose males at 18 and 24 months (mid- and high-dose males at 1 year showed slight increases as did mid-dose males at 2 years). Also, cholesterol levels were increased (statistically significant) in high-dose males at 2 years (a slight decrease was noted at 18 months) and total bilirubin was increased in high-dose females at 2 years. Organ weights determined at the interim sacrifice showed a slight increase in absolute and relative kidney weights in high-dose males and a slight, dose-related increase in absolute and relative liver weights in treated males. This continued until final sacrifice where similar observations were noted including a statistically significant increase in relative liver weight of high-dose males. Females were not similarly affected. Based on the effects observed at the high-dose, the LEL for systemic toxicity was determined to be 50 mg/kg/day. The NOEL for systemic toxicity was determined to be 10 mg/kg/day). This study was given a core grade of minimum.

In a study conducted by ICI (1988), CD rats (50/sex/dose) were administered acetochlor in the diet at levels of 0, 18, 175 and

1750 ppm (equivalent to 0, 0.67, 6.37 and 66.9 mg/kg/day in males, and 0.088, 8.53 and 92.1 mg/kg/day in females) for 104 weeks. For 52 weeks, and additional 10 males and females received doses of 18 and 175 ppm, and another group of 20 males and females received doses of 0 and 1750 ppm. In males and females, systemic toxicity i the form of reduced body weight gain, decreased food efficiency, ophthalmologic abnormalities, elevated GGT and cholesterol, and increased organ-to-body weight ratios were evident at 1750 ppm. No compound related effects were noted at the low- and mid-dose. Based on the effects observed at the high-dose, the LEL for systemic toxicity was 66.9 mg/kg/day for males and 92.1 mg/kg/day for females. The NOEL for systemic toxicity was 6.37 mg/kg/day for males and 8.53 mg/kg/day for females. This study was given a core grade of minimum.

(See section IV-G for discussion of carcinogenic potential.)

4. Rat Developmental Toxicity Studies

In a rat developmental toxicity study conducted by Monsanto in 1980. Groups of pregnant Charles River COBS CD rats (25/sex) were administered acetochlor orally by gavage as a single daily dose on days 6 through 19 of gestation at dose levels of 0, 50, 200, or 400 mg/kg-day. Matting and/or staining of the anogenital region was noted for rats in the high-dose group (13/25) and excessive salivation was observed in 3 rats as a post-dose response on one occasion. A slight but not dose-related increase in matting and/or staining of the anogenital region was noted in the 50 and 200 mg/kg-day groups. A moderate decrease in mean maternal body weight gain during the treatment period and in the adjusted mean body weight gain on gestation day 20 was noted at 400 mg/kg-day when compared to the control group. Based on the above effects, the maternal NOEL and LEL are 200 and 400 mg/kg-day, respectively. A slight to moderate decrease in mean fetal body weight, although not statistically significant, was noted at 400 mg/kg-day. Mean fetal body weight values at 50 and 200 mg/kg-day were comparable to controls. Based on the decrease in mean fetal body weight, the NOEL and LEL for developmental toxicity were determined to be 200 and 400 mg/kg-day, respectively. This study received a core grade of minimum.

A rat developmental toxicity study was conducted by ICI in 1989. Dose levels tested were 0, 40, 150, or 600 mg/kg-day. Animals were apparently received "timed pregnant" from Charles River Breeding Laboratories, Portage, MI. According to the information provided, the females were mated with males of the same strain and shipped in 2 batches (Group A and B) mated one day apart. "The day of mating, as judged by the appearance of sperm in the vaginal smear or by the presence of a vaginal plug, was considered as Day 0 of gestation." Rats (Group A: 15/dose; Group B: 10/dose) were orally administered acetochlor on gestation days 6 through 15, inclusive. The LEL for maternal toxicity is 600

mg/kg-day based on animals sacrificed moribund, clinical observations, decreased body weight gain during the dosing period and the entire gestation period and corrected body weight gain for gestation day 6 through 20. The NOEL for maternal toxicity is 150 mg/kg-day. The LEL for developmental toxicity is 600 mg/kg-day based on increased resorptions per dam, postimplantation loss, and decreased mean fetal weight. The NOEL for developmental toxicity is 150 mg/kg-day. This study received a core grade of minimum.

5. Rabbit Developmental Toxicity Studies

A rabbit developmental toxicity study was conducted by Monsanto in 1986. Groups of pregnant New Zealand White rabbits (20/dose) were administered acetochlor via gastric intubation in 0.5 ml/kg of corn oil on gestation days 7 through 19 at dose levels of 0, 15, 50, or 190 mg/kg-day. No mortality or spontaneous abortions were observed in any of the groups. There was a statistically significant mean body weight loss during the dosing period (days 7 through 19 of gestation) in the high-dose group. From days 19-29, the mean body weight gain for this group was greater than the control, low- and mid-dose groups. There were no apparent group differences regarding any other parameter. Based on body weight loss, the NOEL and LEL for maternal toxicity were determined to be 50 and 190 mg/kg-day, respectively. There were no apparent compound-related differences regarding any developmental toxicity parameters in any dose group. Therefore, the NOEL for developmental toxicity is equal to or greater than 190 mg/kg-day. This study received a core grade of minimum.

A rabbit developmental toxicity study was conducted by ICI in 1989. Groups (16/dose) of time-mated New Zealand White rabbits were administered acetochlor by gavage on gestation days 6 through 18, inclusive at dose levels of 0, 30, 100, or 300 mg/kg-day. Based on the data provided, no significant effects on either the maternal animal or the fetus were noted at the dose levels tested. Therefore the NOEL for maternal and developmental toxicity was determined to be equal to or greater than 300 mg/kg-day. This study received a core grade of minimum.

6. Two-Generation Reproduction Studies

In a 2-generation reproduction study conducted by Monsanto (1982), groups of Charles River rats were fed acetochlor at levels of 0, 500, 1500, or 5000 ppm (Male: 0, 30.4, 74.1, and 324.5 mg/kg-day; Female: 0, 44.9, 130.1, and 441.5 mg/kg-day) over two generations. A slight decrease (about 20%) in litter size was noted at the high-dose in all matings. The high-dose was also associated with decreased pup body weight gain during lactation for both generations. This effect was also noted in male F2b pups from the mid-dose group. Chronic nephritis was increased in

females of the F1 generation fed 5000 ppm; a slight increase in prostatis in this level may have been related to treatment. Apparent treatment-related increased thyroid weights were noted in low- and mid-dose F1b male pups, in F2b male and female pups, and in mid- and high-dose F1 dams. Liver weights (nonsignificant in males) and liver-to-body-weight ratios were increased in mid- (not statistically significant) and high-dose F1 parents. Pituitary weights were decreased at all doses in F1 adult males (absolute weights were decreased at low- and high-doses) and in low- and high-dose F2b male pups but were increased in low-dose F1b female pups. Decreases were observed for ovary weights for adult F1 females at all dose levels. Based on the decreased body weight gain of F2b pups, the LEL for reproductive toxicity is 1500 ppm (Male: 74.1 mg/kg-day; Female: 130.1 mg/kg-day). The NOEL for reproductive toxicity is 500 ppm (Male: 30.4 mg/kg-day; Female: 44.9 mg/kg-day). Based on changes in absolute and relative organ weight (decreased ovary weights in F1 females, decreased pituitary weights for F1 and F2 males, and increased thyroid weights in F1 and F2b pups), the LEL for systemic toxicity is 500 ppm (Male: 30.4 mg/kg-day; Female: 44.9 mg/kg-day), the lowest dose tested. A NOEL for systemic toxicity was not established. This study received a core grade of minimum.

A 2-generation rat reproduction study was also conducted by ICI. Groups of Sprague-Dawley rats (25/sex/dose) received from Charles River UK Ltd were administered acetochlor in the diet over 2 generations at levels of 0, 18, 175, or 1750 ppm (average of 0, 1.6, 21, and 160 mg/kg-day in males and females). Systemic toxicity, as evidenced by reductions in body weight accompanied by slight reductions in food consumption and increases in relative organ weights, was observed in high-dose parental males and females. Based on these effects, the LEL for systemic toxicity is 1750 ppm (160 mg/kg-day). The NOEL for systemic toxicity is 175 ppm (21 mg/kg-day). Reproductive performance and the rate of physical development of offspring were not affected by the administration of the test material in the diet. However, compound-related reductions in body weight on lactational day 21 and total body weight gain during lactation were observed in high-dose pups from both generations. Based on these results, the LEL for reproductive toxicity is 1750 ppm (160 mg/kg-day). The NOEL for reproductive toxicity is 175 ppm (21 mg/kg-day). This study received a core grade of minimum.

E. Mutagenicity

The results of mutagenicity tests conducted by Monsanto are summarized as follows (1978-1987):

- Acetochlor produced negative results in an Ames test (Salmonella).

- Acetochlor gave no evidence that it induced chromosomal abnormalities in an in vivo bone marrow chromosome test.

- In a rat hepatocyte primary culture/DNA repair test, results were negative for unscheduled DNA synthesis/repair.

- In a mouse lymphoma assay, acetochlor was a positive mutagen only in the presence of S-9 activation.

- In a gene mutation assay with Chinese hamster ovary cells, acetochlor was weakly positive.

The results of mutagenicity tests conducted by ICI (1989 to 1991) are summarized below.

- Acetochlor induced a reproducible, positive, mutagenic response in stain TA1538 of Salmonella typhimurium with metabolic activation at 1000 ug/plate (however, this was less that 2X background mutation, but was significant at $p<0.05$). Significant increases in the number of revertant colonies were not induced in strains TA1535, TA 1537, TA98, and TA100.

- Acetochlor was not clastogenic in a mouse micronucleus test at the doses tested (898 and 1436 mg/kg in males; 1075 and 1719 mg/kg in females).

- Acetochlor was clastogenic in cultured human lymphocytes both in the presence and absence of S9 mix at 100 ug/ml, and in the absence of S9 mix at 50 ug/ml.

- Acetochlor induced weak DNA repair (measured by unscheduled DNA synthesis) in rat hepatocytes derived from animals exposed in vivo at 2000 mg/kg.

- In a dominant lethal assay, acetochlor was adminstered to rats at doses of 1000 and 2000 mg/kg. As a result, fertility was reduced during weeks 2, 3 and 4, as shown by reduced pregnancy incidence, decreased implants per pregnancy incidence, increased preimplantation loss, and decreased live implant per pregnancy. Early and late intrauterine deaths were not affected in this study. Positive evidence of mutagenicity was found at the mid and high dose levels in this study (dose levels were 0, 200, 1000 or 2000 mg/kg).

(See also Section IV-G.)

F. Metabolism/Pharmacokinetics

The disposition of ^{14}C acetochlor was examined in CD Sprague Dawley rats at single oral doses of 10 and 200 mg/kg, and at 10

mg/kg for 14 days. Metabolites of acetochlor were characterized and identified in urine, feces and bile. Acetochlor was well absorbed after oral administration of both 10 and 200 mg/kg. A majority of the radioactive dose (50-60%) was eliminated in male and female rats in urine after 24 hours, with a significant percentage in feces (26-37%). Repeated oral dosing at 10 mg/kg had no significant effect on the disposition of acetochlor. Tissue concentrations after 5 days were highest in those tissues well-perfused with blood, due apparently to the avid binding of ^{14}C acetochlor derived radioactivity to red blood cells (blood:plasma ratio $\geq$ 100). The major biotransformation product in urine at 10 and 200 mg/kg was the mercapturic acid conjugate of acetochlor after removal of the ethoxymethyl side chain. Glucuronide and glutathione conjugates of acetochlor were identified in bile, with the glucuronide conjugate as the major metabolite in bile. Fecal metabolites were complex and difficult to identify. Enterohepatic recirculation of acetochlor was suggested from these studies.

A dermal absorption study was conducted by ICI (1990). Acetochlor was absorbed in a dose and time related manner. Material was easily washed from the skin with little reside remaining. The percent of dose absorbed over 0.5 to 24 hours ranged from 1.4 to 31.4%. Evidence of bioaccumulation was observed in carcass and erythrocytes. Volatilization from the application site was significant at the lowest dose. The study was acceptable.

G. Peer Reviews

RfD Committee Review

Acetochlor was first discussed by the HED RfD Committee on December 12, 1990. An RfD was established based upon a NOEL of 10 mg/kg/day for body and organ weight changed which occurred at 20 mg/kg/day in a two-year feeding study in rats (Monsanto study), using an uncertainty factor of 100. However, the Agency RfD Work Group in their meeting on March 27, 1991 deferred the discussion of this chemical pending the completion of studies then under review by HED. Upon completion of the toxicology data reviews, the RfD was reassessed. It was proposed that an RfD be based upon a NOEL of 2 mg/kg/day (for increased salivation, alanine amino transferase and triglycerides and decreased blood glucose levels generated in a chronic feeding study in dogs (ICI study)) using an uncertainty factor of 100. The RfD was calculated to be 0.02 mg/kg/day.

Carcinogenicity Peer Review

The Health Effects Division Peer Review Committee met on three occasions to discuss and evaluate the weight-of-evidence on acetochlor with particular reference to its carcinogenic potential.

Based on the Monsanto data which was reviewed at the first two peer reviews, acetochlor received a B2 classification based on: the incidence of hepatocellular carcinomas (male and female), of thyroid follicular cell adenomas (males), and of papillary adenomas of nose/turbinate (males and female) in Sprague-Dawley rats; and the incidence of both benign and malignant tumors at multiple sites-hepatocellular carcinomas (male, trend for female), lung carcinomas (female), uterine histiocytic sarcomas (female), benign ovarian tumors (female), and kidney adenomas (trend only for females) in Swiss Albino CD-1 mice. Additionally, acetochlor was determined to be structurally related to analogues that are carcinogenic. The SAP concurred with the Peer Review Committee's classification of acetochlor as a group B2 carcinogen.

When the Committee reviewed the ICI study data at the third Peer Review, it was unanimously concluded that classification for acetochlor should remain B2. This was based on the appearance of multiple tumors in both sexes in CD rats (nasal epithelium adenoma, thyroid follicular cell adenoma, benign chondroma of femur, and basal cell tumor of stomach), and of pulmonary adenomas in both sexes of CD-1 mice due to acetochlor exposure; hepatocytic adenomas/carcinomas combined were also noted in male mice.

It was concluded that for the purpose of risk characterization, a low dose extrapolation model applied to the experimental animal tumor data should be used for quantification of human risk (Q_1^*). For quantification, the Committee recommended separate calculations for both sexes of rats using the combined incidence for nasal tumors (benign and malignant) for each sex. The separate values would then be combined using appropriate statistical methods. The estimated risk based upon both sexes, combined by means of the geometric mean was 1.7×10^{-2} mg/kg/day[1].

Based on the total weight of evidence, it was also determined by the Peer Review Committee that acetochlor presents a mutagenicity concern. According to the ICI studies, acetochlor is clastogenic *in vitro*, induces DNA repair in response to DNA damage *in vivo* (UDS), and has suggestive activity in a Salmonella assay. Earlier submitted studies from Monsanto also demonstrated that acetochlor is mutagenic in the Chinese hamster ovary (CHO) and mouse lymphoma gene mutation assays. Results from ICI and Monsanto do not show clastogenic activity *in vivo* (mouse micronucleus and rat bone marrow aberration assays). The positive UDS result was

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[1]A Q_1^* of 0.01 mg/kg/day was previously calculated based on Monsanto study data (see B. Fisher memo dated 7/21/89). For all practical purposes the two Q_1^* values are essentially the same. However, to be consistent with our practice of providing a worst case risk assessment, 0.017 was use in the risk calculations (see also Section VII).

determined to be particularly significant since relatively few compounds that had been considered by the Peer Review Committee were positive in this assay, it was an in vivo result, and the primary analogue, alachlor, was also positive in this assay. The overall mutagenicity concern would support a concern for carcinogenicity. Based on the total weight of evidence, it was recommended that acetochlor be tested in a dominant lethal assay and an alkaline elution or UDS assay in germ cell tissue (in vivo).

NOTE: The dominant lethal assay was conducted as requested (see section IV-E). **Based on the results of this study and the recommendations of the HED Peer Review Committee, a heritable translocation assay has been requested.**

V. RESIDUE CHEMISTRY DATA SUMMARY

A. Nature of the Residue in Plants and Animals

Metabolism studies were independently submitted by Monsanto and ICI. All studies were reviewed and found to be acceptable. The qualitative nature of the residue in corn is adequately understood. The residues to be regulated are parent acetochlor and its 2-ethyl-6-methylamine(EMA)- and 2-(1-hydroxyethyl)-6-methyl-alanine(HEMA)-producing metabolites. Another metabolite, N-(6-ethyl-3-hydroxy-2-methylphenyl)oxamic acid ("metabolite 57") was identified (only in the ICI study) and was present at slightly higher levels in corn grain, forage and fodder. **It was determined that "metabolite 57" need not be included in the tolerance expression at this time. However, further toxicity testing of this metabolite was requested as result of this Peer Review.**

Results from studies to determine the nature of the residue in ruminants and poultry were submitted and reviewed. However, it was determined that meat, milk, poultry and egg tolerances were not needed. Low residue levels are expected in the animal feed items, and thus little transfer to edible animal commodities is expected.

These conclusions were the outcome of the HED Metabolism Committee review of acetochlor, held on September 15, 1993.

B. Enforcement Methodology

Analytical methodology suitable for regulatory purposes has been successfully validated by the Agency. Samples are extracted with methanol/water and then subjected to pressure hydrolysis. The extract is partitioned with methylene chloride, and after several clean-up steps, EMA and HEMA residues are quantified by HPLC using an oxidative coulometric electrochemical detector. The limit of quantification for this method is 0.02 ppm.

C. Residue Field Trial Data

Residue data from 24 field trials conducted by Monsanto during 1984 and 1985. In these trials, acetochlor was applied preemergence to corn at rates of 1.5 to 6 lb ai/A (0.5 to 2X). ICI submitted additional data from trials conducted at 13 locations in 1988. The application rate used in these trials was 1.5 lb ai/A. These trials were conducted in locations throughout the U.S. Details of the analytical methodology were included in the study reports, and was found adequate. The data from these trials adequately support tolerance levels of 0.05 ppm, 1.0 ppm, and 1.5 ppm on field corn, forage and fodder, respectively. In corn treated 2.5 lb ai/A (0.8 X), residues of metabolite 57 detected in grain were all <0.01 ppm. Residues in forage, silage and fodder ranged from <0.01 to 0.39 ppm. Storage stability data demonstrate the stability of EMA- and HEMA-producing metabolites in grain, forage and fodder under frozen storage for over 4 years. Additionally, data are available which support the stability of acetochlor parent under frozen storage in forage for 3 years, in grain and processed commodities for 2 years, and in soil for 2 years. Storage stability data support analyses of metabolite 57 (not to be regulated at this time) in corn RACs for one year.

Several processing studies were conducted by ICI and Monsanto where corn treated with acetochlor at 2 to 7 times the maximum application rate was processed to it various food and feed processed fractions. Neither acetochlor nor its EMA and HEMA-producing metabolites concentrated in corn processed fractions. Additionally, processing study data show that metabolite 57 does not concentrate in corn processed fractions.

D. Confined and Field Rotational Crop Studies

Acceptable confined rotational crop studies were conducted on lettuce, radish and wheat planted from 30 to 120 days after radiolabeled acetochlor was applied to sandy loam soil at 1X the proposed rate. Because the three required confined rotational crop studies all showed significant (>0.01 ppm) acetochlor residues up to 365 days post treatment, rotational crop tolerances were determined to be necessary unless the product label is amended to include plant back restrictions.

Field rotational crop studies for wheat, sorghum and soybeans were submitted, subsequently reviewed and found acceptable. Acetochlor was applied at rates of 1 to 5X and residues remaining after 3 to 14 month intervals were determined. Based on these data, it was concluded that the appropriate rotational crop tolerances are as follows: soybean grain, forage and at 0.1, 0.7 and 1.0 ppm, respectively; wheat grain, forage and straw at 0.02, 0.5 and 0.1 ppm, respectively; sorghum grain, forage, silage and hay at 0.02, 0.1, 0.1, 0.05, and 0.2 ppm, respectively. A label

modification for acetochlor to restrict rotation of crops other than soybeans, sorghum or wheat other will be needed.

At the September 15, 1993 HED Metabolism Committee meeting it was determined that the tolerance expression for rotational crops should include acetochlor and its HEMA-, EMA-producing metabolites. The Committee recommended that the HMEA-producing metabolites should be included in any risk assessment, although not to be included in the tolerance expression. Therefore, the following tolerances were used in the dietary risk assessment: soybean grain, forage, and hay at 0.15, 1.0, and 1.5 ppm, respectively; wheat grain, forage and straw at 0.03, 0.6 and 0.2 ppm, respectively; and sorghum grain, forage, fodder, silage and hay at 0.03, 0.1, 0.1, 0.1, and 0.2 ppm, respectively (see section VII below).

VI. OCCUPATIONAL EXPOSURE

To satisfy data requirements for mixers, loaders and applicators, and reentry worker exposure data, the Acetochlor Registration Partnership referenced a study conducted by Monsanto (1983). It was determined that the study data were unacceptable and therefore did not fulfill either of these data requirements. However, HED has determined that alachlor biological monitoring data are an acceptable surrogate for acetochlor. HED previously evaluated three alachlor biological monitoring studies and concluded that the dosage of alachlor was 5.4 to 540 ng/kg bwt/lb active ingredient handled when open pour mixing/loading occurred, and 3.4 to 340 ng/kg body weight/lb ai handled when closed loading mining/loading occurred. When acetochlor is used at the maximum label rate of 3.0 lb ai/A and workers wear long pants, long sleeve shirts during mixing/loading and application, and use chemical resistant gloves during mixing/loading, the following worker exposure is expected:

TABLE 2. ESTIMATES OF WORKER EXPOSURE RESULTING FROM PREEMERGENCE USE OF ACETOCHLOR ON CORN

User Type	Annual Acreage	Pounds handled per year	Exposure, mg/kg/yr
Private-Small (open system)	120	360	0.002 to 0.194
Private-Large (closed system)	360	1080	0.004 to 0.367
Commercial (closed system)	1800	5400	0.02 to 1.84

Since acetochlor is applied preemergence and only once yearly, it was concluded that reentry data are not required.

VII. ASSESSMENT OF RISK TO HUMANS

DRES chronic exposure analyses were performed using tolerance level residues and 100 percent crop treated information to estimate the theoretical maximum contribution (TMRC) for the general population and 22 subgroups. The TMRC for the general population for corn uses was 1.7×10^{-5} mg/kg bwt/day, representing 0.1% of the RfD for acetochlor. The TMRC for the soybean, sorghum and wheat rotational crop tolerance levels recommended for risk assessment is 1.1×10^{-4} mg/kg bwt/day, representing 0.5% of the RfD. The total TMRC (corn and rotational crops) for the general population would be 1.3×10^{-4} mg/kg bwt/day, or 0.6% of the RfD (RfD = 0.02 mg/kg bwt/day).

The most highly exposed subgroup, non-nursing infants less than 1 year, has a TMRC from corn uses of 4.9×10^{-5} mg/kg bwt/day, or 0.2% of the RfD. The pending rotational crop tolerances used for risk assessment contributed 3.6×10^{-4} mg/kg bwt/day, or 2% of the RfD. If the proposed tolerances were granted, the TMRC for non-nursing infants would be 4.1×10^{-4} mg/kg bwt/day, representing 2% of the RfD.

Based on a Q_1^* of 0.017 of mg/kg/day, the upper bound cancer risk was calculated to be 2.9×10^{-7} as a result of the proposed field corn tolerances. The upper bound carcinogenic risk for the rotational crop tolerances was calculated to be 1.9×10^{-6}. **The upper bound carcinogenic risk from the corn and rotational crop tolerances was calculated to be 2.2×10^{-6}.**

Workers may be exposed to acetochlor primarily via the dermal route. The additional lifetime carcinogenic risk to workers exposed to acetochlor may be estimated as follows:

Excess cancer risk = Q_1^* (.017 mg/kg/day) x LADE
LADE = exposure (mg/kg/day) x 35/70

TABLE 3. ESTIMATES OF ADDED CANCER RISK TO WORKERS RESULTING FROM PREEMERGENCE USE OF ACETOCHLOR ON CORN

Work Site	Maximum Annual Exposure, mg/kg/yr	Maximum daily exposure, mg/kg/day	LADE mg/kg/day	Risk
small private farm	0.19	5.2×10^{-4}	1.1×10^{-4}	1.8×10^{-6}
large private farm	0.37	1.0×10^{-3}	5.1×10^{-4}	8.6×10^{-6}
commercial	1.8	4.9×10^{-3}	2.5×10^{-3}	4.2×10^{-5}

VIII. CONCLUSIONS

Based on the data available at this time, exposure to acetochlor via the diet is estimated to result in a theoretical maximum exposure accounting for not more than 0.6% of the RfD. Based on a Q_1^* of 0.017 of mg/kg/day, the upper bound cancer risk was calculated to be 2.9×10^{-7} as a result of the proposed field corn tolerances. The upper bound carcinogenic risk for the rotational crop tolerances was calculated to be 1.9×10^{-6}. The upper bound carcinogenic risk from the corn and rotational crop tolerances was calculated to be 2.2×10^{-6}. This is above the generally acceptable level of 1.0×10^{-6}. We note that the dietary exposure/risk assessment is possibly an overestimate due to the assumption that 100% of corn will be treated with acetochlor and that residues will be present at the tolerance level. The estimates also assume that the rotational crops would all be grown in fields where acetochlor treated corn had been grown, which is highly unlikely. Additionally, the risk assessment also assumes that the regulated metabolites, that is the EMA and HEMA producing metabolites of acetochlor, have the same toxicity as acetochlor. The risk assessment for the rotational crops also included HMEA producing metabolites, which are not included in the tolerance expression. The risk assessment is therefore considered to be a worst case analysis. The excess cancer risk to workers ranges from 1.8×10^{-6} to 4.2×10^{-5}. This assessment assumes that acetochlor will be used at the maximum use rates.

The following additional toxicity data are requested for clarification of specific TOX endpoints:

1. A heritable translocation assay for acetochlor

2. The following additional toxicity studies should be performed for metabolite 57:

a) unscheduled DNA synthesis in rat hepatocytes (*in vivo* exposure and *in vitro* culture)

b) cytogenetics assay for aberrations using cultured human lymphocytes

Depending on the findings of the additional mutagenicity studies, a revised risk assessment may be needed.

X. REFERENCES USED

1. IRIS Summary of Acetochlor Chronic Toxicity Study Data as supplied by R. Whiting (HED). December 1993.

2. TOX Oneliners, 12/7/93.

3. 11/12/93 memo of T. McMahon to V. Walters, "Acetochlor: Request for Additional Toxicology Data".

4. 8/31/93 memo of S. Dapson to R. Taylor, "Acetochlor: Review of Proposal for Rotational Crop Tolerances".

5. 5/21/92 memo of G. Ghali to J. Miller, "RfD/Peer Review of Acetochlor".

6. 1/27/92 memo of K. Dearfield to R. Taylor, "Third Peer Review of Acetochlor".

7. 12/30/91 memo of B. Fisher to K. Dearfield, "Acetochlor: Quantitative Risk Assessment-CD Rat Study".

8. 8/5/85 memo of W. Teeters to R.Taylor, "Review of TOX Data Submitted in Support of Tolerances for Acetochlor".

9. 1/24/94 memo of M. Flood to R. Taylor, "PP No. 3F2966, 1F4011; Acetochlor Product Chemistry Data"

10. 1/11/94 memo of M. Flood to R. Taylor, "PP No. 3F4232, Acetochlor Rotational Crop Tolerances"

11. 11/24/93 memo of M. Flood to R. Taylor, "PP No. 3F2966/PP No. 1F4011. Acetochlor Registration Partnership. Response to CBTS memo dated 7/12/93".

12. 11/24/93 memo of M. Flood to R. Taylor, "PP No. 3F4232. Acetochlor Rotational Crop Tolerances for Soybeans, Wheat and Sorghum".

13. 9/30/93 memo of M. Flood to HED Metabolism Committee, "Summary of Findings of HED Metabolism Committee Meeting Held September 15, 1993".

14. 9/14/93 memo of M. Flood to D. Edwards, "Acetochlor: Metabolism in Corn, Rotated Crops, and Animals".

15. 7/12/93 memo of M. Flood to R. Taylor, "Acetochlor Registration Partnership. Acetochlor EC Herbicide for Use on Field Corn".

16. 5/24/93 memo of O. Odiott to R. Taylor, "Review of Data Supporting Registration of Acetochlor".

17. 6/14/89 memo of C. Lunchick to R. Taylor, "Acetochlor Nondietary Exposure Assessment Based on Alachlor Biological Monitoring Data".

18. 12/14/93 memo of J. Wintersteen to R. Taylor, "Dietary Exposure Analysis for Acetochlor through the Proposed Use on Field Corn".

19. 12/14/93 memo of J. Wintersteen to R. Taylor, "Dietary Exposure Analysis for Acetochlor through the Proposed Rotational Crop Tolerances".

20. 1/25/94 memo of J. Wintersteen, "Correction to Dietary Exposure Analysis for Acetochlor".

41177

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

MAY 24 1993

MEMORANDUM

SUBJECT: Review of data supporting registration of Acetochlor, Reg.No. 66478-E

FROM: Olga Odiott, Biologist
Occupational and Residential Exposure Branch
Health Effects Division (H7509C)

TO: Robert Taylor, Product Manager 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

THRU: Mark I. Dow, Section Head
Special review and Reregistration Section II
Occupational and Residential Exposure Branch
Health Effects Division (H7509C)

Larry Dorsey, Chief 5/24/93
Occupational and Residential Exposure Branch
Health Effects Division (H7509C)

Please find below OREB review of:

DP Barcode: D187735

Pesticide Chemical Code: 121601

EPA Reg. No.: 66478-E

I. BACKGROUND

To expedite the registration of Acetochlor, ICI Americas and Monsanto have formed the Acetochlor Registration Partnership. The companies are relying on pooled data to support the Partnership' registration applications for Acetochlor.

OREB has been requested to determine if the proposed registration of Acetochlor EC Herbicide, Reg. No. 66478-E, is supported by reentry data (40 CFR 158.390, guidelines series 132 and 133) . The registrants are relying on the following data to satisfy the requirements for guideline series 133-3 and 133-4: " Arras, D. et al, 1983, Applicator Exposure Study with Harness Herbicide, Monsanto Report # MSL-2887.

The cited study is a Mixer/Loader/Applicator Exposure study, and therefore cannot be used to satisfy requirements for reentry data. The study could be cited relative to requirements for guidelines 231 and 232 which deal with worker dermal and inhalation exposure at outdoor sites; however, the study is not acceptable to support registration. It should be noted that the Agency has surrogate data on a biological monitoring study that was reviewed and considered acceptable to conduct a Mixer/Loader/Applicator Exposure Assessment for this chemical (Memorandum from C. Lunchick dated June 14,1989: Acetochlor Nondietary Exposure Assessment Based on Alachlor Biological Monitoring Data). Therefore the data requirements for guidelines 231 and 232 are satisfied.

II. RECOMMENDATION

Although Acetochlor is classified as a B2 carcinogen, based on the proposed use pattern (preemergence/preplant application), reentry data (guideline series 132 and 133) are not required for this product registration. The general reentry and PPE provisions specified by the Worker Protection Standard for products in category II, should provide adequate protection from any potential exposure.

cc: O. Odiott, OREB
Correspondence File
Chemical File (121601)
Circulation

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

JUN 14 1989

MEMORANDUM

SUBJECT: Acetochlor Nondietary Exposure Assessment Based on Alachlor Biological Monitoring Data

TO: R. Taylor
Product Manager 25
Registration Division

FROM: Curt Lunchick
Review Section 1
Non-Dietary Exposure Branch
Health Effects Division (H7509C)

THRU: Michael Firestone, Section Head
Review Section 1
Non-Dietary Exposure Branch
Health Effects Division (H7509C)

THRU: Charles L. Trichilo, Ph.D., Chief
Non-Dietary Exposure Branch
Health Effects Division (H7509C)

Please find below the NDEB review of .....

HED Project #: 9-0247

Reg. File/Rec #: 234022 and 234026

Registration #:

Caswell #: 3B

Company Name: Monsanto

Date Received: 10/28/88 Action Code: 101 and 711

Date Completed: 6/14/89 Reviewing Time: 10 Days

Deferral to : _____ Biological Analysis Branch/BEAD

_____ Science Analysis and Coordination Branch

_____ TB - Insecticide/Rodenticide Branch

__X__ TB - Herbicide/Fungicide Branch

1.0 INTRODUCTION

Monsanto submitted a document on October 3, 1988 to support the registration of two acetochlor products - (Rationale in Support of the Registration of Harness Herbicide and Top-Hand Herbicide, Kuntsman, J.L., Monsanto, July 25, 1988). The document contains toxicology, dietary exposure, nondietary exposure, and economic/agronomic benefits rationales intended to support the registration of Harness and Top-Hand. Both products contain acetochlor as the active ingredient with Top-Hand also containing [redacted] as a safener to protect corn plants from the herbicidal activity of acetochlor. Monsanto is seeking to register both products for use as a herbicide on corn. This assessment is limited to the nondietary exposure aspect of the registration request. Assessment of the dietary aspect is deferred to the Dietary Exposure Branch/HED, assessment of toxicology to Toxicology Branch II/HED, and assessment of the benefits to the Biological and Economic Analysis Division.

2.0 MONSANTO ALACHLOR NONDIETARY EXPOSURE STUDIES

Monsanto proposes to support the nondietary exposure requirements for the registration of acetochlor by utilizing alachlor biological monitoring data as a surrogate for acetochlor. During the Special Review of alachlor, Monsanto submitted three biological monitoring studies designed to quantify the internal dosage of mixers/loaders and applicators treating corn with alachlor (Klein, A.J., et al., Report No. MSL-4207, November 1984, Accession No. 256623/4; Danhous, R.G., et al., Report No. MSL-5320, January 1986; and Danhous, R.G., et al., Report No. MSL-5398, February 1986). The three studies were concluded to be scientifically valid and were incorporated into the Agenoy's nondietary exposure assessment of alachlor. The Agency exposure assessment did not rely solely on the biological monitoring data but also incorporated into the assessment passive dosimetry data from alachor and surrogate chemical studies. The primary rationale for the Agency action was to expand the number of data points from the small numbers of replicates in the biological monitoring studies to increase the predictive value of the exposure assessment. An underlying factor to this decision was the sole use of enclosed tractor cabs in the biological monitoring studies. Open cab application also occurs and would not be represented in any assessment based only on the biological monitoring data. Based on the reviews of studies MSL-4207 and MSL-5398 (Lunchick, C., EAB No. 60901, May 26, 1987) the internal dosage for individuals open pour mixing/loading and then applying alachlor was estimated to range from 5.4 to 540 ng/kg body weight/lb ai handled. The review of study MSL-5320 (Lunchick, C., EAB No. 60901, May 26, 1987) concluded that the use of a closed loading system during mixing/loading and then applying alachlor would produce an internal dosage of 3.4 to 340 ng/kg body weight/lb ai handled.

The use of surrogate data to estimate handler (mixer/loader and applicator) exposure is a well- established practice and is discussed in detail in Subdivision U of the Pesticide Assessment Guidelines. Surrogate data are feasible with passive dosimetry because the amount of pesticide impinging on the skin or clothing is not dependent on the chemical structure of the pesticide. Application rate, application method, personal work habits, and environmental conditions have been shown to be variables that most significantly affect dermal exposure. The internal dosage of a pesticide is additionally dependent on the dermal absorption of the pesticide and other pharmacokinetic factors. This chemical specificity of internal dosage therefore limits the feasibility of surrogate biological monitoring data, which is an indicator of internal dose.

3.0 METABOLISM OF ALACHLOR AND ACETOCHLOR

The use of alachlor biological monitoring data as a surrogate for acetochlor would be acceptable if the metabolic fate of the two chemicals are sufficiently similar. Monsanto uses this rationale in the support document. A rat metabolism study (Livingston, C., The Metabolism of Acetochlor in the Rat; Report No. MSL-2824, 1983) and a monkey metabolism study (Livingston, C., The Metabolism of Acetochlor in Monkey Urine Obtained from Dermal Penetration Studies, Report No. MSL-3208, 1983) were referenced but not provided with the acetochlor submission. Monsanto references Sharp, D. (Herbicides: Chemistry, Degradation, and Mode of Action, ed. P. Kearney and D. Kaufman, Marcel Dekker, N.Y., 1988) to conclude that acetachlor metabolism is similar to that of alachlor.

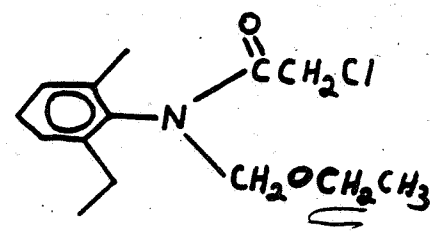
Referencing of data without submission of the data is insufficient to permit HED to evaluate the submission and draw a conclusion. Monsanto had previously submitted the Livingston rat metabolism study for acetochlor and a rat metabolism study (MSL-3198) for alachlor. Both studies have been evaluated by HED and will form the basis of this evaluation. The acetochlor monkey metabolism study is not in HED's Caswell file and no further use of the study will be made for the purpose of this evaluation.

The acetochlor study was evaluated by HED and determined to be a Guideline study (Saunders, S., The Metabolism of Acetochlor in the Laboratory Rat, August 3, 1985). Rats were orally administered a single dose of 10 or 400 mg/kg. Another group of rats received daily doses of 10 mg/kg/day for 14 days followed by a single dose of 10 mg/kg of radiolabeled acetochlor. Elimination of labeled material was monitored for 7 days after the last dose. Elimination via the lungs was minimal at 0.04 percent. A total of 77 percent of the material was excreted within 48 hours with the elimination being biphasic. The half-life of the rapid phase was 5.4 to 10.4 hours and the half-life of the slow phase was 5 to 12 days. Acetochlor was extensively metabolized with <1

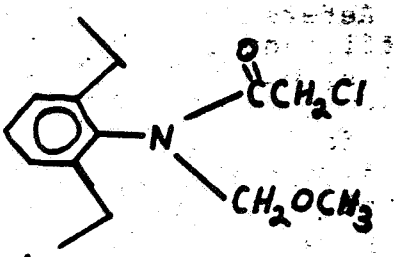
percent of the administered compound excreted unchanged in the feces. The early metabolites were mainly mercapturates and the later metabolites were sulfoxides, sulfones, and sulfates. Approximately twenty metabolites were identified. After 7 days, a total of 86 percent of acetochlor was excreted among the repeat dose rats. The urinary route was the major route of excretion for the repeat dose rats accounting for 64 percent of the total acetochlor with feces accounting for 22 percent. Tissue retention was minimal with the red blood cells accounting for the only significant amounts (2.5%) of the administered dose (see Attachment No. 1).

The alachlor rat metabolism study was evaluated as part of the Special Review of Alachlor. The Position Document 1 and Position Document 2/3 for alachlor described the results of the study. The study indicated that alachlor is rapidly metabolized and eliminated as conjugates of mercapturic acid, glucuronic acid, and sulfate in urine and feces. Urine excretion accounted for 45 percent of the alachlor administered and feces accounted for 46 percent. Approximately 89 percent of the dosages were eliminated during the study which was of a 10-day duration. The elimination of alachlor was biphasic with most occurring within 48 hours with a half-life of 0.2 to 10.6 hours. The slow phase had a half-life of 5 to 16 days. Elimination via the lungs was minimal. Alachlor retention in the tissue was predominantly in the blood and blood-containing organs.

The metabolic fates of the two compounds do appear to be similar. The similarity would be expected based on structural similarity as illustrated below:



ACETOCHLOR



ALACHLOR

The similarity of the two compounds also appears to manifest itself in similar oncogenic effects. Alachlor induced statistically significant oncogenic responses in the rat at the nasal turbinates, stomach, and thyroid. The HED review of the acetochlor chronic rat study (EHL-83107) concluded that statistically significant oncogenic responses occurred in the nasal turbinates and thyroid. The Alachlor Position Document 4 defines alachlor as a B2 oncongen with a Q* of 8×10^{-2} $(mg/kg/day)^{-1}$. The acetochlor Toxchem file of March 27, 1989 estimates the Q* for acetochlor to be 1×10^{-2} $(mg/kg/day)^{-1}$.

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similarities between acetochlor and alachlor in chemical structure, metabolic fate, and oncogenic potential, HED believes the use of alachlor biological monitoring data as a surrogate for acetochlor is reasonable.

4.0 ANNUAL NONDIETARY DOSAGE ESTIMATES FOR ACETOCHLOR

As discussed in Section 2.0, HED evaluated the three alachlor biological monitoring studies and concluded that the dosage of alachlor was 5.4 to 540 ng/kg body weight/lb ai handled when open pour mixing/loading occurred and 3.4 to 340 ng/kg body weight/lb ai handled when closed loading mixing/loading occurred. These dosage estimates assume the use of long pants and long sleeve shirts during mixing/loading and application and the use of chemical resistant gloves during mixing/loading. Monsanto has submitted labels for Harness and Top-Hand that require a Restricted Use classification, tumorigenic warning, requirement for the use of mechanical transfer devices (closed systems) when treating 300 acres or more annually and the use of long pants, long sleeved shirts, and during mixing/loading chemical resistant gloves and eye protection.

The Monsanto registration submission contains a benefits assessment for acetochlor. Harness will permit a maximum application rate of 1.75 lb ai/acre on corn and Top-Hand will permit a maximum application rate of 3.0 lb ai/acre on corn. Typical use of a pesticide is at rates less than the label maximum. The Monsanto assessment also predicts acetochlor to penetrate the corn herbicide market to the extent that by 1993 Harness will replace 15 percent of the combined alachlor, metolachlor, and thiocarbamate market and Top-Hand will replace 15 to 100 percent of the alachlor market segment depending on soil types. Based on this economic assessment, HED believes that by 1993, after 5 years of commercialization, acetochlor use on corn will be similar to other broadleaf herbicides such as alachlor or atrazine.

The average corn acreage in the United States is approximately 195 acres per farm. Assuming typical ground boom application equipment with a boom length of 25 to 35 feet, a private farmer can treat 100 to 120 acres in a day. As was done with alachlor, HED will conduct an exposure assessment for a small private farmers treating 120 acres of corn with acetochlor and for a large private farmer testing 360 acres of corn with acetochlor over a 3-day period. Commercial applicators are expected to treat corn with acetochlor over the preemergent application time window for a total of 15 days. Assuming 120 acres/day for 15 days, the commercial applicator will treat 1800 acres of corn with acetochlor in a year.

A private farmer treating 120 acres/year with Harness at the maximum application rate of 1.75 lb ai/acre will handle 210 lb ai/yr. Top-Hand, with a maximum application rate of 3.0 lb ai/acre will require 360 lb ai/yr to treat 120 acres. The annual internal dosage to a small private farmer handling Harness and using open pour loading will be:

LOW ESTIMATE = 5.4 ng/kg/lb ai x 210 lb ai/yr = 1.1 ug/kg/yr
HIGH ESTIMATE = 540 ng/kg/lb ai x 210 lb ai/yr = 113 ug/kg/yr

If Top-hand is used at the label maximum rate of 3.0 lb ai/acre, the farmer would receive the following dosages of acetochlor:

LOW ESTIMATE = 5.4 ng/kg/lb ai x 360 lb ai/yr = 1.9 ug/kg/yr
HIGH ESTIMATE = 540 ng/kg/lb a.i. x 360 lb ai/yr = 194 ug/kg/yr

Large private farmers treating 360 acres/yr will be required to use mechanical transfer devices. If Harness is used at the maximum application rate of 1.75 lb ai/acre, the farmer will handle 630 lb ai/yr. A total of 1080 lb ai/yr would be handled if Top-Hand would be applied at the 3.0 lb ai/acre label maximum rate. The annual dosage to Harness would be as follows:

LOW ESTIMATE = 3.4 ng/kg/lb ai x 630 lb ai/yr = 2.1 ug/kg/yr
HIGH ESTIMATE = 340 ng/kg/lb ai x 630 lb ai/yr = 214 ug/kg/yr

The annual dosage to Top-Hand would be as follows:

LOW ESTIMATE = 3.4 ng/kg/lb ai x 1,080 lb ai/yr = 3.7 ug/kg/yr
HIGH ESTIMATE = 340 ng/kg/lb ai x 1,080 lb ai/yr = 367 ug/kg/yr

Commercial applicators would be expected to apply acetochlor for up to 15 days during the preemergent herbicide application period. If the applicator averages 120 acres/day, the amount of active ingredient handled if Harness is applied at the label maximum would be 3150 lb ai/yr. If the acetochlor was applied as Top-Head at the label maximum rate the amount of active ingredient handled would be 5400 lb ai/yr. A commercial applicator who mixes, loads, and applies Harness would receive the following dosages:

LOW ESTIMATE = 3.4 ng/kg/lb ai x 3150 lb ai/yr = 10.7 ug/kg/yr

HIGH ESTIMATE = 340 ng/kg/lb ai x 3150 lb ai/yr = 1070 ug/kg/yr

The commercial applicator mixing, loading, and applying Top-Hand would receive the following dosage:

LOW ESTIMATE = 3.4 ng/kg/lb ai x 5,400 lb ai/yr = 18.4 ug/kg/yr
HIGH ESTIMATE = 340 ng/kg/lb ai x 5,400 lb ai/yr = 1,840 ug/kg/yr

5.0 CONCLUSION

Monsanto has submitted a rationale for the use of alachlor biological monitoring data as a surrogate to support the registration of two acetochlor products, Harness and Top-Hand, for use on corn. A review of the supporting data including a comparison of the metabolism data for alachlor and acetochlor supports the conclusion that alachlor biological monitoring data are an acceptable surrogate for acetochlor. This conclusion is based on the similar pharmacokinetics of the two structurally-related compounds.

Based on the proposed label maximum use rates, HED estimates annual acetochlor internal dosage as follows:

? lb ai

User Type	Annual Acreage	Harness	Top-Hand
Private-Small	120	1.1 to 113 ug/kg/yr	1.9 to 194 ug/kg/yr
Private-Large	360	2.1 to 214 ug/kg/yr	3.7 to 367 ug/kg/yr
Commercial	1800	10.7 to 1070 ug/kg/yr	18.4 to 1840 ug/kg/yr

The Monsanto risk management label proposals of Restricted-Use classification, requirement of mechanical transfer device if treating more than 300 acres annually, and the protective clothing requirements are identical to those required by the Agency for Lasso (alachlor) and are acceptable pending further risk-benefit analysis.

Curt Lunchick

Curt Lunchick
Nondietary Exposure Branch
Health Effects Division (H7509C)

cc: Correspondence file
Acetochlor file
Circulation
TB-HFAS
SACB

ATTACHMENT 1

004586

Study: The Metabolism of Acetochlor in the Laboratory Rat

Accession No.: 071971/071972

Sponsor/Contracting Lab.: Monsanto/Hazelton Raltech Inc.

Report No./Date/Submitted: MSL-2624/5-83/9-22-83

Author: D. Stephen Saunders Jr., Ph.D. DSS 7/31/85 TJP 8/3/85

Material

Heterogeneous mixture of 12-C, 13-C, and 14-C-Acetochlor, lot no. 2179029, [illegible]. Specific activity of 14-C label = 9.8 mCi/mmole.

Methods

The methods employed in this study were determined to be adequate by this reviewer. A photocopy of the submitted methods is attached to this review.

The study was conducted with Charles River CD SD rats, divided into four experimental groups: Group A received a single oral dose by gavage of 400 mg/kg radiolabeled acetochlor. Elimination of radiolabel by the pulmonary route was monitored in this group. Group B rats were given a single dose of 10 mg/kg, and Group C rats were given a single dose of 400 mg/kg. Group D received daily doses of 10 mg/kg for 14 days, followed by a single dose of 10 mg/kg of radiolabeled test substance. For all test groups, elimination of label was monitored for 7 days after the last dose.

Also, the structural formulas for several of the principal metabolites were identified by conventional analytical techniques.

Results

A. Excretion- Expired air was collected from animals of group A (400 mg/kg by gavage). These animals excreted an average of 0.04% of the administered dose over 7 days by exhalation. Because of the insignificant release by this route, expired air was not monitored in subsequent analyses.

In all of the treatment groups, acetochlor was rapidly excreted, as more than 70% of the administered dose was excreted within 48 hours (Table 1 of this review). The distribution of metabolites between urine and feces favored the fecal route in group B males (10 mg/kg single dose), however females excreted approximately equal amounts of label by either route. In contrast, animals from group C (400 mg/kg single dose) and group D (10 mg/kg repeated dose) excreted a larger proportion of the administered dose through the urine.

Table 1. Distribution of Excreted Dose (%)[a,b]

Group		Urine 0-2 days	Urine 0-7 days	Feces 0-2 days	Feces 0-7 days	Total 0-2 days	Total 0-7 days
B	Male	29.4	31.5	47.2	50.1	76.6	81.6
	Female	41.3	43.4	39.2	40.4	81.0	83.8
C	Male	42.5	46.7	26.0	28.9	68.5	75.6
	Female	46.5	49.7	24.7	26.6	71.2	76.3
D	Male	53.6	59.4	24.5	25.6	80.2	85.2
	Female	68.1	67.8	18.9	19.3	85.0	87.1

[a]data excerpted from submitted study.

[b]percent excreted days 0-2 calculated by reviewer.

Whole-body elimination of acetochlor was biphasic with a rapid and a slow phase. This type of excretion pattern is consistent with a two compartment model of distribution. Rapid excretion would be predicted from well-perfused organs such as heart, liver and kidney, and a longer half-life would be expected for excretion from tissues that do not receive as much blood flow such as fat. However, studies on tissue residues (see section C of this review) indicate that approximately 2.5% of the administered dose was associated with red blood cells, apparently due to binding to hemoglobin. The long half-life (approx. 180 hours) determined for the slow phase of excretion correlates with the half-life of red blood cell turnover in the rat. This fact led the investigators to speculate that the erythrocyte was the slow phase compartment. Repeated doses of acetochlor had little effect on the excretion kinetics as can be seen by comparisons of groups B and D. The half-lives for both the rapid and slow phases were about 30% longer for animals given the single high dose (group C) than for either of the low dose groups. This effect is consistent with saturation of metabolic enzymes of excretory mechanims. Kinetic data are presented in table 2.

Table 2. Kinetic Constants for Excretion of (14-C)-Acetochlor[a]

Group		t-1/2 (rapid)	t-1/2 (slow)
B	Male	7.1 hours	161.9 hours
	Female	5.6	182.4
C	Male	10.4	249.3
	Female	9.3	286.4
D	Male	7.1	128.6
	Female	5.4	186.3

[a]data excerpted from submitted study.

B. Metabolic Pathway- Acetochlor was extensively metabolized, with less than 1% of the administered dose excreted unchanged into the feces and no unmetabolized acetochlor detectable in the urine. Approximately 20 different metabolites were characterized from urine and feces. The most common metabolites excreted at early time points (<24 hours) were mercapturates. At later time points the relative proportion of mercapturates decreased as the proportion of other sulfur-containing metabolites (sulfoxides, sulfones, sulfates) increased. Based on these data it is apparent that an early step in the metabolism of acetochlor is conjugation with glutathione. The proposed metabolic pathway for acetochlor and identified structures of metabolites (photocopied from the submitted study) are depicted in figures 68-70, appended.

C. Tissue Residues- The only tissue which retained significant amounts of radiolabeled acetochlor was the red blood cell. Acetochlor apparently bound covalently to hemoglobin, as determined by gel electrophoresis. The amount of label retained by other tissues was proportional to tissue mass and/or degree of perfusion. Relatively little label was retained in body fat, suggesting that bioaccumulation due to fat storage is not a factor with this compound. These data are depicted in table 3.

Table 3. Tissue Residues of 14-C Acetochlor[a]

	Group B		Group C		Group D	
Tissue	Male	Female	Male	Female	Male	Female
Brain	2743[b] (0.005)[c]	3263 (0.007)	15316 (0.006)	15429 (0.007)	2471 (0.003)	2809 (0.006)
Heart	20885 (0.024)	24000 (0.026)	107407 (0.026)	89873 (0.022)	29677 (0.027)	27209 (0.026)
Kidney	12468 (0.028)	13067 (0.025)	62500 (0.033)	65658 (0.032)	12491 (0.025)	12083 (0.022)
Liver	12342 (0.157)	13900 (0.134)	46094 (0.148)	50414 (0.135)	10881 (0.125)	10919 (0.104)
Lung	25035 (0.036)	24112 (0.033)	113409 (0.035)	135114 (0.040)	20839 (0.023)	18692 (0.027)
Spleen	27246 (0.019)	23256 (0.013)	151612 (0.018)	146087 (0.021)	25000 (0.012)	23800 (0.015)
GI tract	3209 (0.032)	2558 (0.026)	12440 (0.029)	13356 (0.032)	3467 (0.027)	2208 (0.020)
GI contents	1252 (0.061)	623 (0.025)	10420 (0.093)	5266 (0.052)	4710 (0.132)	812 (0.020)

(cont'd next page)

Table 3. Tissue Residues of 14-C Acetochlor (con't.)

Tissue	Group B Male	Group B Female	Group C Male	Group C Female	Group D Male	Group D Female
Eyes	ND -	ND -	8616 (0.0003)	8395 (0.0007)	ND -	ND -
Gonads	1602 (0.004)	ND -	6303 (0.005)	50480 (0.002)	1154 (0.003)	ND -
Fat	1314 (0.031)	1783 (0.059)	9774 (0.092)	11590 (0.110)	1125 (0.014)	1218 (0.047)
Muscle	2517 (0.273)	2110 (0.229)	9277 (0.245)	10640 (0.284)	1948 (0.212)	2072 (0.225)
Femur	2700 **	3314 **	14770 **	20670 **	3338 **	3566 **
Sternum	4872 **	5393 **	28960 **	29600 **	4298 **	4480 **
Whole blood	173000 (2.54)	166000 (2.45)	766000 (2.77)	811000 (2.95)	131000 (1.95)	142000 (2.10)
Plasma	684 **	660 **	3671 **	4684 **	1016* **	1012* **
Total % Retained	3.23	3.04	3.50	3.69	2.53	2.79

[a]data excerpted from submitted study.

[b]dpm/g tissue, calculated by reviewer from average organ weights.

[c]percent of administered dose.

ND = Not detectable

*data not included in Group D summary table, obtained by reviewer from raw data.

**total body mass of this tissue has not been estimated for the rat.

Discussion and Conclusion

Acetochlor was rapidly eliminated from the rat, with >70% of the administered dose excreted within 48 hours for most of the groups. Animals given a single high dose (Group C, 400 mg/kg) or repeated low doses (Group D, 10 mg/kg for 15 consecutive days) appeared to preferentially eliminate radiolabel via the urine, with little difference between sexes. Group B males (single dose of 10 mg/kg) appeared to excrete more label in the feces than in urine, whereas females excreted approximately equal amounts in urine or feces. The kinetics of excretion were biphasic, with a rapid phase ($t_{1/2}$ = 5.4-10.4 hours) and a slow phase ($t_{1/2}$ = 103.6-203.4 hours). Animals given the high dose (400 mg/kg) appeared to have longer half-lives for both phases, consistent with saturation of biliary and/or excretion mechanisms.

Acetochlor was extensively metabolized, with <1% of the administered compound excreted unchanged in the feces. An early step in the proposed metabolic pathway is conjugation with glutathione, and the majority of the excreted metabolites were mercapturic acid derivatives. The remainder of excreted metabolites were other sulfur-containing derivatives of acetochlor such as sulfates, sulfoxides and sulfones.

The only tissue which accumulated significant amounts of acetochlor was the red blood cell, which retained about 2.5% of an administered dose. This percentage was not dose-dependent (although the absolute amount retained obviously was) since similar percentages were retained by all three dosage groups. A slightly smaller percentage was retained by group D animals as compared to group B animals. This effect is consistent with competition for target receptor sites between labeled and unlabeled chemical, and induction of metabolic and/or excretory mechanisms. This conclusion is supported by the findings that group D rats, compared to group B animals, had slightly higher levels of radioactivity retained in the plasma in conjunction with a higher percentage of administered dose excreted in the urine at 2 days and a slightly higher percentage excreted overall at 2 or 7 days (Tables 1 and 3). The radioactivity was determined to be covalently bound to the hemoglobin fraction of the erythrocyte. Since a significant amount of label was bound even after 14 consecutive doses of unlabeled chemical (group D), these data suggest that a cumulative effect of acetochlor on red blood cell function is possible.

Classification: Core-Guideline

RIN 2556-94

Acetochlor

Page_____ is not included in this copy.

Pages 38 through 41 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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

MEMORANDUM

JAN 13 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Assessment of Corn Herbicide Reduction with the Registration of Acetochlor

FROM: Allen L. Jennings, Director
Biological and Economic Analysis Division (7503W)

TO: Stephen Johnson, Acting Director
Registration Division (7505C)

COMMERCIAL/FINANCIAL INFORMATION IS NOT INCLUDED

The Acetochlor Registration Partnership (Monsanto/Zeneca) asserts in a letter dated January 6, 1994 to Assistant Administrator Goldman that in the fifth year of commercialization, acetochlor will significantly reduce the amount of corn herbicides used by [redacted]" Using documents submitted in support of registration by the Partnership, Monsanto Agricultural Company, and our available sources, we attempted to determine if these projections are legitimate.

Our review of the available data indicate that acetochlor is likely to decrease the amount of corn herbicides introduced into the environment over time. However, we are unable to validate the Partnership's assertion that within five years of commercialization, over [redacted] of corn herbicides will be reduced. Information contained in the support documents submitted by the Partnership to illustrate this benefit are inadequate, incomplete, and unsubstantiated. We found it nearly impossible to determine whether or not the claims being made are representative of what could occur within the five year time frame. Furthermore, we suspect that numerous undisclosed assumptions have been made by the Partnership in preparing their analysis. Without knowing those assumptions, we have no way of determining the validity of the Partnership's claims and how they may affect their projections and our analysis of their projections.

In the support document titled 'Information to Support the Registration of Acetochlor, July 15, 1993', the Partnership maintains that "by 1998, acetochlor will reduce the yearly amount of [corn] herbicide[s] applied by [redacted] and that "assuming a rate of penetration of [redacted] the cumulative reduction by 1998 will be [redacted] of corn herbicides." The alternatives expected to be displaced consist of alachlor, metolachlor, EPTC, butylate, atrazine, cyanazine, 2,4-D, and dicamba. Data tables in the document which contain estimates of current herbicide use are unreferenced. In addition, the Partnership did not include cyanazine use estimates in these. When we compare Agency estimates of these herbicides used in corn to the Partnership's estimates, severe discrepancies result. For example, the difference between their estimates and ours for amount of individual herbicides used approached 20 million pounds in two instances.

Additionally, when the Partnership's estimates for the reduced use of the alternative herbicides are extrapolated to the fifth year of commercialization of acetochlor, we are unable to determine what mathematical method was used. We have made numerous attempts to verify these projections to no avail. We simply have not been given enough information to determine quantitatively to what extent the alternative herbicides use will be reduced. However, we believe that there will be fewer pounds of corn herbicides applied if acetochlor penetrates the market. Acetochlor will be used in most situations at rates lower than those currently used for the primary herbicides it will replace, alachlor, EPTC, butylate, and metolachlor. At the currently proposed rates, acetochlor rates are approximately [redacted] less than alachlor, EPTC and butylate, and are [redacted] less than metolachlor. Furthermore, acetochlor's ability to control selected broadleaf weed species and triazine resistant weeds offers the opportunity to reduce the use of the triazines, dicamba, and 2,4-D.

The Partnership projects that over the initial five years of commercialization, acetochlor will penetrate the market at the rate of [redacted] per year. While we have no way of predicting this with any level of confidence, we suspect that [redacted] per year is an over estimation of market infiltration. Although we can not foresee what new chemicals may enter the market, it is likely that in this five year time frame new herbicides will be introduced. In fact, the data presented by the Partnership for market share penetration does not include some recently registered competing herbicides, namely dimethenamid, flumetsulam, nicosulfuron, and primisulfuron. That being the case, it is likely that their market share predictions are over estimated and therefore, their estimations of reduced herbicide use are likely to be inflated.

The Partnership estimates, and we agree, that the alternative most likely to result in the largest reduction of use is alachlor. Being that the registrant of alachlor, Monsanto Agricultural Company, is one of the members pursuing registration of acetochlor we suspect that through marketing, a large portion of the current alachlor market will shift to acetochlor. The other alternatives, metolachlor, EPTC, butylate, atrazine, cyanazine, dicamba, and 2,4-D, will likely encounter varying degrees of reduced use. Since acetochlor use rates are for the most part lower than the primary alternatives, alachlor, EPTC, butylate, and metolachlor, overall herbicide use reduction is likely to occur. However, pesticide use reduction does not necessarily translate into pesticide risk reduction. We defer to HED and EFED to determine the relative risk associated with acetochlor versus the alternatives it may potentially replace.

Conclusions

It is true that the number of pounds of herbicides used for weed control in corn will be reduced with the registration of acetochlor. However, we are unable to determine with the information presented by the Partnership, whether or not [redacted] of herbicides will be introduced into the environment cumulatively within five years of commercialization of acetochlor. We suspect that it may be an over estimation for a number of reasons. First, the data included as supporting evidence were incomplete and unsubstantiated. Secondly, because some recently introduced chemicals were left out of the analysis of market share projections, namely dimethenamid and flumetsulam, the forecasted market share is likely to be overstated. Lastly, many assumptions have been made by the Partnership in preparing their market projections that we are unable to verify. That being the case, we are incapable of confirming many of the Partnership's claims.

INTEGRATED RISK INFORMATION SYSTEM

Chemical Name: Alachlor
CASRN: 15972-60-8

Last Revised: 01/01/92

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in the Oral RfD, Inhalation RfC and Carcinogenicity Assessment Sections represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The Regulatory Actions Section may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents, which are available in each section of the chemical files.

Category (section)	Status	Last Revised
Oral RfD Assessment	Available	12/01/88
Inhalation RfC Assessment	empty	
Carcinogenicity Assessment	Under Rev	
Drinking Water Health Advisories	Available	03/01/88
U.S. EPA Regulatory Actions	Available	01/01/92
Supplementary Data	empty	

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name: Alachlor
CASRN: 15972-60-8

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Oral RfD Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in the Carcinogenicity Assessment Section of this file when a review of that evaluation is completed.

RfD ASSESSMENT SUMMARY TABLE

Crit. Dose: 1 mg/kg-day [Study 1 NOAEL]
UF: 100 MF: 1 RfD: 1E-2 mg/kg-day Confidence: High

Crit Effect: (1) Hemosiderosis, hemolytic anemia

	NOAEL (Study 1)	LOAEL (Study
Reported	1.0 mg/kg-day	3.0 mg/kg-day
ADJ	1.0 mg/kg-day	3.0 mg/kg-day
Study Type	1-Year Dog Study; Gelatin Capsule	1-Year Dog Study; Gelatin Capsule
Reference	Monsanto Company, 1984a	Monsanto Company, 1984a

1) Monsanto Company, 1984a
1-Year Dog Study; Gelatin Capsule

Critical Effect: Hemosiderosis, hemolytic anemia

Defined Dose Levels:
NOAEL= 1.0 mg/kg-day
NOAEL(ADJ)= 1.0 mg/kg-day
LOAEL= 3.0 mg/kg-day
LOAEL(ADJ)= 3.0 mg/kg-day

Conversion Factors: none

DISCUSSION OF PRINCIPAL AND SUPPORTING STUDIES

Monsanto Company. 1984a. MRID No. 00148923. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Alachlor was administered in gelatin capsules to 6 dogs/sex/group at levels of 0, 1.0, 3.0, and 10.0 mg/kg/day for 1 year. The principal toxic effects noted

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

tained to the hematology parameters studied and are described as hemolytic ıia. This diagnosis was supported by lower RBC counts, hematocrit, and ɔglobin as well as hemosiderosis in several organs. The effect was ɜ-related and was observed only in males; the females at the high dose appeared to have some trend toward developing the same effects.

Hepatotoxic effects were noted in a 6-month dog study at all levels (5, 25, and 75 mg/kg/day).

UNCERTAINTY AND MODIFYING FACTORS

UNCERTAINTY FACTORS:

The customary 100 UF was used for extrapolation from laboratory animals to humans.

ADDITIONAL COMMENTS / STUDIES

Data Considered for Establishing the RfD:

1) 1-Year Feeding - dog: Principal study - see previous description; core grade minimum

6-Month Feeding - dog: NOEL=none; LEL=5 mg/kg/day (hepatoxicity) (Monsanto , 1981a)

2-Year Feeding (oncogenic) - rat: Systemic NOEL=2.5 mg/kg/day; (ocular lesions and hepatoxicity); Systemic LEL=15 mg/kg/day; core grade minimum (Monsanto Co., 1984b)

4) 3-Generation Reproduction - rat: NOEL=10 mg/kg/day; LEL=30\mg/kg/day (kidney effects in pups); core grade minimum (Monsanto Co., 1981b)

5) Teratology - rat: No teratogenic effects, fetotoxic effects at 400 mg/kg/day, maternal toxicity at 150 mg/kg/day (Monsanto Co., 1980)

Data Gap(s): Teratology, second species

CONFIDENCE IN THE RfD

Study: High Data Base: High RfD: High

The study on which the RfD is based is of high quality and sufficient duration. In addition, there are generally good toxicologic studies available on alachlor which, overall, provide high confidence in the data base. High confidence in the RfD follows.

EPA DOCUMENTATION AND REVIEW

- ırce Document: This assessment is not presented in any existing U.S. EPA ument.

.er EPA Documention: Office of Pesticide Programs Files

Agency Work Group Review: 03/11/86

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Verification Date: 03/11/86

EPA CONTACTS

William Burnam / OPP -- (703)305-4791

George Ghali / OPP -- (703)305-7490

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Monsanto Company. 1984b. MRID No. 00139021, 00141060, 40284001. Available from EPA. Write to FOI, EPA, Washington, D.C. 20460.

Monsanto Company. 1981b. MRID No. 00075062. Available from EPA. Write to FOI, EPA, Washington, D.C. 20460.

Monsanto Company. 1980. MRID No. 00043645. Available from EPA. Write to FOI, EPA, Washington, D.C. 20460.

Monsanto Company. 1981b. MRID No. 00028564, 00087479, 00100659. Available from EPA. Write to FOI, EPA, Washington, D.C. 20460.

REVISION HISTORY

12/88 RfD Add Com: Core graded added to studies 1, 3 and 4

Alachlor

REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

stance Name: Alachlor
CN: 15972-60-8

Status: empty

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name: Alachlor
CASRN: 15972-60-8

Status: Under Rev

Note: A risk assessment for this substance/agent is under review by an EPA work group.

Agency Work Group Review: 04/01/87, 04/22/87, 07/11/88

DRINKING WATER HEALTH ADVISORIES

stance Name: Alachlor
RN: 15972-60-8

The Office of Water provides Drinking Water Health Advisories (HAs) as technical guidance for the protection of public health. HAs are not enforceable Federal standards. HAs are concentrations of a substance in drinking water estimated to have negligible deleterious effects in humans, when ingested, for a specified period of time. Exposure to the substance from other media is considered only in the derivation of the lifetime HA. Given the absence of chemical-specific data, the assumed fraction of total intake from drinking water is 20%. The lifetime HA is calculated from the Drinking Water Equivalent Level (DWEL) which, in turn, is based on the Oral Chronic Reference Dose. Lifetime HAs are not derived for compounds which are potentially carcinogenic for humans because of the difference in assumptions concerning toxic threshold for carcinogenic and noncarcinogenic effects. A more detailed description of the assumptions and methods used in the derivation of HAs is provided in the Health Advisory Background Document.

ONE-DAY HEALTH ADVISORY FOR A CHILD

Note: No appropriate data are available to derive a One-day HA; therefore, it is recommended that the Ten-day HA of 0.1 mg/L be used as the One-day HA.

TEN-DAY HEALTH ADVISORY FOR A CHILD

	1E-1 mg/liter
LOAEL:	10 mg/kg-day
UF:	1000 allows for interspecies and intrahuman variability with the use of a LOAEL from an animal study
Assumptions:	1 L/day water consumption for a 10-kg child
Principal Study:	Monsanto Company, 1984

Discussion: Dutch Belted rabbits (18/dosage group) were artificially inseminated and administered alachlor in mineral oil by gavage at 0, 10, 30, or 60 mg/kg/day on days 6 through 27 of gestation. Despite the use of mineral oil, there was little evidence of laxative-cathartic effects. The high-dose group had a high rate of preimplantation loss (49%), increased incidences of fetuses with presacral vertebrae, and increased litters with major vessel variations at the high dose. An increase was noted in the incidence of fetuses with rudimentary and full 13th rib in all dose groups. Based on the rib effects, a dose-response increase was seen. Therefore, the LOAEL for this study is 10 mg/kg/day.

LONGER-TERM HEALTH ADVISORY FOR A CHILD

Note: A Longer-term Health Advisory has not been determined for alachlor because it has been shown to produce cancer in less than 5.6 months in rats (at same rate as did the lifetime exposure).

LONGER-TERM HEALTH ADVISORY FOR AN ADULT

Note: A Longer-term Health Advisory has not been determined for alachlor because it has been shown to produce cancer in less than 5.6 months in rats (at

the same rate as did the lifetime exposure).

DRINKING WATER EQUIVALENT LEVEL / LIFETIME HEALTH ADVISORY

DWEL: 3.5E-1 mg/liter
Basis: Oral RfD verified on: 03/11/86
Lifetime HA: none mg/liter
Assumptions: 2 L/day water consumption for a 70-kg adult

Principal Study: Monsanto Company, 1984

Discussion: See oral RfD. The assessment for the potential human carcinogenicity of alachlor is currently under review. Until this review is completed a Lifetime HA is not recommended.

ORGANOLEPTIC PROPERTIES

No data available

ANALYTICAL METHODS FOR DETECTION IN DRINKING WATER

Determination of alachlor is by a liquid-liquid extraction gas chromato-graphic procedure.

WATER TREATMENT

Data are available on the removal of alachlor from potable water using conventional treatment and adsorption. The use of air stripping has also been considered.

EPA DOCUMENTATION AND REVIEW OF HAs

Source Document: U.S. EPA. 1984. Special Review: Position Document 1. Office of Pesticide Programs.

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Scientific Advisory Panel review of HAs in January, 1986.

EPA CONTACTS

Amal Mahfouz / OST -- (202)260-9568

Edward V. Ohanian / OST -- (202)260-7571

BIBLIOGRAPHY

Monsanto Company. 1984a. MRID No. 00148923. Available from EPA. Write to FOI, EPA, Washington, D.C. 20460.

U.S. EPA. 1984. Special Review: Position Document 1. Office of Pesticide Programs.

REVISION HISTORY

)8 HA Data: Health Advisory added

U.S. EPA REGULATORY ACTIONS

Substance Name: Alachlor
CASRN: 15972-60-8

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in the Oral RfD, Inhalation RfC and Carcinogen Assessment Sections, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in the Regulatory Action Background Document.

SAFE DRINKING WATER ACT (SDWA)

Maximum Contaminant Level Goal

Value: 0 mg/L
Status/Year: Final 1991
Econ/Tech?: No, does not consider economic or technical feasibility
Reference: 56 FR 3526 (01/30/91)

Contact: Health and Ecological Criteria Division / (202)260-7571
Safe Drinking Water Hotline / (800)426-4791

Discussion: An MCLG of 0 mg/L for alachlor is promulgated based upon carcinogenic potential (B2).

Maximum Contaminant Level (MCL)

Value: 0.002 mg/L
Status/Year: Final 1991
Econ/Tech?: Yes, does consider economic or technical feasibility
Reference: 56 FR 3526 (01/30/91)

Contact: Drinking Water Standards Division / OGWDW / (202)260-7575
Safe Drinking Water Hotline / (800)426-4791

Discussion: EPA has set an MCL equal to the PQL, which is associated with a lifetime individual risk of 2E-3.

Monitoring Requirements

All systems initially monitored for four consecutive quarters every 3 years repeat monitoring dependent upon detection, vulnerability status and system size.

U.S. EPA REGULATORY ACTIONS

lytical Methods

roextraction/gas chromatography (EPA 505); nitrogen-phosphorus detector/gas matography (EPA 507); gas chromat- ographic/mass spectrometry (EPA 525): = 0.002 mg/L.

Best Available Technology

Granular activated carbon.

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTCIDE ACT (FIFRA)

Pesticide Active Ingredient Registration Standard

Status: Issued 1984
Reference: Alachlor Pesticide Registration Standard. November, 1984 (NTIS No. PB86-179835).

Contact: Registration Branch / OPP / (703)305-5447

ticide Active Ingredient Special Review

ion: Final Regulatory Decision - PD 4
r: 1987
Econ/Tech?: No, does not consider economic or technical feasibility
Reference: 51 FR 36166 (10/08/86)

Contact: Special Review Branch / OPP / (703)308-8010

Summary of Regulatory Actions: The 1987 PD4 is for dietary and applicator risk. The PD4 for ground water is deferred until 1991. Required restricted use label warning and closed systems for large-scale mixer/loaders; criterion of concern: oncogenicity.

REVISION HISTORY

01/92 Reg Data: Regulatory actions updated

SUPPLEMENTARY DATA

Substance Name: Alachlor
CASRN: 15972-60-8

Status: empty