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

JUN 26 1986

MEMORANDUM

JUN 26 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Alachlor

FROM: Esther Rinde, Ph.D. E. Rinde 5/20/86
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769c)

TO: Robert Taylor
Product Manager #25
Fungicide-Herbicide Branch
Registration Division (TS-767c)

The Toxicology Branch Peer Review Committee met on March 25, 1986 to discuss and evaluate the weight-of-the-evidence on Alachlor, with particular reference to consideration of whether there is agreement on its classification as a B-2 carcinogen.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with peer review unless otherwise stated).

Theodore M. Farber	Theodore M. Farber
Reto Engler	
Louis Kasza	
Bertram Litt	
Gary Burin	
Laurence Chitlick	W. Teeters for L. Chitlick
Bruce Means	
William Marcus	
Robert Beliles	
Esther Rinde	E. Rinde

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A. Individuals in Attendance (continued)

2. Reviewers: (Non-panel members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Judith Hauswirth — Judith W. Hauswirth

3. Peer review members in absentia: (Committee members who were not able to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

John A. Quest — John A. Quest

Richard Hill — Arnold G. Barnes

Stephen Johnson

Anne Barton — Anne Barton

B. Material Reviewed:

The material available for review consisted of the following:

A. DER: A chronic Feeding study of Alachlor in Rats. Bio/Dynamics.

B. DER: A chronic Study of Alachlor Administered in feed to Long-Evans Rats. Monsanto Environmental Health Laboratory.

C. DER: A Special Chronic Feeding Study with Alachlor in Long-Evans Rats. Monsanto.

D. Tumor incidence table for the three rat studies combined; also DER on Monsanto's reevaluation of submucosal gland hyperplasia seen in study reviewed under Part 5.b. of Peer Review Memo (3/17/86).

E. DER: An 18 Month Oncogenic Study in Mice. Bio/dynamics.

F. Sher,S.P., R.D. Jensen and D.L. Bokelman. Spontaneous Tumors in Control F344 and Charles River CD Rats and Charles River CD-1 and B6C3HF1 Mice. Toxicology Letters 11: 103-110, 1982.

G. Homburger,F., A.B. Russfield, J.H. Weisburger, S. Lim, S.P. Chak and E.K. Weisburger. Aging Changes in CD-1 HaM/ICR Mice reared Under Standard Laboratory Conditions. J. Natl. Cancer Inst. 55: 37-45, 1975.

H. Historical Control Data from Bio/dynamics on Lung Tumors and Liver Tumors in CD-1 Mice.

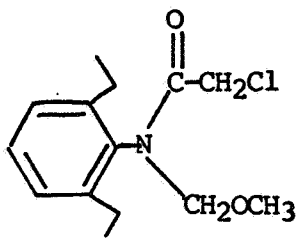
I. Table: Q_1^* Potency Estimates for Alachlor Based on Rat Tumor Data (from the PD-1).

A copy of the information reviewed is appended to this panel report.

C. Background Information:

Alachlor (2-chloro-2'6' diethyl-N-(methoxymethyl)-acetanilide) is registered for use as a selective herbicide for the control of many preemergent broadleaf weeds and grasses. In December 1984, a Special Review Position Document 1 was issued on alachlor, in which the Agency concluded Alachlor is a class B_2 oncogen based on the proposed EPA Guidelines, and that "the weight of the evidence demonstrates that alachlor is oncogenic to laboratory animals and, in the absence of data on humans, it is prudent to treat alachlor as a probable human carcinogen".

A Special Review Position Document 2,3 (PD 2,3) is now being prepared on alachlor; it was felt that it would be beneficial at this time to reevaluate alachlor through the peer review process prior to issuing the PD 2,3.



ALACHLOR

D. Evaluation of Oncogenicity Evidence for Alachlor:

1. A Chronic Feeding Study of Alachlor in Rats:

Bio/dynamics administered alachlor (Lasso Technical) in the diet to groups of 50 male and 50 female Long-Evans rats at concentrations of 0, 100, 300, or 1000 ppm (0, 14, 42 and 126 mg/kg/day, respectively) for 812 to 813 days (males) and 741 to 744 days (females). Two different lots of the technical alachlor were used during the study: Lot #XHI-167, stabilized with 0.5% epichlorohydrin* (for the first 11 months of the study) and Lot #MHK-6, [redacted] (for the remainder of the study). The following incidence of tumors were observed.

STUDY # 1

Tumor Site and Type	Sex	Dose (mg/Kg/day) 0	14	42	126
Stomach:					
leiomyosarcoma	M	0/49	0/50	0/50	1/50
	F	0/50	0/50	0/50	1/49
osteosarcoma	M	0/49	0/50	0/50	3/50
	F	0/50	0/50	0/50	4/49
gastric adenocarcinoma	M	0/49	0/50	0/50	2/50
	F	0/50	0/50	0/50	1/49
malignant mixed gastric tumor	M	0/49	0/50	0/50	11/50
	F	0/50	0/50	1/50	17/49
Thyroid:					
follicular adenoma	M	1/48	0/50	1/49	11/50
	F	0/49	0/44	2/46	2/49
follicular carcinoma	M	0/48	0/50	0/49	2/50
	F	0/49	0/44	0/46	2/49
Nasal Turbinates respiratory epithelium:					
adenomas	M	0/46	0/46	10/41	23/42
	F	0/49	0/47	4/42	10/48
carcinomas	M	0/46	0/46	1/41	0/42
	F	0/49	0/47	1/42	0/48

*Epichlorohydrin is carcinogenic for male Wistar rats and Sprague-Dawley rats: When given in drinking water it causes forestomach tumors (squamous cell papillomas and carcinomas) in male Wistar rats (Konishi et al. Gann 71:922-923, 1980); by inhalation it causes squamous carcinomas of the nasal cavity (Laskin, et al. J. Natl. Cancer Inst. 65:751-755, 1980). The effect of epichlorohydrin on tumor formation in this study is not known.

Nasal turbinate tumors (mainly benign) were significantly increased in both males ($p<0.001$) and females ($p<0.02$) at the mid dose level (42 mg/kg/d) and above.

Stomach malignant tumors increased significantly ($p<0.001$) in both sexes at the high dose level.

Thyroid follicular tumors (adenomas and carcinomas) were significantly increased in males at the high dose level ($p<0.001$).

The lowest dose of alachlor tested in this study probably exceeded a MTD as evidenced by high mortality, compared to controls. Increases in organ weights (liver, kidney, spleen, et al.) were also noted, as were gross findings, at all dose levels, indicative of a compound related effect.

2. A Chronic Feeding Study of Alachlor in Rats:

Monsanto administered technical alachlor (94.13%) in the diet to groups of 50 male and 50 female Long-Evans rats at concentrations of 0, 0.5, 2.5 and 15.0 mg/kg/day for 25 to 26 months. The alachlor was stabilized with [redacted] Epichlorohydrin was not used as a stabilizer. The following incidence of tumors/lesions was observed.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

STUDY #2

Tumor Type and Site	Sex	Dose (mg/kg/day) Control 0	Low 0.5	Medium 2.5	High 15.0
Thyroid follicular adenoma	M	2/49	4/50	3/49	4/49
	F	1/49	1/49	0/49	2/47
carcinoma	M	1/49	0/50	1/49	2/49
	F	3/49	1/49	1/49	1/49
Thymus lymphosarcoma	M	0/49	0/50	1/46	0/50
	F	0/48	1/50	2/48	3/43
Adrenal pheochromocytoma benign	M	8/50	7/50	2/50	6/50
	F	1/49	1/50	3/50	5/49
malignant	M	2/50	2/50	0/50	2/50
	F	1/49	0/50	0/50	0/49
Nose/Turbinates respiratory epithelium adenoma	M	0/45	0/48	0/45	11/45
	F	0/42	0/44	1/47	9/48
neurofibroma	M	0/45	1/48	0/45	0/45
	F	0/42	0/44	0/47	0/48
submucosal gland adenoma	M	0/45	0/48	1/45	0/45
	F	0/42	0/44	0/47	0/48
epith. hyperplasia/ metaplasia	M	1/45	1/48	1/45	1/45
	F	0/42	0/44	0/47	2/48
submucosal gland hyperplasia	M	2/45	1/48	3/45	21/45
	F	2/42	5/44	5/47	11/48

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Nasal turbinate tumors were significantly elevated ($p<0.01$) in both males and females at 15 mg/kg/day (the highest dose tested). One female rat in the mid dose group also had this tumor and one male in this group had a submucosal gland adenoma.

Thymus lymphosarcomas and adrenal pheochromocytomas were significantly increased ($p<0.05$) in the high dose females.

There was a non-significant increase in thyroid follicular cell tumors in the high dose male group.

> The highest dose tested probably exceeded a MTD in female rats, as evidenced by a 16% increase in mortality over that in the control. (In male rats, high mortality in the corresponding control group may have obscured an increased mortality in high dose males.)

Monsanto was requested to reevaluate the submucosal gland hyperplasia seen in both males and females. Experimental Pathology Laboratories, Inc. (EPL) performed a histological reevaluation; their report indicated that the submucosal nasal lesions (hyperplasia) were not neoplastic, however their analysis reflected a slightly higher incidence of adenomas of the nasal cavity. EPL's diagnosis is compared with that of Monsanto in the table below.

	Nasal turbinate adenomas			
	EPL's data		Monsanto's data	
Group (mg/kg/day)	Males	Females	Males	Females
0	0/44	0/42	0/45	0/42
0.5	0/47	0/42	0/48	0/44
2.5	0/44	1/47	0/45	1/47
15.0	15/45	14/48	11/45	9/48

3. A Special Chronic Feeding Study With Alachlor

In a study performed by Monsanto, alachlor was administered in the diet to Long-Evans rats at a concentration of 126 mg/kg/day. After a period of exposure (5-8 months) sufficient to induce ocular lesions (as confirmed by the consulting ophthalmologist) the treated animals were divided into 3 groups[1]. Group I animals were designated to remain on the treatment diet until the end of the two-year study period; group II animals were selected, based on the status of their ocular lesions, for interim sacrifice; and group III animals, based on predicted potential recovery from ocular lesions, were placed on untreated diets for the remainder of the study period. The control group from Study #2 discussed above under section 2 can also be considered here since the two studies were run concurrently.

[1]The grouping process was by design selective for susceptibility for ocular lesions and not a random selection, however, 99% of the females were affected with these lesions by month 13 of the study.

STUDY #3

		Control	Group I	Group III
Nasal turbinates				
respiratory epithelium adenoma	M	0/45	42/61	10/17
	F	0/42	11/25	19/46
carcinoma	M	0/45	7/61	0/17
	F	0/42	2/25	1/46
Thymus lymphosarcoma	M	0/49	1/68	1/16
	F	0/48	0/25	1/43
Adrenal pheochromocytoma benign	M	8/50	8/70	2/20
	F	1/49	0/31	2/48
malignant	M	2/50	2/70	1/20
	F	0/49	0/31	0/48
Thyroid follicular adenoma	M	2/49	8/69	1/20
	F	1/49	4/31	3/49
carcinoma	M	1/49	10/69	1/20
	F	3/49	0/31	1/49
Stomach				
mixed carcino-sarcoma	M	0/50	3/68	0/20
	F	0/50	19/31	0/49
anaplastic sarcoma	M	0/50	1/68	0/20
	F	0/50	3/31	0/49
adenocarcinoma	M	0/50	0/68	0/20
	F	0/50	10/31	0/49
leiomyosarcoma	M	0/50	0/68	0/20
	F	0/50	10/31	0/49
undiff. sarcoma	M	0/50	0/68	0/20
	F	0/50	16/31	2/49
undiff. carcinoma	M	0/50	0/68	0/20
	F	0/50	3/31	0/49
Brain neuroepithelioma	M	0/50	1/70	0/20
	F	0/50	1/31	1/49

(continued)

STUDY #3 (continued)

		Control	Group I	Group III
Liver				
hepatoma	M	1/50	3/70	0/20
	F	0/50	1/31	0/49
neoplastic nodule	M	0/50	0/70	0/70
	F	0/50	1/31	1/49
hepatocellular carcinoma	M	2/50	2/70	0/20
	F	0/50	2/31	1/49

Note that nasal turbinate adenomas developed in rats exposed to alachlor for only 5-6 months at the beginning of the study (Group III).

The MTD was exceeded in female rats, as evidenced by a statistically significant increase in mortality; (In males, this single dose tested probably approached MTD.)

Monsanto submitted a reevaluation of the neuroepitheliomas seen in this study; electron microscopy of such a tumor from one of the animals showed "intermediate fiber typical of keratin", from which Monsanto concluded that the tumor was epithelial, not neural. C.I.I.T. also reevaluated all three brain tumors and concluded that they were extensions of nasal adenocarcinomas and not brain tumors. However, a discrepancy in animal numbers and diagnoses remains to be resolved before either Monsanto's or C.I.I.T.'s conclusions can be accepted (J. Hauswirth Memo). Monsanto has been informed of this discrepancy.

4. An 18 Month Oncogenic Study in Mice

In a study performed by Bio/dynamics, alachlor (Lasso technical)* was administered in the diet to groups of fifty male and fifty female CD-1 mice at dosages corresponding to the following levels: 0, 26, 78 and 260 mg/kg/day. The incidence of pertinent non-neoplastic and neoplastic changes are tabulated below.

STUDY #4

		Dose (mg/kg/day)			
		Control 0	Low 26	Mid 78	High 260
Lung bronchiolar-alveolar	M	6/50	1/50	4/50	10/50
adenoma	F	2/50	4/50	7/50	10/50
carcinoma	M	3/50	5/50	7/50	2/50
	F	1/50	1/50	1/50	1/50
fibrosarcoma	M	0/50	0/50	0/50	0/50
	F	0/50	0/50	0/50	1/50
congestion	M	1/50	13/50	13/50	12/50
	F	5/50	5/50	12/50	16/50
Liver adenoma	M	5/50	1/50	4/50	7/50
	F	0/50	0/50	0/50	1/50
carcinoma	M	0/50	3/50	1/50	4/50
	F	0/50	0/50	1/50	0/50
Uterus leiomyoma	F	0/50	2/50	0/50	0/50
leiomyosarcoma	F	1/50	0/50	2/50	3/50
endometrial carcinoma	F	0/50	1/50	0/50	0/50
endometrial polyp	F	1/50	3/50	0/50	3/50
granular cell myoblastoma	F	0/50	0/50	0/50	1/50

INERT INGREDIENT INFORMATION IS NOT INCLUDED

*Alachlor was supplied in two batches:
Lot XHI-167 used during the first 11 months of the study was stabilized with 0.5% epichlorohydrin; Lot MHK-6, used during the last 7 months, was stabilized [redacted]

The major target organ for oncogenicity was the lung. The incidence of lung bronchioalveolar tumors was significantly increased in the high dose females ($p<0.05$) and was also significant ($p<0.01$) for the high dose females which died in extremis during the study. The incidence of lung tumors in females which died during the study was:

Control	0/30
Low	1/17
Mid	3/27
High	7/35

The MTD was probably reached or slightly exceeded at the high-dose in female mice, as evidenced by slight increase in mortality, 10% body weight depression, an increase in thyroid follicular atrophy and in kidney chronic interstitial fibrosis.

Monsanto submitted an addendum to this study on 2/25/85. The report contains an evaluation done by Bio/dynamics on the nasal turbinates of mice in the control and high dose group. Tissues from all remaining animals were examined (originally only 10 mice/sex/group had been examined). No nasal turbinate tumors were found.

5. Historical Control Information

Historical control data on lung tumors in CD-1 mice could be found in the open literature:

I MSD Study: Sher et al. Toxicology Letters 11:103-110, 1982.

N - animals:	M	1232	N - groups:	M	24	Age:	81-105 weeks
	F	1240		F	24		
adenoma	M	0-38%					
	F	0-41%					
adenocarcinoma	M	0-16%					
	F	0-12%					

II Homburger Data: Homburger et al. J. Natl. Cancer Inst. 35:37-43, 1975.

N - animals	M	99
	F	102

		18 months
adenoma	M	2
	F	4
adenocarcinoma	M	-
	F	1

The MSD study duration was too long, so that comparisons based on these controls could not be made, however the study length from which the Homburger Data was derived, was appropriate. These latter control values were exceeded in the treated animals of study #4; furthermore, the Homburger data appear to indicate that the response seen in concurrent male controls was high, which could be masking the true response in the treated males.

Additional historical control data obtained from Bio-dynamics on the incidence of lung and liver tumors in CD-1 mice for concurrently run studies were discussed but were also found to be inappropriate because the length of the studies was 23-25 months, exceeding the 18 months of the Alachlor study.

Historical control data for the rats was requested from Monsanto, but has not been made available at this time.

E. Additional Toxicology Data on Alachlor:

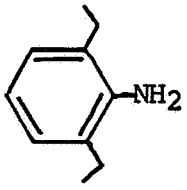
1. Metabolism:

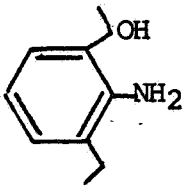
Fourteen metabolites of alachlor have been found in the urine and 13 in feces of Sprague-Dawley rats fed alachlor. Only three of these were found in both urine and feces (Figure 1 & 2). Approximately 89% of the radioactivity is eliminated in urine and feces (1:1) within four days; the rate of elimination is biphasic. Mercapturic acid, glucuronic acid, sulfate conjugation and side chain hydroxylation are important metabolic pathways in the rat. One metabolite found in rat urine, N-[2-ethyl-6-(1-hydroxyethyl)-phenyl]-N-(methoxymethyl)-2(methylsulfonyl)acetamide (metabolite XII), was mutagenic in the Ames salmonella assay, both with and without metabolic activation.

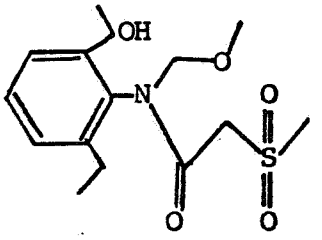
In Rhesus monkeys, 5 conjugates were identified in urine only (Figure 3) when alachlor was given intravenously: 92-94% of the total radioactivity was excreted in the urine during the first 24 hours and 91-94% in the feces during the first 48 hours (9-10:1). Studies via 2 other routes (intramuscular and topical) were considered unacceptable.

In human biomonitoring studies, metabolites which contained diethyl aniline (DEA) and hydroxy-ethyl, ethyl aniline (HEEA) moieties of alachlor were identified in urine.

Note that metabolites with both the HEEA and DEA moieties were found in both humans and rats (metabolite XII also contains the HEEA moiety); and while Monsanto claims that the monkey is a "better model for man in the case of alachlor"* in monkeys, only metabolites with the DEA moiety were found.

DEA: 

HEEA: 

Metabolite XII: 

2. Non-Oncogenic Toxicological Effects

The acute oral LD_{50}'s in the rat of alachlor (90%) and technical alachlor are 2.3 g/kg and 0.93-1.2 g/kg, respectively. In mice the acute oral LD_{50} of technical alachlor is 2.1 g/kg.

In a 3-generation reproduction study in Charles River Sprague-Dawley CD rats, the NOEL was 10 mg/kg based on kidney effects (chronic nephritis, hydronephrosis) seen in F_2 adult males and F_{3b} male pups.

In a one year subchronic beagle dog study the NOEL was 1 mg/kg/day based on hemosiderosis seen in liver, kidney and spleen of dogs in the 3 and 10 mg/kg/day groups.

Alachlor was not teratogenic to rats at 400 mg/kg/day (HDT).

A NOEL for non-neoplastic toxicity was established for alachlor in a 2-year chronic feeding/oncogenicity study in Long-Evans rats. The NOEL was 2.5 mg/kg/day based upon molting of retina pigmentation and increased mortality rate in the females and abnormal disseminated foci in male liver.

*[Monsanto's Rebuttal to Alachlor PD-1]

3. Mutagenicity:

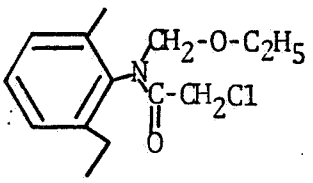
The results of mutagenicity testing conducted on alachlor are summarized in the following table.

Test	Core Classification	Result	Comments
Ames Assay	acceptable	negative	a positive response was seen at 5000 ug/plate in TA 1535 but the response was not repeated for consecutive doses.
Gene mutation in CHO cells HGPRT locus	acceptable	negative	
In-vivo bone marrow chromosome aberration assay	acceptable	negative	no structureal or numerical chromosomal aberrations
In-vivo - in vitro hepatocyte DNA repair assay	acceptable	positive	positive at highest dose tested (1.0g/kg/day) - "weakly genotoxic"
DNA damage in B. subtilis M45 and H17	acceptable	negative	did not cause DNA damage. (20-20,00 ug/plate)

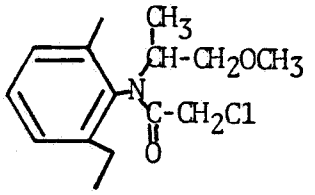
As noted in the metabolism section of this report one metabolite of alachlor tested positive in the Ames assay (TA 100 - both with and without metabolic activation over six test doses).

4. Structure-Activity Correlations:

Alachlor is structurally related to metolachlor and acetochlor, structures of which are shown below.



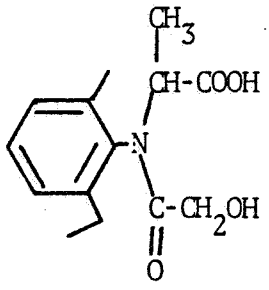
ACETOCHLOR



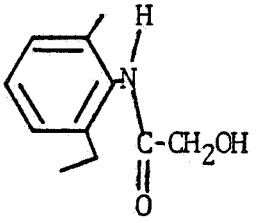
METOLACHLOR

Acetochlor is weakly mutagenic toward CHO/HGPRT cells both with and without metabolic activation in a gene mutation assay. It was also positive to mouse lymphoma (L5178Y) cells in the presence of metabolic activation. When fed to Sprague-Dawley rats at levels of 500, 1500 and 5000 ppm (25, 75, and 250 mg/kg/day, respectively) in the diet, in a chronic 2-year study, acetochlor caused a statistically significant increase in hepatocellular carcinomas (not adenomas) at the high dose in males, and in thyroid follicular cell adenomas, also in the high dose males. When fed to Swiss albino CD-1 mice for 2 years at these same dosage levels, acetochlor caused a statistically significant increase in combined adenomas and carcinomas of the lung at all doses tested in female mice (like alachlor) and in total benign tumors of the ovary in the mid dose females. Acetochlor was evaluated in Peer Review as a class B_2 carcinogen. The structure of identified metabolites in rat urine and feces are shown in Figures 4 and 5.

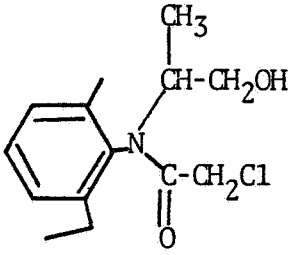
Limited mutagenicity data are available on metolachlor. It has been reported to be negative in the Ames salmonella assay and did not have any effects on fertility, zygote or embryo survival in the in vivo developing sperm mouse assay. Metolachlor, when fed to CD rats at levels of 30, 300 and 3000 ppm caused an increase in proliferative liver lesions (neoplastic nodules) in the high dose female rats. In this study nasal turbinate tumors were seen in two high dose males and one high dose female. Metolachlor was negative for oncogenicity in the mouse. Metolachlor has been evaluated in Peer Review as a class C carcinogen. Identified metabolites of-metolachlor are shown below:



Urine & Feces



Urine only



Feces only

F. Weight of Evidence Considerations:

The committee considered the following facts regarding toxicology data on alachlor to be of importance in a weight of evidence determination of oncogenic potential.

1. Administration of alachlor in the diet to Long-Evans rats is associated with statistically significant increases in incidence over the control in the following tumors:

   Nasal turbinate tumors (mostly benign) at mid and high doses, in both sexes.

   Thyroid follicular tumors in male rats.

   Malignant stomach tumors in male and female rats.

2. Administration of alachlor in the diet to female CD-1 mice is associated with a statistically significant increase in lung tumors (bronchiolar-alveolar adenomas and carcinomas) in female mice.

3. Alachlor was tested in several in vitro and in vivo assays for mutagenicity and/or DNA damage. Of these only the in vivo - in vitro hepatocyte DNA repair assay was positive - and only at the HDT. It was judged, therefore, to be "weakly genotoxic", however a metabolite of alachlor was found to be positive in the Ames Test (Strain TA 100), both with and without metabolic activation over 6 test doses.

4. The metabolite referred to above is a moiety common to metabolites found in both humans and rats (but not in monkeys). This data is significant in-so-much as Monsanto maintains that the monkey is a "better model for man in the case of alachlor" [Monsanto's Rebuttal to Alachlor PD-1].

5. Acetochlor is structurally related to alachlor. Acetochlor when fed in the diet to Sprague-Dawley rats caused increases in:

   °Hepatocellular carcinomas at the high dose level in males.

   °Thyroid follicular cell adenomas in high dose males

   Acetochlor when fed to CD-1 mice caused increases in:

   °Combined adenomas and carcinomas of the lung at all doses tested in female mice (statistically significant increase at high dose).

   °Uterine histiocytic sarcomas at all doses in female mice.

   °Total benign tumors of the ovary in mid dose females.

6. Metolachlor, another structurally related herbicide, when fed to CD rats, caused an increase in liver neoplastic nodules in the high dose females. In this same study, nasal turbinate tumors were seen in 2 high dose males and 1 high dose female, however metolachlor was negative for oncogenicity in the mouse.

G. Classification of Oncogenic Potential:

Criteria contained in the final draft of the proposed EPA Guidelines (12/1/85) for classifying a carcinogen were considered. These Guidelines state that "Sufficient evidence of carcinogenicity indicates that there is an increased incidence of malignant tumors or combined malignant and benign tumors: a) in multiple species [MET] or strains; b) in multiple experiments [MET] (e.g., with different routes of administration or using different dose levels; or c) to an unusual degree in a single experiment with regard to high incidence [MET], unusual site or type of tumor [MET], or early age of onset [MET]. Additional evidence may be provided by data on dose-response effects [MET], as well as information from short-term tests [partially MET] or on chemical structure [MET]".

Alachlor met all but one of the criteria specified for the B-2 classification, any of which alone can be sufficient for such a classification. That is, alachlor produced an increased incidence in malignant, or combined malignant and benign, nasal turbinate tumors (and other tumor types) in Long-Evans rats in three different experiments at more than one dose level via dietary administration. Alachlor also produced a statistically significant increase in lung tumors in female CD-1 mice at 2 dose levels. In another experiment with Long-Evans rats, nasal turbinate tumors occured after only 5-6 months of exposure. The tumor incidence was as high as 50% and tumor site was unusual; i.e., not an increase of a normal high background tumor type. Additionaly, a metabolite of alachlor was mutagenic in the Ames Test at 6 dose levels.

Acetochlor and metolachlor are two herbicides which are structurally related to alachlor. Acetochlor when fed to CD-1 mice produced an increased incidence in combined adenomas and carcinomas of the lung (like alachlor) at all doses (as well as other tumor types). Metolachlor when fed to CD rats, caused an increased incidence of neoplastic nodules in females at the high dose; metolachlor was negative for oncogenicity in the mouse.

The committee concluded that the data available for alachlor (from animal studies) is sufficient for its classification as a B-2 "Probable Human Carcinogen".

H. Major Rebuttals by Monsanto

The committee also addressed the following major points:

1. It is contended that the rat is not the appropriate model for assessing potential effects on humans; rather the monkey is more appropriate.

   The committee disagrees since for this chemical it appears that the rat produces metabolites similar to those observed in man. Moreover, these very metabolites belong to the class of alachlor metabolites which seem to have mutagenic activity (refer to sections on Metabolism and Mutagenicity).

H. Major Rebuttals (continued)

2. It is contended that nasal turbinate tumors are strain specific (Long-Evans Rat).

IBT has a ~~1~~ 2 strain although invalid.

The committee found no evidence that this is anything other than conjecture - ~~no other rat strain has been tested~~. Furthermore, nasal turbinate tumors were not the only response in Long-Evans rats.

3. It is contended that the "effects" are not seen in monkey and dog.

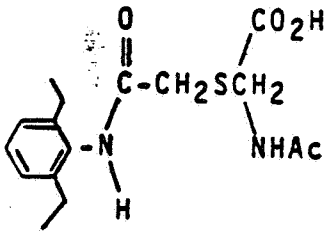
The committee concluded that data for subchronic (less than lifetime) exposure of other species can not refute oncogenic effect in a lifetime study.

4. It is contended that the mouse study did not show any oncogencic effect for alachlor.

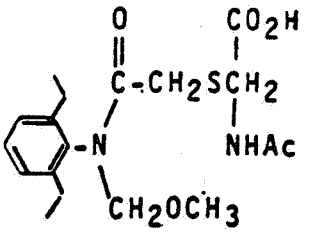
The committee disagrees with this conclusion (see review of mouse study, section D.4)

EPA's detailed response to Monsanto's Rebuttal is appended to this panel report.

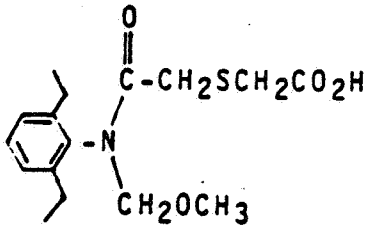
FIGURE 3 METABOLITES OF ALACHLOR



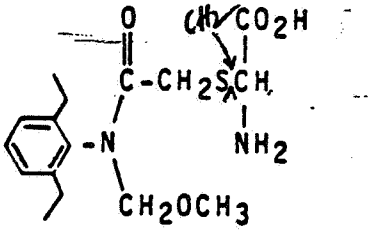
Secondary Mercapturate (4)



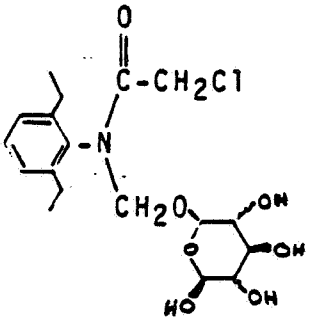
Tertiary Mercapturate (5)



Thioacetic Acid Conjugate (6)



Cysteine Conjugate (7)



Glucuronide Conjugate (8)