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

JUN 16 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Reregistration of Pendimethalin. **Nature of the Residue in Sweet Corn.** List A Case No. 0187. Chemical No. 108501. CBRS No. 11582; DP BARCODE D189207; MRID 42686401.

FROM: Paula A. Deschamp, Biologist
Reregistration Section I
Chemistry Branch II: Reregistration Support
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THRU: William O. Smith, Acting Section Head
Reregistration Section I
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TO: Terri Stowe
Reregistration Branch
Special Review and Reregistration Division (H7508W)

Attached is the review of a sweet corn metabolism study submitted by American Cyanamid Company in response to the 1985 Guidance Document and subsequent Agency reviews. This information was reviewed by Acurex Environmental Corp. under supervision of CBRS, HED. The data assessment has undergone secondary review in the Branch and has been revised to reflect Branch policies.

The corn metabolism study is insufficient to satisfy requirements for plant metabolism, but is upgradeable provided that acceptable storage stability and radiovalidation data are submitted.

We recommend that the registrant receive a copy of this review in its entirety.

If you need additional input, please advise.

Attachment 1: Pendimethalin CBRS No. 11582; DP BARCODE D189207. Registrant's Response to Residue Chemistry Data Requirements.

cc: PADeschamp (CBRS), Circulate, Pendimethalin Reg. Std. File, SF, Acurex Environmental Corp.
cc: RF (Without attachment).

H7509C:CBRS:PAD:pad:CM#2:Rm804A:703-305-6227:06/14/93
RDI: WSmith:06/14/93 MMetzger:06/14/93 EZager:06/14/93

PENDIMETHALIN
~~(Chemical Code 108501)~~
(CBRS No. 11582; DP Barcode D189207)

TASK 3

Registrant's Response to Residue Chemistry Data Requirements

April 30, 1993

Contract No. 68-DO-0142

Submitted to:

U.S. Environmental Protection Agency
Arlington, VA 22202

Submitted by:

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PENDIMETHALIN

(Chemical Code 108501)

(CBRS No. 11582; DP Barcode D189207)

Registrant's Response to Residue Chemistry Data Requirements

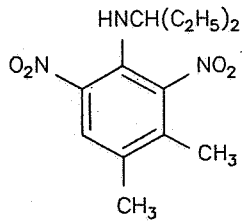
Task 3

BACKGROUND

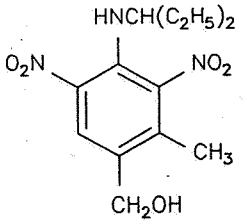
The Pendimethalin Guidance Document dated 3/85 and the Pendimethalin Reregistration Standard Update dated 3/90 required new plant metabolism data. Data were required depicting the nature of the residue of [^{14}C]pendimethalin in three dissimilar food crops using a characterized test substance applied at levels sufficiently high to permit characterization of ^{14}C-residues. Analyses of representative samples from these tests were required using enforcement methodologies. In response, American Cyanamid submitted four previously submitted metabolism studies on sweet corn, peanut hulls, and potato tubers, and one new metabolism study on soybeans that were reviewed and found inadequate (R. Loranger and R. Perfetti, CB Nos. 6570, 6603, 6604, and 7153, dated 1/29/91). The Agency review required new metabolism studies and provided specific guidance as follows:

> Additional metabolism studies are required in which pendimethalin radiolabeled with ^{14}C in the phenyl ring is applied to plants at rates equal to at least the maximum rates on product labels. Provided significant phytotoxicity does not occur, even higher application rates are preferred to increase the level of radioactivity available for analysis. One study should be conducted on sweet corn with examinations of vegetative parts and grain from (1) plants treated pre-emergence and (2) plants treated post-emergence as late in the growing season as practical. A second study is needed on a plant in which the edible portion grows in the soil, i.e., potatoes or peanuts.

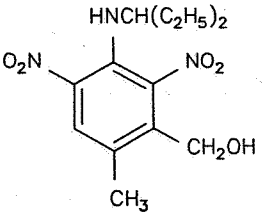
American Cyanamid subsequently submitted data pertaining to the metabolism of [^{13}C/^{14}C]pendimethalin in potatoes. Deficiencies in the potato metabolism study (P. Deschamp, CBRS No. 10678, 2/1/93) because application was not made at rates $>$1x have been resolved. Cyanamid's argument that at least a 6x study would be required for sufficient radioactivity for further characterization/identification of residues in potato tubers has been found acceptable (P. Deschamp, CBRS No. 11797, D190778, 6/93).



Pendimethalin



3,5-Dinitrobenzyl alcohol



2,4-Dinitrobenzyl alcohol

American Cyanamid has submitted the final report on their sweet corn metabolism study (1993; MRID 42686401), and this submission is evaluated herein. The Conclusions and Recommendations stated in this review pertain only to the nature of the residue of pendimethalin in plants.

The 1990 Update indicated that the currently preferred enforcement methods include Methods I, II, III, and IV in PAM, Vol. II. These GC methods employ Florisil cleanup, and electron capture detection, and determine pendimethalin and its 3,5-dinitrobenzl alcohol metabolite (3,5-DNBA).

Tolerances are currently defined as the combined residues of pendimethalin [N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine] and its metabolite 4-[(1-ethylpropyl)amino]-2-methyl-3,5-dinitrobenzyl alcohol (40 CFR §180.361[a] and [c]). 3-[(1-ethylpropyl)amino]-6-methyl-2,4-dinitrobenzyl alcohol is also regulated in peanut hulls in addition to the parent and the 3,5-dinitrobenzyl alcohol metabolite (40 CFR §180.361[b]).

No Codex MRLs exist for pendimethalin residues. Therefore, no compatibility questions exist with respect to Codex MRLs.

CONCLUSIONS

1. The corn metabolism study is insufficient to satisfy requirements for plant metabolism, but is upgradeable provided that acceptable storage stability and radiovalidation data are submitted.

2a. Postemergence application of [U-^{14}C-pendimethalin at 1x the maximum registered rate resulted in total radioactive residues of 0.02 ppm in sweet corn grain/cobs 81 days after treatment.

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2b. Chloroform-soluble, aqueous soluble, and insoluble fractions from extraction of corn grain contained 9%, 38% and 53% of the TRR, respectively. Additional aqueous-soluble residues were released from post extraction solids by cellulase hydrolysis (26%). No chromatographic analysis was conducted.

2c. Residues in chloroform-soluble, aqueous soluble, and insoluble fractions extracted from whole corn plants and stalks/husks harvested at all posttreatment intervals following postemergence application at 1x were adequately identified/characterized.

2d. Unaltered pendimethalin, the only residue identified, was isolated from $CHCl_3$ extracts. Pendimethalin comprised 1.22-5.11% of the TRR in whole corn plants harvested 14, 30, and 60 days posttreatment and 1.5% of the TRR in stalks/husks. harvested 81 days posttreatment. Organosoluble residues were adequately identified/characterized.

2e. Methanol/water-soluble residues extracted from whole corn plants (14-, 30-, 60-day) comprised 42-63% TRR. HPLC analysis resolved both distinct peaks and broad overlapping regions (no baseline separation) consisting of unidentified polar components. At the 30- and 60-day harvest intervals, none of the peaks accounted for >0.057 ppm. Methanol/water-soluble residues were adequately identified/ characterized.

2f. Post extraction solids from whole corn plants (14 and 60-day) accounted for 46% of the TRR. Sequential cellulase, acid, and base hydrolysates partitioned to EtOAc (5.72%; 0.158 ppm) and aqueous (40.53%; 1.113 ppm) fractions. HPLC of these fractions resolved both distinct peaks and poorly resolved regions consisting of unidentified polar components. None of the peaks accounted for >0.413 ppm. Residues in post extraction solids were adequately identified/characterized.

3. No supporting storage stability data were provided to determine whether or not the basic profile of radiolabeled residues in stalks/husks and cobs/grain was significantly altered during frozen storage for up to 466 days and 345 days, respectively.

4. Radiovalidation data were not provided with this corn metabolism study. Representative samples from plant metabolism studies must be analyzed using a currently accepted or proposed enforcement analytical method in order to ascertain that the method will determine all possible residues of concern.

RECOMMENDATIONS

The registrant should be informed that the corn metabolism study does not satisfy the data requirements for plant metabolism for reasons stated in Conclusions 3 and 4 above. This corn metabolism study may be upgraded provided that acceptable radiovalidation and storage stability data are submitted.

DETAILED CONSIDERATIONS

Qualitative Nature of the Residue in Plants

In response to outstanding data requirements, American Cyanamid Company submitted data (1993; MRID 42686401) pertaining to the metabolism of [^{13}C/^{14}C]pendimethalin in sweet corn. Whole corn plants, stalk/husk, and grain/cob samples were collected from plants treated postemergence or preemergence at 1x (4 lb/gal EC; 2.0 lb ai/A). The plants were treated with uniformly ring-labeled [^{14}C]pendimethalin diluted with 3-methyl labeled [^{13}C]pendimethalin to a final specific activity of 3.95 μCi/mg (8,770 dpm/μg); radiochemical purity was 96.9%. Whole plant samples were collected at 14-, 30-, and 60-day intervals, and stored frozen at approximately -20 °C for 4-526 days. Stalks/husks and cobs/grain collected at harvest were stored frozen at approximately -20 °C for 16-466 days and 22-345 days, respectively. Extracts were also stored at 0-5 °C prior to analysis for an unspecified interval. No supporting storage stability data were provided.

Total Radioactive Residues (TRR)

Levels of radioactivity in all solid samples were determined in triplicate by combustion and subsequent liquid scintillation spectrometry (LSS). TRRs in corn commodities are presented in Table 1. The validated limit of detection was 0.01 ppm for stalks, cobs, and foliage.

Table 1. Summary of TRRs in corn fractions treated at 1x with [^{13}C/^{14}C]pendimethalin.

Substrate	Application	PTI (days)[a]	TRR (ppm)[b]
Whole plant	post-emergence	14a; 14b	2.74; 5.19
		30	0.32
		60	0.20
	pre-emergence	30	0.42
		60	0.18
Stalks/husks	post-emergence	81	0.22
	pre-emergence	91	0.26
Cobs/grain	post-emergence	81	0.02
	pre-emergence	91	0.02

[a]PTI=posttreatment interval. [b]These values were used to calculate %TRRs in subsequent analyses; the 2.74 ppm value was used for whole plants treated postemergence.

Extraction/Hydrolysis/Characterization of Residues

Radioactive residues were extracted from cobs/grain, whole plants, and stalks/husks with methanol:water:chloroform (11:5:5; v/v); these results are summarized in Tables 2, 3 and 4. Radioactivity in the aqueous and organic phases was assayed by LSS; post extraction solids

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were air dried and combusted. Extracts were analyzed by HPLC. Solids from cob/grain samples were hydrolyzed with cellulase, but the resulting fractions were not analyzed by chromatographic techniques. Solids from some whole plants and stalks/husks were hydrolyzed sequentially with cellulase, 1N HCl, 6N HCl, and 1N NaOH, each followed by liquid/liquid partitioning with EtOAc; selected fractions were analyzed by 2D-TLC and HPLC as described in Tables 2, 3 and 4.

TLC R_f values (for six different solvent systems) and HPLC retention times were reported for 12 reference standards. The MeOH/water fraction from the 14-day whole plant sample and $CHCl_3$ fraction from the 91 day stalk/husk sample were codeveloped by TLC using six reference standards, (CL 202,588; CL 202,345; CL 202,347; CL 239,336; CL 239,335; and CL 206,923); chemical names were not provided by the registrant. Only pendimethalin (CL 92,553) and 3,5-DNBA (CL 202,347) were codeveloped with each of the other sample extracts analyzed. Representative TLC and HPLC radiochromatograms were provided.

Table 2. Distribution of TRR in corn grain/cob from plants treated postemergence or preemergence at 1x with [$^{13}C/^{14}C$]pendimethalin.

Substrate	Fraction	%TRR	PPM	Characterization/Identification
Grain/cob[a] Postemergence 81 day PTI 0.02 ppm TRR	$CHCl_3$	8.96	0.002	No chromatographic analysis conducted
	MeOH/water	38.32	0.008	No chromatographic analysis conducted
	Solids	52.72	0.011	
	Aqueous Cellulase Hydrolysate	26.30	0.005	No chromatographic analysis conducted
	Solids	26.42	0.005	No further analysis

[a]Extraction scheme and analysis results for grain/cobs treated preemergence and PTI=91 were similar to results presented for grain/cobs treated postemergence and PTI=81.

Table 3. Distribution of TRR in extracts from whole corn plants treated postemergence or preemergence at 1x with [$^{13}C/^{14}C$]pendimethalin.

Substrate	Fraction	%TRR	PPM	Characterization/Identification
Whole plant[a] Postemergence 14 day PTI 2.74 ppm TRR	$CHCl_3$	11.34	0.311	5.11% of TRR (0.140 ppm) was identified as unchanged parent by 2-D TLC and HPLC; and 6 peaks were partially resolved by HPLC, each ≤3.3% of TRR (0.01-0.09 ppm)
	MeOH/water	42.42	1.164	HPLC analysis resulted in one polar peak (1.68% of TRR, 0.046 ppm) and two polar broad overlapping regions comprising 12.79% of TRR (0.351 ppm) and 27.94% of TRR (0.767 ppm); HPLC analysis after each cellulase and acid digestion, quaternary amine solid phase extraction and acetylation, showed improved separation (but not baseline) of the broad overlapping regions, the most successful being the solid phase extraction which resulted in 5 partially resolved regions comprising 2.4-17.2% of TRR (0.123-0.893 ppm)
	Solids	46.24	1.269	
	Aqueous Cellulase Hydrolysate	10.70	0.293	Partitioning yielded an EtOAc fraction (1.02% of TRR; 0.028 ppm) and an aqueous fraction (9.68% of TRR; 0.265 ppm); HPLC analysis of each of these fractions yielded a single peak (<2% of TRR) and a cluster of unresolved peaks (each <4% of TRR); no single peak >0.085 ppm
	Solids	35.54	0.974	
	Aqueous Acid (1N HCL) Hydrolysate	10.49	0.287	Partitioning yielded an EtOAc fraction (2.3% of TRR; 0.063 ppm) and an aqueous fraction (8.2% of TRR; 0.225 ppm); HPLC analysis of each of these fractions yielded resolution of a single peak (<2% of TRR) and a cluster of 3-6 unresolved peaks each <5% of TRR; no single peak >0.133 ppm
	Solids	25.06	0.687	
	Aqueous Acid (6N HCL)	5.80	0.159	Partitioning yielded an EtOAc fraction (1.32% of TRR; 0.036 ppm) and an aqueous fraction (4.48% of TRR; 0.123 ppm); HPLC analysis of each of these fractions yielded 4-5 unresolved peaks (each <3% of TRR); no single peak >0.06 ppm
	Solids	19.26	0.528	
	Aqueous Base (1N NaOH) Hydrolysate	19.26	0.528	Partitioning yielded an EtOAc fraction (1.08% of TRR; 0.030 ppm) and an aqueous fraction (18.18% of TRR; 0.498 ppm); HPLC analysis of the aqueous fraction yielded one polar peak comprising 15.04% of TRR (0.413 ppm) and several unresolved peaks
	Solids	0	0	N/A
Whole plant[a], Postemergence 30 day PTI 0.32 ppm TRR	$CHCl_3$	11.77	0.038	1.77% of TRR (0.006 ppm) was identified as unchanged parent by 2-D TLC and HPLC; 1 distinct polar peak resolved by HPLC comprised 2.32% of TRR (0.008 ppm); 2 partially resolved regions comprising 2.52 and 5.15% of TRR (0.008, 0.017 ppm)
	MeOH/water	42.29	0.135	1 distinct polar peak resolved by HPLC comprised 10.03% of TRR (0.032 ppm); 3 partially resolved regions comprising 0.57-17.75% of TRR (0.002-0.057 ppm)
	Solids	45.94	0.147	none
Whole plant[a] Postemergence 60 day PTI 0.20 ppm TRR	$CHCl_3$	4.67	0.01	1.22% of TRR (0.003 ppm) was identified as unchanged parent by 2-D TLC and HPLC; 2 distinct and 3 unresolved peaks (HPLC), none of which was >0.003 ppm
	MeOH/water	63.21	0.129	HPLC analysis revealed 6 poorly resolved peaks in 2 zones, none of which accounted for >0.031 ppm
	Solids	33.12	0.066	Partitioning analysis after each cellulase, 1N/6N HCl, and NaOH digestion yielded EtOAc and aqueous fractions containing a total of 6.9% (0.014 ppm) and 24.3% (0.049 ppm) of the TRR, respectively; none of the fractions contained >0.015 ppm

[a]Extraction scheme and analysis results for whole plants treated preemergence and harvested 14, 30 and 60 days posttreatment were similar to results presented for whole corn plants treated postemergence and harvested 14, 30, and 60 days posttreatment.

Table 4. Distribution of TRR in extracts of corn stalks/husks from plants treated postemergence or preemergence at 1x with [$^{13}C/^{14}C$]pendimethalin.

Substrate	Fraction	%TRR	PPM	Characterization/Identification
Stalks/husks*, Postemergence 81 day PTI 0.22 ppm TRR	$CHCl_3$	8.23	0.018	1.5% of TRR (0.003 ppm) was identified as unchanged parent by 2-D TLC and HPLC; 1 distinct polar peak resolved by HPLC comprised 1.66% of TRR (0.004 ppm), and 2 peaks partially resolved by HPLC comprised 1.56 and 3.51% of TRR (0.003 and 0.008 ppm)
	MeOH/water	57.13	0.126	HPLC analysis resulted in one polar peak (15.71% of TRR, 0.035 ppm) and three polar broad overlapping regions comprising 11.02-18.05% of TRR (0.024-0.040 ppm); HPLC analysis after cellulase digestion did not show improved separation of the overlapping regions.
	Solids	34.64	0.076	
	Aqueous Cellulase Hydrolysate	7.72	0.017	Partitioning yielded an EtOAc fraction (0.73% of TRR; 0.002 ppm) and an aqueous fraction (6.99% of TRR; 0.015 ppm); HPLC analysis of the aqueous fraction yielded resolution of a single peak (3.06% of TRR; 0.007 ppm) and a cluster of unresolved peaks comprising as much as 2.98% of TRR (0.006 ppm)
	Solids	26.92	0.059	
	Aqueous Acid (1N HCl) Hydrolysate	9.53	0.021	Partitioning yielded an EtOAc fraction (2.11% of TRR; 0.005 ppm) and an aqueous fraction (7.41% of TRR; 0.016 ppm); C18 solid phase extraction resulted in nonretained residues (in application solvent) and an MeOH fraction that were analyzed by HPLC; analysis of the nonretained residues yielded partial resolution of two peaks comprising 1.52 and 1.35% of TRR (approximately 0.003 ppm each) and a cluster of unresolved peaks comprising as much as 1.23% of TRR
	Solids	17.40	0.038	
	Aqueous Acid (6N HCl)	5.92	0.013	No chromatographic analysis conducted
	Solids	11.48	0.025	
	Aqueous Base (1N NaOH) Hydrolsate	11.03	0.024	No chromatographic analysis conducted
	Solids	0.45	0.001	No further analysis

*Extraction scheme and analysis results for stalks and husks treated preemergence and PTI=91 were similar to results presented for stalks and husks treated postemergence and PTI=81.

Soluble lignin, hemicellulose, and cellulose were extracted from stalks/husks according to a Marco et al. procedure. The samples were blended with methanol/water/chloroform (11/5/5; v/v) and then reblended with $CHCl_3$. The solid residues were then refluxed/hydrolyzed in an acid mixture (1N HCl and thioglycolic acid). The acid fraction was associated with hemicellulose. The remaining solids were then base hydrolyzed (2N NaOH), and the precipitate was associated with cellulose, and the basic fraction with soluble lignin.

In addition, the registrant extracted starch from stalks/husks by the following procedure. The samples were blended with methanol:water:chloroform (11:5:5; v/v) and then reblended with $CHCl_3$. The solid residues were then digested with DMSO/water and washed with ethanol; the resulting DMSO/water fraction was associated with starch.

In summary, residues of parent were isolated from $CHCl_3$ extracts of whole corn plants (1.77-5.11% of the TRR) and stalks/husks (1.5% of the TRR). Chromatographic analyses of all other extracts with reference standards did not result in identification of any other ^{14}C-residues. Low levels of radioactivity in cobs/grain (0.02 ppm) prevented adequate characterization of ^{14}C-residues.

This sweet corn metabolism study is insufficient to satisfy data requirements for plant metabolism. The study may be upgradeable, provided that acceptable storage stability and radiovalidation data are submitted.

References

42686401 Zdybak, J. (1993) Pendimethalin (CL 92,553): Metabolism of (carbon 14)-CL 92,553 in Sweet Corn under Field Conditions: Lab Project Number: XBL 91045: RPT00114: M91P553CA1. Unpublished study prepared by XenoBiotic Labs, Inc. in coop with Pan-Agricultural Labs, Inc. 263 p.

Agency Memoranda

CBRS No.: 10678
Subject: Nature of the residue in potatoes
To: L. Rossi
From: P. Deschamp
Dated: 2/1/93
MRID(s): 42467801

CB Nos.: 6570, 6603, 6604, and 7153
Subject: Plant metabolism of pendimethalin
To: R. Engler
From: R. Loranger
Dated: 1/29/91
MRID(s): 41469901