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

SEP 24 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Reregistration of Pendimethalin. **Poultry Metabolism, Residue Analytical Methods, Storage Stability Data.** List A Case No. 0187. Chemical No. 108501. Addendum to CBRS No. 10678; DP BARCODE D183220; MRIDs 42467802, 42471902, 42471903 and 42471901.

FROM: Paula A. Deschamp, Section Head
Reregistration Section I
Chemistry Branch II: Reregistration Support
Health Effects Division (H7509C)

THRU: Edward Zager, Chief
Chemistry Branch II: Reregistration Support
Health Effects Division (H7509C)

TO: Lois Rossi/Terri Stowe
Reregistration Branch
Special Review and Reregistration Division (H7508W)

Attached is the review of poultry metabolism, alfalfa storage stability, and analytical method validation data submitted by American Cyanamid in response to the 1985 Guidance Document, the 1990 Reregistration Standard Update, and subsequent reviews. This information was reviewed by Acurex Environmental under supervision of CBRS, HED. The data assessment has undergone secondary review in CBRS and has been revised to reflect Branch policies.

The poultry metabolism data fulfill the guideline requirements, provided that acceptable radiovalidation data are submitted. The ruminant metabolism study submitted by the registrant has been determined to be inadequate, but possibly upgradeable, by CBTS (F. Griffith; CBTS Nos. 7595/7596 dated 3/5/91 and D170619, CBTS Nos. 8859/8860 dated 4/29/92). The results of both the poultry and ruminant metabolism studies indicate that minimal transfer of radioactivity occurs. Since new uses are pending for animal feed items, and ruminant metabolism is being reviewed by CBTS, CBTS will determine the need for animal feeding studies in conjunction with PP#3F2788.

Additional data must be provided before the alfalfa storage stability data and residue analytical method M-1609 can be considered adequate. It is recommended that a copy of this review be sent to the Registrant.

If you need additional input, please advise.

Attachment 1: Pendimethalin Addendum to CBRS No. 10678; DP BARCODE D183220. Registrant's Response to Residue Chemistry Data Requirements.

cc: PADeschamp (CBRS), Circulate, Pendimethalin Reg. Std. File, SF, Acurex Corporation, Francis Griffith, PP#3F2788.
cc: RF (Without attachment).

H7509C:CBRS:PAD:pad:CM#2:Rm804A:703-305-6227:09/17/93
RDI: MMetzger:09/22/93

PENDIMETHALIN
(Chemical Code 108501)
(Addendum to CBRS No. 10678; DP Barcode D183220)

TASK 3

Registrant's Response to Residue Chemistry Data Requirements

January 20, 1992

Contract No. 68-DO-0142

Submitted to:

U.S. Environmental Protection Agency
Arlington, VA 22202

Submitted by:

Acurex Environmental Corporation
Eastern Regional Operations
4915 Prospectus Drive
P.O. Box 13109
Research Triangle Park, NC 27709

43

PENDIMETHALIN

(Chemical Code 108501)

(Addendum to CBRS No. 10678; DP Barcode D183220)

REGISTRANTS RESPONSE TO RESIDUE CHEMISTRY DATA REQUIREMENTS

Task-3

BACKGROUND

Pendimethalin was the subject of a Residue Chemistry Chapter issued 7/84 and a Reregistration Standard Update dated 3/90. The Pendimethalin Guidance Document dated 3/85 did not require metabolism data for poultry because poultry feed items did not contain any detectable residues of pendimethalin and its 3,5-dinitrobenzyl alcohol metabolite (3,5-DNBA). However, the 1990 Update stated that current guidelines require additional data on the metabolism of pendimethalin in poultry. The Update also required storage stability data on all samples used to determine the magnitude of the residue and data on FDA multiresidue methodology. In response to the Update, American Cyanamid submitted (1992; MRID 42467802, 42471901 and 42471903) data pertaining to the metabolic fate of [^{14}C]pendimethalin in poultry tissues and eggs, storage stability data on alfalfa, and supporting method recovery data on soybean hay. The Conclusions and Recommendations stated herein pertain only to data requirements for poultry metabolism, residue analytical methods and storage stability. The registrant also submitted (1992; MRID 42471902) data pertaining to multiresidue methods that have been forwarded to FDA for review.

The qualitative nature of the residue in livestock is not adequately understood. Data on the nature of the residue in ruminants have been found insufficient (F. Griffith; CBTS Nos. 7595/7596 dated 3/5/91 and D170619, CBTS Nos. 8859/8860 dated 4/29/92). There are no tolerances established for pendimethalin residues in/on animal products. There are no adequate tolerance enforcement methods for animal commodities in PAM, Vol. II.

The qualitative nature of the residues of pendimethalin in plants adequately understood. The terminal residues in potato tubers and sweet corn consist of unaltered pendimethalin; however, additional storage stability and method validation data are needed to fulfill plant metabolism data requirements. 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 metabolite (40 CFR §180.361[b]). 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 the parent pendimethalin and its alcohol metabolite, 3,5-DNBA in plant commodities.

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

CONCLUSIONS

1a. The poultry metabolism study is insufficient to satisfy requirements for livestock metabolism, but is upgradeable provided that acceptable radiovalidation data are submitted. Representative samples from livestock (poultry or ruminant) 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.

1b. Poultry received [^{14}C]pendimethalin at 10 ppm in the diet for seven consecutive days (100x the maximum theoretical dietary burden). Total radioactive residues were 0.205 ppm in liver, <0.01 ppm in muscle, 0.035 ppm in skin/fat and 0.035 ppm in eggs.

1c. In skin/fat, 82.3% (0.027 ppm) of the total radioactivity was extractable. TLC and HPLC analysis of the MeOH-2 fraction (14.9% TRR; 0.005 ppm) detected the presence of low radioactivity associated with several polar components. TLC and HPLC analysis of the MeOH-3 fraction (21.9% TRR; 0.007 ppm) indicated the presence of parent (15.7% TRR; 0.005 ppm) and essentially no other component.

1d. In eggs, 77.3% (0.028 ppm) of the total radioactivity was extractable. TLC and HPLC analysis of the ACN fraction (40.1% TRR; 0.014 ppm) detected pendimethalin (5.3% TRR; 0.002 ppm). Several unidentified polar radioactive components in chromatographic regions designated zones A through F, accounted for 1.7-11.5% of the TRR (<0.01 ppm each). Hexane soluble residues (21.38% TRR; 0.008 ppm) were not further characterized.

1e. In liver, 89.62% (0.21 ppm) of the total radioactivity was extractable. TLC and HPLC analysis of the MeOH/H_2O fraction (10.65% TRR; 0.024 ppm) detected a trace amount of parent (<1% TRR) and several other components more polar in nature than the parent, each of which accounted for <8% TRR. TLC and HPLC analysis of the $CHCl_3$ fraction detected polar components and a trace amount of parent. The major HPLC peak in the $CHCl_3$ fraction corresponded to the acid metabolite of pendimethalin (CL 202,078) that accounted for 2.3% of the TRR (0.005 ppm). Enzyme/acid released aqueous fractions from post-extraction solids (total of 65.09% TRR; 0.15 ppm) were analyzed by HPLC. Residues segregated to three zones with the major zone containing 12.87-18.98% TRR (0.03-0.04 ppm). None of the components present in this zone corresponded with the R_t of known standards.

1f. The parent compound, pendimethalin, was detected in eggs (5% TRR), liver (1.10% TRR), and skin/fat (15.7% TRR). The 3,5-DNBA metabolite was detected in trace amounts (≤6% TRR) in eggs and skin/fat. The data suggest that pendimethalin is metabolized via hydroxylation to its 3,5-DNBA metabolite and subsequently to more polar components via amination and dealkylation.

5

2. The submitted pendimethalin and 3,5-dinitrobenzyl alcohol metabolite recoveries from soybean hay using method M-1609 could not be adequately assessed. The registrant must provide sample chromatograms and calculations in addition to the recovery results. In addition, the registrant did not provide method recovery data on soybean straw from method M-1609; these data are still required.

3. The submitted alfalfa stability data are adequate pending submission of a detailed description of method M-1930.01. These data indicate that residues of pendimethalin and its 3,5-DNBA metabolite are stable in alfalfa green forage, hay and seed stored at approximately -10 °C for up to 24 months. Method M-1930.01, a modification of method M-1930 was used to determine residues of pendimethalin and its 3,5-DNBA metabolite in alfalfa forage, hay, and seed. A complete description of Method M-1930.01 was not provided. If these stability data are to be used to support residue data a complete description of method M-1930.01 must be submitted.

RECOMMENDATIONS

We recommend that the registrant receive a copy of this review and be informed that the poultry metabolism study is sufficient to satisfy requirements for livestock metabolism, provided that acceptable radiovalidation data are submitted. Additional data are also needed to upgrade alfalfa storage stability data, and validation data for Method M-1609.

The registrant should also be reminded that sample storage conditions and intervals must be submitted for all required and previously submitted residue data for plant commodities (raw and processed foods and feeds). Storage stability data in support of previously submitted residue data are required for only those samples deemed useful for tolerance assessment.

The ruminant metabolism study submitted by the registrant has been determined to be inadequate, but possibly upgradeable, by CBTS (F. Griffith; CBTS Nos. 7595/7596 dated 3/5/91 and D170619, CBTS Nos. 8859/8860 dated 4/29/92). The results of both the poultry and ruminant metabolism studies indicate that minimal transfer of radioactivity occurs. Since new uses are pending for animal feed items, and ruminant metabolism is being reviewed by CBTS, CBTS will determine the need for animal feeding studies in conjunction with PP #3F7888; 171-4(j) data need not be Called-In at this time.

DETAILED CONSIDERATIONS

Qualitative Nature of the Residue in Animals

Poultry. American Cyanamid (1992; MRID 42467802) submitted data pertaining to the metabolism of uniformly phenyl-labeled [^{14}C]pendimethalin in laying hens. Three groups of five (groups A, B, and C) and two groups (groups D and E) of 10 laying hens were orally

administered gelatin capsules. Hens received either 0 ppm (group A), 0.5 ppm (group B), or 10 ppm (groups C, D, and E) of [^{14}C]pendimethalin in the feed for 7 consecutive days. The feeding levels were 5x (group B) and 100x (groups C, D, and E) the maximum theoretical dietary exposure based on tolerances of 0.1 ppm for pendimethalin in beans, corn grain and peanuts. The [^{14}C]pendimethalin had a specific activity of 4.01 μCi/mg (8,894 dpm/μg) and a radiochemical purity of 98%. Daily egg samples were pooled, homogenized, and stored frozen (approximately -20 °C). The control and the four groups of treated hens were sacrificed within 24 hours after the last dose and samples of liver, muscle (combined breast and thigh), and skin with adhering fat were collected and pooled according to each replicate group. All samples were stored frozen (approximately -15 °C) until analysis. Analyses of eggs were completed within 3-6 months after sacrifice. Analyses of skin/fat and liver samples were completed within 2 to 7 and 2 to 8 months, respectively.

Total Radioactive Residues (TRR)

Triplicate aliquots of liver and muscle from groups A, B, and C were combusted and radioassayed by liquid scintillation spectrometry (LSS). Triplicate aliquots of eggs from groups A, B and C were radioassayed directly by LSS. Triplicate aliquots of skin/fat were soaked in hexane overnight prior to radioassay by LSS. Residual radioactivity in the remaining skin/fat solids were determined by combustion and LSS. Dark colored fractions and solids were combusted in single or duplicate aliquots. The validated limit of detection was 0.01 ppm. Total radioactive residue levels in liver, muscle, and skin/fat from hens treated with [^{14}C]pendimethalin at 10 ppm were 0.205, <0.01, and 0.035 ppm, respectively. Residues in eggs increased throughout the dosing period and were 0.035 ppm by the seventh day.

Extraction and Hydrolysis of Residues

The distribution of ^{14}C-activity in extracts of eggs and tissues from hens dosed with [^{14}C]pendimethalin at 10 ppm are summarized in Tables 1 through 3. All percentages assigned to fractions in the tables are based upon the TRR in the tissues and were normalized to 100% by the registrant. Tissue and egg fractions were stored at 0-5 °C prior to analysis.

Homogenized whole eggs (0.036 ppm) were extracted (3x) with acetonitrile(ACN)/hexane (1:1, v/v). After each solvent extraction, the mixture was centrifuged, the filtrate was collected, and the solids were re-extracted. The resulting filtrates were combined and separated into ACN and hexane fractions. The ACN fraction was concentrated prior to analysis by HPLC and TLC. The hexane fraction was not analyzed further because of low levels (<0.01 ppm) of residues. The remaining solid fraction was air dried and treated with protease (in potassium phosphate, approximately pH 7, 37 °C, 24 hours) resulting in hydrolysate and solid fractions that were radioassayed but not analyzed further.

Ground liver was extracted with methanol(MeOH)/water/chloroform($CHCl_3$) (11:5:5, v/v/v) resulting in $CHCl_3$, MeOH/H_2O, and solid (PES-1) fractions. The $CHCl_3$ fraction was

7 XO

concentrated and, after cooling (0-5 °C) for several days, separated into two layers. The lower layer was concentrated and centrifuged, and the resulting supernatant was subjected to TLC and HPLC. The MeOH/H_2O fraction was concentrated and centrifuged, and the resulting supernatant was analyzed by TLC and HPLC.

Table 1. Distribution of radioactivity in extracts of eggs from hens dosed with [^{14}C]pendimethalin at 10 ppm for 7 days.

Fraction	% TRR[a]	ppm
Hexane	(21.38)[b]	(0.008)
ACN	(40.08)[c]	(0.014)
Solids (enzyme hydrolyzed)		
Hydrolysate	(15.84)	(0.006)
PES	22.69	0.008
Total Extractable	77.3	0.028

[a]TRR of egg sample was 0.036 ppm. [b]Numbers in parenthesis were added to obtain the "total extractable" sum. [c]Subjected to TLC and HPLC analysis.

The PES-1 liver fraction was subjected to protease hydrolysis (under the same conditions as described for egg solids) resulting in PES-2 and hydrolysate fractions. The hydrolysate was partitioned with ethyl acetate (EtOAc). The resulting EtOAc fraction was not characterized further. The aqueous fraction was concentrated and centrifuged, and the resulting supernatant was applied to a C_{18} cartridge. Two fractions of a water eluate and one of a MeOH eluate were collected, combined, and concentrated. The concentrate was centrifuged and the resulting supernatant was analyzed by HPLC. The PES-2 fraction was subjected to acid hydrolysis (1 N HCl; refluxed at approximately 110 °C for one hour) resulting in PES-3 and hydrolysate fractions. The hydrolysate was partitioned with EtOAc resulting in an aqueous fraction and an EtOAc fraction that was not characterized further. The aqueous fraction was applied to a C_{18} Sep-Pak cartridge that was eluted with MeOH. The MeOH eluate was concentrated and analyzed by HPLC. The PES-3 fraction was subjected to acid hydrolysis (6 N HCl, refluxed for approximately 1 hour at 110 °C) resulting in a PES-4 and a hydrolysate fraction. The hydrolysate was partitioned with EtOAc resulting in EtOAc and aqueous fractions. The aqueous fraction was concentrated and applied to a C_{18} cartridge. Residues were eluted with MeOH, concentrated, reapplied to a C_{18} cartridge, and eluted again with MeOH. The resulting eluate fraction was concentrated and analyzed by HPLC.

Skin/fat was extracted sequentially with hexane and MeOH resulting in hexane-1, MeOH-1, and PES-1 fractions. The MeOH-1 fraction was concentrated and partitioned with hexane resulting in hexane-2 and MeOH-2 fractions. The MeOH-2 fraction was concentrated, cooled (0-5 °C) to precipitate the fat, and the resulting supernatant was concentrated and analyzed by TLC and HPLC. Hexane-1 and hexane-2 fractions were combined, concentrated, centrifuged, and the supernatant was partitioned with MeOH. The resulting

8 A

MeOH-3 fraction was concentrated and analyzed by TLC and HPLC. The PES-1 fraction was subjected to protease hydrolysis under the conditions already described. The hydrolysis mixture was filtered and the resulting hydrolysate and solid fractions were not characterized further.

Table 2. Distribution of radioactivity in liver extracts from hens dosed with [^{14}C]pendimethalin at 10 ppm for 7 days.

Fractions	%TRR[a]	ppm
MeOH/H_2O	(10.65)[b,c]	(0.024)
$CHCl_3$	(7.24)[b]	(0.017)
Solids (PES-1; enzyme hydrolyzed)	82.10	0.189
Hydrolysate	27.10	0.062
EtOAc	(1.31)	(0.003)
Aqueous	(25.79)[d]	(0.059)
PES-2 (acid hydrolyzed; 1 N HCL)	55.00	0.127
Hydrolysate	20.92	0.048
EtOAc	(2.69)	(0.006)
Aqueous	(18.23)[d]	(0.042)
PES-3 (acid hydrolyzed; 6 N HCL)	34.08	0.078
Hydrolysate	23.71	0.055
EtOAc	(2.64)	(0.006)
Aqueous	(21.07)[d]	(0.048)
Total Extractable	89.62	0.206

[a]TRR of liver sample was 0.23 ppm. [b]Subjected to TLC and HPLC analysis. [c]Numbers in parenthesis were added to obtain the "total extractable" sum. [d]Subjected to HPLC analysis.

Table 3. Distribution of radioactivity in skin/fat extracts from hens dosed with [^{14}C]pendimethalin at 10 ppm for 7 days.

Fractions	%TRR[a]	ppm
Hexane-1[b]	33.66	0.011
MeOH-1	29.38	0.010
Hexane-2[b]	14.24	0.005
MeOH-2	(14.91)[c,d]	(0.005)
Hexane-3	(26.28)	(0.009)
MeOH-3	(21.85)[c]	(0.007)
PES-1 (enzyme hydrolysis)	36.95	0.012
Hydrolysate	(19.21)	(0.006)
PES-2	17.74	0.006
Total Extractable	82.3	0.027

[a]TRR of skin/fat sample was 0.033 ppm. [b]Hexane-1 and hexane-2 fractions were combined and partitioned with MeOH resulting in hexane-3 and MeOH-3 fractions [c]Subjected to TLC and HPLC analysis. [d]Numbers in parenthesis were added to obtain the "total extractable" sum.

9/18

Characterization of Residues

Selected fractions of egg and tissues were subjected to purification and qualitative analyses by one-and two-dimensional TLC. Analyses were conducted on silica gel plates using six solvent systems. Reference standards were spotted alongside the samples and were visualized under ultraviolet light. Radiochromatograms were obtained using a radioactivity detector. Characterization of selected fractions was conducted on a HPLC system equipped with a radiometric detector and a UV absorbance detector at 280 nm. Samples were eluted using an acidic H_2O:ACN gradient. HPLC characterization of aqueous and organic fractions from eggs and tissues is presented in Table 4. Reference standards were subjected to HPLC analysis under the same conditions as the samples. Representative TLC chromatograms and HPLC radiochromatograms were provided. Reference standards used are presented in Table 5.

In eggs, 77.3% (0.028 ppm) of the total radioactivity was extractable. TLC analysis of the ACN fraction (40.1% TRR; 0.014 ppm) indicated the presence of the parent and other components characterized as polar because of their low R_f values. HPLC analysis of the ACN fraction confirmed the presence of pendimethalin (5.3% TRR; 0.002 ppm). Several unidentified radioactive components in chromatographic regions designated zones A through F, accounted for 1.7 - 11.5% of the TRR (<0.01 ppm each). The registrant stated that hexane soluble residues (21.38% TRR; 0.008 ppm) could not be assayed due to the low levels of radioactive residues present coupled with matrix interference.

10 18

Table 4. HPLC characterization of residues in aqueous and organic fractions from eggs and tissues of hens dosed with [^{14}C]pendimethalin at 10 ppm for 7 days.

Chromatographic Regions (Zones)	HPLC Rt (minutes)	Egg		Liver		Skin/fat	
		%TRR	ppm	%TRR	ppm	%TRR	ppm
A	0 - 10	1.72	0.001	2.13	0.005	0.0	0.0
B	10 - 17	0.0	0.0	0.39	0.001	0.0	0.0
C	16 - 24	6.71	0.002	1.26	0.003	0.72	0.0
D[a]	16 - 30	11.47	0.004	56.34	0.129	0.0	0.0
E[b]	28 - 36	5.29	0.002	6.77	0.016	0.0	0.0
F[c]	35 - 39	6.1	0.002	0.0	0.0	0.78	0.0
G[d]	35 - 47	5.32	0.002	1.10	0.003	15.69	1.005

[a]Zone D includes retention time for CL 202,078. [b]Zone E includes retention times for CL 202,588, CL 202,345, CL 239,336, CL 206,923, CL 206,925, and CL 239,335. [c]Zone F includes retention times for CL 99,900 and CL 202,347. [d]Registrant stated that zone G "includes parent".

In liver, 89.62% (0.21 ppm) of the total radioactivity was extractable. TLC analysis of the MeOH/H_2O fraction (10.65% TRR; 0.024 ppm) indicated the presence of polar residues that remained at the origin; no parent was detected. HPLC analysis of the same fraction detected a trace amount of parent (<1% TRR) and several other components more polar in nature than the parent, each of which accounted for <8% TRR. TLC analysis of the $CHCl_3$ fraction detected polar components and no parent. The major HPLC peak in the $CHCl_3$ fraction corresponded to the acid metabolite of pendimethalin (CL 202,078) that accounted for 2.3% of the TRR (0.005 ppm). The three enzyme/acid released aqueous fractions (total of 65.09% TRR; 0.15 ppm) were each analyzed by HPLC. In all cases, residues segregated to three zones (A, D, and E) and zone D contained the majority of the radioactivity. Residues confined to zone D accounted for 12.87-18.98% TRR (0.03-0.04 ppm). None of the components present in Zone D corresponded with the R_f of known standards. The registrant does not believe this polar material can be further resolved.

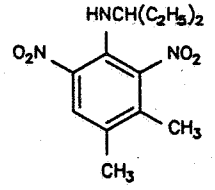
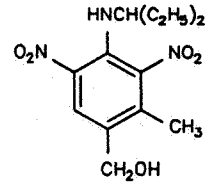
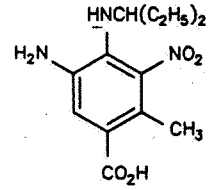
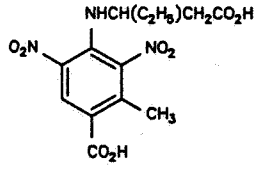
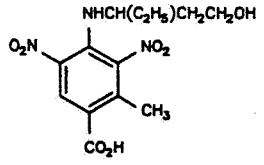
In skin/fat, 82.3% (0.027 ppm) of the total radioactivity was extractable. TLC and HPLC analysis of the MeOH-2 fraction (14.9% TRR; 0.005 ppm) detected the presence of low radioactivity associated with several polar components. TLC and HPLC analysis of the MeOH-3 fraction (21.9% TRR; 0.007 ppm) indicated the presence of parent (15.7% TRR; 0.005 ppm) and essentially no other component.

In summary, the qualitative nature of the pendimethalin residue in poultry is adequately understood. The terminal residues consist of the parent compound, trace amounts of 3,5-DNBA, and a pendimethalin acid metabolite (CL 202,345). The parent compound, pendimethalin was detected in eggs (5.32% TRR), liver (1.10% TRR) and in skin with adhering fat (15.7% TRR). The 3,5-DNBA metabolite was detected in trace amounts ($\leq$6% TRR) eggs and in skin/fat. The acid metabolite of pendimethalin (CL 202,345 was detected in liver (2.3% TRR).

Additional data are, however, required to upgrade this study. Representative samples from the 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.

12 15

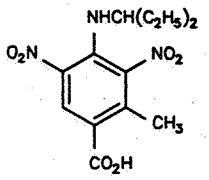
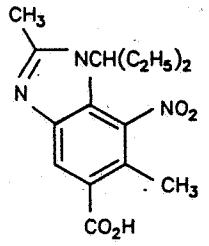
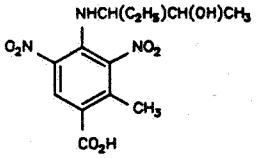
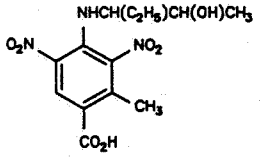
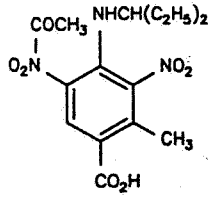
Table 5. Structures of reference standards with HPLC retention times.

Chemical Name[a] (common name or code)	Chemical Structures	HPLC R_t (min)
N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine (Pendimethalin; CL 92,553)		40.70[b]
4-[(1-ethylpropyl)amino]-2-methyl-3,5-dinitrobenzyl alcohol (3,5-DNBA; CL 202,347)		36.02[b]
  (CL 202,078)		27.32
  (CL 202,588)		30.57
4-[(1-ethyl-3-hydroxypropyl) amino]-3,5-dinitro-o-toluic acid (CL 202,345)		30.67[b]

(continued)

1370

Table 5. (continued)

4-[(1-ethylpropyl)amino]-3,5-dinitro-o-toluic acid (CL 99,900)		36.72[b]
  (CL 206,925)		32.32
  (CL 239,336)		31.87[b]
  (CL 239,335)		31.83[b]
  (CL 206,923)		31.13

[a]Chemical names are referenced from 1984 Residue Chemistry Chapter. Because registrant did not include chemical names with this submission, a conflict between the Chapter and the present submission concerning the structure of CL 202,078 could not be resolved. [b]These compounds were previously identified in rat tissues and/or urine.

14

Residue Analytical Methods

In response to soybean residue data requirements set forth in the 1985 Guidance Document, American Cyanamid submitted data (1987; MRID 40185101) that were reviewed by the Agency (D. Edwards, CBRS Nos. 5494 and 5495, dated 9/8/89) and conditionally accepted pending receipt of method recovery data and a description of method M-1609. The registrant responded (1986; MRID 41431001) by submitting an adequate method description and validation data on soybean forage. The Agency concluded (E. Zager, CBRS Nos. 7507 and 7517, 4/24/91) that the submitted validation data (method M-1609) on soybean forage are not sufficient to support the available data on soybean hay and straw. The registrant subsequently submitted validation data (1986; MRID 41982701) on wheat straw that were deemed inadequate (E. Zager, CBRS No. 8515 and Addendum to CBRS No. 8118, 5/15/92) to validate method M-1609 for soybean straw and hay analyses.

Subsequently, American Cyanamid Company (1992; MRID 42471901) has submitted method recoveries of pendimethalin and the 3,5-DNBA metabolite from soybean hay using method M-1609. These results are summarized in Table 6. The registrant did not provide sample chromatograms or calculations; therefore, assessment of these data could not be completed. The registrant must provide sample chromatograms and calculations, along with recovery results, in order to facilitate review of these data. The registrant did not provide method recovery data on soybean straw from method M-1609; these data are still required.

Table 6. Recoveries of pendimethalin and 3,5-DNBA from soybean hay using method M-1609.

Fortification Compound	No. of Samples	Fortification Level	Percent Recovery
pendimethalin	3	0.10	95, 91, 91
	1	1.0	92
3,5-DNBA	3	0.10	126, 75, 70
	1	1.0	109

Storage Stability Data

Currently, no tolerances exist for pendimethalin residues in/on alfalfa commodities. The current submission contains storage stability data on alfalfa submitted to expand the storage stability data base for pendimethalin.

American Cyanamid (1992; MRID 42471903) submitted data depicting the frozen storage stability of pendimethalin and its 3,5-DNBA metabolite in alfalfa seed, forage, and hay.

15

Untreated control samples were fortified at 0.5 ppm and stored at approximately -10 °C for up to 24 months. Residues were determined using method M-1930.01, a modification of method M-1930. A complete description of method M-1930.01 was not provided. If these stability data are to be used to support residue data, a complete description of method M-1930.01 must be submitted.

Storage stability and method recoveries are summarized in Table 7. The submitted data indicate that residues of pendimethalin and its 3,5-DNBA metabolite are stable in alfalfa green forage, hay, and seed stored at approximately -10 °C for up to 24 months.

16B

Table 7. Storage stability and concurrent method recoveries of pendimethalin and its 3,5-DNBA metabolite from alfalfa samples fortified and stored frozen (ca. -10 °C).

Commodity	Fortification Compound	Percent Recovery for Indicated Storage Interval (months)						Concurrent Method Recoveries
		0	3	6	12	18	24	
Alfalfa forage	Pendimethalin	107, 96	87, 116	84, 91	96, 94	95, 88	85, 80	76-104
	3,5-DNBA	100, 103	103, 125	76, 87	85, 85	88, 79	77, 66	74-101
Alfalfa hay	Pendimethalin	81, 91	91, 98	94, 88	97, 95	88, 87	109, 101	82-108
	3,5-DNBA	95, 92	85, 67	70, 68	81, 86	72, 63	71, 78	64-102
Alfalfa seed	Pendimethalin	85, 85	98, 95	91, 91	91, 92	97, 94	100, 96	82-105
	3,5-DNBA	69, 76	93, 84	72, 76	81, 89	89, 77	93, 81	79-104

References

Citations for the MRID documents referenced in this review are presented below. Submissions reviewed in this document are indicated by shaded type.

40185101 Tondreau, R.; Gingher, B. (1987) Soybean Residue Studies with Prowl (R) Herbicide in Illinois and Minnesota: Lab. Rept. No. CY2. Unpublished compilation prepared by American Cyanamid Co. 37 p.

41431001 Tondreau, R. (1986) Validation of Method M-1609 for the Determina- tion of CL 92,553 and CL 202,347 Residues in Soybean Plants: Lab Project Number: C-2667: M-1609. Unpublished study prepared by American Cyanamid Co. 13 p.

41982701 American Cyanamid Co. (1986) Validation of Method M-1624 for the Determination of CL 92,553 and CL 202,347 Residues in Wheat Straw: Lab Project Number: C-2692: M-1624. Unpublished study. 13 p.

42471901 Tondreau, R.; Boyd, J. (1992) Addendum: Soybean Residue Studies with Prowl Herbicide (Concurrent recovery tests from Soybean Hay): Lab Project Number: C2827: C2828: C2676. Unpublished study prepared by American Cyanamid Co. 5 p.

42471902 Witkonton, S. (1992) Pendimethalin (CL 92,553): Characteristics of Pendimethalin and its Alcohol Metabolite (CL 202,347) Through FDA Multiresidue Methods: Lab Project Number: C-3852. Unpublished study prepared by American Cyanamid Co. 61 p.

42467802 Zdybak, J. (1992) Pendimethalin (CL 92,553): Metabolic Fate of Carbon-14 Labeled CL 92,553 in Tissues and Eggs of the Laying Hen: Lab Project Number: PD-M 29-40. Unpublished study prepared by XenoBiotic Labs, Inc. and Hazleton Wisc., Inc. 187 p.

42471903 Witkonton, S. (1992) Pendimethalin (CL 92,553): Freezer Stability of CL 92,553 and CL 202,347 in Alfalfa Green Forage, Hay, and Seed Over a 24-Month Period: Lab Project Number: C-3873. Unpublished study prepared by American Cyanamid Co. 63 p.

CYANAMID

424678-ØØ

American Cyanamid Company
Agricultural Research Division
P.O. Box 400
Princeton, NJ 08543-0400
(609) 799-0400

August 28, 1992

Ms. Terri Stowe
Special Review and Reregistration Division
Office of Pesticide Programs (H7508C)
Document Processing Desk (RS-0187)
U.S. Environmental Protection Agency
Crystal Station #1, Westfield Bldg., Third Floor
2805 Jefferson Davis Highway
Arlington, VA 22202

RE: Pendimethalin Registration Standard Case #0187
Plant and Poultry Metabolism Studies on Pendimethalin

Dear Ms. Stowe:

In a letter addressed to American Cyanamid Company and dated March 8, 1991, the Agency discussed residue chemistry requirements for pendimethalin. The Agency stated that two plant metabolism studies were needed, one on sweet corn (preemergence and postemergence) and one on either potatoes or peanuts. Although American Cyanamid still contended (letter from Gingher to Rossi, dated April 15, 1991) that sufficient data had already been supplied regarding the metabolism of pendimethalin in plants, American Cyanamid agreed to conduct the above-mentioned studies on corn and potatoes using ring-labeled pendimethalin. In communications with the Agency, American Cyanamid understands that these metabolism studies will satisfy requirements for reregistration on the labeled raw agricultural commodities as well as any new registrations on raw agricultural commodities, providing that the metabolic profile is consistent with the earlier findings.

Volume 3 of this submission contains the potato metabolism study conducted for postemergence-applied pendimethalin. The results of this study are similiar to those of previously reported plant metabolism studies, namely, that only trace quantities of pendimethalin are detected in the mature tuber and that all other pendimethalin-derived residues were insignificant.

Volume 1, Exhibit 1, of this submission contains a letter from XenoBiotic Laboratories, Inc., the contract laboratory performing the metabolism study on sweet corn, in which they notify American Cyanamid of their inability to meet the August 31, 1992, EPA submission date. As discussed in the letter, the in-life phase has been completed and

19

CYANAMID

characterization of radioactivity is in progress; however, the contract laboratory requires additional time in order to complete this difficult identification. To provide XenoBiotics time to properly complete the study and for packaging of the report for submission to the Agency, American Cyanamid is requesting an extension of the submission date to March 1, 1993.

Volume 4 of this submission contains the metabolism study conducted on laying hens. This study is being supplied as a result of the data call-in notice issued on September 4, 1990, and as confirmed in the Rossi letter dated February 6, 1991.

Please contact me should you have any questions regarding this submission.

Respectfully submitted,

Mark W. Galley
Manager
U.S. Plant Regulatory Affairs

MWG:gc
Enclosures

20

PLANT AND POULTRY METABOLISM STUDIES
IN SUPPORT OF THE REREGISTRATION OF PROWL® HERBICIDE

Date Submitted: 8/28/92 MRID No. Volume 2

Title

Transmittal Document

Transmittal Date

August 28, 1992

Submitted by

American Cyanamid Company
Agricultural Research Division
P.O. Box 400
Princeton, NJ 08543-0400

21

TRANSMITTAL DOCUMENT

Volume 2

DATE: 8/28/92

Submitted By: American Cyanamid Company
Agricultural Research Division
P.O. Box 400
Princeton, New Jersey 08543-0400

In Support Of: Plant and Poultry Metabolism Studies in Support of the Reregistration of PROWL® herbicide.

PROWL® herbicide technical EPA Reg. No. 241-245.
PROWL® 4E herbicide EPA Reg. No. 241-243.

Volume	TITLE	MRID No.
1	Administrative Material	No Data
2	Transmittal Document	No Data
3	Pendimethalin (CL 92,553): Metabolism of Carbon-14 Labeled CL 92,553 in Potatoes Under Field Conditions (Guideline No. 171-4 (a)(2))	42467801
4	Pendimethalin (CL 92,553): Metabolic Fate of Carbon-14 Labeled CL 92,553 in Tissues and Eggs of the Laying Hen (Guideline Series 171-4)	42467802

Company Official: Mark W. Galley

Company Name : American Cyanamid Company

Company Contact: Mark W. Galley

®Registered Trademark of American Cyanamid Company

22

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs

SEP 10 1992

AMERICAN CYANAMID COMPANY
AGRICULTURAL RESEARCH DIVISION
P.O. BOX 400
PRINCETON, NJ 085430400

Report of Analysis for Compliance with PR Notice 86-5

Thank you for your transmittal of 09/04/92. Our staff has completed a preliminary analysis of the material. The results are provided as follows:

Your submittal was found to be in full compliance with the standards for submission of data contained in PR Notice 86-5. A copy of your bibliography is enclosed, annotated with Master Record ID's (MRIDs) assigned to each document submitted. Please use these numbers in all future references to these documents. Thank you for your cooperation. If you have any questions concerning this data submission, please raise them with the cognizant Product Manager, to whom the data have been released.

23

SEP 14 1992

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs

AMERICAN CYANAMID COMPANY
AGRICULTURAL RESEARCH DIVISION
P.O. BOX 400
PRINCETON, NJ 085430400

Report of Analysis for Compliance with PR Notice 86-5

Thank you for your transmittal of 09/10/92. Our staff has completed a preliminary analysis of the material. The results are provided as follows:

Your submittal was found to be in full compliance with the standards for submission of data contained in PR Notice 86-5. A copy of your bibliography is enclosed, annotated with Master Record ID's (MRIDs) assigned to each document submitted. Please use these numbers in all future references to these documents. Thank you for your cooperation. If you have any questions concerning this data submission, please raise them with the cognizant Product Manager, to whom the data have been released.

24 27

Volume 2

MRID #:

424719-00

TRANSMITTAL DOCUMENT

Submitted By: American Cyanamid Company
Agricultural Research Division
P.O. Box 400
Princeton, New Jersey 08543-0400

REGULATORY ACTION WHICH SUBMISSION SUPPORTS: Pendimethalin Data Call-In
Case #0187
Chemical # 108501

TRANSMITTAL DATE:

CONTENTS OF SUBMISSION:

MRID #	Location in Submission	Content
-	Volume 1	Administrative Materials
-	Volume 2	Transmittal Document
42471901	Volume 3	Addendum: Soybean Residue Studies with PROWL® herbicide. (Concurrent recovery tests from soybean hay)
42471902	Volume 4	Pendimethalin (CL 92,553): Characteristics of Pendimethalin and its Alcohol Metabolite (CL 202,347) Through FDA Multiresidue Methods. Guideline #171-4c (Residue Analytical Method)
42471903	Volume 5	Pendimethalin (CL 92,553): Freezer Stability of CL 92,553 and Cl 202,347 in Alfalfa Green Forage, Hay and Seed Over a 24-Month Period. Guideline #171-4e (Storage Stability)

W. A. Steller

COMPANY OFFICIAL/CONTACT: W. A. Steller
(609) 799-0400

COMPANY NAME: American Cyanamid Company

®Registered Trademark of American Cyanamid Company

25 28

DATA SUBMITTED IN RESPONSE TO THE PENDIMETHALIN
REGISTRATION STANDARD

Date Submitted: 9/3/92 MRID No. Volume 2

Title

Transmittal Document

Transmittal Date

Submitted by

American Cyanamid Company
Agricultural Research Division
P.O. Box 400
Princeton, NJ 08543-0400

26 29

CYANAMID

American Cyanamid Company
Agricultural Research Division
P.O. Box 400
Princeton, NJ 08543-0400
(609) 799-0400

September 2, 1992

Ms. Lois Rossi, Chief
Reregistration Branch (H7508C)
Special Review and Reregistration Division
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Re: July 27, 1992 Letter of L. Rossi to B. Gingher
Pertaining to Pendimethalin

Dear Ms. Rossi:

For your convenience we will address the issues raised in the referenced letter point by point.

AGENCY's point 1 from Acurex review: "The registrant must provide supporting method recovery data on soybean straw and hay using method M-1609, because method M-1609 was used to collect residue data".

American Cyanamid Company's response: As we have indicated previously, method M-1609 had been completely validated for analysis of wheat straw. In addition concurrent recoveries were conducted on soybean hay as the field samples were assayed. We have included documentation (Cyanamid memo - J. Boyd to D. Little 9/1/92) in Volume 3.

AGENCY's point 2 from Acurex review: "The registrant must analyze representative samples of plant tissues containing residues of pendimethalin and its 3,5-dini-trobenzyl alcohol metabolite by multiresidue Protocols C and E from PAM Vol. I, Appendix II."

American Cyanamid Company's response: We have successfully analyzed a non-fatty food (green beans) and a typical fatty food (pecan meats) utilizing the methods described in PAM, Volume 1. These analyses are described in report C-3852 titled "Pendimethalin (CL,92,553): Characteristics of Pendimethalin and its Alcohol Metabolite (CL 202,347) Through FDA Multiresidue Methods" included as Volume 4.

27380

AGENCY's point 3 from Acurex review: "If radiolabeled validation of existing analytical methodology for plant and animals indicates a major portion of the total radioactive residue is not recovered and identified by these methods, radio labeled validation of new proposed analytical methodology will be required".

American Cyanamid Company's response: This statement implies a new data requirement. However, we would comment that this statement is irrelevant since we are in the process of performing additional plant metabolism studies to convince the AGENCY that the current tolerance expressions are a measure of the total toxic residue that warrants regulation.

AGENCY's point 4 from Acurex review: "The registrant must provide additional storage stability data on almond hulls and potato tubers for the 3, 5 DNBA metabolite, and for both parent and metabolite on raisins".

American Cyanamid Company firmly believes that the storage stability data reported in "Pendimethalin (CL 92,553): Summary of Ongoing Freezer Stability studies on CL 92,553 and CL 202,347 (metabolite) Residues in Several Different Types of Commodities" submitted on March 1, 1988 and assigned MRID #40535101 and the storage periods for all our residue studies documented in "Summary of Previously Submitted Data in Response to EPA Review of Storage Stability Related to Guideline 171-4 Requirements, submitted on April 2, 1992, and assigned MRID #42266301 demonstrate the following fact: We have submitted sufficient storage stability data to demonstrate that during freezer storage pendimethalin and its CL 202,347 (metabolite) are stable in all of the typical types of commoditites (watery crop, oily crop, green and dry foliage) during the storage periods encountered in our residue studies.

In addition we are submitting a recently concluded storage stability study conducted on alfalfa commodities which will also be part of a new tolerance petition for alfalfa. This report (C-3873) titled "Pendimethalin (CL 92,553): Freezer Stability of CL 92,553 and CL 202,347 in Alfalfa Green Forage, Hay and Seed Over a 24-Month Period" is included in Volume 5.

AGENCY's point 5 from Acurex review: "The registrant must submit sample storage conditions and intervals for all required and previously submitted residue data for plant commodities (raw and processed foods and feeds). Storage stability data in support of previously submitted residue data are required for only those samples deemed useful to tolerance assessments".

We believe that we have submitted these data for all the raw agriculture commodities (RAC's) for which we currently have tolerances in the previously referred to submission of April 2, 1992, assigned MRID #42266301. We do not have or need any processed food or feed additive tolerances because the residue levels in the RAC is so low that concentration into any processed food would not result in residues higher than the 408 tolerance for the RAC, hence 409 tolerances are not required.

JA 861

AGENCY's point 6 from Acurex review: "The nature of the residue in plants and animals is not adequately understood. If the requested data on plant and animal metabolism indicate the presence of additional metabolites of toxicological concern, data depicting the stability of those residues during storage will be required".

American Cyanamid Company's response: After the AGENCY reviews the additional studies we are conducting, we believe the AGENCY will conclude that the current tolerance expressions are a measure of the total toxic residue that warrants regulation and that there is no reasonable expectation of finite residues in meat or milk. Hence, storage stability data on other metabolites is a moot point.

We appreciate your efforts to aid us through the reregistration process for our important product, PROWL® herbicide, and will continue to work diligently with the AGENCY to complete the process.

Sincerely,

William A. Steller
Special Assistant to Executive
Director of Regulatory & Scientific Affairs
U.S. Regulatory Affairs

WAS:ceb
Encl.

®Registered Trademark of American Cyanamid Company

29888