7-28-93
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 28 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Pendimethalin: Reregistration-Toxicological Data Requirements

TOX Chem No.: 454BB
PC No.: 108501
DP Code: D170935
Submission No: S4066583

FROM: William B. Greear, M.P.H. William B. Greear 6/1/93
Review Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Walter Waldrop/Terri Stowe, PM Team 71
Reregistration Branch
Special Review and Reregistration Division (H7508W)

THRU: Marion P. Copley, D.V.M., Section Head
Review Section II, Toxicology Branch I
Health Effects Division (H7509C) 6/17/93

I. CONCLUSIONS

The toxicological data base is adequate and will support the reregistration of pendimethalin.

II. REQUESTED ACTION

Walter Waldrop, of the SRRD (Reregistration Branch), in a memorandum generated in early 1993, has requested that Tox I clarify the status of the toxicological data requirements for the reregistration of pendimethalin.

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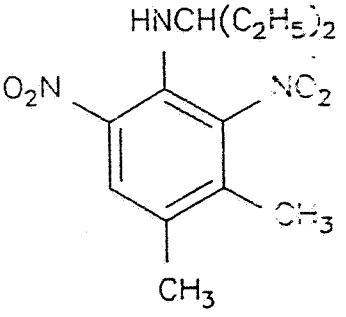
III. PRODUCT INFORMATION — Pendimethalin, No. 454BB
Updated June 1993

Pendimethalin (3,4-xylidine, N-(1-ethylpropyl)-2,6-dinitro) is a herbicide plant growth regulator and is used to control germinating weeds. It is applied using both ground and aerial equipment and depends on mechanical and natural (rain) means for soil incorporation to be effective. Pendimethalin has both terrestrial food crop and nonfood uses. Tolerances have been established for residues of pendimethalin on several raw food crops under 40 CFR 180.361. Nonfood-crop uses include both ornamentals and tobacco. Pendimethalin's proprietary name is PROWL®. The current formulation is PROWL 4E (42.3% a.i.), Registration No. 241-243. Its chemical structure is as follows:

PENDIMETHALIN



The Chemical Abstracts Service Registry Number is 40487-42-1, and the TOX Chem No. is 454BB. The PC No. is 108501. It is a list A chemical.

IV. DATA REQUIREMENTS (40 CFR 158.340)

Pendimethalin, No. 454BE
Updated June 1993

Technical	Required	Satisfied
81-1 Acute Oral Toxicity	Y	Y
81-2 Acute Dermal Toxicity	Y	Y
81-3 Acute Inhalation Toxicity	Y	Y
81-4 Primary Eye Irritation	Y	Y
81-5 Primary Dermal Irritation	Y	Y
81-6 Dermal Sensitization	Y	Y
81-7 Acute Delayed Neurotoxicity (Hen)	N	-
82-1 Subchronic Oral (Rodent)	Y	Y
82-1 Subchronic Oral (Nonrodent)	Y	Y1
82-2 21-Day Dermal	Y	Y
82-3 90-Day Dermal	N	-
82-4 90-Day Inhalation	N	-
82-5 90-Day Neurotoxicity (Hen)	N	-
82-5 90-Day Neurotoxicity (Mammal)	-	-
83-1 Chronic Toxicity (Rodent)	Y	Y
83-1 Chronic Toxicity (Nonrodent)	Y	Y
83-2 Carcinogenicity (rat)	Y	Y
83-2 Carcinogenicity (mouse)	Y	Y
83-3 Developmental Toxicity (rat)	Y	Y
83-3 Developmental Toxicity (rabbit)	Y	Y
83-4 Reproduction	Y	Y
83-5 Chronic/Carcinogenicity	-	-
84-2 Mutagenicity - Gene Mutation	Y	Y
84-2 Mutagenicity - Structural Chromosomal Aberration	Y	Y
84-4 Mutagenicity - Other Genotoxic Effects	Y	Y
85-1 General Metabolism	Y	Y
85-2 Dermal Penetration	N	-
86-1 Domestic Animal Safety	N	-

[1] The chronic dog study satisfies the requirement for the 90-day dog study.

Y = Yes; N = No.

V. TOXICOLOGY PROFILE

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TB-1
TOX ONELINERS MEEETING GUIDELINE REQUIREMENTS

CASWELL#: 454BB

P.C. CODE 108501- N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 06/11/93

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
83-1(a) and 83-2(a) Feeding/oncogenic-2 year Species: rat Hazleton Lab America HLA 6123-112; 4/20/87	Pendimethalin 91.9% (lot AC 3528-129-1)	401744-01	Levels tested in diet of Crl:CD(SD)Br str: 0, 100, 50, 5000 ppm (0, 5, 25, 250 mg/kg/day). Systemic NOEL = 100 ppm (5 mg/kg/day). Sys. LOEL = 500 ppm (25 mg/kg/d). based on pigmentation of thyroid follicular cells in male & female. At 5000 ppm - decr. survival and body weight gain in males. In females - decr. food consumption; incr. GGT, cholesterol, liver weight, liver/body wt. ratio, absolute & relative thyroid weight, icterus, dark adipose tissue, dark thyroids. In males & females - follicular cell hyperplasia in the tyroid. Possible increase in thyroid follicular cell adenoma at 5000 ppm (refer to peer review).		Min (Chronic & Onco) 008606
83-1(a) and 83-2(b) Chronic/onco feeding Species: mice Interntl. Res. and Develop. Co IKI-028; 10/15/88	Pendimethalin 92.6% (batch AC 5213-72A	409099-01	Levels tested in the diet of Crl:CD-1 strain: 0, 100, 500 & 5000 ppm (M - 0, 12.3, 62.3 and 622.1 mg/kg/day F_ 0, 15.6, 78.3 & 806.9 mg/kg/d). NOEL = 500 ppm. LOEL = 5000 ppm - incr. mortality in females, decr. body wt. in females, incr. absolute thyroid, liver and gall bladder wts and/or relative body and brain weight ratios in males and females, amyloidosis in males.		Min. (carcinogen) 008606 Suppl- chroni 008606
83-1(b) Feeding-2 year Species: dog Litton Bionetics Inc. 20755; 12/79	Prowl (Ac-92,553 Tech.)	244444 244445 00067519	NOEL = 12.5 mg/kg/day. LEL = 50 mg/kg/day (increase in serum alkaline phosphatase and increased liver weight, hepatic lesions		Minimum 001035
83-3(a) Developmental Toxicity Study Species: rat Hazleton 362-155; 8/17/79	Pendimethalin Tech.	241595 00025752 417252-02	Teratogenic NOEL>500 mg/kg/day(HDT)Fetotoxic NOEL > 500 mg/kg/day Levels tested = 125, 250, 500 mg/ kg. Upgarded to Minimum. Individual CDFA - EPA Review, 2/15/89: Agreement that the coregrade be changed from guideline to supplementary. Individual animal data were reevaluated (DER 008558 - 5/9/91) allowing an upgrade to Minimum.		Guideline 000544 Supplementary 007751 Minimum 008558
83-3(b) Developmental Toxicity Study Species: rabbit Hazleton 362-164; 5/11/82	Pendimethalin Tech 92.2%	248659	NOEL > 60 mg/kg/day (HDT). Levels tested = 0, 15, 30, 60 mg/kg		Minimum 002406
83-4 Reproduction-2 generation Species: rat Toxicology labs Ltd. CBG/2/90 7/12/90	AC 92553 92.6% (Pendimethalin)	417252-03	Doss levels: 500, 2500 & 5000 ppm (males: 34, 172 & 344 mg/kg/day; females: 43, 216 and 436 mg/kg/day) in Sprague-dawley strain. Reprod. NOEL = 500 ppm (43 mg/kg/day). Reprod LOEL = 2500 ppm (216 mg/kg/day) based on decrease in pup weight. Parental NOEL = 500 ppm 34 mg/kg/d). Parental LOEL = 2500 ppm (172 mg/kg/day) based on decrease in body weight gain & food consumption.		Minimum 008558 Nov 93

Conversion from ppm in diet (ppm) to dose (mg/kg/day) changed from DER 417252 Based on 1991 letter with time-weighted mean intake

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TOX ONELINERS MEEETING GUIDELINE REQUIREMENTS

P.C. CODE 108501- N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 06/11/93

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT
82-1(a) Feeding-3 month Species: rat American Cyanamid Co. AX-86-1; 1/28/86	Pendimethalin (AC 92,553 Tech). 92.1%	261305	Thyroid function study in male rats. NOEL = 500 ppm. LEL = 5,000 ppm (decr. in hematocrit & hemoglobin in males, decreased body wt. gain & food consumption, & hypertrophy of the liver accompanied by increased liver weights). Levels tested: 100,500 and 5,000 ppm in Charles River CD(SD)Br Age - 4 wks. Mean body wt. - 100-115 (M); 87-103 (F)		Guideline 005311
82-2 Dermal-3 week Species: rabbit Food and Drug Research Lab 1613; 8/24/73	Pendimethalin Tech.	00026663	NOEL > 1 g/kg (HDT). Levels tested = 250, 500, 1000 mg/kg		Minimum 000544
82-2 Dermal-3 week Species: rabbit	Prowl (4E - 43.8% a.i.)		Slight to moderate erythema and edema at 2 ml/kg/24 hours.		Minimum 000543
84-4 Mutagenic-reverse mutation Species: salmonella American Cyanamid Co. 0166; 10/28/85	Pendimethalin tech (92.2%	260403 00153768	Positive in Salmonella typhimurium; strains TA1538 and TA98, with S-9 activation.Large response in TA 1538 (reproducible), small response in TA98. Dose response to top dose. Some precipitation at top dose.		Acceptable 005828 009809
84-4 Mutagenic-DNA repair test Species: Pharmakon Res. Inst. Inc. PH311-AC-002-85; 10/25/85	Pendimethalin Tech. 91.2%	260403 000153771	Negative to 3000 ug/well, => 6000 ug/mL were cytotoxic.		Acceptable 005828 009809
84-2(b) Mutagenic-chromosome aberr. Species: Pharmakon Res. Inst. Inc. PH320-AC-001-85; 10/17/85	Pendimethalin Tech 92.9%	260403 000153770	Negative. CHO: 5 to 25 ug/mL without activation, 12.5 to 100 ug/mL with activation.		Acceptable 005828
84-4 Mutagenic-(HGPRT) Species: CHO cell Pharmakon Res. Inst. Inc. PH-314-AC001-85; 10/17/85	Pendimethalin tech. 92.2%	260403 00153369	Negative with S9. Inconclusive with/without S9, although suggestive increases were obtained w/o activation at levels up to 10 ug/mL. Dose levels were inadequate. Unacceptable (New PR Doc. No.)		Acceptable (w/ S9) 005828 Unacc (- S9) 009809

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P.C. CODE 108501- N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 06/11/93

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-4 Mutagenic-micronucleus assay Species: mice Microbiological Associates T9801.122004; 06/07/91	AC 92,533 (pendimethalin 92.98%)	420278-01	Negative. Dose levels: 625 & 1250 mg/kg in ICR strain.		Acceptable 009821
85-1 Metabolism Species: rat American Cyanamid Co. 2-463; 11/7/73	Prowl (radiolabelled CL 92,553 (parent))	000446275	The following metabolites were present in either urine, muscle, blood, fat, kidney or liver. The metabolites identified by code (See review for structures) were as follows: CL 92,553; CL99,900; CL 113,066; CL 113,071; CL 113,072; CL 202,078 CL 202,345 ; CL 202,347 no additional data required at this tim		Supplementary 004026 new doc.
81-1 Acute oral LD50 Species: rat American Cyanamid Co. A-72-4; 6/1/72	Pendimethalin tech. 98.7%	00026657	LD50 (M) = 1250 mg/kg. LD50 (F) = 1050 mg/kg.	3	Minimum 000543
81-1 Acute oral LD50 Species: rat American Cyanamid Co. A-72-4; 6/1/72	Pendimethalin Tech. 93%		LD50 = 2140 mg/kg.	3	Minimum 000543
81-1 Acute oral LD50 Species: mice American Cyanamid Co. A-72-4; 6/1/72	Pendimethalin Tech.	00026657	LD50 > 1620 mg/kg (M). LD50 > 1340 mg/kg (F).	3	Minimum 004026
81-1 Acute oral LD50 Species: rat American Cyanamid Co. A-73-133; 11/28/73	Pendimethalin Tech.	00072802	LD50 = 2140 (1330-4430) mg/kg	3	Minimum 004026
81-1 Acute oral LD50 Species: rat American Cyanamid Co. T-0169; 10/05/89	Pursuit plus EC, 30.1% (Pendi-30.1%; Imazethapyr 2.1%)	413981-03	LD50 (M) = 3281 mg/kg. LD50 (F) = 3247 (2073-4264) mg/kg. LD50 (combined) = 3247 (2073-4264) mg/kg.	3	Guideline 008830

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TOX ONELINERS MEEETING GUIDELINE REQUIREMENTS

P.C. CODE 108501- N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 06/11/93

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-2 Acute Dermal LD50 Species: rabbit American Cyanamid Co. A-72-4; 6/1/72	Pendimethalin Tech. 93%	00026657	LD50 > 5000 mg/kg (HDT).	3	Minimum 000543
81-2 Acute Dermal LD50 Species: rabbit American Cyanamid Co. T-0613; 10/31/89	Pursuit plus EC, 30.1% (Pendi-30.1%; Imazethapyr 2.1%)	413981-04	LD50 > 2000 mg/kg.	3	Guideline 008838
81-3 Acute inhalation LC50 Species: rat Affiliated Medical research 122-1968-43; 10/24/73	Pendimethalin Tech 15% Aq. sol	00073342	LC50 > 320 mg/L (nominal conc.).	4	Minimum 000543 004026
81-3 Acute inhalation LC50 Species: rat Biosearch Inc. 89-6690A; 07/12/89	Pursuit plus EC, 30.1% (Pendi-30.1%; Imazethapyr 2.1%)	413981-04	LC50 > 5.54 mg/L	4	Guideline 008838
81-4 Primary eye irritation Species: rabbit American Cyanamid Co. A-72-4; 6/1/72	Pendimethalin tech. 93%	00026657	Slight conjunctival irritation.	3	Minimum 000543
81-4 Primary eye irritation Species: rabbit American Cyanamid Co. A-73-133; 11/28/73	Pendimethalin Tech.	00072802	Slight irritation (unwashed eyes).	3	Minimum 004026
81-4 Primary eye irritation Species: rabbit American Cyanamid Co. T-0161; 10/09/89	Pursuit plus EC, 30.1% (Pendi-30.1%; Imazethapyr 2.1%)	413981-06	Corneal involvement or irritation clearing in 7 days or less.	3	Guideline 008838

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TOX ONELINERS MEEETING GUIDELINE REQUIREMENTS

P.C. CODE 108501- N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 06/11/93

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-4 Primary eye irritation Species: rabbit American Cyanamid Co. T-0389; 01/31/92	Pendimethalin, 60%	425535-02	Opacity at 21 days.	1	Guideline 010135
81-5 Primary dermal irritation Species: rabbit American Cyanamid Co. A-72-4; 6/1/72	Pendimethalin 93%		No irritation.	4	Minimum 000543
81-5 Primary dermal irritation Species: rabbit American Cyanamid Co. T-0162; 10/20/89	Pursuit plus EC, 30.1% (Pendi-30.1%; Imazethapyr 2.1%)	413981-07	Mild or slight irritant.	4	Guideline 008838
81-6 Dermal sensitization Species: guinea pig Bioresearch Inc. 85-4639A; 8/1/85	Pendimethalin Tech. 92.2%	260403	Nonsensitizing		Minimum 005828
81-6 Dermal sensitization Species: guinea pig Dawson Research Corp. DRC 4915; 07/09/89	Pursuit plus EC, 30.1% (Pendi-30.1%; Imazethapyr 2.1%)	413981-08	It did not sensitize guinea pigs.		Guideline 008838
81-6 Dermal sensitization Species: guinea pig Food and Drug Research Lab 8100; 11/16/84	Prowl 42.3%	261505	Not a sensitizer. Dose levels: 0.4 mL of 30% for induction and challenge. Treatment: induction 1/week for 3 weeks; challenge 2 weeks later.		Guideline 009875

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VI. DATA GAPS

None.

VII. ACTION TAKEN TO REMOVE DATA GAPS AND OBTAIN ADDITIONAL INFORMATION

None.

VIII. REFERENCE DOSE (RfD)

The oral RfD is 0.04 mg/kg/day based on a NOEL of 12.5 mg/kg/day determined in a 2-year dog study utilizing an uncertainty factor of 300 and a modifying factor of 1. The verification date for the Agency RfD workgroup review is September 16, 1987. It is anticipated that of new RfD workgroup review of pendimethalin will be forthcoming.

IX. PENDING REGULATORY ACTIONS

There are no pending regulatory actions against this pesticide at this time that TB-I is aware of.

X. TOXICOLOGICAL ISSUES

A. The Peer Review Committee on Carcinogenicity met on 3/18/92 and decided that pendimethalin was a Group C - possible human carcinogen and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk (see memorandum of William Greear and Ester Rinde dated 7/27/92).

B. A letter dated from Barbara Gingher of the American Cyanamide Company provided data on the time-weighted mean consumption of pendimethalin in the two-generation reproduction study - Study No. CBG/2/90; 7/12/90 (see the Supplemental Reproduction DER attached). These data are adequate and will be incorporated into the one-liners

[These data were only recently (6/93) provided to the Tox I-Reviewer for evaluation.]

C. Although the metabolism study is supplementary, no additional data is required at this time.

NOTE: It is recommended that this memorandum be submitted to the registrant in its entirety. If the registrant wishes to support a hormonal mechanism for thyroid tumors however other metabolism/pharmakinetic data, as identified in the Peer Review Document (7/27/92), would need to be submitted.

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55963:I:WP5.0:Greear:C.Disk:KENCO:11/28/90:de:VO:EK:CL
55963:WP5.1:Greear:1/3/91:MPC

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Reviewed by: William B. Greear, M.P.H.
Review Section IV, Toxicology Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M.
Review Section IV, Toxicology Branch I (H7509C) Marion Copley 9/17/93

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DATA EVALUATION REPORT-SUPPLEMENTAL

Study Type: Two-Generation Reproduction
Study-Guideline Series 83-4

TOX. Chem. No.:454BB
MRID No.: 417252-03*
PC No.: 108501

Test Material: AC92,533

Synonyms: Pendimethalin

Study Number: CBG/;2/90

Sponsor: American Cyanamid Company
Princeton, NJ 08543-0400

Testing Facility: Toxicol Laboratories Limited
Ledburg, U. K.

Title of Report: Dietary Rat Two-Generation Reproduction Toxicity Study with AC 92,553

Author: L. F. H. Irvine, P. Boughton

Report Issued: July 12, 1990

Conclusions: NOEL (parental) = 500 ppm (M ≈ 34 mg/kg/day; F=43 mg/kg/day)
LEL (parental) = 2500 pm (decreased body weight gain and food consumption in males and females ≈ 216 mg/kg/day ≈ 172 mg/kg/d
NOEL (reproduction) = 500 ppm (≈ 43 mg/kg/day)
LEL (reproduction = 2500 ppm decrease in number of pups born and pup body weight ≈ 216 mg/kg/day)

Classification: Core-Minimum

Study Acceptability: The study satisfies the requirements for a Guideline Series 83-4 Two-Generation

New Data: In a letter dated November 1, 1991, Barbara Gingher (attached) of the American Cyanamide Company has submitted the time-weighed-mean of pendimethalin as requested. The data are presented below in Table 1. Table 2 represents the means to be used for calculations of intake for risk assessment.

* - Original MRID No. provided, no new MRID No. is available.

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Table

Time-Weighed-Mean Consumption of Pendimethalin[1]

Period	Generation	Mean Calculated Intake (mg/kg/day) ±S.D. 500 ppm	2500 ppm	5000 ppm
Males:				
Pre-mating	P1	36±6	173±25	343±45
	F1	42±13	215±70	437±139
Post-mating	P1/F1	25±1	128±6	259±13
Females:				
Pre-mating	P1	40±5	195±21	389±37
	F1	46±10	236±50	484±88
Pregnancy (both a & b litters)	P1/F1	33±2	168±7	343±19

Table 2	500 ppm	2500 ppm	5000 ppm
Males [2]	34 mg/kg/day	172 mg/kg/day	346 mg/kg/day
Females [3]	43 mg/kg/day	216 mg/kg/day	436 mg/kg/day

[1]Table extracted from Memorandum of B. Gingler, American Cyanamide Company, 11/1/91

2 Means of P1, F1 pre and post mating intake

3 Means of P1, F1 Pre mating intake

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CYANAMID

NO 40 CFR 158 DATA ARE IN THIS SUBMISSION

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American Cyanamid Company
Agricultural Research Division
P O Box 400
Princeton, NJ 08540
(609) 799-0400

November 1, 1991

Ms. Terri Stowe
Special Review and Reregistration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Crystal Mall, Bldg. No. 2
1921 Jefferson Davis Highway
Arlington, VA 22202

Re: Pendimethalin Registration Standard
Case # 0187; Submission of Information
Required by an EPA Letter Dated September 27, 1991

Dear Ms. Stowe:

American Cyanamid is providing the information required by an EPA letter which we received on October 4, 1991 (attached). In the letter, Toxicology Branch I stated a need for certain time weighted mean consumption values related to a rat reproduction study with pendimethalin (MRID #41725203). These are provided below:

Period	Generation	Mean Calculated Intake (mg/kg/day) ± S.D. 500 ppm	2500 ppm	5000 ppm
Males:				
Pre-mating	P1	36 ± 6	173 ± 25	343 ± 45
	F1	42 ± 13	215 ± [illegible]	43[illegible] ± 139
Post-mating	P1/F1	25 ± 1	128 ± 6	259 ± 13
Females:				
Pre-mating	P1	40 ± 5	195 ± 21	389 ± 37
	F1	46 ± 10	236 ± 50	484 ± 88
Pregnancy (both a & b litters)	P1/F1	33 ± 2	168 ± [illegible]	343 ± 19

We believe that this table provides the information requested in your letter and hope that it is helpful in the evaluation of pendimethalin. If you have any other questions concerning this study, please call me at Extension 2234.

Respectfully submitted,

Barbara Gingher

Barbara Gingher
Product Registrations Manager
U.S. Regulatory Affairs

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