9-24-91

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

008606

SEP 24 1991

SEP 24 91

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Pendimethalin - Review of Reformatted Data and the Chronic Feeding/Carcinogenicity Studies in Rats and Mice (EPA ID No. 108501, Case No. 0187)

PC Code No.: 108501
Tox Chem. No.: 454BB
Project Nos.: 0-1025
1-0072
1-1261
Record No.: 262230
Submission No.: S396025

FROM: William B. Greear, M.P.H. William B. Greear 9/10/91
Review Section III, Toxicology Branch I
Health Effects Division (H7509C)

TO: B. Baker/Terri Stowe, PM Team 74
Reregistration Branch
Special Review and Reregistration Division (H7508W)

THRU: Marion P. Copley, D.V.M., Section Head
Review Section III, Toxicology Branch I
Health Effects Division (H7509C)
Marion Copley 9/12/91

I. CONCLUSIONS

A. The reformatted data have been evaluated in conjunction with the rat chronic feeding/carcinogenicity study (#HLA Study No. 6123-112, April 20, 1987) and mouse chronic feeding/carcinogenicity study (IRDC #141-028, October 5, 1988). The rat study is Core-Minimum for both chronic toxicity (83-1) and carcinogenicity (83-2). The mouse study is Core-Supplementary for chronic toxicity (83-1) and Core-Minimum for carcinogenicity (83-2). The sponsor should address the apparent

discrepancy in survival data in the rat study and submit the time weighted mean consumption values for the test material for each dose level and sex.

B. Concerning the dermal sensitization study on PROWL Herbicide, Toxicology Branch I (TB-I) is only capable of determining whether data gaps exist by examining HED files. It is suggested that whenever RD receives and evaluates a toxicological study that HED be informed with respect to the results of the study (a DER would be adequate) and its status in satisfying a data requirement. This would ensure that the company is provided with correct, up-to-date information on the status of their toxicological data base.

C. The historical control data submitted by the sponsor have been assigned MRID No. 419097-01.

II. REQUESTED ACTION

SRRD has requested that TB-I review the sponsor's submission of the reformatted data for the following studies:

- "Chronic Dietary Toxicity and Oncogenicity Study in Rats Fed with AC 92,553," HLA Study No. 6123-112, April 10, 1987.

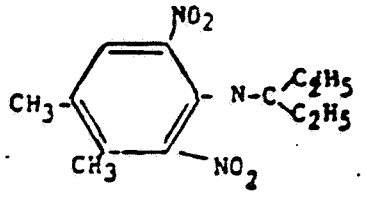
- "Chronic Dietary Toxicity and Oncogenicity Study with AC 92,553 in Mice," IRDC #141-028, October 5, 1988.

In addition, under a cover letter dated March 27, 1991, Barbara Gingher of the American Cyanamid Company has submitted historical control data on the incidence of thyroid proliferative lesions in Sprague-Dawley rats as requested by TB-I. B. Gingher also indicates that a new 2-year chronic/carcinogenic study in rats has been completed and will be submitted the end of June. (The study has not yet been received.) B. Gingher indicated that the dermal sensitization requirement for PROWL Herbicide has already been satisfied by submission of a study (FDRL #8100) on February 11, 1986 and was assigned MRID No. 00157149. A letter from EPA dated December 19, 1986 informed the sponsor that the study was acceptable.

III. Product Information

Pendimethalin, No. 454BB
Updated September 1991

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% ai), EPA Registration No. 241-243. Its chemical structure is as follows:



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

008606

IV. Data Requirements (40 CFR 158.340)

Pendimethalin, No. 454BB
Updated September 1991

Formulation (PROWL Herbicide, EPA Registration No. 241-243)	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
Technical		
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	-
81-8 Acute Neurotoxicity (Rat)	R	-
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 (Rat)	R	-
82-6 28-Day Neurotoxicity (Hen)	N	-
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

Y = Yes; N = No; R = Reserved

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

Technical (cont'd)	Required	Satisfied
85-1 General Metabolism	Y	Y
85-2 Domestic Animal Safety	N	-
85-3 Dermal Penetration	N	-
85-4 Visual System Studies	N	-

Y = Yes; N = No.

008606

V. TOXICOLOGY PROFILE

Pendimethalin, #454BB

Updated September, 1991

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

TOXCHEM NO. 4548B- N-(1-Ethylpropyl)-3 4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 09/10/91

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	CORRGRADE/ DOCUMENT#
83-1(b) Feeding-2 year Species: dog Litton Bionetics Inc. 2075- 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(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, .5, 30, 60 mg/kg		Minimum 002406
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	NOEL = 500 ppm. LEL = 5,000 ppm (decrease in hematocrit and hemoglobin in males, decreased body weight gain and food consumption, and 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
84-2(b) Mutagenic-DNA repair test Species: Pharmakon Res. Inst. Inc. PH311-AC-002-85; 10/25/85	Pendimethalin Tech. 91.2%	260403	Negative.		Acceptable 005828
84-2(b) Mutagenic-chromosome aberr. Species: Pharmakon Res. Inst. Inc. PH320-AC-001-85; 10/17/85	Pendimethalin Tech 92.9%	260403	Negative.		Acceptable 005828
84-4 Mutagenic Species: microorganisms American Cyanamid Co. 6/10/77	Prowl Tech.	230618 00067519	No mutagenicity at 1000 ug/plate (highest dose)		Acceptable 000545

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/SACB
TOX ONELINERS MEETING GUIDELINE REQUIREMENTS

TOXCHEM NO. 454BB- N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 09/10/91

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-4 Mutagenic- host med. Species: mice American Cyanamid Co. 6/10/77	Prowl Tech.	230618	No mutagenicity at l6.6 mg/mouse (highest dose)		Acceptable 000545
84-4 Mutagenic-reverse mutation Species: salmonella American Cyanamid Co. 0166; 10/28/85	Pendimethalin tech (92.2%	260403	Positive in Salmonella typhimurium; strains TA1538 and TA98, with S-9 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	Negative with S9. Inconclusive without S9.		Acceptable (w S9)
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

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/SACB
TOX ONELINERS MEETING GUIDELINE REQUIREMENTS

TOXCHEM NO. 4548B- N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 09/10/91

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
81-3 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
81-4 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
81-5 Primary dermal irritation Species: rabbit American Cyanamid Co. A-72-4; 6/1/72	Pendimethalin 93%		No irritation.	4	Minimum 000543
81-6 Dermal sensitization Species: guinea pig Bioresearch Inc. 85-4639A; 8/1/85	Pendimethalin Tech. 92.2%	260403	Nonsensitizing		Minimum 005828

Current Date 6/20/11

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Chr/onco - Rat (Carcino)	Pendimethalin	MRID # 401744-01	Strain Crl: CD(SD)BR; tested in diet at 0, 100, 500, 5000 ppm (0, 5, 25, 250 mg/kg/day).		Minimum (Chr) (Onco) ↑ Carcino.
Hazleton Lab. Am. Inc. Madison, Wi	Lot# AC 352849-1	401744-01	NOEL = 100 ppm		
HLA 6123-112	91.9% Pure		LEL = 500 ppm based on pigmentation of thyroid follicular cells in males and females		
4/20/87			at 5000 ppm - sl. decr survival and BWG in males. In females - decr food consumption; incr GGT, Chol, liver wt, icterus, dark adipose tissue, dark thyroids	liver/Body wt, ; In fem 5000 ppm	rT Thyroid wt (abs & rel), - follicular cell hyperplasia in Thyroid
		~~401744-01~~	Possible incr. Thyroid follicular cell ade. at (refer to peer rev.)		
Chr/onco - mouse	Pendimethalin	409099-01	Strain: Crl: CD-1 tested in diet at 0, 100, 500 and 5000 ppm (males = 0, 12.3, 62.3 and 622.1 mg/kg/day) (females = 0, 15.6, 78.3 and 806.9 mg/kg/day)		Minimum (Carcinogenic), Supplementary (chronic)
IRDC	Batch # AC 5313-73A		NOEL = 500 ppm		
141-028	92.6% Pure		LEL = 5000 ppm - incr. mitotic idx in females, decr. body wt in females, incr. abs. thyroid, liver and gallbladder weights and/or relative body and brain weight ratios in males and females, acanthocytosis in males		
10/5/88					

9098

Page 4 of 4

VI. DATA GAPS

Technical

83-3 - Developmental Toxicity - Rodent (upgradable)
83-4 - Reproduction (not upgradable)

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

The sponsor needs to be informed of the aforementioned data gaps on pendimethalin (technical) unless appropriate DERS are in RD files.

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.

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

According to the document "Guidance for the Reregistration of Pesticide Products Containing Pendimethalin" (EPA, 1985), the Agency will not allow any significant new uses* to be established for pendimethalin until the toxicological data gaps have been satisfied. Since publication of the Registration Standard document, the rat developmental toxicity study and the rat multigeneration reproduction study have been downgraded to Supplementary data because of several deficiencies. The rat developmental toxicity study can be upgraded with the submission of individual animal data. The multigeneration reproduction study needs to be repeated since histopathological examination was not conducted on abnormal parental lesions with emphasis on the reproductive organs. In addition, the results of the 2-year rat study indicate increases in thyroid proliferative lesions and must be examined by the Peer Review Committee for Carcinogenicity. Currently, TB-I is awaiting additional submission of data from the sponsor which was to be available the end of June.

---

*"Significant new use" is defined in 44 FR 27934, May 11, 1979. In the case of a new food or feed use, the Agency will generally consider as significant an increase in the Theoretical Maximum Residue Contribution of greater than 1 percent.

Reviewed By: William B. Greear, M.P.H. William B. Greear 3/5/91
Review Section II, Toxicology Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. [signature] 3/25/91
Review Section II, Toxicology Branch I (H7509C)

008606

DATA EVALUATION REPORT

Study Type: Guideline Series 83-5
Combined Chronic Feeding/
Carcinogenicity - Mouse

TOX Chem No.: 454BB

Test Material: AC 92,553

MRID No.: 409099-01

Synonyms: Pendimethalin

Study Number: 141-028

Sponsor: American Cyanamid

Testing Facility: IRDC
Mattawan, MI 49071

Title of Report: Chronic Dietary Toxicity and Oncogenicity Study with AC 92,553 in Mice.

Author: Dale E. Johnson

Report Issued: October 5, 1988

Conclusions:

NOEL = 500 ppm (Males: 62.3 mg/kg/day; Females: 78.3 mg/kg/day)

LEL = 5000 ppm [Males: 622.1 mg/kg/day; Females 806.9 mg/kg/day (increased mortality in females, decreased body weight in females, increased absolute thyroid, liver, and gallbladder weights and/or relative body and brain weight ratios in males and females, amyloidosis in males)].

Carcinogenicity - Negative

Classification:

Carcinogenicity (Core-Minimum)

Chronic Toxicity (Core-Supplementary) - Clinical chemistry and urinalysis were not conducted.

The study fulfills the requirement for a Guideline Series 83-2 Carcinogenicity Study. The study does not meet the requirements for a Guideline Series 83-1 Chronic Toxicity Study in Rodents.

A. Materials:

1. Test Compound - AC 92,533, Description: A rust powder; Batch No.: AC5213-72A, Purity: 92.6%.

2. Test Animals - Species: Mouse; Strain: Charles River CD-1; Age: 42 days; Weight: 18 to 29 g (M), 14 to 25 g (F); Source: Charles River Breeding Laboratories, Inc., Portage, MI.

B. Study Design:

1. Animal Assignment - Animals were assigned randomly (by computer) to the following test groups:

Test Group	Dose in Diet (ppm)	Main Study 18 Months Male	Main Study 18 Months Female	Interim Sac 12 Months Male	Interim Sac 12 Months Female
Control #1	0	55	55		
Control #2	0	55	55	10	10
Low (LDT)	100	55	55	10	10
Mid (MDT)	500	55	55	10	10
High (HDT)	5000	55	55	10	10

The mice were acclimated to laboratory conditions for a period of 14 days. During the study, the mice were individually housed in stainless steel, suspended wire mesh cages in a temperature (72 ± 1 °F), humidity (52 ± 8.5%), and light (12 hours on/12 hours off) controlled room.

2. Diet Preparation - Test diets were prepared at weekly intervals. A premix was prepared by grinding the required amount of the test material with a small amount of the basal diet (Certified Rodent Chow No. 5002). This premix was added to an additional amount of diet and mixed in order to yield the required amount of the test material in the test diets. The homogeneity of the 100 and 5000 ppm diets were analyzed by taking samples from the top, middle, and bottom of each side of the blender. A second and third set of samples were placed in glass food jars and stored under normal laboratory conditions for 7 and 14 days. These sets were analyzed for stability. The concentrations of the test material in the test diets were analyzed from all groups for each weekly preparation for the first 4 weeks. Thereafter, samples from a group selected at random each week were analyzed.

Results - By visual inspection, the 100 ppm preparations were clearly not homogenous. By chemical analysis, the

homogeneity of the 100 ppm preparations were "unacceptably" variable for the first month of study. The lowest assay value from each of the six points of sampling was 74 percent. However, the mean of the six determinations was between 93 and 100 percent. The homogeneity of the 5000 ppm diet ranged from 91 to 106 percent. The average concentrations found in the 100 and 5000 ppm test diets stored for 14 days were within 3 percent of the initial day 0 average concentrations. Average concentration found in all analyzed diets taken periodically ranged from 83 to 106 percent for the 100 ppm group, 88 to 111 percent for the 500 ppm group, and 92 to 105 percent for the 5000 ppm group target levels.

3. Animals received food and water ad libitum.

4. Statistics - One-way analysis of variance (ANOVA) and Bartlett's test for homogeneity of variance were used to analyze body weights, food consumption, hematological parameters, and absolute and relative (to body and brain) organ weights. Treatment groups were compared to both control groups or to control group 2 for 12-month hematological parameters and interim sacrifice organ weights, by sex, using the appropriate t-statistic (for equal or unequal variance). Dunnett's multiple comparison tables were used to determine the significance of the differences. All statistical tests were two-tailed with levels of significance of $p < 0.05$ and $p < 0.01$. Survival data and time to tumor data were analyzed using the computer program of Thomas, Breslow, and Gart. The program includes the following statistical procedures: Kaplan-Meier and standards method for survival curves, Cox's test for linear trend in proportions, and both Cox's test and Gehan-Breslow's generalized Kruskal-Wallis test for comparing survival distributions. The incidence of microscopic lesions was compared using the chi-square test criterion with Yates' correction for 2 x 2 contingency tables.

5. Quality assurance inspections were conducted throughout the study. The Quality Assurance Statement was signed by Margery J. Wirth on September 28, 1988.

C. Methods and Results:

1. Observations - Animals were inspected at least twice daily for signs of toxicity and mortality.

   Results - The incidences of death and moribund sacrifice are provided in Table 1 below.

Table 1. Mortality

Group (ppm)	N	Week 1-13	14-26	27-39	40-52	53-65	66-79	0-79
Male								
Control 1 (0)	55				2	3	8	13 (24%)
Control 2 (0)	65		2	1		1	4	8 (12%)
Low (100)	65			1	1	4	8	14 (22%)
Mid (500)	65	1		1	2		6	10 (15%)
High (5000)	65	2				4	13	19 (29%)
Female								
Control 1 (0)	55					2	4	6 (11%)
Control 2 (0)	65					1	10	11 (17%)
Low (100)	65			2	2	3	7	14 (22%)
Mid (500)	65			3	2	5	6	16 (25%)
High (5000)	65		1	1	2	5	13	22 (34%)

Mortality was increased ir the 5000 ppm female group when compared to controls (Statistical analysis was not provided). From initiation of treatment, 100 percent of the males and females in the 500 and 5000 ppm groups exhibited dark yellow and dark orange urine. Yellow discoloration of the hair was also observed in a majority of the animals in the 5000 ppm group during Weeks 15 to 78. Yellow staining of the ventral/anogenital area was noted in several males in the 5000 ppm group during Weeks 5 to 26.

2. Body Weight - Individual body weights were recorded initially, weekly for the first 14 weeks, biweekly until week 26, and monthly thereafter.

   Results - Body weights were slightly decreased (but statistically significant, 6-10%) in females in the 5000 ppm group at several intervals when compared to females in the control group (see Table 2 below). These may not be biologically significant since they are based on means of only 1 to 2 grams difference.

3. Food Consumption and Compound Intake - Consumption was determined weekly for the first 14 weeks, biweekly until week 26, and monthly thereafter, and mean daily diet consumption was calculated.

   Results - Very slight (< 10%) differences in food consumption occurred in the treatment groups when compared to controls and are not considered to be biologically significant. Mean compound intake for males in the 100, 500, and 5000 ppm groups was 12.3, 62.3, and

622.1 mg/kg bwt/day, respectively. Mean compound intake was 15.6, 78.3, and 806.9 mg/kg bwt/day for females in the 100, 500, and 5000 ppm groups, repectively.

Table 2. Body Weight (g)

Group (ppm)		Week 1	6	13	26	38	52	78
Male								
Control	1 (0)	27	32	35	37	39	40	39
Control	2 (0)	27	32	35	38	40	41	40
Low	(100)	27	33	35	39	40	41	40
Mid	(500)	26	32	35	37	39	40	38[3]
High	(5000)	27	32	35	37	38	40	40
Female								
Control	1 (0)	22	27	29	32	34	34	36
Control	2 (0)	21	27	29	32	34	34	35
Low	(100)	22	27	29	31	34	34	34
Mid	(500)	21	26	29	31	32	34	36
High	(5000)	21	26	28	30[1,3]	31[2,3]	33[1,4]	34

[1]Significantly different from Control Group 1 at $p < 0.05$.
[2]Significantly different from Control Group 1 at $p < 0.01$.
[3]Significantly different from Control Group 2 at $p < 0.05$.
[4]Significantly different from Control Group 2 at $p < 0.01$.

4. Ophthalmological Examinations - All animals were examined at 12, and 18 months.

Results - Unremarkable.

5. Blood was collected from 10 animals/sex in the control 2, 100, 500, and 5000 ppm groups at 12 months and on 10 animals/sex from all groups at 18 months for hematology analysis. The CHECKED (X) parameters were examined.

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*

X Total plasma protein (TP)
X Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB conc. (MCHC)
X Mean corpuscular volume (MCV)
X Reticulocytes (if signs of anemia are present)

Results - Unremarkable.

Note: Clinical chemistries were not conducted.

6. Sacrifice and Pathology - All animals that died, the 10 animals/sex in the control 2, 100, 500, and 5000 ppm groups sacrificed at 12 months, and all surviving animals at terminal sacrifice were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
X	Tongue	X	Aorta*	XX	Brain*
X	Salivary glands*	XX	Heart*	X	Periph. nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	XX	Spleen*	X	Eyes (optic n.)*
X	Jejunum*	X	Thymus*		Glandular
X	Ileum*		Urogenital	XX	Adrenals*
X	Cecum*	XX	Kidneys*		Lacrimal gland
X	Colon*	X	Urinary bladder*	X	Mammary gland*
	Rectum*	XX	Testes*	X	Parathyroids*
XX	Liver*		Epididymides	XX	Thyroids*
X	Gallbladder*	X	Prostate		Other
X	Pancreas*	X	Seminal vesicle	X	Bone*
	Respiratory	XX	Ovaries	X	Skeletal muscle*
X	Trachea*	X	Uterus*	X	Skin
XX	Lung*	X	Vagina	X	All gross lesions and masses

a. Organ Weight - At the 12-month sacrifice, males in the 5000 ppm group had statistically significant increases in the liver/gallbladder weight (30%) and relative body (28%) and brain weight ratios (29%) (see Table 4 below). Females in the 5000 ppm group exhibited a significant increase in the relative liver/gallbladder body weight ratio (17%) and slight (not statistically significant) increases in the absolute liver/gallbladder weight (11%) and relative brain weight ratio (10%). At terminal sacrifice, males and females in the 5000 ppm group exhibited statistically significant increases in the liver/gallbladder weight (M = 15 to 21%, F = 17 to 18%) [see Table 5]. In addition, the liver/ gallbladder body weight ratio was significantly increased (M = 15 to 21%, F = 19 to 22%) in the 5000 ppm group. The liver/gallbladder brain weight ratio was also significantly increased (M = 15 to 22%, F = 15 to 19%) in the 5000 ppm group. Males in the 500 ppm group had a significant increase (10%) in the liver/gallbladder body weight ratio. Males in the 100 ppm group exhibited significant increases of 18, 18, and 21 percent for the liver/gallbladder weight, body weight ratio, and brain weight ratio, respectively. The thyroid weight was significantly

increased (33%) in females in the 5000 ppm group. In addition, the thyroid body weight ratio was significantly increased (M = 15%, F = 24%) in the 5000 ppm group. The thyroid brain weight ratio was also significantly increased (M = 16%, F = 18 to 19%) in the 5000 ppm group. The thyroid body weight ratio was significantly increased (14%) in males in the 500 ppm group. The pituitary weight was significantly (statistical) increased in males in the 500 and 5000 ppm groups; however, mean weights were identical to controls. The pituitary body weight ratio was significantly increased (M = 26%, F = 17%) in the 5000 ppm group and in females in the 500 ppm group (27%). The pituitary brain weight ratio was significantly increased by 27 and 28 percent in males in the 500 and 5000 ppm groups, respectively.

b. Gross Pathology - Unremarkable for deaths and animals sacrificed up to 12 months. There was a slight increase in mildly congested thyroids in males in the 5000 ppm group during the interval 12-month to terminal sacrifice. The incidence was 3/36 (8.3%) when compared to zero incidence in all other male groups. One female in the 5000 ppm group had a mildly congested thyroid and one had an enlarged thyroid. Two females in the 500 ppm group had enlarged thyroids (one mild, one moderate). No other macroscopic changes in the thyroid of any other female group were noted.

Table 4. Organ Weight; Body and Brain Weight Ratios: 12-Month Sacrifice

	Group (ppm)							
	Males				Females			
Parameter	0	100	500	5000	0	100	500	5000
Liver (g)*	2.10	2.01	2.22	2.71[1]	1.96	1.77	1.82	2.18
Liver/Body Weight (% x 10)	5.23	5.18	5.41	6.71[1]	5.91	5.30	5.60	6.93[1]
Liver/Brain (%)	4.07	4.07	4.28	5.25[1]	3.85	3.56	3.55	4.25

*Includes gallbladder.
[1]Significantly different at $p < 0.01$.

Table 5. Organ Weight; Body and Brain Weight Ratios: Terminal Sacrifice

Parameter	Group (ppm) Males 0 (Control 1) 0 (Control 2)	100	500	5000	Females 0 (Control 1) 0 (Control 2)	100	500	5000
Liver (g)*	2.40 (2.29)	2.71[3]	2.40	2.77[2,4]	2.12 (2.15)	2.14	2.30	2.51[2,3]
Liver/Body Weight (% x 10)	6.15 (5.70)	6.75[3]	6.29[3]	6.92[2,4]	5.97 (6.10)	6.23	6.47	7.28[2,4]
Liver/Brain Weight (% x 10^{-2})	4.58 (4.30)	5.21[3]	4.60	5.26[1,4]	3.92 (4.03)	4.14	4.24	4.62[2,3]
Pituitary (mg)	3 (3)[1]	3	3[1]	3[2]	4 (4)	4	4	4
Pituitary/ Body Weight (% x 10^{3})	6.43 (7.91)	7.47	8.38[2]	8.13[1]	11.4 (11.5)	13.1	11.5	13.3[1]
Pituitary/ Brain (% x 10)	4.75 (5.86)[1]	5.77	6.05[1]	6.10[2]	7.48 (7.59)	8.63	7.37	8.26
Thyroid* (mg)	6 (6)	6	7	7	6 (6)	6	7	8[2,4]
Thyroid/Body Weight (% x 10^{3})	16.4 (15.5)	15.2	17.7[3]	17.8[3]	18.1 (18.0)	19.0	19.7	22.4[2,4]
Thyroid/ Brain (% x 10)	12.1 (11.6)	11.5	12.8	13.4[3]	11.9 (11.8)	12.5	12.7	14.1[2,4]

*Includes gallbladder.
[1]Significantly different from control group 1 at $p < 0.05$.
[2]Significantly different from control group 1 at $p < 0.01$.
[3]Significantly different from control group 2 at $p < 0.05$.
[4]Significantly different from control group 2 at $p < 0.01$.

c. Microscopic Pathology

1) Non-neoplastic - Two males exhibited hepatocellular hypertrophy in the 5000 ppm group (incidence: 2/12 (17%) in the time interval 0 to 12 months. Corresponding liver lesions were not observed in any of the male groups during the 12- to 18-month period. [The author indicated that this may explain the elevated liver weights.] When considering all deaths and animals sacrificed on schedule, there was an increased incidence of amyloidosis in several tissues (i.e., gastrointestinal tract, heart, kidney, liver, lung, parathyroid, thyroid, etc.) in males in the 5000 ppm group (see Table 6 below). [The incidence of amyloidosis in males was 21.8, 29.0, 29.0, and 40.0%, respectively, in the control No. 2, 100, 500 and 5000 ppm groups. The incidence of amyloidosis in females was 18.2, 27.3, 38.2 and 20.0%, respectively, in the control No. 2, 100, 500 and 5000 ppm groups.]

Table 6. Incidence (%) of Amyloidosis in Males (0 to 78 Weeks)

	Group (ppm)				
	0[1]	0[2]	100	500	5000
Adrenal	3/13 (23)	7/61 (11)	11/63 (17)	15/64 (23)	20/64 (31)
Cecum	1/13 (8)	2/65 (3.0)	3/65 (5.0)	1/65 (2.0)	9/65 (14)
Colon	1/13 (8)	0/65 (0)	2/65 (3.0)	1/65 (2.0)	10/65 (15)
Duodenum	2/13 (15)	4/65 (6.0)	8/65 (12)	10/65 (15)	15/65 (23)
Heart	3/13 (23)	5/65 (7.7)	12/65 (18)	15/65 (23)	21/65 (32)
Jejunum	2/13 (15)	7/65 (11)	10/65 (15)	11/65 (17)	17/65 (26)
Kidney	3/13 (23)	6/65 (9.2)	13/65 (20)	15/65 (23)	20/65 (31)
Liver	3/13 (23)	2/65 (3.1)	7/65 (11)	7/65 (11)	14/65 (22)
Lung	3/13 (23)	2/65 (3.1)	7/65 (11)	10/65 (15)	13/65 (20)
Lymph Node, Mesenteric	2/12 (17)	10/64 (16)	6/62 (10)	8/62 (13)	16/61 (26)
Parathyroid	0/11 (0)	0/47 (0)	4/46 (8.7)	5/52 (9.6)	6/47 (13)
Thyroid	3/13 (23)	4/65 (6.2)	11/64 (17)	13/65 (20)	19/64 (30)
Tongue	3/13 (23)	4/65 (6.2)	8/65 (12)	12/65 (18)	14/65 (22)

2) Neoplastic - Unremarkable.

D. Discussion:

Female mortality was increased in the 5000 ppm group. From initiation of treatment to termination, 100 percent of the males and females in the 500 and 5000 ppm groups had dark yellow/orange urine. Yellow discoloration of the hair was observed in a majority of animals in the 5000 ppm group. Males in the 5000 ppm group also exhibited yellow staining of the ventral/anogenital area during Weeks 5 to 26. This discoloration can probably be attributed to carry through of the color in the urine and/or direct contact with the test material in the diet. Body weight was slightly (6 to 10%) decreased in females in the 5000 ppm group at several intervals when compared to controls. Males, and to a lesser part females, in the 5000 ppm group at the 12-month sacrifice displayed a statistically significant increase in the absolute liver/gallbladder weight and/or relative body or brain weight ratio. At termination, males and females in the 5000 ppm group exhibited statistically significant increases in the absolute liver/gallbladder weight and relative body and brain weight ratios. Although slight but statistically significant increases were observed in the absolute liver/gallbladder weight and/or relative body and/or brain weight ratios in males in the 500 and 100 ppm group, the increases were not considered to be significant. A few males in the 5000 ppm group exhibited hypertrophy of the liver at the 12-month sacrifice. No hypertrophy of the liver was observed at terminal sacrifice; therefore, the finding is of questionable biological relevance. [It is noted that in a 3-month rat study (#AX-AC-1) liver weights were elevated and hypertrophy of the liver was noted. In addition, in a 2-year dog study (#20755), liver weight was elevated, alkaline phosphatase was increased and liver lesions were noted. The liver is apparently being affected by administration of the test material. Because liver weight increases associated with microscopic changes have occurred in rodent as well as in nonrodent studies, the increased weight changes are considered to be biologically significant and of toxicological portent.] Pituitary organ to body and brain weight ratios were quite variable. Without any significant microscopic lesion of the pituitary, very little significance can be accorded the variable increases in organ (pituitary) and organ weight ratios in males in the 500 and 5000 ppm groups. The absolute thyroid weight and body and brain weight ratios were significantly (statistically) increased in females in the 5000 ppm group and the relative thyroid body and brain weight ratios were increased (statistically significant) in males in the 5000 ppm group at terminal sacrifice; however, no microscopic lesions attributable to administration of the test material were evident. Because thyroid lesions (pigmentation of the follicular cells, discolored colloid and follicular cell adenomas) have been observed in a second rodent species, the rat, the increased

absolute and relative thyroid weights are considered to be compound-related. One microscopic lesion, amyloidosis, appeared to be significantly increased in several organs/tissues of males in the 5000 ppm group. This is a frequent, spontaneous lesion in aged mice. Nevertheless, it is apparent that administration of the test material at 5000 ppm to males significantly increased the incidence and severity of amyloidosis in several organs/tissues. This may have occurred by accelerating the aging process by inducing stress at the 5000 ppm dose level. There were no increases in the incidence of neoplastic lesions that could be related to administration of the test material.

[The MTD in females was achieved as indicated by the increase in mortality and decreased body weight (6-10%). It did not appear that an MTD was reached in males. However, the high dose in the males (5000 ppm) is near the limit dose (7000 ppm); therefore, the study does not have to be repeated.]

Comments:

Clinical chemistry and urinalyses should have been conducted in order to further elucidate changes which may have been occurring in the liver. This is a deficiency in the study.

8606

64751:I:WP5.0:Greear:C.Disk:KEVRIC:01/25/91:tlc:WO:EK:CL:WO:DD
R:62842:WP5.0:Greear:C.Disk:KEVRIC:03/04/91:aw:wo:DD:aw

Reviewed By: William B. Greear, M.P.H. William B. Greear 4/5/91
Review Section II, Toxicology Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. Marion Copley 8/24/91
Review Section II, Toxicology Branch I (H7509C)

008606

DATA EVALUATION REPORT

Study Type: Guidelines Series 83-5 - Combined Chronic Feeding/ Oncogenicity - Rat

TOX Chem No.: 454BB

Accession No.: N/A

MRID No.: 401 744-01

Test Material: Pendimethalin

Synonyms: Prowl, AC 92,553, Herbadox, Penoxalin, N-(1-Ethyl-propyl)-3,4-dimethyl-2,6-dinitrobenzeneamine, N-(1-Ethyl-propyl)-2,6-dinitro-3,4-xylidine [CAS No. 40487-42-1]

Study No.: HLA Study No. 6123-112

Sponsor: American Cyanamid Company

Testing Facility: Hazleton Laboratories America, Inc.
Madison, WI 53704

Title of Report: Chronic Dietary Toxicity and Oncogenicity Study in Rats Fed with AC 92,553.

Author: Robert H. Weltman

Report Issued: April 20, 1987

Conclusions:

NOEL = 100 ppm (≈5 mg/kg/day)
LEL = 500 ppm (≈25 mg/kg/day) (based on pigmentation of thyroid follicular cells in males and females)

In addition, at 5000 ppm, survival in males was slightly decreased and body weight gain was decreased. There was decreased food consumption, increased gamma glutamyl transferase and cholesterol, increase in liver weight and/or liver body and brain weight ratios, increase in right thyroid weight and/or thyroid body and/or brain weight ratios, generalized icterus, dark adipose tissue in females, diffusely dark thyroids, and follicular cell hyperplasia of the thyroid.

Note: The sponsor should address the apparent discrepancy in survival data. The sponsor should also submit the time weighted mean consumption values of the test material for each dose level and sex.

Carcinogenicity potentially positive for thyroid follicular cell adenomas pending further analysis of data by HED's Peer Review Committee.

Classification

Core-Minimum. This study satisfies the requirements for a Guideline Series 83-1 (Chronic Feeding) and 83-2 (Carcinogenicity) studies.

Justification of Classification

The study is classified Core-Minimum because the time weighted mean values of the test material was not reported for each dose level and sex.

Attachment

A. Materials:

1. Test Compound - AC 92,553; Description: brownish-orange, crystalline solid; Lot No.: AC 3528-129-1; Purity: 91.9%; Contaminants: Not reported.

2. Test Animals - Species: Rat; Strain: Crl:CD(SD)BR; Age: Weanlings; Mean Group Weight: Males (149.2-151.4 g), females (127.8-129.8 g); Source: Kingston Facility of Charles River Laboratories, Wilmington, MA.

B. Study Design:

1. Animal Assignment - The animals were randomly assigned to the following groups:

Test Group	Dose in Diet (ppm)	Main Study 24 Months		Interim Sacrifice 12 Months	
		Male	Female	Male	Female
Control	0	55	55	10	10
Low	100	55	55	10	10
Mid	500	55	55	10	10
High	5000	55	55	10	10

The animals were housed singly in one room in suspended stainless steel, screen-bottom cages placed on racks with absorbent pan liners. Pan liners were changed twice weekly, and the cages and racks were cleaned every 2 weeks. The rats were maintained in an environment with a room temperature of 70 ± 3 °F, relative humidity of 50 ± 20 percent and a light/dark cycle of 12 hours. The air was changed 10 times per hour.

2. Diet Preparation - Diets were prepared independently at weekly intervals. The test substance was mixed with a small amount of the basal diet (Purina Rodent Chow #5002), and then more of the basal diet was added to form a premix. The premix was then mixed with the appropriate amount of the basal diet to obtain the desired dietary concentrations. The test diets were stored in polycarbonate cages at refrigerated temperature. Three sets of six randomly selected samples of each test diet were taken. One set was assayed for homogeneity, two sets were placed in the animal room, and one set was analyzed after 7 days and the second set was analyzed after 14 days for stability testing.

Results - At 100 and 5000 ppm, the percent of the nominal concentration found at six sampling sites ranged from 90.7 to 102.6 percent. The concentration of the test material in the diets after 14 weeks ranged from 94.7 to 124.5 percent of the nominal concentration.

3. Animals received food and water ad libitum.

4. Statistics - For homogeneous data, one-way analysis of variance (ANOVA) was used to statistically analyze body weight, body weight gain, food consumption, clinical chemistry, hematology, urine pH, volume and specific gravity, organ weight, organ-to-body weight ratio, and organ to brain weight ratio. If ANOVA was significant, Dunnett's t-test was used for pairwise comparison between groups. For heterogeneous data, the Kruskal-Wallis H-test ANOVA was used for analysis. If significant, the Nemenyi-Kruskal-Wallis test for multiple comparison or the Wilcoxon-Mann-Whitney two-sample rank test was used in the analysis. Trend analysis was also used.

5. Quality assurance inspections were conducted throughout the study. The Quality Assurance Statement was signed by a person (name is illegible) for S. Kramlich on February 19, 1987.

C. Methods and Results:

1. Observations - The animals were observed twice daily for clinical signs of toxicity and death. At least once a week the animals were removed from their cages and were carefully examined for abnormalities. The animals were also palpated at this time.

Results - The sponsor provided a table on the "adjusted percent survival at 104 weeks" (see Table 1 below).

Table 1. Adjusted Percent Survival at 104 Weeks

AC 92,553 (ppm)			
0	100	500	5000
	Males		
36	38	42	29
	Females		
42	53	46	56

Table 2 below provides survival data at 104 weeks which was compiled from the pathology tables 20, 21, and 22 which listed animals as being a) interim sacrificed; b) moribund/death sacrifice; and c) terminal sacrifice.

Table 2. Survival at 104 Weeks (Number Alive/N) N = 55[1]

0	100	500	5000
Males			
19/55 (34.5%)	21/55 (38.2%)	22/55 (40.0%)	15/55 (27.3%)
Females			
23/55 (41.8%)	28/55 (50.9%)	24/55 (43.6%)	31/55 (56.4%)

[1] N = 55 animals remaining after interim sacrifice.

Survival of males in the 5000 ppm group was slightly reduced when compared to the control and the remaining treated groups. There are discrepancies between the sponsor's "Adjusted Percent Survival" table and the pathology tables 20, 21, and 22. The differences are not more than one animal/group; however, the differences require explanation. The term "adjusted" should be defined by the sponsor. Males in the 5000 ppm group were pale, sensitive to the touch, wheezed, and were urine-stained. Females in the 5000 ppm group were thin.

2. Body Weight - Recorded initially, weekly through week 14, once every 2 weeks for the next 26 weeks, and every 4 weeks thereafter.

Results - Males in the 5000 ppm group exhibited statistically significant decreases in body weight when compared to controls on Weeks 1 to 104. Females in the 5000 ppm group had statistically significant decreases in body weight when compared to controls on Weeks 1 to 100. Decreases in mean cumulative body weight gain of males and females in the 5000 ppm group were observed throughout the test period when compared to controls. Mean cumulative body weight gain was decreased in males and females by 10.7 and 25.4 percent, respectively, at 13 weeks when compared to controls. At termination, mean cumulative body weight was decreased by 29.7 and 15.8 percent, respectively, in males and females when compared to controls. Mean cumulative body weight gain in females in the 500 ppm group was decreased by approximately 3, 8, 9, and 10 percent at 13, 26, 52, and 80 weeks, respectively (see Table 3 below), when compared to control.

Table 3. Mean Cumulative Body Weight Gain (g) and (Percent Loss) Relative to Controls

Group (ppm)	Interval (Week) 0 - 6	0 - 13	0 - 26	0 - 52	0 - 80	0 - 104
Male						
Control (0)	260.8	376.7	465.4	591.7	590.3	531.8
Low (100)	257.1 (-1.4)	375.5 (-0.3)	475.3 (9.9)	608.1 (2.8)	649.2 (10.0)	607.7 (14.3)
Mid (500)	264.2 (1.3)	382.5 (1.5)	476.5 (11.1)	614.0 (3.8)	639.0 (8.3)	565.1 (6.3)
High (5000)	229.5 (-12.0)	336.3 (-10.7)	421.2 (-9.5)	535.7 (-9.5)	524.6 (-11.1)	374.1 (-29.7)
Female						
Control (0)	116.2	170.2	220.7	324.9	395.4	330.1
Low (100)	120.3 (3.5)	171.3 (0.3)	218.2 (-1.1)	320.0 (-1.5)	380.7 (-3.7)	376.3 (14.0)
Mid (500)	117.6 (1.2)	164.9 (-3.1)	202.4 (-8.3)	295.9 (-8.9)	357.9 (-9.5)	363.5 (10.1)
High (5000)	91.6 (-21.0)	126.9 (-25.4)	153.1 (-30.6)	209.1 (-35.6)	253.3 (-35.9)	278 (-15.8)

3. Food Consumption and Compound Intake - Recorded initially, weekly through week 14, once every 2 weeks for the next 26 weeks, and every 4 weeks thereafter.

Results - Food consumption was significantly decreased in males (approximately 9%) and females (approximately 12%) in the 5000 ppm group at several time intervals when compared to controls (see Table 4 below). Data were not submitted on mean compound intake.

Table 4. Mean Food Consumption (g/animal/week) and Percent Loss Relative to Controls

Group (ppm)	Week 1	6	13	26	52	80	104
Males							
Control (0)	177.0	203.9	196.5	184.6	193.4	187.1	183.1
Low (100)	177.9 (0.5)	206.1 (1.0)	195.1 (-0.7)	191.9 (4.0)	197.6 (2.2)	199.3 (6.5)	185.5 (1.3)
Mid (500)	177.6 (0.3)	205.9 (1.0)	197.7 (-0.6)	188.4 (2.0)	196.8 (1.8)	199.9 (6.5)	186.5 (1.9)
High (5000)	177.7 (0.4)	194.9* (-4.4)	178.2* (-9.3)	190.8. (3.4)	187.3 (-3.2)	172.0 (-8.1)	133.3* (-28.3)
Control (0)	135.4	144.6	135.5	136.4	147.1	158.7	131.4
Low (100)	142.2* (5.0)	151.3 (4.6)	135.2 (-0.2)	138.3 (1.4)	147.5 (0.3)	150.9 (-4.9)	148.1 (12.7)
Mid (500)	133.0 (-1.7)	148.8 (2.9)	131.0 (-3.3)	128.9 (-5.5)	143.1 (-2.8)	149.7 (-5.7)	141.1 (7.4)
High (5000)	140.3 (3.6)	137.1 (-5.1)	118.7* (-12.4)	121.4* (-11.0)	129.1 (-12.2)	138.2* (-12.9)	134.6 (2.2)

*Statistically significant at $p \leq 0.05$.

4. Ophthalmalogical examinations were not conducted.

5. Blood was collected at 3, 6, 12, 18, and 24 months from 10 randomly selected rats/sex/group via the orbital sinus. Blood was taken from the same animals that were used for sacrifice and necropsy. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)		Total plasma protein (TP)
X	Hemoglobin (HGB)	X	Leukocyte differential count
X	Leukocyte count (WBC)		Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)		Mean corpuscular HGB conc. (MCHC)
X	Platelet count		Mean corpuscular volume (MCV)
X	Reticulocyte count		

Results - At 3 months, there were statistically significant increases in platelet count in males at 5000 ppm and in eosinophils in males at 500 and 5000 ppm. At 12 months, males in the 100 and 5000 ppm groups exhibited statistically significant decreases in HCT, HGB, and RBC. Females in the 500 and 5000 ppm groups exhibited statistically significant decreases in HGB. At 24 months, males in the 500 and 5000 ppm groups exhibited a statistically significant decrease in HCT. HGB was also significantly decreased in males in the 5000 ppm group. The differences listed above were sporadic, did not appear to be dose-related, and were not of significant magnitude to be of biological importance.

b. Clinical Chemistry

X	Electrolytes	X	Other
X	Calcium	X	Albumin (A)
	Chloride		Blood creatinine
	Magnesium	X	Blood urea nitrogen
	Phosphorus	X	Cholesterol
X	Potassium	X	Globulins (G)
	Sodium	X	Glucose
	Enzymes	X	A/G ratio
X	Alkaline phosphatase	X	Total bilirubin
	Cholinesterase		Direct bilirubin
	Creatinine phosphokinase	X	Triglycerides
X	Lactic acid dehydrogenase	X	Total protein
X	Serum alanine aminotransferase (SGPT)		
X	Serum aspartase aminotransferase (SGOT)		
X	Gamma glutamyl transpeptidase (GGT)		

Results - At 3 months, males and females exhibited statistically significant increases in GGT and cholesterol. In addition, males in the 5000 ppm group had significant increases in total protein, albumin, and calcium. At 6 months, males and females had significant increases in GGT and cholesterol. At 12 months, there were significant increases in cholesterol in males and females in the 5000 ppm group. Females also exhibited significant increases in GGT and total protein. GGT was elevated in males in the 5000 ppm group; however, it was not statistically significant. At 18 months, males in the 500 and 5000 ppm group had significant increases in alkaline phosphatase. Females in the 5000 ppm group had significant increases in total protein and albumin. There was also a non-significant increase in GGT. At 24 months, males and females in the 5000 ppm group had an increase (not significant) in GGT. Increases in GGT and cholesterol in males and females are the only parameters considered to be of biological significance (see Table 5 below).

Table 5. Clinical Chemistry Values

Group (ppm)	Cholesterol (mg/dL)					GGT (IU/L)				
Month	3	6	12	18	24	3	6	12	18	24
Males										
Control (0)	52	70	88	113	148	1.0	2.9	1.8	4.4	2.5
Low (100)	52	69	109	105	123	1.3	3.3	1.4	1.4	1.6
Mid (500)	56	66	90	146	95	1.6	2.8	1.1	2.5	1.4
High (5000)	86*	109*	118*	144	134	2.4*	4.0*	2.4	4.8	4.2
Females										
Control (0)	68	74	88	100	87	1.1	2.7	1.6	1.5	1.7
Low (100)	68	87	84	92*	80	1.7	2.5	1.7	1.5	2.1
Mid (500)	71	75	88	85	82	1.8	2.8	1.5	1.3	1.7
High (5000)	87*	105*	121*	109	100	4.1*	4.8*	2.9	2.9	3.3

*Statistically significant at $p < 0.05$.

6. Urinalysis - Urine was collected from 10 randomly selected rats/sex/group at 3, 6, 12, 18, and 24 months. The CHECKED (X) parameters were examined.

X		X	
X	Appearance	X	Glucose
	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood
X	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen

Results - Males and females in the 5000 ppm group had urine that was primarily amber at all sampling times, whereas animals in the lower dose groups had urine that was straw or yellow in color.

7. Sacrifice and Pathology - All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed in animals at the 12- and 24-month sacrifices.

X	Digestive
X	Tongue
X	Salivary glands*
X	Esophagus*
X	Stomach*
X	Duodenum*
X	Jejunum*
X	Ileum*
X	Cecum*
X	Colon*
X	Rectum*
XX	Liver*
	Gallbladder*
X	Pancreas*
	Respiratory
X	Trachea*
XX	Lung*

X	Cardiovasc./Hemat.
X	Aorta*
XX	Heart*
X	Bone marrow*
X	Lymph nodes*
XX	Spleen*
XX	Thymus*
	Urogenital
XX	Kidneys*
X	Urinary bladder*
XX	Testes*
	Epididymides
X	Prostate
X	Seminal vesicle
XX	Ovaries
X	Uterus*
X	Vagina

X	Neurologic
XX	Brain*
X	Periph. nerve*
X	Spinal cord (3 levels)*
XX	Pituitary*
X	Eyes (optic n.)*
	Glandular
XX	Adrenals*
	Lacrimal gland
X	Mammary gland*
X	Parathyroids*
XX	Thyroids
	Other
X	Bone*
X	Skeletal muscle*
X	Skin
X	All gross lesions and masses

a. Organ Weight - At the 12-month and terminal sacrifices there were several statistically significant increases in organ weight or relative organ to body weight or organ to brain weight ratios (see Table 6). One finding of significance was the liver weight change. At the 12-month sacrifice, the liver/body weight ratio was increased (36%) in males in the 5000 ppm group.

The liver body weight and brain weight ratios were significantly increased by 15 and 28 percent, respectively, in females in the 5000 ppm group. A second finding of significance was increases in thyroid weight and thyroid body and brain weight ratios at 12 months. Males in the 5000 ppm group exhibited statistically significant increases of 50, 62, and 48 percent, respectively, in the right thyroid weight and right thyroid body weight and brain weight ratios. Females in the 5000 ppm group exhibited significant increases of 6 and 42 percent, respectively, in the right thyroid weight and thyroid body weight ratio. Males in the 5000 ppm group also had a significant increase (35%) in the left thyroid body weight ratio. Thyroid weight and thyroid body and brain weight ratios were not significantly increased in animals in the test groups at terminal sacrifice.

Table 6. Organ Weights and Organ Weight Ratios

	Males (ppm)				Females (ppm)			
Parameter	0	100	500	5000	0	100	500	5000
12-Month Sacrifice								
Liver Weight (g)	18.6	20.2	22.3	22.9[1]	10.8	10.4	10.8	11.0[1]
Liver/Body Weight (% x 100)	2.61	2.65	2.85	3.54[1]	2.45	2.37	2.58	3.36[1]
Liver/Brain Weight (%)	8.46	9.45	10.0	10.5	5.47	5.27	5.51	5.65
Rt. Thyroid Weight (g)	.018	.020	.020	.027[1]	.016	.014	.016	.017[1]
Rt. Thyroid/Body Weight (% x 100)	.0026	.0027	.0025	.0042[1]	.0036	.0032	.0037	.0051[1]
Rt. Thyroid/Brain Weight (%)	.0085	.0095	.0089	.0126[1]	.0081	.0071	.0079	.0087
L. Thyroid Weight (g)	.018	.018	.019	.023[1]	.026	.015	.013	.013
L. Thyroid/Body Weight (% x 100)	.0026	.0024	.0024	.0035[1]	.0059	.0033	.0031	.0041
L. Thyroid/Brain Weight (%)	.0083	.0084	.0085	.0106	.0129	.0074	.0066	.0069
Terminal Sacrifice								
Liver Weight (g)	18.8	17.2	19.5	19.0[1]	11.7	12.1	12.0	13.9[1]
Liver/Body Weight (% x 100)	3.05	2.40	2.76	3.78[1]	3.27	2.36	2.52	3.77[1]
Liver/Brain Weight (%)	8.64	7.79	8.88	8.81	5.58	6.18	6.12	7.16[1]

[1] Statistically significant at $p < 0.05$.

b. Gross Pathology - At 12 months, there was an increase in the incidence of accentuated liver lobular pattern in males in the 500 and 5000 ppm group and diffusely dark adipose tissue of males and females in the 5000 ppm group. In animals that died or were sacrificed moribund prior to termination, there was an increase in the incidence of light focal areas of the lung in females in the 5000 ppm group and diffusely dark thyroids of males and females in the 5000 ppm group. At terminal sacrifice, there was an increase in diffusely dark thyroids in males and females in the 5000 ppm group and generalized icterus in males and females in the 5000 ppm group (see Table 7 below).

Table 7. Gross Pathology and Percent Incidence (%)

	Males (ppm)				Females (ppm)			
Lesion	0	100	500	5000	0	100	500	5000
Interim Sacrifice								
Liver-accentuated lobular structure	3/10 (30)	3/10 (30)	6/10 (60)	8/10 (80)	2/10 (20)	1/10 (10)	0/10	0/10
Adipose tissue-dark	0/10	0/10	0/10	2/10 (20)	0/10	0/10	0/10	6/10 (60)
Thyroid diffusely dark	0/10	0/10	0/10	10/10 (100)	0/10	0/10	0/10	10/10 (100)
Died/Moribund Sacrifice								
Lung-light focal areas	0/36	0/34	0/40	0/37	0/32	0/27	1/32 (3.2)	6/24 (25)
Thyroid-diffusely dark	0/36	1/34 (3.0)	1/33 (3.0)	24/40 (60)	0/32	0/27	1/31 (3.2)	16/24 (67)
Terminal Sacrifice								
Thyroid-diffusely dark	0/19	0/21	1/22 (45)	14/15 (93)	0/23	0/28	0/24	31/31 (100)
Generalized icterus	0/19	0/21	0/22	1/15 (6.7)	0/23	0/28	0/24	11/31 (35)

c. Microscopic Pathology

1) Non-neoplastic - At the 12-month interim sacrifice, in those animals dying or sacrificed moribund and at terminal sacrifice, there was an increase in pigmentation of the follicle cells

accompanied by varying degrees of colloid depletion and discolored colloid in the thyroids of males and females in the 500 and 5000 ppm groups (see Table 8 below). The overall incidence of thyroid follicular cell hyperplasia was increased in males and females in the 5000 ppm group.

Table 8. Non-neoplastic Microscopic Pathology and Percent Incidence (%)

Lesion	Males (ppm)				Females (ppm)			
	0	100	500	5000	0	100	500	5000
Interim Sacrifice								
Thyroid-pigmentation of follicle cells	0/10	0/10	0/10	10/10 (100)	0/10	0/10	0/10	10/10 (100)
Thyroid-discolored colloid	0/10	0/10	0/10	9/10 (90)	0/10	0/10	0/10	10/10 (100)
Thyroid-follicular cell hyperplasia	0/10	0/10	0/10	1/10 (10)	0/10	0/10	0/10	0/10.
Deaths and Unscheduled Sacrifices								
Thyroid-pigmentation of follicle cells	0/36	0/34	2/33 (6.1)	35/40 (88)	0/32	0/37	1/31 (3.0)	22/24 (92)
Thyroid-discolored colloid	0/36	0/34	0/33	29/40 (73)	0/32	0/37	0/31	15/24 (63)
Thyroid follicular cell hyperplasia	3/36 (8.3)	3/34 (8.8)	0/33	4/40 (10)	8/32 (25)	9/37 (24)	8/31 (26)	5/24 (21)
Terminal Sacrifice								
Thyroid-pigmentation of follicle cells	0/19	0/21	1/22 (4.5)	15/15 (100)	0/23	0/28	0/24	31/31 (100)
Thyroid-discolored colloid	0/19	0/21	0/22	10/15 (67)	0/23	0/28	0/24	17/31 (55)
Thyroid follicular cell hyperplasia	4/19 (21)	4/21 (19)	4/22 (18)	6/15 (40)	2/23 (8.7)	1/28 (3.6)	3/24 (13)	6/31 (19)

2) Neoplastic - There was an increased incidence of follicular cell adenoma in males and females in the 5000 ppm group. The increase were not

statistically significant. It was also noted that only one case of follicular cell carcinoma occurred in the study and was present in the male 5000 ppm group. (See Table 9 below for the total incidence of thyroid follicular cell hyperplasia, adenoma, and carcinoma.)

Table 9. Thyroid Lesions Day 0-Termination and Percent Incidence (%)

	Males (ppm)				Females (ppm)			
Lesion	0	100	500	5000	0	100	500	5000
Follicular cell								
- Hyperplasia	7/65 (10.8)	7/65 (10.8)	4/65 (6.2)	11/65 (16.9)	2/65 (3.1)	1/65 (1.5)	3/65 (3.1)	8/65 (12.3)
- Adenoma	3/65 (4.6)	2/65 (3.1)	3/65 (4.6)	8/65 (12.3)	1/65 (1.5)	1/65 (1.5)	1/65 (1.5)	7/65 (10.8)
- Carcinoma	0/65	0/65	0/65	1/65 (1.5)	0/65	0/65	0/65	0/65

D. Discussion:

Survival of males in the 5000 ppm group was slightly decreased. Body weight gain of males and females in the 5000 ppm group was reduced when compared to controls at all time intervals. Body weight gain of males and females in the 5000 ppm group was reduced by 10.7 and 25.4 percent, respectively, at week 13, when compared to controls. Food consumption was significantly decreased in males and females in the 5000 ppm group at several intervals. At week 13, food consumption of males and females in the 5000 ppm group was decreased by 9.3 and 12.4 percent, respectively, when compared to controls. Hematology was not affected by administration of the test material. Gamma glutamyl transferase was significantly increased in males and females in the 5000 ppm group at 3 and 6 months. Cholesterol was increased in males and females in the 5000 ppm group at 3, 6, and 12 months. Gamma glutamyl transferase was also increased (but not significantly) at 24 months. The urine of males and females in the 5000 ppm group was amber in color compared to straw or yellow color of animals in all other groups. This was probably due to the disposition of the yellow pigment in the test material. The liver to body weight ratio was increased at 12 months in males in the 5000 ppm group. At terminal sacrifice, the absolute weight of the liver was significantly increased in males and females in the 5000 ppm group. In addition, the liver body weight and brain weight ratios were significantly increased in females in the 5000 ppm group. There was also an increase in the absolute thyroid weight and thyroid body and brain weight ratios in males in the 5000 ppm group at the 12-month interim sacrifice. Females exhibited an increase in the thyroid body

weight ratio at 12 months. Although significant increases in thyroid weight or body and brain weight ratios were not observed at terminal sacrifice, the increased thyroid weight was probably related to administration of the test material since the thyroid appears to be a target tissue when examined microscopically. At 12 months, there was an increase in the incidence of accentuated liver lobular pattern in males in the 500 and 5000 ppm groups. However, this macroscopic lesion was not present at an increased incidence in females at 12 months or in males and females at terminal sacrifice. This observation did not correspond to microscopic pathology and is probably of little biological significance. Dark adipose tissue was observed only in females in the 5000 ppm group and was probably treatment-related. A generalized icterus was observed only in males and females in the high-dose group. The incidence was much higher in females (35%) than in males (6.7%). At the interim sacrifice, the thyroids of all 10 males and 10 females in the 5000 ppm group were diffusely dark. Most of the animals in the 5000 ppm group had diffusely darkened thyroids at terminal sacrifice and in animals that were not sacrificed on schedule. A few animals in the 100 and 500 ppm group (approximately 3%) had diffusely dark thyroids. The majority of the males and females in the 5000 ppm group had pigmentation of the follicular cells of the thyroid and discolored colloid in the thyroid. A few animals in the 500 ppm group had pigmentation of the follicular cells of the thyroid. There was an increase in follicular cell hyperplasia of the thyroid in males (11/65; 17%) and females (8/65; 12%) in the 5000 ppm group when compared to males (7/65; 11%) and females (2/65; 3%) in the control group. Follicular cell hyperplasia did not appear to be significantly increased in males and females in the 100 and 500 ppm groups. The incidence of follicular cell adenoma was increased in males (8/65; 12%) and females (7/65; 11%) in the 5000 ppm group when compared to males (3/65; 5%) and females (1/65; 2%) in the control group. The increases were not statistically significant. Follicular cell carcinoma occurred in one male in the 5000 ppm group and may be related to treatment.

The sponsor should address the apparent discrepancy in survival data as noted in this review. The historical control data are attached.

[The MTD was achieved as indicated by decreases in body weight gain and slightly increased mortality in males in the 5000 ppm group.]

PENDIMETHALIN

Page_____ is not included in this copy.

Pages 38 through 47 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

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

____ The document is not responsive to the request.

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