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

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OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of Pendimethalin

FROM: William Greear, M.P.H and W. Greear 6/17/92
Marion Copley D.V.M., Section Head Marion Copley 7/3/92
Review Section IV, Toxicology Branch I
Health Effects Division (H7509C)

and
Esther Rinde, Ph.D. E. Rinde
Manager, Carcinogenicity Peer Review Committee
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Robert Taylor
Product Manager #25
Registration Division (H7505C)

The Health Effects Division Carcinogenicity Peer Review Committee met on 03/18/92 to discuss and evaluate the weight-of-the-evidence on pendimethalin with particular reference to its carcinogenic potential.

The Peer Review Committee agreed that pendimethalin should be classified as 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.

A. Individuals in Attendance:

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

Karl Baetcke

Marcia Van Gemert

Reto Engler

Robert Beliles

Lucas Brennecke

William L. Burnam

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Marion Copley

George Ghali

Richard Hill

Hugh Pettigrew

John Quest

Yin-Tak Woo

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

William Greear[1] 6/17/92

Bernice Fisher

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Penelope Fenner-Crisp

Kerry Dearfield

Julie Du

Jean Parker

Esther Rinde

William Sette

4. Other Attendees: (Observers)

Eve Andersen (Clement)
Ann Clevenger (HED)

[1] Also a member of the PRC for this chemical. Signature indicates concurrence with the peer review unless otherwise noted.

B. Material Reviewed:

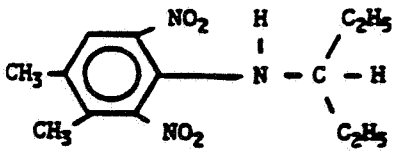
The material available for review consisted of DER's, one-liners, and other data summaries prepared by William Greear; tables and statistical analysis by Bernice Fisher. The material reviewed is attached to the file copy of this report. The data reviewed are based on studies submitted to the Agency by American Cyanamid.

C. Background Information:

Pendimethalin, N-(1-ethylpropyl)-3,4-dimethyl-2,6 dinitrobenzenamine is a dinitroaniline herbicide registered for use on corn, rice, beans, peanuts, soybeans, cotton, sorghum, and sunflowers for the control of certain broadleaf weeds and grassy weed species. Pendimethalin is available as a technical material at 90% ai. It is also registered by the trade name PROWL®. End use formulations are a 1% and 10% granular and 2.98 lbs/gal, 3.0 lbs/gal, and 4.0 lbs/gal emulsifiable concentrate. The American Cyanamid Company produces pendimethalin. Following the Data Call-In Notice of the first Registration Standard of March 1985, a multigeneration study and two chronic studies in rodents were received.

The Caswell (or Tox Chem) Number of pendimethalin is 454BB.
The Chemical Abstracts Registry Number (CAS No.) is 40487-42-1.
The PC Number is 108501.

The structure of pendimethalin is



D. Evaluation of Carcinogenicity Evidence:

1. Rat Carcinogenicity Study No. 1

Reference: Weltman, R.H., "Chronic Dietary Toxicity and Oncogenicity Study in Rats Fed AC 92,553," April 20, 1987. MRID Number: 4010744-01, Study Number: HLA 6123112. Testing Facility: Hazleton Laboratories, Inc., Madison, WI.

a. Experimental Design

Technical pendimethalin (91.9% ai) was administered in the diet to groups of 55 male and 55 female Crl:CD (SD)BR rats at 0 (control), 100, 500, or 5000 ppm (approximately 0, 5, 25 or 250 mg/kg/day) for 24 months. Additional groups of 10 animals/sex/dose were assigned to the 12-month interim sacrifice.

b. Discussion of Tumor and Hyperplasia Data

Both males and females had a significant, dose-related, increasing trend in thyroid follicular cell adenomas and a significant increase using pair wise comparisons between the controls and 5000 ppm group. (See Tables 1 and 2) Both males and females had a significantly increased trend for thyroid follicular cell hyperplasia, which was significant in pairwise comparisons at the high dose for females only. There was no statistically significant increase in carcinomas.

Table 1. Pendimethalin- Sprague-Dawley Male Rats (1987) Thyroid Follicular Cell Tumor and Hyperplasia Rates* and Peto's Prevalence Test Results

	Dose (ppm)			
Lesions	0	100	500	5000
hyperplasia (%)	7/64(11)	7/62(11)	4/64(6)	10[a]/64(16)
p =	0.028*	0.421	0.870(n)	0.121
adenomas (%)	3/64(5)	2/62(3)	3[b]/64b(5)	8/64(13)
p =	0.003**	0.720(n)	0.491	0.038*
carcinomas (%)	0/64(0)	0/62(0)	0/64(0)	1/64[c](2)
p** =	0.252	1.000	1.000	0.500

[a] First hyperplasia observed at week 53, dose 5000 ppm.
[b] First adenoma observed at week 53, dose 500 ppm.
[c] First carcinoma observed at week 93, dose 5000 ppm.

Table 2. Pendimethalin - Sprague-Dawley Female Rats (1987), Thyroid Follicular Cell Hyperplasia and Adenoma Tumor Rates* and Peto's Prevalence Test Results

	Dose (ppm)			
Lesions	0	100	500	5000
Hyperplasia (%)	1/34(13)	1/44(2)	3/37(8)	8[a]/45(18)
p=	0.004**	0.560(n)	0.161	0.027*
Adenomas (%)	1/41(2)	1/49(2)	1/43(2)	7[b]/53(13)
p=	0.002**	0.560	0.510	0.036*

[a] First hyperplasia observed at week 88, dose 5000 ppm.
[b] First adenoma observed at week 53, dose 5000 ppm.

*Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.
** Resultant p values based on application of Exact Trend test and Fisher's Exact test for pair-wise comparisons with control and each dose level. Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If * then $p<.05$ and if ** then $p<.01$. (n) = negative change from control.

The sponsor has submitted historical control data from 13 separate 2-year studies conducted from 1985 to 1990 at the testing laboratory, Hazleton-Wisconsin, Inc., in Sprague-Dawley rats. The incidence of adenomas in male (12.3%) and female (10.8%) rats in the 5000 ppm group exceeded the historical control ranges for males (0 to 8.1%; mean - 3.2%) and for females (0 to 5.7%; mean - 1.8%). The incidence of adenomas and carcinomas combined in the male 5000 ppm group (13.8%) exceeded the historical control range (0 to 8.1%, mean 3.3%).

c. Non-neoplastic Lesions

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. This was also observed 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 and females in the 5000 ppm group when compared to males and females 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 (see Tables 1 and 2).

There was an increase in absolute and relative thyroid weight primarily in males (up to about 62% over controls) at 5000 ppm at the interim sacrifice. However, increased thyroid weights were not observed at terminal sacrifice.

The absolute and relative liver weights also were increased in both sexes at 5000 ppm. Increases were noted for GGT and total cholesterol at 5000 ppm.

There appeared to be a slight decrease in survival in the high dose males (36, 38, 42 and 29% for control through high dose). Statistical analysis showed a significant dose-related decreasing trend in survival in male rats.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The dosing was considered to be adequate for assessing the carcinogenic potential of pendimethalin. There were body weight gain depressions of 10.7% and 25.4% in males and females in the 5000 ppm group, respectively, at 13 weeks when compared to controls. Also, at the end of two years, body weight gain depressions in male and female rats in the 5000 ppm group were 29.7% and 15.8%, respectively, when compared to controls.

2. Rat Carcinogenicity Study No. 2

Reference: "Effects of Chronic Dietary Administration of AC 92,553 on the Function and Structure of Male Rat Thyroids," September 10, 1991. MRID Number 420478-02, Study Number: HLA 362-191, Testing Facility: Hazleton Laboratories America, Inc.

a. Experimental Design

Technical pendimethalin (92.6%) was administered in the diet to groups of 50 male Crl:CD(SD)BR rats at 0 (control), 1250, 2500, 3750 or 5000 ppm (approximate doses of 0, 51, 103, 154 or 213 mg/kg/day) for 24 months. Additional groups of 15 males/dose were sacrificed after receiving 1, 13, 26, 39 or 52 weeks of compound in the diet. Only males were tested.

b. Discussion of Tumor Data

The incidences of thyroid follicular cell adenomas and carcinomas in male rats are shown below.

Thyroid Follicular Cell Tumors and Hyperplasia in Male Rats (1990 study)

	Dose (ppm)				
Lesion	0	1250	2500	3750	5000
adenoma	4[a]/90(4)**	7/85(8)	7/88(8)	6/89(7)	15/89(17)**
carcinoma	1/60(2)	1/54(2)	4/58(7)	3[b]/59(5)	2/59(3)
combined tumors	5/90(6)**	8/85(9)	11/88(12)	9/89(10)	17/89(19)**
hyperplasia	0/90(0)*	0/85(0)	0/88(0)	2/89	2[c]/89

* Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a] first adenoma at week 27. [b] first carcinoma at week 67.
[c] first hyperplasia at week 53

Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level.

* $p < 0.05$ ** $p < 0.01$

There was a significant trend ($p<0.01$) for follicular cell adenomas and adenoma/carcinomas combined. Since the adenomas are responsible for significance in combined values, only adenomas will be discussed further. In addition, pairwise comparisons produced significant differences in adenomas between the control and 5000 ppm groups at the $p \leq 0.01$ level.

The incidence of adenomas in males in the 5000 ppm group (17%) exceeded the historical control range for males (0 to 8.1%, mean 3.2%).

c. Non-neoplastic Lesions

Non-neoplastic lesions were observed in the thyroid and liver. In the thyroid there was a treatment-related increase in follicular cell hypertrophy, hyperplasia and pigment, follicular cysts and a possible decreased colloid (see Table 4). Absolute thyroid weights were increased from 57 to 144% in the 2500 ppm and up when compared to controls. This was seen as early as week 14 in the 3750 ppm group.

Table 4. Select Non-neoplastic Thyroid Follicular Lesions (%)

Lesion	0 ppm	1250 ppm	2500 ppm	3750 ppm	5000 ppm
Hypertrophy	4	1	**8**	**17**	**34**
Hyperplasia	0	0	0	**2**	**2**
Pigment	53	54	**66**	**73**	**71**
Colloid decreased	2	4	**5**	**7**	**16**
Cysts	0	**3**	**3**	**8**	**5**
Colloid increased	1	1	1	**3**	**2**

N = 120, 116, 119, 120, 119 for controls to high dose (total animals examined for the study). **BOLD - most likely treatment related increase.**

In the liver there was a treatment related increase in eosinophilic and basophilic foci of cellular alteration, hepatocellular enlargement and hepatocellular intracytoplasmic eosinophilic inclusions in groups at 2500 ppm and above. There was also an increase in periportal vacuolization at 3750 ppm and 5000 ppm. Liver weight (relative) was increased in all groups treated with pendimethalin starting at week 1.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The body weights were statistically decreased at 2500 ppm and above when compared to controls. The decrease was greater than 10% during weeks 40-104.

3. Rat Chronic Feeding/Carcinogenicity Study No. 3

Reference: "A 24-month Oral Toxicity and Carcinogenicity Study of Compound AC 92,553 in Rats," August 21, 1974. MRID Number: 00059468, Study Number: 72R-746, Testing Facility: Bio/dynamics, Inc.

This study is "Invalid" and cannot be used in data analysis.

4. Mouse Carcinogenicity Study No. 1

Reference: Johnson, D.E., "Chronic Dietary Toxicity and Oncogenicity Study With AC 92,553 in Mice," October 5, 1988. MRID Number: 409099-01, Study Number: 141-028, Testing Facility: International Research and Development Corporation, Mattawan, MI.

a. Experimental Design

Pendimethalin technical was administered in the diet to groups of 55 male and 55 female CD-1 mice at 0 (control), 100, 500, or 5000 ppm (approximate doses, males - 0, 12.3, 62.3 or 622.1 mg/kg/day; females - 0, 15.6, 78.3 or 806.9 mg/kg/day) for 18 months. A second control group of 55 male and female mice each was included in the study. Additional groups of 10 mice/sex/dose were assigned to the 12-month sacrifice.

b. Discussion of Tumor Data

There were no increases in neoplasms reported for any dosed group.

c. Non-Neoplastic Lesions

Amyloidosis occurring in multiple tissues was increased in males and females in the 5000 ppm group. There was an increase in absolute and relative thyroid weight in females (33% and 24% over controls) and relative thyroid weight in males (9% over controls) treated at 5000ppm. Absolute and relative liver weights were also increased in all male treated groups and females in the 5000 ppm group.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Adequate toxicity to test carcinogenic potential was achieved in females. Survival at 18 months was decreased in females in the 5000 ppm group (66%) when compared to controls (89%). Males and females in the 5000 ppm group exhibited increases in the liver/ gallbladder weight, liver/ gallbladder body weight ratio, and/or the liver/ gallbladder brain weight ratio at 12 months and at termination. On microscopic examination of the liver, no differences could be discerned among control and treated groups. The thyroid weight, thyroid body weight ratio, and/or thyroid brain weight ratio was increased in males and females in the 5000 ppm group. Organ weight, organ/body, and organ/brain weight ratio changes in male mice in the 5000 ppm group are not

considered to be adequate evidence to indicate that adequate toxicity was achieved. However, 5000 ppm is near the limit dose of 7000 ppm.

5. Mouse Chronic Feeding/Carcinogenicity Study No. 2

Reference: "An 18-month Carcinogenicity Study of AC 92,553 in Mice," April 2, 1974. MRID Number 00040301, Project Number: 71R-747, Testing Facility: Bio/dynamics, Inc.

This study is "Invalid" and can not be used in data analysis.

E. Additional Toxicology Data on Pendimethalin

1. Hormonal Mechanism Studies

a. A 92-day Thyroid Function Study in male rats, strain CD[Crl:CD(SD)] (HLA 6123-112, 8/5/91) was conducted at dose levels of 0, 100 or 5000 ppm (0, 4.98 or 245.4 mg/kg/day). A NOEL could not be determined. The LEL was 100 ppm based on decreases in T_3 and T_4 levels. In addition, at 5000 ppm there were: increases in TSH levels; decreases in body weight and body weight gain; increase in the incidence and severity of hypertrophy of thyroid follicular epithelial cells; and increases in absolute and relative thyroid weight.

TABLE 5 Levels of Serum TSH, T_3 and T_4 in Male Rats (% increase or decrease)

Day Dose (ppm)	15	29	57	92
TSH (ng/ml)				
0	4.35	4.02	3.87	4.90
100	3.99 (-.08)	4.69 (16.7)	4.67 (20.7)	4.20 (-1.4)
5000	5.12 (17.8)	7.66* (90.5)	6.62* (71.0)	6.65 (35.7)
T_3 (ng/ml)				
0	69.69	86.96	71.07	65.71
100	57.42* (-17.6)	67.17* (-19.8)	71.08 (0.0)	66.11 (0.6)
5000	41.91 (-39.9)	63.94* (-26.5)	58.43* (-17.8)	54.14* (-17.6)
T_4 (ug/ml)				
0	4.26	4.01	4.03	4.62
100	3.74 (-12.2)	3.82 (-4.7)	3.30* (-18.1)	3.32* (-28.1)
5000	1.37* (-67.8)	1.34* (-66.6)	1.08* (-73.2)	1.35* (-70.8)

* $p < 0.05$

b. A 2-year Chronic Feeding Study[2] in male rats, strain Crl:CD(SD)BR (HLA 362-191, 9/10/91) was conducted at dose levels of 0, 1250, 2500, 3750 or 5000 ppm (0, 51, 103, 154 or 213 mg/kg/day). The systemic NOEL could not be determined. The LEL was less than or equal to 1250 ppm based on the finding of decreased colloid and an increase of cysts in the thyroid follicles as well as increased liver weight. The levels of T_3 and T_4 were erratic. The NOEL based on thyroid function was 3750 ppm (not definitive) due to an increase in TSH at 5000 ppm. In addition, at 2500 ppm there was an increase in pigment and hypertrophy of follicular cells. At 3750 ppm and above, there was also hyperplasia of follicular cells. Thyroid follicular adenomas, GGT and cholesterol were increased at 5000 ppm.

c. The registrant has submitted a draft report of a 2 week study indicating that the decreases in T_3 and T_4 were not due to decreased synthesis. Peer review committee did not review this study.

d. The registrant plans to conduct a study of thyroid hormone clearance to further elucidate the mechanism for depression of T_3 and T_4.

2. Metabolism

When ^{14}C-radiolabeled pendimethalin was administered to rats, about 70 percent of the radioactivity was excreted in the feces and 20 percent in the urine within 24 hours. The excretion of radioactivity in the urine peaked at 6 to 12 hours wherein 11.2 percent of the dose was excreted. In feces, the peak excretion interval was between 12 and 24 hours wherein 46.6 percent of the dose was excreted. The maximum residual radioactivity in the tissues was found in the 6-hour samples (except for fat at 12 hours). The levels of radioactivity detected in liver, kidney, muscle, fat, and blood at 6 hours were 29.8, 16.9, 1.3, 12.2, and 5.4 ppm, respectively. Within 96 hours, the radioactivity found in the tissues was 0.3 ppm or less, except for fat which was 0.9 ppm. The major portion of the radioactivity that was excreted in the feces was identified as the parent compound.

Pendimethalin is metabolized in rats mainly through oxidation of the 4-methyl group attached to the benzene ring as well as oxidation of the alkyl side chain of this N-substituted dinitroaniline compound (MRID No. 000446275, Study No. 2-463).

3. Mutagenicity

Pendimethalin has been tested in several mutagenicity studies. Acceptable tests fulfill all three categories for mutagenicity testing. The following studies have been conducted:

In Vitro Cytogenetics-CHO - Negative results were obtained when pendimethalin was tested at levels up to 25 ug/plate without metabolic (S9) activation and

[2] This is the same study discussed in D.2.

100 ug/mL with metabolic activation (MRID No. 00153770, Study No. PH-320-AC-001-85). Acceptable.

DNA Repair (Unscheduled DNA synthesis) - Negative results were obtained when tested when pendimethalin was tested between 30 and 3000 ug/well (MRID No. 00153771, Study No. PH 311-AC-002-85). Acceptable.

Salmonella assay - Positive results were obtained in strains TA1538 (large increase) and TA98 (frame-shift mutations) with metabolic (S9) activation. No evidence of mutagenic activity was evident in strains TA1535, TA1537 and TA100. These results are based on several replicates. Dose levels ranged from 50 to 5000 ug/plate (MRID No. 00153768, Study No. 0166). Acceptable.

CHO/HGPRT Assay - Negative results were obtained at dose levels up to 80 ug/mL with metabolic (S9) activation. Inconclusive results, though suggestive increases, were obtained at levels up to 10 ug/mL without metabolic activation (MRID No. 00153769, Study No. PH-314-AC001-85). Unacceptable; need higher concentrations.

Host-Mediated Assay - Tested a prepared nitrosamine sample (C194269) found in the technical Prowl product. Negative results were obtained at dose levels up to 16.6 mg/mouse (MRID No. 00067519, Study No. N/A). Unacceptable; many questions, no toxicity.

Host-Mediated Assay - The question of the mutagenicity of pendimethalin (a process intermediate PROWL, 76.2% plus 15% nitrosamine) in this study has not been resolved. Dose levels used were 20.0 and 26.8 mg/mouse (MRID No. 00067519, Study No. N/A). Unacceptable.

Dominant Lethal - Pendimethalin was negative at the highest dose level tested of 2500 ppm (MRID No. 00026673, Study No. 2006). Unacceptable.

Salmonella/E. Coli assay - Pendimethalin was negative when tested at levels up to 1000 ug/disc or plate with and without metabolic activation (MRID No. 00067519, Study No. N/A). Unacceptable; strains unspecified.

The three acceptable tests meet the initial testing requirement for mutagenicity testing in the three categories of gene mutations, structural chromosomal aberrations and other genotoxic effects. The positive Salmonella results indicate that pendimethelin has genotoxic activity. An assay for germ cell effects or interaction is required to follow-up the Salmonella results.

Currently a mutagenicity study titled "Micronucleus Cytogenetic Assay in Mice with AC 92,553 Lab Study" No. T9801, June 7, 1991, D. L. Putman, M. J. Morris, Microbiological Associates, Inc., MRID #42027801 is under review. The results of this micronucleus test will not impact on the Salmonella follow-up requirement.

4. Developmental Toxicity

Pendimethalin did not produce developmental effects in rats, when given by gavage at doses up to 500 mg/kg (MRID No. 00025752, Study No. 362-155) or in rabbits at doses up to 60 mg/kg by gavage (MRID No. N/A, Study No. 362-164); however, maternal mortality and embryotoxicity (resorptions) were observed at 125 mg/kg in a rabbit pilot study (MRID No. N/A, Study No. 362-163).

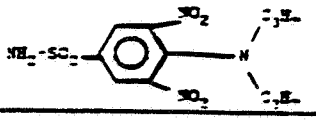
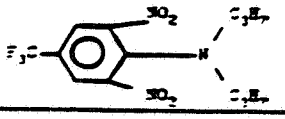
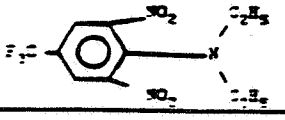
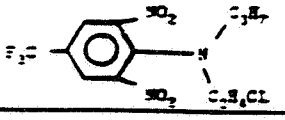
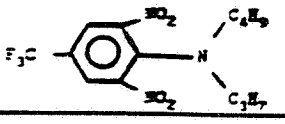
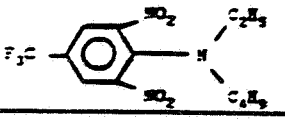
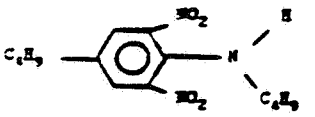
5. Structure-Activity Correlations

Pendimethalin is structurally related to oryzalin, trifluralin, benfluralin, fluchloralin, profluralin, ethalfluralin, and butralin. The primary difference between pendimethalin and the others is the methyl group present in pendimethalin as compared to the F_3C or $NH\text{-}SO_2$- group in most of the others. This difference limits the usefulness of the structure-activity comparisons.

Oryzalin was associated with increased mammary tumors (adenomas, fibroadenomas, and adenocarcinomas) in female F344 rats, thyroid follicular cell adenomas and carcinomas in male and female F344 rats, and skin tumors (fibromas and fibrosarcomas-males; papillomas, keratoacanthomas, and squamous cell sarcomas-males and females; and basal cell adenomas, preputial gland adenomas, sebaceous gland adenomas, Zymbal's gland adenomas and trichoepitheliomas-males and females) in F344 rats (MRID Nos. 00026779 and 00070569, Study Nos. R167 and R177). Oryzalin was categorized as a group "C" carcinogen with a Q* of 1.3×10^{-1} $(mg/kg/day)^{-1}$ (based on the occurrence of mammary gland tumors (adenomas, fibroadenomas and adenocarcinomas combined) in female rats) by the HED Peer Review Committee. Trifluralin was associated with an increase in transitional cell carcinomas of the renal pelvis and thyroid follicular cell adenomas and carcinomas in male F344 rats, urinary tract tumors (transitional cell papillomas and carcinomas of the bladder) in female F344 rats (MRID No. 00044337, Study Nos. R-87 and R-97). Trifluralin was categorized as a group "C" carcinogen by the HED Peer Review Committee. The Q* was calculated to be 7.7×10^{-3} $(mg/kg/day)^{-1}$. Ethalfluralin was associated with increased mammary gland tumors (fibroadenomas) in female Fischer 344 (MRID No. N/A, Study Nos. R267 and R277). Profluralin has been associated with increased liver tumors (hepatoma B) in male CD-1 mice (MRID No. N/A, Study No. 381-006). Ethalfluralin, benfluralin, fluchloralin, butralin and profluralin have not been examined by the HED Peer Review Committee.

Oryzalin produced sister chromatid exchanges following intraperitoneal administration to hamsters. Trifluralin was weakly positive in an Ames test, negative in two CHO tests, negative in one SCE test, but positive in another SCE test, and negative in a sex-linked recessive lethal test in Drosophila. Ethalfluralin was positive in two Ames tests with and without metabolic activation. It was also positive for the induction of chromosomal aberrations in an in vitro cytogenetics assay with CHO cells with metabolic activation. Butralin was positive in an Ames test with metabolic activation and in a mouse lymphoma assay with and without metabolic activation. (See Figure 1 for structurally related compounds.)

FIGURE 1. Structurally Related Compounds

Structure	Name Tox Chem #/CAS #	Classification
	Oryzalin (Surflan) 623A/19044-88-3	Group C with Q* Rat + Thyroid, Mammary, Skin Mouse negative study
	Trifluralin (Treflan) 589/1582-09-8	Group C with Q* Rat + Kidney, Bladder, Thyroid Mouse negative study
	Benfluralin (Benefin) 130/1861-40-1	NA Rat inconclusive study Mouse inconclusive study
	Fluchloralin (Basalin) 460B/33245-39-5	NA Rat invalid study Mouse invalid study
	Profluralin (Tolban) 271BB/26399-36-0	NA Rat negative study Mouse + Hepatoma
	Ethalfluralin (Sonalan) 453B/55283-68-6	NA Rat + Mammary Mouse negative study
	Butralin (Dibutalin) 125E/33629-47-9	NA Rat negative study Mouse no studies

* Positive cancer study

NA Not applicable or not evaluated

6. Acute, Subchronic, and Chronic Toxicity Studies

The acute oral LD_{50} of pendimethalin in male and female rats is 1250 mg/kg and 1050 mg/kg, respectively (Toxicity Category III). The acute dermal LD_{50} in rabbits is greater than 5000 mg/kg (Toxicity Category III). The acute inhalation LC_{50} for a 15 percent aqueous solution of the technical in rats was greater than 320 mg/L for a 4-hour exposure. Pendimethalin causes slight dermal and eye irritation in rabbits (Toxicity Category III) but is not a skin sensitizer. In a cataractogenicity study in chickens, the NOEL was determined to be greater than 3000 ppm.

Pendimethalin was administered to rats in a 90-day feeding study at dose levels of 0, 100, 500, and 5000 ppm in the diet. At the 5000 ppm dose level, there was a decrease in the hematocrit and hemoglobin in males, decreased body weight gain and food consumption, and hypertrophy of the liver accompanied by increased liver weights. The NOEL was 500 ppm. In a 90-day study in dogs, the NOEL was determined to be greater than 62.5 mg/kg/day (ASALIS) when pendimethalin was administered by gavage. In a 21-day dermal study in rabbits, the NOEL was determined to be greater than 1000 mg/kg. In a 30 day feeding study in mice, the NOEL was determined to be greater than 2000 ppm (ASALIS).

Although not discussed at the PR meeting, the HED file noted that the NOEL for the 2-year dog study (#20755, MRID 00067519) was not 12.5 mg/kg/day and the LEL was 50 mg/kg/day based on increases in serum alkaline phosphatase, increased liver weiught and hepatic lesions.

A three-generation reproduction study was conducted in rats using dose levels of 500 and 5000 ppm pendimethalin in the diet. The NOEL was determined to be 500 ppm based on reduced litter size and pup body weight and a decrease in the survival index.

F. Weight of Evidence Considerations

The Committee considered the following facts regarding the toxicology data on pendimethalin in a weight-of-the-evidence determination of carcinogenic potential:

1. There is positive evidence for benign thyroid tumors in rats. In rat study No. 1, pendimethalin was associated with a statistically significant increased trend and pairwise comparison at 5000 ppm for thyroid follicular cell adenomas in both male and female Sprague-Dawley rats. In rat study No. 2, there was also a statistically significant increased trend and pairwise comparison at 5000 ppm for thyroid follicular cell adenomas, but only male rats were tested. Thyroid follicular cell hyperplasia showed positive dose trends in the two studies.

2. The incidence of thyroid follicular cell adenomas and carcinomas in males and adenomas in females was outside the range reported for historical controls at the testing laboratory for all 13 studies.

3. The dosing was adequate for assessing carcinogenic potential, but the dose in rat study No. 1 may have been excessive, as indicated by the increased mortality in males.

4. Pendimethalin was not associated with increases in neoplasms when fed to CD-1 mice at doses up to 5000 ppm. The study appeared to have been adequately conducted.

5. Pendimethalin was positive in a Salmonella assay for frame shift mutations. Negative results were found in a structural chromosomal aberration test (in vitro cytogenetic CHO assay), and in a DNA repair (UDS) assay.

6. The thyroid follicular cell tumor response is also seen in two other members of this class of compounds. Oryzalin was associated with thyroid follicular cell tumors (adenomas and carcinomas) in male and female F344 rats. Trifluralin was associated with thyroid follicular cell tumors (adenomas) in male F344 rats. However, these are structural features of these analogs that lead one to think they may not be predictors of this chemical's behavior.

7. The PRC determined that there is some evidence that the thyroid tumors could be attributed to a disruption of the thyroid-pituitary hormonal balance. In a 92-day feeding study in male rats, there was evidence of a hormonal effect on the thyroid that included decreases in T_3 and T_4 at 100 and 5000 ppm and a marked increase in TSH at 5000 ppm. There was evidence for goitrogenic activity in vivo since there was follicular cell hypertrophy, increased pigmentation, decreased colloid, and increased thyroid weight. Also, there was evidence of progression from hypertrophy to hyperplasia and adenomas.

However, the PRC determined that there was insufficient evidence to conclude with certainty if the neoplasms observed were necessarily due to thyroid-pituitary imbalance and if so, by what particular mechanism. The PRC suggests that the following types of tests will fill this data gap:

tests to determine specific evidence for reduced hormone synthesis or increased clearance of T_4 from the serum

tests to determine whether the thyroid effects are reversible

tests to determine whether iodine carrier proteins are interrupted

tests to determine whether increased biliary excretion of T_4 may have lead to the decreased T_4 levels.

tests to determine whether glucuronide conjugates in the liver are involved, as indicated by UDP-glucuronosyltransferase activity levels

tests to determine whether liver enzyme induction mechanisms are involved, as evidenced by histological changes

The PRC also recommended:

a comparative DNA binding test, which would only be useful if similar tests with trifluralin are positive

tests to examine the possible role of genotoxicity, especially in light of the strong Salmonella result (TA 1538, TA98)

G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity.

The Peer Review Committee agreed that the classification for pendimethalin should be 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 .

This decision was based on the statistically significant increased trend and pairwise comparison between the high dose group and controls for thyroid follicular cell adenomas in male and female rats. This study was conducted using adequate doses for the determination of carcinogenic activity. Pendimethalin induces gene mutations, but not aberrations or DNA damage/repair based on acceptable studies. Structurally related compounds showed evidence of tumorigenic activity.

The PRC was requested to consider the possibility of using the threshold model for thyroid neoplasms for pendimethalin (see Appendix). While it was suggestive, the evidence was not sufficient to support hormonal mechanisms for thyroid neoplasms.

REFERENCES FOR LIVER-INDUCED EFFECTS ON THYROID-PITUITARY STATUS

Brown, C.G. et al. 1987. Effects of toxic doses of a novel histamine (H2) antagonist on the rat thyroid. Fd. Chem. Toxicol 25:787-794.

Canan, P.G. and DeGrout, L.J. 1991. The effect of hepatic enzyme-inducing drugs on thyroid hormones and the thyroid gland. Endocrin? Rev.

Comer, C.P. et al. 1985. Changes in thyroid function and liver UDP glucuronosyl transferase activity in rats following a novel imidazole. Toxicol Appl Pharmacol 80:427-436.

McClain, R.M. et al. 1989. The effect of phenobarbital on the metabolism and excretion of thyroxine in rats. Toxicol Appl Pharmacol 98:216-228.

Senler, D.E. et al. 1989. The effects of chronic ingestion of spironolactone on seven thyrotropin and thyroid hormones in the male rat. Toxicol Appl Pharmacol 98:263-268.

APPENDIX

Taken from the Amitrole Draft Peer Review Document
(Rinde to Yowell 11/20/89)
and adapted by William Greear for pendimethalin.

The following guidance is given in the Agency's DRAFT Policy Document (Thyroid Follicular Carcinogenesis: Mechanistic and Science Policy Considerations, SAB Review Draft, May 1988):

"Studies over the last several decades in multiple laboratories and using a number of different treatment regimens (eg., iodine deficiency) have demonstrated the significance of long-term thyroid-pituitary hormonal imbalance in thyroid carcinogenesis. A consistent progression of events is noted: reduction in thyroid hormone concentrations, elevation in TSH levels, cellular hypertrophy and hyperplasia, nodular hyperplasia, and neoplasia. Hyperplasia and sometimes neoplasia of the pituitary may also be seen. A block in any of the early steps acts as a block for subsequent steps including tumor development, and cessation of treatment at an early stage in the progression results in regression toward normal thyroid structure and function. Based on these observations ..... the Agency concludes that:

a. thyroid follicular cell tumors may arise from long-term disturbances in thyroid-pituitary feedback under conditions of reduced circulating thyroid hormone and elevated TSH levels:

b. the steps leading to these tumors are expected to show thresholds, such that the risks of tumor development are minimal when thyroid-pituitary homeostasis exists; and

c. models that assume thresholds may be used to assess the risks of thyroid follicular cell tumors where there is evidence of thyroid-pituitary hormonal imbalance."

Two basic questions must be addressed before this policy is applied.

"The first is a qualitative issue which addresses whether it is reasonable to presume that the neoplasms are due to thyroid-pituitary imbalance. A corollary issue is the extent to which other carcinogenic mechanisms can be discounted. The second question concerns the procedures to be employed in estimating the risks of these agents."

"The answers to the first question allow one to assign chemicals producing thyroid tumors to one of three categories. The assignation is based upon knowledge as to whether the chemical disrupts thyroid-pituitary feedback, whether tumors other than thyroid follicular cell (and relevant pituitary) tumors are found, and whether mechanisms other than thyroid-pituitary imbalance may apply to the observed tumor response."

2. Determination of whether neoplasms are due to thyroid-pituitary imbalance

The document goes on to describe the three factors which should be considered in making this determination (answering the first question, or "qualitative issue"). These are addressed as they apply to Pendimethalin follows:

FACTOR I. Consideration of whether the thyroid tumors associated with administration of Pendimethalin can be attributed to disruption of the thyroid-pituitary hormonal balance. (In addressing this factor, the Policy states, six indicators should be considered.)

a. Goitrogenic activity in vivo:

Thyroid follicular cell hypertrophy was observed in males (only sex tested) in the 92-day thyroid function study and in the 2-year rat study no 2. In the 2-year rat study no. 1 there was **increased pigmentation of the follicular cells** and **discolored colloid of the thyroid** in males and females. There was **decreased colloid** in the follicles in males (only sex tested) in the 2-year rat study no. 2. **Thyroid follicular cell hyperplasia** was observed in rats in the 2-year chronic/carcinogenicity feeding study no. 1 (both sexes) and study no. 2. There was a dose-related **increase in absolute and relative thyroid weight** in males (only sex tested) in the 92-day hormonal mechanism study. In both 2-year rat studies (no. 1 and 2) there was also increased absolute and/or relative thyroid weight (males and females when tested). There were also significant increases in the absolute and/or relative thyroid weight in the chronic/carcinogenicity mouse study no. 1.

b. Clinical chemistry changes (eg., reduced thyroid hormone and increased TSH serum concentrations):

In the 92-day hormonal mechanism study, T_3 and T_4 were significantly elevated in males (only sex tested) and TSH was significantly decreased. In the 2-year rat study no.2 there was an increase in TSH in males (only sex tested) but T_3 and T_4 levels were quite variable.

c. Specific evidence of reduced hormone synthesis (eg., inhibited iodine uptake) or increased thyroid hormone clearance (eg., enhanced biliary excretion):

No information is available other than a reported decrease in colloid in the follicles in males (only sex tested) in the 2-year rat study no. 2.

d. Evidence of progression (eg., hypertrophy/hyperplasia, nodular hyperplasia - neoplasia):

There is possible evidence of progression in both 2-year rat studies based on increases in hypertrophy and/or hyperplasia and adenomas of the thyroid follicular cells. There is no evidence of progression to malignancy. Only hypertrophy was apparent in the 92-day rat study.

e. Reversibility of lesions after exposure is terminated:

There is no information.

f. SAR to other thyroid tumorigens:

It is structurally related to Trifluralin and Oryzalin with reservations noted in the SAR section or this document.

Based on the overall judgment of the six indicators in Factor I, it may be concluded that there is suggestive evidence that the thyroid tumors in the rat associated with administration of Pendimethalin may be due to a disruption in the thyroid-pituitary status.

FACTOR II. Consideration of the extent to which genotoxicity may account for the observed tumor effects.

The mutagenicity data on Pendimethalin are equivocal. There are some possible indications of mutagenic activity in the point mutation tests (frame shift). Although one host mediated assay was negative a second test is being questioned. A second Ames test, HGPRT (CHO), dominant lethal, in vitro cytogenetics (CHO) and DNA repair are negative.

FACTOR III. Evaluation of neoplasms in addition to thyroid follicular tumors, including pituitary tumors.

No other treatment-related neoplastic lesions were observed in any study.

3

Conclusions: As indicated above, based on the overall judgment of the six indicators in Factor I and III, it may be concluded that there is suggestive evidence that the thyroid tumors in the rat associated with administration of Pendimethalin may be due to a disruption in the thyroid-pituitary status. Factors II is equivocal.

3. Factors to be Considered in Determining Method to be Used in Estimating the Risks of Pendimethalin

Again, this guidance is taken from the Amitrole Peer Review Document and revised for Pendimethalin. The Committee is requested to consider these points when determining which method is to be used for estimating the carcinogenic risk for Pendimethalin.

Guidance given in the EPA DRAFT policy on Thyroid Neoplasia for proceeding with the quantitation of risk is as follows:

a. "Threshold considerations should be applied in dose-response assessments for those chemical substances where (1) only thyroid tumors (and relevant pituitary tumors) have been produced; (2) the tumors can be attributed to a disruption in thyroid-pituitary hormonal homeostasis; and (3) potential mechanisms other than thyroid-pituitary imbalance (eg., genotoxicity) can be disregarded.
b. Special attention should be given to chemicals (1) that have induced thyroid tumors (and relevant pituitary tumors) that may be due to thyroid-pituitary imbalance, and (2) where there is also evidence of either a genotoxic potential or the induction of neoplasms at sites other than the thyroid (or pituitary). Generally, those cases will be approached using various principles laid out in the EPA Guidelines for Carcinogen Risk Assessment. A strong rationale must be articulated for handling these agents otherwise.
c. For those chemicals producing thyroid tumors that do not seem to be acting via thyroid-pituitary hormonal inhibition, dose-response assessments will be performed in accordance with the EPA Guidelines for Carcinogen Risk Assessment."

Greear, Disk I° FILES,PENDIMET.PR

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

FILE COPY

March 3, 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review Meeting on **PENDIMETHALIN**

FROM: Esther Rinde, Ph.D. E.R.
Manager, Carcinogenicity Peer Review
Health Effects Division (H7509c)

TO: Addressees

Attached for your review is a package on **Pendimethalin** prepared by **William Greear.**

A meeting to consider the carcinogenicity classification of **Pendimethalin** is scheduled for **Wednesday, March 18, 1992,** at **10:00 am in Room 815, CM2.**

Addressees

P. Fenner-Crisp
W. Burnam
R. Engler
R. Hill
R. Beliles
K. Baetcke
L. Brennecke
M. Van Gemert
M. Copley
K. Dearfield
J. Parker
H. Pettigrew
W. Sette
G. Ghali
B. Fisher
J. Dc
Y. Woo
J. Quest
E. Saito (for microfiche-with one-liner)
A. Clevenger
E. Andersen
W. Greear

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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Peer Review of Pendimethalin

Tox. Chem # 454BB
PC # 108501

FROM: William B. Greear, M.P.H. William B. Greear 3/3/92
Review Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Esther Rinde, Ph.D.
Manager, Peer Review for Carcinogenicity
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

THRU: Marion P. Copley, D.V.M., Section Head Marion P. Copley 3/3/92
Review Section IV, Toxicology Branch I
Health Effects Division (H7509C)

and

Karl Baetcke, Ph.D., Branch Chief Karl D. Baetcke 3/3/92
Toxicology Branch I
Health Effects Division (H7509C)

Attached are Sections C, D, E, F and H for incorporation into the Peer Review Document on Pendimethalin.

The issues of concern are benign exocrine thyroid tumors occurring in male and female rats and support for a hormonal mechanism.

March 4, 1992

Pendimethalin, Qualitative Risk Assessment for the 2-Year Sprague-Dawley Rat Dietary Study (1987) and 2-Year Sprague-Dawley Male Rat Dietary Study (1991) are attached after Attachment NO. 7 - one-liners.

005525

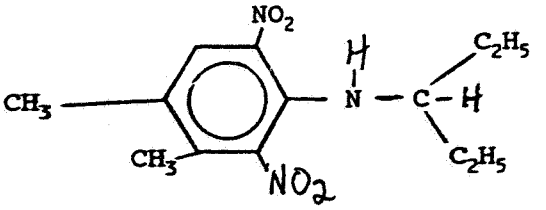
Table of Contents

A and B. Not part of this document - To be completed by the Peer Review Committee.

C. Background Information

Pendimethalin, N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine is a dinitroaniline herbicide registered for use on corn, rice, beans, peanuts, soybeans, cotton, sorghum, and sunflowers for the control of certain broadleaf weeds and grassy weed species. Pendimethalin is available as a technical material at 90% ai. It is also registered by the trade name PROWL®. End use formulations are a 1% and 10% granular and 2.98 lbs/gal, 3.0 lbs/gal, and 4.0 lbs/gal emulsifiable concentrate. The American Cyanamid Company produces pendimethalin. Following the Data Call-In Notice of the first Registration Standard of March 1985, a multigeneration study and two chronic studies in rodents were received.

The Tox Chemistry Number of pendimethalin is 454BB. The Chemical Abstracts Number is 40487-42-1. The PC Number is 108501.



Structure of Pendimethalin

D. Evaluation of Carcinogenicity Evidence

1. Rat Chronic Feeding/Carcinogenicity Study No. 1

Reference: Weltman, R.H., "Chronic Dietary Toxicity and Oncogenicity Study in Rats Fed AC 92,553," April 20, 1987. MRID Number: 4010744-01, Study Number: HLA 6123-112. Testing Facility: Hazleton Laboratories, Inc., Madison, WI.

a. Experimental Design

Technical pendimethalin (91.9% ai) was administered in the diet to groups of 55 male and 55 female Crl:CD (SD)BR rats at 0 (control), 100, 500, or 5000 ppm (approximately 0, 5, 25 or 250 mg/kg/day) for 24

months. Additional groups of 10 animals/sex/dose were assigned to the 12-month interim sacrifice.

b. Discussion of Tumor Data

Table 1. shows the incidences of thyroid follicular cell adenomas and carcinomas in male and female rats. There were increased incidences of adenomas, and adenomas and carcinomas combined in the male 5000 ppm group and an increase in the incidence of adenomas in the female 5000 ppm group. Statistics will be provided by SACB.

TABLE 1. Incidences (%) of Thyroid Follicular Cell Tumors in Sprague-Dawley Rats[1]

	Dose Level (ppm)			
	0	100	500	5000
Males				
Adenoma	3/65 (4.6)*	2/65 (3.1)	3/65 (4.6)	8/65 (12.3)
Carcinoma	0/65 (0)	0/65 (0)	0/65 (0)	1/65 (1.5)
Combined	3/65 (4.6)*	2/65 (3.1)	3/65 (4.6)	9/65 (13.8)
Females				
Adenoma	1/65 (1.5)*	1/65 (1.5)	1/65 (1.5)	7/65 (10.8)
Carcinoma	0/65 (0)	0/65 (0)	0/65 (0)	0/65 (0)
Combined	1/65 (1.5)	1/65 (1.5)	1/65 (1.5)	7/65 (10.8)

* Significant trend ($p < 0.05$); Cochran-Armitage and Fisher.
1 Data abstracted from table 26 and 27 of the study report.

There was a significant trend ($p < 0.05$) for follicular cell adenomas and follicular cell adenomas and carcinomas combined in males. In the females, there was a significant trend ($p < 0.05$) for follicular cell adenomas. Pairwise comparisons produced no significant differences at the $p<0.05$ level. There were no increases of thyroid follicular cell tumors at 100 or 500 ppm.

The sponsor has submitted historical control data from 13 separate 2-year studies conducted from 1985 to 1990 at the testing laboratory, Hazleton-Wisconsin, Inc., in Sprague-Dawley rats (see Attachment Nos. 1 and 2). The incidence of adenomas in male (12.3%) and female (10.8%) rats in the 5000

ppm group exceeded the historical control ranges for males (0 to 8.1%; mean - 3.2%) and for females (0 to 5.7%; mean - 1.8%). The incidence of adenomas and carcinomas combined in the male 5000 ppm group (13.8%) exceeded the historical control range (0 to 8.1%, mean 3.3%).

c. Non-Neoplastic Lesions

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. This was also observed 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 (see Table 2). This is consistent with the increase in absolute and relative thyroid weight in primarily males (up to about 62 % over controls) at 5000 ppm at the interim sacrifice. However, increased thyroid weights were not observed at treminal sacrifice. The absolute and relative liver weight weights were also increased in both sexes at 5000 ppm. Increases were noted for GGT and total cholesterol at 5000 ppm.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The dosing was considered to be adequate for assessing the carcinogenic potential of pendimethalin, based on body weight gain depressions of 10.7 and 25.4 percent in males and females in the 5000 ppm group, respectively, at 13 weeks when compared to controls. At the end of 2 years, body weight gain depressions in male and female rats in the 5000 ppm group were 29.7 and 15.8 percent, respectively, when compared to controls. In addition, there appeared to be a slight decrease in survival in the high dose males (36, 38, 42 and 29 % for control through high dose).

TABLE 2. Non-Neoplastic Microscopic Pathology of the Thyroid in Sprague-Dawley Rats and Percent Incidence (%)

Lesion	Male (ppm)				Female (ppm)			
	0	100	500	5000	0	100	500	5000
Interim Sacrifice								
Pigmentation of follicle cells	0/10	0/10	0/10	10/10 (100)	0/10	0/10	0/10	10/10 (100)
Discolored colloid	0/10	0/10	0/10	9/10 (90)	0/10	0/10	0/10	10/10 (100)
Follicular cell hyperplasia	0/10	0/10	0/10	1/10 (10)	0/10	0/10	0/10	0/10
Deaths and Unscheduled Sacrifices								
Pigmentation of follicle cells	0/36	0/34	2/33 (6.1)	35/40 (88)	0/32	0/37	1/31 (3)	22/24 (92)
Discolored colloid	0/36	0/34	0/33	29/40 (73)	0/32	0/37	0/31	15/24 (63)
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								
Pigmentation of follicle cells	0/19	0/21	1/22 (4.5)	15/15 (100)	0/23	0/28	0/25	31/31 (100)
Discolored colloid	0/19	0/21	0/22	10/15 (67)	0/23	0/28	0/24	17/31 (55)
Follicular cell hyperplasia	4/19 (21)	4/21 (19)	4/22 (18)	6/15 (40)	2/23 (9)	1/28 (4)	3/24 (13)	6/31 (19)

2. Rat Chronic Feeding/Carcinogenicity Study No. 2

Reference: "Effects of Chronic Dietary Administration of AC 92,553 on the Function and Structure of Male Rat Thyroids," September 10, 1991. MRID Number 420478-02, Study Number: HLA 362-191, Testing Facility: Hazleton Laboratories America, Inc.

a. Experimental Design

Technical pendimethalin (92.6%) was administered in the diet to groups of 50 male Crl:CD(SD)BR rats at 0 (control), 1250, 2500, 3750 or 5000 ppm (approximate doses, 0, 51, 103, 154 or 213 mg/kg/day) for 24 months. Additional groups of 15 males/dose were sacrificed after receiving 1, 13, 26, 39 or 52 weeks of compound in the diet.

b. Discussion of Tumor Data

Table 3 shows the incidences of thyroid follicular cell adenomas and carcinomas in male rats. there were increases of adenomas, and adenomas/carcinomas combined in the male 5000 ppm group. Statistics will be provided by SACB.

TABLE 3 Thyroid Tumors in Male Rats

	0 ppm	1250 ppm	2500 ppm	3750 ppm	5000 ppm
Follicular cell adenoma[1]	4/90(4)**	7/85(8)	7/88(8)	6/89(7)	15/89(17)**
Follicular cell carcinoma[2]	1/60(2)	1/54(2)	4/58(7)	3/59(5)	2/59(3)
Follicular cell tumors	5/90(6)**	8/85(9)	11/88(12)	9/89(10)	17/89(19)**

1 Denominator represents animals at risk, survivors after occurrence of first tumor.
Adenoma - first tumor at week 27.
2 Carcinoma - first tumor at week 67.
Trend noted at controls, pair-wise comparison noted at dose group
** $p < 0.01$

There was a significant trend ($p<0.01$) for follicular cell adenomas and adenoma/carcinomas combined. Since the adenomas are responsible for and significance in combined values, only adenomas will be discussed. In addition, pairwise comparisons produced significant differences between the control and 5000 ppm groups at the $p \leq 0.01$ level.

The incidence of adenomas in males in the 5000 ppm group (17%) exceeded the historical control range for males (0 to 8.1%, mean 3.2%).

c. Non-neoplastic Lesions

Non-neoplastic lesions were observed in the thyroid and liver. In the thyroid there was a treatment related increase in follicular cell hypertrophy, hyperplasia and pigment, follicular cysts and a possible decreased colloid (see table 4). Absolute thyroid weights were increased from 57 to 144 % in the 2500 ppm and up when compared to controls. This was seen as early as week 14 in the 3750 ppm group.

TABLE 4 Select Non-neoplastic Thyroid Follicular Lesions (%)

Lesion	0 ppm	1250 ppm	2500 ppm	3750 ppm	5000 ppm
Hypertrophy	4	1	**8**	**17**	**34**
Hyperplasia	0	0	0	**2**	**2**
Pigment	53	54	**66**	**73**	**71**
Colloid decreased	2	**4**	**5**	**7**	**16**
Cysts	0	**3**	**3**	**8**	**5**
Colloid increased	1	1	1	**3**	**2**

N = 120, 116, 119, 120, 119 for controls to high dose (total animals examined for the study).
BOLD - most likely treatment related increase.

In the liver there was a treatment related increase in eosinophilic and basophilic foci of cellular alteration, hepatocellular enlargement and hepatocellular intracytoplasmic eosinophilic inclusions in groups at 2500 ppm and above. There was also an increase in periportal vacuolization at 3750 ppm and 5000 ppm (see table 10 of the DER. Liver weight (relative) was increased in all groups treated with Pendimethalin starting at week 1.

3. Rat Chronic Feeding/Carcinogenicity Study No. 3

Reference: "A 24-month Oral Toxicity and Carcinogenicity Study of Compound AC 92,553 in Rats," August 21, 1974. MRID Number: 00059468, Study Number: 72R-746, Testing Facility: Bio/dynamics, Inc.

This study is "Invalid" and can not be used in data analysis.

4. Mouse Carcinogenicity Study No. 1

Reference: Johnson, D.E., "Chronic Dietary Toxicity and Oncogenicity Study With AC 92,553 in Mice," October 5, 1988. MRID Number: 409099-01, Study Number: 141-028, Testing Facility: International Research and Development Corporation, Mattawan, MI.

a. Experimental Design

Pendimethalin technical was administered in the diet to groups of 55 male and 55 female CD-1 mice at 0 (control), 100, 500, or 5000 ppm (approximate doses, males - 0, 12.3, 62.3 or 622.1 mg/kg/day; females - 0, 15.6, 78.3 or 806.9 mg/kg/day) for 18 months. A second control group of 55 male and female mice was included in the study. Additional groups of 10 mice/sex/dose were assigned to the 12-month sacrifice.

b. Discussion of Tumor Data

There were no increases in neoplasms reported for any dosed group.

c. Non-Neoplastic Lesions

Amyloidosis occurring in multiple tissues was increased in males and females in the 5000 ppm group. There was an increase in absolute/relative thyroid weight in females (33/24 % over controls) and relative thyroid weight in males (9 % over controls). Absolute and relative liver weights were also increased in all male treated groups and females in the 5000 ppm group.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Survival at 18 months was decreased in females in the 5000 ppm group (66%) when compared to controls (89%). Males and females in the 5000 ppm group exhibited increases in the liver/ gallbladder weight, liver/ gallbladder body weight ratio, and/or the liver/ gallbladder brain weight ratio at 12 months and at termination. On microscopic examination of the liver, no differences could be discerned among control and treated groups. The thyroid weight, thyroid body weight ratio, and/or thyroid brain weight ratio was increased in males and females in the 5000 ppm group. Adequate toxicity to test carcinogenic potential was achieved in females in the 5000 ppm group as indicated by an increase in mortality. Organ weight, organ/body, and organ/brain weight ratio changes in male mice in the 5000 ppm group are not considered to be adequate evidence to indicate that adequate toxicity was achieved. The HDT of 5000 ppm is near the limit dose of 7000 ppm.

5. Mouse Chronic Feeding/Carcinogenicity Study No. 2

Reference: "An 18-month Carcinogenicity Study of AC 92,553 in Mice," April 2, 1974. MRID Number 00040301, Project Number: 71R-747, Testing Facility: Bio/dynamics, Inc.

This study is "Invalid" and can not be used in data analysis.

E. Additional Toxicology Data on Pendimethalin

1. Hormonal Mechanism Studies

a. A 92-day Thyroid Function Study in male rats, strain CD[Crl:CD(SD)] (HLA 6123-112, 8/5/91) was conducted at dose levels of 0, 100 or 5000 ppm (0, 4.98 or 245.4 mg/kg/day). A NOEL could not be determined. The LEL was 100 ppm based on decreases in T3 and T4 levels. In addition, at 5000 ppm there are: increase in TSH levels; decreases in body weight and body weight gain;increase in the incidence and severity of hypertrophy of thyroid follicular epithelial cells; and increases in absolute and relative thyroid weight.

TABLE 5 Levels of Serum TSH, T_3 and T_4 in Male Rats (% increase or decrease)

Weeks Dose (ppm)	15	29	57	92
TSH (ng/ml)				
0	4.35	4.02	3.87	4.90
100	3.99 (-.08)	4.69 (16.7)	4.67 (20.7)	4.20 (-1.4)
5000	5.12 (17.8)	7.66* (90.5)	6.62* (71.0)	6.65 (35.7)
T_3 (ng/ml)				
0	69.69	86.96	71.07	65.71
100	57.42* (-17.6)	67.17* (-19.8)	71.08 (0.0)	66.11 (0.6)
5000	41.91 (-39.9)	63.94* (-26.5)	58.43* -17.8)	54.14* (-17.6)
T_4 (ug/ml)				
0	4.26	4.01	4.03	4.62
100	3.74 (-12.2)	3.82 (-4.7)	3.30* (-18.1)	3.32* (-28.1)
5000	1.37* (-67.8)	1.34* (-66.6)	1..8* (73.2)	1.35* (-70.8)

* p <0.05

b. A 2-year Chronic Feeding Study in male rats, strain Crl:CD(SD)BR (HLA 362-191, 9/10/91) was conducted at dose levels of 0, 1250, 2500, 3750 or 5000 ppm (0, 51, 103, 154 or 213 mg/kg/day). The systemic NOEL could not be determined. The LEL was less than or equal to 1250 ppm based on the finding of decreased colloid and an increase of cysts in the thyroid follicles as well as increased liver weight. The NOEL based on thyroid function was 3750 ppm (not definitive) due to a decrease in TSH at 5000 ppm. In addition, at 2500 ppm there was an increase in pigment and hypertrophy of follicular cells. At 3750 ppm and above, there was also hyperplasia of follicular cells. Thyroid follicular adenomas, GGT and cholesterol were increased at 5000 ppm.

2. Metabolism

When ^{14}C-radiolabeled pendimethalin was administered to rats, about 70 percent of the radioactivity was excreted in the feces and 20 percent in the urine within 24 hours. The excretion of radioactivity in the urine peaked at 6 to 12 hours wherein 11.2 percent of the dose was excreted. In feces, the peak excretion interval was between 12 and 24 hours wherein 46.6 percent of the dose was excreted. The maximum residual radioactivity in the tissues was found in the 6-hour samples (except for fat at 12 hours). The levels of radioactivity detected in liver, kidney, muscle, fat, and blood at 6 hours were 29.8, 16.9, 1.3, 12.2, and 5.4 ppm, respectively. Within 96 hours, the radioactivity found in the tissues was 0.3 ppm or less, except for fat which was 0.9 ppm. The major portion of the radioactivity that was excreted in the feces was identified as the parent compound. Pendimethalin is metabolized in rats mainly through oxidation of the 4-methyl group attached to the benzene ring as well as oxidation of the alkyl side chain of this N-substituted dinitroaniline compound (MRID No. 000446275, Study No. 2-463).

Pendimethalin is rapidly eliminated from the body with 70 percent being excreted in the feces primarily unchanged as parent compound and 20 percent in the urine within 24 hours. It is mainly metabolized through oxidation of the 4-methyl group on the benzene ring and the alkyl side chain.

3. Mutagenicity

Pendimethalin has been tested in several mutagenicity studies. Acceptable tests fulfill all three categories for mutagenicity testing. The following studies have been conducted:

Study	Status
Gene Mutation	
Ames-Salmonella/E.Coli	Acceptable
Ames-Salmonella	Acceptable
CHO/HGPRT	Acceptable (W S9)
Host-Mediated	Unclassified
Host-Mediated	Acceptable
Structural Chromosomal Aberration	
Dominant Lethal	Unacceptable
In Vitro Cytogenetics-CHO	Acceptable
Other Genotoxic Effects	
DNA Repair	Acceptable

a. Ames test - Salmonella/E. Coli (strains unspecified) - Pendimethalin was negative when tested at levels up to 1000 ug/disc or plate with and without metabolic activation (MRID No. 00067519, Study No. N/A).

b. Ames test - Salmonella - Positive results were obtained in strains TA1538 and TA98 (frame-shift mutations) with metabolic (S9) activation. No evidence of mutagenic activity was evident in strains TA1535, TA1537 and TA100. Dose levels ranged from 50 to 5000 ug/plate (MRID No. N/A, Study No. 0166).

c. CHO/HGPRT Assay - Negative results were obtained at dose levels up to 80 ug/mL with metabolic (S9) activation. Inconclusive results were obtained at levels up to 10 ug/mL without metabolic activation (MRID No. N/A, Study No. PH-314-AC001-85).

d. Host-Mediated Assay - Negative results were obtained at dose levels up to 16.6 mg/mouse (MRID No. N/A, Study No. N/A).

e. Host-Mediated Assay - The question of the mutagenicity of pendimethalin[1] in this study has not been resolved. Dose levels used were 20.0 and 26.8 mg/mouse (MRID No. 00067519, Study No. N/A).

f. Dominant Lethal - Pendimethalin was negative at the highest dose level tested of 2500 ppm (MRID No. N/A, Study No. 2006).

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[1]A "crude process PROWL C194,269, 99% purity"

g. In Vitro Cytogenetics-CHO - Negative results were obtained when pendimethalin was tested at levels up to 25 ug/plate without metabolic (S9) activation and 100 ug/mL with metabolic activation (MRID No. N/A, Study No. PH-320-AC-001-85).

h. DNA Repair - Negative results were obtained when tested when Pendimethalin was tested between 30 and 3000 ug/well (MRID No. N/A, Study No. PH 311-AC-002-85).

No data gaps exist for mutagenicity testing. The Dynamac reviewer recommended that in vivo assays designed to detect gene mutations (e.g., mouse spot test) be conducted. Additional in vitro mammalian cell culture assays (e.g., mouse lymphoma assay) were recommended using a different system so that the question of gene mutation potential in mammalian cells could be resolved. [See document "Overview Pendimethalin (Prowl) Mutagenicity", January 22, 1987, TOX ID No. 005828.] Currently a mutagenicity study titled "Micronucleus Cytogenetic Assay in Mice with AC 92,553 Lab Study" No. T9801, June 7, 1991, D. L. Putman, M. J. Morris, Microbiological Associates, Inc., is under review. The projected contract completion date is Early March 1992.

4. Developmental Toxicity

Pendimethalin did not produce developmental effects in rats, when given by gavage at doses up to 500 mg/kg (MRID No. 00025752, Study No. 362-155) or in rabbits at doses up to 60 mg/kg by gavage (MRID No. N/A, Study No. 362-164); however, maternal mortality and embryotoxicity (resorptions) were observed at 125 mg/kg in a rabbit pilot study (MRID No. N/A, Study No. 362-163).

5. Structure-Activity Correlations

Pendimethalin is structurally related to oryzalin, trifluralin, benfluralin, fluchloralin, profluralin, ethalfluralin, and butralin. The primary difference between pendimethalin and the others is the methyl group present in pendimethalin as compared to the F_3C or $NH-SO_2-$ group in most of the others. This difference limits the usefulness of the structure-activity comparisons. Oryzalin was associated with increased mammary tumors (adenomas, fibroadenomas, and adenocarcinomas) in female F344 rats, thyroid gland tumors (follicular cell adenomas and carcinomas) in male and female F344 rats, and three types of skin tumors (fibromas and fibrosarcomas-males; papillomas, keratoacanthomas, and squamous cell sarcomas-males and females; and basal cell adenomas, preputial gland adenomas, sebaceous gland adenomas, Zymbal's gland

adenomas and trichoepitheliomas-males and females) in F344 rats (MRID Nos. 00026779 and 00070569, Study Nos. R167 and R177). Oryzalin was categorized as a group "C" carcinogen with a Q* of 1.3×10^{-1} $(mg/kg/day)^{-1}$ (based on the occurrence of mammary gland tumors (adenomas, fibroadenomas and adenocarcinomas combined) in female rats) by the HED Peer Review Committee. Trifluralin was associated with increased tumors of the renal pelvis (transitional cell carcinomas) and follicular cell adenomas and carcinomas in male F344 rats, urinary tract tumors (transitional cell papillomas and carcinomas of the bladder) in female F344 rats (MRID No. 00044337, Study Nos. R-87 and R-97). Trifluralin was categorized as a group "C" carcinogen by the HED Peer Review Committee. The Q* was calculated to be 7.7×10^{-3} $(mg/kg/day)^{-1}$. Ethalfluralin was associated with increased mammary gland tumors (fibroadenomas) in female Fischer 344 (MRID No. N/A, Study Nos. R267 and R277). Profluralin has been associated with increased liver tumors (hepatoma B) in male CD-1 mice (MRID No. N/A, Study No. 381-006). Ethalfluralin, benfluralin, fluchloralin, butralin and profluralin have not been examined by the HED Peer Review Committee.

Oryzalin produced sister chromatid exchanges following intraperitoneal administration to hamsters. Ethalfluralin was positive in two Ames Tests with and without metabolic activation. It was also positive for the induction of chromosomal aberrations in an in vitro cytogenetics assay with CHO cells with metabolic activation. Butralin was positive in an Ames Test with metabolic activation and in a mouse lymphoma assay with and without metabolic activation. (See Figure 1 for structurally related compounds.)

Pendimethalin Tox review 009525

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39-46

Attachment #1

Table 2.
Historical Control Data for Thyroid Proliferative Lesions in the Sprague-Dawley Rat

	Hazleton - Wisconsin (1985-1990)			Hazleton - Washington (1985-1990)			Charles River (1977-1985)		
	Incidence	%	Range	Incidence	%	Range	Incidence	%	Range
Males									
Follicular Cell Hyperplasia	NA	NA	NA	2/835	0.2	0-1.7	NA	NA	NA
Follicular Cell Adenoma	26/821	3.2	0-8.1	35/835	4.2	0-12.0	11/866	1.3	0-5.3
Follicular Cell Carcinoma	1/821	0.1	0-2.0	17/835	2.0	0-6.7	14/866	1.6	0-8.2
Follicular Cell Adenoma and Carcinoma	27/821	3.3	0-8.1	ND	ND	ND	ND	ND	ND
Females									
Follicular Cell Hyperplasia	NA	NA	NA	2/834	0.2	0-3.0	NA	NA	NA
Follicular Cell Adenoma	15/815	1.8	0-5.7	7/834	0.8	0-2.1	4/869	0.5	0-1.8
Follicular Cell Carcinoma	0/815	0.0	0.0	8/834	1.0	0-2.1	11/869	1.3	0-9.1
Follicular Cell Adenoma and Carcinoma	15/815	1.8	0-5.7	ND	ND	ND	ND	ND	ND

NA = not available
ND = not determined, due to inability to exclude possible redundancy

HAZLETON WISCONSIN, INC.

UNAUDITED

HISTORICAL CONTROL DATA FOR THYROID NEOPLASMS IN THE SPRAGUE-DAWLEY RAT

1985 - 1990

Symbols Prefacing Neoplastic Findings

B = Primary, benign neoplasm
M = Primary, malignant neoplasm
N = Metastatic neoplasm
I = Locally invasive neoplasm
X = Other neoplasm

Study Code	R(SD)C1		R(SD)C2		R(SD)C3		R(SD)C4		R(SD)C5		R(SD)C7		R(SD)C8		R(SD)C9	
Year Completed	1990		1985		1988		1987		1986		1987		1985		1985	
Study Duration (weeks)	104		104		104		104		104		104		104		104	
Pathologist Code	6		39		39		39		39		29		39		29	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Tumor Type																
Thyroid																
B - Follicular cell adenoma	3/37	1/30	1/60	0/60	0/60	0/60	3/60	1/60	3/90	1/90	2/70	4/70	3/65	2/65	4/60	2/60
M - Follicular cell carcinoma	0/37	0/30	0/60	0/60	0/60	0/60	0/60	0/60	0/90	0/90	0/70	0/70	0/65	0/65	0/60	0/60
B - "C" cell adenoma	2/37	2/30	1/60	3/60	0/60	1/60	1/60	2/60	2/90	2/90	2/70	4/70	2/65	3/65	5/60	3/60
M - "C" cell carcinoma	0/37	0/30	0/60	0/60	0/60	0/60	0/60	0/60	0/90	0/90	1/70	0/70	0/65	0/65	1/60	0/60

Study Code	R(SD)C10		R(SD)C11		R(SD)C12		R(SD)C14		R(SD)C15			
Year Completed	1987		1986		1985		1987		1989			
Study Duration (weeks)	104		104		106		104		104			
Pathologist Code	42		39		42		42		39		Totals	
	M	F	M	F	M	F	M	F	M	F	M	F
Tumor Type												
Thyroid												
B - Follicular cell adenoma	3/65	1/65	0/80	1/79	1/49	1/51	1/65	1/65	2/60	0/60	26/821	15/815
M - Follicular cell carcinoma	0/65	0/65	0/80	0/79	1/49	0/51	0/65	0/65	0/60	0/60	1/821	0/815
B - "C" cell adenoma	9/65	6/65	3/80	8/79	2/49	5/51	6/65	7/65	2/60	1/60	37/821	47/815
M - "C" cell carcinoma	1/65	0/65	0/80	0/79	2/49	0/51	1/65	0/65	0/60	0/60	6/821	0/815

(AMCYATHY.HCD)
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Reviewed By: William B. Greear, M.P.H. William B. Greear 7/7/91
Review Section II, Toxicology Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. Marion Copley 8/26/91
Review Section II, Toxicology Branch I (H7509C)

003605

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 Male	Main Study 24 Months Female	Interim Sacrifice 12 Months Male	Interim Sacrifice 12 Months 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.

51

(25)

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* (-28.0)
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)		

55

29

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	72*	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		X		X	
	Digestive		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*	XX	Thymus*		Glandular
X	Ileum*		Urogenital	XX	Adrenals*
X	Cecum*	XX	Kidneys*		Lacrimal gland
X	Colon*	X	Urinary bladder*	X	Mammary gland*
X	Rectum*	XX	Testes*	X	Parathyroids*
XX	Liver*		Epididymides	XX	Thyroids
	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 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. 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) 0	100	500	5000	Females (ppm) 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

61

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.]

Table 2.
Historical Control Data for Thyroid Proliferative Lesions in the Sprague-Dawley Rat

	Hazleton - Wisconsin (1985-1990)			Hazleton - Washington (1985-1990)			Charles River (1977-1985)		
	Incidence	%	Range	Incidence	%	Range	Incidence	%	Range
Males									
Follicular Cell Hyperplasia	NA	NA	NA	2/835	0.2	0-1.7	NA	NA	NA
Follicular Cell Adenoma	26/821	3.2	0-8.1	35/835	4.2	0-12.0	11/866	1.3	0-5.3
Follicular Cell Carcinoma	1/821	0.1	0-2.0	17/835	2.0	0-6.7	14/866	1.6	0-8.2
Follicular Cell Adenoma and Carcinoma	27/821	3.3	0-8.1	ND	ND	ND	ND	ND	ND
Females									
Follicular Cell Hyperplasia	NA	NA	NA	2/834	0.2	0-3.0	NA	NA	NA
Follicular Cell Adenoma	15/815	1.8	0-5.7	7/834	0.8	0-2.1	4/869	0.5	0-1.8
Follicular Cell Carcinoma	0/815	0.0	0.0	8/834	1.0	0-2.1	11/869	1.3	0-9.1
Follicular Cell Adenoma and Carcinoma	15/815	1.8	0-5.7	ND	ND	ND	ND	ND	ND

NA = not available
ND = not determined, due to inability to exclude possible redundancy

(37)

63

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TABLE 3

HISTORICAL CONTROL DATA FOR THYROID NEOPLASMS IN THE SPRAGUE-DAWLEY RAT

HAZLETON WISCONSIN, INC. (1985-1990)

[redacted]

HAZLETON WISCONSIN, INC.

UNAUDITED

HISTORICAL CONTROL DATA FOR THYROID NEOPLASMS IN THE SPRAGUE-DAWLEY RAT

1985 - 1990

Symbols Prefacing Neoplastic Findings

B = Primary, benign neoplasm
M = Primary, malignant neoplasm
N = Metastatic neoplasm
I = Locally invasive neoplasm
X = Other neoplasm

Study Code	R(SD)C1		R(SD)C2		R(SD)C3		R(SD)C4		R(SD)C5		R(SD)C7		R(SD)C8		R(SD)C9	
Year Completed	1990		1985		1988		1987		1986		1987		1985		1985	
Study Duration (weeks)	104		104		104		104		104		104		104		104	
Pathologist Code	6		39		39		39		39		29		39		29	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Tumor Type																
Thyroid																
B - Follicular cell adenoma	3/37	1/30	1/60	0/60	0/60	0/60	3/60	1/60	3/90	1/90	2/70	4/70	3/65	2/65	4/60	2/60
M - Follicular cell carcinoma	0/37	0/30	0/60	0/60	0/60	0/60	0/60	0/60	0/90	0/90	0/70	0/70	0/65	0/65	0/60	0/60
B - "C" cell adenoma	2/37	2/30	1/60	3/60	0/60	1/60	1/60	2/60	2/90	2/90	2/70	4/70	2/65	3/65	5/60	3/60
M - "C" cell carcinoma	0/37	0/30	0/60	0/60	0/60	0/60	0/60	0/60	0/90	0/90	1/70	0/70	0/65	0/65	1/60	0/60

Study Code	R(SD)C10		R(SD)C11		R(SD)C12		R(SD)C14		R(SD)C15		Totals	
Year Completed	1987		1986		1985		1987		1989			
Study Duration (weeks)	104		104		104		104		104			
Pathologist Code	42		39		42		42		39			
	M	F	M	F	M	F	M	F	M	F	M	F
Tumor Type												
Thyroid												
B - Follicular cell adenoma	3/65	1/65	0/80	1/79	1/49	1/51	1/65	1/65	2/60	0/60	26/821	15/815
M - Follicular cell carcinoma	0/65	0/65	0/80	0/79	1/49	0/51	0/65	0/65	0/60	0/60	1/821	0/815
B - "C" cell adenoma	9/65	6/65	3/80	0/79	2/49	5/51	6/65	7/65	2/60	1/60	37/821	47/815
M - "C" cell carcinoma	1/65	0/65	0/80	0/79	2/49	0/51	1/65	0/65	0/60	0/60	6/821	0/815

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(39)

TABLE 4

HISTORICAL CONTROL DATA FOR THYROID LESIONS IN THE SPRAGUE-DAWLEY RAT

HAZLETON WASHINGTON (1985-1990)

HISTORICAL HISTOPATHOLOGY DATA
Rat, Sprague-Dawley, Dietary
Study Durations 104 Weeks

TERM, FOUND DEAD, AND MORIBUND SACRIFICED ANIMALS	1988	1989	1989	1987/88	1988	1988	1988			
MALE ANIMALS	A	B	C	D	E	F	G			TOTAL
THYROID Number Examined	49	60	59	65	70	48	48			399
Follicular Cell Hyperplasia	0	1	0	0	0	0	0			1
Percent (%)	0.0	1.7	0.0	0.0	0.0	0.0	0.0			0.3
Follicular Cell Adenoma	2	4	1	3	2	3	2			17
Percent (%)	4.1	6.7	1.7	4.6	2.9	6.3	4.2			4.3
Follicular Cell Carcinoma	2	4	0	0	2	0	1			9
Percent (%)	4.1	6.7	0.0	0.0	2.9	0.0	2.1			2.3
"C" Cell Hyperplasia	11	0	16	2	2	4	4			39
Percent (%)	22.4	0.0	27.1	3.1	2.9	8.3	8.3			9.8
"C" Cell Adenoma	6	4	7	7	6	2	7			39
Percent (%)	12.2	6.7	11.9	10.8	8.6	4.2	14.6			9.8
"C" Cell Carcinoma	3	6	2	1	2	0	0			14
Percent (%)	6.1	10.0	3.4	1.5	2.9	0.0	0.0			3.5
FEMALE ANIMALS	A	B	C	D	E	F	G			TOTAL
THYROID Number Examined	50	60	60	66	69	48	49			402
Follicular Cell Hyperplasia	0	0	0	2	0	0	0			2
Percent (%)	0.0	0.0	0.0	3.0	0.0	0.0	0.0			0.5
Follicular Cell Adenoma	1	1	0	1	1	0	0			4
Percent (%)	2.0	1.7	0.0	1.5	1.4	0.0	0.0			1.0
Follicular Cell Carcinoma	0	1	0	0	0	1	0			2
Percent (%)	0.0	1.7	0.0	0.0	0.0	2.1	0.0			0.5
"C" Cell Hyperplasia	16	0	31	6	6	4	0			63
Percent (%)	32.0	0.0	51.7	9.1	8.7	8.3	0.0			15.7
"C" Cell Adenoma	5	7	11	5	7	6	2			43
Percent (%)	10.0	11.7	18.3	7.6	10.1	12.5	4.1			10.7
"C" Cell Carcinoma	1	6	3	5	3	2	0			20
Percent (%)	2.0	10.0	5.0	7.6	4.3	4.2	0.0			5.0

HISTORICAL HISTOPATHOLOGY DATA
Rat, Sprague-Dawley, Dietary
Study Duration: 104 Weeks

TERM, FOUND DEAD, AND MORIBUND SACRIFICED ANIMALS

	1986	1987	1985	1987	1987	1987	1987	1987	
MALE ANIMALS	H	I	J	K	L	M	N	O	TOTAL
THYROID — Number Examined	50	50	49	50	50	50	49	50	436
Follicular Cell Hyperplasia	0	0	0	1	0	0	0	0	1
Percent (%)	0.0	0.0	0.0	1.1	0.0	0.0	0.0	0.0	0.2
Follicular Cell Adenoma	2	2	0	1	6	4	2	1	18
Percent (%)	4.0	4.0	0.0	1.1	12.0	8.0	4.1	2.0	4.1
Follicular Cell Carcinoma	3	1	0	2	0	2	0	0	8
Percent (%)	6.0	2.0	0.0	2.3	0.0	4.0	0.0	0.0	1.8
"C" Cell Hyperplasia	8	10	6	9	5	4	2	2	46
Percent (%)	16.0	20.0	12.2	10.2	10.0	8.0	4.1	4.0	10.6
"C" Cell Adenoma	1	6	3	8	1	4	1	0	24
Percent (%)	2.0	12.0	6.1	9.1	2.0	8.0	2.0	0.0	5.5
"C" Cell Carcinoma	0	2	0	1	3	1	4	4	15
Percent (%)	0.0	4.0	0.0	1.1	6.0	2.0	8.2	8.0	3.4
FEMALE ANIMALS	H	I	J	K	L	M	N	O	TOTAL
THYROID — Number Examined	48	50	49	89	50	48	50	48	432
Follicular Cell Hyperplasia	0	0	0	0	0	0	0	0	0
Percent (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Follicular Cell Adenoma	1	0	1	0	0	0	1	0	3
Percent (%)	2.1	0.0	2.0	0.0	0.0	0.0	2.0	0.0	0.7
Follicular Cell Carcinoma	1	1	1	0	1	1	0	1	6
Percent (%)	2.1	2.0	2.0	0.0	2.0	2.1	0.0	2.1	1.4
"C" Cell Hyperplasia	2	8	9	3	2	3	8	1	36
Percent (%)	4.2	16.0	18.4	3.4	4.0	6.3	16.0	2.1	8.3
"C" Cell Adenoma	1	5	7	6	5	2	4	1	31
Percent (%)	2.1	10.0	14.3	6.7	10.0	4.2	8.0	2.1	7.2
"C" Cell Carcinoma	2	1	1	0	3	1	3	1	12
Percent (%)	4.2	2.0	2.0	0.0	6.0	2.1	6.0	2.1	2.8

(42)

TABLE 5

HISTORICAL CONTROL DATA FOR THYROID NEOPLASMS IN THE SPRAGUE-DAWLEY RAT

CHARLES RIVER LABORATORIES (1977-1985)

CHARLES RIVER CD® RAT, MALE: 24 MONTHS

TABLE 1 Continued
SUMMARY OF NEOPLASTIC LESIONS

LOCATION & TUMOR	# EXAM.	# TUMOR	PERCENT	RANGE
LIVER	880			
neoplastic nodule		15	1.7	0-12.0
liver nodules		32	3.6	0-23.6
nodular hepatocellular proliferation		10	1.1	0- 6.1
hepatocellular adenoma		7	0.8	0- 3.5
hepatocellular carcinoma		19	2.2	0-11.1
hepatoma		12	1.4	0-10.9
cholangioma		1	0.1	0- 1.0
hemangioma		1	0.1	0- 1.1
lipoma		2*	0.2	0- 2.2
fibrous histiocytoma (M)		1	0.1	0- 1.3
PANCREAS (EXOCRINE)	867			
adenoma (NOS)		4	0.5	0- 1.4
acinar cell adenoma		5	0.6	0- 4.1
PANCREAS (ENDOCRINE)	867			
islet cell adenoma		33	3.8	0- 8.0
islet cell carcinoma		14	1.6	0- 9.0
islet cell tumor		3*	0.3	0- 3.5
URINARY SYSTEM				
KIDNEY	880			
tubular cell adenoma		3*	0.3	0- 3.0
renal neoplasia (NOS)		1	0.1	0- 1.0
carcinoma (NOS)		1	0.1	0- 1.1
mixed cell tumor		1	0.1	0- 1.3
nephroblastoma		1	0.1	0- 1.3
lipoma		1	0.1	0- 1.1
hamartoma		2	0.2	0- 1.8
URINARY BLADDER	860			
REPRODUCTIVE SYSTEM				
TESTIS	880			
interstitial cell tumor (B)		31	3.5	0-12.0
interstitial cell tumor (M)		1	0.1	0- 1.1
interstitial cell tumor (NOS)		23	2.6	0- 9.1
gonadal stromal sarcoma (NOS)		1	0.1	0- 1.0
gonadal stromal tumor (NOS)		1	0.1	0- 1.0
seminoma (B)		1	0.1	0- 1.3
hemangioma		1	0.1	0- 1.2
PROSTATE	869			
adenocarcinoma		2	0.2	0- 1.4
carcinoma (NOS)		2	0.2	0- 1.3
fibrosarcoma		1	0.1	0- 1.3
leiomyosarcoma		1	0.1	0- 1.3
ENDOCRINE SYSTEM				
PITUITARY GLAND	859			
adenoma (NOS)		327	38.1	26.3-50.0
basophil adenoma		1	0.1	0- 1.3
adenoma, pars intermedia		1	0.1	0- 1.0
adenocarcinoma		33	3.9	0-24.7
carcinoma (NOS)		2*	0.2	0- 2.8
THYROID GLAND	866			
follicular cell adenoma		11	1.3	0- 5.3
follicular cell carcinoma		14	1.6	0- 8.2
C-cell adenoma		25	2.9	0- 6.8
medullary carcinoma		9	1.1	0- 7.0
Hurthle cell adenoma		1	0.1	0- 1.2
adenoma (NOS)		5*	0.6	0- 5.6
follicolomedullary carc.		1	0.1	0- 1.0
carcinoma, undif.		8*	0.9	0- 8.2
PARATHYROID GLAND	499			
adenoma		9	1.8	0- 4.3
ADRENAL GLAND	878			
cortical adenoma		29	3.3	0-21.0
adenoma (NOS)		3	0.3	0- 1.8
carcinoma (NOS)		3	0.3	0- 1.3
pheochromocytoma (B)		53	6.0	0-18.0
pheochromocytoma (M)		3	0.3	0- 2.2
pheochromocytoma (NOS)		15	1.7	0-10.0

70

TABLE 2 — Continued
SUMMARY OF NEOPLASTIC LESIONS

009525

LOCATION & TUMOR	# EXAM.	# TUMOR	PERCENT	RANGE
MUSCULOSKELETAL SYSTEM				
SKELETAL MUSCLE	877			
BONE	790			
osteosarcoma		1	0.1	0- 11.1
RESPIRATORY SYSTEM				
TRACHEA	725			
LUNG	877			
CIRCULATORY SYSTEM				
HEART	877			
endocardial sarcoma		1	0.1	0- 11.0
DIGESTIVE SYSTEM				
SALIVARY GLAND	838			
ESOPHAGUS	786			
STOMACH	878			
adenocarcinoma		1	0.1	0- 11.1
basal cell carcinoma		2*	0.2	0- 22.0
leiomyoma		1	0.1	0- 11.3
leiomyosarcoma		1	0.1	0- 11.3
SMALL INTESTINE	878			
leiomyoma		1	0.1	0- 11.3
leiomyosarcoma		1	0.1	0- 11.3
LARGE INTESTINE	876			
leiomyosarcoma		1	0.1	0- 11.3
LIVER	880			
neoplastic nodules		12	1.4	0- 22.0
liver nodule		23	2.6	0-200.0
nodular hepatocellular proliferation		4	0.5	0- 22.0
hepatocellular adenoma		2	0.2	0- 11.3
hepatocellular carcinoma		15	1.7	0-100.0
hepatoma		2	0.2	0- 11.8
cholangioma		1	0.1	0- 11.3
cholangiocarcinoma		1	0.1	0- 11.3
hemangiosarcoma		1	0.1	0- 11.3
PANCREAS (EXOCRINE)	853			
adenoma (NOS)		1	0.1	0- 11.2
PANCREAS (ENDOCRINE)	853			
islet cell adenoma		8	0.9	0- 44.0
islet cell carcinoma		6	0.7	0- 33.0
islet cell tumor		4	0.5	0- 77.3
URINARY SYSTEM				
KIDNEY	880			
tubular cell adenoma		1	0.1	0- 11.0
renal cell adenoma		1	0.1	0- 11.3
hemangioma		1	0.1	0- 11.1
URINARY BLADDER	861			
adenomatous polyp		1	0.1	0- 11.4
REPRODUCTIVE SYSTEM				
OVARY	875			
granulosa cell tumor (NOS)		6	0.7	0- 55.1
granulosa cell tumor (B)		2	0.2	0- 11.4
fibroma		1	0.1	0- 11.3
fibrosarcoma		1	0.1	0- 11.1
UTERUS	815			
endometrial stromal polyp		39	4.8	1.3-12.2
adenoma (NOS		2	0.2	0- 11.3
adenocarcinoma (NOS)		1	0.1	0- 11.4
endometrial carcinoma		1	0.1	0- 11.0
carcinoma in situ		1	0.1	0- 11.8
leiomyoma		2	0.2	0- 11.3
leiomyosarcoma		4	0.5	0- 22.1
hemangioma		2*	0.2	0- 22.2
endometrial sarcoma		1	0.1	0- 11.0
sarcoma, undifferentiated		1	0.1	0- 11.2
sarcoma (NOS)		1	0.1	0- 11.1
ENDOCRINE SYSTEM				
PITUITARY GLAND	865			
adenoma (NOS)		492	57.0	35.7-78.2
clear cell adenoma		1	0.1	0- 11.0
adenocarcinoma		52	6.0	0-88.7
carcinoma (NOS)		8	0.9	0- 55.6
THYROID GLAND	869			
follicular cell adenoma		4	0.5	0- 11.8
follicular cell carcinoma		11	1.3	0- 89.1
C-cell adenoma		36	4.1	0-133.5
medullary carcinoma		10	1.2	0- 44.0
adenoma (NOS)		3	0.3	0- 22.2
carcinoma, undif.		5*	0.6	0- 55.6

(71) (45)

TABLE 7
EXPANDED TABLE OF TESTICULAR TUMORS IN CD® RATS: 24 MONTHS

TUMOR		GROUP										
	N=	A 80	B 80	C 86	D 75	E 75	F 100	G 90	H 55	I 89	J 25	K 35
interstitial cell tumor (B)		—	—	2	2	2	6	4	—	—	9	6
interstitial cell tumor (M)		—	—	—	—	—	—	1	—	—	—	—
interstitial cell tumor (NOS)		3	7	—	—	—	—	—	5	8	—	—

TABLE 8
EXPANDED TABLE OF THYROID TUMORS IN CD® RATS: 24 MONTHS

MALE

TUMOR		GROUP										
	N=	A 78	B 80	C 86	D 75	E 71	F 100	G 90	H 53	I 85	J 25	K 35
follicular cell adenoma		—	1	1	2	1	—	—	—	—	4	2
follicular cell carcinoma		—	1	—	2	—	—	—	2	7	1	2
C-cell adenoma		3	—	4	2	1	5	—	—	—	5	5
medullary carcinoma		—	1	—	1	—	7	—	—	—	—	—
carcinoma, undifferent.		—	—	—	—	—	—	8	—	—	—	—
adenoma, (NOS)		—	—	—	—	—	—	5	—	—	—	—

FEMALE

TUMOR		GROUP										
	N=	A 78	B 80	C 86	D 75	E 74	F 98	G 90	H 55	I 86	J 23	K 34
follicular cell adenoma		1	—	1	—	—	—	—	1	—	—	1
follicular cell carcinoma		—	—	—	—	—	2	—	5	4	—	—
C-cell adenoma		1	1	1	4	3	8	—	—	—	8	11
medullary carcinoma		—	—	2	3	2	3	—	—	—	—	—
carcinoma, undifferent.		—	—	—	—	—	—	5	—	—	—	—
adenoma, (NOS)		1	—	—	—	—	—	2	—	—	—	—

(16)

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009525

DATA EVALUATION REPORT

STUDY TYPE: 2-year onco - rat(male)(83-5)
TOX. CHEM NO: 454BB
PC No.: 108501
TEST MATERIAL: Pendimethalin
MRID NO.: 420278-02

SYNONYMS: AC 92,553

STUDY NUMBER: HLA 362-191

SPONSOR: American Cyanamid

TESTING FACILITY: Hazleton Laboratories America, Inc. Rockville, Maryland

TITLE OF REPORT: Effects of chronic dietary administration of AC 92,553 on the function and structure of male rat thyroids.

AUTHOR(S): D.E. Bailey

REPORT ISSUED: 9/10/91

CONCLUSION: NOEL systemic < 1250 ppm (51 mg/kg/day)
LEL < 1250 ppm based on non-neoplastic thyroid follicular cell changes and increased liver weight. In addition there was an increase in thyroid weight and non-neoplastic liver pathology at 2500 ppm and above. There was a decrease in body weight gain at 3750 ppm. At 5000 ppm (213 mg/kg/day) GGT and total cholesterol were increased.
Thyroid function NOEL = 3750 ppm (154 mg/kg/day)(not definitive).
LEL = 5000 ppm based on a TSH increased.
Thyroid pathology NOEL < 1250 ppm.
LEL ≤ 1250 ppm based on decreased colloid and increase of cysts. At 2500 ppm (103 mg/kg/day) there was an increase of pigment and hypertrophy of follicular cells. At 3750 ppm and above there was also hyperplasia. Thyroid follicular adenomas were increased at 5000 ppm.

Male Sprague Dawley (Crl:CD(SD)BR) rats were exposed to 0, 1250, 2500, 3750 or 5000 ppm (approximately 0, 51, 103, 154 or 213 mg/kg/day) in the diet for up to 2 years.

Classification: core-supplementary, does not satisfy the guideline requirements for a chronic/oncogenicity rodent study due to the study design and purpose of this study.

Special Review Criteria (40 CFR 154.7) - There is an increase in male thyroid tumors.

A. MATERIALS:

1. Test compound: Pendimethalin (AC 92,533). Description - yellowish-orange solid, Lot # - AC 5213-72A, Purity - 92.6%, stored in ambient conditions.

2. Test animals: Male, Species: Rat, Strain: Sprague Dawley (Crl:CD(SD)BR), Age: 36 days old, Weight (range): 121.9-169.5 gm, Source: Charles River Labs, Portage, Michigan. Acclimatization: 1 week. Animals were individually housed in environmentally controlled rooms.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned by a computer generated weight randomization program to the test groups as noted in table 1. Animals were exposed to the test compound in the diet daily for 2 years.

TABLE 1 Experimental design, males only

Test Group	ppm in diet	weeks on diet for interim and final sacrifices 1	13	26	39	52	104
1 Cont.	0	15	15	15	15	15	50
2 Low (LDT)	1250	15	15	15	15	15	50
3 Mid 1(MDT1)	2500	15	15	15	15	15	50
4 Mid 2(MDT2)	3750	15	15	15	15	15	50
5 High (HDT)	5000	15	15	15	15	15	50

2. Compound/diet preparation

Pendimethalin/diets were prepared weekly. Adjustment was made for purity. Compound was crushed in a mortar and pestle then premixed in a blender with about 200 grams of feed. This was added to additional feed in a mixer resulting in the final test diet. Prior to the study samples of the 1250 and 5000 ppm test diets were taken at preparation, and 7 and 14 days and submitted to the sponsor for analysis. All levels were sampled weekly.

Results - Stability, homogeneity and concentration appeared to be adequate based on data presented in the study.

3. Animals received food (Purina lab rodent chow #5002) and water ad libitum.

4. Statistics - The procedures utilized in analyzing the numerical data are in attachment 1 taken from the study report.

5. Signed GLP and quality assurance statements are present.

C. METHODS AND RESULTS:

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

   Toxicity/Mortality (survival) - Survival did not appear to be affected by treatment with 52, 36, 40, 36 and 40% survival for controls to the high dose.
   Signs of toxicity were sporadic, not dose related and were not considered treatment related. Urine in treatment groups was slightly orange to darker orange/brown. This was probably due to the test material (metabolites).

2. Body weight - Animals were weighed weekly.

   Body weight gain for the 104 weeks of the study are decreased 8, 14, 21 % for the 2500, 3750 and 5000 ppm groups, respectively, when compared to controls. As can be seen in table 3 (table 3B taken from the study report) weight gain is statistically decreased in 2500 ppm and above. However, this statistical decrease is only greater than 10% of controls at 5000 ppm (15 - 36 % throughout most of the study), and at 2500 ppm (11 %) and 3750 ppm (25%) after week 39 for the rest of the first year.

   TABLE 3 (taken from the study report)

TABLE 3B
MEAN BODY WEIGHT CHANGE (G)
CHRONIC DIETARY OF AC 92,553

HLA 362191

GROUP AND DOSE LEVEL (PPM)		WEEK 0 - 1	0 - 13	0 - 26	0 - 39	0 - 52	0 - 104
				MALES			
1	MEAN	60 3	406 5	512 3	568 9	625 5	558 5
	S D	5 17	42 63	59 46	75 39	81 51	104 10
.000	N	125	110	95	80	65	26
2	MEAN	61 1	397 2	505 9	565 2	614 9	569 4
	S D	5 56	45 27	57 95	69 14	81 90	130 41
1250.000	N	125	109	94	79	63	18
3	MEAN	56 4*	386 1*	488 2*	541 8	592 1*	511 3
	S D	6 11	39 01	49 59	57 96	71 53	128 11
2500.000	N	125	110	94	79	64	21
4	MEAN	49 4*	374 0*	472 0*	526 7*	569 1*	481 0
	S D	8 16	34 64	49 10	58 72	73 52	115 63
3750.000	N	125	110	94	79	64	19
5	MEAN	44 9*	348 7*	446 2*	492 4*	528 4*	439 4*
	S D	7 66	33 36	46 27	49 18	57 80	129 34
5000 000	N	125	110	95	79	64	20

* Significantly different from control value, $p \leq 0.05$.

73
75

(49)

3. Food consumption and compound intake - Food consumption was measured weekly.

Food consumption (g/animal) (see table 4 taken from the study) was decreased statistically in the 5000 ppm group from week 1 - 26, in the 2500 and 3750 ppm groups from week 1 - 13. None of these decreases were greater than 8 %and were therefore probably not related to treatment.

TABLE 4 (taken from the study report)

TABLE 4B HLA 362191
MEAN TOTAL FOOD CONSUMPTION AND STANDARD DEVIATIONS (G)
CHRONIC DIETARY OF AC 92.553

GROUP AND DOSE LEVEL (PPM)		WEEK 1	1 - 13	1 - 26	1 - 39	1 - 52	1 - 104
				MALES			
1	MEAN	161 3	2388 7	4693 4	6968 4	9312 7	18598 6
	S D	11.52	126.91	272 85	403 60	551 66	837 99
000	N	124	70	55	39	32	7
2	MEAN	182 3	2372 6	4687 9	7035 2	9382 2	18731 5
	S D	9.83	131 50	251 63	351 36	518 10	706 96
1250 000	N	123	70	59	45	29	2
3	MEAN	157 8	2316 6 *	4624 1	6986 0	9373 8	18436 0
	S D	10.72	139 76	294 13	399 83	539 41	1453 53
2500 000	N	99	74	58	42	31	3
4	MEAN	151 9 *	2266 2 *	4582 7	6948 3	9234 3	19134 6
	S D	18 69	144 71	299 16	426 73	621 13	486 87
3750 000	N	68	49	38	28	21	3
5	MEAN	146 8 *	2220 6 *	4510 8 *	6806 5	9073 8	18009 2
	S D	21 69	122 55	273 49	413 35	471 35	1703 51
5000 000	N	65	48	32	24	18	2

* Significantly different from control value. $p \leq 0.05$.

Compound intake - based on body weight and food consumption was presented in ranges with the highest consumed dose during the first 2 weeks of the study, decreasing for the next 14 weeks and plateauing for the remainder of the study. The time weighted average (calculated by the EPA reviewer)are presented in table 5.

009525

TABLE 5 Compound Intake - Time Weighted Average (mg/kg/day)

Concentration in Diet (ppm)	1250	2500	3750	5000
Dose week 1-13	85	168	211	338
week 1-104	51	103	154	213

4. Ophthalmological examination - This was not mentioned

5. Blood was collected from the 15 rats (fasted) scheduled for interim (weeks 1, 14, 27, 40, 53 and 104) and terminal sacrifices for clinical analysis (hematology was not performed). The CHECKED (X) parameters were examined.

   a. Hematology not performed

   b. Clinical Chemistry - general

X	Electrolytes:	X	Other:
X	Calcium*	X	Albumin*
X	Chloride*		Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
	Phosphorous*	X	Cholesterol*
X	Potassium*	X	Globulin and A/G ratio
X	Sodium*	X	Glucose*
	Enzymes	X	Total (and direct) bilirubin
X	Alkaline phosphatase (ALK)	X	Total serum Protein (TP)*
	Cholinesterase (ChE)		Triglycerides
	Creatinine phosphokinase*		Serum protein electrophoreses
X	Lactic acid dehydrogenase (LAD)		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
X	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic and chronic studies

Results - There was an increase in serum total cholesterol and GGT at most time points in the 5000 ppm group (see table 6). Statistical changes at other doses and in other parameters were probably not treatment-related since they only occurred at sporadic time points, were not dose related or were within the normal range for this species.

77

(5)

TABLE 6 Selected clinical chemistry values for week 40

Parameter	0 ppm	1250 ppm	2500 ppm	3750 ppm	5000 ppm
Tot. Chol. (mg/dl)	67	110*	104*	115*	142*
GGT (U/L)	1	1	2	2	3*

* $p \geq 0.05$

c. Clinical Chemistries - Thyroid function

In addition to the above the following thyroid function tests were also performed at weeks 1, 14, 27, 40 and 53:
triiodothyronine (T3)
reverse T3 (rT3)
thyroxine (T4)
thyroid stimulating hormone (TSH)

Free T3 and free T3 were also determined at week 53.

Results - Attached table 6A from the study report presents the thyroid function data.

- TSH (5000 ppm) was statistically increased (%) at 1 and 14 weeks of the study. Subsequent time point values, although increased were not statistical.
- T4 and free T4 (5000 ppm) were only statistically depressed at 53 weeks although there was evidence of depression at other time points. T4 was also decreased ($p < 0.05$) in the 2500 ppm group at 40 and 53 weeks but not 3750 ppm. It was increased however in the 3750 ppm group at 27 weeks.
- Changes in T3, rT3 and free T3 did not appear to be related to treatment since they were sporadic with regard to dose or time, or were of a small magnitude.

6. Urinalysis - not performed

7. Sacrifice and Pathology

Fifteen rats selected at random were sacrificed at each of the following times:weeks 1, 14, 27, 40 and 53. The remainder were sacrificed at 104 weeks. All animals that died and that were sacrificed on schedule were subject to gross pathological examination. Livers were weighed following trimming and thyroid/parathyroids were trimmed and fixed prior to weighing. The following tissues were preserved in 10% neutral-buffered formalin, and processed for histologic examination:

78

(52)

Thyroid/parathyroid
Liver
Gross lesions

a. Organ weight - As can be seen in table 7, absolute thyroid weight is consistently increased in males treated with 2500 ppm and above. Statistical significance however is apparent only at 14 and 26 weeks. Relative thyroid weights are statistically significant throughout most of the study at 3750 ppm and above.

TABLE 7 Organ weight - Absolute Thyroid (g)[a]

Week	0 ppm	1250 ppm	2500 ppm	3750 ppm	5000 ppm
1	.022	.020	.025	.024	.022
14	.026	.028	.030 (15%)	.032* (23%)	.032* (23%)
26	.035	.038 (9%)	.045* (28%)	.048* (37%)	.051* (46%)
40	.043	.049 (14%)	.049 (14%)	.050 (16%)	.050 (16%)
53	.050	.057 (14%)	.057 (14%)	.056 (12%)	.060 (20%)
104	.054	.056	.132[b]	.096[b]	.085[b]

* $p \geq 0.05$
a Does not include unscheduled deaths and moribund sacrifices.
b Standard deviations for these values were very large.

TABLE 8 Organ Weight - Relative Liver (to body weight)[1]

Week	0 ppm	1250 ppm	2500 ppm	3750 ppm	5000 ppm
1	3.609	4.036*	4.298*	4.410*	4.815*
14	2.529	2.950*	3.117*	3.262*	3.622*
26	2.452	2.800*	3.042*	3.431*	3.620*
40	2.362	2.728*	2.777*	3.084*	3.518*
53	2.487	2.647	3.048*	3.382*	3.472*
104	2.771	2.992*	3.460	3.789*	4.305*

* $p \geq 0.05$
1 Does not include unscheduled deaths and moribund sacrifices.

As can be seen in table 8, relative liver weight is increased in all groups at almost all time periods. Absolute liver weight is also statistically increased (8 - 55%) in a dose related manner in all groups throughout most of the study.

b. Gross pathology

Changes in thyroid gross pathology were first noted at the 14 week sacrifice and consisted of dark thyroid (2/15 rats) and enlarged thyroid (1/15 rats) at the high dose. By 27 weeks these observations had increased in frequency and occurred at 2500 ppm and above. Enlarged livers were also noted in these groups. These changes continued until term.

c. Microscopic pathology

Non-neoplastic lesions were observed in the thyroid and liver. In the thyroid there was a treatment related increase in follicular cell hypertrophy, hyperplasia and pigment, follicular cysts and a possible decreased colloid (see table 9).

TABLE 9 Select non-neoplastic thyroid follicular lesions (%)

Lesion	0 ppm	1250 ppm	2500 ppm	3750 ppm	5000 ppm
Hypertrophy	4	1	**8**	**17**	**34**
Hyperplasia	0	0	0	**2**	**2**
Pigment	53	54	**66**	**73**	**71**
Colloid decreased	2	**4**	**5**	**7**	**16**
Cysts	0	**3**	**3**	**8**	**5**
Colloid increased	1	1	1	**3**	**2**

N = 120, 116, 119, 120, 119 for controls to high dose (total animals examined for the study.

BOLD - most likely treatment related increase.

The following discussion of the individual thyroid follicular lesions is supported by table 12 at the end of this DER.

Hypertrophy increases occur as early as 1 week in the 2500 ppm (and above) group with a dose related response. Although the response appears to

temporarily diminish by week 26, there is a strong response by week 104 in the same treatment groups.

Hyperplasia increased only slightly at 3750 and 5000 ppm. Due to the low incidence it is difficult to characterize it as to time on study.

Pigment does not occur in any animals until week 26. At this time it occurred in all groups including controls. However, there was a marked increase at 3750 ppm and 5000 ppm (40%, 40%, 47%, 100% and 100% for controls to high dose). At week 40, the 2500 ppm treatment animals were also 100 % affected. By week 53 almost all animals in all groups had pigment in the thyroids (including controls).

Decreased colloid occurred sporadically throughout the study 7%, 33%, 33%, 33% and 80 % for controls to high dose). As the study progressed the incidence decreased and the lowest dose affected increased. By 53 weeks there were no cases.

Cysts did not occur in any control animals. Increases were present in all treated groups. The low dose animals were not affected until 53 weeks. They occurred sporadically in higher doses as early as 26 weeks, however.

Increased colloid was present in all groups and occurred sporadically throughout the study (1%, 1%, 1%, 3% and 2% for controls to high dose). It is difficult to determine if this effect is treatment related.

In the liver there was a treatment related increase in eosinophilic and basophilic foci of cellular alteration, hepatocellular enlargement and hepatocellular intracytoplasmic eosinophilic inclusions in groups at 2500 ppm and above. There was also an increase in periportal vacuolization at 3750 ppm and 5000 ppm (see table 10).

The incidence of **eosinophilic cellular** alteration is comparable among control and treated groups up to 52 weeks. At 104 weeks the incidence is increased at 2500 ppm and above (15, 22, 40, 67 and 40 % for control to high dose).

The incidence of **basophilic cellular alteration** is increased at 2500 ppm and above for unscheduled deaths and is also increased at 104 weeks.

Hepatocellular enlargement increased as early as 14 weeks in the 5000 ppm group, 26 weeks in the 3750 ppm group and 40 weeks in the 2500 ppm group. This lesion does not occur in the control and 1250 ppm groups.

The incidence of **hepatocellular intracytoplasmic** eosinophilic inclusions is observed as early as 26 weeks in the 3750 ppm and 5000 ppm groups and 40 weeks in the 2500 ppm group. This lesion is not observed in the 1250 ppm and controls.

By 14 weeks and clearly by 26 weeks, there appears to be a dose-related increase in the incidence of **periportal vacuolization** at 3750 ppm and above.

TABLE 10 Select non-neoplastic liver lesions in per cent

Lesion	0 ppm	1250 ppm	2500 ppm	3750 ppm	5000 ppm
Eosinophilic cellular alteration	6	3	**10**	**10**	**12**
Basophilic cellular alteration	6	9	**21**	**18**	**18**
Hepatocellular enlargement	0	0	**5**	**14**	**18**
Intracytoplasmic inclusions	0	0	**3**	**16**	**28**
Periportal vacuolization	2	0	0	**7**	**16**

N = 125, 124, 125, 125, 125 for controls to high dose (total animals examined for the study.
BOLD - most likely treatment related increase.

Neoplastic lesions (Thyroid follicular cell adenomas) are presented in table 11.

TABLE 11 Thyroid Tumors in Male Rats

	0 ppm	1250 ppm	2500 ppm	3750 ppm	5000 ppm
Follicular cell adenoma[1]	4/90(4)**	7/85(8)	7/88(8)	6/89(7)	15/89(17)**
Follicular cell carcinoma[2]	1/60(2)	1/54(2)	4/58(7)	3/59(5)	2/59(3)
Follicular cell tumors	5/90(6)**	8/85(9)	11/88(12)	9/89(10)	17/89(19)**

1 Denominator represents animals at risk, survivors after occurrence of first tumor.
Adenoma - first tumor ar week 27.
2 Carcinoma - first tumor at week 67.
Trend noted at controls, **pair-wise comparison** noted at dose group
** $p < 0.01$

The treatment related thyroid tumor response is limited to the 5000 ppm group and consists solely of follicular cell adenoma. This is consistent with an earlier rat oncogenicity study.

Historical control data are attached to this DER.

DISCUSSION

This was a well conducted and reported study. The treatment levels were mg/kg/day in the diet. Body weight gain was decreased greater than 10 % from 3750 ppm. The decrease in food consumption was minimal and probably not related to treatment.

Clinical chemistries (other than thyroid tests) that appeared to be affected by treatment included total cholesterol, increased at all dose levels and GGT, increased at 2500 ppm and above. The cholesterol increase is statistically significant, especially at the 5000 ppm dose. GGT is increased slightly from 2500 ppm and above and may be related to treatment.

The thyroid function test results were not as conclusive as those obtained in a 92 day study. One explanation for this is the age of the rat at initiation of treatment. The 92 day study started with 13 week old rats while those in this study were only 5 weeks old. TSH does however appear to be increased at 5000 ppm. Liver weight is increased at all doses and thyroid is also increased statistically from 2500 ppm and above. There is evidence of thyroid follicular effects (histologically) at all doses (decreased colloid and increased cysts). Pigment and hypertrophy of the follicular cells occurred at 2500 ppm. Hyperplasia was present to a limited extent only at 3750 and 5000 ppm. Thyroid follicular cell adenomas were increased only at 5000 ppm. Carcinomas were not increased. The earliest adenoma was observed at 26 weeks in the control group.

TABLE 12 Select Non-neoplastic Thyroid Follicular Lesions (%)

LESION	PPM Week	0	1250	2500	3750	5000
Hypertrophy	1	7	7	27	40	53
	14	7	0	0	13	53
	26	0	0	0	0	0
	40	0	0	0	0	20
	53	0	0	0	0	7
	104	8	0	30	44	45
	UD	5	8	0	15	20
Hyperplasia	1	0	0	0	0	0
	14	0	0	0	0	0
	26	0	0	0	0	0
	40	0	0	0	7	7
	53	0	0	0	0	0
	104	0	0	0	0	0
	UD	0	0	0	4	4
Pigment	1	0	0	0	0	0
	14	0	0	0	0	0
	26	40	40	47	100	100
	40	40	47	100	100	100
	53	93	100	100	100	100
	104	100	100	100	100	100
	UD	60	68	80	89	80
Colloid decreased	1	7	33	33	33	80
	14	7	0	7	13	27
	26	0	0	0	0	0
	40	0	0	0	7	20
	53	0	0	0	0	0
	104	0	0	0	0	0
	UD	0	0	0	0	0
Cysts	1	0	0	0	0	0
	14	0	0	0	0	0
	26	0	0	0	7	0
	40	0	0	0	7	7
	53	0	7	7	13	0
	104	0	0	5	11	15
	UD	0	8	4	11	13

UD - animals found dead of sacrifices moribund
N = 15 for weeks 1, 14, 26, 40 and 53
N = 26, 18, 20, 18, 20 for week 104 (control to high dose)
N = 19, 25, 24, 27, 25 for UD animals (control to high dose)
BOLD - most likely treatment related increase.

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Pendimethalin Tox review 009525

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Pages 85 through 90 are not included.

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85-90

Attachment #5

Reviewed By: William B. Greear, M.P.H. William B. Greear
Review Section IV, Toxicology Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. Marion Copley 3/27/92
Review Section IV, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT

Study Type: 92-Day Thyroid Function Study - Rats (Related to 83-1, 83-2, Study No. HLA 6123-112)

TOX Chem No: 454BB
PC No.: 108501
MRID No.: 420546-01

Test Material: AC 92,553, 92.6 percent pure

Synonyms: Pendimethalin, PROWL; N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine

Study Number: T-0270

Sponsor: American Cyanamid Company
Princeton, NJ 08543

Testing Facility: Toxicology Department
American Cyanamid Company
Agricultural Research Division
Princeton, NJ 08543-0400

Title of Report: 92-Day Thyroid Function Study in Albino Rats with AC 92,553

Author: Joel E. Fischer

Report Issued: August 5, 1991

Conclusions: NOEL < 100 ppm (4.98 mg/kg/day)
LEL = 100 ppm (based on decreases in T_3 and T_4)

In addition, at 5000 ppm (245.4 mg/kg/day), there were decreases in body weight, body weight gain, increases in TSH levels, in absolute and relative thyroid weight and in the incidence and severity hypertrophy of thyroid follicular epithelial cells.

Classification: Supplementary based on design and intent.

G

A. Materials

1. Test Compound - AC 92,553; Description: orange-yellow crystals; Lot No.: 5213-72A; Purity: 92.6 percent; Contaminants: not reported.

2. Test Animals - Species: rat; Strain: CD[Crl:CD(SD)]; Age: 13 weeks at start of feeding; Weight: males - 430 to 507 g, females - not tested; Source: Charles River Breeding Laboratories, Inc., Wilmington, MA.

B. Study Design:

1. Animal Assignment - Animals were randomly assigned to the following test groups.

92-Day Thyroid Function Study

Test Group	Dose in Diet (ppm)	Day of Sacrifice 15 No. Males	29 No. Males	57 No. Males	92 No. Ma
Control	0	20	20	20	20
Low	100	20	20	20	20
High	5000	20	20	20	20

The rats were acclimatized to laboratory conditions for 5 weeks prior to start of feeding. The rats were individually housed in stainless-steel suspended cages with screen bottoms in a room at a temperature of 72 °F ± 4 °, relative humidity of 50 percent ± 2 percent and a 12-hour on/12-hour off light cycle. Food (Purina Certified Rodent Chow #5002 and water were provided ad libitum.

2. Diet Preparation - The diets were prepared by adding the proper amount of AC 92,553 to an initial premix of basal diet and blending in a Waring blender for 1 to 2 minutes. The premix was added to approximately 2 kg of basal diet and mixed for 2 to 3 minutes in a Hobart mixer. The amount was then transferred to a large Readco bowl mixer or Davis ribbon blender. The remainder of the basal diet was added and blended for 10 to 15 minutes. The test diets were prepared weekly and the test diet concentrations were adjusted to correct for the purity of the test material. At initiation of the study, batches of low- and high-concentration diets were analyzed for

92

homogeneity by measuring the top, middle, and bottom concentrations from left to right. Stability was determined by analyzing the diets from feed exposed for 8 days in the rat room.

Results - The concentration of the test substance (homogeneity sample) found in the 100 ppm test diet ranged from 89.7 to 109.0 percent with a mean of 97.5 percent and a coefficient of variation of 7.1 percent. The concentration of the test substance (homogeneity samples) found in the 5000 ppm diet ranged from 97.2 to 106.5 percent with a mean of 101.4 percent and coefficient of variation of 0.1 percent. The concentration of the test substance from the 100 ppm stability samples taken from feeders exposed for 8 days in the animal room averaged 92.4 percent. Stability samples taken from the 5000 ppm diet after 8 days averaged 106.1 percent. The average test diet concentration in the 100 ppm weekly diet ranged from 85.6 to 109.3 percent with a mean of 96.9 percent of the nominal concentration. The average test diet concentration in the 5000 ppm diet ranged from 94.5 to 110.5 percent with a mean of 101.4 percent of the nominal concentration.

3. Statistics - One-way analysis of variance (ANOVA) was used to analyze the following data: body weight, body weight gain, food consumption, TSH, T_3, T_4, thyroid gland weight, and thyroid gland-body weight ratios. If ANOVA was significant, then a Dunnett's t-test was used for pairwise comparisons between the treated and control groups. The level of significance was at the 5.0 percent probability level. It should be noted that data for TSH are also presented as adjusted data by removing outlying data points (points $\pm$ 1.5 SD) to reduce data variability. Excluded points are identified in the individual animal data tables.

C. Methods and Results:

1. Observations - All animals were inspected for mortality and signs of toxicity. Once a week each rat was removed from its cage and carefully examined for abnormalities and clinical signs of toxicity.

Results - Two rats, one control (#17) and one rat (#151) in the 100 ppm group died on Days 15 and 39, respectively. No cause of death was evident. No other deaths occurred. Most of the treated rats had yellow-to-amber colored urine beginning on Day 2 in the 5000 ppm group and on Day 8 in the 100 ppm animals. Additionally, several animals in the 5000 ppm group had yellow stained

coats. (This has been observed in previous studies and is believed to be a result of contact with metabolites of the test substance or the test substance itself.)

2. Body Weight - Individual animal body weights were determined initially (Day 0), and weekly thereafter.

Results - Body weight was significantly decreased in the 5000 ppm at the majority of the measurement periods when compared to the controls. The decrease ranged from 4.4 percent at Week 3 to 6.5 percent at Week 6. Body weights of the control and 5000 ppm group were not significantly different after Week 10: Body weight gain was significantly decreased (≈20%) in males in the 5000 ppm group when compared to controls over the length of the study. Body weight gain of rats in the 100 ppm group were decreased by approximately 8.7 percent when compared to controls over the length of the study (see Table 1).

Table 1: Body Weight and Percent (%) Decrease and Body Weight Gain Compared to Controls

Dose Level (ppm)	0	3	6	9	13	Initial-13
0	467.5	531.9	578.1	619.2	665.4	193.8
100	469.5	526.0	575.8	594.2	644.5	177.0
		(1.0)	(0.4)	(4.0)	(3.0)	(-8.7)
5000	471.5	508.7*	540.7*	582.6*	633.2	154.4*
		(4.4)	(6.5)	(5.9)	(4.8)	(-20)

* $p < 0.05$

3. Food Consumption and Compound Intake - Individual food consumption data were collected weekly.

Results - Food consumption was statistically decreased by approximately 30, 2.7, 6.9, and 8.2 percent for males in the 5000 ppm group at Weeks 1, 2, 4, and 7. In general, food consumption was only slightly decreased in males in the 5000 ppm group at most measurement intervals when compared to the controls. Food consumption was decreased by approximately 5 percent in the males in the 100 ppm group when compared to controls at Week 1, but was otherwise comparable to the controls. The time weighted average compound intake was 4.98 and 245.4 mg/kg/day of the test substance in the 100 and 5000 ppm groups of animals, respectively.

4. Blood samples were collected from 20 rats per dose level on Day 15, 29, 57, and 92 of the study by cardiac puncture and allowed to clot for 1 hour at room temperature, centrifuged and the serum separated into 4 aliquots of approximately 1 mL each and the samples frozen and stored at -80 °C. Animals were not fasted overnight. The samples were shipped to Hazleton Laboratories, Inc. in Vienna, VA for analysis of thyroid stimulating hormone (TSH), triiodothyronine (T_3) and thyroxine (T_4).

   Results - There were statistically significant increases in TSH in males in the 5000 ppm group on Day 29 (91%) and Day 57 (71%) and an increase (not significant) on Day 92 of approximately 66 percent. T_3 levels were significantly decreased by approximately 18 to 40 percent at all measurement intervals during the study in males in the 5000 ppm group. T_3 levels in males in the 100 ppm group were significantly decreased by 18 and 23 percent on Days 15 and 29, respectively. Levels of T_3 in males in the 100 ppm group was comparable to controls on Days 57 and 92. T_4 levels were significantly decreased by approximately 67 to 73 percent at all measurement intervals during the study in males in the 5000 ppm group when compared to controls. Levels of T_4 were significantly decreased by approximately 18 to 28 percent in males in the 100 ppm group on Days 57 and 92 when compared to controls. T_4 levels of males in the 100 ppm group were comparable to controls on Days 15 and 29 (see Table 2). Figures 1, 3 and 4 from the study report are attached to this DER.

5. Sacrifice and Pathology - Twenty rats per group were sacrificed at Days 15, 29, 57, and 92. Thyroid glands were removed intact, attached to the trachea. Thyroid and adjacent tissues were fixed in 10 percent neutral phosphate-buffered formalin. After at least 24 hrs of fixation, the thyroid lobes were carefully dissected from the trachea and connective tissue, blotted dry on filter paper and the combined weight of the left and right lobes recorded. All samples of thyroid gland were submitted to W.R. Brown, D.V.M., Ph.D., veterinary pathologist, New Britain, PA for processing and histological evaluation. The tissues were cut, blocked in paraffin, sectioned to 4 to 6 μ, mounted on slides, stained with H&E and examined microscopically.

95

TABLE 2 Levels of Serum TSH, T_3 and T_4 in Male Rats (% increase or decrease)

Weeks / Dose (ppm)	15	29	57	92
		TSH (ng/ml)		
0	4.35	4.02	3.87	4.90
100	3.99 (-.08)	4.69 (16.7)	4.67 (20.7)	4.20 (-1.4)
5000	5.12 (17.8)	7.66* (90.5)	6.62* (71.0)	6.65 (35.7)
		T_3 (ng/ml)		
0	69.69	86.96	71.07	65.71
100	57.42* (-17.6)	67.17* (-19.8)	71.08 (0.0)	66.11 (0.6)
5000	41.91 (-39.9)	63.94* (-26.5)	58.43* -17.8)	54.14* (-17.6)
		T_4 (ug/ml)		
0	4.26	4.01	4.03	4.62
100	3.74 (-12.2)	3.82 (-4.7)	3.30* (-18.1)	3.32* (-28.1)
5000	1.37* (-67.8)	1.34* (-66.6)	1.08* (73.2)	1.35* (-70.8)

* p <0.05

Results

a. Organ Weight - See attached Table 5.7.1 taken from the study report. There was a dose-related increase in the absolute and relative thyroid weights of males in the 100 and 5000 ppm groups when compared to controls at all measurement intervals. The increase in absolute thyroid weight ranged from 6.9 to 14.5 percent of control values for animals in the 100 ppm group and from 23.8 to 35.5 percent of control values for animals in the 5000 ppm group. Relative thyroid to body weight decreased from 0 to 16.7 percent of control values for animals in the 100 ppm group and from 30.8 to 50.0 percent of control values for animals in the 5000 ppm groups. Statistically significant increases were observed in only the 5000 ppm group, but at all measurement intervals when compared to controls.

b. Histopathology - There was an increase in the incidence and severity (slight-to-moderate) of hypertrophy of thyroid follicular epithelial cells in males in the 5000 ppm on Day 57 (70%) and Day 92

(80%) when compared to controls on Day 57 (20%) and Day 92 (20%). (See Table 3.)

Table 3. Incidence of Hypertrophy of the Thyroid Follicular Epithelial Cells in Males

	Day 15			Day 29		
Dose level (ppm)	0	100	5000	0	100	5000
No. Animals	20	19	20	20	20	20
Hypertrophy						
- minimal	5	3	6	3	3	4
- slight	0	0	1	0	0	2
- moderate	0	0	0	0	0	0
- total incidence	5/20 (25)[1]	3/19 (16)	7/20 (35)	3/20 (15)	3/20 (15)	3/20 (15)
	Day 57			Day 92		
No. Animals	20	19	20	20	20	20
Hypertrophy						
- minimal	3	2	4	3	4	6
- slight	1	2	8	1	1	5
- moderate	0	0	2	0	0	4
- total incidence	4/20 (20)	4/19 (22)	14/20 (71)	4/20 (20)	5/20 (25)	16/20 (80)

[1]percent incidence

D. Discussion

The preparation of the diet was adequate with respect to weekly concentrations, homogeneity of the diets and stability of the diets stored over an 8-day period at room temperature. Most of the rats in the 2 treatment groups had yellow to amber colored urine that was attributed to staining with the metabolites of the test substance or with the test substance itself. Rats in the 5000 ppm group also had yellow stained coats. Mortality was not affected by administration of the test material and no signs of clinical toxicity were apparent. Body weight was significantly

decreased in rats in the 5000 ppm group over most of the measurement intervals. Body weight gain was significantly decreased (≈ 20%) in rats in the 5000 ppm group when compared to controls. Body weight gain was only slightly decreased (≈9%) in the 100 ppm group when compared to controls. Food consumption was significantly decreased in rats in the 5000 ppm group at most measurement intervals when compared to controls. The decreases were considered to be only marginal. The 30 percent decrease at Week 1 was significant but can probably be related to a decrease in palatability. Serum TSH levels were significantly increased in the 5000 ppm group when compared to controls. Serum T_3 and T_4 levels were significantly decreased in rats in the 5000 ppm groups at all measurement intervals. Serum T_3 levels were also significantly decreased in rats in the 100 ppm group on Days 15 and 29. Serum T_4 levels were significantly decreased in the 100 ppm group on Days 57 and 92. Thyroid absolute and relative weights were decreased in a dose-response relationship at many measurement intervals. Statistical significance was only achieved at the 5000 ppm level. Thyroids of rats in the 5000 ppm group exhibited an increase in the incidence and severity of hypertrophy of follicular epithelial cells at Days 57 and 92.

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Pages 99 through 102 are not included.

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99-102

Attachment #6

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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] 3/20/91
Review Section II, Toxicology Branch I (H7509C)

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.

103

009525

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.

009525

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	9	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 in 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

106

(80)

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 6, 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)*		Total plasma protein (TP)
X	Hemoglobin (HGB)*	X	Leukocyte differential count
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)*	X	Mean corpuscular HGB conc. (MCHC)
X	Platelet count*	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, 13, and 21 percent for the liver/gallbladder weight, body weight ratio, and brain weight ratio, respectively. The thyroid weight was significantly

108

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. 009525

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

112

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.

Attachment 1

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

TOXCHEM NO. 4548B- N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 03/02/92

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
83-1(a) and 83-2(a) Feeding/oncogenic-2 year Species: rat Bio/dynamics Inc. 72R-746; 8/21/74	Prowl Tech.	112849 246347 246348			Invalid 000544 001223 002255
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- chronic 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
83-2(b) Oncogenic-18 month Species: mice Bio/dynamics Inc. 72R-747; 4/27/74	Prowl Tech.	00040301	Negative for carcinogenicity. Levels tested = 100, 500, 2500 ppm		Invalid 000544 001223
83-3(a) Developmental Toxicity Study Species: rat IBT B2324; 12/12/72	Pendimethalin Tech.	00027237	IBT - Invalid. Dynamac Corporation contract No. 68-01-6561. Accepted by EPA: 6/11/82 Maternal NOEL > 500 mg/kg (HDT). Develop NOEL > 500 mg/kg (HDT).		003032

(83)

114

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

TOXCHEM NO. 454BB- N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 03/02/92

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
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(a) Developmental Toxicity Study Species: rat IBT 81374(A); 7/20/72	Pendimethalin Tech (AC 92,553)				Invalid 004026
83-3(b) Developmental Toxicity Study Species: rabbit Hazleton 362-163; 5/6/82	Pendimethalin Tech. 92.2%	248659	Pilot study - Determined that maternal deaths and resorptions occur at 125 mg/kg/day and above.		Supplementary 002406
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
83-4 Reproduction-3 generation Species: rat Bio/dynamics Inc. 72R-748; 4/27/74	Pendimethalin Tech.	112849 246347 246348 00040304	Reproduction NOEL = 500 ppm Reproduction LEL = 5000 ppm (reduced litter size; reduced survival index, reduced pup weight). Levels tested = 500, 5000 ppm CDFA - EPA Review, 2/25/89: Agreement that the coregrade be changed from minimum to supplementary.		Minimum 000544 Supplementary 007751
83-4 Reproduction-2 generation Species: rat Toxicology labs Ltd. CBG/2/90 7/12/90	AC 92553 92.6% (Pendimethalin)	417252-03	Dose levels: 500, 2500 & 5000 ppm (males: 25, 125 & 250 mg/kg/day; females: 35, 175 and 350 mg/kg/day) in Sprague-dawley strain. Reprod. NOEL = 500 ppm (35 mg/kg/day). Reprod LOEL = 2500 ppm (217 mg/kg/day) based on decrease in pup weight. Parental NOEL = 500 ppm (25 mg/kg/d). Parental LOEL = 2500 ppm (125 mg/kg/day) based on decrease in body weight gain & food conumption.		Minimum 008558
82-1(a) Feeding-3 month Species: rat Bio/dynamics Inc. 72R-746; 8/21/74	Prowl Tech.	112849 00059468	3 month interim report: of a 24 month study Systemic NOEL = 500 ppm. Systemic LEL = 2500 ppm (5000 ppm) decreased body weight. Levels tested = 0, 100, 500, 2500 (5000) ppm, 2500 ppm in diet raised to 5000 ppm on day 35.		000544 Supplementary 004026

009525

69

113

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

TOXCHEM NO. 4548B- N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 03/02/92

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
82-1(a) Feeding-3 month Species: rat Pharmacopathics Res. Lab 6/1/73	Prowl Tech.	00059469	NOEL > 2500 (5000) ppm (only dose tested) 2500 ppm diet increased to 5000 ppm after 6 weeks. Study designed for possible reactions in male mammary glands.		Supplementary 004026
82-1(a) Feeding-3 month Species: rat Bio/dynamics Inc. 73R-869; 9/14/73	Prowl Tech.	00059468	NOEL > 2500 (500) ppm (HDT) 2500 ppm in diet increased to 5000 ppm after 8 weeks. Levels tested: 0, 25, 50, 100, 500, 2500 (5000) ppm. Study designed for reactions in male mammary glands.		Supplementary 004026
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
82-1(b) Feeding-3 month Species: dog Food and Drug Research Lab 1421; 9/12/73	Pendimethalin Tech.	00026672 00040305	NOEL > 2500 ppm (62.5 mg/kg) by gavage		000544
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
Inhalation-21 day Species: rat Food and Drug Research Lab 2935; 1/6/75	Prowl (AC 92,5553 with tobacco trated herbicide	00031974	NOEL > 9 mg/L		Invalid 004026

009525

90

211

TOXCHEM NO. 4548B- N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 03/02/92

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Feeding-30 day Species: rat American Cyanamid Co. A-72-4; 6/1/72	Prowl (AC 92,553 Tech)	000106754	NOEL = 1600 ppm. LEL = 3200 ppm (increased liver weight). Levels tested = 800, 1600, 3200 ppm.		Supplementary 004026
Feeding-30 day Species: mice American Cyanamid Co. A-72-4; 6/1/72	Prowl (AC 92,553 Tech.)	000106754	NOEL > 2000 ppm (HDT). Levels tested = 500, 1000, 2000 ppm.		Supplementary 004026
90 day oral Species: dog American Cyanamid Co. A-72-4; 6/1/72	Prowl (AC 92.553 Tech.)	000106754	NOEL not determined. Levels tested = 125, 250, 1000 mg/kg		Supplementary 004026
Feeding-14 day Species: mice American Cyanamid Co. A-72-4; 6/1/72	Prowl (AC 92,553 Tech.)	000106754	NOEL < 4000 ppm (LDT) (decreased food consumption, decreased body weight gain). Levels tested = 4000, 8000, 16000 ppm.		Supplementary 004026
Feeding-14 day Species: rat American Cyanamid Co. A-72-4; 6/1/72	Prowl (AC 92,553 Tech.)	000106754	NOEL > 6400 ppm (LDT) (decreased food consumption and decreased body weight). Levels tested = 6,400, 12,800 ppm		Supplementary 004026
84-4 Mutagenic Species: microorganisms American Cyanamid Co. 5/10/77	Prowl Tech.	230618 00067519	No mutagenicity at 1000 ug/plate (highest dose)		Acceptable 000545
84-4 Mutagenic- host med. Species: mice American Cyanamid Co. 5/10/77	Prowl Tech.	230618	No mutagenicity at 16.6 mg/mouse (highest dose)		Acceptable 000545
84-4 Mutagenic-dominant lethal test Species: rat Food and Drug Research Lab 2006; 10/5/73	Prowl Tech.	00026673	Non mutagenic 2500 ppm (HDT		Unacceptable 000544

TOXCHEM NO. 4548B- N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 03/02/92

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-4 Mutagenic- host med. Species: mice American Cyanamid Co. 7/73	Prowl intermediate 76.2% (lot# AC 2174-114).	230618 00067519	NOTE: The test chemical is process intermediate in Prowl production claimed to typify the product prior [redacted] Host-mediated assays (2 replicates) using mice as host and a histidine dependent strain of S. typhimurium (his G-46) as indicator were conducted according to the methods of Legator and Malling. Mice were dosed at 20.0 and 26.8 milligrams per mouse (mice weight about 20-25 grams). The reviewer did not agree with the stated conclusion that the test compound was nonmutagenic in the assay as performed. The reviewer raised several questions which apparently have yet to be addressed by the registrant.		Unclassified
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
84-2(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-(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)
Registration standard	Pendimethalin				004026

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TOXCHEM NO. 454BB- N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine FILE LAST PRINTED: 03/02/92

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
5-1 etabolism pecies: rat merican Cyanamid Co. -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		Supplementary 004026
ataractogenicity pecies: chicken BT 580-09771; 1/5/77	Prowl tech.	00054244	NOEL > 3000 ppm (HDT). Levels tested = 1000 & 3000 ppm 17 day evaluation of diet stability.		003033 Supplementary 000545
etabolites			Caswell #455C (CL 99,900) 4[(1-ethylpropyl) amino]-3,5-dinitro-o-toluic acid. Caswell #221I (CL 113,071) 4[(1-carboxymethyl) propyl] amino]-3,5-dinitro-o-toluic acid Caswell #223A (CL 113,072) 4[(1-ethyl-2-hydroxypropyl) amino]-3,5-dinitro-o-toluic acid. Caswell #223B (CL 202,345) 4[(1-ethyl-3-hydroxypropyl) amino]-3,5-dinitro-o-toluic acid Caswell #224A (CL 202,347) 4[(1-ethylpropyl) amino]-2-methyl-3,5-dinitrobenzyl. Caswell #224B (CL 94,269) N-(1-ethylpropyl) 2,6-dinitro-N- nitroso-3,4-xylidine		

009525

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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Pendimethalin, Qualitative Risk Assessment -
2-Year Sprague-Dawley Rat Dietary Study (1987) &
a 2-Year Sprague-Dawley Male Rat Dietary Study
(1991)

Caswell no.454BB

From: Bernice Fisher, Biostatistician Bernice Fisher 3/92
Science Support & Special Review Section
Science Analysis & Coordination Branch
Health Effects Division (H7509C)

To: William Greear, Pharmacologist
Review Section II
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Health Effects Division (H7509C)

Thru: Kerry L. Dearfield, Ph.D., Acting Section Head
Science Support & Special Review Section
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Kerry Dearfield 3.4.92

Summary

The qualitative risk assessment of pendimethalin was based upon 2 two-year chronic feeding/oncogenicity studies in Sprague-Dawley rats. The first (1987) study included both male and female rats and the second (1991) one contained only males. In the first (1987) study the rats were fed 0, 100, 500 and 5000 ppm. and in the second (1991) one, the males were fed 0, 1250, 2500, 3750 and 5000 ppm. of pendimethalin.

The first (1987) study allocated 65 males/females to each dose group and selected 10 of them for an interim sacrifice at week 53. The next (1991) study allocated 125 males to each dose group and selected 15 of them for interim sacrifices at weeks 2, 14, 27, 40 and 53 weeks.

The statistical evaluation of mortality in the first (1987) study indicated a significant dose related decreasing trend in survival in male rats. In females there was no incremental mortality with increasing doses of pendimethalin.

In the second (1991) study, male rats did not have any significant differential mortality with dose increments of pendimethalin.

Male rats had a significant dose related increasing trend in thyroid follicular adenomas and in the combined thyroid follicular adenomas and/or carcinomas in the 1987 study. Both tumor rate categories also were significantly increased in the pair-wise comparison of controls and the highest (5000 ppm.) dose group. In second (1991) study, statistical evaluations repeated the same significant outcomes in male rats as were observed in the first (1987) study.

The female rats in the 1987 study had a significant dose related increasing trend in thyroid follicular adenomas and also a significant increase in the adenomas in the pair-wise comparison of controls and the highest (5000 ppm.) dose group.

Background

A 2-year chronic toxicity/oncogenicity study in Sprague-Dawley rats was conducted by Hazleton Laboratories America, Inc. for American Cyanamid Company (HLA 6123-112 and MRID no. 4010744-01) and issued in April, 1987.

The study design assigned in a random manner groups of 65 males/females to dose levels of 0, 100, 500 and 5000 ppm. of pendamethalin. An interim sacrifice of 10 males/females was made in each of the sex/dose categories.

Another 2-year chronic toxicity/oncogenicity study in Sprague-Dawley male rats was also conducted by Hazelton Laboratories America, Inc. for American Cyanamid Company (HLA 362-191 and MIRD no. 420278-02) and issued in September,1991.

The study design assigned in a random manner groups of 125 males to dose levels of 0, 1250, 2500, 3750 and 5000 ppm. of pendimethalin. Interim sacrifices of 15 males in each dose level were made at weeks 2, 14, 27, 40 and 53.

Survival Analysis

In male rats, there was a statistically significant increasing trend in mortality with incremental doses of pendimethalin (Table 1) in the 1987 study. In the 1991 study, the males did not have any significant differential survival among the dose levels of pendimethalin (Table 6).

The female rats in the 1987 study, had statistically significant dose related increasing survival and also a significant increase in the pair-wise comparison of controls and the highest (5000 ppm.) dose group (Table 2).

The statistical evaluation of mortality in the rat studies was based upon the Thomas, Breslow and Gart computer program.

Tumor Analysis

Male rats had a significant increasing dose related trend in thyroid follicular cell adenomas and in the combined thyroid follicular adenomas and/or carcinomas in both the 1987 and the 1991 studies. Also in the pair-wise comparison of controls and the 5000 ppm. groups, there was a significant increase in thyroid follicular cell adenomas and in the combined thyroid follicular cell adenomas and/or carcinomas again in both the 1987 and the 1991 studies. See attached Tables 3 and 7 for further details.

In both the 1987 and the 1991 studies, male rats had a significant increasing dose related trend in follicular cell hyperplasia (Tables 4 and 8).

Female rats in the 1987 study, had significant dose related increasing trends in follicular cell adenomas and in hyperplasia rates. They also had significant increases in the adenomas and hyperplasia in the pair-wise comparisons of controls and the highest (5000 ppm.) dose groups (Table 5).

The above statistical analysis of tumor or lesion rates was based upon either Peto's Prevalence Tests or the Cochran-Armitage Trend test (or Exact Trend) and Fisher's Exact test for pair-wise comparisons of controls and each dose group, dependent upon whether or not there was significant statistical evidence of differential mortality with increasing doses of pendamethalin.

Table 1. Pendimethalin - Sprague-Dawley Rat Study (1987), Male Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (ppm)	Weeks 1-26	27-52	53[a]	53-78	79-105[b]	Total
0	0/65	1/65	10/64	10/54	25/44	36/55(65)*
100	1/65	2/64	10/62	6/52	25/46	34/55(62)
500	0/65	1/65	10/64	6/54	26/48	33/55(60)
5000	1/65	0/64	10/64	12/54	27/42	40/55(73)

[+] Number of animals that died during interval/Number of animals alive at the beginning of the interval.

( ) percent

[a] Interim sacrifice at week 53.
[b] Final sacrifice at week 105.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 2. Pendimethalin - Sprague-Dawley Rat Study (1987), Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-26	27-52	53[a]	53-78	79-105[b]	Total
0	1/65	0/64	10/64	12/54	19/42	32/55(58)[n*]
100	0/65	1/65	10/64	7/54	19/47	27/55(49)
500	2/65	4/63	10/59	9/49	16/40	31/55(56)
5000	0/65	2/65	10/63	6/53	16/47	24/55(44)[n*]

[+] Number of animals that died during interval/Number of animals alive at the beginning of the interval.

( ) percent

[a] Interim sacrifice at week 53.
[b] Final sacrifice at week 105.

[n] Negative trend or negative change from control.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 3. Pendimethalin - Sprague-Dawley Male Rats (1987), Thyroid Follicular Cell Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (ppm)			
	0	100	500	5000
Tumors				
Adenomas	3/64	2/62	3[a]/64	8/64
(%)	(5)	(3)	(5)	(13)
p=	0.003**	0.720(n)	0.491	0.038*
Carcinomas	0/64	0/62	0/64	1[b]/64
(%)	(0)	(0)	(0)	(2)
p++=	0.252	1.000	1.000	0.500
Both	3/64	2/62	3/64	9/64
(%)	(5)	(3)	(5)	(14)
p=	0.001**	0.720(n)	0.540	0.027*

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a] First adenoma observed at week 53, dose 500 ppm.
[b] First carcinoma observed at week 93, dose 5000 ppm.

n Negative change from control.

** Resultant p values based on application of Exact Trend test and Fisher's Exact test for pair-wise comparisons with control and each dose level.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

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Table 4. Pendimethalin - Sprague-Dawley Male Rats (1987), Thyroid Follicular Cell Hyperplasia Only Rates* and Peto's Prevalence Test Results (p values)

	Dose (ppm)			
	0	100	500	5000
Hyperplasia only (%)	7/64 (11)	7/62 (11)	4/64 (6)	10[a]/64 (16)
p=	0.028*	0.421	0.870(n)	0.121

* Number of animals with hyperplasia/Number of animals examined, excluding those that died before observation of the first lesion.

[a] First hyperplasia observed at week 53, dose 5000 ppm.

n Negative change from control.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 5. Pendimethalin - Sprague-Dawley Female Rats (1987), Thyroid Follicular Cell Hyperplasia and Adenoma Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (ppm)			
	0	100	500	5000
Lesions				
Hyperplasia only (%)	1/34 (13)	1/44 (2)	3/37 (8)	8[a]/45 (18)
p=	0.004**	0.560(n)	0.161	0.027*
Adenomas only (%)	1/41 (2)	1/49 (2)	1/43 (2)	7[b]/53 (13)
p=	0.002**	0.560	0.510	0.036*

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first lesion.

[a] First hyperplasia observed at week 88, dose 5000 ppm.
[b] First adenoma observed at week 53, dose 5000 ppm.

n Negative change from control.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then p<.05 and if ** then p<.01.

Table 6. Pendimethalin - Sprague-Dawley Rat Study (1991), Male Mortality Rates* and Cox or Generalized K/W Test Results

Dose (ppm)	Interim Sacrifices					Deaths on Study			
	Weeks								
	2	14	27	40	53	1-52	53-78	79-105[a]	Total
0	15/125	15/110	15/95	15/80	15/65	0/65	7/50	17/43	24/50 (48)
1250	15/125	15/109	15/94	15/79	15/64	2/65	4/48	26/44	32/50 (64)
2500	15/125	15/110	15/94	15/79	15/64	1/65	1/49	28/48	30/50 (60)
3750	15/125	15/110	15/94	15/79	15/64	1/65	9/49	22/40	32/50 (64)
5000	15/125	15/110	15/95	15/79	15/64	1/65	6/49	23/43	30/50 (60)

* Number of animals that died during interval/Number of animals alive at the beginning of the interval.

( ) percent

[a] Final sacrifice at week 105.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

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Table 7. Pendimethalin - Sprague-Dawley Male Rats (1991), Thyroid Follicular Cell Tumor Rates* and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	1250	2500	3750	5000
Tumors					
Adenomas	4[a]/90	7/85	7/88	6/89	15/89
(%)	(4)	(8)	(8)	(7)	(17)
p=	0.007**	0.236	0.255	0.366	0.006**
Carcinomas	1/90	1/85	4/88	3[b]/89	2/89
(%)	(1)	(1)	(5)	(3)	(2)
p=	0.200	0.737	0.177	0.306	0.496
Both	5/90	8/85	11/88	9/89	17/89
(%)	(6)	(9)	(12)	(10)	(19)
p=	0.004**	0.247	0.087	0.196	0.005**

* Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a] First adenoma observed at week 27, dose 0 ppm.
[b] First carcinoma observed at week 67, dose 3750 ppm.

Note: Significance of trend denoted at Cotrol.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 8. Pendamethalin - Sprague-Dawley Male Rats (1991), Thyroid Follicular Cell Hyperplasia Only Rates* and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	1250	2500	3750	5000
Hyperplasia only (%)	0/90 (0)	0/85 (0)	0/88 (0)	2[a]/89 (2)	2/89 (2)
p=	0.024*	1.000	1.000	0.245	0.245

* Number of animals with hyperplasia/Number of animals examined, excluding those that died before observation of the first lesion.

[a] First hyperplasia observed at week 53, dose 5000 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * ther p<.05 and if ** then p<.01.

References

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