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

JUN - 1 1994

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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Subject: DPX-D732-66; Terbacil. Review of a Combined Chronic/Oncogenicity Study in Rats. DP Barcode D197159 Submission No S454225 MRID 429876-01

To: Andrew Eartman, PM #71, Tox Chem # 821A
Reregistration Branch
Special Review and Reregistration Division (7508W)

From: Joycelyn E. Stewart, Ph.D., Head,
Section II, Toxicology Branch I,
Health Effects Division (H7509C) 5/20/94

Thru: Karl P. Baetcke, Ph.D., Chief,
Toxicology Branch I,
Health Effects Division (H7509C) 5/24/94

Registrant: E.I. duPont de Nemours and Company
Wilmington, DE 19880-0038

Action Requested: Review a two year rat chronic/oncogenicity study submitted in response to the Registration Standard Data Call-In Notice. The information herein was submitted as 6(a)(2) data.

Executive Summary: When technical terbacil (97.4% a.i.) was administered to male and female Crl:CD BR(SD) rats at dietary levels of 0, 25, 1500 or 7500 ppm (equivalent to 0, 0.9, 58, and 308 mg/kg/day in males and 0, 1.4, 83, and 484 mg/kg/day in females). no evidence of carcinogenic potential was observed. Dosing was adequate based on significantly decreased body weight gain during the first year in males receiving 7500 ppm (13%) and females receiving 1500 ppm (18%) and 7500 ppm (39%).

Seventy rats/sex/group were used in the study. Ten/sex/group were sacrificed by study design at 12 months. Excessive mortality in most groups necessitated sacrifice at 23 months.

At 1500 ppm, a significant increase in the mean liver to body weight ratio was observed in females at twelve months (16%) and at study termination (21%). At study termination the liver weight increase was accompanied by a marginal increase in centrilobular hepatocyte hypertrophy and a 20% decrease in mean body weight in females.

1 of 20

011006

At 7500 ppm, significant increases in relative liver weight were seen in both sexes at 12 and 23 months and mean liver weight in males was 20% increased compared to controls. In addition, there was an increase in centrilobular hypertrophy and fatty changes in livers in both sexes as well as increases in biliary hyperplasia and serum cholesterol in the females. Eosinophilic foci of cellular alteration in the liver were increased in incidence in dosed groups of males and females, but this is of doubtful significance since it was not accompanied by any corroborative toxicological evidence such as dose response, hepatic enzyme elevation or increased incidence of hepatocellular tumors.

The NOEL for systemic effects was 25 ppm and the LEL was 1500 ppm, based on the liver pathology and body weight gain decrement in female rats.

This study is core-Guideline and satisfies Subdivision F guideline requirements for a chronic/oncogenicity study.

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DATA EVALUATION REPORT

DPX-D732-66 (TERBACIL)

Study Type: Chronic Oral/Oncogenicity Two-Year Feeding Study in Rats

Prepared for:

Office of Pesticide Programs
Health Effects Division
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Contract Number: 68D10075
Work Assignment Number: 3-50
Clement Number: 214
Project Officer: Caroline Gordon

3

TX1006

TERBACIL

Chronic Oral Toxicity/Oncogenicity Study in Rats: 83-5

EPA Reviewer: Joycelyn E. Stewart, Ph.D.
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Signature: Joycelyn E Stewart
Date: 5/17/1994

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Review Section IV, Toxicology Branch I
Health Effects Division (7509C)

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Date: 5/23/94

DATA EVALUATION REPORT

STUDY TYPE: Chronic Oral/Oncogenicity Feeding Study - Rat (83-5)

TOX. CHEM. NO.: 821A

P.C. CODE: 021701

MRID NO.: 429876-01

TEST MATERIAL: DPX-D732-66; Technical Terbacil

SYNONYMS: 3-tert-Butyl-5-chloro-6-methyluracil; IN D732-66

STUDY NUMBER: Dupont HLR 453-93

SPONSOR: E.I. du Pont de Nemours and Company, Inc

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714

TITLE OF REPORT: Combined Chronic Toxicity/Oncogenicity Study with DPX-D732-66 (Terbacil) - Two Year Feeding Study in Rats

AUTHOR: Malek, D.E.

REPORT ISSUED: October 22, 1993

EXECUTIVE SUMMARY: In a two-year chronic toxicity/carcinogenicity study, technical Terbacil was administered in feed to groups of 70 male and 70 female Crl:CD®BR (Sprague-Dawley) rats at levels of 0, 25, 1500, or 7500 ppm (approximate doses for males of 0, 0.9, 58 and 308 mg/kg/day a.i. and for females 0, 1.4, 83, and 484 mg/kg/day a.i.). Ten animals/sex/group were sacrificed by study design at 12 months.

Excessive mortality (not compound or dose-related) in most groups necessitated sacrifice at 23 months. Dosing was adequate based on significantly decreased weight gain compared to controls during the first year of the study in males receiving 7500 ppm (13%) and females receiving 1500 ppm (18%) and 7500 ppm (39%).

At 1500 ppm, a significant increase in the mean liver-to-body weight ratio was observed in females at 12 months (16%) and at study termination (21%). At termination, the liver weight increase was accompanied by a marginal increased incidence of centrilobular hepatocyte hypertrophy (minimal)

4

and a 20% decreased mean body weight (not significant) in females. At 7500 ppm, significant increases in liver-to-body weight ratios were seen in both sexes at 12 and 23 months and mean liver weight in males was 20% increased compared to controls at termination. An increase in centrilobular hypertrophy and fatty changes were seen in both sexes at the high dose and an increase in biliary hyperplasia was observed in high-dose females. Increased serum cholesterol concentrations were observed in 7500-ppm females throughout the study. Eosinophilic foci of cellular alteration in the liver were increased in incidence in dosed groups of males and females (significant trend) but this is of equivocal importance because it was not accompanied by hypertrophic or hyperplastic changes or hepatocellular tumors. **The systemic LEL of 1500 ppm is based on liver effects and decreased body weight gain in females. The NOEL is 25 ppm.**

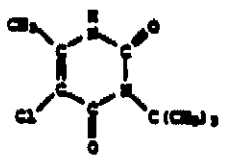
There was no evidence of carcinogenic potential. Dosing was adequate based on decreased weight gains in both sexes.

The study is core guideline and satisfies the guideline requirements for a chronic/carcinogenicity feeding study (83-5) in rats.

Special Review Criteria: (40 CFR 154.7) None

A. MATERIALS

1. Test Material: Terbacil 2,4 (1H, 3H) - Pyrimidinedione, 5-chloro-3-(1,1-dimethylethyl)-6-methyl
   Description: light tan solid
   Lot/Batch #: TO3038970
   Purity: 97.4% a.i.
   Stability of compound: Stable, based on analyses conducted during the study
   CAS number: 5902-51-2
   Structure:



2. Vehicle and/or positive control: diet

3. Test animals

   Species: Rat
   Strain: Crl:CD®BR
   Age and weight: 50 days old at study initiation; group mean body weights males--293.6-299.1 g, females--198.9-200.3 g. At receipt (day 21) weights ranged from 46.9-89.6 g for males and 44.7-89.6 g for females.
   Source: Charles River Laboratories, Raleigh, NC
   Housing: Stainless steel, wire-mesh cages suspended above cage boards

5.1

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Environmental conditions: Temperature: 23±2°C
Humidity: 50±10%
Air changes: Not reported
Photoperiod: 12-hour light/dark cycle

Acclimation period: 29 days. During acclimation animals were weighed 5 times and health was monitored.

B. STUDY DESIGN

1. Animal assignment

Animal assignment: Animals selected on the basis of normal body weight gain, normal clinical signs and ophthalmic findings were assigned to the following groups using a computerized stratified randomization procedure.

TABLE 1. Study Design

Test Group	Dose level (ppm)	No. of Animals: Main study (24 Months) Male	Main study (24 Months) Female	Interim Sacrifice (12 Months) Male	Interim Sacrifice (12 Months) Female
Control	0	60	60	10	10
Low dose (LDT)	25	60	60	10	10
Medium dose (MDT)	1500	60	60	10	10
High dose (HDT)	7500	60	60	10	10

Rationale for Dose Selection: A 4-week range finding study was conducted with groups of 10 rats/sex at dietary levels of 0, 3500, 5000, or 7500 ppm 97.4% pure technical terbacil. Body weight gains in the dosed groups of males were decreased 12, 20, and 23% compared to controls and in females gains were 18, 12, and 19% lower than controls at 3500, 5000, and 7500 ppm, respectively.

In a previous 2-year study with 80% wettable powder terbacil, rats were fed dietary levels of 0, 50, 250, or 2500 ppm terbacil (a.i.); the high dose was gradually increased to 10,000 ppm after 28 weeks. Decreased body weights were seen at 10,000 ppm and there was a slight increase in relative liver weights. Enlarged centrilobular hepatocytes with vacuolation were observed at the one year sacrifice and after 2 years. The histologic liver changes were minimal at 250 ppm. In a 90-day study with 0, 100, 500, or 5000 ppm of 80% wettable powder, increased absolute liver weights were seen in both sexes at 5000 ppm and hepatocellular hypertrophy was seen at 500 and 5000 ppm.

2. Diet preparation and analysis

Diets were prepared weekly by mixing appropriate amounts of Terbacil with Purina Certified Rodent Diet #5002 in a high speed mixer for 3 minutes; diets were refrigerated until used. Homogeneity and stability were tested at study start. During the study, the test compound was analyzed for purity at 4 study intervals (day 3, 16, 205, 526, and 706). At 9 study intervals samples of diets were analyzed for concentration.

Results - Homogeneity Analysis: The coefficients of variance were 1.0, 1.0, and 2.5% for duplicate samples at 3 levels of the mixer at dietary levels of 25, 1500, and 7500 ppm. The range of concentrations were 96-105% of nominal for all samples.

Stability Analysis: The test compound was completely stable in diets for 14 days at room temperature or refrigerated.

Concentration Analysis: At 9 intervals of analysis diets were $92.2 \pm 9.1\%$, $103.1 \pm 8.8\%$ and $100 \pm 4.1\%$ of nominal at 25, 1500, or 7500 ppm, respectively. At 1500 and 7500 ppm diets were generally within 5% of nominal. Diets at 25 ppm were 85 to 105% of nominal.

3. Animals received food and water *ad libitum*.

4. Statistics: Body weights, body weight gains, organ weight data and clinical laboratory data were analyzed by one-way ANOVA and pairwise comparisons were made with Dunnett's test. If clinical laboratory data and organ weight data had unhomogeneous variance with Bartlett's test for homogeneity, non-parametric statistical methods were employed. Clinical observations were evaluated by the Fisher exact test with the Bonferroni correction followed by the Cochran-Armitage trend test. Neoplastic, preneoplastic and nonneoplastic histologic findings were evaluated with the Fisher exact test and the Cochran-Armitage trend test. Eosinophilic foci were analyzed by logistic regression with dose and age as variables.

5. A signed and dated quality assurance statement was present.
A signed and dated GLP statement was present.

C. METHODS AND RESULTS

1. Observations

All animals were inspected at least once daily for signs of toxicity and mortality. At each weighing animals were individually examined for abnormal behavior and appearance.

Results - Table 2 summarizes mortality and percent survival at selected intervals. Because of excessive mortality in the control and 25 ppm groups of females between 18 and 21 months, the study was terminated at 23 months. Decreased survival was not related to

Table 2. Mortality and (Percent Survival) in Rats Fed Terbacil for 2 Years[a]

Week	Dietary level (ppm) 0	25	1,500	7,500
		Males		
51	4 (94)	3 (96)	7 (90)	5 (93)
79	22 (63)	19 (68)	23 (62)	20 (67)
95	37 (38)	36 (40)	38 (37)	35 (42)
101	46 (23)	46 (23)	43 (28)	40 (33)
		Females		
51	4 (94)	4 (94)	2 (97)	0 (100)
79	23 (62)	25 (58)	19 (68)	18 (70)
95	41 (32)	39 (35)	35 (42)	31 (48)
101	45 (25)	45 (25)	39 (35)	33 (45)

[a]Week 51 survival was based on 70 animals/sex/group; others based on 60/sex/group due to Interim Sacrifice.

Source: Study HLR 453-93. Tables 14 and 15, pp 126-131.

dosing. Survival was greater in groups receiving 1500 and 7500 ppm than in controls.

No clinical signs related to dosing were observed. The signs occurring in both control and treated groups including hair loss, sore paws, fur staining, and eye discharge were sporadic and common signs in rats.

2. Body weight

Body weights were recorded weekly for the first three months and every other week thereafter.

Results - Tables 3 and 4 summarize mean body weight data and body weight gain data at representative study intervals. Body weights were significantly decreased in males receiving 7500 ppm and in females receiving 1500 and 7500 ppm throughout most of the study. In the first year of the study mean weights in males receiving 7500 ppm were 7-9% lower than controls and in females receiving 1500 and 7500 ppm were about 4-9% and 10-21% lower than controls, respectively. Mean weight gain decrements were seen primarily in the first year of the study.

At 51 weeks, body weight gain in males receiving 7500 ppm was 13% lower than control gain and in females receiving 1500 and 7500 ppm gains were 18% and 39% lower than in controls.

3. Food consumption and compound intake

Food consumption was measured at each weighing interval and was corrected for the amounts of spillage. From these data, daily diet consumption was calculated. Food efficiency and compound intake were calculated from food consumption and body weight data.

Results -

a. Food consumption - Mean weekly food consumption was comparable in all groups of males or females when treated groups were compared to controls.

b. Compound consumption - Mean compound intakes at 25, 1500, and 7500 ppm were 0.94, 58, and 305 mg/kg/day in males, respectively, and 1.36, 83 and 484 mg/kg/day in females at the same doses.

Food efficiency in males receiving 7500 ppm was 91% and 88% of control efficiency between initiation and 91 or 357 days. In females receiving 1500 ppm, overall food efficiency was 95 and 88% of control for 13 or 51 weeks and at the 7500-ppm dose was 73 and 59% of control at the same intervals.

Table 3. Mean Body Weights and (Percent of Control) in Rats Fed Terbacil for Two Years

Week	Dietary level (ppm)			
	0	25	1,500	7,500
		Males		
0	298.3	299.1 (100)	298.0 (100)	293.6 (98)
13	611.9	610.6 (100)	601.3 (98)	568.3* (93)
27	726.8	721.4 (99)	717.5 (99)	673.0* (93)
51	825.7	818.9 (99)	814.6 (99)	754.7* (91)
79	895.2	888.8 (99)	865.8 (97)	805.2* (90)
101	808.1	830.1 (103)	810.5 (100)	773.8 (96)
		Females		
0	199.0	198.9 (100)	201.9 (101)	200.3 (101)
13	314.6	315.4 (100)	302.3 (96)	284.7* (90)
27	371.4	365.6 (98)	346.2* (93)	317.5* (86)
51	444.0	432.3 (97)	403.7* (91)	350.2* (79)
79	553.0	493.1 (89)	454.3* (82)	412.5* (75)
101	526.9	491.1 (93)	442.9 (84)	422.2 (80)

*Satistically significantly different from control value, $p<0.05$.

Source: Study HLR 453-93. Tables 2 and 3, pp 101-104.

Table 4. Mean Cumulative Weight Gain at Selected Intervals in Rats Fed Terbacil for Two Years

Days	Dietary level (ppm) 0	25	1,500	7,500
			Males	
0-91	313.6	311.4	303.3	274.7*
0-357	527.6	520.1	516.9	461.2*
357-706	7.3	16.1	53.4	25.0
0-706	515.4	532.7	528.8	485.5
			Females	
0-91	116.1	116.4	100.4*	84.4*
0-357	246.2	232.6	202.1*	149.9*
357-706	110.3	87.4	75.6	77.2
0-706	331.9	296.7	248.0	225.3*

*Significantly different from control value, $p<0.05$.

Source: Study HLR 453-93. Tables 4 and 5, pp 105-108.

4. Ophthalmoscopic examinations

Eyes were examined at pretest (day 19) and for all surviving animals prior to the 1 year sacrifice and terminal sacrifice. Examinations were conducted after mydriasis by using an indirect ophthalmoscope.

Results - Six males and three females were excluded from the study because of preexisting ocular lesions (primarily focal retinopathy). At the 12-month evaluation, sporadic ocular lesions were found (retinal atrophy, chomodacryorrhea, phthisis bulbi) but no increased incidence was seen with dose. No primary ocular findings related to dosing were seen at termination. Pale ocular fundi were seen in 9 dosed rats (3/group) and 2 controls prior to termination.

5. Clinical Pathology

Blood was collected by orbital sinus puncture from 10 fasted rats/sex/group at 3, 6, 12, and 18 months and from all surviving rats at termination (23 months) for hematology and clinical chemistry analysis. The CHECKED (X) parameters were examined.

a. Hematology

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
Blood clotting measurements
(Thromboplastin time)
(Clotting time)
(Prothrombin time)

X Leukocyte differential count*
X Mean corpuscular HGB (MCH)
X Mean corpusc. HGB conc. (MCHC)
X Mean Corpusc. volume (MCV)
X Reticulocyte count

* Required for subchronic and chronic studies

Results - No toxicologically important changes in hematology parameters were observed. Slight but significant decreases in hemoglobin concentrations were sporadically seen in high-dose males and females as compared to controls but all values were within the normal range and no effect on RBC count or other red cell indices consistently accompanied the changes.

b. Clinical Chemistry

Electrolytes	Other
X Calcium*	X Albumin*
X Chloride*	Albumin/globulin ratio
Magnesium	X Blood creatinine*
X Phosphate*	X Blood urea nitrogen*
X Potassium*	X Globulins
X Sodium*	X Total protein*
Enzymes	X Glucose*
	Total bilirubin
X Alkaline phosphatase (ALP)	Triglycerides
Cholinesterase	X Cholesterol*
X Creatinine phosphokinase	Serum protein electrophoreses
Lactic acid dehydrogenase	
X Serum alanine aminotransferase (also SGPT)*	
X Serum aspartate aminotransferase (also SGOT)*	
Gamma glutamyl transferase (GGT)	
Glutamate dehydrogenase	

* Required for subchronic and chronic studies

Results - Table 5 presents mean data for serum cholesterol levels. In females receiving 7500 ppm, a moderate but significant increase in cholesterol was seen at all intervals of blood sampling. A marginally significant increase was seen at 18 months in females receiving 1500 ppm terbacil. A slight increase was observed in 7500 ppm males at 18 and 23 months but no clear dose-response relationship was apparent and only the increase at 18 months was statistically significant compared to control. The increases in high-dose females were considered compound related but not clearly of biologic importance; the increase in high-dose males at 18 months was not considered dose related. No toxicologically important effects on other clinical chemistry parameters were observed.

6. Urinalysis

Overnight urine specimens were collected from 10 rats/sex/group on the day prior to blood samples for clinical laboratory analysis. The CHECKED (X) parameters were examined.

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

Results - No toxicologically important alteration of urinary parameters were observed in dosed males or females.

Table 5. Mean Cholesterol Levels (mg/dL) ± SD at Selected Intervals in Rats Fed Terbacil for Two Years

Month	Dietary level (ppm) 0	25	1,500	7,500
		Males		
3	106 ± 77	80 ± 8	76 ± 15	95 ± 9
6	139 ± 109	106 ± 17	100 ± 23	121 ± 26
12	114 ± 69	85 ± 22	102 ± 32	114 ± 28
18	111 ± 24	165 ± 89	130 ± 67	157 ± 48*
23	137 ± 61	153 ± 78	130 ± 28	179 ± 98
		Females		
3	87 ± 19	86 ± 20	109 ± 14	124 ± 28**
6	104 ± 17	108 ± 35	129 ± 32	148 ± 39**
12	92 ± 17	86 ± 25	113 ± 37	158 ± 30**
18	91 ± 18	88 ± 33	127 ± 39**	124 ± 14**
23	127 ± 32	173 ± 98	165 ± 48	172 ± 40*

*Significantly different from control value ($p<0.05$) using the Mann-Whitney U Criteria test.
**Significantly different from control ($p<0.05$) by Dunnett criteria test.

Source: Study HLR 453-93. Tables 20 and 21, pp 142-147.

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.

Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue	X Aorta*	XX Brain*+
X Salivary glands*	XX Heart*	X Peripheral nerve* (sciatic nerve)
X Esophagus*	X Bone marrow*	X Spinal cord* (three levels)
X Stomach*	X Lymph nodes*	X Pituitary*
X Duodenum*	XX Spleen*	X Eyes*
X Jejunum*	X Thymus*	Glandular
X Ileum*	Urogenital	X Adrenal gland*
X Cecum*	XX Kidneys*+	X Lacrimal gland
X Colon*	X Urinary bladder*	X Mammary gland*
X Rectum*	XX Testes*+	X Parathyroids*++
XX Liver*+	X Epididymides	X Thyroids*++
Gall bladder*	X Prostate	Other
X Pancreas*	X Seminal vesicles	X Bone*
Respiratory	X Ovaries*+	X Skeletal muscle*
X Trachea*	X Uterus*	X Skin
X Lung*	X Vagina	X All gross lesions and masses*
X Nose		
Pharynx		
Larynx		

* Required for subchronic and chronic studies.
\+ Organ weight required for subchronic and chronic studies.
++ Organ weight required for non-rodent studies.

Note: All tissues were microscopically examined for control- and high-dose groups and from all animals that died or were sacrificed moribund. In the low- and mid- dose groups liver kidneys, lungs, gross lesions and target organs were also examined for survivors.

Results -

a. Organ weight - Table 6 summarizes data on liver weights and liver-to-body weight ratios at the interim and terminal sacrifices. At 12 months, the mean liver weight in high-dose males was increased 9% compared to controls (non-significant) but the liver-to-body weight ratio was increased 28% ($p<0.05$). The mean body weight in the ten high-dose males at interim sacrifice was decreased to 86% of control ($p<0.05$). Liver weights and liver-to-body weight ratios were increased in females receiving 1500 and 7500 ppm at the 12 month sacrifice. Relative liver weights were 16 and 48% increased compared to controls ($p<0.05$) at 1500 and 7500 ppm. Mean body weights at sacrifice were significantly decreased (20%, $p<0.05$) in the high dose females but were slightly increased compared to controls at 1500 ppm.

011006

Table 6. Liver Weights and Liver-to-Body Weight Ratio ± SD and (Percent Increase Compared to Control)[a]

Dietary Levels (ppm)	12 Months		23 Months	
	Grams	Percent	Grams	Percent
		Males		
0	21.5±4.4	2.69±0.3	18.4±2.6	2.35±0.4
25	19.8±2.0 (-8)	2.59±0.3 (-4)	19.0±2.8 (3)	2.41±0.5 (3)
1500	22.7±2.9 (6)	2.79±0.3 (4)	19.3±3.6 (5)	2.43±0.4 (3)
7500	23.5±3.4 (9)	3.43±0.2* (28)	22.1±3.3* (20)	3.02±0.5* (29)
		Females		
0	10.2±1.7	2.56±0.3	13.1±3.9	2.70±0.6
25	10.1±1.7 (-1)	2.66±0.2 (4)	12.4±3.5 (-5)	2.81±0.7 (4)
1500	13.2±1.9* (29)	2.98±0.3* (16)	13.4±3.3 (2)	3.27±0.7* (21)
7500	12.1±2.2 (19)	3.78±0.4* (48)	13.9±3.1 (6)	3.57±0.7* (32)

*Significantly different from control ($p<0.05$) by Dunnett's criteria test.

Source: Study HLR 453-93. Tables 24 and 27, pp 154-157.

At the terminal sacrifice, absolute and relative (to body) liver weights were increased in males receiving 7500 ppm and mean body weights were 7% lower than controls (nonsignificant); the relative liver weights in 7500-ppm males were 28% and 29% higher than controls at the interim and terminal sacrifices, respectively. Liver-to-body weight ratios at termination were increased 21 and 32% above controls in females that received 1500 and 7500 ppm, respectively: however, mean terminal body weights were decreased 16% and 19% in the 1500 and 7500 ppm doses when compared to controls. No important effects on organ weights were seen in the other organs evaluated. In evaluating kidney weights at study termination, outlier values (>10 g) were censored by the study authors since these values were caused by severe glomerulonephritis.

b. Gross pathology - The only finding of note was discoloration of the liver which occurred in 14-17 females/group (including controls) and in 8 control males and 14 or 15 males/dosed group. Other findings were infrequent and none were dose-related.

c. Microscopic pathology -

1) Non-neoplastic - The liver was identified as the target organ. Table 7 summarizes the incidence of nonneoplastic liver lesions.

At the interim sacrifice, minimum/mild centrolobular hepatocyte hypertrophy was observed in 8/10 males and all 10 females receiving 7500 ppm terbacil; no controls low-dose or mid-dose rats had the finding at 12 months. Eosinophilic foci of cellular alteration were observed in 3/10 control males and 5/10 high-dose males. Centrilobular fatty changes were slightly increased in dosed males.

In the main study, the incidences of findings were tabulated for animals that died or were sacrificed moribund and for animals at terminal sacrifice combined. An increased incidence of centrilobular hepatocyte hypertrophy was observed in both sexes receiving 7500 ppm in the main study and at interim sacrifice. The severity was minimal at 12 months and minimal in the main study. An increased incidence of centrilobular fatty change was seen in both segments of the study which was minimal or mild and seen primarily in the high dose groups of both sexes. An increase in liver inflammation or focal necrosis was observed in the main study for high-dose males and biliary hyperplasia incidence was increased for high dose females. Eosinophilic foci of cellular alteration was increased in all dosed groups in the main study.

Table 7. Nonneoplastic Lesions in the Livers of Rats fed Terbacil for up to 25 Months

Lesion	Dietary Levels (ppm)							
	Males				Females			
	0	25	1500	7500	0	25	1500	7500
				12-Month Sacrifice				
No. Examined	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Biliary Hyperplasia	3	3	1	2	3	1	5	4
Centrilobular hypertrophy	0	0	0	8*	0	0	0	10*
Centrilobular fatty change	1	2	3	3	0	0	2	0
Eosinophilic foci of cellular alteration	3	0	1	5	1	0	0	0
				Main Study				
No. examined	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
Biliary hyperplasia	34	30	34	33	23	21	27	42*
Centrilobular hypertrophy	0	0	0	11*	0	0	1	14*
Inflammation/focal necrosis	6	6	2	12*	6	7	5	5
Centrilobular fatty change	3	6	7	19*	1	3	4	8*
Eosinophilic foci of cellular alteration^	6	17*	27*	23*	7	14	12	20*

*Significant trend ($p<0.05$) by the Cochran-Armitage test or significant by the Fisher exact test at the low-dose when compared to control.
^Significant for all doses in males but not females when analyzed by logistic regression with age and dose as variables.

Source: Study No. HLR 453-93 Tables 32-35, pp 173-201.

No nonneoplastic findings in other sites were considered related to compound administration. The incidence of glomerulonephropathy was greater than 80% in most groups; its severity was somewhat increased in high-dose males compared to controls; 32% of controls and 48% of high-dose males had moderate/severe glomerulonephropathy. The finding was also more severe in males than in females which is a common finding in rats.

2) Neoplastic - No increase in neoplastic findings related to dosing were observed. Hepatocellular adenoma/carcinoma incidence (combined) was 5% or less in all groups which normal for this strain. The incidences of hepatocellular adenomas and carcinomas were 0, 2, 1, 2, and 0, 0, 0, 1 in control, low, mid-, and high-dose males, respectively. In females the incidences of hepatocellular adenomas were 2, 0, 2, and ;era in the control, low, mid-, and high-dose groups. No hepatocellular carcinomas were reported in females.

D. DISCUSSION

The design and conduct of the study were acceptable. A peer review of the pathology report, which reviewed 10% of the rats in each group for gross and microscopic observations and all neoplasms in the study, was conducted. The reviewing pathologist agreed with the study pathologists diagnoses, interpretations and conclusions. Tissue recovery rate was good based on NTP standards and good tissue preservation was evident for virtually all tissues not autolyzed prior to necropsy. Tabulations of data were clear and grades of lesions as well as incidence were reported. A detailed protocol was available as well as protocol amendments.

Although the males may have been able to tolerate a higher dose based on minimal effects on body weights, we assess that dosing was adequate based on a significant ($p<0.05$) decreased weight gain (13%) in males receiving 7500 ppm during the first 52 weeks when compared to controls. The liver appears to be the target organ. Liver weights (absolute and relative-to-body weight) were increased in males receiving 7500 ppm terbacil and in females receiving 1500 or 7500 ppm terbacil at both 12 and 23 months. The increased liver weights were not accompanied by any changes in clinical chemistry parameters in males, but centrilobular fatty changes were seen in both sexes receiving 7500 ppm. None of the histologic liver changes were moderate or severe. The biological importance of the statistically significant increased incidence of eosinophilic foci in the livers of males receiving 25 and 1500 ppm is equivocal since all findings were minimum or slight and there was no corroborative toxicology such as dose-response elevation of hepatic enzymes or increased incidence of hepatocellular tumors. In high dose females, serum cholesterol levels were slightly but significantly increased compared to controls throughout the study. An examination of liver enzymes and P-450 would have been useful to determine if the liver effects were adaptive or adverse.

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Based on the decreased body weight gains and effects on liver weights and liver histopathology, the LELs in males and females were 7500 ppm and 1500 ppm, respectively. The NOEL is 25 ppm.

E. STUDY DEFICIENCIES

There were no study deficiencies that would affect interpretation of the results.

END