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DATA EVALUATION REPORT

STUDY TYPE: Oncogenicity Study in Rats

ACCESSION NUMBER: N/A

TOX. CHEM. NO.: 428

TEST MATERIAL: Terrazole® Technical
Lot No. S035012 (98.8% Pure)
Brown liquid

MRID NO.: 407479-01

SYNONYMS: 5-ethoxy-3-trichloromethyl-1,2,4-thiadiazole

STUDY NUMBER(S): 798-210

SUBMITTED BY: Uniroyal Chemical Company, Inc.

TESTING FACILITY: Hazleton Laboratories America, Inc.

TITLE OF REPORT: Oncogenicity Study in Rats with Terrazole® Technical

AUTHOR(S): Janet A. Trutter

REPORT ISSUED: June 23, 1988

CONCLUSIONS: Groups of Crl:CD®BR albino rats from Charles River Laboratories were dosed in their feed at nominal concentrations of 0, 100, 640, and 1280 ppm. Their calculated doses (based on food consumption) were 4.81, 30.43, and 63.38 mg/kg/day for males; and 5.90, 38.45, and 83.65 mg/kg/day for females.

The incidence of clinical signs, including tissue masses and wart-like lesions, was comparable for all groups. Depressed body weight gain was significant (>10%) in the high-dose males for only a few weeks at the beginning of the study. The high-dose females had depressed weight gain almost throughout the study which gradually progressed to 28% by the end of the study, while the mid-dose females had depressions of 10-16% during the latter half of the study. At 13 weeks, body weight gain was decreased 9% in the high-dose males, and 8% and 20% in the mid and high-dose females, respectively (compared to controls).

Food consumption and food efficiency were depressed in the high-dose females over the course of the study, but within normal ranges for all other groups. Food consumption at 13 weeks was decreased 7% in the high-dose males, and 10% and 18% in the mid and high-dose females, respectively (compared to controls).

The hematology data were not fully evaluable. There were no anomalous group values, other than marked neutrophilia in the mid and high-dose females which was of uncertain significance. One high-dose male was found to have myelocytes, metamyelocytes, and band neutrophils in its circulating blood at week 79, which correlated with a histopathologic evaluation of leukemia.

Gross lesions included dilated renal pelvis (20%) in the high-dose males which died on study, and pale areas (30%), cysts (18%), and masses (46%) in the livers of high-dose females. Organ weight anomalies included increased absolute and relative liver weights in the mid and high-dose males, and in the high-dose

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PRD-18

females. The relative organ weight data in the high-dose females were skewed by the substantial decrease in body weight gain.

Karyomegaly (nuclear enlargement, which is an indication of increased cellular turnover) was found in the absence of inflammation in the renal tubule cells of most low-dose, and virtually all mid and high-dose males and females. There was no subsequent increase in kidney tumors. Other non-neoplastic lesions included hepatocytomegaly, clear, basophilic, and eosinophilic cellular alteration, cholangiectasis, centrilobular pigmentation, and spongiosis hepatis of the liver; and testicular interstitial cell hyperplasia. There was a correlation between increased lesion incidences and elevated liver weights in the mid and high-dose males and the high-dose females.

Dose-related increases in thyroid tumors were seen in high-dose males, particularly when adenomas and carcinomas are considered together. It is not clear whether this was due to a direct or indirect (i.e. enhanced by excretion of thyroid hormones due to accelerated liver metabolism) carcinogenic effect.

Although increased incidences of mammary gland tumors were found in females, there was no evidence of biologically significant carcinogenicity. The mammary tumors were probably age-related, and the aging process may have been accelerated by physiological stress.

Biologically significant carcinogenicity was observed in the liver and testes, with the females having more liver tumors than the males. Bile stasis may have been a consequence of, or a factor in tumor formation. Cholangiocarcinoma (bile duct carcinoma), a rare liver tumor, was seen in 1 low-dose and 1 high-dose male, and in 8 high-dose females. It was the cause of death in 1 male (week 96) and 5 females (first death at week 81) at the high-dose.

Among the high-dose males, hepatocellular adenoma incidence was of doubtful biological significance, and carcinoma counts were within normal limits. The hepatocellular adenoma and carcinoma incidences were low in the high-dose females which died on study, but biologically significant at the terminal sacrifice.

Thus, in females, cholangiocarcinoma was seen mostly in the animals which died on study, while the liver adenomas and carcinomas were seen mostly at the end of the study. There was a good correlation between the high incidence of cholangiocarcinoma in females and centrilobular pigmentation.

The incidence of testicular interstitial cell hyperplasia was increased in the high-dose males which died on study and in those sacrificed terminally. This corresponded to interstitial cell tumor which was statistically significant in the rats examined terminally (7 of 19) and for the overall study (10 of 50).

The defined doses for this study are as follows:

Systemic NOAEL = 100 ppm (4.8/5.90 mg/kg/day, M/F, LDT) - renal tubule cell karyomegaly.

Systemic LOAEL = 640 ppm (4.8/5.90 mg/kg/day, M/F, LDT) - decreased body weight gain (F), increased absolute and relative liver weight (M),renal tubule cell karyomegaly (M&F), hepato-

PRD-19

cytomegaly (M), spongiosis hepatis (M), cholangiectasis (F), and centrilobular pigmentation (F).

Terrazole has carcinogenic potential in the livers of female rats, and the testes of male rats, and possibly in the thyroid of male rats. It can also induce cholangiocarcinoma, a rare tumor, predominantly in female rats.

STUDY CLASSIFICATION: This study is classified CORE MINIMUM. The hematology data were not fully evaluable for weeks 53 and 79 because no absolute counts were reported for erythrocytes, total and differential leukocytes, and platelets. Although it was not required, it would have been prudent to perform some clinical chemistry studies, especially a liver function battery. Considering the profound depression in weight gain in the high-dose females (28%), it was surprising that only a few animals were clinically observed to be "thin." Obvious typographical errors in Table 7A (clinical signs for group 2 females on page 132) should have been caught during Quality Assurance review. No historical control tumor data were supplied for comparison. Although the EPA Guidelines do not require them, they would have been useful in evaluating tumor incidence.

The mid-dose level (640 ppm) is defined as the Maximum Tolerated Dose (MTD) on the basis of decreased body weight gain in females (10-16%); increased absolute and relative liver weight (males); renal tubule cell karyomegaly in both sexes; liver lesions including hepatocytomegaly (males), spongiosis hepatis (males), cholangiectasis (females), and centrilobular pigmentation (females); and testicular interstitial cell tumor (males). Although this dose was well tolerated systemically (double the dose was not lethal), it nevertheless meets the criteria for an MTD.

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PRD-20

PROTOCOL: A 104-week oncogenicity study was performed using groups of 50 male (126.0-221.4 g) and 50 female (114.7-175.8 g) 4-week old Crl:CD®BR albino rats from Charles River Laboratories, Kingston, New York. The rats were individually housed during the study, and food (certified chow) and water were available ad libutum. The automatic watering system was replaced by water bottles between study weeks 6 and 24 due to problems in the water valves.

The rats were dosed in their feed at concentrations of 0 (vehicle control), 100, 640, and 1280 ppm (groups 1 through 4, respectively). Fresh diets were prepared weekly, and stored at room temperature. The rats were observed daily for clinical signs. Twice weekly they were examined closely and palpated for masses. Body weights were measured prior to study initiation, and body weights and food consumption were measured weekly for weeks 1-14, and monthly thereafter. During study week 89, 75% of the screened animals were positive for pinworms. The genus and species involved were not considered to have any impact on the study.

The test diets were analyzed for test article homogeneity and stability prior to study initiation and during the first week of the study. Initial chemical extraction difficulties were resolved by a new methodology, and had no impact on the study. Dose concentration analyses were performed during weeks 1, 2, 3, 4, 12, 24, 36, 48, 60, 72, 84, 96, and 104. Hematology studies were performed according to the following regimen:

Parameter	Week/s	Groups	Number/Group
Leukocytes, differential	53,79	1 & 4	10 males
Leukocytes, differential	103	1,2,3,4	10 males
Leukocytes, differential	53	1 & 4	10 females
Leukocytes, differential	79,103	1,2,3,4	10 females
Leukocytes, absolute	103	1,2,3,4	10/sex
Erythrocytes	103	1,2,3,4	10/sex
Hemoglobin	103	1,2,3,4	10/sex
Hematocrit	103	1,2,3,4	10/sex
nRBC's	103	1,2,3,4	10/sex
Cell morphologies	103	1,2,3,4	10/sex
Mean corpuscular volume	103	1,2,3,4	10/sex
Mean corpuscular hemoglobin	103	1,2,3,4	10/sex
Mean corpuscular hemoglobin conc.	103	1,2,3,4	10/sex
Platelets	103	1,2,3,4	10/sex

Reticulocytes were not counted. Tail blood was used for smears at weeks 53 and 79, and retro-orbital sinus blood was used at week 103. Blood was collected from the tail or vena cava of rats sacrificed moribund. No clinical chemistry or urinalysis parameters were evaluated.

At the end of the study, all survivors were sacrificed with sodium pentobarbital and exsanguination. All rats were necropsied, including those which died on study or were sacrificed moribund. The following tissues were preserved for all animals, and evaluated histopathologically for the control and high-dose groups, as well as all rats found dead or sacrificed during the study. The organs marked with an asterisk (*) were also weighed at necropsy for 10 rats/sex/group.

PRD-21

* Adrenals	Cecum
Pancreas	Rectum
Pituitary	* Kidneys
Thymus	* Liver
Thyroid and parathyroids	Lungs
Bone marrow (femur)	Trachea
* Brain (medulla/pons, cerebellar cortex, stem)	Lymph nodes (mandibular, mesenteric, regional)
Eyes (both)	Skin
Spinal cord (cervical, mid-thoracic, lumbar)	Mammary gland (female only)
Nerve (sciatic)	Skeletal muscle
Heart	Urinary bladder
Aorta (thoracic)	* Testes (w/ epididymides)
Spleen	Seminal vesicles
Salivary gland (mandibular)	Prostate
Esophagus	Ovaries (with fallopian tubes)
Stomach	Uterus
Duodenum	Vagina
Jejunum	Cervix
Ileum	Gross lesions
Colon	Masses with regional tissue

RESULTS: Initial concerns over stability were allayed when a better method of extraction was found. Analyses demonstrated that the feed formulations of terrazole were homogeneous, and stable for periods of at least 1 week at room temperature. Dose concentration analyses (excluding those with extraction problems) ranged from -16% to +7% of nominal, but were generally within ±10%. Over the course of the study, mean doses were within 5% of nominal. The calculated doses based on food consumption were as follows:

Nominal Dose (ppm)	Calculated Mean Dose (mg/kg/day) Weeks 1-4	Weeks 5-13	Weeks 14-54	Weeks 58-104	Weeks 1-104
			MALES		
0	-	-	-	-	-
100	8.09	5.80	4.25	3.58	4.81
640	51.43	36.71	26.94	22.56	30.43
1280	98.09	74.77	57.74	49.57	63.38
			FEMALES		
0	-	-	-	-	-
100	8.76	7.22	5.64	4.32	5.90
640	54.16	45.78	37.12	29.68	38.45
1280	106.65	94.15	83.24	69.64	83.65

PRA-22

The cause of death for 1 male and 5 females which died on study was attributed to cholangiocarcinoma, a rare liver tumor which will be discussed later. The mortality pattern over the course of the study was similar for all groups:

	MALES				FEMALES			
Dose (ppm):	0	100	640	1280	0	100	640	1280
Found dead	15	12	18	24	16	15	19	14
Sacrificed moribund	5	15	6	7	11	14	6	10
Accidental deaths	0	1	1	0	0	1	1	1
Total	20	28	25	31	27	30	26	25

Depressed body weight gain exceeded 10% in the high-dose males between weeks 6 and 11, and gradually approached control values thereafter. Depressed body weight gain in the high-dose females was 10% at week 2 and progressed to 28% by the end of the study. Depressed body weight gain in the mid-dose females ranged from 10-16% between week 50 and the end of the study. At 13 weeks, body weight gain was decreased 9% in the high-dose males, and 8% and 20% in the mid and high-dose females, respectively (compared to controls).

Food consumption was within a normal range for the males, but was depressed approximately 14% in the high-dose females over the course of the study. At 13 weeks, food consumption was decreased 7% in the high-dose males, and 10% and 18% in the mid and high-dose females, respectively (compared to controls). Food efficiency was reduced in the high-dose females, but was comparable for all other groups. The incidence of clinical signs, including tissue masses and wart-like lesions, was comparable for all groups.

At week 103, there was a marked neutrophilia in the mid-dose (+220%) and high-dose (+228%) females concurrent with constant lymphocyte counts, which resulted in leukocytosis (+56% and +51%, respectively). These findings were not dose-related, however, and the significance of this finding is uncertain. There were no dose-related effects found in erythrocyte or platelet counts at termination.

The interpretation of the hematology data was hampered by the failure of the laboratory to report absolute counts for total and differential leukocytes, erythrocytes, and platelets for weeks 53 and 79. The blast cell counts were zero. Blast forms are not released into peripheral blood, so this designation is presumed to be for myelocytes, which are mentioned in the clinical pathology report (page 42). Neutrophilic myelocytes differentiate into metamyelocytes (which were also counted), then band neutrophils, and finally neutrophils. There was no evidence of a neutrophilic left-shift (i.e. release of immature neutrophils) except in one high-dose male (No. B45881) which had 12% myelocytes, 16% metamyelocytes, and 21% band neutrophils at week 79. This finding correlated with a histopathologic evaluation of leukemia.

Gross lesions included dilated renal pelvis (20%) in the high-dose males which died on study; and pale areas (30%), cysts (18%), and masses (46%) in the livers of high-dose females which died on study and in those sacrificed terminally. As expected, more of the females sacrificed terminally had mammary masses than those which died on study, but there was no clear dose relationship.

PRD-23

The following table summarizes the percentages of change in organ weights compared to the controls. The values followed by asterisks are considered biologically significant. The relative organ weight changes reflect the lack of body weight gain change in the males and the marked changes in the females.

	MALES (%)			FEMALES (%)		
Dose (ppm):	100	640	1280	100	640	1280
ABSOLUTE ORGAN WEIGHT CHANGES						
Liver	+8	+31*	+42*	+4	+14	+76*
Kidney	-2	-2	-5	-4	-7	-1
Brain	-1	0	0	-2	-1	-5
Testes	-4	+16	+16	--	--	--
Adrenal	+23	+262	+5	-22	-25	-21
RELATIVE ORGAN WEIGHT CHANGES						
Terminal body weight	[-3]	[+3]	[-3]	[-7]	[-12]	[-29]
Liver	+3	+27*	+38*	+15	+27	+242*
Kidney	-7	-5	-9	+6	+4	+42
Brain	-6	-3	-2	+13	+13	+40
Testes	0	+14	+17	--	--	--
Adrenal	+16	+247	+3	-7	-11	+17

In the males, the absolute and relative liver weights were significantly increased in the mid and high-dose groups beyond that expected as a normal metabolic response to a toxic agent. Absolute and relative testes weights were increased somewhat in the mid and high-dose males, but the change was not dose-related. The marked increase in mid-dose male adrenal weights was considered to be an artifact since it was not dose-related. There were no dose-related effects on kidney or brain weights.

In the females, decreased body weight gain (29%) at the high-dose resulted in a significant, but exaggerated, increase in relative liver weight (242%). Apparent increases in kidney, brain, and adrenal weights in the high-dose females were not true organ weight anomalies, but rather were due to marked decreases in body weight gain.

The following table summarizes the significant non-neoplastic histopathologic lesions. Those that are biologically significant are marked with asterisks (*).

PRA-24

Non-Neoplastic Lesions

Dose (ppm):	MALES 0	100	640	1280	FEMALES 0	100	640	1280
UNSCHEDULED DEATHS								
LIVER:								
Hepatocytomegaly	1/20	0/28	6/25*	15/31*	2/27	3/30	1/26	16/25*
Cellular alteration, clear	3/20	3/28	1/25	6/31*	0/27	1/30	0/26	6/25*
Cellular alteration, bas.	3/20	0/28	2/25	10/31*	5/27	9/30	12/26*	15/25*
Cellular alteration, eos.	4/20	1/28	4/25	16/31*	3/27	3/30	0/26	8/25*
Cellular alteration, all	7/20	3/28	6/25	21/31*	7/27	12/30	12/26	17/25*
Spongiosis hepatis	2/20	2/28	8/25*	10/31*	0/27	0/30	0/26	2/25
Centrilob. pigmentation	0/20	0/28	0/25	2/31	0/27	0/30	7/26	23/25*
KIDNEY:								
Tubule cell karyomegaly	0/20	13/28*	25/25*	30/31*	0/27	21/30*	26/26*	25/25*
TESTES:								
Interst. cell hyperplasia	1/20	1/28	2/25	7/31*			—	
TERMINAL SACRIFICE								
LIVER:								
Hepatocytomegaly	5/30	5/22	10/25	19/19	5/23	4/20	14/24	21/25
Cholangiectasis	17/30	14/22	13/25	10/19	6/23	4/20	8/24	14/25*
Centrilob. pigmentation	0/30	0/22	0/25	2/19	0/23	0/20	3/24	22/25*
KIDNEY:								
Tubule cell karyomegaly	0/30	18/22*	25/25*	19/19*	0/23	18/20*	24/24*	25/25*
TESTES:								
Interst. cell hyperplasia	3/30	4/22	4/25	11/19*			—	
TOTAL								
LIVER:								
Hepatocytomegaly	6/50	5/50	16/50	34/50	7/50	7/50	15/50	37/50
Cellular alteration, eos.	18/50	13/50	27/50*	30/50*	8/50	11/50	14/50	29/50*
Cholangiectasis	20/50	24/50	17/50	17/50	8/50	6/50	15/50*	18/50*
Centrilob. pigmentation	0/50	0/50	0/50	4/50	0/50	0/50	10/50*	45/50*
KIDNEY:								
Tubule cell karyomegaly	0/50	31/50*	50/50*	49/50*	0/50	39/50*	50/50*	50/50*
TESTES:								
Interst. cell hyperplasia	4/50	5/50	6/50	18/50*			—	

The liver and testes histopathologic lesions will be discussed later along with the neoplastic lesions since they could have been preludes to cancer.

The karyomegaly (nuclear enlargement) found in the renal tubule cells was an indication of increased cellular turnover following toxic insult. It was clearly compound-related, with most of the low-dose and virtually all the mid and high-dose animals of both sexes being affected. Although this lesion can be a prelude to neoplasia, there was no subsequent increase in kidney tumors. There were no corresponding signs of inflammation.

The following tables summarize the neoplastic liver lesions found in the males and females. Hepatocytomegaly incidence is included for the sake of reference (asterisks indicate biological significance).

PRA-25

Liver Neoplasia - Males

Dose (ppm):	0	100	640	1280
UNSCHEDULED DEATHS				
Hepatocytomegaly	1/20	0/28	6/25*	15/31*
Adenoma, hepatocellular	0/20 0%	0/28 0%	0/25 0%	4/31 13%
Carcinoma, hepatocellular	0/20 0%	1/28 4%	1/25 4%	1/31 3%
Cholangiocarcinoma	0/20 0%	0/28 0%	0/25 0%	1/31 3%
Adenoma and/or carcinoma, hepatocellular	0/20 0% p= <0.05	1/28 4%	1/25 4%	5/31 16%
TERMINAL SACRIFICE				
Hepatocytomegaly	5/30	5/22	10/25	19/19
Adenoma, hepatocellular	1/30 3%	0/22 0%	0/25 0%	4/19 21%
Carcinoma, hepatocellular	1/30 3%	0/22 0%	1/25 4%	0/19 0%
Cholangiocarcinoma	0/30 0%	1/22 5%	0/25 0%	0/19 0%
Adenoma and/or carcinoma, hepatocellular	2/30 7% p= <0.05	0/22 0%	1/25 4%	4/19 21%
TOTAL				
Hepatocytomegaly	6/50	5/50	16/50	34/50
Adenoma, hepatocellular	1/50 2% p= <0.01	0/50 0%	0/50 0%	8/50 16% 0.0154
Carcinoma, hepatocellular	1/50 2%	1/50 2%	2/50 4%	1/50 2%
Cholangiocarcinoma	0/50 0%	1/50 2%	0/50 0%	1/50 2%
Adenoma and/or carcinoma, hepatocellular	2/50 4% p= <0.01	1/50 2%	2/50 4%	9/50 18% 0.0256

PRD-26

Liver Neoplasia - Females

Dose (ppm):	0	100	640	1280
UNSCHEDULED DEATHS				
Hepatocytomegaly	2/27	3/30	1/26	16/25*
Adenoma, hepatocellular	0/27 0%	0/30 0%	0/26 0%	3/25 12%
Carcinoma, hepatocellular	0/27 0%	0/30 0%	0/26 0%	1/25 4%
Cholangiocarcinoma	0/27 0%	0/30 0%	0/26 0%	8/25 32%
	p= <0.01			0.0014
Adenoma and/or carcinoma, hepatocellular	0/27 0%	0/30 0%	0/26 0%	4/25 16%
	p= <0.01			0.0467
TERMINAL SACRIFICE				
Hepatocytomegaly	5/23	4/20	14/24	21/25
Adenoma, hepatocellular	2/23 9%	1/20 5%	2/24 8%	9/25 36%
	p= <0.01			0.0264
Carcinoma, hepatocellular	0/23 0%	0/20 0%	0/24 0%	11/25 44%
	p= <0.01			0.0002
Cholangiocarcinoma	0/23 0%	0/20 0%	0/24 0%	3/25 12%
Adenoma and/or carcinoma, hepatocellular	2/23 9%	1/20 5%	2/24 8%	20/25 80%
	p= <0.01			0.0001
TOTAL				
Hepatocytomegaly	7/50	7/50	15/50	37/50
Adenoma, hepatocellular	2/50 4%	1/50 2%	2/50 4%	12/50 24%
	p= <0.01			0.0038
Carcinoma, hepatocellular	0/50 0%	0/50 0%	0/50 0%	12/50 24%
	p= <0.01			0.0001
Cholangiocarcinoma	0/50 0%	0/50 0%	0/50 0%	11/50 22%
	p= <0.01			0.0003

PRA-27

Adenoma and/or carcinoma, hepatocellular	2/50	1/50	2/50	24/50
	4%	2%	4%	48%
	p= <0.01			0.0001

Significance of trend (Cochran-Armitage Trend Test) is denoted under the control data if there is a significant trend.

Significance of pairwise comparison with control (Fisher's Exact Test) is listed under the dose group data if there is a significant change.

The correlation between the non-neoplastic liver lesions (hepatocytomegaly; clear, basophilic and eosinophilic cellular alteration; cholangiectasis; and centrilobular pigmentation) and tumor incidences suggests that they could have been preludes to cancer, although there is no way of confirming this. There was a correlation between the increased lesion incidences and elevated liver weights in the mid and high-dose males and the high-dose females. Bile statis could have been a contributing factor in tumor formation, but more likely it was a consequence of tumor impingement. The significance of spongiosis hepatis (a cellular change in response to injury) is uncertain. There would have been a better understanding of the compound-induced hepatotoxicity if clinical chemistry studies had been performed.

Among the high-dose males, there were small increases in hepatocellular adenomas in the unscheduled deaths (first seen at week 84) and at the terminal sacrifice. The adenoma incidence (8 of 50) was statistically significant only when all animals were considered. Carcinoma counts were within normal limits. The death of one high-dose male which died on study (week 96) was attributed to cholangiocarcinoma, a rare tumor. A low-dose male also had a cholangiocarcinoma.

The female rats had more liver neoplasia than did the males. Those which died on study had low adenoma and carcinoma incidence, but 8 of 25 of the high-dose females had cholangiocarcinoma, a rare tumor (first seen at week 81). Five female deaths were attributed to cholangiocarcinoma. The high-dose animals sacrificed terminally had significant increases in adenoma (9 of 25) and carcinoma (11 of 25) incidence, and 3 also had cholangiocarcinoma. Thus, in females, cholangiocarcinoma was seen mostly in the animals which died on study, while the adenomas and carcinomas were seen mostly at the end of the study.

There was a good correlation between the high incidence of cholangiocarcinoma in females and centrilobular pigmentation which affected 23 of 25 females, but only 2 of 31 males. It is unfortunate that no bilirubin measurements were taken. It is likely that the centrilobular pigmentation was due to bile pigment deposition (e.g. bilirubin, etc.) as a consequence of biliary blockage.

No laboratory historical control data were provided, but the non-neoplastic liver lesions and liver tumor incidences appear to exceed literature historical control values.

The following table summarizes the neoplastic thyroid lesions found in the males and females, and includes findings of follicular cell hyperplasia for the sake of reference:

Thyroid Neoplasia - Males

Dose (ppm):	0	100	640	1280
UNSCHEDULED DEATHS				
Hyperplasia, follicular cell	0/20 0%	0/28 0%	0/25 0%	0/30 0%
Adenoma, follicular cell	2/20 10%	1/28 4%	4/25 16%	6/30 20%
Carcinoma, follicular cell	0/20 0%	1/28 4%	1/25 4%	3/30 10%
Adenoma and/or carcinoma, follicular cell	2/20 10%	2/28 8%	5/25 20%	9/30 30%
TERMINAL SACRIFICE				
Hyperplasia, follicular cell	0/30 0%	1/20 5%	1/24 4%	0/19 0%
Adenoma, follicular cell	4/30 13% p=	5/20 25%	3/24 13%	8/19 42% 0.0270
Carcinoma, follicular cell	0/30 0% p=	0/20 0%	5/24 21% 0.0134	1/19 5%
Adenoma and/or carcinoma, follicular cell	4/30 13% p= <0.01	5/20 25%	8/24 33%	9/19 47% 0.0112
TOTAL				
Hyperplasia, follicular cell	0/50 0%	1/48 2%	1/49 2%	0/49 0%
Adenoma, follicular cell	6/50 12% p= 0.05	6/48 13%	7/49 14%	14/49 29% 0.0349
Carcinoma, follicular cell	0/50 0% p= 0.05	1/48 2%	6/49 12%	4/49 8% 0.0563
Adenoma and/or carcinoma, follicular cell	6/50 12% p= <0.01	7/48 15%	13/49 27%	18/49 37% 0.0038

PRD-29

Thyroid Neoplasia - Females

Dose (ppm):	0	100	640	1280
UNSCHEDULED DEATHS				
Hyperplasia, follicular cell	0/27 0%	1/30 3%	1/25 4%	2/25 8%
Adenoma, follicular cell	0/27 0%	1/30 3%	0/25 0%	1/25 4%
Carcinoma, follicular cell	1/27 4%	1/30 3%	0/25 0%	1/25 4%
Adenoma and/or carcinoma, follicular cell	1/27 4%	2/30 7%	0/25 0%	2/25 8%
TERMINAL SACRIFICE				
Hyperplasia, follicular cell	0/23 0%	0/1 0%	0/0 0%	1/25 4%
Adenoma, follicular cell	0/23 0%	0/1 0%	0/0 0%	3/25 12%
Carcinoma, follicular cell	0/23 0%	0/1 0%	0/0 0%	0/25 0%
Adenoma and/or carcinoma, follicular cell	0/23 0%	0/1 0%	0/0 0%	3/25 12%
TOTAL				
Hyperplasia, follicular cell	0/50 0%	1/31 3%	1/25 4%	3/50 6%
Adenoma, follicular cell	0/50 0%	1/31 3%	0/25 0%	4/50 8%
Carcinoma, follicular cell	1/50 2%	1/31 3%	0/25 0%	1/50 2%
Adenoma and/or carcinoma, follicular cell	1/50 2%	2/31 6%	0/25 0%	5/50 10%

Significance of trend (Cochran-Armitage Trend Test) is denoted under the control data if there is a significant trend.

Significance of pairwise comparison with control (Fisher's Exact Test) is listed under the dose group data if there is a significant change.

PRD-30

The incidences of thyroid follicular cell hyperplasia, adenoma, and carcinoma in females were low in all groups. There was little or no follicular cell hyperplasia in the male groups, but a statistically significant increase in follicular cell adenoma incidence was seen in the high-dose males at terminal sacrifice and for the study as a whole. A significant trend was seen in the incidence of follicular cell carcinoma at the terminal sacrifice and for the study as a whole, but the dose-relationship was not clear (incidence was highest at the mid-dose). The incidence of follicular cell adenoma and/or carcinoma (i.e. combined) in the high-dose group was statistically significant at the terminal sacrifice and for the study as a whole.

Historical primary thyroid tumor incidence in many rat strains can range from 5% to 36%. The data were insufficient to clearly show whether the dose-related incidences of combined adenomas and carcinomas were due to a direct or indirect (i.e. enhanced by excretion of thyroid hormones due to accelerated liver metabolism) carcinogenic effect.

The following table summarizes the neoplastic testes lesions, and includes interstitial cell hyperplasia for the sake of reference:

Testes Neoplasia - Males

Dose (ppm):		0	100	640	1280
UNSCHEDULED DEATHS					
Hyperplasia, interstitial cell		1/20	1/28	2/25	7/31
		5%	4%	8%	23%
	p=	<0.05			
Tumor, interstitial cell		0/20	1/28	0/25	3/31
		0%	4%	0%	10%
TERMINAL SACRIFICE					
Hyperplasia, interstitial cell		3/30	4/22	4/25	11/19
		10%	18%	16%	58%
	p=	<0.01			0.0005
Tumor, interstitial cell		0/30	3/22	4/25	7/19
		0%	14%	16%	37%
	p=	<0.01			0.0006
TOTAL					
Hyperplasia, interstitial cell		4/50	5/50	6/50	18/50
		8%	10%	12%	36%
	p=	<0.01			0.0007
Tumor, interstitial cell		0/50	4/50	4/50	10/50
		0%	8%	8%	20%
	p=	<0.01			0.0013

PRD-31

Significance of trend (Cochran-Armitage Trend Test) is denoted under the control data if there is a significant trend.

Significance of pairwise comparison with control (Fisher's Exact Test) is listed under the dose group data if there is a significant change.

The incidence of testicular interstitial cell hyperplasia was increased in the high-dose males which died on study and in those sacrificed terminally. This corresponded to interstitial cell tumor which was statistically significant in the rats examined terminally (7 of 19) and for the overall study (10 of 50). Interstitial cell tumor incidence should have been low in this strain of rat, and in fact no tumors were seen in the control animals. The low and mid-dose groups had similar tumor incidence which suggests a compound-related effect, but not necessarily a dose-related effect. No laboratory historical control data were provided, and there are no good tumor incidence data in the open literature.

The following table summarizes the neoplastic mammary lesions.

Mammary Gland Neoplasia - Females

Dose (ppm):	0	100	640	1280
UNSCHEDULED				
Adenoma	1/26 4%	0/30 0%	0/26 0%	0/25 0%
Fibroadenoma	4/26 15%	9/30 30%	5/26 19%	11/25 44%
p=				0.0257
Carcinoma	7/26 27%	6/30 20%	9/26 35%	9/25 36%
Fibroma	0/26 0%	0/30 0%	0/26 0%	1/25 4%
Adenoma, fibroadenoma, carcinoma, and/or fibroma	11/26 42%	11/30 37%	13/26 50%	15/25 60%
TERMINAL				
Adenoma	0/23 0%	0/16 0%	0/20 0%	1/25 4%
Fibroadenoma	5/23 22%	9/16 56%	12/20 60%	12/25 48%
p=				0.0541
Carcinoma	8/23 35%	6/16 38%	6/20 30%	6/25 24%

PRD-32

Fibroma	0/23 0%	1/16 6%	0/20 0%	1/25 4%
Adenoma, fibroadenoma, carcinoma, and/or fibroma	11/23 48%	13/16 81%	15/20 75%	15/25 60%
TOTAL				
Adenoma	1/49 2%	0/46 0%	0/46 0%	1/50 2%
Fibroadenoma	9/49 18% p= <0.05	18/46 39%	17/46 37%	23/50 46% 0.0030
Carcinoma	15/49 31%	12/46 26%	15/46 33%	15/50 30%
Fibroma	0/49 0%	1/46 2%	0/46 0%	2/50 4%
Adenoma, fibroadenoma, carcinoma, and/or fibroma	22/49 45%	24/46 52%	28/46 61%	30/50 60%

Significance of trend (Cochran-Armitage Trend Test) is denoted under the control data if there is a significant trend.

Significance of pairwise comparison with control (Fisher's Exact Test) is listed under the dose group data if there is a significant change.

The only statistically significant neoplasia found in the mammary gland was fibroadenoma. Despite significance of trend for fibroadenoma for the study as a whole ($p < 0.05$), there was no clear evidence of dose-related incidence at any point in the study. The adenoma, carcinoma, and fibroma counts were comparable for all dosed and control groups, and except for carcinomas, were of low incidence. The incidence of adenoma, fibroadenoma, carcinoma, and/or fibroma was comparable for all dosed and control groups. Thus, there was no evidence of carcinogenicity in the mammary gland. Compared to the open literature, the tumor incidence was within normal limits.