

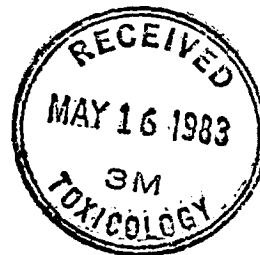


HAZLETON LABORATORIES AMERICA, INC.

8200 LEESBURG TURNPIKE, VIENNA, VIRGINIA 22180, U.S.A.

May 13, 1983

William C. McCormick, III
Toxicologist
Toxicology Services
Medical Department/3M
220-2E 3M Center
St. Paul, Minnesota 55101



Dear Bill:

Enclosed are four copies of the final report for Project No. 154-158, Pilot Rat Teratology Study with T-3351. With copy of this letter, I am forwarding one copy of the report to Marshall Johnson.

If you have any comments or questions, please contact me.

Best regards.

Sincerely,

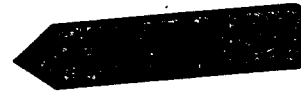
LAWRENCE T. WETZEL, Ph.D.
Staff Scientist
Department of Toxicology

LTW:sm
Enclosure

cc: E. Marshall Johnson

PILOT TERATOLOGY STUDY IN RATS

T-3551



FINAL REPORT

Submitted to
3M Company
St. Paul, Minnesota

May 13, 1983



SUBJECT: Pilot Teratology Study in Rats
Project No. 154-158

We, the undersigned, hereby declare that the work was performed under our supervision, according to the procedures herein described.

Study Director:


LAWRENCE T. WETZEL, Ph.D.
Staff Scientist
Department of Toxicology

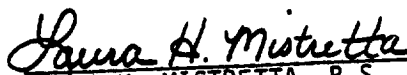
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tlh

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HAZLETON LABORATORIES AMERICA, INC.

9200 LEESBURG TURNPIKE, VIENNA, VIRGINIA 22180, U.S.A.

SPONSOR: 3M Company

DATE: May 13, 1983

MATERIAL: T-3551 

SUBJECT: FINAL REPORT
Pilot Teratology Study in Rats
Project No. 154-158

SUMMARY

T-3351, suspended in corn oil at concentrations intended to deliver 1, 5, 10, or 20 mg/kg/day (Groups 2, 3, 4, and 5, respectively), was administered by oral intubation to four groups of mated female Sprague-Dawley SD[®] rats on gestation Days 6 through 15. A fifth group (Group 1) of mated females served as the control group and received the vehicle only.

No Group 5 females survived to cesarean section on gestation Day 20. Treatment-related clinical observations in Groups 4 and 5 included hunched and thin appearance of the animals. In addition, tremors and convulsions as well as prostration and anorexia were noted in Group 5 animals. Body weight gain of the dams during gestation was less in Groups 3, 4, and 5 compared to control, with a significant reduction in weight gain occurring in Groups 4 and 5. A significant decrease in food consumption occurred in Groups 4 and 5. Apparent treatment-related ulcerated areas on the glandular and/or nonglandular stomach mucosa were found during necropsy of Group 5 females.

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Analysis of individual and mean uterine data demonstrated no effect of T-3351 on fetal mortality or fetal viability. Mean fetal weight was comparable for either sex in all groups. External, visceral, and skeletal abnormalities were generally similar for all groups. One Group 3 fetus was found to have a small eye upon external examination. Another Group 3 fetus had fused hind limbs and anal atresia. Skeletal examination confirmed the external limb anomaly.

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INTRODUCTION

This study was designed to determine the maternal and embryo/fetal toxicity of T-3551 when administered by gavage to pregnant rats during the period of fetal organogenesis for the purpose of setting dosage levels for an expanded teratology study. The rats were placed in breeding on January 11, 1983, and cesarean sections were completed on February 3, 1983. This report presents the methods and results from this study.

CONTROL AND TEST MATERIALS

The vehicle and control material, Duke's[®] Corn Oil (C. F. Sauer Co., Richmond, Virginia), Lot 80235, was received on May 28, 1982 and was stored at room temperature.

The test material, T-3351, a white powder, was received from the sponsor on January 5, 1983, and was stored at room temperature. The test material was assumed to be 100% active compound. Information on methods of synthesis and stability, as well as data on composition or other characteristics which define the test material, are on file with the sponsor.

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TEST ANIMALS

Sexually mature, cesarean-derived Sprague-Dawley Cr1:CD[®](SD)BR rats were chosen for this study because they are sensitive to a number of agents which are known to be embryotoxic and/or teratogenic. Rats have historically been used in safety evaluation studies of this type and are required by the regulatory agencies. Thirty-six male and thirty-six female thirteen-week old rats were received from Charles River Breeding Laboratories, Kingston, New York, on December 22, 1982. The rats were held in quarantine for two weeks, during which time a health status examination was performed by a staff veterinarian.

The rats were housed one male and one female per cage during breeding. Following confirmation of mating, the females were housed individually in elevated wire-mesh cages with food (Purina Rodent Laboratory Chow[®] 5001) and tap water available ad libitum. The females were uniquely identified by ear tag after mating was confirmed. Temperatures in the study room ranged from 71 to 76°F with a relative humidity between 37 and 65%.

METHODS

Mating Period

During the mating period, one female was paired with one male until mating was confirmed or until two weeks had elapsed. Daily vaginal examinations of each female were performed to detect the presence and

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viability of sperm or the presence of a copulatory plug. The day of observation of sperm or copulatory plug was designated as "Day 0" of gestation.

Groups and Dosage Levels

Upon confirmation of mating, each female was assigned to one of the following groups.

<u>Group</u>	<u>Dose^a</u> <u>mg/kg/day</u>	<u>Number of Females</u>
1	0	6
2	1	6
3	5	7
4	10	7
5	20	7

^a Based on individual animal body weights at each weighing interval during the dosing period.

The females were placed in the dose groups one at a time beginning with the high-dose group and continuing sequentially through the control group until all mated females were assigned to a group.

All males were sacrificed via carbon dioxide asphyxiation and discarded without necropsy once a sufficient number of matings were confirmed.

Compound Preparation and Administration

Suspensions of the test material in the corn oil vehicle were prepared on a weight per volume basis. The required amount of compound

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for each level was weighed on an electronic Arbor 126 balance and transferred to a 7 ml homogenizer. Approximately 5 ml of corn oil was added and the test material was ground into a fine suspension with a teflon pestle. This suspension was transferred to a beaker and any remaining compound in the homogenizer was rinsed into the beaker. Additional corn oil was added to the suspension to produce the desired concentration and the suspension was mixed on a stirrer for approximately ten minutes. Prepared suspensions were mixed with a magnetic stirrer during dosing.

Females were given the appropriate dosing suspension or vehicle by oral intubation on a daily basis beginning on Day 6 and continuing through Day 15 of gestation. The test material was administered orally because of the relative ease and accuracy of dosing.

Fresh dosing suspensions were prepared weekly and stored under refrigeration (approximately 41°F). Samples of each test mixture as well as the vehicle were sent to the sponsor for analysis.

Maternal Observations and Records

All animals were examined twice daily for mortality and morbidity (from day of receipt through study termination) and once daily for clinical signs of toxicity and pharmacologic effects (throughout gestation). Body weights and food consumption were recorded on Days 0, 6, 8, 12, 16, and 20 of gestation.

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Cesarean Sacrifice and Tissue Preservation

A gross necropsy was performed on all animals (found deads, moribund sacrifices, and terminal sacrifices). The uterus and ovaries from found dead animals and animals sacrificed because of moribundity were removed and examined for the number of implantation sites and corpora lutea, respectively. Prior to gestation Day 20, surviving females were assigned random numbers and all personnel performing cesarean sections and/or external, visceral, or skeletal examinations of the fetuses were unaware of the dose level from which the animals were derived. On Day 20 of gestation, all surviving females were weighed and sacrificed by carbon dioxide asphyxiation.

The uterus from each female was weighed and examined for the number and placement of uterine implantation sites, number of live and dead fetuses, early and late resorbing fetuses, and any abnormalities. The uterus of each animal was reweighed after the contents were removed. The ovaries were examined for the number of corpora lutea. Each live fetus was sexed, weighed, and examined for external abnormalities. Findings were recorded.

Beginning at the ovarian end of the right uterine horn, the first six fetuses, regardless of sex, were selected for further evaluation. After the external examination was completed, the first fetus was identified with a tag and fixed in Bouin's solution for soft tissue evaluation (Wilson, et al., 1965). The next two fetuses were eviscerated, tagged, and processed for skeletal examination using a

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technique modified from that reported by Staples (Staples and Schnell, 1964). This sequence was repeated until a maximum of six fetuses had been selected.

Statistical Analyses

Mean maternal body weight gains (Days 6-16 and 0-20), total food consumption, gravid uterine weight, terminal body weight minus gravid uterine weight, resorption incidence, percent males, and fetal viability were analyzed in the following order. Levene's test for homogeneity of variances (Levene, 1960; Draper and Hunter, 1969) was performed and if the variances proved to be homogeneous, the data were analyzed by one-way classification analysis of variance (ANOVA) (Winer, 1971). If the variances proved to be heterogeneous, a series of transformations was performed until variance homogeneity was achieved. These transformations were: $\log_{10}$, square (x^2), square root ($x^{1/2}$), reciprocal ($1/x$), angular (arcsine $x^{1/2}$), and rank, in that order. If rank transformation was ineffective in removing variance heterogeneity, ANOVA of ranked data was completed. If ANOVA of untransformed or transformed data was significant, Dunnett's t-test (Dunnett, 1955 and 1964) was used for control vs. compound-treated group mean comparisons. If ANOVA was not significant, the analysis was complete.

Mean number of fetuses with visceral variants per litter and skeletal variants per litter were analyzed by Fisher's exact test for proportions (Fisher, 1950).

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In addition to the above data, analysis of covariance (ANCOVA) (Winer, 1971) was used to analyze mean fetal weights. The litter was used as the experimental unit.

Levene's tests and ANOVA were evaluated at the 5.0% one-tailed probability level. Control vs. compound-treated group mean comparisons were evaluated at the 5.0% two-tailed probability level.

Statistical references are appended to this report, and statistically significant differences, as indicated by the aforementioned tests, are designated throughout this report by the term "significant" and/or as follows:

S+ = Significantly higher than the control value.

S- = Significantly lower than the control value.

Specimen, Raw Data, and Final Report Storage

All specimens, raw data, and the final report are stored in the archives of Hazleton Laboratories America, Inc.

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RESULTS - MATERNAL DATA

Clinical Signs

Summary clinical signs are presented in Table 1.

Treatment-related clinical observations were noted in the Groups 4 and 5 animals during the treatment and posttreatment phases. These included hunched and thin appearance and rough haircoat in both groups, and tremors, convulsions, prostration, and anorexia in the Group 5 females.

Mortality

All Group 5 females were found dead or sacrificed in a moribund condition prior to cesarean section on Day 20 of gestation. All other animals survived to Day 20 of gestation.

Body Weights

Individual and mean body weights and body weight changes are presented in Appendix 1. Mean weight values and body weight changes are presented in Table 2.

Lower mean body weight values were noted in the treated groups. Decreased body weight gain during gestation was noted in Groups 3, 4, and 5, with significant decreases noted in Groups 4 and 5. (Due to the number of deaths in Group 5, body weight change values could not be determined for Days 0-20.)

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Food Consumption

Individual and mean food consumption values are presented in Appendix 2. Mean food consumption values are presented in Table 3.

Decreased food consumption was noted in all treated groups in a dose-related fashion. Significantly lower total food consumption values (Days 0-20) were noted in Groups 3 and 4. (Due to the number of deaths in Group 5, total food consumption values could not be determined.)

Gross Pathology

Summary gross pathology findings are presented in Table 4.

Treatment-related findings were noted in the Group 5 rats and included ulcerated-like areas on the glandular or nonglandular stomach mucosa.

Uterine Weights

Individual and mean uterine weights are presented in Appendix 3. Summary uterine weights are presented in Table 5.

The terminal body weights minus the gravid uterine weights were lower in the treated groups when compared to the control group; however, no statistical differences were noted. The gravid uterine weights were comparable between the control and treated groups.

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RESULTS - CESAREAN DATA

Individual and mean ovarian, uterine, and litter data are presented in Appendix 4. Individual and mean live fetal data are presented in Appendix 5. Summary ovarian, uterine, and litter data are presented in Table 6.

Pregnancy Rates, Corpora Lutea, Uterine Implantations, and Implantation Efficiency

Pregnancy rates were 100 percent for Groups 2, 3, and 5; 83 percent for Group 1, and 86 percent for Group 4. The mean number of corpora lutea and uterine implantations were comparable for all groups. The implantation efficiency for the control group was low; however, this may be attributed to two animals which had implantation efficiencies of 38.4 and 35.7 percent.

Fetal Viability, Weight, and Sex

The mean incidence of resorptions was similar for Groups 1-4. The mean incidence of fetal viability was comparable between the control group and Groups 2, 3, and 4, as were mean fetal weights and the percent males per litter.

Fetal Development

Individual visceral findings are presented in Appendix 6; individual skeletal findings are presented in Appendix 7. Mean incidence values

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for visceral and skeletal findings are presented in Table 7 (based on number of fetuses) and Table 8 (based on number of litters).

External anomalies were noted in two Group 3 fetuses at cesarean section. These included a small right eye in one fetus, and short and thickened tail, no external genital/anal opening and hind legs which were joined from the pelvis to the feet in the other fetus. All remaining fetuses appeared normal.

There was no apparent treatment-related increase in the incidence of visceral or skeletal variants or anomalies. Incompletely descended testes were noted in two Group 4 fetuses. Skeletal anomalies noted in one Group 3 fetus included a small pubis, fused ischia, and cojoined hind limbs. This fetus was the one for which the tail and hind limb external abnormalities were noted.

Table 1
Clinical Observations During Gestation
Pilot Teratology Study of T-3551 in Rats

<u>Observation</u>	<u>Group 1</u>			<u>Group 2</u>			<u>Group 3</u>			<u>Group 4</u>			<u>Group 5</u>		
	<u>0-5</u>	<u>6-15</u>	<u>16-20</u>	<u>0-5</u>	<u>6-15</u>	<u>16-20</u>	<u>0-5</u>	<u>6-15</u>	<u>16-20</u>	<u>0-5</u>	<u>6-15</u>	<u>16-20</u>	<u>0-5</u>	<u>6-15</u>	<u>16-20</u>
Number which appeared normal	6	5	5	6	5	6	7	7	7	7	2	3	6		
Alopecia		1	1							1	1		1	1	
Hunched										2	1		5		5
Rough haircoat										1	1		6		4
Bloody crust					1					2	1		6		6
Thin										1	1		7		5
Urine stains													4		4
Tremors													1		
Convulsions													3		3
Prostrate													3		3
Anorexia													6		5
Soft feces													1		
Bloody discharge from vagina															1

Table 2
Mean Maternal Body Weights and Body Weight Change
Pilot Teratology Study of T-3551 in Rats

Group and Dose Level		Body Weight (g)						Body Weight Change ($\pm$ g)	
		Day of Gestation						Days of Gestation	
		0	6	8	12	16	20	6-16	0-20
1 0 mg/kg	Mean	231.67	256.38	260.96	280.92	303.22	355.36	46.84	123.60
	S.D.	13.831	9.187	12.574	13.102	20.915	33.795	16.308	26.087
2 1 mg/kg	Mean	216.53	243.78	246.60	266.08	289.38	348.43	45.60	131.90
	S.D.	8.640	12.094	11.064	18.994	16.705	23.213	9.297	15.259
3 5 mg/kg	Mean	231.16	253.44	253.79	262.24	291.21	350.90	37.77	119.74
	S.D.	10.085	10.692	8.578	9.340	9.111	16.306	9.800	15.426
4 10 mg/kg	Mean	228.75	254.33	254.85	262.15	266.08	333.75	4.37 ^{S-}	105.00
	S.D.	19.401	18.145	20.020	21.046	24.184	26.277	22.593	13.301
5 20 mg/kg	Mean	228.29	245.06	238.70	202.73	175.05	-	-64.50 ^{S-}	-
	S.D.	14.039	13.923	9.242	6.388	5.720	-	17.593	-

Table 3
Mean Food Consumption Values
Pilot Teratology Study of T-3551 in Rats

Group and Dose Level		Food Consumption (gm/day)					Total Food Consumption
		Day of Gestation					Days of Gestation
		6	8	12	16	20	0-20
1 0 mg/kg	Mean	23.73	20.13	21.55	21.10	26.05	457.12
	S.D.	2.501	4.132	3.597	4.145	4.284	58.499
2 1 mg/kg	Mean	20.88	18.50	19.85	19.27	27.00	410.80
	S.D.	4.330	4.159	2.874	2.430	2.211	29.452
3 5 mg/kg	Mean	21.47	16.47	16.60	17.66	24.81	397.83S-
	S.D.	1.923	2.735	1.880	1.269	1.585	23.480
4 10 mg/kg	Mean	21.61	16.90	17.46	10.91	22.11	365.09S-
	S.D.	2.006	1.615	5.336	3.879	3.021	41.840
5 20 mg/kg	Mean	19.31	14.13	4.74	0.32	-	-
	S.D.	2.741	2.743	4.028	0.240	-	-

Table 4
Summary Gross Pathology Findings
Pilot Teratology Study of T-3551 in Rats

<u>ORGAN AND DESCRIPTION</u>	Dose Level	Group: $\frac{1}{0}$	$\frac{2}{1}$	$\frac{3}{5}$	$\frac{4}{10}$	$\frac{5}{20}$
Number of animals examined		6	6	7	7	7
Number of animals with no gross lesions		6	5	7	7	2
STOMACH						
Ulcerated-like areas/dark foci on glandular mucosa						3
Smooth glandular mucosa						1
Ulcerated-like areas on nonglandular mucosa						1
VAGINA						
Red discharge						1
HEART						
Enlarged atria						1
LIVER						
Mass on median lobe adhered to diaphragm			1			
DIAPHRAGM						
Small hole			1			

Table 5
 Mean Terminal Body Weights, Gravid Uterine Weights, and
 Terminal Body Weights Minus Gravid Uterine Weights
 Pilot Teratology Study of T-3551 in Rats

<u>Group and Dose Level</u>		<u>Terminal Body Weight</u>	<u>Gravid Uterine Weight</u>	<u>Terminal Body Weight Minus Gravid Uterine Weight</u>
1 0 mg/kg	Mean	355.36	62.82	292.54
	S.D.	33.795	28.982	9.634
2 1 mg/kg	Mean	348.43	72.45	281.93
	S.D.	23.213	8.097	30.878
3 5 mg/kg	Mean	350.90	74.71	276.19
	S.D.	16.306	12.846	10.211
4 10 mg/kg	Mean	333.75	74.78	258.97
	S.D.	26.277	12.312	19.333
5 20 mg/kg	Mean	-	-	-
	S.D.	-	-	-

Key to Table 6

Pregnancy Rate (percent) = (number of pregnant females/number of females which showed evidence of copulation) x 100.

Survival Rate (percent) = (number of females surviving to Day 20/number of females which showed evidence of copulation) x 100.

Mean Implantation Efficiency (percent) = Group mean of ([resorptions per litter/corpora lutea per litter] x 100).

Mean Incidence of Resorptions (percent) = Group mean of ([resorptions per litter/implantations per litter] x 100).

Mean Incidence of Fetal Viability (percent) = Group mean of ([live fetuses per litter/implantations per litter] x 100).

Table 6
Summary of Ovarian, Uterine, and Litter Data
Pilot Teratology Study of T-3551 in Rats

	Group: Dose Level (mg/kg):	1 0	2 1	3 5	4 10	5 20
Number of females with mating confirmed		6	6	7	7	7
Number of females pregnant		5	6	7	6	7
Pregnancy rate (%)		83	100	100	86	100
Number of females surviving to Day 20		6	6	7	7	0
Survival rate		100	100	100	100	0
Mean number of:						
Corpora lutea		15.2	15.5	15.7	16.3	14.0 ^a
Implantations		11.0	13.7	13.7	13.5	10.7
Resorptions		0.6	0.5	1.0	0.3	-
Fetuses - dead		0.0	0.0	0.0	0.0	-
- live		10.4	13.2	13.0	13.2	-
Indices calculated on a per litter basis:						
Mean implantation efficiency (%) ^b		70.0	88.2	89.1	83.1	-
Mean resorption incidence (%)		4.1	3.6	7.0	2.6	-
Mean incidence of fetal mortality (%)		0.0	0.0	0.0	0.0	-
Mean incidence of fetal viability (%)		95.9	96.4	93.0	97.4	-
Live fetuses						
Mean body weight (g)						
Males - unadjusted		3.70	3.35	3.51	3.43	-
- covariance adjusted		3.65	3.36	3.53	3.47	-
Females - unadjusted		3.48	3.25	3.34	3.30	-
- covariance adjusted		3.48	3.26	3.34	3.29	-
Percent males		42.3	50.7	54.6	59.2	-

^a The ovaries of two animals were too autolyzed to count corpora lutea.

^b Data analyzed following rank transformation.

Table 7
Mean Incidence Values for Visceral and Skeletal Findings
Pilot Teratology Study of T-3551 in Rats

	Group: Dose Level (mg/kg):	$\frac{1}{0}$	$\frac{2}{1}$	$\frac{3}{5}$	$\frac{4}{10}$
Visceral Examination					
Number of fetuses examined		10	12	14	12
Number and percent of fetuses having one or more visceral variants		1/10.0	2/16.7	2/14.3	2/16.7
Number and percent of fetuses with:					
Dilated ureter(s)		1/10.0	2/16.7	1/ 7.1	0/ 0.0
Undilated ureter		0/ 0.0	0/ 0.0	1/ 7.1	0/ 0.0
Incompletely descended testis		0/ 0.0	0/ 0.0	0/ 0.0	2/16.7
Number and percent of fetuses having one or more visceral anomalies		0/ 0.0	0/ 0.0	0/ 0.0	0/ 0.0
Skeletal Examination					
Number of fetuses examined		18	24	28	24
Number and percent of fetuses having one or more skeletal variants		13/72.2	15/62.5	22/78.6	14/58.3
Number and percent of fetuses with:					
Skull - incomplete closure (less than 75%)		0/ 0.0	3/12.5	0/ 0.0	2/ 8.3
- interparietal incomplete ossification		6/33.3	13/54.2	13/46.4	6/25.0
- supraoccipital - incomplete ossification		7/38.9	13/54.2	14/50.0	7/29.2
- nonfused		0/ 0.0	2/ 8.3	2/ 7.1	0/ 0.0
- nonossified		1/ 5.6	0/ 0.0	0/ 0.0	1/ 4.2
- hyoid - incomplete		0/ 0.0	0/ 0.0	4/14.3	1/ 4.2
- nonossified		0/ 0.0	8/33.3	0/ 0.0	1/ 4.2
- parietals irregularly ossified		3/16.7	9/37.5	0/ 0.0	2/ 8.3
- zygoma incomplete		0/ 0.0	2/ 8.3	0/ 0.0	0/ 0.0

Table 7 - Continued
 Mean Incidence Values for Visceral and Skeletal Findings
 Pilot Teratology Study of T-3551 in Rats

	Group: Dose Level (mg/kg):	1 0	2 1	3 5	4 10
Rib cage - sternebrae bipartite		1/ 5.6	0/ 0.0	0/ 0.0	3/12.5
- ribs irregularly ossified		0/ 0.0	0/ 0.0	0/ 0.0	1/ 4.2
Vertebral column - thoracic centra - incomplete		1/ 5.6	0/ 0.0	0/ 0.0	2/ 8.3
- nonfused		4/22.2	0/ 0.0	0/ 0.0	0/ 0.0
- lumbar arch irregularly ossified		0/ 0.0	0/ 0.0	2/ 7.1	0/ 0.0
- sacral arch - incomplete		0/ 0.0	1/ 4.2	0/ 0.0	1/ 4.2
- nonossified		1/ 5.6	0/ 0.0	0/ 0.0	0/ 0.0
- caudals 3		1/ 5.6	0/ 0.0	0/ 0.0	0/ 0.0
Pelvic girdle - ischium incomplete		1/ 5.6	0/ 0.0	0/ 0.0	0/ 0.0
- ischium and pubis irregularly ossified		0/ 0.0	0/ 0.0	2/ 7.1	0/ 0.0
- pubis nonossified		1/ 5.6	0/ 0.0	0/ 0.0	0/ 0.0
<u>Bone alignment</u>					
Sternebrae checkered		1/ 5.6	0/ 0.0	0/ 0.0	1/ 4.2
Fused ribs, malaligned thoracic centra and arches		0/ 0.0	0/ 0.0	1/ 3.6	0/ 0.0
Angulated ribs		1/ 5.6	3/12.5	17/60.7	0/ 0.0
Extra rib(s)		2/11.1	1/ 4.2	1/ 3.6	3/12.5
Femur short		0/ 0.0	0/ 0.0	1/ 3.6	3/12.5
Number and percent of fetuses having one or more skeletal anomalies		0/ 0.0	0/ 0.0	1/ 3.6	0/ 0.0
Number and percent of fetuses with:					
<u>Bone alignment</u>					
Fused ischia and cojoined hind limbs; pubis small		0/ 0.0	0/ 0.0	1/ 3.6	0/ 0.0

Key to Table 8

Mean Incidence of Visceral Anomalies (percent) = Group mean of ([number of fetuses with anomalies per litter/number of fetuses examined visceraally per litter] x 100).

Mean Incidence of Visceral Variants (percent) = Group mean of ([number of fetuses with variants per litter/number of fetuses examined visceraally per litter] x 100).

Mean Incidence of Skeletal Anomalies (percent) = Group mean of ([number of fetuses with anomalies per litter/number of fetuses examined skeletally per litter] x 100).

Mean Incidence of Skeletal Variants (percent) = Group mean of ([number of fetuses with variants per litter/number of fetuses examined skeletally per litter] x 100).

Table 8
Mean Incidence of Visceral and Skeletal Findings per Litter
Pilot Teratology Study of T-3551 in Rats

	Group: $\frac{1}{0}$	$\frac{2}{1}$	$\frac{3}{5}$	$\frac{4}{10}$
Dose Level (mg/kg):				
Visceral				
Number of litters examined	5	6	7	6
Mean values calculated on a per litter basis				
Number of fetuses with variants	0.2	0.3	0.3	0.3
Incidence of variants	10.0	17.5	14.6	16.7
Number of fetuses with anomalies	0.0	0.0	0.0	0.0
Incidence of anomalies	0.0	0.0	0.0	0.0
Skeletal				
Number of litters examined	5	6	7	6
Mean values calculated on a per litter basis				
Number of fetuses with variants	2.6	2.5	3.1	2.5
Incidence of variants	71.6	62.5	78.6	58.3
Number of fetuses with anomalies	0.0	0.0	0.1	0.0
Incidence of anomalies	0.0	0.0	3.6	0.0

Key to Appendix 1

P = Pregnant
NP = Not Pregnant
C = Cesarean Delivery, Preceded by Day of Gestation
FD = Found Dead, Preceded by Day of Gestation
MS = Moribund Sacrifice, Preceded by Day of Gestation

Appendix 1
Individual and Mean Maternal Body Weights^a
Pilot Teratology Study of T-3551 in Rats

Maternal Number	Date of Mating	Disposition	Body Weight (grams) - Day of Gestation					Weight Change (grams)		
			0	6	8	12	16	20	6-16 ^b	0-20
Group 1 - 0 mg/kg										
20736	1/11/83	NP, 20-C	(201.3)	(230.1)	(230.8)	(234.5)	(239.9)	(248.3)	(9.8)	(47.0)
20737	1/11/83	P, 20-C	217.3	243.0	246.3	269.5	286.1	322.4	43.1	105.1
20738	1/11/83	P, 20-C	224.4	256.5	250.9	267.4	280.8	318.0	24.3	93.6
20739	1/12/83	P, 20-C	238.9	259.3	265.8	280.8	300.6	361.8	41.3	122.9
20740	1/12/83	P, 20-C	226.0	254.6	264.0	288.0	318.9	385.8	64.3	159.8
20741	1/13/83	P, 20-C	252.2	268.5	277.8	298.9	329.7	388.8	61.2	136.6
Mean			231.76	256.38	260.96	280.92	303.22	355.36	46.84	123.60
S.D.			13.831	9.187	12.574	13.102	20.915	33.795	16.308	26.087
Group 2 - 1 mg/kg										
20743	1/11/83	P, 20-C	212.5	232.4	240.7	262.1	290.9	339.0	58.5	126.5
20744	1/11/83	P, 20-C	222.9	255.4	260.9	281.1	301.3	364.8	45.9	141.9
20745	1/11/83	P, 20-C	216.5	245.0	239.3	259.1	277.6	336.6	34.6	120.1
20746	1/12/83	P, 20-C	210.4	240.4	240.6	252.4	281.1	329.0	40.7	118.6
20747	1/12/83	P, 20-C	230.1	260.7	260.7	296.2	315.3	388.2	54.6	158.1
20748	1/13/83	P, 20-C	206.8	230.8	237.4	245.6	270.1	333.0	39.3	126.2
Mean			216.53	243.78	246.60	266.08	289.38	348.43	45.60	131.90
S.D.			8.640	12.094	11.064	18.994	16.705	23.213	9.297	15.259
Group 3 - 5 mg/kg										
20730	1/11/83	P, 20-C	223.3	248.3	253.3	267.1	291.7	345.4	43.4	122.1
20751	1/11/83	P, 20-C	216.8	240.1	240.3	260.8	286.9	342.5	46.8	125.7
20752	1/11/83	P, 20-C	245.4	270.6	262.0	249.4	295.6	344.5	25.0	99.1
20753	1/12/83	P, 20-C	238.6	258.7	257.3	255.6	284.6	349.3	25.9	110.7
20754	1/12/83	P, 20-C	228.8	254.2	246.7	262.4	288.1	353.3	33.9	124.5
20755	1/13/83	P, 20-C	238.7	259.7	265.0	279.2	309.3	385.7	49.6	147.0
20756	1/14/83	P, 20-C	226.5	242.5	251.9	261.2	282.3	335.6	39.8	109.1
Mean			231.16	253.44	253.79	262.24	291.21	350.90	37.77	119.74
S.D.			10.085	10.692	8.578	9.340	9.111	16.306	9.800	15.426

^a Only pregnant animals were included in group mean. Numbers within parentheses were excluded from mean calculations.

^b Data analyzed following rank transformation.

Appendix 1 - Continued
Individual and Mean Maternal Body Weights^a
Pilot Teratology Study of T-3551 in Rats

Maternal Number	Date of Mating	Disposition	Body Weight (grams) - Day of Gestation					Weight Change (grams)		
			0	6	8	12	16	20	6-16 ^b	0-20
Group 4 - 10 mg/kg										
20757	1/11/83	P, 20-C	214.6	248.2	237.6	260.3	266.9	335.8	18.7	121.2
20758	1/11/83	P, 20-C	206.4	226.9	223.5	225.7	225.6	290.5	-1.3	84.1
20759	1/11/83	P, 20-C	237.9	268.9	269.3	283.5	299.3	349.8	30.4	111.9
20760	1/12/83	P, 20-C	246.2	266.9	269.4	274.1	267.1	342.3	0.2	96.1
20761	1/12/83	NP, 20-C	(229.1)	(239.5)	(238.9)	(225.2)	(199.6)	(229.1)	(-39.9)	(0.0)
20762	1/13/83	P, 20-C	253.0	272.8	272.1	276.3	277.9	365.6	5.1	112.6
20763	1/13/83	P, 20-C	214.4	242.3	257.2	253.0	259.7	318.5	17.4	104.1
Mean			228.76	254.33	254.85	262.15	266.08	333.75	4.37 ^{S-}	90.00
S.D.			19.401	18.145	20.020	21.046	24.184	26.277	22.593	41.502
Group 5 - 20 mg/kg										
20764	1/11/83	P, 14-FD	233.7	250.4	243.3	199.2			-80.5	
20765	1/11/83	P, 17-FD	226.5	246.1	230.9	191.7	165.6		-74.4	
20766	1/11/83	P, 17-MS	224.2	255.0	250.2	209.4	180.6		-48.20	
20767	1/11/83	P, 20-FD	211.1	219.2	233.2	199.7	171.0		-41.6	
20768	1/12/83	P, 19-FD	224.9	245.0	232.3	203.4	175.7		-58.6	
20769	1/12/83	P, 18-FD	221.4	237.2	230.0	209.3	178.6		-83.70	
20770	1/13/83	P, 18-FD	256.2	262.5	251.0	206.4	178.8			
Mean			228.29	245.06	238.70	202.73	175.05		-64.50 ^{S-}	
S.D.			14.039	13.923	9.242	6.388	5.720		17.593	

^a Only pregnant animals were included in group mean. Numbers within parentheses were excluded from mean calculations.

^b Data analyzed following rank transformation.

Appendix 2
Individual and Mean Food Consumption Values
Pilot Teratology Study of T-3551 in Rats

Maternal Number	Food Consumption (gm/day)					Total Food Consumption (g)
	Day of Gestation					Days
	6	8	12	16	20	0-20
Group 1 - 0 mg/kg						
20736	22.6	18.8	16.9	14.2	17.4	366.8
20737	25.4	22.6	22.2	24.6	27.6	494.8
20738	21.5	15.1	19.5	19.8	27.8	427.4
20739	21.2	19.2	20.2	19.4	28.5	437.5
20740	27.7	27.0	27.4	23.6	26.7	531.2
20741	24.0	18.1	23.1	25.0	28.3	485.0
Mean	23.73	20.13	21.55	21.10	26.05	457.12
S.D.	2.501	4.132	3.597	4.145	4.284	58.499
Group 2 - 1 mg/kg						
20743	19.3	18.1	19.4	20.1	27.3	418.4
20744	21.9	20.2	20.4	19.3	28.5	444.0
20745	19.3	15.4	17.9	16.5	24.7	382.9
20746	24.3	25.9	22.5	23.2	29.4	404.9
20747	21.5	14.4	23.3	19.6	28.2	441.5
20748	19.0	17.0	15.6	16.9	23.9	373.1
Mean	20.88	18.50	19.85	19.27	27.00	410.80
S.D.	4.330	4.159	2.874	2.430	2.211	29.452

Appendix 2 - Continued
Individual and Mean Food Consumption Values
Pilot Teratology Study of T-3551 in Rats

Maternal Number	Food Consumption (gm/day)					Total Food Consumption (g)
	Day of Gestation					Days
	6	8	12	16	20	0-20
Group 3 - 5 mg/kg						
20750	21.5	21.3	19.2	19.0	24.8	423.5
20751	19.4	15.4	17.5	18.2	23.7	384.9
20752	22.2	15.4	14.7	17.0	26.5	396.3
20753	22.6	14.2	14.5	15.8	26.2	389.4
20754	25.6	13.7	17.0	17.0	23.8	400.4
20755	22.7	19.0	18.3	19.4	26.3	429.7
20756	18.3	16.3	15.0	17.2	22.4	360.6
Mean	21.76	16.47	16.60	17.66	24.81	397.83 ^{S-}
S.D.	2.385	2.735	1.880	1.269	1.585	23.480
Group 4 - 10 mg/kg						
20757	18.8	17.0	16.8	12.6	22.8	355.2
20758	19.4	15.4	28.2	10.9	23.4	396.7
20759	21.7	19.9	18.0	15.9	23.3	398.6
20760	24.1	17.9	17.6	8.9	20.7	368.8
20761	21.0	15.3	10.6	3.6	15.9	276.7
20762	23.3	16.8	15.6	11.4	23.8	376.3
20763	23.0	16.0	15.4	13.1	24.9	383.3
Mean	21.61	16.90	17.46	10.91	22.11	365.09 ^{S-}
S.D.	2.006	1.615	5.336	3.879	3.021	41.840

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Appendix 2 - Continued
 Individual and Mean Food Consumption Values
 Pilot Teratology Study of T-3551 in Rats

Maternal Number	Food Consumption (gm/day)					Total Food Consumption (g)
	Day of Gestation					Days
	6	8	12	16	20	0-20
Group 5 - 20 mg/kg						
20764	15.3	18.7	1.3	-	-	-
20765	20.5	11.1	1.2	0.2	-	-
20766	21.2	14.5	3.8	0.6	-	-
20767	15.8	16.8	12.4	0.2	-	-
20768	22.0	12.4	5.8	0.3	-	-
20769	19.0	12.1	6.8	0.6	-	-
20770	21.4	13.3	1.9	0.0	-	-
Mean	19.31	14.13	4.74	0.32		
S.D.	2.741	2.743	4.028	0.240		

Appendix 3
 Individual Terminal Body Weights, Gravid Uterine Weights, and
 Terminal Body Weights Minus Gravid Uterine Weights
 Pilot Teratology Study of T-3551 in Rats

<u>Maternal Number</u>	<u>Terminal Body Weight (g)</u>	<u>Gravid Uterine Weight (g)</u>	<u>Terminal Body Weight Minus Gravid Uterine Weight</u>
Group 1 - 0 mg/kg			
20736	Not Pregnant		
20737	322.4	32.9	289.5
20738	318.0	32.8	285.2
20739	361.8	71.3	290.5
20740	385.8	97.7	288.1
20741	388.8	79.4	309.4
Mean	355.36	62.82	292.54
S.D.	33.795	28.982	9.634
Group 2 - 1 mg/kg			
20743	339.0	62.7	312.0
20744	364.8	80.9	283.9
20745	336.6	72.0	264.6
20746	329.0	80.9	248.1
20747	388.2	63.3	324.9
20748	333.0	74.9	258.1
Mean	348.43	72.45	281.93
S.D.	23.213	8.097	30.878

Appendix 3 - Continued
 Individual Terminal Body Weights, Gravid Uterine Weights, and
 Terminal Body Weights Minus Gravid Uterine Weights
 Pilot Teratology Study of T-3551 in Rats

<u>Maternal Number</u>	<u>Terminal Body Weight (g)</u>	<u>Gravid Uterine Weight (g)</u>	<u>Terminal Body Weight Minus Gravid Uterine Weight</u>
Group 3 - 5 mg/kg			
20750	345.4	73.0	272.4
20751	342.5	77.6	264.9
20752	344.5	56.1	288.4
20753	349.3	68.8	280.5
20754	353.3	85.0	268.3
20755	385.7	95.5	290.2
20756	335.6	67.0	268.6
Mean	350.90	74.71	276.19
S.D.	16.306	12.846	10.211
Group 4 - 10 mg/kg			
20757	335.8	72.6	263.2
20758	290.5	61.2	229.3
20759	349.8	65.3	284.5
20760	342.3	86.4	255.9
20761	Not Pregnant		
20762	365.6	92.8	272.8
20763	318.5	70.4	248.1
Mean	333.75	74.78	258.97
S.D.	26.277	12.312	19.333

Appendix 3 - Continued
Individual Terminal Body Weights, Gravid Uterine Weights, and
Terminal Body Weights Minus Gravid Uterine Weights
Pilot Teratology Study of T-3551 in Rats

<u>Maternal Number</u>	<u>Terminal Body Weight (g)</u>	<u>Gravid Uterine Weight (g)</u>	<u>Terminal Body Weight Minus Gravid Uterine Weight</u>
Group 5 - 20 mg/kg			
20764	-	-	-
20765	-	-	-
20766	-	-	-
20767	-	-	-
20768	-	-	-
20769	-	-	-
20770	-	-	-

Appendix 4
Individual and Mean Ovarian, Uterine, and Litter Data
Pilot Teratology Study of T-3551 in Rats

<u>Maternal Number</u>	<u>Ovarian Corpora Lutea</u>	<u>Uterine Implantations</u>	<u>Implantation^a Efficiency (%)</u>	<u>Early Resorptions</u>	<u>Resorption Incidences (%)</u>	<u>Number of Fetuses</u> <u>Dead</u> <u>Alive</u>		<u>Fetal Mortality (%)</u>	<u>Fetal Viability (%)</u>	
Group 1 - 0 mg/kg										
20736	Not Pregnant									
20737		13	5	38.4	0	0.0	0	5	0.0	100.0
20738		14	5	35.7	0	0.0	0	5	0.0	100.0
20739		16	14	87.5	1	7.1	0	13	0.0	92.8
20740		16	16	100.0	0	0.0	0	16	0.0	100.0
20741		17	15	88.2	2	13.3	0	13	0.0	86.7
Mean	15.2	11.0	70.0	0.6	4.1	0.0	10.4	0.0	95.9	
S.D.	1.64	5.52	30.47	0.89	6.00	0.00	5.08	0.00	6.01	
Group 2 - 1 mg/kg										
20743	14	13	92.9	2	15.4	0	11	0.0	84.6	
20744	16	14	87.5	0	0.0	0	14	0.0	100.0	
20745	15	14	93.3	0	0.0	0	14	0.0	100.0	
20746	18	16	88.9	1	6.3	0	15	0.0	93.8	
20747	15	11	73.3	0	0.0	0	11	0.0	100.0	
20748	15	14	93.3	0	0.0	0	14	0.0	100.0	
Mean	15.5	13.7	88.2	0.5	3.6	0.0	13.2	0.0	96.4	
S.D.	1.38	1.63	7.71	0.84	6.30	0.00	1.72	0.00	6.29	
Group 3 - 5 mg/kg										
20750	15	13	86.7	0	0.0	0	13	0.0	100.0	
20751	15	14	93.3	0	0.0	0	14	0.0	100.0	
20752	15	12	80.0	2	16.7	0	10	0.0	83.3	
20753	17	15	88.2	3	20.0	0	12	0.0	80.0	
20754	16	15	93.8	1	6.7	0	14	0.0	93.3	
20755	19	17	89.5	1	5.9	0	16	0.0	94.1	
20756	13	12	92.3	0	0.0	0	12	0.0	100.0	
Mean	15.7	13.7	89.1	1.0	7.0	0.0	13.0	0.0	93.0	
S.D.	1.89	3.35	4.82	1.15	8.28	0.00	1.91	0.00	8.28	

^a Data analyzed following rank transformation.

Appendix 4 - Continued
Individual and Mean Ovarian, Uterine, and Litter Data
Pilot Teratology Study of T-3551 in Rats

<u>Maternal Number</u>	<u>Ovarian Corpora Lutea</u>	<u>Uterine Implantations</u>	<u>Implantation^a Efficiency (%)</u>	<u>Early Resorptions</u>	<u>Resorption Incidences (%)</u>	<u>Number of Fetuses</u>		<u>Fetal Mortality (%)</u>	<u>Fetal Viability (%)</u>
						<u>Dead</u>	<u>Alive</u>		
Group 4 - 10 mg/kg									
20757	15	13	86.7	0	0.0	0	13	0.0	100.0
20758	14	13	92.9	1	7.7	0	12	0.0	92.3
20759	16	10	62.5	0	0.0	0	10	0.0	100.0
20760	16	15	93.8	0	0.0	0	15	0.0	100.0
20761	Not Pregnant								
20762									
20763	18	17	94.4	0	0.0	0	17	0.0	100.0
	19	13	68.4	1	7.7	0	12	0.0	92.3
Mean	16.3	13.5	83.1	0.3	2.6	0.0	13.2	0.0	97.4
S.D.	1.86	2.35	14.08	0.52	3.98	0.00	2.48	0.00	3.98
Group 5 - 20 mg/kg									
20764	14	13							
20765	12	11							
20766	16	13							
20767	b	3	-						
20768	b	10	-						
20769	15	14							
20770	13	11							
Mean	14.0	10.7							
S.D.	1.58	3.68							

^a Data analyzed following rank transformation.

^b Ovaries were too autolyzed to count corpora lutea.

Appendix 5
Individual and Mean Live Fetal Data
Pilot Teratology Study of T-3551 in Rats

Maternal Number	Sex		Percent Males	Mean Weight (grams)			
	Number of Males	Number of Females		Males		Females	
				Unadjusted	Adjusted	Unadjusted	Adjusted
Group 1 - 0 mg/kg							
20736	Not Pregnant						
20737	2	3	40.0	4.1		3.7	
20738	2	3	40.0	3.3		3.4	
20739	8	5	61.6	3.3		3.1	
20740	5	11	31.3	3.8		3.5	
20741	5	8	38.5	4.0		3.7	
Mean	4.4	6.0	42.3	3.70	3.65	3.48	3.48
S.D.	2.51	3.47	11.39	0.381	0.127	0.249	0.089
Group 2 - 1 mg/kg							
20743	4	7	36.4	3.4		3.3	
20744	9	5	64.3	3.5		3.4	
20745	7	7	50.0	3.2		3.0	
20746	9	6	60.0	3.1		3.0	
20747	4	7	36.4	3.4		3.3	
20748	8	6	57.2	3.5		3.5	
Mean	6.8	6.3	50.7	3.35	3.36	3.25	3.26
S.D.	2.32	0.82	12.03	0.164	0.106	0.207	0.082
Group 3 - 5 mg/kg							
20750	7	6	53.9	3.3		3.3	
20751	6	8	42.9	3.4		3.3	
20752	8	2	80.0	3.4		3.4	
20753	4	8	33.4	3.6		3.1	
20754a	5	8	38.5	3.8		3.5	
20755	12	4	75.0	3.8		3.6	
20756	7	5	58.4	3.3		3.2	
Mean	7.0	5.9	54.6	3.51	3.53	3.34	3.34
S.D.	2.58	2.34	17.90	0.219	0.099	0.172	0.075

^a Sex of one pup could not be determined.

Appendix 5 - Continued
 Individual and Mean Live Fetal Data
 Pilot Teratology Study of T-3551 in Rats

Maternal Number	Sex		Percent Males	Mean Weight (grams)			
	Number of Males	Number of Females		Males		Females	
				Unadjusted	Adjusted	Unadjusted	Adjusted
Group 4 - 10 mg/kg							
20757	6	7	46.2	3.7		3.3	
20758	7	5	58.4	3.2		3.2	
20759	6	4	60.0	3.8		3.6	
20760	8	7	53.4	3.4		3.2	
20761	Not Pregnant						
20762	12	5	70.6	3.2		3.3	
20763	8	4	66.7	3.3		3.2	
Mean	7.8	5.3	59.2	3.43	3.47	3.30	3.29
S.D.	2.23	1.34	8.83	0.258	0.111	0.155	0.082

Group 5 - 20 mg/kg

20764	Found Dead - Day 14
20765	Found Dead - Day 17
20766	Moribund Sacrifice - Day 17
20767	Found Dead - Day 20
20768	Found Dead - Day 19
20769	Found Dead - Day 18
20770	Found Dead - Day 18

Appendix 6
Individual Visceral Findings for Each Litter
Pilot Teratology Study of T-3551 in Rats

	Group 1 - 0 mg/kg					Group 2 - 1 mg/kg					
	2	2	2	2	2	2	2	2	2	2	2
	0	0	0	0	0	0	0	0	0	0	0
	7	7	7	7	7	7	7	7	7	7	7
Animal	3	3	3	4	4	4	4	4	4	4	4
Number:	7	8	9	0	1	3	4	5	6	7	8
Number of fetuses examined by Wilson's technique	2	2	2	2	2	2	2	2	2	2	2
Number of fetuses within normal limits	2	2	2	1	2	2	2	1	1	2	2
Number of fetuses having one or more visceral variants	0	0	0	1	0	0	0	1	1	0	0
Percent of fetuses having one or more visceral variants (%)	0.0	0.0	0.0	50.0	0.0	0.0	0.0	50.0	50.0	0.0	0.0
Number of fetuses with:											
Dilated ureter(s)				1				1	1		
Number of fetuses having one or more visceral anomalies	0	0	0	0	0	0	0	0	0	0	0
Percent of fetuses having one or more visceral anomalies	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

	Group 3 - 5 mg/kg							Group 4 - 10 mg/kg					
	2	2	2	2	2	2	2	2	2	2	2	2	2
	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	7	7	7	7	7	7	7	7	7	7	7	7
Animal	5	5	5	5	5	5	5	5	5	6	6	6	6
Number:	0	1	2	3	4	5	6	7	8	9	0	2	3
Number of fetuses examined by Wilson's technique	2	2	2	2	2	2	2	2	2	2	2	2	2
Number of fetuses within normal limits	2	2	2	2	2	2	2	2	1	2	2	1	2
Number of fetuses having one or more visceral variants	0	2	0	0	0	0	0	0	1	0	0	1	0
Percent of fetuses having one or more visceral variants (%)	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	50.0	0.0	0.0	50.0	0.0
Number of fetuses with:													
Dilated ureters		1											
Undilated ureter		1											
Incompletely descended testis									1			1	
Number of fetuses having one or more visceral anomalies	0	0	0	0	0	0	0	0	0	0	0	0	0
Percent of fetuses having one or more visceral anomalies (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Appendix 7
Individual Skeletal Findings for Each Litter
Pilot Teratology Study of T-3551 in Rats

	Group 1 - 0 mg/kg					Group 2 - 1 mg/kg					
	2	2	2	2	2	2	2	2	2	2	2
	0	0	0	0	0	0	0	0	0	0	0
	7	7	7	7	7	7	7	7	7	7	7
Animal	3	3	3	4	4	4	4	4	4	4	4
Number:	7	8	9	0	1	3	4	5	6	7	8
Number of fetuses examined	3	3	4	4	4	4	4	4	4	4	4
Number of fetuses within normal limits	2	0	0	1	2	2	3	0	1	2	1
Number of fetuses having one or more skeletal variants	1	3	4	3	2	2	1	4	3	2	3
Percent of fetuses having one or more skeletal variants (%)	33	100	100	75	50	50	25	100	75	50	75
Number of fetuses with:											
Lagging Ossification											
Skull - incomplete closure (less than 75%)								2		1	
- intraparietal incomplete ossification			2	3	1	2		4	3	2	2
- supraoccipital - incomplete ossification	1	2	2	1	1	2	1	3	3	1	3
- nonfused								1		1	
- nonossified		1									
- hyoid - nonossified						1		4		1	2
- parietals irregularly ossified				3		1	1	4	1	1	1
- zygoma incomplete								2			
Rib cage - sternebrae bipartite		1									
Vertebral column - thoracic centra - incomplete		1									
- nonfused		1	2		1						
- sacral arch - incomplete									1		
- nonfused		1									
- caudals <3		1									
Pelvic girdle - ischium incomplete		1									
- pubis nonossified		1									
Bone Alignment											
Sternebrae checkered					1						
Angulated ribs			1					2	1		
Extra ribs			2					1			
Number of fetuses having one or more skeletal anomalies	0	0	0	0	0	0	0	0	0	0	0
Percent of fetuses having one or more skeletal anomalies (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Appendix 7 - Continued
Individual Skeletal Findings for Each Litter
Pilot Teratology Study of T-3551 in Rats

	Group 3 - 5 mg/kg							Group 4 - 10 mg/kg						
	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Animal	5	5	5	5	5	5	5	5	5	5	6	6	6	6
Number:	0	1	2	3	4	5	6	7	8	9	0	2	3	3
Number of fetuses examined	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Number of fetuses within normal limits	2	1	0	0	0	3	0	2	1	3	2	1	1	1
Number of fetuses having one or more skeletal variants	2	3	4	4	4	1	4	2	3	1	2	3	3	3
Percent of fetuses having one or more skeletal variants (%)	50	75	100	100	100	25	100	50	75	25	50	75	75	75
Number of fetuses with:														
Lagging Ossification														
Skull - incomplete closure (less than 75%)									2					
- interparietal incomplete ossification		2	1	4	2		4	1		1		3	1	
- supraoccipital - incomplete ossification		2	2	4	2		4	1			2	2	2	
- nonfused			1		1						1			
- nonossified												1		
- hyoid - incomplete				2	2									
- nonossified								1						
- parietals irregularly ossified												2		
Rib cage - sternebrae bipartite								1	1					1
- ribs irregularly ossified											1			
Vertebral column - thoracic centra - incomplete								1			1			
- lumbar arch irregularly ossified	2													
- sacral arch incomplete													1	
Pelvic girdle - ischium and pubis irregularly ossified						2								

Appendix 7 - Continued
Individual Skeletal Findings for Each Litter
Pilot Teratology Study of T-3551 in Rats

	Group 3 - 5 mg/kg							Group 4 - 10 mg/kg						
	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Animal	5	5	5	5	5	5	5	5	5	6	6	6	6	6
Number:	0	1	2	3	4	5	6	7	8	9	0	2	3	3
Bone Alignment														
Sternebrae checkered					1									
Fused ribs; malaligned thoracic centra and arches					1									
Angulated ribs	2	3	4	2	2		4							
Extra ribs					1									
Femur short					1				2		1	1	1	
Number of fetuses having one or more skeletal anomalies	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Percent of fetuses having one or more skeletal anomalies	0.0	0.0	0.0	0.0	25	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Number of fetuses with:														
Bone Alignment														
Fused ischia and cojoined hind limbs; pubis small					1									

Appendix 8
References
Pilot Teratology Study of T-3551 in Rats
STATISTICAL METHODS/LABORATORY PROCEDURES

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