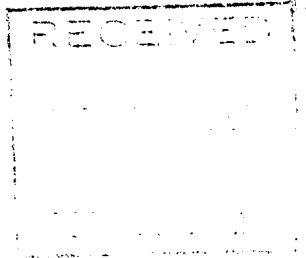


AR226-0282



Special Lens Oral Teratology Study of
T-2999CoC in Rats

Experiment No.:

0680TR0020

Conducted At:

Safety Evaluation Laboratory
Riker Laboratories, Inc.
St. Paul, Minnesota

Dosing Period:

February 9, 1981 through
March 26, 1981

Study Director:

E. G. Gortner

E. G. Gortner 12-22-81
E. G. Gortner Date
Senior Research Technologist
Animal Reproduction-Teratolgy
Study Director

Elden G. Lamprecht 12/22/81
E. G. Lamprecht, DVM, PhD Date
Research Veterinary Pathologist

Marvin T. Case 12/22/81
M. T. Case, DVM, PhD Date
Manager, Pathology-Toxicology
Safety Evaluation Laboratory

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Summary

This special rat teratology study was conducted specifically to evaluate rat lenses exposed to T-2999CoC during the period of organogenesis. The objectives of the study were to determine a no-effect dose level of the lens abnormality reported in a previous teratology study and to describe the appearance of the lens abnormality in weanling rats. Groups of time mated female rats were orally dosed with T-2999CoC at 0, 25, 2.5 or 0.25 mg/kg/day on days 6 through 15 of gestation. Approximately one-half of the females were killed on day 20 of gestation while the rest of the females were allowed to litter and raise their pups to weaning.

Since this study was conducted, the lens findings have been found not to be abnormal. The lens findings observed are interpreted as a freehand sectioning artifact of a normal area of lens fiber degeneration. The lens artifact was observed in fetuses of all dose groups, including the control group. The 25 mg/kg/day dose group incidence of the artifact was significantly higher than the control group incidence. The histological appearance of the lens findings were the same in all dose groups including the control group. The differences among the dose group incidences were due to the manner and frequency in which the artifact was created and the limitations inherent in its visualization. T-2999CoC in utero exposed rat fetuses did not have compound-related lens changes.

Weanling rat pups which had been exposed in utero to T-2999CoC did not have lens nucleus abnormalities. The finding of no lens nucleus abnormalities in weanlings supports the conclusion that the lens findings in the rat fetuses were an artifact and not a teratogenic change.

The fetal lens findings observed under the dissecting microscope were artifact. T-2999CoC in utero exposed fetuses and weanlings did not have compound-related lens changes.

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T-2999CoC^a was labeled a teratogen of the lens because abnormalities were observed at the 75, 37.5 and 25 mg/kg/day dose pathology study (Riker Experiment Number 0680TR0010). The T-2999CoC study^b were to determine a no-effect dose level of ^c and to describe the appearance of the lens abnormality. The study was sponsored by the 3M Commercial Chemical Minnesota and was conducted by the Safety Evaluation Laboratories, Inc., St. Paul, Minnesota. Six sets of ^d and list of the principal participants and supervisory ^e found in Appendices I and II respectively.

As study were conducted according to the Good Laboratory Practices and the Safety Evaluation Laboratory Standard (see Appendix III for Quality Assurance Unit statement). For specimens, raw data and a copy of the final report is Safety Evaluation Laboratory's record archives.

Dawley derived CD rats were obtained from Charles River, Wilmington, Massachusetts, and assigned cages according to random numbers table. The rats, ranging in weight from were then divided into four groups of 72 animals each. The ^f in six sets and the body weight data were interpreted in the rats were housed individually in hanging stainless steel ^g floors and fronts in a temperature and humidity controlled ^h water were available ad libitum. The lights were on a 12 hour

observed daily from day 3 through 20 of gestation for abnormal body weights were recorded on days 3, 6, 9, 12, 15 and 20 of ⁱ or groups were dosed with T-2999CoC suspended daily in corn ^j and 0.25 mg/kg/day. The suspensions were administered daily ^k use volume of 5 mg/kg by oral intubation with a syringe ^l l-tipped intubation needle to the rats on days 6 through 15 ^m indicated by sperm-positive vaginal smear). T-2999CoC ⁿ ed by 3M Commercial Chemical Division, St. Paul, Minnesota

half of the females were killed on gestational day 20. All ^o re fixed in Bouin's fixative and the heads were freehand ^p lson technique. The presence of lens findings were ^q e dissecting microscope. Fetal specimens with visible lens ^r lded in paraffin, sectioned at 5-6 microns, stained with ^s in and examined histologically. The remaining females were

al grade FM-3422)
er 0680TR0020)

y Chow, Ralston Purina Co., St. Louis, MO

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allowed to litter in plastic shoe box cages bedded with ground corn cobs. On day 21 of lactation the eyes of the weanlings were examined by slit lamp biomicroscopy or indirect ophthalmoscopy. The weanling rats were then killed and their eyes were fixed in 10% buffered formalin, imbedded in paraffin, sectioned at 5-6 microns, stained with hematoxylin and eosin and evaluated histologically.

Results and Discussion

The first objective of this special lens teratology study was to determine a no-effect dose level of the lens abnormality reported in a previous teratology study. Since this study was conducted, the lens findings have been found not to be abnormal. The lens findings observed under the dissecting microscope are interpreted as a freehand sectioning artifact of a normal area of lens fiber degeneration. The fetal rat lens finding was incorrectly interpreted as a teratogenic change in Riker Experiment Number 0680TR0010 and, therefore, the first objective of this study was not valid.

The fetal lens findings were observed to occur in individual fetuses of all dose groups including the control group. The lens findings were localized to the area of the embryonal nucleus, although a variety of morphological appearances were present within that location. The range of morphological appearances as observed under the dissecting microscope included: a discoloration of the lens near the anteroventral region extending from beneath the lens epithelium to half-way through the lens posteriorly, a cleft at the anteroventral lens region or a combination of lens discoloration and the presence of a cleft.

Histologically, the cleft was a space opened up at the vestage of the lens vesicle remnant and consisted of a separation of primary lens fibers of the embryonal nucleus from the lens epithelial cells. The dark streak discoloration of the embryonal nucleus resulted from either the lens being freehand sectioned across the area of normal primary lens fiber degeneration or an artifact being created in the lens during freehand sectioning accentuating the area of normal primary lens fiber degeneration.

The differences in the appearance of the lens artifact in individual fetuses and differences among the dose group incidences were largely due to the manner and frequency in which the artifact was created and the limitations inherent in its visualization. Statistically significant differences occurred among the incidences of fetuses observed to have the lens artifact. The 25 mg/kg/day dose group incidence was significantly higher than the 0 mg/kg/day dose group incidence (Table 1). The artifact was the same in all dose groups regardless of the morphological appearance described under the dissecting microscope and regardless of the statistical comparisons among the group incidences of the artifact. T-2999CoC in utero exposed fetuses did not have compound-related changes in their lenses.

The second objective of this special lens teratology study was to describe the appearance of the lens abnormality in weanling rats which had been exposed in utero to T-2999CoC. Again, since the fetal lens finding was an artifact, this objective also was not valid. All eyes of the weanling rats were observed by either slit lamp biomicroscopy or indirect ophthalmoscopy. Neither a lens cleft nor a fetal lens nuclear opacity were observed in any of the lenses of any of the weanlings in the control or compound-treated offspring. One high dose weanling did have a lens opacity, but the opacity did not involve the fetal nucleus (Table 2). The crystalline appearance of the centers of the weanling lenses in all dose groups made histologically sectioned and stained specimens unsuitable for evaluation of individual lens fibers. The finding of no lens nucleus abnormalities in weanlings supports the conclusion that the lens finding in the rat fetuses were an artifact and not a teratogenic change.

T-2999CoC was maternally toxic to the pregnant dams of the 25 mg/kg/day dose level in both study replicates. The compound caused the toxicity of reduced mean body weight gain during the dosing interval. The mean weight gained between days 9 and 12 of gestation for the 25 mg/kg/day dose group was significantly lower than the weight gained by the 0 mg/kg/day dose group during that same interval (Table 3).

No compound-related clinical signs were observed in any of the three compound treated groups. Six intubation deaths occurred during the study (Appendix V). One 25 mg/kg/day dose group dam died during parturition.

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Table 1

Special Lens Oral Teratology Study of T-2999CoC in Rats
Results of Dissecting Microscopic Observations of
Gestational Day 20 Fetal Lens

Dose Group	Dams	Fetuses Examined	Dams Having Fetuses With Lens Findings		Fetuses with Lens Findings	
			N	%	N	%
0 mg/g/day	28	292	13	46	41	14
25 mg/g/day	22	225	18	82 ^a	55	24 ^a
2.5 mg/g/day	27	271	18	67	59	22 ^a
0.25 mg/g/day	26	279	14	54	41	16

^a-Significantly higher than the control (Chi-square with Yates correction p <0.05)

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Table 2

Special Lens Oral Teratology Study of T-2999CoC in Rats
 Results of Ocular Examination Findings of Pups at Day 21 of Lactation

Dose Group	No. of Dams	Total Number of Pups	No Abnorm. Found	Abnorm. Found	Findings
0 mg/kg/day	29	291	288	3	Corneal Opacity Bilateral corneal ulcer with opacity Left eye grossly enlarged - 2 X normal size, lens may be absent
25 mg/kg/day	30	263	262	1	Opaque area of lens - 1 to 3 o'clock
2.5 mg/kg/day	28	266	263	3	Questionable cloudy area of cornea
0.25 mg/kg/day	26	211	209	2	Corneal opacity

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Table 3

Special Lens Oral Teratology Study of T-2999CoC in Rats
 Mean Body Weight Gain (g) of Pregnant Rats
 Between Weighings with Standard Deviations

First Replicate

	DAY	6	9	12	15	20
0 mg/kg/day	MEAN	29	24	21	26	70
	STAN. DEV	10.9	7.9	8.0	15.5	29.1
25 mg/kg/day	MEAN	31	21	10 ^a	27	70
	STAN. DEV	16.9	11.5	13.9	16.1	24.6
2.5 mg/kg/day	MEAN	33	23	14	30	65
	STAN. DEV	10.0	4.5	13.3	13.7	30.2
0.5 mg/kg/day	MEAN	31	22	15	31	64
	STAN. DEV	9.4	7.4	12.3	17.9	29.9

Second Replicate

	DAY	6	9	12	15	20
0 mg/kg/day	MEAN	30	21	30	25	70
	STAN. DEV	5.1	6.6	6.3	6.9	22.4
25 mg/kg/day	MEAN	29	19	22 ^a	23	71
	STAN. DEV	11.8	8.3	6.7	7.1	15.3
2.5 mg/kg/day	MEAN	29	21	26 ^a	28	76
	STAN. DEV	5.8	5.7	7.0	7.1	12.4
0.25 mg/kg/day	MEAN	32	20	28	23	68
	STAN. DEV	7.8	6.0	6.7	7.1	26.9

^a Significantly lower than the control (Dunnett's t test $p < 0.05$)

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Appendix I

TITLE: Protocol for a Special Lens Oral Teratology Study of T-2999CoC^a in Rats

OBJECTIVE: A purified grade of T-2999CoC was teratogenic to the eye and caused developmental lens abnormalities at 75, 37.5 and 25 mg/kg/day in a rat teratology study (Riker Experiment Number 0680TR0010). The objectives of the study are to determine a no-effect dose level of the lens abnormality and to describe the appearance of the lens abnormality in the weanling rats. The study will be conducted according to the 1978 Good Laboratory Practice Regulations and the Safety Evaluation Laboratory's Standard Operating Procedures.

SPONSOR: 3M Commercial Chemical Division, St. Paul, Minnesota.

TESTING FACILITY: Safety Evaluation Laboratory, Riker Laboratories, Inc., St. Paul, Minnesota.

STUDY DIRECTOR: E. G. Gortner

START OF DOSING: February, 1981.

TEST SYSTEM: One hundred and ninety-two sexually mature, time mated Sprague-Dawley derived female rats from Charles River Breeding Laboratories will be housed in hanging stainless steel cages with wire mesh floors and fronts in a temperature and humidity controlled room. This strain of rat will be used because it was used in the previous teratology study and time mated females are readily available. Purina Laboratory Chow and water will be available ad libitum. The lights will be on a 12 hour light/dark cycle.

TEST SYSTEM IDENTIFICATION: Each animal will be ear tagged and that number will be indicated on the outside of the cage.

RANDOMIZATION: The animals will be assigned cages according to a computer-generated random numbers table.

CONTROL ARTICLE: Corn oil.

TEST ARTICLE: T-2999CoC^a.

ANALYTICAL SPECIFICATIONS: The test article composition and purity will be determined by the Sponsor (3M Commercial Chemical group) prior to the start of the study and at the end of dosing.

^a FM-3924 (technical grade FM-3422)

DOSAGE LEVELS AND EXPERIMENT DESIGN: The test article will be suspended in corn oil daily. The test article suspension and the control articles will be administered by oral intubation to the rats on days 6 through 15 of gestation according to the following:

<u>Dose Group</u>	<u>Dose Level</u>	<u>Group Size</u>
High	25 mg/kg/day	48 ♀
Mid	2.5 mg/kg/day	48 ♀
Low	0.25 mg/kg/day	48 ♀
Control	0 mg/kg/day	48 ♀

The oral route of administration will be used because teratogenicity resulted by this route in the previous teratology study. No dietary contaminants are known to interfere with the test article.

The animals will be observed daily from day 3 through 20 of gestation for abnormal clinical signs. Body weights will be recorded on days 3, 6, 9, 12, 15 and 20 of pregnancy and the rats will be dosed accordingly using a constant dose volume of 5 ml/kg of body weight.

Approximately one-half of the females will be killed on day 20 of gestation. All of their pups will be fixed in Bouin's solution and the heads will be free-hand sectioned by the Wilson technique. The presence of eye abnormalities will be determined using the dissecting microscope. Select eye sections can be sent to histopath for microscopid examination. The remaining females will be allowed to litter. On day 21 of lactation the eyes of neonates will be examined to determine the presence of lens abnormalities.

DATA ANALYSIS AND FINAL REPORT: The proposed statistical method to be used for analysis of the data is the Chi-square for percent of abnormalities. The proposed date for the final report is 2-3 months after day 21 of lactation and the pup eye exam has been completed (approximately second quarter, 1981).

Amendment to the Protocol for a Special Lens
Oral Teratology Study of T-2999CoC in Rats

An additional number of rats will be added to this study. The 96 new animals will be divided among the dose groups as follows:

<u>Dose Group</u>	<u>Dose Level</u>	<u>No. of Animals</u>
High	25 mg/kg/day	24
Mid	2.5 mg/kg/day	24
Low	0.25 mg/kg/day	24
Control	0 mg/kg/day	24

The reason for this amendment is a reduced number of pregnant animals in the first two groups of animals.

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Appendix II

List of Principal Participating Personnel

<u>NAME</u>	<u>FUNCTION</u>
Edwin G. Gortner	Study Director
Elden G. Lamprecht	Veterinary Pathologist
Gary C. Pecore	Supervisor - Animal Care
Vinkateswa Pothapragoda	Commercial Chemical - Analytical
Loren O. Wiseth	Technician

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STATEMENT OF QUALITY ASSURANCE

STUDY NUMBER: 0680TR0020TITLE: SPECIAL LENS ORAL TERATOLOGY STUDY OF
T 2999CoC in Rats

Audits and/or inspections were performed by the Riker Compliance Audit unit for the above titled study, and reported to the study director and to management as follows:

<u>Date Performed</u>	<u>Date Reported</u>
12 February 1981	12 February 1981
23 February 1981	24 February 1981
18 March 1981	23 March 1981
18 March 1981	24 March 1981
31 March 1981	6 April 1981
25 & 27 April 1981	29 April 1981
21 December 1981	21 December 1981

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D. P. Loewner
Compliance Audit
Riker Laboratories, Inc.

12/22/81

Date

APPENDIX IV

Test and/or Control Article Characterization

for

T-2999CoC

1. The identity strength, uniformity, composition, purity or other pertinent characterizations of the test and/or control substances have been determined and documented as of 8 Jan 81 *.
2. The method of synthesis or origin of the test and control substances, including their amount and the method of bioassay (if applicable) is documented.
yes X no
3. The stability of the test and/or control substances have been determined or will be determined as of Completion of the Study.

The above information and documentation are located in the sponsor's records.

E. W. Baker
Sponsor

Jan 16, 1981
Date

*CCD Analytical Req. No. 16474 October 28, 1980

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Special Lens Oral Teratology Study of T-2999CoC in Rats

Individual Body Weights (g) with Mean Body Weights
and Standard Deviations for Pregnant Animals

	Replicate 1						
DAY	3	6	9	12	15	20	

0 MG/KG/DAY							
N1R	1130	185	220	247	275	298	341
N1R	1132	202	221	250	277	308	369
N1R	1133	194	220	246	272	304	382
N1R	1134	230	251	264	291	317	377
N1R	1150	195	215	230	227	232	235
N1R	1151	170	212	242	262	290	337
N1R	1152	208	231	248	262	273	282
N1R	1153	206	226	242	268	295	376
N1R	1154	187	217	240	254	260	276
N1R	1179	192	218	244	269	303	386
N1R	1180	221	249	267	293	327	416
N1R	1181	184	211	226	247	283	345
N1R	1182	224	246	266	289	324	407
N1R	1198	206	226	249	256	261	271
N1R	1199	206	229	255	284	317	392
N1R	1200	200	228	255	278	318	395
N1R	1201	207	225	265	284	318	407
N1R	1202	193	211	226	253	284	359
N1R	1218	197	216	243	264	302	393
N1R	1414	175	226	252	282	309	407
N1R	1415	183	219	233	256	228	339
N1R	1416	201	240	274	298	330	422
N1R	1417	172	205	229	252	262	331
N1R	1433	174	224	245	251	307	403
N1R	1434	174	204	225	249	273	345
N1R	1435	157	160	205	222	262	357
N1R	1436	192	232	268	288	316	413
N1R	1453	178	223	248	275	301	397
N1R	1454	173	211	228	235	266	345
MEAN	193	221	245	266	292	362	
STAN. DEV	17.4	16.7	15.9	19.6	27.5	47.9	

NON PREGNANT ANIMALS

N1R 1131	181	208	227	244	240	248	
N1R 1170	194	223	240	259	263	273	
N1R 1171	195	208	230	245	249	270	
N1R 1178	209	235	248	0 ^a	0	0	
N1R 1219	191	219	242	250	252	266	
N1R 1413	184	219	233	232	241	279	
N1R 1437	184	225	249	228	251	258	

^a Animal died

Appendix V (Continued)

Special Lens Oral Teratology Study of T-2999CoC in Rats

Individual Body Weights (g) with Mean Body Weights
and Standard Deviations for Pregnant Animals

		Replicate 2					
DAY		3	6	9	12	15	20

0 MG/KG/DAY							
N1R	1461	216	239	259	278	302	370
N1R	1462	185	211	230	253	274	340
N1R	1463	179	205	232	267	285	354
N1R	1464	193	220	241	274	299	383
N1R	1465	187	219	240	268	298	355
N1R	1481	235	260	296	320	345	437
N1R	1482	213	235	265	293	318	398
N1R	1483	186	211	237	262	286	369
N1R	1484	203	231	252	277	298	378
N1R	1485	195	224	249	288	317	410
N1R	1501	177	203	229	253	278	356
N1R	1502	199	224	249	271	293	350
N1R	2374	196	237	262	299	339	418
N1R	2375	183	206	235	266	296	370
N1R	2376	210	241	269	297	331	402
N1R	2378	199	230	253	284	307	374
N1R	2394	214	244	259	287	312	349
N1R	2395	204	232	258	290	319	421
N1R	2396	195	221	240	265	296	366
N1R	2397	217	249	273	305	330	382
N1R	2398	210	245	268	303	332	417
N1R	2414	187	213	233	275	298	377
N1R	2415	186	226	244	284	307	398
N1R	2422	189	220	235	261	285	349
N1R	2423	225	259	280	314	341	431
N1R	2425	222	252	267	299	325	406
N1R	2426	212	250	256	285	311	310
N1R	2442	172	207	221	235	233	238
N1R	2443	208	246	265	298	327	416
N1R	2445	200	231	240	271	298	372
N1R	2446	215	238	251	288	311	383
N1R	2462	194	230	243	277	310	380
N1R	2463	174	205	215	238	251	298
MEAN		199	229	250	280	305	374
STAN. DEV		15.7	16.4	17.7	19.9	24.4	40.3

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NON PREGNANT ANIMALS

N1R	2377	184	208	231	236	248	256
N1R	2424	196	236	253	283	315	394
N1R	2444	197	223	227	238	248	262

Special Lens Oral Teratology Study of T-2999CoC in Rats

Individual Body Weights (g) with Mean Body Weights
and Standard Deviations for Pregnant Animals

		Replicate 1					
DAY		3	6	9	12	15	20

25 MG/KG/DAY							
01R	1135	212	241	265	275	317	392
01R	1136	214	228	238	234	243	258
01R	1137	238	261	278	281	307	388
01R	1138	160	203	216	214	222	241
01R	1156	192	223	238	251	264	305
01R	1158	237	269	290	317	348	429
01R	1172	162	163	200	214	253	331
01R	1173	201	237	251	257	265	277
01R	1184	214	248	261	272	288	381
01R	1186	199	226	239	254	276	366
01R	1187	198	225	246	268	301	369
01R	1204	179	196	207	222	246	308
01R	1206	212	241	263	0 ^a	0	0
01R	1221	235	257	267	281	294	375
01R	1418	186	241	260	279	314	400
01R	1419	160	201	213	216	261	331
01R	1420	195	248	278	297	321	389
01R	1421	164	209	226	233	266	342
01R	1422	167	210	233	255	275	352
01R	1438	170	208	229	263	278	357
01R	1439	192	232	246	261	283	355
01R	1440	190	226	254	266	290	372
01R	1441	191	166	231	250	259	367
01R	1442	181	229	258	228	296	382
01R	1455	191	218	242	223	286	374
MEAN		194	224	245	255	281	352
STAN. DEV		23.3	26.1	22.9	27.4	28.6	45.8

NON PREGNANT ANIMALS

01R	1139	224	237	246	252	270	272
01R	1155	224	250	260	247	256	270
01R	1157	187	198	220	220	214	237
01R	1159	192	223	236	220	230	233
01R	1183	215	238	253	254	272	287
01R	1185	219	236	235	240	246	265
01R	1203	142	205	219	238	246	255
01R	1205	210	226	230	235	253	261
01R	1207	219	233	240	240	249	265
01R	1220	208	222	236	0 ^a	0	0
01R	1456	156	185	199	200	206	233

^a Animal died

Appendix V (Continued)

Special Lens Oral Teratology Study of T-2999CoC in Rats

Individual Body Weights (g) with Mean Body Weights
and Standard Deviations for Pregnant Animals

		Replicate 2					
DAY		3	6	9	12	15	20

25 MG/KG/DAY							
01R	1466	181	203	229	258	275	343
01R	1468	242	280	300	328	356	442
01R	1469	205	236	255	281	299	381
01R	1470	186	205	230	248	266	323
01R	1486	158	208	222	247	270	362
01R	1487	200	225	244	275	288	366
01R	1488	199	225	246	279	303	381
01R	1489	203	239	250	278	303	405
01R	1490	207	234	256	278	274	358
01R	1503	204	234	253	273	295	361
01R	1504	192	224	257	291	318	414
01R	2379	189	223	237	260	276	338
01R	2380	214	247	272	296	328	390
01R	2381	202	228	251	270	292	343
01R	2382	195	219	234	253	267	294
01R	2383	199	229	249	271	295	352
01R	2399	183	171	217	239	266	332
01R	2400	195	230	250	264	293	360
01R	2401	194	217	233	257	281	343
01R	2402	188	239	269	290	311	385
01R	2403	199	220	234	250	279	354
01R	2416	233	260	279	305	336	415
01R	2417	222	258	275	301	330	412
01R	2428	219	250	256	275	291	334
01R	2430	203	246	263	289	319	383
01R	2431	208	241	263	293	320	399
01R	2447	191	195	225	241	266	348
01R	2448	213	249	259	267	288	342
01R	2449	206	247	249	252	281	349
01R	2450	189	211	224	247	274	343
01R	2464	193	225	237	254	279	353
01R	2465	196	228	243	266	293	371
MEAN		200	230	249	271	294	365
STAN. DEV		15.6	20.9	18.5	20.8	23.0	31.5

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NON PREGNANT ANIMALS

01R	1467	184	215	234	251	263	287
01R	2427	196	226	228	229	240	255
01R	2429	195	230	241	239	250	268
01R	2451	192	228	234	225	237	255

Appendix V (Continued)

Special Lens Oral Teratology Study of T-2999CoC in Rats

Individual Body Weights (g) with Mean Body Weights
and Standard Deviations for Pregnant Animals

		Replicate 1						
DAY		3	6	9	12	15	20	Σ

2.5 MG/KG/DA								
P1R	1140	190	215	234	232	243	254	
P1R	1142	227	246	270	265	271	271	
P1R	1144	209	238	267	300	328	405	
P1R	1160	201	232	255	261	276	277	
P1R	1161	194	224	252	266	292	327	
P1R	1162	196	223	249	257	288	320	
P1R	1164	182	207	225	218	230	235	
P1R	1188	229	258	272	293	314	385	
P1R	1189	177	196	217	238	271	347	
P1R	1190	198	230	253	281	322	411	
P1R	1191	205	230	251	274	311	395	
P1R	1192	214	243	261	282	319	401	
P1R	1208	181	200	221	246	277	341	
P1R	1209	225	250	268	293	330	412	
P1R	1210	249	287	314	333	381	470	
P1R	1211	205	228	247	264	278	327	
P1R	1223	209	240	261	275	317	390	
P1R	1423	166	215	243	278	294	400	
P1R	1424	177	223	252	236	295	394	
P1R	1425	178	223	242	273	292	375	
P1R	1426	135	196	218	220	246	335	
P1R	1443	157	195	217	218	261	339	
P1R	1444	170	205	230	243	284	369	
P1R	1445	197	238	274	292	307	382	
P1R	1446	153	199	221	244	258	329	
P1R	1447	182	215	236	239	287	377	
P1R	1457	181	215	236	230	275	337	
P1R	1458	152	190	211	230	264	327	
MEAN		191	224	246	260	290	355	
STAN. DEV		26.0	22.1	23.0	28.6	31.7	53.2	

NON PREGNANT ANIMALS

P1R 1141	177	206	219	223	245	252	
P1R 1143	167	207	239	246	256	273	
P1R 1163	194	217	239	241	252	260	
P1R 1174	190	205	215	227	237	246	
P1R 1175	147	184	196	211	213	223	
P1R 1212	179	197	227	0 ^a	0	0	
P1R 1222	191	217	226	0 ^a	0	0	
P1R 1427	183	214	232	234	239	258	

^a Animal died

Appendix V (Continued)

Special Lens Oral Teratology Study of T-2999CoC in Rats

Individual Body Weights (g) with Mean Body Weights
and Standard Deviations for Pregnant Animals

DAY	Replicate 2					
	3	6	9	12	15	20

2.5 MG/KG/DA						
P1R 1471	194	223	247	244	298	388
P1R 1472	234	268	283	315	337	439
P1R 1473	185	210	237	267	290	359
P1R 1474	196	223	246	271	300	386
P1R 1475	179	209	233	258	283	355
P1R 1491	209	248	262	290	317	398
P1R 1492	195	212	243	259	285	348
P1R 1493	205	235	261	283	315	400
P1R 1494	218	251	269	305	335	410
P1R 1495	205	225	245	269	298	380
P1R 1505	193	223	243	270	290	361
P1R 1506	191	214	240	269	286	369
P1R 2384	189	213	243	268	302	361
P1R 2385	209	245	262	295	328	404
P1R 2386	233	256	282	313	345	434
P1R 2387	192	226	243	272	296	358
P1R 2388	191	220	247	268	297	356
P1R 2404	226	257	281	316	350	432
P1R 2406	200	223	248	274	305	373
P1R 2407	202	231	253	285	310	398
P1R 2408	205	234	253	282	315	392
P1R 2418	196	223	241	265	292	356
P1R 2419	225	249	278	304	333	412
P1R 2433	196	239	249	271	302	390
P1R 2434	222	264	277	303	330	406
P1R 2453	194	225	246	272	299	373
P1R 2454	203	232	248	267	284	335
P1R 2455	217	244	265	286	315	413
P1R 2456	211	243	256	283	295	348
P1R 2466	199	229	239	263	292	371
P1R 2467	197	225	245	270	300	384
MEAN	204	233	254	279	307	384
STAN. DEV	13.9	16.1	14.5	18.1	18.9	27.2

NON PREGNANT ANIMALS

P1R 2405	192	220	242	245	256	272
P1R 2432	199	233	238	247	257	270
P1R 2435	202	240	262	277	304	336
P1R 2436	224	259	273	271	281	289
P1R 2452	198	228	240	242	249	261

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Special Lens Oral Teratology Study of T-2999CoC in Rats

Individual Body Weights (g) with Mean Body Weights
and Standard Deviations for Pregnant Animals

DAY	Replicate 1					
	3	6	9	12	15	20
0.25 MG/KG/D						
Q1R 1146	197	216	234	261	293	357
Q1R 1148	215	249	276	306	339	395
Q1R 1166	210	235	262	288	314	369
Q1R 1168	199	226	247	248	248	262
Q1R 1177	222	243	251	266	265	286
Q1R 1193	213	236	259	286	320	396
Q1R 1194	185	202	213	214	230	244
Q1R 1195	215	239	263	287	325	412
Q1R 1196	200	225	241	263	294	353
Q1R 1197	215	247	274	295	306	402
Q1R 1213	208	227	246	266	299	368
Q1R 1214	197	224	242	257	259	275
Q1R 1215	212	238	246	269	311	384
Q1R 1216	207	233	251	277	307	391
Q1R 1217	185	212	228	247	274	332
Q1R 1224	205	237	259	274	312	385
Q1R 1225	218	251	267	296	325	339
Q1R 1428	175	218	244	250	301	377
Q1R 1429	176	199	232	250	282	369
Q1R 1430	206	242	263	265	274	289
Q1R 1431	208	251	282	273	334	429
Q1R 1432	170	203	232	216	284	369
Q1R 1448	196	236	259	288	300	361
Q1R 1449	211	244	281	294	328	426
Q1R 1450	187	237	269	286	318	417
Q1R 1451	204	257	286	294	339	438
Q1R 1452	186	228	253	252	312	409
MEAN	201	232	254	269	300	364
STAN. DEV	14.1	15.5	18.0	23.0	27.9	52.7

NON PREGNANT ANIMALS

Q1R 1145	176	203	234	251	260	266
Q1R 1147	183	207	232	243	245	251
Q1R 1149	172	187	194	217	228	242
Q1R 1165	199	228	254	270	283	279
Q1R 1167	196	241	257	264	272	278
Q1R 1169	192	221	244	257	255	258
Q1R 1176	192	220	246	263	0 ^a	0
Q1R 1459	182	213	242	246	255	277
Q1R 1460	177	225	251	237	256	269

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^a Animal died

Special Lens Oral Teratology Study of T-2999CoC in Rats

Individual Body Weights (g) with Mean Body Weights
and Standard Deviations for Pregnant Animals

		Replicate 2					
DAY	3	6	9	12	15	20	

0.25 MG/KG/D							
Q1R	1476	216	248	283	324	345	454
Q1R	1477	202	227	252	286	303	386
Q1R	1478	187	217	237	273	296	369
Q1R	1479	214	243	268	300	331	408
Q1R	1480	222	249	273	299	318	387
Q1R	1496	208	229	243	273	308	383
Q1R	1497	238	265	285	314	332	389
Q1R	1498	204	233	249	255	263	278
Q1R	1500	182	212	233	261	294	357
Q1R	1508	200	231	253	279	304	378
Q1R	2389	209	242	267	299	332	410
Q1R	2390	184	201	207	228	252	261
Q1R	2391	208	246	266	310	334	413
Q1R	2392	187	218	237	265	290	362
Q1R	2393	200	234	257	289	313	383
Q1R	2409	193	226	254	281	310	394
Q1R	2410	206	229	252	281	307	376
Q1R	2411	213	240	257	292	321	429
Q1R	2412	212	240	260	287	298	351
Q1R	2413	205	229	254	288	313	397
Q1R	2420	190	245	272	306	332	425
Q1R	2421	189	219	244	269	282	316
Q1R	2437	185	211	225	250	270	322
Q1R	2438	208	246	261	280	281	300
Q1R	2439	192	238	255	287	313	398
Q1R	2440	206	244	255	279	301	351
Q1R	2441	208	241	256	279	302	363
Q1R	2457	196	224	239	272	300	382
Q1R	2458	193	229	242	264	290	363
Q1R	2459	212	246	276	302	324	396
Q1R	2460	173	223	237	265	284	285
Q1R	2461	187	224	246	277	300	379
Q1R	2468	236	278	293	318	340	459
Q1R	2469	190	220	236	259	288	368
MEAN	202	234	254	282	305	373	
STAN. DEV	14.6	15.4	17.8	20.6	22.0	45.8	

NON PREGNANT ANIMALS

Q1R 1499	191	219	226	230	234	243
Q1R 1507	180	201	212	215	223	234

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