AR226-0463

Oral Teratology Study of T-2998CoC in Rats

Experiment No.:	0681TR0110
Conducted At:	Safety Evaluation Laboratory Riker Laboratories, Inc. St. Paul, Minnesota
Dosing Period:	April 6, 1981 through April 16, 1981
Study Director:	E. G. Gortner

E. B. Gortner 12-15-81

E. G. Gortner Date
Senior Research Technologist
Animal Teratology Reproduction

Eldon G Lamprecht 12-15-81

E. G. Lamprecht, DVM, PhD Date
Research Veterinary Pathologist

Marvin T Case 12/15/81

M. T. Case, DVM, PhD Date
Manager, Pathology-Toxicology
Safety Evaluation Laboratory

003034

Summary

Oral administration of T-2998CoC at doses of 0, 150, 50, 1.5 and 0.05 mg/kg/day to pregnant Sprague-Dawley rats during days 6 through 15 of gestation (period of organogenesis) was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams. The compound did not cause abnormal gross, internal, or skeletal malformations of the fetuses. T-2998CoC was not teratogenic in the rat.

T-2998CoC administration was maternally toxic to the 150 mg/kg/day dose group animals. It caused significantly low mean body weights during the dosing interval. Toxic clinical signs and deaths occurred in only the 150 mg/kg/day dose group.

Introduction

This teratology study[a] in rats was conducted to evaluate the embryotoxic and teratogenic effects of orally administered T-2998CoC[b]. The study was sponsored by 3M Commercial Chemical Division, St. Paul, Minnesota and was conducted by the Safety Evaluation Laboratory, Riker Laboratories, Inc., St. Paul, Minnesota. Two sets of compound administration groups were dosed between April 6 and April 16, 1981. The protocol and list of the principal participants and supervisory personnel can be found in Appendices I and II respectively.

All portions of this study were conducted according to the Good Laboratory Practice (GLP) regulations and the Safety Evaluation Laboratory Standard Operating Procedures (see Appendix III for Quality Assurance Unit statement). The storage location for specimens, raw data and a copy of the final report is maintained in the Safety Evaluation Laboratory's record archives.

Methods

Time mated Sprague Dawley derived CD rats were obtained from Charles River Breeding Laboratory, Wilmington, Massachusetts, and assigned cages according to a computer-generated random numbers table. The rats, ranging in weight from 167 to 230 grams, were then divided into four groups of 22 animals each. The rats were housed individually in hanging stainless steel cages with wire mesh floors and fronts in a temperature and humidity controlled room. Food[c] and water were available ad libitum. The lights were on a 12 hour light/dark cycle.

The animals were observed daily from day 3 through day 20 of gestation for abnormal clinical signs. Body weights were recorded on days 3, 6, 9, 12, 15 and 20 of gestation and the rats dosed accordingly using a constant dose volume of 5 ml/kg of body weight. The five groups were dosed with T-2998CoC dissolved in distilled water daily at 0, 150, 5, 1.5 or 0.05 mg/kg/day. T-2998CoC was administered daily by oral intubation with a syringe equipped with a ball-tipped intubation needle to the rats on days 6 through 15 of gestation (day 0 indicated by sperm-positive vaginal smear). T-2998CoC analysis was provided by 3M Commercial Chemical Division, St. Paul, Minnesota (Appendix IV).

All surviving animals were sacrificed on day 20 by cervical dislocation and the ovaries and uterus, including its contents, were examined immediately to determine the following: number of corpora lutea, number of viable fetuses, number of resorption sites, pup weights and sex, and any gross fetal abnormalities. Approximately two-thirds of the fetuses were preserved in alcohol for clearing and staining of the skeleton with alizarin red to detect skeletal abnormalities. Approximately one-third of the fetuses were fixed in Bouin's solution for subsequent free-hand sectioning by the Wilson technique to determine visceral abnormalities. In order to evaluate lens findings seen under the dissecting microscope, all eye sections with findings, plus select eye sections without lens findings were inbedded in paraffin, sectioned at 5-6 microns, stained with hematoxylin and eosin and examined histologically.

[a] Riker Experiment No. 0681TR0110
[b] FC-143
[c] Purina Laboratory Chow, Ralston Purina Co., St. Louis, MO

Results and Discussion

T-2998CoC administered during the period of organogenesis was toxic to the high dose group (150 mg/kg/day) rats in causing low mean body weights during the dosing period. At gestational days 9, 12 and 15 (Table 1, Appendix V), the high dose group rats weighed significantly less than controls (0 mg/kg/day). The mean maternal body weights of the intermediate (5 mg/kg/day), mid (1.5 mg/kg/day), and low (0.05 mg/kg/day) dose groups were not different from the controls throughout the study.

Abnormal clinical signs were observed and deaths occurred only in the high dose group. Three rats in the high dose group died. All three of the rats that died were ataxic and two of the rats were pale for one to two days before death. The surviving high dose rats did not have abnormal clinical signs and signs of toxicity did not occur in lower dose animals.

T-2998CoC was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams. The mean number of male, female, total and dead fetuses, the mean number of resorption sites, implantation sites, corpora lutea and mean fetus weights of the four T-2998CoC dose groups were not significantly different from the control (Table 2, Appendix VI).

T-2998CoC did not cause compound-related abnormal gross fetal findings (Table 3), nor did T-2998CoC treatment produce fetal skeletal malformations (Table 4, Appendix VII). A significant higher incidence of the skeletal finding of one sternebrae missing occurred in the high dose group. One sternebrae missing is a minor skeletal aberration and was not considered a malformation in this study. Further, the incidence of the finding of one sternebrae missing was not different among the control group and the lower three treatment groups. The incidences of skeletal findings associated with delayed ossification and rib aberrations were not different among the five treatment groups.

A fetal lens finding was 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 anteriocentral region extending from beneath the lens epithelium to half-way through the lens posteriorly, a cleft at the anteriocentral lens region or a combination of lens discoloration and the presence of a cleft.

The lens findings observed under the dissecting microscope were interpreted histopathologically as either a freehand sectioning artifact of a normal area of primary lens fiber degeneration. 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 and sectioning accentuating the area of normal primary lens fiber degeneration. The

differences in the appearance of the lens artifact in individual fetuses and even among dose groups were largely due to the manner and frequency in which the artifact was created and the limitations inherent in visualizing the artifact under the dissecting microscope. Histologically, the lens artifact was the same in all dose groups regardless of the morphological appearance described under the dissecting microscope. T-2998CoC in utero exposed fetuses did not have compound-related changes in their lenses.

Table 1

Oral Teratology Study of T-2998CoC in Rats
Mean Material Body Weights with Standard Deviations

Dose Groups	DAY	3	6	9	12	15	20
0 mg/kg/day	MEAN	196	223	251	276	310	380
	STAN. DEV	16.1	23.4	21.4	20.6	22.3	27.6
150 mg/kg/day	MEAN	202	229	226[a]	259[a]	282[a]	361
	STAN. DEV	14.0	16.1	29.5	20.6	23.5	28.6
5 mg/kg/day	MEAN	201	225	252	277	312	390
	STAN. DEV	12.1	13.9	14.6	17.1	20.0	30.0
1.5 mg/kg/day	MEAN	196	219	245	269	301	369
	STAN. DEV	15.3	14.6	16.5	15.5	17.9	26.7
0.05 mg/kg/day	MEAN	199	225	249	273	306	380
	STAN. DEV	13.8	16.2	18.2	21.0	23.2	32.4

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

003039

Table 2

Oral Teratology Study of T-2998CoC in Rats
Mean Litter Data and Fetus Weights with Standard Deviations[a]

Dose Groups	GRP	NO. OF ANIMALS	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESORPTION SITES	IMPLANTATION SITES	CORPORA LUTEA	MEAN WT. FETUS(G)
0 mg/kg/day		20	4.9	4.9	9.8	0.0	0.5	10.3	11.4	4.4
	STAN	DEV	1.8	1.8	2.5	0.0	0.8	2.5	1.6	0.4
150 mg/kg/day		14	4.9	5.1	10.0	0.0	0.6	10.6	11.1	4.2
	STAN	DEV	2.1	2.2	3.3	0.0	1.0	3.1	1.9	0.3
5 mg/kg/day		21	5.2	5.2	10.4	0.0	0.5	11.0	11.3	4.3
	STAN	DEV	2.2	2.4	1.9	0.0	0.8	1.7	1.6	0.3
1.5 mg/kg/day		19	3.7	4.8	8.5	0.0	1.1	9.6	10.1	4.3
	STAN	DEV	1.8	2.5	3.6	0.0	1.5	2.8	2.5	0.4
0.05 mg/kg/day		21	5.1	4.9	10.0	0.0	0.4	10.5	11.0	4.3
	STAN	DEV	1.9	2.2	2.8	0.2	1.2	2.2	1.8	0.2

[a] Treatment groups were not significantly different from the control group (Dunnett's t test $p < 0.05$)

Table 3

Oral Teratology Study of T-2998CoC in Rats
Number of Fetuses with Gross Findings[a]

Findings	0 mg/kg/day	150 mg/kg/day	5 mg/kg/day	1.5 mg/kg/day	0.05 mg/kg/day
Total Fetuses Examined	196	140	219	162	211
Runted	1	---	---	---	---
Small	---	---	---	2	---
Umbilical hernia	---	---	---	---	1
Total Normal Fetuses	195	140	219	160	210
Total Abnormal Fetuses	1	0	0	2	1

[a] Treatment groups were not significantly different from the control group (Chi-square $p < 0.05$)

003041

Table 4

Oral Teratology Study of T-2998CoC in Rats
Number and Percent of Fetuses with Skeleton Findings

Skeleton Findings	0 mg/kg/day		150 mg/kg/day		5 mg/kg/day		1.5 mg/kg/day		0.05 mg/kg/day	
Fontanelle not closed	24	(18)	18	(19)	17	(11)	15	(13)	20	(14)
Hole in frontal							1	(1)		
Frontals not ossified	17	(13)	14	(15)	5	(3)	9	(8)	9	(6)
Parietals not ossified	17	(13)	14	(15)	5	(3)	9	(8)	9	(6)
Interparietals not ossified	17	(13)	13	(14)	2	(1)	6	(5)	3	(2)
Sternebrae not ossified	40	(67)	64	(67)	101	(67)	71	(63)	95	(64)
Sternebrae bipartite			1						5	(3)
Sternebrae asymmetrical	14	(10)	10	(10)	12	(8)	13	(12)	18	(12)
One sternebrae missing	20	(15)	30	(31)[a]	29	(19)	19	(17)	22	(15)
Two sternebrae missing	9	(7)	7	(7)	8	(5)	2	(2)	3	(2)
Four sternebrae missing							1	(1)		
13 ribs	2	(1)	2	(2)	4	(3)	1	(1)	6	(4)
13 ribs spurred	4	(3)	10	(10)	5	(3)	6	(5)	6	(4)
Wavy ribs	7	(5)	7	(7)	3	(2)	6	(5)	3	(2)
Protrusion on ribs	6	(4)	7	(7)	4	(3)	4	(4)	3	(2)
One body vertebrae bipartite	35	(26)	15	(16)	30	(20)	17	(15)	25	(17)
Two bodies vertebrae bipartite	6	(4)	2	(2)	14		2	(2)	6	(4)
Three bodies vertebrae bipartite	1				3	(2)			2	(1)
One body of vertebrae missing			1							
Total Number of Fetuses	136		97		150[b]		112[b]		148	
Total Abnormal Fetuses	126	(93)	88	(92)	136	(91)	93	(83)	127	(86)
Total Normal Fetuses	10	(7)	9	(8)	14	(9)	19	(17)	21	(14)

[a] Significantly higher than the control group (Chi-square $p < 0.05$)
[b] Results from one fetus are missing
( ) = percent of total examined

003042

Table 5

Oral Teratology Study of T-2998CoC in Rats
Number and Percent of Fetuses with Internal Findings

Internal Findings	0 mg/kg/day		150 mg/kg/day		5 mg/kg/day		1.5 mg/kg/day		0.05 mg/kg/day	
Fetuses with lens findings	5	(8)	11	(26)[a]	2	(3)	6	(12)	5	(8)
A dark streak in the lens of one eye			2	(5)					2	(3)
A dark streak & cleft in the lens of one eye			3	(7)						
A cleft in the lens of one eye	5	(8)	5	(12)	1	(1)	6	(12)	2	(3)
A cleft in the lens of both eyes			1	(2)	1	(1)			1	(2)
Hydronephrosis					1	(1)				
Enlarged renal pelvis	17	(29)	1	(2)[a]	4	(6)[a]	9	(18)	10	(16)
Abdominal cavity full of blood	2	(3)	3	(7)	3	(4)	1	(2)	3	(5)
Total Normal Fetuses	38	(63)	30	(70)	59	(87)	37	(76)	46	(73)
Total Abnormal Fetuses	22	(37)	13	(30)	9	(13)	12	(24)	17	(27)
Total Fetuses Examined	60		43		68		49		63	

[a] Significantly different from the control group (Chi-square $p < 0.05$)
( ) = percent of total examined

003043

Appendix I

TITLE: Protocol for Oral Teratology Study of T-2998CoC[a] in Rats (Riker Experiment Number 0681TR0110).

OBJECTIVE: A teratology study will be used to evaluate the embryotoxic and teratogenic effects of orally administered T-2998CoC to pregnant rats during the period of organogenesis. The procedure complies with the general recommendations of the FDA issued in January, 1966 ("Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use"). The study will be conducted according to the 1978 Good Laboratory Practice Regulations and 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: April, 1981.

TEST SYSTEM: One hundred and ten sexually mature, time mated Sprague-Dawley derived female rats from Charles River Breeding Laboratory 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 of historical control data 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-2998CoC.

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.

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

[a] FC-143

Dose Level	Group Size
150 mg/kg/day	22
5 mg/kg/day	22
1.5 mg/kg/day	22
0.05 mg/kg/day	22
0 mg/kg/day	22

The oral route of administration will be used because metabolism studies showed radiolabeled T-2998CoC was well absorbed. No dietary contaminants are known to interfere with the test article.

The animals will be observed daily from day 3 through day 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 dosed accordingly using a constant dose volume of 5 ml/kg of body weight.

The females will be killed on day 20 and the ovaries, uterus and its contents will be examined to determine: number of corpora lutea, number of fetuses (live and dead), number of resorption sites, number of implantation sites, pup weight and gross abnormalities. Approximately one-third of the pups will be fixed in Bouin's solution for subsequent free-hand sectioning by the Wilson technique to determine any visceral abnormalities using a dissecting microscope. Select eye sections can be sent to histopath for microscopic examination as deemed necessary by the study director. The remaining approximately two-thirds of the pups will be fixed in ethyl alcohol for subsequent skeletal examination after clearing and staining with alizarin red.

DATA ANALYSIS AND FINAL REPORT: The proposed statistical methods to be used for analysis of the data are: Dunnett's t test for dam and pup weights, number of fetuses, number of resorption sits, number of implantation sites and number of corpora lutea; Chi square for percent abnormalities. The proposed date for the final report is 2-3 months after detailed pup examinations have been completed (approximately third quarter, 1981).

Amendment to Protocol

The control article for Experiment Number 0681TR0110 (oral teratology study of T-2998CoC in rats) will be changed from corn oil to water. The test article will not be suspended in corn oil daily as noted in the protocol, but solutions will be made by dissolving T-2998CoC in water by Dr. V. Pothapragada and the solution for the whole study will be submitted to 3M Commercial Chemical group for clearance before the start of the study and at the end of dosing.

003045

Appendix II

List of Principal Participating Personnel

NAME	FUNCTION
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

STATEMENT OF QUALITY ASSURANCE

STUDY NUMBER: 0681TR0110

TITLE: Oral Teratology Study of T 2998CoC 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:

Date Performed	Date Reported
9,14,16 April 1981	21 April 1981
20 April 1981	21 April 1981
20 August 1981	28 August 1981
7 December 1981	14 December 1981
14 December 1981	14 December 1981

Dave L. Stevens
Compliance Audit
Riker Laboratories, Inc.

14 December 1981
Date

003047

Appendix IV

Prestudy and Poststudy Analysis of T-2998CoC Distilled Water Solutions[a]

Dose Level	Expected	Analysis	
		Prestudy[a]	Poststudy
0 mg/kg	0.0 mg/ml	0.0 ppm	0.00 ppm
150 mg/kg	30.0 mg/ml	30.328 mg/ml	31.0 mg/ml
5 mg/kg	1.0 mg/ml	0.983 mg/ml	0.92 mg/ml
1.5 mg/kg	0.3 mg/ml	0.268 mg/ml	0.33 mg/ml
0.05 mg/kg	0.01 mg/ml	0.0087 mg/ml	0.0092 mg/ml

[a] Pregnant rats were dosed at 5 ml/kg T-2998CoC

003048

Appendix V

Oral Teratology Study of T-2998CoC in Rats
Individual Body Weights (g) and Mean Body Weights
With Standard Deviations For Pregnant Rats

DAY		3	6	9	12	15	20
0 MG/KG/DAY							
N1R	2997	223	243	264	292	321	402
N1R	2998	194	219	247	281	315	383
N1R	3000	186	214	243	261	292	350
N1R	3001	199	222	252	288	325	414
N1R	3002	193	216	239	261	291	356
N1R	3003	170	223	261	290	331	415
N1R	3004	167	144	188	218	254	341
N1R	3005	186	217	251	276	312	374
N1R	3006	185	208	244	266	297	373
N1R	3007	177	211	236	259	297	363
N1R	3052	191	220	252	277	314	401
N1R	3053	218	253	278	301	327	366
N1R	3054	226	261	289	303	347	432
N1R	3055	209	235	267	291	327	399
N1R	3056	208	237	268	292	327	396
N1R	3057	207	236	270	295	325	397
N1R	3058	194	222	243	267	289	354
N1R	3059	191	216	232	251	286	345
N1R	3061	204	239	266	288	330	403
N1R	3062	191	214	236	261	286	341
MEAN		196	223	251	276	310	380
STAN. DEV		16.1	23.4	21.4	20.6	22.3	27.6
NON PREGNANT ANIMALS							
N1R	2999	196	219	231	248	258	280
N1R	3060	188	207	225	235	236	253

Appendix V (Continued)

Oral Teratology Study of T-2998CoC in Rats

Individual Body Weights (g) and Mean Body Weights
With Standard Deviations For Pregnant Rats

DAY		3	6	9	12	15	20
150 MG/KG/DA							
01R	3008	214	236	256	271	297	372
01R	3011	185	215	179	228	256	337
01R	3012	197	220	244	259	271	337
01R	3013	198	231	246	267	280	346
01R	3015	215	235	201	261	301	383
01R	3016	194	224	239	252	271	355
01R	3017	197	230	181	0[a]	0	0
01R	3018	188	219	209	250	270	339
01R	3063	214	241	252	267	300	385
01R	3064	208	233	236	272	296	395
01R	3065	225	254	259	279	304	409
01R	3068	193	219	223	256	253	345
01R	3069	200	228	223	264	295	382
01R	3070	182	195	200	211	234	303
01R	3071	230	264	272	294	317	369
01R	3073	197	218	188	0[a]	0	0
MEAN		202	229	226	259	282	361
STAN. DEV		14.0	16.1	29.5	20.6	23.5	28.6
NON PREGNANT ANIMALS							
01R	3009	194	220	174	223	242	263
01R	3010	189	209	173	229	252	269
01R	3014	183	207	205	207	238	257
01R	3066	187	201	153	0[a]	0	0
01R	3067	192	223	228	225	239	251
01R	3072	199	215	207	224	236	253

[a] Animal died

003050

Appendix V (Continued)

Oral Teratology Study of T-2998CoC in Rats
Individual Body Weights (g) and Mean Body Weights
With Standard Deviations For Pregnant Rats

DAY		3	6	9	12	15	20
5 MG/KG/DAY							
P1R	3019	205	225	241	264	297	371
P1R	3020	192	215	243	268	301	374
P1R	3021	182	205	235	260	294	375
P1R	3022	182	211	245	274	308	397
P1R	3023	198	221	253	273	313	385
P1R	3024	208	232	268	289	323	410
P1R	3025	214	241	266	300	338	434
P1R	3026	189	206	233	259	292	355
P1R	3027	192	214	237	266	297	381
P1R	3028	213	231	257	282	322	394
P1R	3029	200	225	257	278	319	388
P1R	3074	206	228	254	279	309	385
P1R	3075	214	241	258	288	320	396
P1R	3076	192	208	237	259	290	368
P1R	3077	191	219	241	266	295	375
P1R	3078	210	248	273	302	345	458
P1R	3079	222	247	280	313	345	413
P1R	3080	198	229	252	282	312	383
P1R	3081	225	247	276	305	345	445
P1R	3083	197	210	231	249	272	324
P1R	3084	200	224	251	271	306	384
MEAN		201	225	252	277	312	390
STAN. DEV		12.1	13.9	14.6	17.1	20.0	30.0
NON PREGNANT ANIMALS							
P1R	3082	209	222	250	264	269	278

003051

Appendix V (Continued)

Oral Teratology Study of T-2998CoC in Rats
Individual Body Weights (g) and Mean Body Weights
With Standard Deviations For Pregnant Rats

	DAY	3	6	9	12	15	20
1.5 MG/KG/DA							
Q1R	3030	178	202	224	258	291	368
Q1R	3031	183	210	236	261	293	357
Q1R	3032	212	227	259	272	325	415
Q1R	3033	185	211	241	261	291	360
Q1R	3034	190	213	242	271	306	390
Q1R	3036	179	209	234	252	286	350
Q1R	3037	190	218	241	259	292	352
Q1R	3038	209	235	268	291	327	412
Q1R	3039	213	236	266	293	328	405
Q1R	3040	193	222	250	283	298	340
Q1R	3085	198	220	243	271	302	373
Q1R	3086	184	209	235	261	281	319
Q1R	3088	198	214	239	264	299	379
Q1R	3089	196	221	241	261	278	331
Q1R	3091	173	194	219	241	271	348
Q1R	3092	189	204	223	254	285	356
Q1R	3093	229	251	275	298	326	372
Q1R	3094	221	244	273	289	321	390
Q1R	3095	203	222	249	274	311	385
MEAN		196	219	245	269	301	369
STAN. DEV		15.3	14.6	16.5	15.5	17.9	26.7
NON PREGNANT ANIMALS							
Q1R	3035	186	212	237	252	271	265
Q1R	3087	186	203	230	235	249	261
Q1R	3090	191	212	225	244	242	255

003052

Appendix V (Concluded)

Oral Teratology Study of T-2998CoC in Rats
Individual Body Weights (g) and Mean Body Weights
With Standard Deviations for Pregnant Rats

DAY		3	6	9	12	15	20
0.05 MG/KG/D							
R1R	3041	212	241	263	292	323	403
R1R	3042	203	232	251	276	304	364
R1R	3043	198	222	237	267	299	370
R1R	3045	207	237	267	298	337	413
R1R	3046	183	205	225	245	280	358
R1R	3047	197	214	236	260	296	360
R1R	3048	196	221	250	280	320	406
R1R	3049	191	221	257	280	314	387
R1R	3050	180	212	238	256	286	341
R1R	3051	226	250	279	312	354	424
R1R	3096	221	250	269	292	328	414
R1R	3097	188	206	226	249	281	367
R1R	3098	200	212	233	254	289	355
R1R	3099	189	218	235	252	274	314
R1R	3100	183	212	237	255	286	359
R1R	3101	188	204	227	245	287	352
R1R	3102	207	242	268	293	325	405
R1R	3103	218	253	280	295	332	430
R1R	3104	179	207	227	247	274	338
R1R	3105	205	234	260	290	322	409
R1R	3106	212	236	264	287	320	406
MEAN		199	225	249	273	306	380
STAN. DEV		13.8	16.2	18.2	21.0	23.2	32.4
NON PREGNANT ANIMALS							
R1R	3044	183	196	211	222	231	246

Appendix VI

Oral Teratology Study of T-2998CoC in Rats
Individual Litter Data with Mean Fetus Weights

ANIMAL		VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESOR PTION SITES	IMPLAN TATION SITES	CORPRA LUTEA	MEAN FETUS WT(G) AVG	M	F
0 mg/kg/day											
N1R	2997	6	3	9	0	0	9	10	4.9	4.9	4.9
N1R	2998	4	6	10	0	1	11	13	3.8	3.9	3.8
N1R	2999	NOT PREGNANT									
N1R	3000	5	5	10	0	0	10	11	4.3	4.5	4.1
N1R	3001	6	6	12	0	0	12	13	4.5	4.6	4.4
N1R	3002	4	6	10	0	0	10	10	4.2	4.3	4.1
N1R	3003	6	5	11	0	0	11	12	4.8	4.7	4.9
N1R	3004	6	4	10	0	3	13	14	4.0	4.0	4.0
N1R	3005	5	4	9	0	2	11	12	4.8	4.9	4.6
N1R	3006	9	4	13	0	0	13	13	4.2	4.2	4.1
N1R	3007	6	3	9	0	1	10	11	4.5	4.4	4.6
N1R	3052	6	5	11	0	0	11	11	4.4	4.5	4.3
N1R	3053	1	1	2	0	1	3	9	5.4	5.5	5.3
N1R	3054	5	8	13	0	1	14	14	4.0	4.0	4.0
N1R	3055	4	7	11	0	1	12	14	3.9	4.0	3.8
N1R	3056	4	7	11	0	0	11	10	4.5	4.6	4.4
N1R	3057	6	3	9	0	0	9	11	4.9	4.9	4.8
N1R	3058	3	3	6	0	0	6	9	4.6	4.7	4.5
N1R	3059	4	4	8	0	0	8	10	4.2	4.4	3.9
N1R	3060	NOT PREGNANT									
N1R	3061	7	5	12	0	0	12	12	4.4	4.5	4.2
N1R	3062	2	8	10	0	0	10	10	4.0	4.2	3.9
	MEAN	4.9	4.9	9.8	0.0	0.5	10.3	11.4	4.4		
	STAN. DEV.	1.8	1.8	2.5	0.0	0.8	2.5	1.6	0.4		

Appendix VI (Continued)

Oral Teratology Study of T-2998CoC in Rats
Individual Litter Data with Mean Fetus Weights

ANIMAL	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESOR PTION SITES	IMPLAN TATION SITES	CORPRA LUTEA	MEAN FETUS WT(G) AVG	M	F
150 mg/kg/day										
01R 3008	4	7	11	0	2	13	12	3.9	4.0	3.9
01R 3009	NOT PREGNANT									
01R 3010	NOT PREGNANT									
01R 3011	5	3	8	0	1	9	9	4.4	4.5	4.3
01R 3012	5	5	10	0	0	10	10	4.1	4.2	4.1
01R 3013	7	2	9	0	0	9	10	4.2	4.3	3.9
01R 3014	NOT PREGNANT									
01R 3015	4	7	11	0	1	12	12	4.4	4.7	4.3
01R 3016	3	5	8	0	2	10	10	4.5	4.5	4.5
01R 3017	DEAD									
01R 3018	3	4	7	0	3	10	9	4.7	4.9	4.5
01R 3063	6	8	14	0	0	14	14	3.8	3.9	3.8
01R 3064	6	6	12	0	0	12	14	3.9	4.0	3.8
01R 3065	10	5	15	0	0	15	14	3.8	3.8	3.8
01R 3066	DEAD									
01R 3067	NOT PREGNANT									
01R 3068	5	7	12	0	0	12	12	4.0	3.9	4.0
01R 3069	4	8	12	0	0	12	11	4.0	4.1	3.9
01R 3070	6	3	9	0	0	9	10	3.9	3.9	3.7
01R 3071	1	1	2	0	0	2	9	4.3	4.4	4.3
01R 3072	NOT PREGNANT									
01R 3073	DEAD									
MEAN	4.9	5.1	10.0	0.0	0.6	10.6	11.1	4.2		
STAN. DEV.	2.1	2.2	3.3	0.0	1.0	3.1	1.9	0.3		

003055

Appendix VI (Continued)

Oral Teratology Study of T-2998CoC in Rats
Individual Litter Data with Mean Fetus Weights

ANIMAL	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESOR PTION SITES	IMPLAN TATION SITES	CORPRA LUTEA	MEAN FETUS WT(G) AVG	M	F
5 mg/kg/day										
P1R 3019	3	6	9	0	1	10	10	3.4	3.3	3.4
P1R 3020	4	5	9	0	0	9	10	3.8	3.9	3.6
P1R 3021	3	7	10	0	2	12	14	4.1	4.4	4.0
P1R 3022	6	7	13	0	0	13	12	5.0	5.3	4.8
P1R 3023	5	5	10	0	0	10	11	4.2	4.2	4.2
P1R 3024	3	9	12	0	1	13	14	4.4	4.4	4.5
P1R 3025	9	5	14	0	0	14	14	4.3	4.3	4.2
P1R 3026	2	6	8	0	0	8	9	4.6	4.8	4.6
P1R 3027	7	2	9	0	2	11	11	4.5	4.6	4.1
P1R 3028	8	2	10	0	0	10	11	4.5	4.5	4.4
P1R 3029	4	5	9	0	0	9	10	4.6	4.7	4.5
P1R 3074	4	6	10	0	0	10	10	4.2	4.2	4.1
P1R 3075	7	5	12	0	0	12	13	4.5	4.7	4.1
P1R 3076	8	4	12	0	0	12	13	4.0	4.0	4.0
P1R 3077	1	11	12	0	1	13	11	4.2	4.5	4.2
P1R 3078	5	8	13	0	0	13	13	4.3	4.4	4.2
P1R 3079	6	3	9	0	0	9	10	4.5	4.6	4.4
P1R 3080	5	4	9	0	2	11	11	4.3	4.3	4.2
P1R 3081	9	3	12	0	0	12	12	4.5	4.6	4.3
P1R 3082	NOT PREGNANT									
P1R 3083	6	1	7	0	2	9	9	4.3	4.3	4.3
P1R 3084	4	6	10	0	0	10	10	4.4	4.5	4.3
MEAN	5.2	5.2	10.4	0.0	0.5	11.0	11.3	4.3		
STAN. DEV.	2.2	2.4	1.9	0.0	0.8	1.7	1.6	0.3		

003056

Appendix VI (Continued)

Oral Teratology Study of T-2998CoC in Rats
Individual Litter Data with Mean Fetus Weights

ANIMAL		VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESORPTION SITES	IMPLANTATION SITES	CORPRA LUTEA	MEAN FETUS WT(G) AVG	M	F
1.5 mg/kg/day											
Q1R	3030	3	8	11	0	1	12	11	4.0	4.1	4.0
Q1R	3031	4	5	9	0	1	10	11	4.4	4.6	4.2
Q1R	3032	5	8	13	0	0	13	12	4.6	4.5	4.7
Q1R	3033	5	6	11	0	0	11	11	4.5	4.6	4.4
Q1R	3034	5	5	10	0	0	10	11	4.6	4.7	4.5
Q1R	3035	NOT PREGNANT									
Q1R	3036	2	7	9	0	0	9	9	4.1	4.2	4.1
Q1R	3037	2	4	6	0	2	8	9	3.7	3.5	3.8
Q1R	3038	5	5	10	0	1	11	12	5.1	5.4	4.9
Q1R	3039	6	4	10	0	1	11	10	4.9	5.1	4.6
Q1R	3040	1	1	2	0	5	7	6	4.6	5.1	4.2
Q1R	3085	5	5	10	0	2	12	14	4.4	4.5	4.3
Q1R	3086	1	0	1	0	5	6	8	3.4	3.4	0.0
Q1R	3087	NOT PREGNANT									
Q1R	3088	5	6	11	0	0	11	11	3.9	4.1	3.8
Q1R	3089	3	1	4	0	1	5	8	4.5	4.5	4.6
Q1R	3090	NOT PREGNANT									
Q1R	3091	5	4	9	0	1	10	11	4.0	4.1	3.8
Q1R	3092	1	8	9	0	0	9	9	4.2	4.4	4.1
Q1R	3093	1	2	3	0	0	3	4	4.0	4.7	3.7
Q1R	3094	5	5	10	0	1	11	10	4.4	4.5	4.2
Q1R	3095	6	8	14	0	0	14	14	4.0	4.2	3.8
MEAN		3.7	4.8	8.5	0.0	1.1	9.6	10.1	4.3		
STAN. DEV.		1.8	2.5	3.6	0.0	1.5	2.8	2.5	0.4		

Appendix VI (Concluded)

Oral Teratology Study of T-2998CoC in Rats
Individual Litter Data with Mean Fetus Weights

ANIMAL		VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESORPTION SITES	IMPLANTATION SITES	CORPORA LUTEA	MEAN FETUS AVG	FETUS M	WT (G) F
0.05 mg/kg/day											
R1R	3041	4	7	11	0	0	11	11	4.7	5.0	4.5
R1R	3042	5	3	8	0	0	8	8	4.3	4.3	4.3
R1R	3043	4	6	10	0	0	10	11	4.6	4.7	4.5
R1R	3044	NOT PREGNANT									
R1R	3045	5	6	11	0	0	11	11	4.1	4.1	4.0
R1R	3046	6	4	10	0	0	10	10	4.4	4.6	4.1
R1R	3047	4	3	7	0	2	9	9	4.5	4.6	4.3
R1R	3048	3	9	12	0	1	13	15	4.4	4.6	4.3
R1R	3049	7	3	10	0	0	10	10	4.3	4.4	4.2
R1R	3050	3	2	5	0	0	5	8	4.5	4.5	4.4
R1R	3051	5	6	11	0	0	11	11	4.7	4.9	4.4
R1R	3052	6	7	13	0	0	13	13	4.0	4.1	4.0
R1R	3057	7	5	12	0	0	12	11	4.1	4.3	3.9
R1R	3058	6	5	11	0	0	11	10	4.2	4.3	4.1
R1R	3059	1	1	2	0	5	7	13	4.4	4.2	4.6
R1R	3100	7	2	9	1	0	10	10	4.2	4.4	3.6
R1R	3101	3	9	12	0	0	12	12	4.0	4.2	3.9
R1R	3102	7	4	11	0	0	11	11	4.5	4.6	4.3
R1R	3103	9	4	13	0	0	13	11	4.2	4.3	4.0
R1R	3104	3	5	8	0	0	8	9	4.6	4.5	4.6
R1R	3105	6	6	12	0	0	12	12	4.4	4.6	4.3
R1R	3106	7	6	13	0	1	14	14	4.1	4.0	4.2
MEAN		5.1	4.9	10.0	0.0	0.4	10.5	11.0	4.3		
STAN. DEV.		1.9	2.2	2.8	0.2	1.2	2.2	1.8	0.2		

003058

Appendix VII

Oral Teratology Study of T-2998CoC in Rats
Number of Fetuses by Dam with Skeletal Findings

0 mg/kg/day Dam Number	2997	2998	3000	3001	3002	3003	3004	3005	3006	3007	3052	3053	3054	3055	3056	3057	3058	3059	3061	3062
Total Number Fetuses	6	7	7	8	7	8	7	6	9	6	8	1	9	8	8	6	4	6	8	7
Fontanelle not closed	1	3	1	1	2		1		1	1			3	2	3	2		1	1	1
Frontals not ossified					2		1		3	1	1		2	4	2			1		
Parietals not ossified					2		1		3	1	1		2	4	2			1		
Interparietals not ossified					2		1		3	1	1		2	4	2			1		
Holes in pareitals																				1
Sternebrae not ossified	4	5	3	6	5	7	4	1	8	2	7		7	5	5	3	3	5	7	3
Sternebrae asymmetrical	1	2	1			1			2		2		1	1	2			1		
One sternebrae missing			2	1	2		3		2		1			4	1			1	1	2
Two sternebrae missing			2	1	2		1			2									1	
13 ribs			1				1													
13 ribs spurred			1		1		1								1					
Wavy ribs								1		1			2		2					1
Protrusion on ribs	1									1			2		1					1
One body vertebrae bipartite	1	1	1	3	3	4	1	2	5	1	1		2	1	2		2	2	1	2
Two bodies vertebrae bipartite		1				1		1		2								1		
Three bodies vertebrae bipartite													1							
Total Abnormal Fetuses	5	7	7	8	7	7	7	4	9	5	8	0	9	8	8	4	4	6	8	5
Total Normal Fetuses	1	0	0	0	0	1	0	2	0	1	0	1	0	0	0	2	0	0	0	2

Appendix VII (Continued)

Oral Teratology Study of T-2998CoC in Rats

Number of Fetuses by Dam with Skeletal Findings

150 mg/kg/day Dam Number	3008	3011	3012	3013	3015	3016	3018	3063	3064	3065	3068	3069	3070	3071
Total Number Fetuses	8	6	7	6	8	6	5	10	8	10	8	8	6	1
Fontanelle not closed			2	1		1		2	2	2	4	2	2	
Frontals not ossified			1					5		5	1	2		
Parietals not ossified			1					5		5	1	2		
Interparietals not ossified			1					5		5	1	1		
Sternebrae not ossified	1	2	6	4	3	6	4	9	6	6	3	8	5	1
Sternebrae bipartite		1												
Sternebrae asymmetrical		3		2		1				2	1		1	
One sternebrae missing		1			2	1	1	5	1	10	3	3	3	
Two sternebrae missing			1						1		5			
13 ribs					2									
13 ribs spurred	1				4	2		1				1	1	
Wavy ribs			2	1		2		2						
Protrusion on ribs			4	1		1		1						
One body vertebrae bipartite	3	1		1		3			1	2	2	2		
Two bodies vertebrae bipartite			1				1							
One body of vertebrae missing	1													
Total Abnormal Fetuses	5	4	7	6	6	6	4	10	7	10	8	8	6	1
Total Normal Fetuses	3	2	0	0	2	0	1	0	1	0	0	0	0	0

Appendix VII (Continued)

Oral Teratology Study of T-2998CoC in Rats
Number of Fetuses by Dam with Skeletal Findings

5 mg/kg/day Dam Number	3019	3020	3021	3022	3023	3024	3025	3026	3027	3028	3029	3074	3075	3076	3077	3078	3079	3080	3081	3083	3084
Total Number Fetuses	6[a]	6	7	9	7	8	10	6	6	7	6	7	8	8	8	9	6	6	8	5	7
Fontanelle not closed	3		1			1								3	1		1	3	2	2	
Frontals not ossified														2			1		2		
Parietals not osfified														2			1		2		
Interparietals not ossified														1			1				
Sternebrae not ossified	2	5	3	5	3	6	6	4	4	6	4	7	7	5	4	8	4	3	7	3	5
Stenrebrae asymmetrical	1	1				1			1	2		1		1	2				1		1
One sternebrae missing	2	4	2		1	2	5		1		1			3	4		4				
Two sternebrae missing	1	1	3	1			2														
13 ribs									1		1			1	1						
13 ribs spurred					1		2							2							
Wavy ribs														1	1	1					
Protrusion on ribs					3	1											1	1	1	1	4
One body vertebrae bipartite	2	2	1	1		3	1	2	3	3	2	2					1		2	2	2
Two bodies vertebrae bipartite	2	2	2									1							1		
Three bodies vertebrae bipartite			1								1										
Total Abnormal Fetuses	5	6	7	6	6	7	10	4	6	6	6	7	7	8	8	8	6	4	8	4	7
Total Normal Fetuses	1	0	0	3	1	1	0	2	0	1	0	0	1	0	0	1	0	2	0	1	0

[a] Results from one fetus are missing

Appendix VII (Continued)

Oral Teratology Study of T-2998CoC in Rats
Number of Fetuses by Dam with Skeletal Findings

1.5 mg/kg/day Dam Number	3030	3031	3032	3033	3034	3036	3037	3038	3039	3040	3085	3086	3088	3089	3091	3092	3093	3094	3095
Total Number Fetuses	7[a]	6	9	8	7	6	4	7	7	1	7	1	8	3	6	6	2	7	10
Fontanelle not closed				3				1	1				2	1	1	2		2	2
Frontals not ossified				2			1	1				1		1	1		1		1
Parietals not ossified				2			1	1				1		1	1		1		1
Interparietals not ossified				2			1	1				1					1		
Hole in frontal						1													
Sternebrae not ossified	1	5	5	3	4	1	3	5	4	1	6	1	6	1	3	6	2	6	8
Sternebrae asymmetrical	1	1			1		2	2	2		1							1	2
One sternebrae missing		3	3	1	1	1		2			1		3		1		2	1	
Two sternebrae missing				1			1												
Four sternebrae missing									1										
13 ribs								1											
13 ribs spurred				2						1					1	2			
Wavy ribs						2	1	1								1		1	
Protrusion on ribs						3	1												
One body vertebrae bipartite	1		4		2	2		2	3				1			1			1
Two bodies vertebrae bipartite				2															
Total Abnormal Fetuses	2	6	1	7	5	3	4	6	6	1	7	1	8	2	4	6	2	7	9
Total Normal Fetuses	5	0	2	1	2	3	0	1	1	0	0	0	0	1	2	0	0	0	1

[a] Results from one fetus are missing

Appendix VII (Concluded)

Oral Teratology Study of T-2998CoC in Rats
Number of Fetuses by Dam with Skeletal Findings

0.05 mg/kg/day Dam Number	3041	3042	3043	3045	3046	3047	3048	3049	3050	3051	3096	3097	3098	3099	3100	3101	3102	3103	3104	3105	3106
Total Number Fetuses	8	6	7	8	7	5	8	7	4	8	9	8	8	1	6	8	8	9	6	8	9
Fontanelle not closed			1	1				3	1		1	1	2			3	2	1			4
Frontals not ossified								1					1	1	1	1	1				3
Parietals not ossified								1					1	1	1	1	1				3
Interparietals not ossified								1								1	1				
Sternebrae not ossified	3	4	5	2	3	4	5	4	4	3	6	6	5	1	3	5	8	6	3	7	8
Sternebrae bipartite								1	1				1					1		1	
Sternebrae asymmetrical	2					1	1	1			2	1	1		1		1	2	1	2	2
One sternebrae missing		1		3	1	1	2	1	2				2		2		2		3		2
Two sternebrae missing				1	1			1													
13 ribs	2		1										1	1				1			
13 ribs spurred				1				1			2	1				1					
Wavy ribs																	1				2
Protrusion ribs																	2				1
One body vertebrae bipartite	1	2	1		2	2	2		1	1	1		1		2		2	4	1		2
Two bodies vertebrae bipartite	2		1		1											1					1
Three bodies vertebrae bipartite	1															1					
Total Abnormal Fetuses	7	5	6	7	7	4	8	6	4	3	7	6	7	1	4	7	8	8	6	7	9
Total Normal Fetuses	1	1	1	1	0	1	0	1	0	5	2	2	1	0	2	1	0	1	0	1	0

Appendix VIII

Oral Teratology Study of T-2998CoC in Rats
Number of Fetuses by Dam With Internal Findings

0 mg/kg/day Dam Number	2997	2998	3000	3001	3002	3003	3004	3005	3006	3007	3052	3053	3054	3055	3056	3057	3058	3059	3061	3062
Total Number of Fetuses	3	3	3	4	3	3	3	3	4	3	3	1	4	3	3	3	2	2	4	3
A cleft in the lens of one eye											1	1	1	1			1			
Enlarged renal pelvis		1		4				2	1	3			1		2	1		2		
Abdominal cavity full of blood												1				1				
Total Abnormal Fetuses	0	1	0	4	0	0	0	2	1	3	1	1	1	1	2	2	1	2	0	0
Total Normal Fetuses	3	2	3	0	3	3	3	1	3	0	2	0	3	2	1	1	1	0	4	3

Appendix VIII (Continued)

Oral Teratology Study of T-2998CoC in Rats
Number of Fetuses by Dam With Internal Findings

150 mg/kg/day Dam Number	3008	3011	3012	3013	3015	3016	3018	3063	3064	3065	3068	3069	3070	3071
Total Number Fetuses	3	2	3	3	3	2	2	4	4	5	4	4	3	1
A dark streak in the lens of one eye	1								1					
A dark streak & cleft in the lens of one eye									2				1	
A cleft in the lens of one eye		1		2						1			1	
A cleft in the lens of both eyes											1			
Enlarged renal pelvis							1							
Abdominal cavity full of blood									1			1	1	
Total Abnormal Fetuses	1	1	0	2	0	0	1	0	3	1	1	1	2	0
Total Normal Fetuses	2	1	3	1	3	2	1	4	1	4	3	3	1	1

Appendix VIII (Continued)

Oral Teratology Study of T-2998CoC in Rats
Number of Fetuses by Dam With Internal Findings

5 mg/kg/day Dam Number	3019	3020	3021	3022	3023	3024	3025	3026	3027	3028	3029	3074	3075	3076	3077	3078	3079	3080	3081	3083	3084
Total Number Fetuses	2	3	3	4	3	4	4	2	3	3	3	3	4	4	4	4	3	3	4	2	3
A cleft in the lens of one eye							1														
A cleft in the lens of both eyes			1																		
Hydronephrosis																1					
Enlarged renal pelvis							1		1							1	1				
Abdominal cavity full of blood		1											1			1					
Total Abnormal Fetuses	0	1	1	0	0	0	2	0	1	0	0	0	1	0	0	2	1	0	0	0	0
Total Normal Fetuses	2	2	2	4	3	4	2	2	2	3	3	3	3	4	4	2	2	3	4	2	3

Appendix VIII (Continued)

Oral Teratology Study of T-2998CoC in Rats

Number of Fetuses by Dam With Internal Findings

1.5 mg/kg/day	Dam Number	3030	3031	3032	3033	3034	3036	3037	3038	3039	3040	3085	3086	3088	3089	3091	3092	3093	3094	3095
Total Number Fetuses		3	3	4	3	3	3	2	3	3	1	3	0	3	1	3	3	1	3	4
A cleft in the lens of one eye				1	2	1	1				1									
Enlarged renal pelvis					1		1	1	1		1					2		1	1	
Abdominal cavity full of blood																			1	
Total Abnormal Fetuses		0	0	1	2	1	1	1	1	0	1	0		0	0	2	0	1	1	0
Total Normal Fetuses		3	3	3	1	2	2	1	2	3	0	3		3	1	1	3	0	2	4

003067

Appendix VIII (Concluded)

Oral Teratology Study of T-2998CoC in Rats
Number of Fetuses by Dam With Internal Findings

0.05 mg/kg/day Dam Number	3041	3042	3043	3045	3046	3047	3048	3049	3050	3051	3096	3097	3098	3099	3100	3101	3102	3103	3104	3105	3106
Total Number Fetuses	3	2	3	3	3	2	4	3	1	3	4	4	3	1	3	4	3	4	2	4	4
A dark streak in the lens of one eye			1								1										
A cleft in the lens of one eye			1					1													
A cleft in the lens of both eyes												1									
Enlarged renal pelvis	1			1		1				1	2						1	1		1	1
Abdominal cavity full of blood		1	1																		1
Total Abnormal Fetuses	1	1	2	1	0	1	0	1	0	1	3	1	0	0	0	0	1	1	0	1	2
Total Normal Fetuses	2	1	1	2	3	1	4	2	1	2	1	3	3	1	3	4	2	3	2	3	2

DISTRIBUTION LIST

M. T. Case

E. G. Gortner (original + 1)

F. Keller (QA files)

E. G. Lamprecht

E. L. Mutsch → R. A. Nelson → R. E. Ober

W. C. McCormick → F. D. Griffith (2)

W. H. Pearlson

G. R. Steffen → J. D. Henderson → K. L. Ebbens

003069

M. T. Case
E. G. Gortner (original + 1)
F. Keller (Q A Files)
E. G. Lamprecht

E. L. Mutsch → R. A. Nelson → R. E. Ober
W. C. McCormick → F. D. Griffith (2)
W. H. Pearlson
G. R. Steffen → J. D. Henderson → K. L. Ebbens

Amendment to the Final Report of the Oral Teratology
Study of T-2998CoC in Rats
Experiment No.: 0681TR0110
Issued 12/15/81

Please insert the amended page 3 to the above report. Five word changes were made in the last two paragraphs. The study conclusions are not changed by this amendment to the results and discussion section of the report.

E. G. Gortner 12/22/81
E. G. Gortner Date
Senior Research Technologist
Animal Teratology Reproduction

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

Maureen T Case 12/23/81
M. T. Case, DVM, PhD Date
Manager, Pathology-Toxicology
Safety Evaluation Laboratory

003070

Results and Discussion

T-2998CoC administered during the period of organogenesis was toxic to the high dose group (150 mg/kg/day) rats in causing low mean body weights during the dosing period. At gestational days 9, 12 and 15 (Table 1, Appendix V), the high dose group rats weighed significantly less than controls (0 mg/kg/day). The mean maternal body weights of the intermediate (5 mg/kg/day), mid (1.5 mg/kg/day), and low (0.05 mg/kg/day) dose groups were not different from the controls throughout the study.

Abnormal clinical signs were observed and deaths occurred only in the high dose group. Three rats in the high dose group died. All three of the rats that died were ataxic and two of the rats were pale for one to two days before death. The surviving high dose rats did not have abnormal clinical signs and signs of toxicity did not occur in lower dose animals.

T-2998CoC was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams. The mean number of male, female, total and dead fetuses, the mean number of resorption sites, implantation sites, corpora lutea and mean fetus weights of the four T-2998CoC dose groups were not significantly different from the control (Table 2, Appendix VI).

T-2998CoC did not cause compound-related abnormal gross fetal findings (Table 3), nor did T-2998CoC treatment produce fetal skeletal malformations (Table 4, Appendix VII). A significant higher incidence of the skeletal finding of one sternebrae missing occurred in the high dose group. One sternebrae missing is a minor skeletal aberration and was not considered a malformation in this study. Further, the incidence of the finding of one sternebrae missing was not different among the control group and the lower three treatment groups. The incidences of skeletal findings associated with delayed ossification and rib aberrations were not different among the five treatment groups.

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 anteriocentral region extending from beneath the lens epithelium to half-way through the lens posteriorly, a cleft at the anteriocentral lens region or a combination of lens discoloration and the presence of a cleft.

The lens findings observed under the dissecting microscope were interpreted histopathologically as a freehand sectioning artifact of a normal area of primary lens fiber degeneration. 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

cc: M. T. Case
E. G. Gortner (original +1)
F. Keller
E. G. Lamprecht
W. C. McCormick
R. A. Nelson
R. A. Prokop
L. O. Wiseth

TITLE: Protocol for Oral Teratology Study of T2998CoC[a] in Rats (Riker Experiment Number 0681TR0110).

OBJECTIVE: A teratology study will be used to evaluate the embryotoxic and teratogenic effects of orally administered T2998CoC to pregnant rats during the period of organogenesis. The procedure complies with the general recomendations of the FDA issued in January, 1966 ("Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use"). The study will be conducted according to the 1978 Good Laboratory Practice Regulations and 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: April, 1981.

TEST SYSTEM: One hundred and ten sexually mature, time mated Sprague-Dawley derived female rats from Charles River Breeding Laboratory 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 of historical control data 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: T2998CoC.

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.

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

[a] FC-143

Dose Level	Group Size
150 mg/kg/day	22
5 mg/kg/day	22
1.5 mg/kg/day	22
0.05 mg/kg/day	22
0 mg/kg/day	22

The oral route of administration will be used because metabolism studies showed radiolabeled T2998CoC was well absorbed. No dietary contaminants are known to interfere with the test article.

The animals will be observed daily from day 3 through day 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 dosed accordingly using a constant dose volume of 5 ml/kg of body weight.

The females will be killed on day 20 and the ovaries, uterus and its contents will be examined to determine: number of corpora lutea, number of fetuses (live and dead), number of resorption sites, number of implantation sites, pup weight and gross abnormalities. Approximately one-third of the pups will be fixed in Bouin's solution for subsequent free-hand sectioning by the Wilson technique to determine any visceral abnormalities using a dissecting microscope. Select eye sections can be sent to histopath of microscopic examination as deemed necessary by the study director. The remaining approximately two-thirds of the pups will be fixed in ethyl alcohol for subsequent skeletal examination after clearing and staining with alizarin red.

DATA ANALYSIS AND FINAL REPORT: The proposed statistical methods to be used for analysis of the data are: Dunnett's t test for dam and pup weights, number of fetuses, number of resorption sites, number of implantation sites and number of corpora lutea; Chi square for percent abnormalities. The proposed date for the final report is 2-3 months after detailed pup examinations have been completed (approximately third quarter, 1981).

E. G. Gortner 3-4-81
E. G. Gortner Date
Senior Research Technologist
Animal Teratology-Reproduction
Study Director

Elden G Lamprecht 3-4-81
E. G. Lamprecht, DVM, PhD Date
Research Veterinary Pathologist

Marvin T Case 3/4/81
M. T. Case, DVM, PhD Date
Manager, Pathology-Toxicology
Safety Evaluation Laboratory

William C. McCormick 3/9/81
W. C. McCormick, MS Date
Toxicologist
Sponsor Representative

003073