Oral Teratology Study of T-3141CoC in Rabbits

Experiment No.:	0681TB0398
Conducted At:	Safety Evaluation Laboratory Riker Laboratories, Inc. St. Paul, Minnesota
Dosing Period:	September 21, 1981 through November 6, 1981
Study Director:	E. G. Gortner

E. D. Gortner 2-18-82

E. G. Gortner Date
Senior Research Technologist
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Elden G. Lamprecht 2-19-82

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

Summary

Oral administration of distilled water solutions of T-3141CoC at doses of 0, 50, 5 and 1.5 mg/kg/day to pregnant New Zealand White/Minikin rabbits during gestational days 6 through 18 (period of organogenesis) was not embryotoxic and did not affect the ovaries or reproductive tract contents of the does. The compound did not cause gross, internal, or skeletal malformations of the fetuses. T-3141CoC was not teratogenic in the rabbit.

T-3141CoC administration was toxic to only the 50 mg/kg/day dose group pregnant animals. The high dose does, as a group, lost significantly more weight than the 0 mg/kg/day group does. No compound-related toxic clinical signs or deaths occurred in any of the compound-treated groups.

Introduction

A rangefinding study[a] determined that the T-3141CoC[b] was very toxic to pregnant rabbits at dose levels of 100 mg/kg/day and higher. The toxicity resulted in deaths within the first four days of dosing. The 50 mg/kg/day rabbits survived 13 days of dosing but lost a significant amount of body weight early in the dosing interval (days 6-9 gestation). The high dose level for a rabbit teratology study was set at 50 mg/kg/day based on the results of the rangefinding study.

This teratology study[c] in rabbits was conducted to evaluate the embryotoxic and teratogenic effects of orally administered T-3141CoC. 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 September 21 and November 6, 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

Sexually mature New Zealand White/Minikin female rabbits were obtained from Dutchland Laboratories, Inc., Denver, PA, and assigned cages according to a computer-generated random numbers table. The rabbits, ranging in weight from 1041 to 2813 grams, were then divided into four groups of 18 animals each. The rabbits were housed individually in stainless steel cages in a temperature and humidity controlled room. Food[d] and water were available ad libitum. The lights were on a 12 hour light/dark cycle. Each female rabbit was injected with 1 mg of pituitary luteinizing hormone via the ear vein before insemination. The does were then artificially inseminated with 0.5 ml of pooled diluted semen. The day of insemination was designated day 0 of pregnancy.

The animals were observed daily from days 3 through 29 of gestation for abnormal clinical signs. Body weights were recorded on gestational days 3, 6, 9, 12, 15, 18 and 29. The four groups were dosed with T-3141CoC dissolved in distilled water at 0, 50, 5 and 1.5 mg/kg/day. The solutions were administered daily using a constant dose volume of 1 ml/kg by oral intubation with a syringe and rubber catheter on gestational days 6 through 18. T-3141CoC characterization was provided by 3M Commercial Chemical Division, St. Paul, Minnesota (Appendix IV).

[a] Riker Experiment Number 0681RB0331
[b] FC-143
[c] Riker Experiment Number 0681TR0398
[d] Purina Rabbit Chow, Ralston Purina Co., St. Louis, MO

All surviving animals were euthanatized on gestational day 29. 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, fetal weights and sex, and gross fetal abnormalities. The fetuses were then placed in an incubator at 37°C for a 24-hour incubation period. Following the incubation period, all fetuses were killed and examined for internal abnormalities. The fetuses were then preserved in ethyl alcohol for clearing and staining of the skeleton with alizarin red to detect skeletal abnormalities.

Results and Discussion

The oral administration of T-3141CoC to pregnant rabbits during the period of organogenesis caused maternal toxicity only in the high dose group (50 mg/kg/day). The high dose does, as a group, lost significantly more weight than the control group (0 mg/kg/day) between day 6 (the initiation of dosing) and day 9 of the study (Table 1, Appendix V). The high dose does gained weight comparable to the controls after day 9 of gestation. The mid (5 mg/kg/day) and low (1.5 mg/kg/day) dose group mean maternal body weight gains were never significantly different from the control group. The failure of the low dose does to gain body weight comparable to the control group was due to one animal (Q1B2336) which consistantly lost weight during the dosing interval and eventually aborted and died. No compound-related clinical signs were unique to T-3141CoC treatment of pregnant rabbits.

Maternal deaths occurred during the study. Five of the six deaths were terminations due to broken backs or were due to intubation error. No deaths could be attributed directly to compound-related toxicity.

Reproductive function of the does and fetal survival were not affected by compound administration. The conception incidence, the incidences of abortions or does delivering early and the 24 hour incubation mortality incidence of the treated groups were not different from the control group (Table 2).

T-3141CoC was not embryotoxic and did not affect the ovaries or reproductive tract contents of the does. The number of male, female, total and dead fetuses, the mean number of resorption sites, implantation sites, corpora lutea and mean fetus weights of the three compound dosed groups were not significantly different from the control group (Table 3, Appendix VI).

No compound-related major gross fetal malformations were observed in any compound-dosed group. One low dose fetus had a clubbed forepaw (Table 4, Appendix VII). No internal fetal findings were observed (Table 5, Appendix VIII).

T-3141CoC treatment did not cause compound-related fetal skeletal malformations. The incidences of 13 ribs in the high dose group and 13 ribs spurred in the mid dose group were significantly higher than in the control

group (Table 6, Appendix IX). The findings involving the 13th rib are naturally occurring and were not considered malformations. Findings associated with skeletal ossifiction were not different among the four treatment groups. The oral administration of T-3141CoC to pregnant rabbits was not teratogenic at the dose levels tested.

Table 1

Oral Teratology Study of T-3141CoC in Rabbits
Mean Body Weight Gain or Loss (g) With Standard Deviations
of Pregnant Rabbits Between Gestational Day Weighings

Dose Group	DAY	3-6	9	12	15	18	29
0 mg/kg/day	MEAN	43	-1	18	50	48	103
	STAN. DEV	51.3	29.5	23.3	26.4	25.3	137.6
50 mg/kg/day	MEAN	52	-92[a]	31	70	53	166
	STAN. DEV	29.9	73.6	78.0	56.4	50.0	233.6
5 mg/kg/day	MEAN	21	3	6	56	41	200
	STAN. DEV	25.1	64.2	83.1	78.1	51.8	45.4
1.5 mg/kg/day	MEAN	45	-4	-1	29	41	205
	STAN. DEV	41.5	40.1	76.6	66.0	64.7	56.3

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

Table 2

Oral Teratology Study of T-3141CoC in Rabbits
Reproductive Performance and Fetal Mortality[a]

Dose Group	Total Number of Animals	Conception Incidence	%	Incidence of Abortions or Premature Deliveries	%	24 Hour Incubation Mortality Incidence	%
0 mg/kg/day	18	15/18	83	4/15	27	0/49	0
50 mg/kg/day	18	17/18	94	2/17	12	1/74	1
5 mg/kg/day	18	11/17[b]	64	0/11	0	0/71	0
1.5 mg/kg/day	17[c]	9/15[b]	60	1/9	11	1/45	2

[a] Treatment groups were not significantly different from the control group (Chi-square with Yates correction $p < 0.05$)
[b] One or more animals died early in study and pregnancies could not be determined
[c] One of 18 animals was terminated before the initiation of dosing because of a debilitating condition

Table 3

Oral Teratology Study of T-3141CoC in Rabbits
Mean Litter Data and Fetal Weights With Standard Deviations[a]

Dose Group	NO. OF ANIMALS	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESORPTION SITES	IMPLANTATION SITES	CORPORA LUTEA	MEAN WT. FETUS(G)
0 mg/kg/day	11	2.8	1.6	4.5	0.0	0.7	5.2	6.2	41.4
	STAN DEV	1.6	1.1	2.5	0.0	1.0	2.1	1.5	7.6
50 mg/kg/day	14	2.7	2.6	5.3	0.1	0.5	5.9	6.0	41.2
	STAN DEV	1.6	1.2	2.3	0.3	0.8	2.4	2.1	5.0
5 mg/kg/day	11	3.7	2.7	6.5	0.0	0.4	6.8	7.2	43.9
	STAN DEV	1.7	1.4	2.1	0.0	0.5	2.0	2.7	5.5
1.5 mg/kg/day	7	3.6	2.9	6.4	0.0	0.6	7.0	7.9	43.9
	STAN DEV	1.0	1.3	1.4	0.0	0.8	1.6	2.2	4.5

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

Table 4

Oral Teratology Study of T-3141CoC in Rabbits
Number of Fetuses With Gross Findings[a]

	Dose Groups			
	0 mg/kg/day	50 mg/kg/day	5 mg/kg/day	1.5 mg/kg/day
Total fetuses examined	49	74	71	45
Small	3 (6)	1 (1)	2 (3)	2 (4)
Clubbed forepaw				1 (2)

Table 5

Oral Teratology Study of T-3141CoC in Rabbits
Number of Fetuses With Internal Findings[b]

	Dose Groups			
	0 mg/kg/day	50 mg/kg/day	5 mg/kg/day	1.5 mg/kg/day
Total fetuses examined	49	74	71	45

[a] Treatment groups were not significantly different from the control group (Dunnett's t test $p < 0.05$)
[b] No findings were observed in the fetuses examined
( ) = percent of total examined

Table 6

Oral Teratology Study of T-3141CoC in Rabbits
Numbers of Fetuses With Skeletal Findings

	0 mg/kg/day		50 mg/kg/day		5 mg/kg/day		1.5 mg/kg/day	
No. of fetuses examined	49		74		71		45	
Fontanelle not closed	19	(30)	16	(22)	24	(34)	11	(24)
Holes in parietal	1	(2)	1	(1)				
Holes in both parietals							1	(2)
One sternebrae missing					1	(1)		
Sternebrae not ossified	7	(14)	16	(22)	11	(16)	10	(22)
Sternebrae asymmetrical	4	(8)	3	(4)	5	(7)	5	(11)
Extra sternebrae	1	(2)	1	(1)			1	(2)
Sternebrae fused	1	(2)	1	(1)				
13 ribs	8	(16)	28	(38)[a]	21	(30)	9	(20)
13 ribs spurred	3	(6)	12	(16)	18	(25)[a]	7	(16)
13 ribs floating	1	(2)			1	(1)	1	(2)

[a] Significantly higher than the control (Dunnett's t test $p < 0.05$)
( ) = percent of total examined

Appendix I

TITLE: Protocol for Oral Teratology Study of T-3141CoC[a] in Rabbits (Riker Experiment Number 0681TB0398).

OBJECTIVE: A teratology study will be used to evaluate the embryotoxic and teratogenic effects of orally administered T-3141CoC to pregnant rabbits 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: September, 1981.

TEST SYSTEM: Seventy-two sexually mature New Zealand White/Minikin rabbits from Dutchland Laboratories, Inc., will be housed in stainless steel cages with wire mesh floors in a temperature and humidity controlled room. This strain of rabbit will be used because historical control data is available. Purina Rabbit Chow and water will be available ad libitum. The lights will be on a 12 hour/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: Distilled water.

TEST ARTICLE: T-3141CoC.

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. The sponsor is responsible for retaining a reference sample of the test and control article, as required, for GLP compliance.

[a] FC-143

DOSAGE LEVELS AND EXPERIMENT DESIGN: The test article will be dissolved in distilled water daily. The test article solution and control article will be administered by oral intubation to the rabbits on days 6 through 18 of gestation according to the following:

Dose Level	Group Size
50 mg/kg/day	18
5 mg/kg/day	18
1.5 mg/kg/day	18
0 mg/kg/day	18

The oral route of administration will be used because toxicity has been defined by this route in a rangefinder study. No dietary contaminants are known to interfere with the test article.

On the day of breeding, each female will be given an intravenous injection of 1 mg of pituitary luteinizing hormone to induce ovulation. The does will then be artificially inseminated with 0.5 ml of pooled diluted semen collected from New Zealand White/Minikin male rabbits.

The animals will be observed daily from day 3 through day 29 of gestation for abnormal clinical signs. Body weights will be recorded on days 3, 6, 9, 12, 15, 18 and 29 of pregnancy and the rabbits dosed accordingly using a constant dose volume of 1 ml/kg of body weight.

The females will be killed on day 29 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. The pups will be placed in an incubator at 37° C for a 24 hour survival check. The following day the pups will be terminated and their viscera examined for any internal abnormalities. The pups will then be fixed in ethyl alcohol for subsequent skeletal examination after clearing and staining with alizarin red.

SAMPLES FOR POSSIBLE SPONSOR COMPOUND LEVEL ANALYSIS: A blood sample will be taken pre-dose, on day 18 and on day 29 of gestation from the same six rabbits at each dose level. A liver sample will be taken from the same rabbits on day 29 of gestation. The samples will be labeled, frozen and transferred to the sponsor.

These samples are not considered an integral part of the teratology evaluation of T-3141CoC in rabbits, that is they are not per se a part of the teratology study. They were taken at the sponsor's request because they may supply useful supplemental information. The samples will not necessarily be analyzed; the extent to which they are analyzed is a matter of scientific judgement by the sponsor. The results of these analyses, if and when they are completed, will be reported in a separate report. A copy of such report will be sent to the study director for inclusion in the Safety Evaluation Laboratory record archive file. Alternatively, the sponsor can notify Safety Evaluation that the samples will not be analyzed.

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 resporption 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 first quarter, 1982).

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
Venkateswa Pothapragada	Commercial Chemical - Analytical
Larry Winter	Commercial Chemical - Analytical
Loren O. Wiseth	Technician

APPENDIX III

STATEMENT OF QUALITY ASSURANCE

STUDY NUMBER: 0681TB0398

TITLE: Oral Teratology Study of T 3141 CoC in Rabbits

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
14 October 1981	16 October 1981
15 October 1981	21 October 1981
19 October 1981	27 October 1981
3 November 1981	11 November 1981
6 November 1981	11 November 1981
17 November 1981	1 December 1981
12 January 1982	27 January 1982
18 February 1982	19 February 1982

David C. Hamm

Compliance Audit
Riker Laboratories, Inc.

2/14/82
Date

Appendix IV

Oral Teratology Study of T-3141CoC in Rabbits
Test and Control Article Analytical Results

T-3141CoC Commercial Chemical Analytical Report #308

GLC of Methyl Esters

	Prestudy	Poststudy
C_6 Acid	0.2	.2
C_7 Acid	0.6	.4
C_8Acid (all isomers)	97.6	98.4
C_9 Acid	.8	.4
C_{10}Acid	.2	.2
C_x Acid	.5	.4

All values within experimental and integration parameters.

Elemental Analysis

Element	Theo.	Prestudy	Poststudy
F	66.13	66.2	65.9
C	22.27	22.2	22.2
N	3.24	3.5	3.6
H	0.92	0.7	0.7
O by diff.	7.42	7.4	7.6
F^-	0	68 ppm	68 ppm

MW = 431

Spectroscopic

Infrared spectra #16474-1 and 17958-1 are identical and match reference spectra.

NMR spectra H 8386, F 8388-9 (Pre) and F 10163-4 (Post) are identical and match reference spectra. The chain is 79% straight chain, 9% $(CF_3)_2CF^-$ branching and 12% back bone branched.

Conclusions

T-3141CoC has an analysis within specifications, is stable and is representative of commercial material.

Poststudy Control Article Commercial Chemical Analytical Report #294

Control Article	Theoretical mg/ml T-3141CoC	Actual mg/ml T-3141CoC
Distilled water	0.0	0.0

Appendix V

Oral Teratology Study of T-3141CoC in Rabbits Individual Body Weights(g) With Mean Body Weights and Standard Deviations for Pregnant Animals

DAY	3	6	9	12	15	18	29
0 MG/KG/DAY							
N1B	2121	1670	1697	1683	1704	1783	1840	1967
N1B	2122	1862	1905	1895	1909	1963	2047	2187
N1B	2123	2159	2198	2231	2273	2300	2346	2543
N1B	2124	1582	1659	1639	1683	1686	1754	1883
N1B	2127	1675	1670	1569	1612	1674	1718	1833
N1B	2128	1732	1769	1797	1859	1942	2039	2229
N1B	2129	1715	1786	1799	1840	1908	1962	2113
N1B	2686	2269	2317	2321	2314	2335	2422	2473
N1B	2688	2362	2352	2351	2342	2160	2387	2459
N1B	2701	2247	2281	2269	2262	2294	2314	2190
N1B	2702	2445	2490	2496	2528	2619	2650	2569
N1B	2703	2106	2186	2187	2175	2233	2277	2424
N1B	2704	2050	2123	2146	2149	2200	2225	2481
N1B	2717	2254	2279	2220	2227	2216	2327	2508
N1B	2718	1659	1818	1825	1848	1876	1910	2110
MEAN	1993	2016	2031	2050	2100	2148	2251	
STAN. DEV	204.	228.	229.	228.	226.	227.	234.	8
NON PREGNANT ANIMALS								
N1B	2340	1564	1577	1558	1551	1535	1554	1599
N1B	2685	1920	1760	1547	1863	2004	2139	2478
N1B	2687	1503	1574	1600	1589	1618	1691	1721

Appendix V (Continued)

Oral Teratology Study of T-3141CoC in Rabbits Individual Body Weights(g) With Mean Body Weights and Standard Deviations for Pregnant Animals

DAY	3	6	9	12	15	18	29
50 MG/KG/DAY							
018	2125	2232	2348	2122	2042	2094	2234	2464
018	2126	1681	1699	1659	1705	1789	1748	2034
018	2127	1574	1722	1644	1737	1760	1815	1808
018	2128	2270	2317	2175	2157	2246	2144	2499
018	2241	1860	1846	1627	1795	1823	1897	2124
018	2242	1880	1917	1704	1891	1909	1934	2133
018	2243	1571	1611	1543	1626	1677	1724	1965
018	2244	2342	2390	2220	2205	2277	2389	2577
018	2245	1629	1661	1562	1726	1795	1743	1960
018	2250	2046	2145	2118	2152	2270	2309	2537
018	2251	2011	2082	2020	2062	2188	2247	2525
018	2252	2057	2174	2117	2047	2102	2260	2540
018	2253	2413	2524	2547	2572	2660	2691	2902
018	2255	2672	2712	2710	2737	2814	2859	3102
018	2257	2004	2063	1973	1956	2069	0[a]	0
018	2258	1823	1902	1730	1867	1894	1930	2191
018	2259	2152	2242	2276	2230	2229	2226	2511
MEAN	2021	2085	1992	2024	2094	2147	2211	
STAN. DE	310.	227.	246.	332.	322.	333.	412.	5
NON PREGNANT ANIMALS								
018	2113	2158	2227	2153	2177	2141	2043	2226

[a] Animal died - intubation error

Appendix V (Continued)

Oral Teratology Study of T-3141CoC in Rabbits Individual Body Weights(g) With Mean Body Weights and Standard Deviations for Pregnant Animals

DAY	3	6	9	12	15	18	29
5 MG/KG/DAY							
F1B	2329	2277	2302	2221	2257	2281	2340	2483
F1B	2230	1531	1599	1583	1642	1723	1778	1915
F1B	2231	1672	1690	1686	1745	1802	1845	2088
F1B	2332	2256	2130	2321	2099	2205	2541	2764
F1B	2692	2611	2828	2941	2904	2816	2852	2975
F1B	2695	2056	2097	2127	2135	2199	2220	2460
F1B	2709	1675	1696	1747	1792	1835	1875	2072
F1B	2710	2117	2247	2270	2325	2394	2412	2686
F1B	2711	2242	2256	2302	2217	2239	2317	2463
F1B	2712	1996	2075	2135	2201	2279	2300	2526
F1B	2721	2196	2426	2437	2419	2428	2418	2676
MEAN	2108	2159	2162	2168	2225	2269	2369
STAN. DEV.	178	376	382	354	324	325	324	4
NON PREGNANT ANIMALS							
F1B	2345	1441	1963	1915	1969	1984	2018	2100
F1B	2346	1926	2638	2242	2473	2601	2961	2896
F1B	2347	1265	1628	1753	1878	1887	1989	2173
F1B	2348	1642	2056	2129	2224	2263	2281	2463
F1B	2694	2007	2042	0[a]	0	0	0	0
F1B	2696	1650	1717	1695	1716	1720	1772	1879
F1B	2722	1904	1939	1963	1841	1833	1874	1943

[a] Animal died - intubation error

Appendix V (Concluded)

Oral Teratology Study of T-3141CoC in Rabbits Individual Body Weights(g) With Mean Body Weights and Standard Deviations for Pregnant Animals

DAY	3	6	9	12	15	18	29	
1.5 MG/KG/DA								
016	2216	2072	2177	2081	1883	1748	1628	0[a]
016	2037	1838	1918	1952	1995	2060	2123	2401
016	2684	2030	2211	2208	2230	2217	2225	2451
016	2599	2277	2303	2351	2381	2454	2507	2629
016	1709	1637	1648	1674	1692	1762	1819	2047
016	[illegible]	[illegible]	2363	2367	2400	2398	2412	2719
016	[illegible]	[illegible]	2425	2413	2443	2439	2472	2761
016	[illegible]	2715	2805	2815	2843	2878	2853	3010
016	[illegible]	1990	1997	1972	1910	1906	1912	2081
MEAN	2152	2009	2084	2101	2110	2115	2517	
STDV.	DEV.	122.	0128.	0221.	3157.	4176.	4367.	5141. 6
NON PREGNANT ANIMALS								
016	2231	2072	2170	2214	2205	2354	2372	2754
016	2226	1900	1881	1862	1744	1740	1809	1871
016	2349	1717	2129	2198	2277	2327	2275	2337
016	2150	1454	1734	0[b]	0	0	0	0
016	2351	1272	1718	1819	1887	1947	1995	2057
016	1952	1041	1407	1[illegible]7[b]	1565	1625	1703	1874
016	2713	2104	0[b]	0	0	0	0	0
016	2723	1952	1982	0[b]	0	0	0	0

[a] Animal died - aborted four days before death
[b] Animal killed - broken back

Appendix VI

Oral Teratology Study of T-3141CoC in Rabbits
Individual Litter Data With Mean Fetus Weights

0 mg/kg/day

ANIMAL	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESOR PTION SITES	IMPLAN TATION SITES	CORPRA LUTEA	MEAN FETUS WT(G) AVG	M	F
2021	3	2	5	0	1	6	6	42.0	42.0	43.2
2222	2	1	3	0	0	3	8	42.3	41.3	44.2
2223	4	3	7	0	0	7	7	37.3	36.4	38.6
2224	1	0	1	0	1	2	4	54.3	54.3	0.0
2227	ABORTED									
2238	4	3	7	0	0	7	5	39.3	39.7	38.8
2239	0	1	1	0	1	2	4	57.3	0.0	57.3
2240	NOT PREGNANT									
2605	NOT PREGNANT									
2606	5	2	7	0	0	7	6	34.9	34.3	35.8
2607	NOT PREGNANT									
2608	ABORTED									
2701	ABORTED									
2702	Delivered Early									
2703	1	0	1	0	3	4	5	51.8	51.8	0.0
2704	4	2	6	0	0	6	8	39.9	38.9	41.9
2717	4	1	5	0	0	5	7	38.3	38.2	38.9
2718	2	3	6	0	2	8	8	38.7	38.4	38.9

Appendix VI (Continued)

Oral Teratology Study of T-3141CoC in Rabbits
Individual Litter Data With Mean Fetus Weights

50 mg/kg/day

ANIMAL	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESORPTION SITES	IMPLANTATION SITES	CORPRA LUTEA	MEAN FETUS WT(G) AVG	M	F
18 2325	2	3	5	0	0	5	6	40.2	44.1	37.5
18 2326	3	3	6	0	1	7	8	41.8	44.7	39.0
18 2327	ABORTED									
18 2328	3	4	7	1	2	10	10	38.7	36.2	37.1
18 2341	2	3	5	0	0	5	7	37.3	39.9	38.0
18 2342	2	2	4	0	0	4	4	39.4	36.9	41.8
18 2343	3	2	5	0	1	6	8	39.5	40.2	38.4
18 2344	0	1	1	0	1	2	2	47.9	0.0	47.9
18 2689	1	2	3	0	2	5	6	49.9	50.4	49.7
18 2690	3	3	6	0	0	6	8	34.9	34.0	36.5
18 2691	2	3	5	0	0	5	6	44.4	45.4	43.8
18 2692	5	4	9	0	0	9	8	37.5	40.1	34.2
18 2700	3	2	5	0	0	5	7	35.0	34.1	37.5
18 2705	1	0	1	0	0	1	1	45.3	45.3	0.0
18 2707	DEAD									
18 2708	2	3	5	0	0	5	8	46.0	45.7	46.2
18 2719	NOT PREGNANT									
18 2720	ABORTED									

Appendix VI (Continued)

Oral Teratology Study of T-3141CoC in Rabbits
Individual Litter Data With Mean Fetus Weights

5 mg/kg/day

ANIMAL		VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESOR PTION SITES	IMPLAN TATION SITES	CORPRA LUTEA	MEAN FETUS WT(G) AVG	M	F
1B	2329	3	5	8	0	0	8	7	34.2	31.2	36.0
1B	2330	1	1	2	0	1	3	6	50.9	52.2	49.6
1B	2331	6	2	8	0	0	8	7	37.8	37.9	38.1
1B	2332	5	2	7	0	1	8	7	37.2	37.7	35.9
1B	2345	NOT PREGNANT									
1B	2346	NOT PREGNANT									
1B	2347	NOT PREGNANT									
1B	2348	NOT PREGNANT									
1B	2683	4	3	7	0	0	7	5	36.0	36.3	35.5
1B	2684	DEAD									
1B	2685	4	2	6	0	1	7	5	40.1	40.3	39.7
1B	2686	NOT PREGNANT									
1B	2709	2	1	3	0	0	3	3	48.3	48.5	47.7
1B	2710	5	2	7	0	0	7	7	38.0	38.9	35.9
1B	2711	2	5	7	0	1	8	10	34.2	34.3	34.1
1B	2712	6	3	9	0	0	9	13	38.7	39.5	37.0
1B	2721	3	4	7	0	0	7	9	44.0	43.6	44.3
1B	2722	NOT PREGNANT									

Appendix VI (Concluded)

Oral Teratology Study of T-3141CoC in Rabbits
Individual Litter Data With Mean Fetus Weights

1.5 mg/kg/day

ANIMAL		VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESOR PTION SITES	IMPLAN TATION SITES	CORPRA LUTEA	MEAN FETUS WT(G) AVG	M	F
1B	2333	NOT PREGNANT									
1B	2335	NOT PREGNANT									
1B	2336	DEAD									
1B	2349	NOT PREGNANT									
1B	2350	DEAD									
1B	2351	NOT PREGNANT									
1B	2352	NOT PREGNANT									
1B	2697	3	3	6	0	1	7	9	46.2	46.1	46.3
1B	2698	4	1	5	0	0	5	5	34.7	33.9	38.1
1B	2699	4	2	6	0	1	7	7	40.4	40.1	40.9
1B	2700	3	2	5	0	0	5	7	38.8	40.8	35.9
1B	2713	DEAD									
1B	2714	2	5	7	0	0	7	8	37.9	29.3	41.3
1B	2715	4	3	7	0	2	9	7	40.1	39.3	41.1
1B	2716	5	4	9	0	0	9	12	37.7	38.1	37.1
1B	2723	DEAD									
1B	2724	ABORTED									

Appendix VII

Oral Teratology Study of T-3141CoC in Rabbits
Number of Fetuses by Dam With Gross Findings

Dose Group - 0 mg/kg/day

Dam No.	2321	2322	2323	2324	2338	2339	2686	2703	2704	2717	2718
Total fetuses examined	5	3	7	1	7	1	7	1	6	5	6
Small			2		1						

Dose Group - 50 mg/kg/day

Dam No.	2325	2326	2328	2341	2342	2643	2644	2689	2690	2691	2692	2705	2706	2708
Total fetuses examined	5	6	7	6	4	5	1	3	8	5	9	8	2	5
Small			1											

Dose Group - 5 mg/kg/day

Dam No.	2329	2330	2331	2332	2693	2695	2709	2710	2711	2712	2721
Total fetuses examined	8	2	8	7	7	6	3	7	7	9	7
Small	1								1		

Dose Group - 1.5 mg/kg/day

Dam No.	2697	2698	2699	2700	2714	2715	2716
Total fetuses examined	6	5	6	5	7	7	9
Small					2		
Clubbed forepaw		1					

Appendix VIII

Oral Teratology Study of T-3141CoC in Rabbits
Number of Fetuses by Dam With Internal Findings

Dose Group - 0 mg/kg/day

Dam No.	2321	2322	2323	2324	2338	2339	2686	2703	2704	2717	2718
Total fetuses examined	5	3	7	1	7	1	7	1	6	5	6

Dose Group - 50 mg/kg/day

Dam No.	2325	2326	2328	2341	2342	2343	2344	2689	2690	2691	2692	2705	2706	2708
Total fetuses examined	5	6	7	6	4	5	1	3	8	5	9	8	2	5

Dose Group - 5 mg/kg/day

Dam No.	2329	2330	2331	2332	2693	2695	2709	2710	2711	2712	2721
Total fetuses examined	8	2	8	7	7	6	3	7	7	9	7

Dose Group - 1.5 mg/kg/day

Dam No.	2697	2698	2699	2700	2714	2715	2716
Total fetuses examined	6	5	6	5	7	7	9

Oral Teratology Study of T-3141CoC in Rabbits
Number of Fetuses by Dam With Skeletal Findings

Dose Group - 0 mg/kg/day

Dam No.	2321	2322	2323	2324	2338	2339	2686	2703	2704	2717	2718
Number of fetuses examined	5	3	7	1	7	1	7	1	6	5	6
Fontanelle not closed	1	2	4		4		4		3		1
Holes in the parietal			1								
Sternebrae not ossified	1		1		2		1	1		1	
Sternebrae asymmetrical			1				1				2
Extra sternebrae									1		
Sternebrae fused											1
13 ribs	1	1	1	1		1	1			2	
13 ribs spurred			1		1				1		
13 ribs floating										1	

Dose Group - 50 mg/kg/day

Dam No.	2325	2326	2328	2341	2342	2343	2344	2689	2690	2691	2692	2705	2706	2708
Number of fetuses examined	5	6	7	6	4	5	1	3	8	5	9	8	2	5
Fontanelle not closed		2	2	3		2			1			4	1	1
Holes in the parietal			1											
Sternebrae not ossified		1		3	0	3		1	5			1	1	1
Sternebrae asymmetrical					1	1				1				
Extra sternebrae		1												
Sternebrae fused		1												
13 ribs	4	3	7	3	3			3	1			1		3
13 ribs spurred	1	2		2	1	1			2	2				1

Oral Teratology Study of T-3141CoC in Rabbits
Number of Fetuses by Dam With Skeletal Findings

Dose Group - 5 mg/kg/day

Dam No.	2329	2330	2331	2332	2693	2695	2709	2710	2711	2712	2721
Number of fetuses examined	8	2	8	7	7	6	3	7	7	9	7
Fontanelle not closed	2	1	5	2	3	1	1	1	2	5	1
Sternebrae not ossified	1				3	1		3	1	2	
Sternebrae asymmetrical						1		3		1	
One sternebrae missing								1			
13 ribs	7	1	3	3	1	3		1		3	
13 ribs spurred	1		3	3		1		2	2	2	3
13 ribs floating										1	

Dose Group - 1.5 mg/kg/day

Dam No.	2697	2698	2699	2700	2714	2815	2716
Number of fetuses examined	6	5	6	5	7	7	9
Fontanelle not closed		2	3	1	2	1	2
Holes in both parietals							1
Sternebrae not ossified		2	2	1		2	3
Sternebrae asymmetrical			1	1	3		
Extra sternebrae				1			
13 ribs			2	1	1	3	2
13 ribs spurred	1		1	2	1	2	
13 ribs floating							1

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