

Oral Rangefinder Study of T-2999CoC
in Pregnant Rabbits

Experiment No.: 0680RB0019

Conducted At: Safety Evaluation Laboratory
Riker Laboratories, Inc.
St. Paul, Minnesota

Dosing Period: February 1, 1981 to March 13, 1981

Study Director: E. G. Gortner

E. G. Gortner 6-25-81
E. G. Gortner Date
Senior Research Technologist
Animal Teratology Reproduction
Study Director

Elden H. Lamprecht 6-25-81
E. G. Lamprecht, DVM, PhD
Research Veterinary Pathologist

Martin T. Case 6/25/81
M. T. Case, DVM, PhD
Manager, Pathology-Toxicology
Safety Evaluation Laboratory

Introduction

This oral range-finder study^a was conducted to determine the upper dose level of T-2999CoC^b for a subsequent oral teratology study in rabbits. 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. The study was conducted in accordance with the Safety Evaluation Laboratory's Standard Operating Procedures for such studies. The storage location for the raw data and a copy of the final report is maintained in the Safety Evaluation Laboratory's record archives.

Methods

Sixty sexually mature New Zealand White/Minikin derived female rabbits from Dutchland Laboratories, Inc., were used in the study. Each female was injected with 1 mg of pituitary luteinizing hormone via the ear vein before breeding. The does were then artificially inseminated with 0.5 ml of pooled diluted semen. The day of insemination was designated day 0 of pregnancy.

Eight groups of 6 animals were dosed with T-2999CoC suspended daily in corn oil at 100, 75, 50, 25, 15, 12, 9 or 6 mg/kg/day. There were two sets of compound administration groups. Concurrent control animals dosed at 0 mg/kg/day T2999CoC in corn oil were present with both groups. All animals were dosed during days 6 through 18 of gestation by oral intubation with a syringe and rubber catheter using a constant dose volume of 1 ml/kg. The rabbits were housed individually in hanging stainless steel cages with wire mesh floors in a temperature and humidity controlled room. Purina Rabbit Chow and water were available ad libitum. The lights were on a 12 hour light/dark cycle. All animals were observed daily from day 3 of gestation until termination for abnormal clinical signs. Body weights were recorded on days 3, 6, 9, 12, 15, 18 and 29 of gestation and the rabbits were dosed accordingly. All surviving animals were euthanatized on either days 22 or 29 of gestation and each uterus, including its contents, was examined immediately to determine if the animal was pregnant.

Results and Discussion

First Group of Animals

The oral administration of T-2999CoC at doses of 100, 75, 50 or 25 mg/kg/day resulted in compound and dose related deaths and signs of abortion. Over 50% of the females died at the two higher dose levels and compound related deaths also occurred at the two lower dose levels. All dams at each compound dose level aborted or were in the process of resorbing their conceptuses (Table 2). Also all T-2999CoC groups had a negative body weight effect (Table 1). Because of the high death rate and compound related signs of abortion the animals were terminated at gestation day 22 of a 29 day study. All of the dose levels were too high to be tolerated during a rabbit teratology study. Therefore, a second group of animals were dosed at lower dose levels.

^a Riker Experiment No. 0680RB0019

^b FM-3924

Second Group of Animals

The oral administration of T-2999 CoC at doses of 15, 12, 9 or 6 mg/kg/day did not result in compound related deaths. The three deaths in the 9 mg/kg/day group were due to noncompound related events of intubation error, broken back or pneumonia. One surviving female in each of the 15, 12, 9 and 0 mg/kg/day groups aborted or was undergoing resorption (Table 2). However, these abortions and resorptions were not considered to be compound related. Abortions or resorptions did not occur in the 6 mg/kg/day group. All dose groups including the control group had reduced body weight gain at some point during gestation (Table 1), but generally it was more pronounced in the T-2999CoC animals.

Conclusion

The objective of determining an upper dose level for an oral rabbit teratology study was met with the second group of animals. The results suggest that the 15 mg/kg/day dose level would be an appropriate high dose in a rabbit teratology study as there was the toxic effect of reduced body weight gain and absence of compound related deaths. A majority of the conceptuses were maintained throughout pregnancy at the 15 mg/kg/day dose level.

Table 1

Oral Rangefinder Study of T-2999CoC
in Pregnant Rabbits
Mean Body Weight Gain or Loss of
Pregnant Rabbits With Standard Deviations (g)

	Group I					
	Day					
	6	9	12	15	18	
0 mg/kg/day	4	-27	-8	-23	-12	
	22.2	34.9	49.7	62.4	65.8	
100 mg/kg/day	29	-187	-169	-129	-116	
	94.2	71.8	24.6	49.3	*****	
75 mg/kg/day	3	-186	-132	-159	-146	
	10.7	23.8	30.2	22.1	78.5	
50 mg/kg/day	11	-176	-96	-128	-128	
	27.1	49.2	67.1	23.2	25.6	
25 mg/kg/day	22	-184	-98	-84	-76	
	24.5	63.3	56.4	20.2	33.9	
	Group II					
	Day					
	6	9	12	15	18	29
0 mg/kg/day	66	-43	5	3	-6	182
	89.1	37.2	8.9	16.0	45.1	111.2
15 mg/kg/day	59	-122	-52	41	6	209
	51.3	32.1	45.6	22.7	52.1	86.7
12 mg/kg/day	66	-132	-65	-11	42	236
	25.0	36.7	66.3	36.1	49.9	134.0
9 mg/kg/day	110	-149	-101	-77	-44	165
	86.6	84.5	94.4	70.8	182.2	64.1
6 mg/kg/day	71	-86	-32	25	11	243
	36.7	56.8	42.5	70.6	27.1	113.0

Table 2
Oral Rangefinder Study of T-2999CoC in Pregnant Rabbits
Death and Reproduction Results

Dose Group	Number Pregnant	Number Died	Number of Dams Aborted or with Total Resorbed Conceptuses
0 mg/kg/day	6	3	0
100 mg/kg/day	6	6	6
75 mg/kg/day	6	4	6
50 mg/kg/day	6	2	6
25 mg/kg/day	6	1	6
0 mg/kg/day	6	1	1
15 mg/kg/day	6	0	1
12 mg/kg/day	5	0	1
9 mg/kg/day	6	3	3 ^a
6 mg/kg/day	5	0	0

^a Two of the three dams died before the end of the study.

Oral Rangefinder Study of T-2999CoC
in Pregnant Rabbits
Individual Body Weights (g) and
Mean Body Weights With Standard
Deviation for Pregnant Rabbits

	Day					
	3	6	9	12	15	18
0 MG/KG/DAY						
N1B	157	1609	1626	1619	1649	0 ^a 0
N1B	156	2262	2232	2270	2291	2259 2298
N1B	159	2229	2248	2194	2111	0 ^a 0
N1B	160	2585	2568	2593	0 ^a 0	0
N1B	177	2215	2226	2170	2195	2237 2231
N1B	178	2133	2158	2145	2107	2025 1993
MEAN	2189	2193	2165	2071	2174	2161
STAN. DEV	325.	1312.	0314.	2247.	4129.	2182. 9

	Day					
	3	6	9	12	15	18
100 MG/KG/DAY						
01B	161	2056	2029	1860	1659	0 ^a 0
01B	162	1866	1887	1744	1582	1475 1358
01B	163	2513	2477	2339	2159	0 ^a 0
01B	164	2601	2615	1827	1678	0 ^a 0
01B	179	3636	3252	2922	2731	2634 0 ^a
01B	186	2669	2656	1895	1757	1570 0 ^a
MEAN	2257	2286	2098	1928	1893	1358
STAN. DEV	439.	7514.	0454.	7443.	2643.	5*****

^a Died

Appendix I (Continued)

6

Oral Rangefinder Study of T-2999CoC

in Pregnant Rabbits

Individual Body Weights (g) and
Mean Body Weights With Standard
Deviation for Pregnant Rabbits

	Day						
	3	6	9	12	15	18	

75 MG/KG/DAY							
F1B	165	2206	2216	2104	1954	1777	0 ^a
F1B	166	1650	1628	1431	1269	1126	0 ^a
F1B	167	2129	2128	1974	1836	1698	1607
F1B	168	2267	2270	2095	1964	0 ^a	0
F1B	169	1989	2005	1820	1737	1507	1355
F1B	182	0 ^a	0	0	0	0	1
MEAN	2068	2071	1885	1752	1546	1481	
STAN. DEV	265	0271	4278	5285	6290	3178	2

	Day						
	3	6	9	12	15	18	

50 MG/KG/DAY							
Q1B	169	1921	1919	1721	1567	0 ^a	0
Q1B	170	2072	2133	1915	1918	1790	1674
Q1B	171	2739	2723	2512	2329	0 ^a	0
Q1B	172	2197	2202	1997	1924	1816	1714
Q1B	183	2057	2055	1949	1885	1724	1563
Q1B	184	2507	2526	2404	2294	2177	2041
MEAN	2249	2260	2083	1986	1877	1748	
STAN. DEV	311	5304	3307	1285	2203	9205	5

^a Died

Appendix I (Continued)
 Oral Rangefinder Study of T-2999CoC
 in Pregnant Rabbits

Individual Body Weights (g) and
 Mean Body Weights With Standard
 Deviation for Pregnant Rabbits

		Day					
		3	6	9	12	15	18
25 MG/KG/DRY							
R1B	173	2141	2159	1949	1822	1715	1590
R1B	174	1738	1752	1860	1624	1552	1477
R1B	175	2286	2269	2092	1949	1844	1745
R1B	176	2022	2043	1908	1856	1794	1739
R1B	185	2038	2136	1905	1845	1767	1732
R1B	186	2713	2762	2499	2326	0 ^a	0
MEAN		2165	2187	2002	1904	1734	1658
STAN. DEV		323	8331	9280	4232	8112	1118

		Day						
		3	6	9	12	15	18	29
0 MG/KG/DRY								
N1B	515	1763	1960	1820	1832	1841	1869	2111
N1B	516	2181	2184	2198	2189	2175	2096	2413
N1B	517	1838	1947	1903	1916	1896	1822	1848
N1B	518	1579	1769	1713	1725	1746	1754	1840
N1B	525	2819	2968	2788	2791	2797	2749	2966
N1B	536	1923	1920	1965	1960	1918	1939	2246
MEAN		2032	2098	2055	2060	2062	2055	2237
STAN. DEV		422	4460	6295	8389	9387	2307	7421

^a died

Appendix I (Continued)
Oral Rangefinder Study of T-2999CoC
in Pregnant Rabbits

Individual Body Weights (g) and
Mean Body Weights With Standard
Deviation for Pregnant Rabbits

Day							
	3	6	9	12	15	18	29

10 MG/KG/DAY

01B	519	1872	1925	1822	1790	1842	1829	2017
01B	520	2127	2198	2055	1952	1962	1872	1927
01B	521	1940	1973	1825	1718	1725	1696	1979
01B	522	1876	1972	1827	1764	1840	1863	2152
01B	527	1622	1596	1468	1459	1479	1530	1735
01B	538	1848	1968	1907	1904	1983	2028	2269

MEAN 1881 1940 1817 1765 1805 1805 2013
STAN. DEV162. 6192. 8193. 3173. 6185. 3171. 0184. 8

Day							
	3	6	9	12	15	18	29

12 MG/KG/DAY

P1B	523	1794	1821	1753	1817	1764	1806	2031
P1B	524	2171	2222	2050	1961	1940	1984	2195
P1B	525	1768	1867	1721	1610	1601	1681	1806
P1B	526	1686	1766	1650	1569	1606	1642	1721
P1B	539	1962	2038	1890	1823	1796	1749	2109
P1B	540	1879	1944	1794	1680	1679	1776	2193

MEAN 1877 1943 1810 1743 1731 1773 2009
STAN. DEV172. 6166. 6142. 1149. 2129. 8119. 8201. 5

Oral Rangefinder Study of T-2999CoC

in Pregnant Rabbits

Individual Body Weights (g) and
Mean Body Weights With Standard
Deviation for Pregnant Rabbits

Day							
3	6	9	12	15	18	29	

9 MG/KG/DAY

01B	527	2468	2590	2512	2381	2247	1901	0 ^a
01B	528	2629	2673	1832	1783	1782	1871	2686
01B	529	1798	1884	1796	1538	1369	1372	0 ^a
01B	530	1699	1779	1712	1688	1653	1758	1946
01B	541	2634	2300	2645	2638	0 ^a	1	0
01B	542	2648	3111	2940	2800	2751	2675	2768

MEAN 2179 2290 2140 2038 1960 1915 2267
STAN. DEV 501. 6497. 4486. 6476. 6543. 9474. 1439. 8

Day							
3	6	9	12	15	18	29	

6 MG/KG/DAY

R1B	531	1828	1888	1742	1740	1752	1780	1966
R1B	532	1583	1690	1586	1558	1678	1679	1890
R1B	533	2070	2150	2090	1987	1911	1886	2316
R1B	534	1933	2027	1915	1938	1959	1964	2099
R1B	543	2278	2291	2276	2215	2263	2309	2564

MEAN 1938 2009 1922 1888 1913 1924 2167
STAN. DEV 260. 4232. 4273. 4250. 6226. 8240. 8274. 6

^a Died