

Oral Rangefinder Study of T-2999CoC
in Pregnant Rabbits

0680RB.0019

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

February 1, 1981 to March 13, 1981

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Introduction

This oral rangefinder 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.

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Table 1

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

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	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	55.8	
100 mg/kg/day	29	-187	-169	-129	-116	
	94.2	71.8	24.6	49.3	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	24
0 mg/kg/day	66	-43	5	3	-6	182
	59.1	37.3	8.8	16.0	45.1	151.2
15 mg/kg/day	99	-122	-52	41	0	209
	51.3	23.1	45.6	22.7	52.1	86.7
12 mg/kg/day	66	-132	-60	-11	42	236
	25.0	36.7	66.3	30.1	49.9	131.0
9 mg/kg/day	110	-149	-101	-77	-44	165
	80.6	84.5	94.4	70.8	182.2	64.1
6 mg/kg/day	71	-88	-33	25	11	243
	36.7	56.8	49.5	70.6	27.1	113.0

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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.

Appendix I

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Oral Rangefinder Study of T-2999CoC

in Pregnant Rabbits

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

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	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	166	2585	2568	2593	0 ^a 0	0
N1B	177	2215	2226	2170	2195	2237 2231
N1B	178	2133	2158	2145	2167	2025 1953
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	2015	1827	1678	0 ^a 0
01B	179	3036	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*****	

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

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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							
P1B	165	2206	2216	2104	1954	1777	0 ^a
P1B	166	1650	1628	1431	1269	1126	0 ^a
P1B	167	2129	2128	1974	1836	1698	1607
P1B	168	2267	2270	2095	1964	0 ^a	0
P1B	181	1989	2005	1820	1737	1557	1355
P1B	182	0 ^a	0	0	0	0	1
MEAN	2068	2071	1885	1752	1540	1481	
STAN. DEV	265.	8271.	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

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Appendix I (Continued)

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

	Day					
	3	6	9	12	15	18
25 MG/KG/DAY						
R1B	172	2141	2159	1949	1822	1715 1595
R1B	174	1738	1752	1660	1624	1552 1477
R1B	175	2286	2269	2092	1949	1844 1745
R1B	176	2022	2043	1908	1856	1794 1739
R1B	185	2088	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. 7

	Day						
	3	6	9	12	15	18	29
0 MG/KG/DAY							
N1B	515	1762	1900	1820	1832	1841	1869 2111
N1B	516	2181	2184	2198	2189	2175	2096 2413
N1B	517	1823	1947	1903	1916	1896	1922 1846
N1B	518	1679	1769	1713	1725	1746	1754 1840
N1B	525	2819	2868	2788	2791	2797	2749 2966
N1B	526	1923	1926	1905	1901	1918	1939 2246
MEAN	2032	2098	2055	2066	2062	2055	2227
S. AN. DEV	422.	4460.	6395.	8389.	9387.	3357.	7421 6

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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	21	24
10 MG/KG/DAY									
01B	519	1872	1935	1822	1790	1842	1839	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. DEV		162.6	192.8	193.3	173.6	185.3	171.0	184.8	

		Day							
		3	6	9	12	15	18	21	24
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. DEV		172.6	166.6	142.1	149.2	129.8	119.8	201.5	

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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							
Q1B	527	2468	2590	2512	2381	2247	1901
Q1B	528	2629	2673	1832	1783	1782	1871
Q1B	529	1798	1884	1796	1538	1369	1372
Q1B	530	1699	1779	1712	1688	1653	1758
Q1B	541	2634	2300	2045	2038	0 ^a	1
Q1B	542	2048	3111	2940	2800	2751	2675
MEAN	2179	2296	2140	2038	1960	1915	2267
STAN. DEV	501	6497	4486	6476	6543	9474	1439

	Day						
	3	6	9	12	15	18	29
6 MG/KG/DAY							
R1B	531	1828	1888	1742	1740	1752	1780
R1B	532	1583	1690	1586	1558	1678	1679
R1B	533	2070	2150	2090	1987	1911	1886
R1B	534	1933	2027	1915	1938	1959	1964
R1B	543	2278	2291	2276	2215	2263	2309
MEAN	1938	2009	1922	1888	1913	1924	2167
STAN. DEV	260	4232	4273	4250	8226	8240	8274

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