

A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS


\*\*\*\*\*  
 \*THIS STUDY IS NOT INTENDED TO SUPPORT APPLICATIONS FOR\*  
 \*RESEARCH OR MARKETING PERMITS FOR PRODUCTS REGULATED\*  
 \*BY GOVERNMENTAL AGENCIES. THIS IS AN EXPLORATORY/\*  
 \*RANGE-FINDING STUDY AND IS NOT WITHIN THE SCOPE OF\*  
 \*GOOD LABORATORY PRACTICE REGULATIONS.\*  
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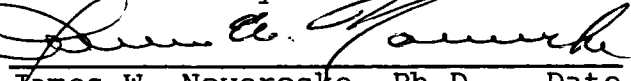
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Safety Assessment Project Number 2453


Department of Product Safety Assessment  
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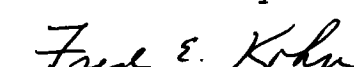
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# A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

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DEPARTMENT OF PRODUCT SAFETY ASSESSMENT

G. D. Searle & Co.  
Skokie, IL

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\*THE SCOPE OF GOOD LABORATORY PRACTICE REGULATIONS.\*  
\*\*\*\*\*

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Study No.: S.A. 2453

Date: January 29, 1985

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Summary:

SC-19129 was administered by diet admix to pregnant rats at intended dosage levels of 125, 250, 500, 750 and 1000 mg/kg/day for 10 consecutive days (days 6 through 15 of gestation). A control group received the standard diet.

Actual average dosage levels of SC-19129 from days 6 through 15 of gestation were 125, 243, 510, 764 and 996 mg/kg/day. No compound-related deaths or clinical signs occurred at any dosage level.

Average maternal body weight gain and food consumption were unaffected at all dosage levels.

Examination of the reproductive status of females at sacrifice revealed no adverse effects of SC-19129 on average numbers of implantations, resorptions, and live or dead fetuses per litter at intended dosage levels of 125, 250, 500 or 750 mg/kg/day. At an intended dosage level of 1000 mg/kg/day, there was an increase in the average number of resorptions.

S.A. 2453

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

### INTRODUCTION

This study was conducted to determine potential toxic effects of SC-19129 as evidenced by clinical signs, body weights, fetal viability, and to provide a basis for dosage level selection in teratology/reproduction studies.

### MATERIALS AND METHODS

Sixty virgin female rats (Charles River COBS CD strain, Portage, MI) approximately eleven weeks of age and weighing 209 to 251 g, were divided into 6 groups of 10 rats each for this study.

Female rats were placed with males (1 or 2 females/male) of the same strain. Each morning during the breeding period, a vaginal lavage was taken from the females. Upon detection of spermatozoa in the vaginal lavage (day 1 of gestation) the mated females were randomly assigned to treatment groups and given an ear tag with a unique number. The females were then housed in individual suspended, stainless steel, wire mesh cages, and given free access to Certified Purina Rat Chow Meal # 5002 and to municipally supplied tap water.

The animal room was set to maintain a  $72^{\circ} \pm 5^{\circ}\text{F}$  temperature and 25% or greater relative humidity with a 12-hour light and 12-hour dark cycle. The study was started on October 17, 1984 and terminated on November 9, 1984.

SC-19129, N-L- $\beta$ -aspartyl-L-phenylalanine,1-methyl ester (Lot #84K-047-101), was given to the 5 groups of rats for 10 consecutive days. SC-19129/Certified Purina Rat Chow Meal # 5002 diet admix preparations were made at levels of 125, 250, 500, 750 and 1000 mg/kg/day. Actual average dosage levels (Tables 4 and 8) were 125, 243, 510, 764, and 996 mg/kg/day. Dosage calculations (Days 6-13, and 13-16) were based upon cumulative average food consumption and body weights of the first animals to reach appropriate stages of gestation (Days 5 and 12, respectively). Historical body weight data was also used to anticipate maternal weight gains. The control group received the standard diet ad libitum.

The identity, strength, purity, and composition of the test article were determined before use in this study. The results of the test article analyses are shown in Appendix B.

Body weights of rats were recorded on days 1, 6, 8, 10, 12, 14, 16, and 21 of gestation. The rats were examined daily for adverse clinical signs throughout the study, sacrificed by CO<sub>2</sub> inhalation on day 21 of gestation, and examined to obtain the numbers of corpora lutea, implantations, resorptions, and live or dead fetuses.

Maternal body weights, body weight changes, and food consumption were analyzed using a one-way analysis of variance, and if the ANOVA F-test was significant at the 5% level, Student's t-tests (using the pooled error variance from the one-way analysis of variance) of control versus the other dose groups were performed. A Bartlett-Box test for homogeneity of variance was done. The Kruskal-Wallis test

was used to analyze the following variables: numbers of implantations, resorptions, and live fetuses per litter. If significant at the 5% level, then the Mann-Whitney U test was used to compare the control to each compound-treated group. Numbers of corpora lutea were not analyzed or tabulated in this report. All t-tests were two-tailed and significance levels achieved have been reported for 5% for t-tests, Bartlett-Box tests, and Mann-Whitney U tests.

The study was conducted at G. D. Searle & Co., and the final report, protocol, raw data, and supporting documents are on file at G. D. Searle & Co., Skokie, Illinois.

A list of the study professionals that participated in the study is as follows:

Laboratory Animal Resources	J. Erickson
Analytical Coordinator	K. Pilipauskas
Biostatistics	P. Sanders
Teratology	G. Chmielewski
Product Development	J. Jiu
Analytical Department	

## RESULTS AND DISCUSSION

From days 6 to 16 gestation, average dosage levels of SC-19129 (Tables 4 and 8) administered by diet admix were 125, 243, 510, 764 and 996 mg/kg/day. No compound-related deaths or clinical signs occurred at any dosage level.

Average maternal body weight gain and food consumption were unaffected at all dosage levels (Tables 1, 3, 5 and 7).

Examination of the reproductive status of females at sacrifice (Tables 2 and 6) revealed that the average numbers of implantations, resorptions, and live or dead fetuses per litter were unaffected by SC-19129 at intended dosage levels of 125, 250, 500 and 750 mg/kg/day. At the intended dosage level of 1000 mg/kg/day, there was a significant increase ( $p < 0.05$ ) in the average number of resorptions compared to that of the control group.

## COMPLIANCE STATEMENT

Although this is a range-finding study and not within the scope of Good Laboratory Practice regulations, the laboratory phase was conducted with the intention of complying with the GLP regulations. One known deviation occurred as follows:

1. Animal room humidity levels fell below protocol specified limits on October 23 and 24, November 1-3, and November 5, 1984.

However, this deviation did not affect the quality or integrity of the study and this report accurately reflects the data obtained during the performance of the study.



TABLE 1

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

## Maternal Body Weights

		(mg/kg/day)				
	Control	125	250	500	750	1000
Average Body Weight (g)						
Day 1	231	232	234	226	233	227
Day 6	255	249	255	248	252	251
Day 8	260	257	261	255	261	259
Day 10	272	265	270	266	270	269
Day 12	273	272	269	265	271	270
Day 14	286	280	282	283	284	285
Day 16	299	294	295	288	296	296
Day 21	365	353	355	351	355	351
Change						
Days 1-6	+ 24	+ 17	+ 21	+ 22	+ 20	+ 24
Days 6-16	+ 44	+ 45	+ 40	+ 40	+ 44	+ 45
Days 16-21	+ 66	+ 59	+ 60	+ 63	+ 59	+ 55
Days 1-21	+134	+121	+121	+125	+123	+125

TABLE 2  
A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS  
Reproductive Status Of Females At Sacrifice

		(mg/kg/day)				
	Control	125	250	500	750	1000
Females						
Total No.	10	10	10	10	10	9 <sup>a</sup>
No. Live Pregnant	10	9	10	9	9	8
No. Live Not Pregnant	0	1	0	1	1	1
Implantations						
Total No.	144	119	142	119	115	118
No./Pregnant Female	14.4	13.2	14.2	13.2	12.8	14.8
Resorptions						
Total No.	3	6	8	5	4	22
No./Pregnant Female	0.3	0.7	0.8	0.6	0.4	2.8*
Fetuses						
Total No.	141	113	134	114	111	96
No. Live	140	113	134	114	111	96
No. Dead	1	0	0	0	0	0
No. Live/Pregnant Female	14.0	12.6	13.4	12.7	12.3	12.0
No. Dead/Pregnant Female	0.1	0.0	0.0	0.0	0.0	0.0

\*Significantly different ( $p < 0.05$ ) from control

<sup>a</sup>One rat (#84-2150) removed from study prior to the initiation of compound administration because of poor health

TABLE 3  
A Range-Finding Study of SC-19129 in Pregnant Rats  
Maternal Food Consumption

	Control	mg/kg/day				
		125	250	500	750	1000
Average Daily Food Consumption (g)						
Days 1-6	21.0	19.8	20.3	20.6	20.7	20.3
Days 6-13	21.8	21.6	20.8	21.5	22.1	21.5
Days 13-16	24.1	23.6	23.8	24.4	24.4	23.8
Days 6-16	22.5	22.2	21.7	22.4	22.8	22.2
Days 16-21	25.6	25.3	25.2	25.6	25.9	25.9

TABLE 4

## A Range-Finding Study of SC-19129 in Pregnant Rats

## Actual Average Maternal Dosage Levels

	Control	mg/kg/day				
		125	250	500	750	1000
Average Dosage Levels (mg/kg/day)						
Days 6-16	0	125	243	510	764	996

TABLE 5

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

## Individual Female Body Weights (g)

## Control Group

Female	Reproductive Status	Gestation Day							
		1	6	8	10	12	14	16	21
84-2100	Pregnant	225	246	251	264	269	274	287	355
84-2101	Pregnant	244	263	269	284	286	288	298	358
84-2102	Pregnant	210	236	243	250	258	259	270	330
84-2103	Pregnant	233	250	249	266	270	275	288	360
84-2104	Pregnant	230	255	257	271	271	282	294	341
84-2105	Pregnant	218	246	251	263	253	282	296	365
84-2106	Pregnant	242	263	269	282	277	303	314	393
84-2107	Pregnant	238	263	268	279	278	297	310	386
84-2108	Pregnant	235	271	279	294	296	317	328	393
84-2109	Pregnant	238	255	268	263	273	283	305	367

TABLE 5 (cont.)

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

Individual Female Body Weights (g)

125 mg/kg/day Group

Female	Reproductive Status	Gestation Day							
		1	6	8	10	12	14	16	21
84-2110	Pregnant	241	260	267	281	288	291	300	344
84-2111	Pregnant	236	259	268	280	281	289	298	360
84-2112	Pregnant	237	245	253	261	269	272	288	350
84-2113	Pregnant	224	244	247	256	260	272	287	354
84-2114	Pregnant	228	242	250	262	269	283	292	365
84-2115	Pregnant	224	252	259	270	278	287	296	363
84-2116	Pregnant	236	262	268	276	282	295	309	370
84-2117	Not Pregnant	226	247	252	259	258	259	256	255
84-2118	Pregnant	231	242	243	250	254	265	287	345
84-2119	Pregnant	234	236	254	252	270	266	290	327

TABLE 5 (cont.)

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

Individual Female Body Weights (g)

250 mg/kg/day Group

Female	Reproductive Status	Gestation Day							
		1	6	8	10	12	14	16	21
84-2120	Pregnant	246	256	266	280	278	286	293	335
84-2121	Pregnant	227	264	270	283	286	286	304	365
84-2122	Pregnant	224	242	244	252	256	259	266	319
84-2123	Pregnant	237	256	261	274	278	284	298	367
84-2124	Pregnant	237	270	271	279	276	296	307	377
84-2125	Pregnant	230	255	261	271	269	286	293	344
84-2126	Pregnant	233	259	265	273	265	298	311	371
84-2127	Pregnant	240	258	263	269	264	282	300	372
84-2128	Pregnant	227	240	240	249	243	255	265	324
84-2129	Pregnant	240	253	266	266	276	285	312	378

TABLE 5 (cont.)

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

Individual Female Body Weights (g)

500 mg/kg/day Group

Female	Reproductive Status	Gestation Day							
		1	6	8	10	12	14	16	21
84-2130	Pregnant	222	245	255	263	265	274	275	301
84-2131	Pregnant	225	245	251	260	269	276	293	355
84-2132	Pregnant	219	250	255	269	272	285	291	362
84-2133	Pregnant	231	262	265	279	270	289	306	369
84-2134	Pregnant	239	249	255	266	266	285	293	366
84-2135	Pregnant	219	235	249	260	248	276	288	348
84-2136	Pregnant	229	246	250	257	257	282	296	370
84-2137	Pregnant	229	251	257	272	267	282	290	356
84-2138	Pregnant	224	250	258	270	267	296	264	332
84-2139	Not Pregnant	240	265	278	282	288	282	276	273



TABLE 5 (cont.)

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

Individual Female Body Weights (g)

750 mg/kg/day Group

Female	Reproductive Status	Gestation Day							
		1	6	8	10	12	14	16	21
84-2140	Pregnant	226	247	256	266	271	282	294	359
84-2141	Not Pregnant	236	266	271	284	279	280	273	276
84-2142	Pregnant	219	239	246	260	263	270	284	351
84-2143	Pregnant	248	275	283	297	292	314	332	410
84-2144	Pregnant	240	266	268	283	276	295	302	332
84-2145	Pregnant	224	237	246	256	252	273	285	348
84-2146	Pregnant	248	263	268	273	271	280	292	360
84-2147	Pregnant	215	234	249	254	249	269	274	316
84-2148	Pregnant	224	238	249	248	262	265	280	332
84-2149	Pregnant	251	273	287	289	301	308	323	391

TABLE 5 (cont.)

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

Individual Female Body Weights (g)

1000 mg/kg/day Group

Female	Reproductive Status	Gestation Day							
		1	6	8	10	12	14	16	21
84-2151	Pregnant	239	268	278	289	295	298	311	375
84-2152	Pregnant	222	246	254	264	273	276	285	343
84-2153	Pregnant	219	240	248	258	242	272	284	343
84-2154	Not Pregnant	235	257	264	273	265	277	272	274
84-2155	Pregnant	229	252	255	263	264	283	291	334
84-2156	Pregnant	227	243	248	262	262	279	285	337
84-2157	Pregnant	236	262	270	284	281	300	314	370
84-2158	Pregnant	209	244	253	263	264	284	292	336
84-2159	Pregnant	234	251	267	265	280	290	306	373

TABLE 6

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

## Individual Fetal Data

## Control group

Animal Number	Reproductive Status	Number of			
		Implant- ations	Resorp- tions	Live Fetuses	Dead Fetuses
84-2100	Pregnant	15	1	14	0
84-2101	Pregnant	13	1	12	0
84-2102	Pregnant	15	0	15	0
84-2103	Pregnant	16	0	15	1
84-2104	Pregnant	12	0	12	0
84-2105	Pregnant	14	0	14	0
84-2106	Pregnant	16	0	16	0
84-2107	Pregnant	16	0	16	0
84-2108	Pregnant	13	0	13	0
84-2109	Pregnant	14	1	13	0

TABLE 6 (cont.)

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

## Individual Fetal Data

125 mg/kg/day group

Animal Number	Reproductive Status	Number of			
		Implant- ations	Resorp- tions	Live Fetuses	Dead Fetuses
84-2110	Pregnant	7	0	7	0
84-2111	Pregnant	13	0	13	0
84-2112	Pregnant	15	1	14	0
84-2113	Pregnant	16	0	16	0
84-2114	Pregnant	15	0	15	0
84-2115	Pregnant	18	4	14	0
84-2116	Pregnant	12	1	11	0
84-2117	Not Pregnant	0	0	0	0
84-2118	Pregnant	14	0	14	0
84-2119	Pregnant	9	0	9	0

TABLE 6 (cont.)

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

## Individual Fetal Data

250 mg/kg/day group

Animal Number	Reproductive Status	Number of			
		Implant- ations	Resorp- tions	Live Fetuses	Dead Fetuses
84-2120	Pregnant	5	0	5	0
84-2121	Pregnant	13	1	12	0
84-2122	Pregnant	13	1	12	0
84-2123	Pregnant	16	0	16	0
84-2124	Pregnant	16	0	16	0
84-2125	Pregnant	16	3	13	0
84-2126	Pregnant	16	1	15	0
84-2127	Pregnant	16	0	16	0
84-2128	Pregnant	15	2	13	0
84-2129	Pregnant	16	0	16	0

TABLE 6 (cont.)

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

## Individual Fetal Data

500 mg/kg/day group

Animal Number	Reproductive Status	Number of			
		Implant- ations	Resorp- tions	Live Fetuses	Dead Fetuses
84-2130	Pregnant	2	0	2	0
84-2131	Pregnant	15	1	14	0
84-2132	Pregnant	15	0	15	0
84-2133	Pregnant	14	0	14	0
84-2134	Pregnant	15	1	14	0
84-2135	Pregnant	14	1	13	0
84-2136	Pregnant	15	1	14	0
84-2137	Pregnant	15	0	15	0
84-2138	Pregnant	14	1	13	0
84-2139	Not Pregnant	0	0	0	0

TABLE 6 (cont.)

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

## Individual Fetal Data

750 mg/kg/day group

Animal Number	Reproductive Status	Number of			
		Implant- ations	Resorp- tions	Live Fetuses	Dead Fetuses
84-2140	Pregnant	15	1	14	0
84-2141	Not Pregnant	0	0	0	0
84-2142	Pregnant	14	0	14	0
84-2143	Pregnant	16	0	16	0
84-2144	Pregnant	5	1	4	0
84-2145	Pregnant	15	1	14	0
84-2146	Pregnant	15	1	14	0
84-2147	Pregnant	6	0	6	0
84-2148	Pregnant	14	0	14	0
84-2149	Pregnant	15	0	15	0

TABLE 6 (cont.)

## A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RATS

## Individual Fetal Data

1000 mg/kg/day group

Animal Number	Reproductive Status	Number of			
		Implant- ations	Resorp- tions	Live Fetuses	Dead Fetuses
84-2151	Pregnant	17	3	14	0
84-2152	Pregnant	17	4	13	0
84-2153	Pregnant	14	2	12	0
84-2154	Not Pregnant	0	0	0	0
84-2155	Pregnant	9	1	8	0
84-2156	Pregnant	15	3	12	0
84-2157	Pregnant	14	2	12	0
84-2158	Pregnant	16	7	9	0
84-2159	Pregnant	16	0	16	0



TABLE 7

## A Range-Finding Study of SC-19129 in Pregnant Rats

Individual Average Daily Food Consumption (g)

Control Group

Female	Reproductive Status	Gestation Period (days)			
		1-6	6-13	13-16	16-21
84-2100	Pregnant	20.6	20.3	23.7	24.4
84-2101	Pregnant	20.2	21.0	24.0	25.2
84-2102	Pregnant	20.0	20.3	22.7	23.2
84-2103	Pregnant	21.0	18.6	22.0	23.8
84-2104	Pregnant	22.4	23.3	23.7	25.2
84-2105	Pregnant	20.4	21.0	23.7	26.4
84-2106	Pregnant	20.8	23.1	25.0	27.0
84-2107	Pregnant	22.0	23.1	24.0	26.0
84-2108	Pregnant	21.6	26.7	27.7	29.4
84-2109	Pregnant	21.2	20.4	24.7	25.8

TABLE 7 (cont.)

## A Range-Finding Study of SC-19129 in Pregnant Rats

Individual Average Daily Food Consumption (g)

125 mg/kg/day Group

Female	Reproductive Status	Gestation Period (days)			
		1-6	6-13	13-16	16-21
84-2110	Pregnant	21.2	21.4	25.3	26.2
84-2111	Pregnant	20.2	20.9	25.3	25.8
84-2112	Pregnant	19.2	20.9	23.3	25.4
84-2113	Pregnant	19.4	20.9	22.0	23.2
84-2114	Pregnant	18.0	20.6	22.0	24.6
84-2115	Pregnant	21.4	23.1	23.0	25.2
84-2116	Pregnant	22.6	26.0	25.3	26.8
84-2117	Not Pregnant	19.6	19.9	16.7	17.4
84-2118	Pregnant	18.8	19.3	24.3	26.8
84-2119	Pregnant	17.0	20.9	22.0	23.8

TABLE 7 (cont.)

## A Range-Finding Study of SC-19129 in Pregnant Rats

Individual Average Daily Food Consumption (g)

250 mg/kg/day Group

Female	Reproductive Status	Gestation Period (days)			
		1-6	6-13	13-16	16-21
84-2120	Pregnant	18.2	20.9	26.7	28.6
84-2121	Pregnant	22.0	22.9	26.3	29.2
84-2122	Pregnant	20.6	20.1	23.0	24.8
84-2123	Pregnant	20.2	21.0	22.3	23.6
84-2124	Pregnant	22.2	22.4	24.0	24.6
84-2125	Pregnant	21.0	21.3	23.3	22.8
84-2126	Pregnant	21.2	20.7	25.3	24.8
84-2127	Pregnant	21.6	19.0	23.3	25.6
84-2128	Pregnant	16.0	18.0	18.3	20.8
84-2129	Pregnant	20.0	21.6	25.0	27.2

TABLE 7 (cont.)

## A Range-Finding Study of SC-19129 in Pregnant Rats

Individual Average Daily Food Consumption (g)

500 mg/kg/day Group

Female	Reproductive Status	Gestation Period (days)			
		1-6	6-13	13-16	16-21
84-2130	Pregnant	21.4	21.6	25.3	28.4
84-2131	Pregnant	20.2	20.4	25.0	26.8
84-2132	Pregnant	20.8	20.9	24.3	27.6
84-2133	Pregnant	22.6	22.1	25.0	25.6
84-2134	Pregnant	20.6	22.4	26.0	28.4
84-2135	Pregnant	20.6	22.6	25.3	27.2
84-2136	Pregnant	18.6	21.0	25.7	27.0
84-2137	Pregnant	20.8	21.4	22.3	24.4
84-2138	Pregnant	19.4	21.1	20.3	15.2
84-2139	Not Pregnant	21.8	25.3	17.0	17.2

TABLE 7 (cont.)

## A Range-Finding Study of SC-19129 in Pregnant Rats

Individual Average Daily Food Consumption (g)

750 mg/kg/day Group

Female	Reproductive Status	Gestation Period (days)			
		1-6	6-13	13-16	16-21
84-2140	Pregnant	20.4	20.6	23.3	25.2
84-2141	Not Pregnant	24.0	23.9	19.3	19.0
84-2142	Pregnant	19.6	20.6	24.0	26.0
84-2143	Pregnant	21.8	24.0	28.7	30.2
84-2144	Pregnant	23.8	24.1	25.7	27.2
84-2145	Pregnant	19.8	21.6	24.7	25.2
84-2146	Pregnant	22.4	21.9	23.0	25.8
84-2147	Pregnant	16.8	21.4	25.3	25.4
84-2148	Pregnant	19.0	20.1	21.0	22.0
84-2149	Pregnant	22.6	24.3	23.7	26.4

TABLE 7 (cont.)

## A Range-Finding Study of SC-19129 in Pregnant Rats

Individual Average Daily Food Consumption (g)

1000 mg/kg/day Group

Female	Reproductive Status	Gestation Period (days)			
		1-6	6-13	13-16	16-21
84-2151	Pregnant	23.2	23.1	24.7	25.6
84-2152	Pregnant	19.2	20.4	21.3	23.8
84-2153	Pregnant	18.0	18.3	22.7	25.8
84-2154	Not Pregnant	20.8	21.1	19.7	18.4
84-2155	Pregnant	21.2	23.3	26.3	28.2
84-2156	Pregnant	18.6	19.9	21.3	23.2
84-2157	Pregnant	20.6	22.6	25.7	27.2
84-2158	Pregnant	20.2	20.9	23.0	24.4
84-2159	Pregnant	21.0	23.6	25.7	29.0

TABLE 8

## A Range-Finding Study of SC-19129 in Pregnant Rats

## Individual Female Dosage Levels

## 125 mg/kg/day Group

Animal #	Average Body Wt. (g) Days 6-16	Average Daily Compound Intake (mg)			Average Dose (mg/kg/day) 6-16
		6-13	13-16	6-16	
84-2110	281	31.7	41.0	34.5	123
84-2111	279	30.9	41.0	33.9	122
84-2112	265	30.9	37.7	33.0	125
84-2113	261	30.9	35.6	32.3	124
84-2114	266	30.5	35.6	32.0	120
84-2115	274	34.2	37.3	35.1	128
84-2116	282	38.5	41.0	39.2	139
84-2117	255	29.5	27.1	28.7	113
84-2118	257	28.6	39.4	31.8	124
84-2119	261	30.9	35.6	32.3	124

TABLE 8 (cont.)

## A Range-Finding Study of SC-19129 in Pregnant Rats

## Individual Female Dosage Levels

## 250 mg/kg/day Group

Animal #	Average Body Wt. (g) Days 6-16	Average Daily Compound Intake (mg)			Average Dose (mg/kg/day) 6-16
		6-13	13-16	6-16	
84-2120	277	61.9	86.5	69.3	250
84-2121	282	67.8	85.2	73.0	259
84-2122	253	59.5	74.5	64.0	253
84-2123	275	62.2	72.3	65.2	237
84-2124	283	66.3	77.8	69.7	246
84-2125	273	63.0	75.5	66.8	245
84-2126	279	61.3	82.0	67.5	242
84-2127	273	56.2	75.5	62.0	227
84-2128	249	53.3	59.3	55.1	222
84-2129	276	63.9	81.0	69.1	250



TABLE 8 (cont.)

## A Range-Finding Study of SC-19129 in Pregnant Rats

## Individual Female Dosage Levels

## 500 mg/kg/day Group

Animal #	Average Body Wt. (g) Days 6-16	Average Daily Compound Intake (mg)			Average Dose (mg/kg/day) 6-16
		6-13	13-16	6-16	
84-2130	263	127.7	163.9	138.5	527
84-2131	266	120.6	162.0	133.0	501
84-2132	270	123.5	157.5	133.7	495
84-2133	279	130.6	162.0	140.0	503
84-2134	269	132.4	168.5	143.2	532
84-2135	259	133.6	163.9	142.7	550
84-2136	265	124.1	166.5	136.8	517
84-2137	270	126.5	144.5	131.9	489
84-2138	268	124.7	131.5	126.8	474
84-2139	279	149.5	110.2	137.7	494

TABLE 8 (cont.)

## A Range-Finding Study of SC-19129 in Pregnant Rats

## Individual Female Dosage Levels

## 750 mg/kg/day Group

Animal #	Average Body Wt. (g) Days 6-16	Average Daily Compound Intake (mg)			Average Dose (mg/kg/day) 6-16
		6-13	13-16	6-16	
84-2140	269	182.5	226.5	195.7	727
84-2141	276	211.8	187.6	204.5	742
84-2142	260	182.5	233.3	197.7	760
84-2143	299	212.6	279.0	232.5	778
84-2144	282	213.5	249.8	224.4	797
84-2145	258	191.4	240.1	206.0	798
84-2146	275	194.0	223.6	202.9	739
84-2147	255	189.6	245.9	206.5	810
84-2148	257	178.1	204.1	185.9	723
84-2149	297	215.3	230.4	219.8	741

TABLE 8 (cont.)

## A Range-Finding Study of SC-19129 in Pregnant Rats

## Individual Female Dosage Levels

## 1000 mg/kg/day Group

Animal #	Average Body Wt. (g) Days 6-16	Average Daily Compound Intake (mg)			Average Dose (mg/kg/day) 6-16
		6-13	13-16	6-16	
84-2151	290	273.0	320.1	287.2	991
84-2152	266	241.1	276.0	251.6	945
84-2153	257	216.3	294.2	239.7	931
84-2154	268	249.4	255.3	251.2	937
84-2155	268	275.4	340.8	295.0	1101
84-2156	263	235.2	276.0	247.5	940
84-2157	285	267.1	333.1	286.9	1006
84-2158	267	247.0	298.1	262.4	984
84-2159	277	279.0	333.1	295.2	1068

## PROTOCOL

1. Study Title: A Range-Finding Study of SC-19129 in Pregnant Rats

\*\*\*\*\*  
\*THIS STUDY IS NOT INTENDED TO SUPPORT APPLICATIONS\*  
\*FOR RESEARCH OR MARKETING PERMITS FOR PRODUCTS\*  
\*REGULATED BY GOVERNMENTAL AGENCIES. THIS IS AN\*  
\*EXPLORATORY/RANGE-FINDING STUDY AND IS NOT WITHIN\*  
\*THE SCOPE OF GOOD LABORATORY PRACTICE REGULATIONS.\*  
\*\*\*\*\*

2. Study Sponsor: G. D. Searle & Co.

3. Facility: G. D. Searle & Co., 4901 Searle  
Parkway, Skokie, Illinois 60077.

4. Proposed Dates:

A. Initiate Breeding: Oct. 17, 1984

B. Initiate Dosing: Oct. 23, 1984

C. Initiate Day 21 Sacrifice: Nov. 7, 1984

5. Purpose: To determine potential toxic effects as evidenced by clinical signs, body weights, and fetal viability, and to provide a basis for dosage level selection in teratology/reproduction studies.

6. Overview of Study Design:

<u>Group</u>	<u>Treatment</u>	<u>Dosage Level (mg/kg/day)</u>	<u>Number of Females/Group</u>
1	Control	0	10
2	SC-19129	125	10
3	SC-19129	250	10
4	SC-19129	500	10
5	SC-19129	750	10
6	SC-19129	1000	10

7. Laboratory Procedures: This is an exploratory/range-finding study and is not within the scope of Good Laboratory Practice Regulations.

8. Proposed Use:

9. Test Article:

- A. Chemical Name: N-L- $\beta$ -aspartyl-L-phenylalanine, l-methyl ester.
- B. Formulation: The appropriate amount of test article will be mixed with diet.
- C. Administration:
  - 1. Route: By diet admix.
  - 2. Duration: The females will receive the SC-19129/diet admix ad libitum from day 6\* through day 15 of gestation. The concentration of SC-19129 in the diet will be adjusted on day 13 of gestation based on average group body weights from day 12 of gestation.
- D. Analysis
  - 1. Test Article
    - a. Identity, strength, purity and composition: Will be determined before use.
    - b. Stability: Will be reported if available.
  - 2. Test Article Carrier Mixture:
    - a. Stability: Will be reported if available.
- E. Storage
  - 1. Test Article: Will be stored in a well-closed, light-resistant container at controlled room temperature.
  - 2. Test article carrier mixture: Will be stored in an appropriate container at controlled room temperature.
- F. Estimated Test Article Requirements: 300 g

\*NOTE - Day 6 SC-19129/diet concentrations will be based on food consumption and body weight data obtained on day 5 from the first rats to reach this stage of gestation.

10. Study Design Conditions:

- A. Animals: Sixty virgin female rats of the Charles River COBS CD strain (Portage, MI.) will be used in this study. The rat is widely used for teratogenic studies, and as such a vast amount of historical control data is available. The rats will be approximately 2 to 3 months of age and weigh 170-270 grams at the start of the study. The rats will be allowed approximately two weeks acclimatization prior to the start of the study.
- B. Husbandry and Diet: Rats will be housed (2 or 3 females/box) in polycarbonate shoe boxes prior to the start of the study. Following mating, the female rats will be housed individually in polycarbonate shoe boxes for the remainder of the study. The rats will have free access to a Certified Purina Rat Chow Diet #5002 and have free access to municipally supplied tap water throughout the study. It is considered that there are no known interfering contaminants in the diet or water. Animal room temperature will be 72° + 5°F and relative humidity will be 25% or greater; both parameters will be monitored. A 12-hour light/12-hour dark cycle will be used throughout the study.
- C. Breeding Procedure: Female rats will be grouped with breeder colony males (1 or 2 females/male) of the same strain and source. Each morning a vaginal lavage will be prepared from each female and examined for the presence of spermatozoa. The presence of sperm in the lavage will indicate a successful mating. The day this occurs will be designated as day 1 of gestation. Once mating has occurred, the females will be randomly assigned to treatment groups by using a block design of random permutation and be given their unique identification numbers using ear tags.

11. Maternal Observations:

- A. Clinical Signs: Animals checked at least once a day and all remarkable signs observed will be recorded.
- B. Mortality: Any rats that die will be examined to verify reproductive status and to possibly determine cause of death.
- C. Body Weight: Females will be weighed on gestation days 1, 6, 8, 10, 12, 14, 16, and 21.

D. Feeder Weight: Measured on days 1, 6, 13, 16, and 21 of gestation.

12. Caesarean Section:

On day 21 of gestation, all females will be sacrificed by CO<sub>2</sub> inhalation. The uterus will be exposed and the numbers of corpora lutea, implantations, resorptions, and live or dead fetuses recorded.

13. Statistical Procedures:

The mean values and standard deviations of each variable will be determined. Food consumption, maternal body weights, and body weight changes will be analyzed by a one-way analysis of variance, Student's t-tests (using the pooled error variance from the one-way analysis of variance) of control vs. the other dose groups (if the F ratio among treatments is significant at the 5% level), and the Bartlett-Box test for homogeneity of variance. All t-tests will be two-tailed. The Kruskal-Wallis test will be used to analyze the following variables: number of implantations, resorptions, live or dead fetuses per litter. If significant at the 5% level, then the Mann-Whitney U test will be used to compare each drug-treated group to the control group. Significance levels achieved will be reported for 5% for t-tests, Mann-Whitney U tests and Bartlett-Box test.

14. Archiving of Materials:

All raw data, supporting documents, protocol, specimens, and the final report will be transferred to the R&D Central File.

15. Protocol Approval

A. J. W. Noveroske, Ph.D.

Study Director

Product Safety Assessment: J. W. Noveroske Oct. 16/84

Date

B. F. N. Kotsonis, Ph.D.

Diplomate, A.B.T.

Director, Toxicology

Product Safety Assessment: F. N. Kotsonis 10/16/84

Date

C. F. E. Kohn, Ph.D.

Senior Director,

Product Safety Assessment: F. E. Kohn 10/16/84

Date

PROTOCOL AMENDMENT  
October 18, 1984

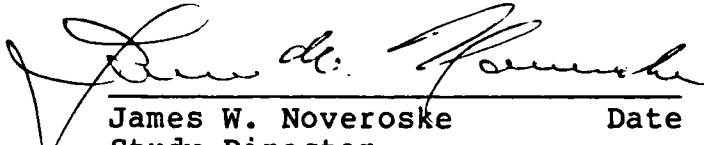
Protocol Amendment #1  
S.A. 2453  
A Range-Finding Study of SC-19129 in Pregnant Rats

The following is a change to the approved protocol:

1. Page 3, Sect. 10.B. - Change "female rats will be housed individually in polycarbonate shoe boxes" to "female rats will be housed individually in suspended, stainless steel, wire mesh cages."

Reason for Change - to avoid feeder spillage, jars used should be secured in cage; difficult in polycarbonate shoe boxes.

Approval:

  
James W. Noveroske      Date  
Study Director

10/18/84

S.A. 2453



APPENDIX B

R&D PRODUCT DEVELOPMENT FUNCTION  
REPORT REVIEW AND RELEASE

Page 1 of 3

DEPARTMENT: Product Development Analytical

DOCUMENT NUMBER: F-307-034-03

TITLE OF REPORT: SC-19129

TYPE OF REPORT: Analytical Summary in Support of Product Safety  
Assessment Study Number 2453

AUTHOR(S):	DATE	REVIEWER(S):	DATE
<u>James Jiu</u>	<u>12/06/84</u>	<u>Daniel L. Sweeney</u>	<u>12-6-84</u>
_____	_____	_____	_____
_____	_____	_____	_____

APPROVAL:	DATE
James Jiu <u>James Jiu</u>	<u>12/06/84</u>
_____	_____

TECHNICAL WRITER:  
Michele Newcomb Michele Newcomb

APPROVAL FOR RELEASE:

<u>R. Baum</u>	<u>12/10/84</u>	<u>R. Baum for L. Hansen</u>	<u>12/10/84</u>
R. Baum, Director	Date	L. Hansen,	Date
Analytical Development		Senior Director	
		Product Development	

NORTH AMERICAN PRECLINICAL RESEARCH AND DEVELOPMENT  
SEARLE PHARMACEUTICALS AND CONSUMER PRODUCTS  
SKOKIE, ILLINOIS

S.A. 2453

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Subject: SC-19129

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Summary Number: F-307-034-03

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ANALYTICAL SUMMARY  
Product Development Analytical Department

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Subject: SC-19129

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Summary Number: F-307-034-03

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Applicable to SA Study Number: 2453

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Test Article Characterization and Stability

Lot 84K-047-101 (formerly 840413) was analyzed using the release methods of testing, released against the current specifications (NS-S84-015-A), and given a re-evaluation period of one year prior to use in this study.

Table 1

	Prior to Hydration(1)		After Hydration(1)
Lot Designation	840413	840413	84K-047-101
Analysis Report #	84N1007	84N1009	84N1058
Completion Date	10/03/84	10/01/84	10/16/84
Identity (HPLC)	Conforms to Standard	Conforms to Standard	Conforms to Standard
Assay (on dried basis)	(Titration) 99.9% n = 3 s = 0.1	(HPLC) 99.0% n = 3 s = 0.3	(HPLC) 100.0% n = 3 s = 0.2
Loss on Drying	0.5%		
Water		0.6%(1)	9.8%(1)

(1) Lot 840413 was hygroscopic. To circumvent percent water variability, this lot was allowed to equilibrate to a more stable water content, and was designated as Lot 84K-047-101.

These results and all other results, coupled with the use of lot 84K-047-101 within its re-evaluation period indicate that lot 84K-047-101 of SC-19129 was suitable for use in this study.

S.A. 2453

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Subject: SC-19129

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Summary Number: F-307-034-03

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Applicable to SA Study Number: 2453

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GLP Compliance Statement

To the best of our knowledge, the support activities provided by the Product Development Analytical Department for this study were conducted in compliance with the Good Laboratory Practices Regulations, as set forth in part 58, 21 CFR.

S.A. 2453

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