

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


 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.

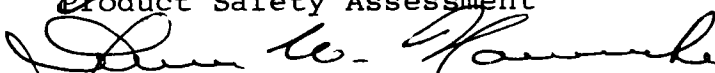
James W. Noveroske and Gary Chmielewski

Safety Assessment Project Number 2454


Department of Product Safety Assessment
 G. D. Searle & Co.
 Skokie, IL

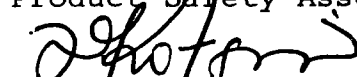
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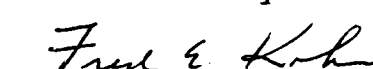
 1/24/85
 Gary Chmielewski, M.A. Date
 Research Teratologist
 Product Safety Assessment

 1/24/85
 James W. Noveroske, Ph.D. Date
 Study Director
 Product Safety Assessment

Approvals:

 1/25/85
 Martin A. Sidor, D.V.M., M.S. Date
 Director,
 Laboratory Animal Resources
 Product Safety Assessment

 1/24/85
 Frank N. Kotsonis, Ph.D. Date
 Diplomate, A.B.T.
 Director, Toxicology
 Product Safety Assessment

 1/25/85
 Fred E. Kohn, Ph.D. Date
 Senior Director,
 Product Safety Assessment

January 24, 1985

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Report Document Number: PS 85S-2454A

DEPARTMENT OF PRODUCT SAFETY ASSESSMENT

G. D. Searle & Co., Skokie, IL

Title: A Range-Finding Study of SC-19129 in Pregnant Rabbits

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Author: James W. Noveroske and Gary Chmielewski

Study No.: S.A. 2454

Date: January 24, 1985

Type of Report: Final

Summary:

SC-19129, was administered once daily by oral intubation to six female rabbits per group from Days 6 through 18 of gestation at dosage levels of 125, 250, 500, 750 and 1000 mg/kg/day. A control group received the vehicle, 0.5% methylcellulose and 0.1% polysorbate 80, in the same dosing regimen as the compound-treated groups.

No compound-related maternotoxic effects occurred at dosage levels of 125, 250, 500 or 750 mg/kg/day. At 1000 mg/kg/day, maternotoxicity was observed as evidenced by weight loss and death of four of six females. Death was preceded by persistent clinical signs of low food intake or not eating.

Examination of the reproductive status of females at Day 28 of gestation revealed no adverse effects on average numbers of implantations, resorptions, or live or dead fetuses per litter.

S.A. 2454

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

INTRODUCTION

The study was conducted 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 a teratology study.

MATERIALS AND METHODS

Thirty-six female rabbits (New Zealand White strain, H.A.R.E., Hewitt, N.J.) approximately 4 months of age and weighing 3.32 to 4.21 kg, were divided into 6 groups of 6 rabbits each for this study.

Each rabbit was artificially inseminated (day 0 of gestation) with approximately six million motile spermatozoa contained in 0.25 ml of 0.9% physiological saline, and then injected intravenously via the marginal ear vein with 50 USP units of chorionic gonadotropin to help induce ovulation. The females were then assigned to treatment groups using a block design of random permutations, and given unique identification numbers using an ear tag. The rabbits were individually housed in stainless steel cages, and given approximately 150 g of Certified Purina Rabbit Chow #5322 per day and had free access to municipally supplied tap water throughout the study.

The animal room was maintained at $65^{\circ}\pm 5^{\circ}\text{F}$ temperature and 25% or greater relative humidity with a 12-hour light and 12-hour dark cycle. The study was started on November 1, 1984 and terminated on November 30, 1984.

SC-19129, N-L- β -aspartyl-L-phenylalanine, l-methyl ester, was given to 5 groups of 6 rabbits each for 13 consecutive days (Days 6 through 18 of gestation) at dosage levels of 125, 250, 500, 750 and 1000 mg/kg/day. SC-19129 was administered orally by gavage as a suspension of 0.5% methylcellulose (w/v) and 0.1% polysorbate 80 (v/v) in distilled water. The doses of SC-19129 Lot #84K-047-101, were prepared as fresh suspensions daily and the quantity (4 ml/kg) administered was based on the most recent body weight. The sixth group of rabbits served as controls and received the vehicle, 0.5% methylcellulose and 0.1% polysorbate 80 in distilled water, in the same volume as the compound-treated rabbits.

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

Body weights of the rabbits were recorded on Days 0, 6, 8, 10, 13, 16, 19, and 28 of gestation. The rabbits were examined daily for adverse clinical signs throughout the study, sacrificed by an overdose of an euthanizing agent injected via the marginal ear vein on Day 28 of gestation, and the uterus examined to obtain the numbers of corpora lutea, implantations, resorptions, and live or dead fetuses.

Maternal body weights and body weight changes 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. Numbers of corpora lutea were not analyzed or reported. The Kruskal-Wallis test was used to analyze the following variables: numbers of implantations, resorptions, and live and dead 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. 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	
Analytical Department	J. Jiu

RESULTS AND DISCUSSION

No compound-related deaths or clinical signs occurred at dosage levels of 125, 250, 500, or 750 mg/kg/day. At 1000 mg/kg/day, three of six animals died and one was sacrificed because of a moribund condition. These deaths were preceded by persistent (5 days or longer) clinical signs of low food intake or not eating. In addition, two animals, one each from the 125 and 250 mg/kg/day groups, aborted but were considered unrelated to treatment.

Average maternal body weight gain of rabbits given 125, 250, 500 or 750 mg/kg/day was unaffected (Tables 1 and 3). At 1000 mg/kg/day, there was a significant loss ($p>0.05$) in average body weight compared to that of the control group. The two animals from the 1000 mg/kg/day group surviving to Day 28 of gestation lost weight until Day 13 of gestation then they started to gain weight again, a trend that continued for the remainder of the study.

Examination of the reproductive status of females at Day 28 of gestation revealed no adverse effects of SC-19129 on average numbers of implantations, resorptions, and live or dead fetuses per litter at dosage levels of 125, 250, 500, and 750 mg/kg/day (Tables 2 and 4). Although only two rabbits from the 1000 mg/kg/day group survived to day 28 of gestation, no adverse effects of SC-19129 on average numbers of implantations, resorptions, and live or dead fetuses per litter were observed.

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. Three known deviations occurred as follows:

1. Although specified in the protocol, animal room temperature and humidity levels were not recorded during the first nine days of the study and twice during the study temperature levels slightly exceeded the range specified in the protocol.
2. One animal of the 500 mg/kg/day dose group was inadvertently dosed on Day 19 of gestation.
3. Three rabbits, one each from the control, 250 and 750 mg/kg/day groups, received slightly different dosage volumes than intended based on their body weights for a period of 2, 6, and 2 days, respectively.

However, these deviations 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 RABBITS

Maternal Body Weights

	Control 0	(mg/kg/day)				
		125	250	500	750	1000
Average Body Weight (Kg)						
Day 0	3.60	3.88	3.66	3.76	3.73	3.57
Day 6	3.61	3.83	3.66	3.74	3.68	3.55
Day 8	3.62	3.82	3.63	3.76	3.71	3.52
Day 10	3.64	3.82	3.62	3.78	3.73	3.26*
Day 13	3.68	3.90	3.75	3.83	3.81	3.06*
Day 16	3.79	3.97	3.85	3.93	3.91	3.01*
Day 19	3.83	4.00	3.91	3.99	3.96	3.21*
Day 28	4.05	4.20	4.19	4.23	4.17	3.81
Change						
Days 0-6	+0.01	-0.05	0.00	-0.02	-0.05	-0.01
Days 6-19	+0.21	+0.17	+0.26	+0.25	+0.27	-0.27*
Days 19-28	+0.22	+0.19	+0.24	+0.24	+0.21	+0.15
Days 0-28	+0.45	+0.33	+0.46	+0.47	+0.43	+0.28

*Significantly different ($p > 0.05$) from control

TABLE 2
A RANGE-FINDING STUDY OF SC-19129 IN PREGNANT RABBITS
Reproductive Status of Females at Sacrifice

	Control	(mg/kg/day)				
	0	125	250	500	750	1000
Females						
Total No.	6	6	6	6	6	6
No. Live Pregnant	6	5	4	6	5	2
No. Live Not Pregnant	0	0	0	0	1	0
No. Sacrificed Pregnant	0	0	1 ^a	0	0	1
No. Died Pregnant	0	0	0	0	0	3
No. Aborted	0	1	1 ^b	0	0	0
Implantations						
Total No.	33	52	40	53	38	19
No./Pregnant Female	5.5	10.4	10.0	8.8	7.6	9.5
Resorptions						
Total No.	1	2	0	2	2	2
No./Pregnant Female	0.2	0.4	0.0	0.3	0.4	1.0
Fetuses						
Total No.	32	50	40	51	36	17
No. Live	32	49	39	51	35	16
No. Dead	0	1	1	0	1	1
No. Live/Pregnant Female	5.3	9.8	9.8	8.5	7.0	8.0
No. Dead/Pregnant Female	0.0	0.2	0.3	0.0	0.2	0.5

^aAnimal sacrificed because of leg injury

^bAnimal died after aborting

TABLE 3

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

Individual Female Body Weights (kg)

Control Group

Female	Reproductive Status	Gestation Day							
		0	6	8	10	13	16	19	28
84-2498	Pregnant	3.38	3.37	3.36	3.32	3.21	3.37	3.40	3.63
84-2499	Pregnant	3.80	3.80	3.82	3.82	3.92	3.93	4.04	4.31
84-2500	Pregnant	3.60	3.73	3.73	3.88	3.90	4.15	4.09	4.24
84-2501	Pregnant	3.46	3.47	3.48	3.54	3.59	3.65	3.72	3.98
84-2502	Pregnant	3.73	3.74	3.77	3.71	3.84	3.87	3.94	4.19
84-2503	Pregnant	3.66	3.58	3.58	3.58	3.62	3.78	3.77	3.94

TABLE 3 (Cont.)

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

Individual Female Body Weight (kg)

125 mg/kg/day Group

Female	Reproductive Status	Gestation Day							
		0	6	8	10	13	16	19	28
84-2504	Pregnant	3.85	3.82	3.88	3.75	3.90	3.95	3.98	4.08
84-2505	Pregnant	3.98	3.94	3.88	3.90	3.93	4.05	4.02	4.24
84-2506	Pregnant	3.92	3.82	3.84	3.87	3.96	3.99	4.05	4.24
84-2507	Pregnant	4.14	4.12	4.10	4.14	4.19	4.26	4.32	4.62
84-2508	Pregnant	3.42	3.46	3.44	3.45	3.54	3.64	3.68	3.81
84-2509	Aborted	3.97	3.81	3.82	3.83	3.87	3.94	3.95	3.98

TABLE 3 (Cont.)

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

Individual Female Body Weights (kg)

250 mg/kg/day Group

Female	Reproductive Status	Gestation Day							
		0	6	8	10	13	16	19	28
84-2510	Pregnant	3.32	3.35	3.35	3.36	3.44	3.50	3.52	3.78
84-2511	Pregnant	3.80	3.76	3.79	3.82	3.87	3.98	4.05	4.29
84-2512	Pregnant	3.34	3.49	3.54	3.48	3.61	3.65	3.76	-- ^a
84-2513	Pregnant	4.21	4.15	4.16	4.23	4.25	4.38	4.39	4.57
84-2514	Pregnant	3.69	3.68	3.53	3.26	— ^b	—	—	—
84-2515	Pregnant	3.60	3.51	3.44	3.55	3.60	3.76	3.84	4.12

--^a Animal died—^b Animal sacrificed

TABLE 3 (Cont.)

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

Individual Female Body Weights (kg)

500 mg/kg/day Group

Female	Reproductive Status	Gestation Day							
		0	6	8	10	13	16	19	28
84-2516	Pregnant	3.75	3.73	3.72	3.77	3.83	3.93	3.97	4.25
84-2517	Pregnant	3.77	3.78	3.84	3.90	3.92	4.05	4.10	4.16
84-2518	Pregnant	4.08	4.03	4.05	4.09	4.14	4.22	4.24	4.54
84-2519	Pregnant	3.70	3.75	3.71	3.72	3.74	3.79	3.87	4.02
84-2520	Pregnant	3.82	3.76	3.81	3.83	3.92	4.05	4.13	4.50
84-2521	Pregnant	3.43	3.38	3.45	3.38	3.46	3.54	3.64	3.89

TABLE 3 (Cont.)

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

Individual Female Body Weights (kg)

750 mg/kg/day Group

Female	Reproductive Status	Gestation Day							
		0	6	8	10	13	16	19	28
84-2522	Pregnant	3.66	3.61	3.58	3.62	3.73	3.84	3.87	4.14
84-2523	Pregnant	3.93	3.91	3.93	3.93	3.99	4.13	4.24	4.42
84-2524	Pregnant	3.93	3.91	3.95	3.95	3.99	4.11	4.06	4.18
84-2525	Pregnant	3.69	3.58	3.61	3.67	3.76	3.84	3.93	4.15
84-2526	Pregnant	3.45	3.41	3.47	3.50	3.56	3.64	3.69	3.95
84-2527	Not Pregnant	3.61	3.53	3.41	3.41	3.50	3.41	3.17	3.62

TABLE 3 (Cont.)

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

Individual Female Body Weights (kg)

1000 mg/kg/day Group

Female	Reproductive Status	Gestation Day							
		0	6	8	10	13	16	19	28
84-2528	Pregnant	3.95	3.83	3.82	3.34	2.92	2.69	-- ^a	--
84-2529	Pregnant	3.81	3.80	3.77	3.63	3.80	3.92	3.96	4.06
84-2530	Pregnant	3.41	3.50	3.41	3.16	2.85	--	--	--
84-2531	Pregnant	3.54	3.53	3.48	3.10	2.83	2.52	— ^b	—
84-2532	Pregnant	3.43	3.45	3.43	3.22	2.73	2.64	2.33	--
84-2533	Pregnant	3.25	3.20	3.22	3.11	3.24	3.29	3.35	3.55

--^a Animal Died—^b Found moribund and sacrificed

TABLE 4

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

Individual Fetal Data

Control Group

Animal Number	Reproductive Status	Number of			
		Implant- ations	Resorp- tions	Live Fetuses	Dead Fetuses
84-2498	Pregnant	3	0	3	0
84-2499	Pregnant	4	0	4	0
84-2500	Pregnant	1	0	1	0
84-2501	Pregnant	6	0	6	0
84-2502	Pregnant	9	1	8	0
84-2503	Pregnant	10	0	10	0

TABLE 4 (cont.)

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

Individual Fetal Data

125 mg/kg/day Group

Animal Number	Reproductive Status	Number of			
		Implant- ations	Resorp- tions	Live Fetuses	Dead Fetuses
84-2504	Pregnant	11	0	11	0
84-2505	Pregnant	11	0	10	1
84-2506	Pregnant	3	0	3	0
84-2507	Pregnant	15	1	14	0
84-2508	Pregnant	12	1	11	0
84-2509	Pregnant	ANIMAL ABORTED			

TABLE 4 (cont.)

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

Individual Fetal Data

250 mg/kg/day Group

Animal Number	Reproductive Status	Number of			
		Implant- ations	Resorp- tions	Live Fetuses	Dead Fetuses
84-2510	Pregnant	7	0	7	0
84-2511	Pregnant	11	0	11	0
84-2512	Pregnant	A N I M A L D I E D			
84-2513	Pregnant	10	0	10	0
84-2514	Pregnant	A N I M A L S A C R I F I E D			
84-2515	Pregnant	12	0	11	1

TABLE 4 (cont.)

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

Individual Fetal Data

500 mg/kg/day Group

Animal Number	Reproductive Status	Number of			
		Implant- ations	Resorp- tions	Live Fetuses	Dead Fetuses
84-2516	Pregnant	10	0	10	0
84-2517	Pregnant	9	0	9	0
84-2518	Pregnant	8	1	7	0
84-2519	Pregnant	6	1	5	0
84-2520	Pregnant	12	0	12	0
84-2521	Pregnant	8	0	8	0

TABLE 4 (cont.)

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

Individual Fetal Data

750 mg/kg/day Group

Animal Number	Reproductive Status	Number of			
		Implant- ations	Resorp- tions	Live Fetuses	Dead Fetuses
84-2522	Pregnant	8	0	8	0
84-2523	Pregnant	10	0	10	0
84-2524	Pregnant	2	0	2	0
84-2525	Pregnant	9	1	8	0
84-2526	Pregnant	9	1	7	1
84-2527	Not Pregnant	0	0	0	0

TABLE 4 (cont.)

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

Individual Fetal Data

1000 mg/kg/day Group

Animal Number	Reproductive Status	Number of			
		Implant- ations	Resorp- tions	Live Fetuses	Dead Fetuses
84-2528	Pregnant		A N I M A L	D I E D	
84-2529	Pregnant	8	0	7	1
84-2530	Pregnant		A N I M A L	D I E D	
84-2531	Pregnant		A N I M A L	S A C R I F I C E D	
84-2532	Pregnant		A N I M A L	D I E D	
84-2533	Pregnant	11	2	9	0

PROTOCOL

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

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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: November 1, 1984
- B. Initiate Dosing: November 7, 1984
- C. Initiate Day 28 Sacrifice: November 29, 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 a Teratology study.
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 | 6 |
| 2 | SC-19129 | 125 | 6 |
| 3 | SC-19129 | 250 | 6 |
| 4 | SC-19129 | 500 | 6 |
| 5 | SC-19129 | 750 | 6 |
| 6 | SC-19129 | 1000 | 6 |
7. Laboratory Procedures: This is an exploratory/range-finding study and is not within the scope of Good Laboratory Practice Regulations.

8. Proposed Clinical Use:

9. Test Article:

- A. Chemical Name: N-L- β -aspartyl-L-phenylalanine, 1-methylester.
- B. Formulation: The appropriate amount of test article will be suspended in 0.5% methylcellulose (w/v), 0.1% polysorbate 80 (v/v) in distilled water.
- C. Administration:
 - 1. Route: Orally by gavage.
 - 2. Frequency: Once daily.
 - 3. Duration: The females will be dosed from day 6 through day 18 of gestation. The quantity of control vehicle or test article suspensions will be based on the most recent body weight.
 - 4. Volume: Both the control vehicle and test article suspensions will be given at 4 ml/kg.
- 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 prepared fresh daily.
- F. Estimated Test Article Requirements: 1200g

10. Study Design Conditions:

- A. Animals: 36 virgin female rabbits of the New Zealand White strain (H.A.R.E., Hewitt, N.J.) will be used in this study. The rabbit is widely used as the non-rodent species for teratogenic studies, and a vast amount of historical control data is available. The rabbits will be approximately 4 months of age and weigh approximately 3 to 5 kg at the start of the study. The rabbits will be allowed approximately 1 month acclimatization prior to the start of the study.
- B. Husbandry and Diet: Rabbits will be individually housed in stainless steel cages during the study. The rabbits will be given approximately 150 g of Certified Purina Rabbit Chow #5322 per day and have free access to municipally supplied tap water throughout the study. No special analyses of feed and water will be performed since no contaminants known to be capable of interfering with the study are reasonably expected to be present. Animal room temperature will be $65^{\circ} \pm 5^{\circ}\text{F}$ 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 rabbits will be artificially inseminated (day 0 of gestation) with semen from breeder colony males of the same strain and source. Each female will then receive 50 USP units of a chorionic gonadotropin intravenously via the marginal ear vein to help induce ovulation. The females will then be assigned to treatment groups by using a block design of random permutations 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 rabbits that die will be examined internally to verify reproductive status and to possibly determine cause of death.
- C. Body Weight: Females will be weighed on gestation days 0, 6, 8, 10, 13, 16, 19, and 28.

D. Food Consumption: Estimated for all females throughout the study.

12. Caesarean Section:

On day 28 of gestation, all females will be sacrificed with an overdose of a euthanizing agent. 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. 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:

[Signature] 10/18/87
Date

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

Diplomate, A.B.T.

Director, Toxicology

Product Safety Assessment:

[Signature] 10/18/87
for Dr. Kotsonis Date

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

Senior Director,

Product Safety Assessment:

[Signature] 10/19/87
for F. Kohn Date

S.A. 2454

APPENDIX B

R&D PRODUCT DEVELOPMENT FUNCTION
REPORT REVIEW AND RELEASE

Page 1 of 3

DEPARTMENT: Product Development Analytical

DOCUMENT NUMBER: F-308-034-04

TITLE OF REPORT: SC-19129

TYPE OF REPORT: Analytical Summary in Support of Product Safety
Assessment Study Number 2454

AUTHOR(S):	DATE	REVIEWER(S):	DATE
<u>James Jiu</u>	<u>12/06/84</u>	<u>Daniel J. 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. 2454

Subject: SC-19129

Summary Number: F-308-034-04

Applicable to SA Study Number: 2454

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.

Subject: SC-19129

Summary Number: F-308-034-04

Applicable to SA Study Number: 2454

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.

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