

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

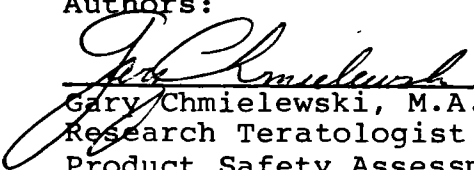
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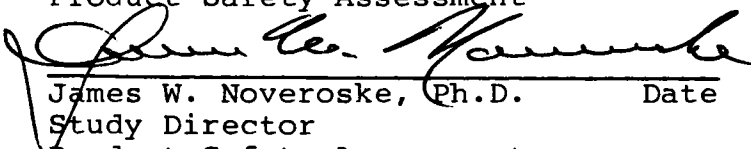
James W. Noveroske and Gary Chmielewski

Safety Assessment Project Number 2609

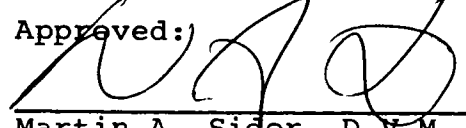
Department of Product Safety Assessment
 G. D. Searle & Co.
 Skokie, IL

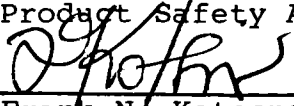
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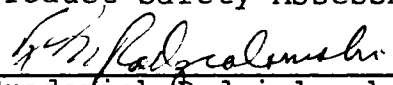

 Gary Chmielewski, M.A. Date 6/5/85
 Research Teratologist
 Product Safety Assessment


 James W. Noveroske, Ph.D. Date 6/5/85
 Study Director
 Product Safety Assessment

Approved:


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 Diplomate, A.B.T.
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 Senior Director,
 Product Safety Assessment

June 5, 1985

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

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

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EXPLORATORY/RANGE-FINDING STUDY AND IS NOT WITHIN
THE SCOPE OF GOOD LABORATORY PRACTICE REGULATIONS.

Author: James W. Noveroske and Gary Chmielewski

Study No.: S.A. 2609

Date: June 5, 1985

Type of Report: Final

Summary:

SC-19129 was administered by diet admix to fifteen rats at an intended dosage level of 1000 mg/kg/day for 10 consecutive days (days 6 through 15 of gestation). A control group received the standard diet.

Actual average dosage level of SC-19129 from days 6 through 15 of gestation was 1071 mg/kg/day. No compound-related deaths or clinical signs occurred.

Average maternal body weight gain and food consumption were not adversely affected.

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.

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

Thirty virgin female rats (Charles River COBS CD strain, Canada) approximately thirteen weeks of age and weighing 239 to 288 g, were divided into 2 groups of 15 rats each for this study.

Female rats were placed with males (1 female/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 February 13, 1985 and terminated on March 8, 1985.

SC-19129, N-L- β -aspartyl-L-phenylalanine, 1-methyl ester (Lot # 84K-047-101), was given for 10 consecutive days. SC-19129/Certified Purina Rat Chow Meal # 5002 diet admix preparation was made at an intended level of 1000 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 was determined before and after 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 CO₂ 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 Student's t-test. The Mann-Whitney U test was used to analyze the numbers of implantations, resorptions, and live fetuses per litter. Numbers of corpora lutea were not analyzed or tabulated in this report. All tests were two-tailed and significance levels achieved have been reported at the 5% level.

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
Teratology	G. Chmielewski
Product Development	J. Jiu
Analytical Department	
Biostatistics	A. MacKenthun

RESULTS AND DISCUSSION

From days 6 to 16 gestation, the actual average dosage level of SC-19129 (Tables 4 and 8) administered by diet admix was 1071 mg/kg/day. No compound-related deaths or clinical signs occurred.

Average maternal body weight gain and food consumption were not adversely affected (Tables 1, 3, 5, and 7).

Examination of the reproductive status of females at sacrifice (Tables 2 and 6) revealed no adverse effects on average numbers of implantations, resorptions, and live or dead fetuses per litter.

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. Two known deviations occurred as follows:

1. Animal room humidity fell below the protocol specified limits February 18, 1985.
2. Animal room temperature fell below protocol specified limits March 4-5, 1985.

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 RATS

Maternal Body Weights

	Control	1000 mg/kg/day
Average Body Weight (g)		
Day 1	265	263
Day 6	285	288
Day 8	296	297
Day 10	307	307
Day 12	316	317
Day 14	325	325
Day 16	342	342
Day 21	403	412
Change		
Days 1-6	+ 19	+ 26
Days 6-16	+ 57	+ 53
Days 16-21	+ 61	+ 70*
Days 1-21	+138	+149

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

TABLE 2

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

Reproductive Status Of Females At Sacrifice

	Control	1000 mg/kg/day
Females		
Total No.	15	15
No. Live Pregnant	14	14
No. Live Not Pregnant	1	1
Implantations		
Total No.	224	220
No./Pregnant Female	16.0	15.7
Resorptions		
Total No.	22	15
No./Pregnant Female	1.6	1.1
Fetuses		
Total No.	202	205
No. Live	202	205
No. Live/Pregnant Female	14.4	14.6

TABLE 3

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

Maternal Food Consumption

	Control	1000 mg/kg/day
Average Daily Food Consumption (g)		
Days 1-6	21.1	21.3
Days 6-13	24.4	23.9
Days 13-16	24.1	24.0
Days 6-16	24.3	23.9
Days 16-21	26.9	27.7

TABLE 4

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

Actual Average Maternal Dosage Levels

	Control	1000 mg/kg/day
Average Dosage Levels (mg/kg/day)		
Days 6-16	0	1071

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
85-221	Pregnant	263	291	296	311	327	328	340	420
85-222	Pregnant	243	254	264	274	287	292	306	373
85-223	Pregnant	252	276	286	295	303	314	327	382
85-224	Pregnant	286	306	314	333	336	349	365	440
85-225	Not Pregnant	269	282	272	296	294	299	306	303
85-226	Pregnant	264	283	291	308	312	328	343	410
85-227	Pregnant	265	281	290	308	320	328	349	412
85-228	Pregnant	269	284	295	299	309	316	334	386
85-229	Pregnant	262	270	286	291	295	299	320	385
85-230	Pregnant	264	287	300	310	317	330	352	411
85-231	Pregnant	279	303	321	330	340	353	370	421
85-232	Pregnant	266	299	314	322	333	340	362	428
85-233	Pregnant	274	291	301	309	320	331	343	415
85-234	Pregnant	255	264	280	290	302	307	333	368
85-235	Pregnant	274	298	309	314	322	328	346	395

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
85-246	Pregnant	242	266	273	284	299	302	308	375
85-247	Pregnant	247	277	288	304	313	319	336	415
85-248	Pregnant	254	299	300	315	325	337	353	434
85-249	Pregnant	256	279	284	299	305	312	331	391
85-250	Pregnant	285	298	304	320	323	332	350	425
85-251	Pregnant	269	285	288	298	308	315	328	407
85-252	Pregnant	273	301	306	318	330	340	358	422
85-253	Pregnant	239	260	269	280	288	295	311	378
85-254	Pregnant	262	284	291	295	305	309	331	403
85-255	Pregnant	288	308	319	328	340	342	364	441
85-256	Pregnant	259	281	286	294	303	316	333	386
85-257	Pregnant	255	302	326	334	348	359	376	447
85-258	Pregnant	279	300	306	318	322	331	355	421
85-259	Not Pregnant	245	252	255	257	261	260	262	266
85-260	Pregnant	267	298	314	315	328	335	349	416

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
85-221	Pregnant	18	1	17	0
85-222	Pregnant	15	0	15	0
85-223	Pregnant	15	1	14	0
85-224	Pregnant	18	1	17	0
85-225	Not Pregnant	0	0	0	0
85-226	Pregnant	16	0	16	0
85-227	Pregnant	14	0	14	0
85-228	Pregnant	16	2	14	0
85-229	Pregnant	16	1	15	0
85-230	Pregnant	16	0	16	0
85-231	Pregnant	11	1	10	0
85-232	Pregnant	16	1	15	0
85-233	Pregnant	18	1	17	0
85-234	Pregnant	20	10	10	0
85-235	Pregnant	15	3	12	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
85-246	Pregnant	16	2	14	0
85-247	Pregnant	13	0	13	0
85-248	Pregnant	15	0	15	0
85-249	Pregnant	16	3	13	0
85-250	Pregnant	17	1	16	0
85-251	Pregnant	17	1	16	0
85-252	Pregnant	17	2	15	0
85-253	Pregnant	16	2	14	0
85-254	Pregnant	17	0	17	0
85-255	Pregnant	17	0	17	0
85-256	Pregnant	13	1	12	0
85-257	Pregnant	15	1	14	0
85-258	Pregnant	16	0	16	0
85-259	Not Pregnant	0	0	0	0
85-260	Pregnant	15	2	13	0

TABLE 7

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

Individual Average Daily Food Consumption (g)

Control Group

Number	Reproductive Status	Gestation Period (days)			
		1-6	6-13	13-16	16-21
85-221	Pregnant	22.8	25.1	22.3	25.4
85-222	Pregnant	15.6	21.3	21.7	24.2
85-223	Pregnant	20.6	22.9	21.7	24.4
85-224	Pregnant	22.6	26.3	26.0	30.0
85-225	Not Pregnant	18.8	19.0	22.7	20.2
85-226	Pregnant	21.4	23.0	23.0	27.0
85-227	Pregnant	20.4	24.7	26.3	27.8
85-228	Pregnant	23.0	23.9	23.0	25.4
85-229	Pregnant	18.4	21.4	20.7	25.0
85-230	Pregnant	22.4	25.7	25.0	26.4
85-231	Pregnant	25.2	28.9	29.0	31.0
85-232	Pregnant	23.2	27.7	25.7	31.2
85-233	Pregnant	20.6	23.3	22.7	25.8
85-234	Pregnant	18.6	24.6	26.7	27.6
85-235	Pregnant	20.4	23.3	24.0	25.4

TABLE 7 (cont.)

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

Individual Average Daily Food Consumption (g)

1000 mg/kg/day Group

Number	Reproductive Status	Gestation Period (days)			
		1-6	6-13	13-16	16-21
85-246	Pregnant	19.2	23.0	21.3	24.8
85-247	Pregnant	18.6	24.1	25.3	30.8
85-248	Pregnant	24.4	26.6	29.3	31.8
85-249	Pregnant	20.4	22.3	23.7	26.2
85-250	Pregnant	23.0	23.9	23.3	26.2
85-251	Pregnant	19.2	22.6	23.7	26.6
85-252	Pregnant	21.0	23.9	24.0	26.8
85-253	Pregnant	21.8	23.6	22.0	25.4
85-254	Pregnant	21.8	23.6	23.3	27.0
85-255	Pregnant	24.0	25.6	23.7	29.4
85-256	Pregnant	19.8	22.6	23.0	27.4
85-257	Pregnant	24.8	28.9	28.7	30.4
85-258	Pregnant	19.2	21.1	22.7	26.0
85-259	Not Pregnant	16.0	17.9	17.0	20.2
85-260	Pregnant	20.4	23.1	22.0	28.4

TABLE 8

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

Individual Female Dosage

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	
85-246	289	318	306	314	1087
85-247	306	333	363	342	1118
85-248	322	367	421	383	1189
85-249	302	308	340	317	1050
85-250	321	329	335	331	1031
85-251	304	312	340	320	1053
85-252	326	329	344	334	1025
85-253	284	326	316	323	1137
85-254	303	326	335	328	1083
85-255	334	353	340	349	1045
85-256	302	312	330	317	1050
85-257	341	399	411	402	1179
85-258	322	292	325	302	938
85-259	258	247	244	246	953
85-260	323	320	316	318	985

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: February 13, 1985
- B. Initiate Dosing: February 19, 1985
- C. Initiate Day 21 Sacrifice: March 6, 1985
5. Purpose: To determine potential toxic effects as evidenced by clinical signs, body weights, and fetal viability.
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 or more
2	SC-19129	1000	10 or more

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- β -aspartyl-L-phenylalanine, 1-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 and day 13 SC-19129/diet concentrations will be based on food consumption and body weight data obtained on day 5 and day 12 from the first rats to reach this stage of gestation.

10. Study Design Conditions:

- A. Animals: Twenty or more virgin female rats of the Charles River COBS CD strain (Canada) 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 3 to 4 months of age and weigh 200-300 grams at the start of the study. The rats will be allowed approximately one week 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 suspended, stainless steel, wire mesh cages 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 $72^{\circ} \pm 5^{\circ}\text{F}$ 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 rats will be housed with breeder colony males (1 female/male) of the same strain. 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 CO₂ 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. Appropriate analyses will be performed if necessary.

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 2/12/85
Date

B. F. N. Kotsonis, Ph.D.
Diplomate, A.B.T.
Director, Toxicology
Product Safety Assessment:

F. N. Kotsonis 2/12/85
Date

C. F. E. Kohn, Ph.D.
Senior Director,
Product Safety Assessment:

F. E. Kohn 2/12/85
Date

PROTOCOL AMENDMENT
March 14, 1985

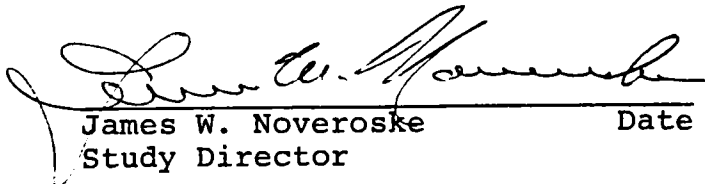
Protocol Amendment #1
S.A. 2609
A Range-Finding Study of SC-19129 in Pregnant Rats

The following is a change to the approved protocol:

1. Page 2, Sect. 9.D.1.a. - Change "Will be determined before use" to "Will be determined before and after use."

Reason for change - To provide data on stability of test article.

Approval:

 Mar. 14, 1985
James W. Noveroske Date
Study Director

S.A. 2609

PROTOCOL AMENDMENT
March 14, 1985

Protocol Amendment #2
S.A. 2609
A Range-Finding Study of SC-19129 in Pregnant Rats

The following is a change to the approved protocol:

1. Page 4, Sect. 13 - Change "The mean values and standard deviations" to "The mean values".

Reason for change - Calculation of standard deviations
not needed to evaluate data variables.

Approval:

 Mar. 14, 1985
James W. Noveroske Date
Study Director

S.A. 2609

PROTOCOL AMENDMENT
May 13, 1985

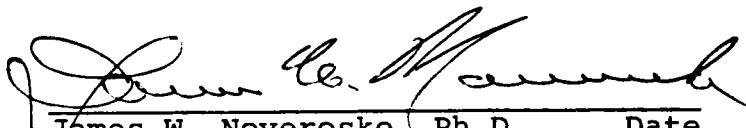
Protocol Amendment #3
S.A. 2609
A Range-Finding Study of SC-19129 in Pregnant Rats

The following is a change to the approved protocol:

1. Page 4, Sect. 13 - Change "The mean values of each variable will be determined. Appropriate analyses will be performed if necessary." to "Maternal body weights, body weight change, and food consumption were analyzed using a Student's t-test. The Mann-Whitney U Test was used to analyze the numbers of implantations, resorptions, and live fetuses per litter. Numbers of corpora lutea were not analyzed or tabulated in this report. All tests were two-tailed and significance levels achieved have been reported at the 5% level."

Reason for change - A thorough analysis of variables was considered necessary.

Approval:


James W. Noveroske, Ph.D. Date
Study Director

5/14/85

S.A. 2609

Appendix B

R&D PRODUCT DEVELOPMENT FUNCTION
REPORT REVIEW AND RELEASE

Page 1 of 3

DEPARTMENT: Product Development Analytical

DOCUMENT NUMBER: F-320-034-08

TITLE OF REPORT: SC-19129

TYPE OF REPORT: Analytical Summary in Support of Product Safety
Assessment Study Number 2609

AUTHOR(S):	DATE	REVIEWER(S):	DATE
<u>James J. [Signature]</u>	<u>08-Mar-85</u>	<u>D. L. [Signature]</u>	<u>5-11-85</u>
_____	_____	_____	_____
_____	_____	_____	_____

TECHNICAL WRITER:

Michele Newcomb Michele Newcomb 3/13/85

APPROVAL:	DATE
<u>[Signature]</u>	<u>13-Mar-85</u>
_____	_____

APPROVAL FOR RELEASE:

<u>[Signature]</u>	<u>3/19/85</u>	<u>[Signature]</u>	<u>3/19/85</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. 2609

B-1

Subject: SC-19129

Summary Number: F-320-034-08

Applicable to SA Study Number: 2609

Test Article Characterization and Stability

Lot 84K-047-101 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

Lot Designation	84K-047-101
Analysis Report #	84N1058
Completion Date	10/16/84
Identity (HPLC)	Conforms to Standard
Assay BY HPLC (on dried basis)	100.0% n = 3 s = 0.2
Water	9.8%

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-320-034-08

Applicable to SA Study Number: 2609

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. 2609

B-3

Revision or Amendment Notice

Searle Research and Development

SEARLE

Notice of change to report stored in R&D Central File

Departmental Document or PSA Study Number S.A. 2609 ✓	R&D Central File Holding Number R-19129-20749-00 ✓
Originating Department Product Safety Assessment ✓	
Report Title A Range-Finding Study of SC-19129 in Pregnant Rats	

Affected
Portion of
Report

Indicate page numbers or text sections and describe how revised version differs from original.

Analytical Report - Appendix B

Reason for Change

The attached analytical report replaces the existing analytical report in Appendix B /

Approval
Signature

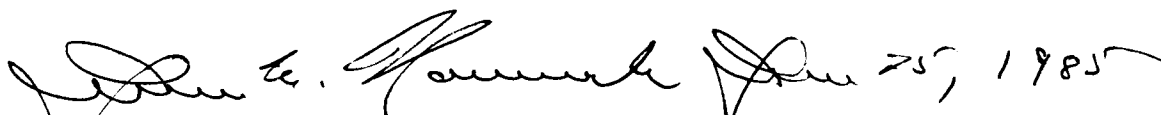
Individual Responsible for Change	Date	Study Dir./ Author/ Dept. Dir.	Date
		<i>[Signature]</i>	6/24/85
Authorized Submitter	Date	R&D CF Information Scientist	Date
<i>[Signature]</i>	6/26/85	<i>[Signature]</i>	6/26/85

REPORT AMENDMENT

A Range-Finding Study of SC-19129 in Pregnant Rats
S.A. 2609
Report Amendment #1

The attached analytical report replaces the existing
analytical report in Appendix B.

Approval:


James W. Noveroske, Ph.D. Date
Study Director

R&D PRODUCT DEVELOPMENT FUNCTION
REPORT REVIEW AND RELEASE

Page 1 of 3

DEPARTMENT: Product Development Analytical

DOCUMENT NUMBER: F-320-034-08A

TITLE OF REPORT: SC-19129

TYPE OF REPORT: Analytical Summary in Support of Product Safety
Assessment Study Number 2609

AUTHOR(S):	DATE	REVIEWER(S):	DATE
<u>James J. J.</u>	<u>20 June '85</u>	<u>Daniel L. Sweeney</u>	<u>6-21-85</u>
_____	_____	_____	_____
_____	_____	_____	_____

TECHNICAL WRITER:

Michele Newcomb Michele Newcomb

APPROVAL:	DATE
<u>James J.</u>	<u>21 June -85</u>
_____	_____

APPROVAL FOR RELEASE:

<u>R. Baum</u>	<u>6/21/85</u>	<u>L. Hansen/sep</u>	<u>6/24/85</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

Justification for Change:

1. Post-study analysis data was added.

Subject: SC-19129

Summary Number: F-320-034-08A

Applicable to SA Study Number: 2609

Test Article Characterization and Stability

Lot 84K-047-101 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

	Pre-Study	Post-Study
Lot Designation	84K-047-101	84K-047-101
Analysis Report	84N1058	85N0283
Completion Date	10/16/84	04/03/85
Identity (HPLC)	Conforms to Standard	Conforms to Standard
Assay by HPLC (on dried basis)	100.0% n = 3 s = 0.2	99.2% n = 3 s = 0.2
Water	9.8%	9.8%

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-320-034-08A

Applicable to SA Study Number: 2609

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.