

REPORT AMENDMENT NUMBER 1


FOUR WEEK DIETARY ADMIX TOXICITY STUDY OF SC-19129
IN THE DOG

S.A. 2449

CHANGE: The attached is an amendment to the original
report.

REASON FOR CHANGE: The original report did not include the
Analytical Summary from the Product
Development Analytical Department and
the Bioavailability Report from the
Department of Drug Metabolism.

APPROVAL:

 7-17-85

James L. Allen, Ph.D. Date
Diplomate, A.B.T.
Study Director
Product Safety Assessment

FOUR WEEK DIETARY ADMIX TOXICITY STUDY OF
SC-19129 IN THE DOG

REPORT AMENDMENT 1

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Report Document Number: PS 85S-2449B

DEPARTMENT OF PRODUCT SAFETY ASSESSMENT
G. D. Searle & Co., Skokie, IL

Title: Four Week Dietary Admix Toxicity Study of SC-19129
in the Dog

Author(s): M. Napier (Analytical Summary)
E. Burton (Bioavailability Report)

Study No.: S.A. 2449

Date: July 17, 1985 Type of Report: Report Amendment No. 1

Summary:

SC-19129 was administered by dietary admix for four weeks to Beagle dogs (3/sex/dosage group) at intended dosages of 0, 250, 500, and 1000 mg/kg.

This report amendment includes the final analytical summary from the Product Development Analytical Department that includes data for test article characterization and stability, and concentration, stability, and homogeneity of the test article in carrier. The data indicate that the test article was stable and was given at the approximate intended concentrations in the diet. In addition, the test article was homogeneously distributed in the diet.

This amendment also includes a report of the test article bioavailability analyses from the Department of Drug Metabolism. The plasma concentration data demonstrate that SC-19129 or its free acid, β -AP, was absorbed at all dose levels by all dogs. Plasma C_{max} and AUC values for β -AP increased with dose and when normalized to the actual doses received by the diet admix route, were proportional to dose. The C_{max} (mean \pm SEM) of the pooled sexes were 5.78 \pm 1.05, 9.30 \pm 1.15 and 23.6 \pm 1.9 on day 28. Steady state plasma levels were attained by day 15 of the study. There was no tendency towards dose accumulation of β -AP in the plasma.

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R&D PRODUCT DEVELOPMENT FUNCTION
REPORT REVIEW AND RELEASE

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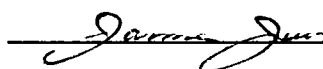
DEPARTMENT: Product Development Analytical

DOCUMENT NUMBER: F-306-034-02A

TITLE OF REPORT: SC-19129

TYPE OF REPORT: Analytical Summary in Support of Product Safety
Assessment Study Number 2449


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		Product Development	

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

Justification for Change:

1. Stability, homogeneity, and concentration data have been added.

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A-1

Subject: SC-19129

Summary Number: F-306-034-02A

Applicable to SA Study Number: 2449

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
Report of Analysis	84N1058	85N0013
Completion Date	10/16/84	01/24/85
Identity (HPLC)	Conforms to Standard	Conforms to Standard
Assay: HPLC (on dried basis)	(HPLC) 100.0% n = 3 s = 0.2	(HPLC) 98.5% n = 3 s = 1.3
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.

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A-2

Subject: SC-19129

Summary Number: F-306-034-02A

Applicable to SA Study Number: 2449

Stability of Test Article in Carrier

The stability of SC-19129 (Lot 84K-047-101) in canine diet admixture (Ralston Purina 5007) was determined by using a stability indicating HPLC method (M84-048-A). Diet admixture samples prepared at dosing concentrations of 1 g and 200 g of SC-19129/kg of canine diet admixture were stored at ambient conditions.

The 1 g/kg dosing concentration samples were prepared over a seventeen day period for days 0, 3, 6, 7, 10, 14, and 17. The 200 g/kg dosing concentration samples were prepared over a seventeen day period for days 0, 2, 6, 7, 10, 14, and 17. The statistics are based on the relative percent recovery values. The results of the analyses are presented in Tables 2 and 3.

For the low dosing concentration, 1 g/kg, Table 2, the results of the linear regression analysis (MINITAB, Reference 1) for the relative percent recovery of SC-19129 versus time, gave a t-ratio value less than the table value, $t = 1.812$ (Reference 2, Table A-4), indicating no significant downward trend. The correlation between the observed recovery values and the predicted recovery values exhibited a normal probability plot (Reference 1 and 3). The results indicate that SC-19129 in canine diet admixture at 1 g/kg, stored at ambient conditions, does not undergo significant degradation for at least seventeen days.

For the high dosing concentration, 200 g/kg, Table 3, the results of the linear regression analysis (MINITAB, Reference 1) for the relative percent recovery of SC-19129 versus time, gave a t-ratio value less than the table value, $t = 1.812$ (Reference 2, Table A-4), indicating no significant downward trend. The correlation between the observed recovery values and the predicted recovery values exhibited a normal probability plot (References 1 and 3). The results indicate that SC-19129 in canine diet admixture at 200 g/kg, stored at ambient conditions, does not undergo significant degradation for at least seventeen days.

Since SC-19129 is stable at low and high dosing concentrations at ambient conditions, all dosing concentrations between 1 g and 200 g of SC-19129/kg of canine diet admixture are considered to be stable for at least seventeen days when stored under equivalent conditions.

Notebook Reference: M. Napier, PDAD-0028, pp. 290-303.

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Subject: SC-19129

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Table 2

Stability of Test Article in Carrier
1 g of SC-19129/kg of Canine Diet Admixture

Time (Days)	Sample	% SC-19129 Recovered	% Relative Recovery
0	3	100.8	100.0
	4	99.9	
	5	100.6	
	6	100.9	
		$\bar{X} = 100.6$	
Reference			
3	1	100.8	100.2
	2	101.0	100.4
6	1	100.1	99.5
	2	99.5	98.9
7	1	97.7	97.1
	2	98.7	98.1
10	1	99.4	98.8
	2	101.5	100.9
14	1	99.8	99.2
	2	98.6	98.0
17	1	99.0	98.4
	2	98.9	98.3
Intercept			99.8
Slope			- 0.0865
t-Ratio			- 1.34
t (0.95, df = 10)			1.812
Correlation: Predicted vs Observed			0.979

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Subject: SC-19129

Summary Number: F-306-034-02A

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Table 3

Stability of the Test Article in Carrier
200 g of SC-19129/kg of Canine Diet Admixture

Time (Days)	Sample	% SC-19129 Recovered	% Relative Recovery
0	3	97.2	
	4	101.3	
	5	98.7	
	6	99.3	100.0
		$\bar{X} = 99.1$	
Reference			
2	1	99.1	100.0
	2	101.4	102.3
6	1	98.5	99.4
	2	101.1	102.0
7	1	99.5	100.4
	2	94.0	94.9
10	1	98.1	99.0
	2	98.3	99.2
14	1	97.3	98.2
	2	94.6	95.5
17	1	99.9	100.8
	2	98.6	99.5
Intercept			100
Slope			- 0.128
t-Ratio			- 1.00
t (0.95, df = 10)			1.812
Correlation: Predicted vs Observed			0.943

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Subject: SC-19129

Summary Number: F-306-034-02A

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Homogeneity of Test Article in Carrier

The homogeneity of SC-19129 (Lot 84K-047-101) in canine diet admixture (Ralston Purina 5007) was determined for the low and the high dosing concentrations during Study Weeks 1 and 4. The analyses were conducted by using a stability indicating HPLC method (M84-048-A).

Product Safety Assessment personnel prepared and sampled the diet admixture during Study Weeks 1 and 4. For Study Week 1 and Study Week 4, nine 1 gram samples were randomly taken from the storage container using a bag trier.

The results of the analyses are presented in Tables 4 and 5.

The results for homogeneity for the Study Week 1, low dosing concentration (Table 4, column 2) were shown to be normally distributed ($\alpha = 0.05$), having a normality correlation coefficient above the table value, $t = 0.912$ (References 1 and 3). The calculated tolerance interval (Reference 2, Table A-6) indicates that with 95% confidence, at least 95% of the future samples should be between 11.1 and 12.5 g/kg diet admixture for the low dosing concentration. This is equivalent to $\pm 5.9\%$. The SC-19129 is considered uniformly distributed in the diet admixture used.

The results for homogeneity for the Study Week 1, high dosing concentration (Table 4, column 4), were shown to be normally distributed ($\alpha = 0.05$), having a normality correlation coefficient above the table value, $t = 0.912$. The calculated tolerance interval indicates that with 95% confidence, at least 95% of future samples should be between 43.6 and 47.8 g/kg diet admixture for the high dosing concentration. This is equivalent to $\pm 4.6\%$. The SC-19129 is considered uniformly distributed in the diet admixture used.

Since the Study Week 1 low and high dosing concentrations are shown to be homogeneous, all the Study Week 1 dosing concentrations are considered homogeneous.

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Subject: SC-19129

Summary Number: F-306-034-02A

Applicable to SA Study Number: 2449

The results for homogeneity for the Study Week 4 low dosing concentration (Table 5, column 2) were shown to be normally distributed ($\alpha = 0.05$), having a normality correlation coefficient above the table value, $t = 0.912$. The calculated tolerance interval indicates that with 95% confidence, at least 95% of the future samples should be between 11.2 and 12.6 g/kg diet admixture for the low dosing concentration. This is equivalent to + 5.9%. The SC-19129 is considered uniformly distributed in the diet admixture used.

The results for the homogeneity for the Study Week 4 high dosing concentration (Table 5, column 4) were shown to be normally distributed ($\alpha = 0.05$), having a normality correlation coefficient above the table value, $t = 0.912$. The calculated tolerance interval indicates that with 95% confidence, at least 95% of the future samples should be between 44.4 and 48.0 g/kg diet admixture for the high dosing concentration. This is equivalent to + 3.9%. The SC-19129 is considered uniformly distributed in the diet admixture used.

Since the Study Week 4 low and high dosing concentrations are shown to be homogeneous, all the Study Week 4 diet admixture dosing concentrations are considered homogeneous.

Additionally, since the Study Week 1 and Study Week 4 diet admixtures are shown to be homogeneous, all diet admixtures prepared for the study are considered homogeneous.

Notebook Reference: M. Napier, PDAD-0028, pp. 236-248, 273-284.

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Table 4

Homogeneity of Test Article in Carrier

Study Week 1

SC-19129, g/kg

Report of Analysis	84-2032		84-2034
Dose	Low		High
Sample		Sample	
G00104	11.6	G00116	46.0
G00105	11.7	G00117	46.3
G00106	11.6	G00118	45.4
G00107	11.8	G00119	45.3
G00108	11.8	G00120	45.7
G00109	12.0	G00121	45.4
G00110	12.0	G00122	46.6
G00111	11.9	G00123	45.8
G00112	11.9	G00124	44.7
\bar{X}	11.8		45.7
s	0.2		0.6
Normality Correlation Coefficient	0.996		0.991
Tolerance Interval	± 0.7		± 2.1

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Table 5

Homogeneity of Test Article in Carrier

Study Week 4

SC-19129, g/kg

Report of Analysis	84-2250		84-2252
Dose	Low		High
Sample		Sample	
G00428	11.5	G00440	45.3
G00429	12.0	G00441	47.3
G00430	12.0	G00442	45.9
G00431	11.8	G00443	45.9
G00432	12.2	G00444	46.2
G00433	12.0	G00445	46.3
G00434	12.0	G00446	46.1
G00435	11.8	G00447	46.6
G00436	12.1	G00448	46.2
\bar{X}	11.9		46.2
s	0.2		0.5
Normality Correlation Coefficient	0.965		0.963
Tolerance Interval	± 0.7		± 1.8

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Concentration of Test Article in Carrier

The concentration of SC-19129 (Lot 84K-047-101) in canine diet admixtures (Ralston Purina 5007) was determined during Study Weeks 1 and 4. The analyses were conducted using a stability indicating HPLC method (M84-048-A).

Product Safety Assessment personnel prepared and sampled the diet admixtures. For Study Week 1 and Study Week 4, three or nine 1 gram samples for each dosing concentration were randomly taken from the storage container using a bag trier.

The dosing concentrations are presented in Chart 1.

The results of the analyses are reported in Tables 6 through 9.

Notebook Reference: M. Napier, PDAD-0028, pp. 236-248, 273-289.
K. Klimovitz, PDAD-0096, pp. 9-24.

Subject: SC-19129

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Chart 1
Dosing Concentrations
SC-19129, g/kg

Study Week	Low	Medium	High
1	12.5	25	50
4	12.5	25	50

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Subject: SC-19129

Summary Number: F-306-034-02A

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Table 6

Concentration of Test Article in Carrier

Study Week 1

Dosing Control Sample

SC-19129, g/kg

Report of Analysis	84-2031
Dose	Dosing Control Sample
Sample	
G00101	Less than 0.04
G00102	Less than 0.04
G00103	Less than 0.04

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Subject: SC-19129

Summary Number: F-306-034-02A

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Table 7
Concentration of Test Article in Carrier
Study Week 1
SC-19129, g/kg

Report of Analysis	84-2032		84-2033		84-2034
Dose	Low		Medium		High
Sample		Sample		Sample	
G00104	11.6	G00113	23.5	G00116	46.0
G00105	11.7	G00114	23.5	G00117	46.3
G00106	11.6	G00115	22.8	G00118	45.4
G00107	11.8			G00119	45.3
G00108	11.8			G00120	45.7
G00109	12.0			G00121	45.4
G00110	12.0			G00122	46.6
G00111	11.9			G00123	45.8
G00112	11.9			G00124	44.7
\bar{X}	11.8		23.3		45.7
S	0.2		0.4		0.6

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Subject: SC-19129

Summary Number: F-306-034-02A

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Table 8
Concentration of Test Article in Carrier
Study Week 4
Dosing Control Sample
SC-19129, g/kg

Report of Analysis	84-2249
Dose	Dosing Control Sample
Sample	
G00425	Less than 0.04
G00426	Less than 0.04
G00427	Less than 0.04

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Subject: SC-19129

Summary Number: F-306-034-02A

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Table 9
Concentration of Test Article in Carrier
Study Week 4
SC-19129, g/kg

Report of Analysis	84-2250		84-2251		84-2252
Dose	Low		Medium		High
Sample		Sample		Sample	
G00428	11.5	G00437	23.9	G00440	45.3
G00429	12.0	G00438	23.4	G00441	47.3
G00430	12.0	G00439	22.7	G00442	45.9
G00431	11.8			G00443	45.9
G00432	12.2			G00444	46.2
G00433	12.0			G00445	46.3
G00434	12.0			G00446	46.1
G00435	11.8			G00447	46.6
G00436	12.1			G00448	46.2
\bar{X}	11.9		23.3		46.2
s	0.2		0.6		0.5

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A-15

Subject: SC-19129

Summary Number: F-306-034-02A

Applicable to SA Study Number: 2449

References:

1. Ryan, Jr., T. A., Joiner, B. L., and Ryan, B. F., "MINITAB Student Handbook", 1976, Wadsworth Publishing Co., Inc.
2. Natrella, M. G., "Experimental Statistics, National Bureau of Standards Handbook 91", 1963, US Government Printing Office
3. Filliben, J., Technometrics, 17 (1), 111 (1975)

Subject: SC-19129

Summary Number: F-306-034-02A

Applicable to SA Study Number: 2449

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.

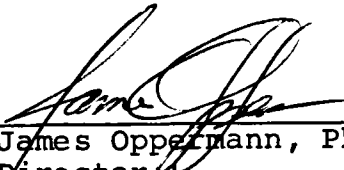
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APPENDIX B

GLP COMPLIANCE STATEMENT

To my knowledge, the study described in the attached report (SA-2449) was conducted in compliance with the Good Laboratory Practices Regulations as set forth in part 58, 21 CFR.

 5/2/85
James Oppermann, Ph.D. Date
Director
Department of Drug Metabolism

S.A. 2449

B-1

Evaluation of the Plasma Concentration Data
from the Four Week Dietary Admix Toxicity Study
of SC-19129 in the Dog, S.A.2449

Document Number: MRC-851-0035

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MRC-851-0035

B-2

**Evaluation of the Plasma Concentration Data
from the Four Week Dietary Admix Toxicity Study
of SC-19129 in the Dog, S.A. 2449**

I. Collection and Analysis of Samples

Plasma samples were collected at 2, 4, 6 and 24 hours after the start of the feeding period on days 1, 15 and 28. Plasma samples were also collected prior to the start of the feeding period (0 hours) on day 1. The concentration of N-L- β -aspartyl-L-phenylalanine (β -AP), the free acid of SC-19129, in each plasma sample was determined by a high performance liquid chromatography (HPLC) procedure (1).

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II. Statistical Analysis

The maximum observed concentration (C_{max}) of β -AP for each dog on each day was obtained by inspection of the plasma concentration data (Table 1). Areas under the plasma concentration-time curves (AUC) from 0 to 6 hours after the initiation of dosing were calculated using the trapezoidal rule. The concentration of β -AP at 0 hours on days 15 and 28 were assumed to be zero for these calculations. The C_{max} and AUC values were normalized by multiplying each value by 250 mg/kg and dividing the product obtained by the measured dose (reference 2, Appendix D) received by each dog on each day. The normalized C_{max} and AUC values were tested for dose, sex and day effects using analysis of variance techniques.

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III. Results and Discussion

A. Absorption of the Test Article:

Studies with [^{14}C]-SC-19129 have indicated that SC-19129 is not detectable in the systemic circulation following oral administration (3). An assay was therefore developed for the free acid, β -AP, in plasma (1).

Individual plasma concentrations of β -AP and individual AUC values are given in Tables 1 and 2, respectively. Mean plasma concentrations of β -AP are given in Table 3 and shown in Figures 1-3. Plasma concentrations of β -AP were measureable in all treated animals on each day, demonstrating absorption of SC-19129 or its free acid, β -AP, at all doses.

B. Relationship of Plasma Concentration to Dosage:

Mean C_{max} values (mcg/ml) for the low, medium and high doses respectively were 6.53 ± 0.80 (\pm standard error of the mean both sexes combined), 13.7 ± 1.7 and 28.1 ± 1.7 on day 1, 7.82 ± 0.57 , 11.8 ± 1.8 and 31.6 ± 3.3 on day 15 and 5.78 ± 1.05 , 9.30 ± 1.15 and 23.6 ± 1.9 on day 28 (Table 4). The mean AUC values ([mcg/ml]hours) for the low, medium and high doses respectively were 23.3 ± 2.8 , 45.9 ± 4.7 and 103 ± 4 on day 1, 31.1 ± 2.7 , 47.7 ± 7.7 and 129 ± 11 on day 15 and 21.7 ± 4.4 , 36.9 ± 5.0 and 95.7 ± 8.0 on day 28 (Table 5). Thus mean C_{max} values (Figure 4) and mean AUC values (Figure 5) for plasma β -AP increased as the dose was increased. Dose proportionality was evaluated using the C_{max} and AUC values normalized by dividing by the respective doses received. The

normalized Cmax (Table 6 and Figure 6) and normalized AUC (Table 7 and Figure 7) values were proportional to dose on all sampling days (Tables 8, 9).

Plasma Cmax and AUC values tended to be somewhat lower (approximately 10-20%, Tables 4, 5) for females than for males. However the average normalized Cmax and averaged normalized AUC values differed by less than 10% between males and females (Tables 6, 7) and were not significantly different between sexes ($p > 0.05$, Tables 8, 9).

C. Relationship of Plasma Concentrations to Duration of Dosing:

Normalized Cmax values (Table 6, Figure 6) did not differ significantly between days ($p > 0.05$, Table 8). A significant ($p < 0.05$, Table 9) treatment day effect was observed for normalized AUC values (Table 7 and Figure 7). Comparisons between days (Duncans multiple range test) indicated no significant difference between days 15 and 28, but day 15 and day 28 normalized AUC values were significantly higher than day 1 values. The results indicate that steady state plasma concentrations were attained by day 15 of the study. The fact that only one out of 53 samples taken at 24 hours after dosing (dog 84-2012, day 1; Table 1) contained a measureable amount of β -AP (> 1.0 mcg/ml) also indicates no tendency towards dose accumulation of β -AP in the plasma as a result of chronic administration.

IV. Conclusions

The plasma concentration data demonstrate that SC-19129 or its free acid, β -AP, was absorbed at all dose levels by all dogs. Plasma Cmax and AUC values for β -AP increased with dose and, when normalized to the actual doses received by the diet admix route, were proportional to dose. Steady state plasma levels were attained by day 15 of the study.

V. Reference

1. Schmidt, R. E., J. Hill and G. L. Schoenhard. Method Development and Validation of the High Performance Liquid Chromatographic Assay for N-L- β -Aspartyl-L-Phenylalanine (β AP) in Dog Plasma. G. D. Searle & Co., Research and Development Division, MRC-842-0079, May, 1985.
2. Allen, J. L., C. D. Port and R. C. Guy. Four Week Dietary Admix Toxicity Study of SC-19129 in the Dog. Research and Development Division, G. D. Searle & Co. PS 85S-2449A, February, 1985.
3. Burton, E., I. Dressler, K. Hoglund and J. Hribar. Pharmacokinetics and Metabolism of [14 C]-SC-19129 in the Rhesus Monkey. Department of Drug Metabolism, Research and Development Division, G.D. Searle & Co., MRC-842-0056, July, 1985.

VI. Tables

MRC-851-0035 S.A. 2449

Table 1

**Individual Animal Plasma Concentrations of β -AP During
the Four Week Dietary Admix Toxicity Study
of SC-19129 in the Dog, S.A. 2449**

Treatment Day	Time After Administration (hours)	Low Dose (250 mg/kg)							
		Males				Females			
		84-2002	84-2003	84-2004	84-2005	84-2006	84-2007		
1	0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0		
	2	2.94	2.57	5.07	2.12	3.68	3.21		
	4	5.27	4.70	8.47 ^b	3.45	5.38	3.76		
	6	7.66 ^b	5.76 ^b	7.77	3.66 ^b	8.41 ^b	5.23 ^b		
	24	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0		
15	2	9.25 ^b	4.05	6.56	4.05	4.11	6.59		
	4	6.40	6.36 ^b	9.28 ^b	6.95 ^b	6.37 ^b	8.68 ^b		
	6	5.64	3.32	5.73	5.40	3.28	6.04		
	24	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0		
28	2	5.29 ^b	4.60 ^b	6.03	1.12	1.77 ^b	4.52		
	4	4.76	4.36	7.66	4.64	<1.0	6.29 ^b		
	6	3.82	3.58	9.25 ^b	7.45 ^b	<1.0	4.30		
	24	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0		

^a The lowest concentration used in the standard curve for this assay is 1.0 mcg/ml, the established sensitivity limit of the assay. Concentration values lower than 1.0 mcg/ml are indicated by <1.0.

^b The indicated value is the C_{max} value.

Table 1 (cont'd)

Individual Animal Plasma Concentrations of β -AP During
the Four Week Dietary Admix Toxicity Study
of SC-19129 in the Dog, S.A. 2449

Treatment Day	Time After Administration (hours)	Medium Dose (500 mg/kg)							
		Males		Females		Males		Females	
		84-2008	84-2009	84-2010	84-2011	84-2012	84-2013	84-2012	84-2013
1	0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
	2	4.99	4.86	5.81	3.48	5.55	5.39	5.55	5.39
	4	8.41 ^b	14.1 ^b	20.7 ^b	13.9 ^b	11.1	8.12	11.1	8.12
	6	7.01	5.61	13.9	10.7	14.2 ^b	11.0 ^b	14.2 ^b	11.0 ^b
	24	<1.0	<1.0	<1.0	<1.0	1.11	<1.0	1.11	<1.0
15	2	5.98	9.75	15.5	6.16	4.57	12.9 ^b	4.57	12.9 ^b
	4	10.7 ^b	15.3 ^b	17.7 ^b	6.23 ^b	7.68 ^b	10.6	7.68 ^b	10.6
	6	6.40	10.4	10.8	3.70	5.62	3.35	5.62	3.35
	24	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
	28	5.61 ^b	7.84	9.16	9.16 ^b	5.78	8.52 ^b	5.78	8.52 ^b
28	2	4.59	9.63 ^b	14.3 ^b	6.96	7.28	4.70	7.28	4.70
	4	2.27	5.38	11.6	3.40	8.56 ^b	3.38	8.56 ^b	3.38
	6	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
	24	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
	28	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0

^a The lowest concentration used in the standard curve for this assay is 1.0 mcg/ml, the established sensitivity limit of the assay. Concentration values lower than 1.0 mcg/ml are indicated by <1.0.

^b The indicated value is the C_{max} value.

Table 1 (cont'd)

**Individual Animal Plasma Concentrations of β -AP During
the Four Week Dietary Admix Toxicity Study
of SC-19129 in the Dog, S.A. 2449**

Treatment Day	Time After Administration (hours)	High Dose (1000 mg/kg)							
		Plasma β -AP Concentration (mcg/ml)							
		Males		Females					
		84-2014	84-2015	84-2016	84-2017	84-2018	84-2019		
1	0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0		
	2	19.6	10.7	12.3	16.8	14.1	14.2		
	4	26.8b	29.5b	30.2	23.5	21.4b	26.8b		
	6	7.66	21.8	32.5b	31.8b	19.2	13.5		
	24	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0		
15	2	28.6	28.3b	18.6	16.5	25.7	17.2		
	4	47.8b	22.9	24.8	21.3	31.8b	28.4b		
	6	23.6	21.0	27.4b	26.0b	28.6	23.6		
	24	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0		
28	2	23.1	16.0	12.0	20.2b	17.6b	12.2		
	4	25.3	26.8b	23.6b	19.2	15.8	18.6		
	6	30.5b	25.1	10.2	15.4	9.69	22.7b		
	24	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0 ^c		

a The lowest concentration used in the standard curve for this assay is 1.0 mcg/ml, the established sensitivity limit of the assay. Concentration values lower than 1.0 mcg/ml are indicated by <1.0.

b The indicated value is the C_{max} value.

c Sample not obtained for analysis.

Table 2

Individual Animal AUC Values During
the Four Week Dietary Admix Toxicity Study
of SC-19129 in the Dog, S.A. 2449

Treatment Group	Animal Number	Sex	AUC [(mcg/ml)hours] ^a		
			Day 1	Day 15	Day 28
Low Dose (250 mg/kg)	84-2002	M	24.1	36.9	23.9
	84-2003		20.3	24.1	21.5
	84-2004		34.9	37.4	36.6
	84-2005	F	14.8	27.4	19.0
	84-2006		26.5	24.2	3.54
	84-2007		19.2	36.6	25.9
	84-2008	M	33.8	39.8	22.7
Medium Dose (500 mg/kg)	84-2009		43.5	60.5	40.3
	84-2010		66.9	77.2	58.5
	84-2011	F	45.5	28.5	35.6
	84-2012		47.5	30.1	34.7
	84-2013		38.0	50.4	29.8
	84-2014	M	100	176	127
High Dose (1000 mg/kg)	84-2015		102	123	111
	84-2016		118	114	81.4
	84-2017	F	112	102	94.2
	84-2018		90.2	144	76.5
	84-2019		95.5	115	84.3

^a Areas under the plasma concentration-time curves from 0 to 6 hours calculated by the trapezoidal rule. The concentrations of β -AP at 0 hours were assumed to be zero for these calculations. The above values are rounded to 3 significant digits.

Table 3

Mean Plasma Concentrations of β -AP During
the Four Week Dietary Admix Study
of SC-19129 in the Dog, S.A. 2449

Treatment Group	Treatment Day	Time After Dosing (hours)	β -AP Plasma Concentrationa (mcg/ml)		
			Males	Females	All Dogs
Low Dose (250 mg/kg)	1	2	3.53 \pm 0.78	3.00 \pm 0.46	3.27 \pm 0.42
		4	6.15 \pm 1.17	4.20 \pm 0.60	5.17 \pm 0.73
		6	7.06 \pm 0.65	5.77 \pm 1.40	6.41 \pm 0.75
	15	2	6.62 \pm 1.50	4.92 \pm 0.84	5.77 \pm 0.86
		4	7.35 \pm 0.97	7.33 \pm 0.69	7.34 \pm 0.53
		6	4.90 \pm 0.79	4.91 \pm 0.83	4.90 \pm 0.51
	28	2	5.31 \pm 0.41	2.47 \pm 1.04	3.89 \pm 0.81
		4	5.59 \pm 1.04	3.64 \pm 1.88	4.62 \pm 1.06
		6	5.55 \pm 1.85	3.92 \pm 2.16	4.73 \pm 1.32
Medium Dose (500 mg/kg)	1	2	5.22 \pm 0.30	4.81 \pm 0.66	5.01 \pm 0.34
		4	14.4 \pm 3.6	11.0 \pm 1.7	12.7 \pm 1.9
		6	8.84 \pm 2.56	12.0 \pm 1.1	10.4 \pm 1.4
	15	2	10.4 \pm 2.8	7.88 \pm 2.55	9.14 \pm 1.78
		4	14.6 \pm 2.1	8.17 \pm 1.29	11.4 \pm 1.8
		6	9.20 \pm 1.40	4.22 \pm 0.71	6.71 \pm 1.32
	28	2	7.54 \pm 1.04	7.82 \pm 1.04	7.68 \pm 0.66
		4	9.51 \pm 2.80	6.31 \pm 0.81	7.91 \pm 1.49
		6	6.42 \pm 2.74	5.11 \pm 1.72	5.77 \pm 1.48
High Dose (1000 mg/kg)	1	2	14.2 \pm 2.7	15.0 \pm 0.9	14.6 \pm 1.3
		4	28.8 \pm 1.0	23.9 \pm 1.6	26.4 \pm 1.4
		6	20.7 \pm 7.2	21.5 \pm 5.4	21.1 \pm 4.0
	15	2	25.2 \pm 3.3	19.8 \pm 3.0	22.5 \pm 2.3
		4	31.8 \pm 8.0	27.2 \pm 3.1	29.5 \pm 4.0
		6	24.0 \pm 1.9	26.1 \pm 1.4	25.0 \pm 1.2
	28	2	17.0 \pm 3.2	16.7 \pm 2.4	16.9 \pm 1.8
		4	25.2 \pm 0.9	17.9 \pm 1.0	21.6 \pm 1.8
		6	21.9 \pm 6.1	15.9 \pm 3.8	18.9 \pm 3.5

a Values are the mean \pm SEM of 3 animals for males or females and of 6 animals for all dogs. Individual animal values are in Table 1.

Table 4

Maximum Observed Plasma Concentrations (Cmax)
of β -AP During the Four Week Dietary Admix Toxicity Study
of SC-19129 in the Dog, S.A. 2449

Treatment Group	Sex	Cmax (mcg/ml) ^a			
		Day 1	Day 15	Day 28	
Low Dose (250 mg/kg)	Male	7.30 \pm 0.80	8.30 \pm 0.97	6.38 \pm 1.45	
	Female	5.77 \pm 1.40	7.33 \pm 0.69	5.17 \pm 1.73	
	All Dogs	6.53 \pm 0.80	7.82 \pm 0.57	5.78 \pm 1.05	
Medium Dose (500 mg/kg)	Male	14.4 \pm 3.6	14.6 \pm 2.1	9.85 \pm 2.51	
	Female	13.0 \pm 1.0	8.94 \pm 2.0	8.75 \pm 0.21	
	All Dogs	13.7 \pm 1.7	11.8 \pm 1.8	9.30 \pm 1.15	
High Dose (1000 mg/kg)	Male	29.6 \pm 1.7	34.5 \pm 6.7	27.0 \pm 2.0	
	Female	26.7 \pm 3.0	28.7 \pm 1.7	20.2 \pm 1.5	
	All Dogs	28.1 \pm 1.7	31.6 \pm 3.3	23.6 \pm 1.9	

^a Values are the mean \pm SEM of 3 animals for males or females and of 6 animals for all Dogs. Individual animal values are in Table 1.

Table 5

Areas Under the Plasma Concentration-Time Curves (AUC)
for β -AP During the Four Week Dietary Admix Toxicity Study
of SC-19129 in the Dog, S.A. 2449

Treatment Group	Sex	AUC [(mcg/ml)hours] ^a					
		Day 1		Day 15		Day 28	
Low Dose (250 mg/kg)	Male	26.4 \pm 4.4		32.8 \pm 4.4		27.4 \pm 4.7	
	Female	20.2 \pm 3.4		29.4 \pm 3.7		16.1 \pm 6.6	
	All Dogs	23.3 \pm 2.8		31.1 \pm 2.7		21.7 \pm 4.4	
Medium Dose (500 mg/kg)	Male	48.1 \pm 9.8		59.2 \pm 10.8		40.5 \pm 10.3	
	Female	43.7 \pm 2.9		36.3 \pm 7.0		33.4 \pm 1.8	
	All Dogs	45.9 \pm 4.7		47.7 \pm 7.7		36.9 \pm 5.0	
High Dose (1000 mg/kg)	Male	107 \pm 5		138 \pm 19		106 \pm 13	
	Female	99.4 \pm 6.7		120 \pm 12		85.0 \pm 5.1	
	All Dogs	103 \pm 4		129 \pm 11		95.7 \pm 8.0	

^a Values are the mean \pm SEM of 3 animals for males or females and of 6 animals for all dogs. The means and standard errors were calculated using unrounded AUC values (calculated by the trapezoidal rule). Individual animal values (rounded) are in Table 2.

Table 6

Maximum Plasma Concentrations Normalized
for Dose Received During the Four Week Dietary Admix Study
of SC-19129 in the Dog, S.A. 2449

Treatment Group	Sex	Normalized Cmax ^a		
		Day 1	Day 15	Day 28
Low Dose (250 mg/kg)	Male	7.74 ± 1.12	11.3 ± 2.2	9.70 ± 1.69
	Female	7.30 ± 1.08	9.86 ± 0.63	21.2 ± 11.6
	All Dogs	7.52 ± 0.70	10.6 ± 1.1	15.4 ± 5.8
Medium Dose (500 mg/kg)	Male	9.88 ± 2.84	9.38 ± 0.09	8.31 ± 0.47
	Female	7.77 ± 1.58	7.67 ± 0.52	10.9 ± 3.2
	All Dogs	8.83 ± 1.53	8.52 ± 0.45	9.62 ± 1.58
High Dose (1000 mg/kg)	Male	7.73 ± 0.30	9.07 ± 1.50	9.16 ± 2.02
	Female	6.73 ± 0.76	7.26 ± 0.43	7.33 ± 0.90
	All Dogs	7.22 ± 0.43	8.17 ± 0.81	8.25 ± 1.07

^a Values are the mean ± SEM of 3 animals for males or females and of 6 animals for all dogs. The individual animal Cmax values (Table 1) were multiplied by 250 ÷ Dose received (reference 2, Appendix D) to obtain the normalized Cmax values.

Table 7

Areas Under the Plasma Concentration-Time Curves
for β -AP Normalized for Dose Received During
the Four Week Dietary Admix Toxicity Study
of SC-19129 in the Dog, S.A. 2449

Treatment Group	Sex	Normalized AUC ^a		
		Day 1	Day 15	Day 28
Low Dose (250 mg/kg)	Male	28.3 \pm 6.0	44.9 \pm 9.2	41.8 \pm 5.2
	Female	26.2 \pm 3.6	39.2 \pm 1.4	49.7 \pm 19.4
	All Dogs	27.3 \pm 3.2	42.0 \pm 4.4	45.7 \pm 9.2
Medium Dose (500 mg/kg)	Male	32.4 \pm 7.8	37.6 \pm 1.6	34.1 \pm 1.6
	Female	26.0 \pm 5.2	31.9 \pm 3.7	40.6 \pm 10.2
	All Dogs	29.2 \pm 4.4	34.7 \pm 2.2	37.4 \pm 4.8
High Dose (1000 mg/kg)	Male	27.9 \pm 1.3	36.3 \pm 4.1	35.0 \pm 5.4
	Female	25.0 \pm 1.7	30.4 \pm 3.2	31.6 \pm 5.8
	All Dogs	26.4 \pm 1.2	33.3 \pm 2.7	33.3 \pm 3.6

^a Values are the mean \pm SEM of 3 animals for males or females and of 6 animals for all dogs. The individual animal values (Table 2) were multiplied by $250 \div$ dose received (reference 2, Appendix D) to obtain the normalized AUC values.

Table 8
Analysis of Variance of Plasma β -AP
Normalized Cmax Values

Effect	d.f.	Sum of Squares	F-statistic ^a	P-value
Dose	2	102.1	1.44	0.2757
Sex	1	2.355	0.07	0.8012
Dose*Sex	2	55.23	0.78	0.4815
Animal (Dose*Sex)	12	426.4	-----	-----
Day	2	96.74	1.86	0.1769
Sex*Day	2	92.06	1.77	0.1913
Dose*Day	4	102.6	0.99	0.4331
Sex*Dose*Day	4	85.41	0.82	0.5237
Error	24	623.0	-----	-----

^a Dose, Sex and Dose*Sex effects tested against Animal (Dose*Sex) sum of squares. All other effects tested against Error sum of squares.

Table 9

Analysis of Variance of 0-6 Hour Plasma
 β -AP Normalized AUC Values

Effect	d.f.	Sum of Squares	F-statistic ^a	P-value
Dose	2	491.8	1.40	0.2852
Sex	1	50.99	0.29	0.6005
Dose*Sex	2	37.72	0.11	0.8994
Animal (Dose*Sex)	12	2115.	----	-----
Day	2	1265.	5.18	0.0135*
Sex*Day	2	224.3	0.92	0.4130
Dose*Day	4	278.2	0.57	0.6875
Sex*Dose*Day	4	93.38	0.19	0.9407
Error	24	2933.	----	-----

^a Dose, Sex and Dose*Sex effects tested against Animal (Dose*Sex) sum of squares. All other effects tested against Error sum of squares.

* Significant at the 0.05 level.

VII. Figures

MRC-851-0035 S.A. 2449

-19-

B-21

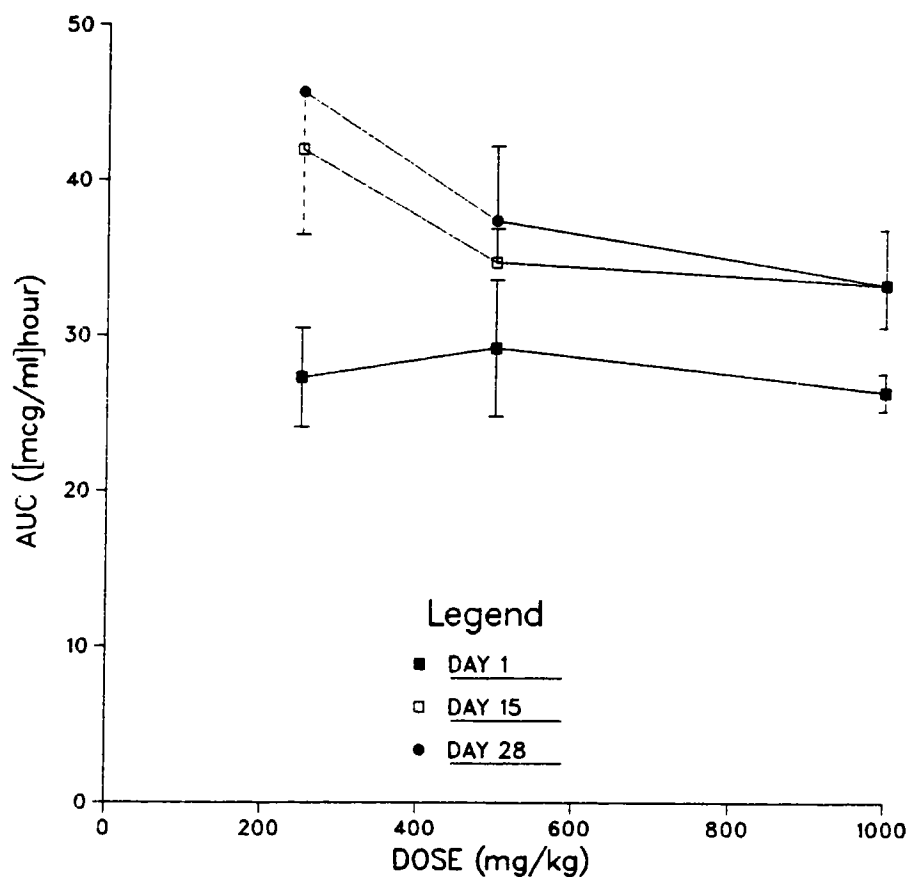


Figure 7. Mean normalized AUC values on days 1 (■), 15 (□) and 28 of study S.A. 2449. Abscissa: intended dose administered (mg/kg). Ordinate: mean normalized AUC ([mcg/ml] hours X [250 mg/kg ÷ Dose received (mg/kg)]). The vertical bars indicate the standard errors of the means. Full standard error bars have been omitted where overlaps with adjoining curves would occur.

MRC-851-0035 S.A. 2449

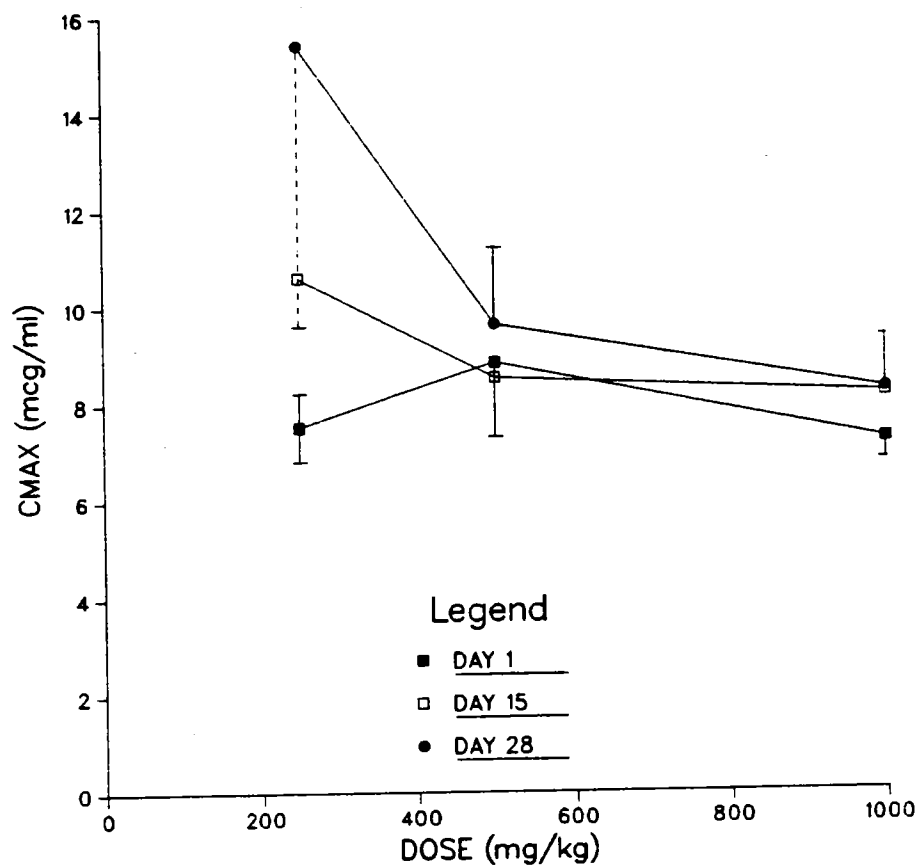


Figure 6. Mean normalized Cmax values on days 1 (■), 15 (□) and 28 of study S.A. 2449. Abscissa: intended dose administered (mg/kg). Ordinate: mean normalized Cmax (mcg/ml X [250 mg/kg ÷ Dose received (mg/kg)]). The vertical bars indicate the standard errors of the mean. Full standard error bars have been omitted where overlaps with adjoining curves would occur.

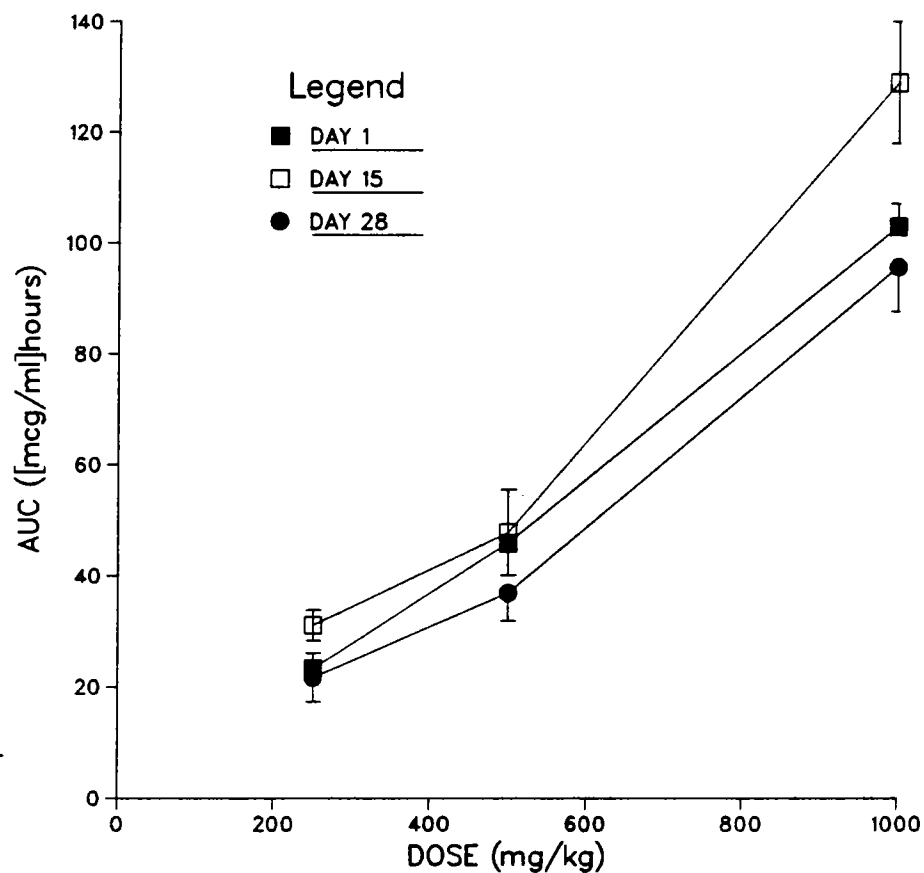


Figure 5. Mean plasma AUC values on days 1 (■), 15 (□) and 28 (●) of study S.A. 2449. Abscissa: intended dose administered (mg/kg). Ordinate: mean area under the plasma concentration-time curve (AUC) of β -AP ([mcg/ml]hours). The vertical bars indicate the standard errors of the means.

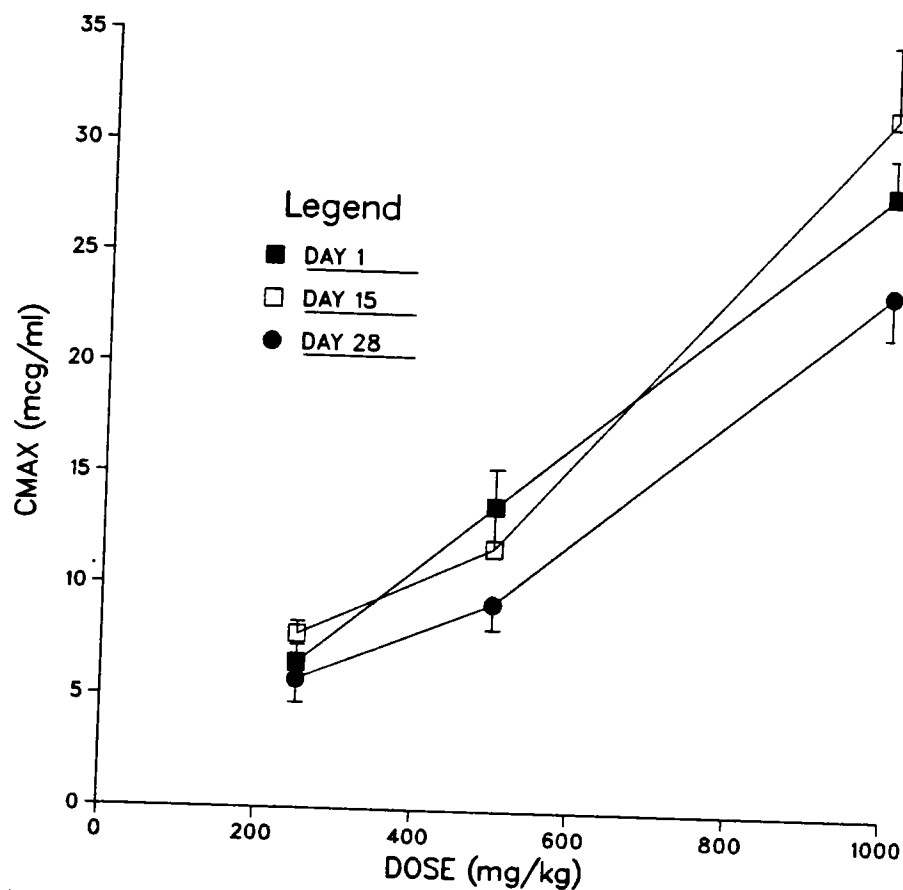


Figure 4. Mean plasma Cmax values on days 1 (■), 15 (□) and 28 (●) of study S.A. 2449. Abscissa: intended dose administered (mg/kg). Ordinate: mean peak plasma concentration (Cmax) of β -AP (mcg/ml). The vertical bars indicate the standard errors of the means.

FOUR WEEK DOG STUDY, S.A. 2449
PLASMA CONCENTRATIONS OF beta-AP
DAY 28

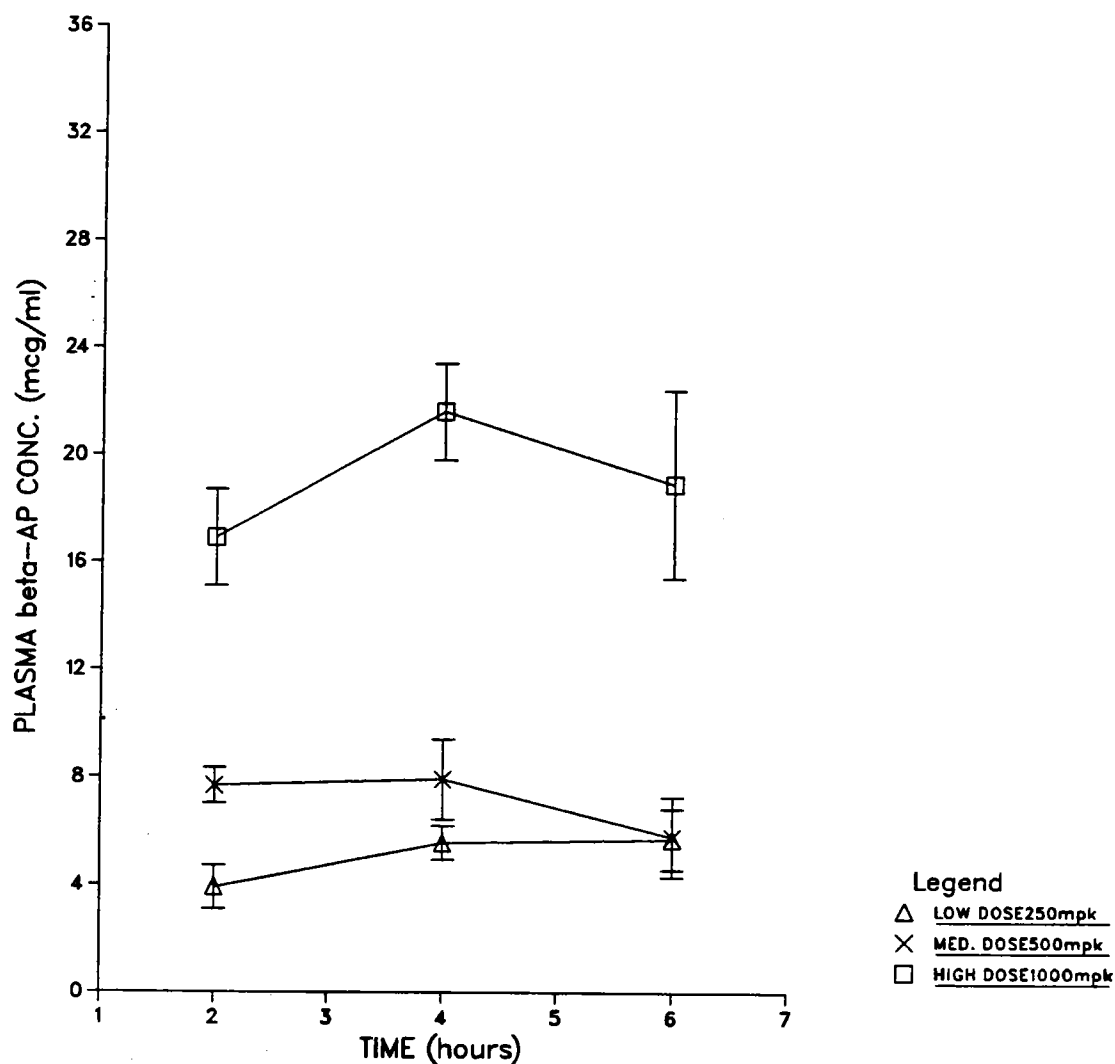


Figure 3. Mean plasma concentrations of β -AP for doses of 250 (Δ), 500 (\times) and 1000 (\square) mg of SC-19129 on day 28 of study S.A. 2449. Abscissa: time after initiation of dose administration (hours). Ordinate: concentration of β -AP in plasma (mcg/ml). The vertical bars indicate the standard errors of the means.

FOUR WEEK DOG STUDY, S.A. 2449
PLASMA CONCENTRATIONS OF β -AP
DAY 15

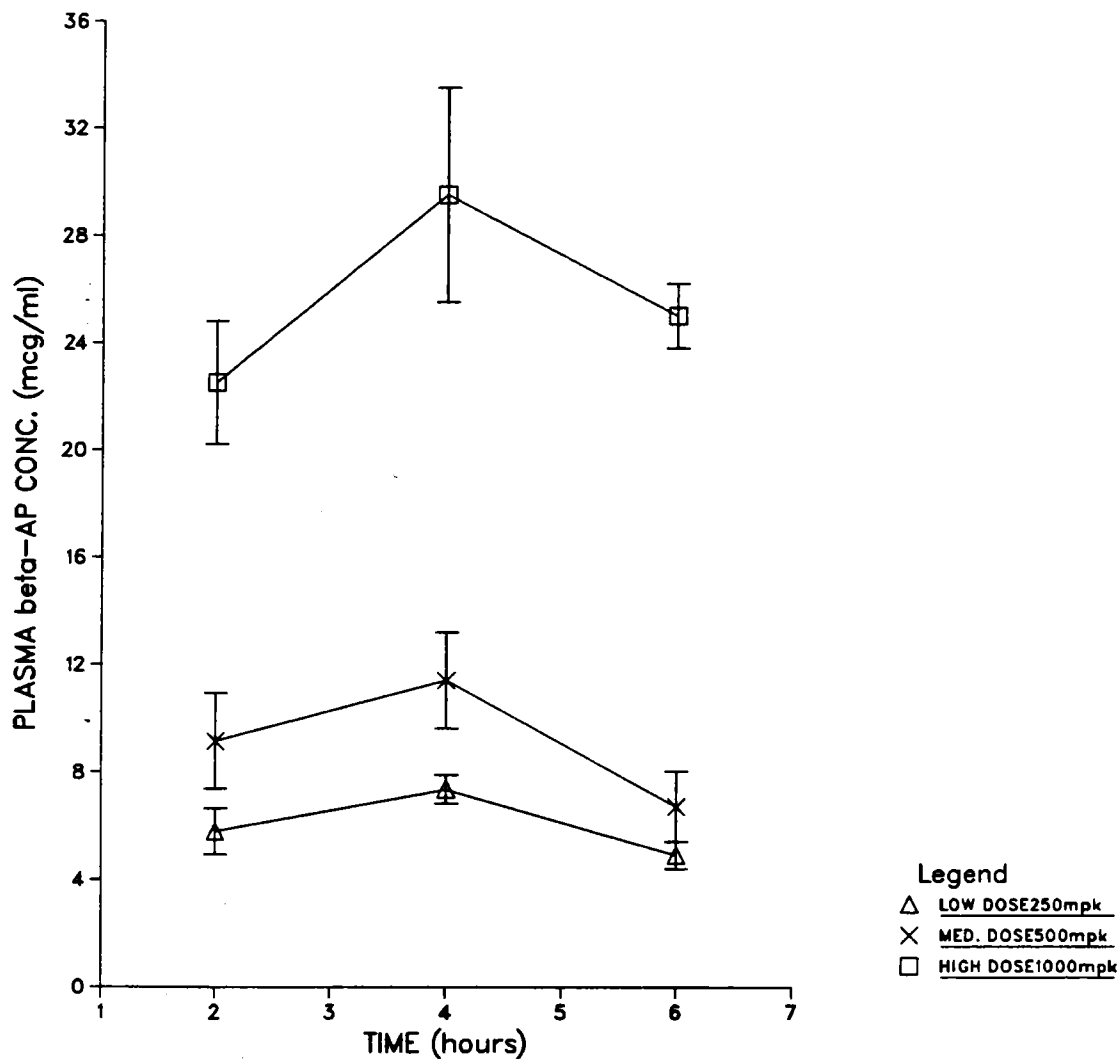


Figure 2. Mean Plasma concentrations of β -AP for doses of 250 (Δ), 500 (x) and 1000 (\square) mg of SC-19129 on day 15 of study S.A. 2449. Abscissa: time after initiation of dose administration (hours). Ordinate: concentration of β -AP in plasma (mcg/ml). The vertical bars indicate the standard errors of the means.

FOUR WEEK DOG STUDY, S.A. 2449
PLASMA CONCENTRATIONS OF beta-AP
DAY 1

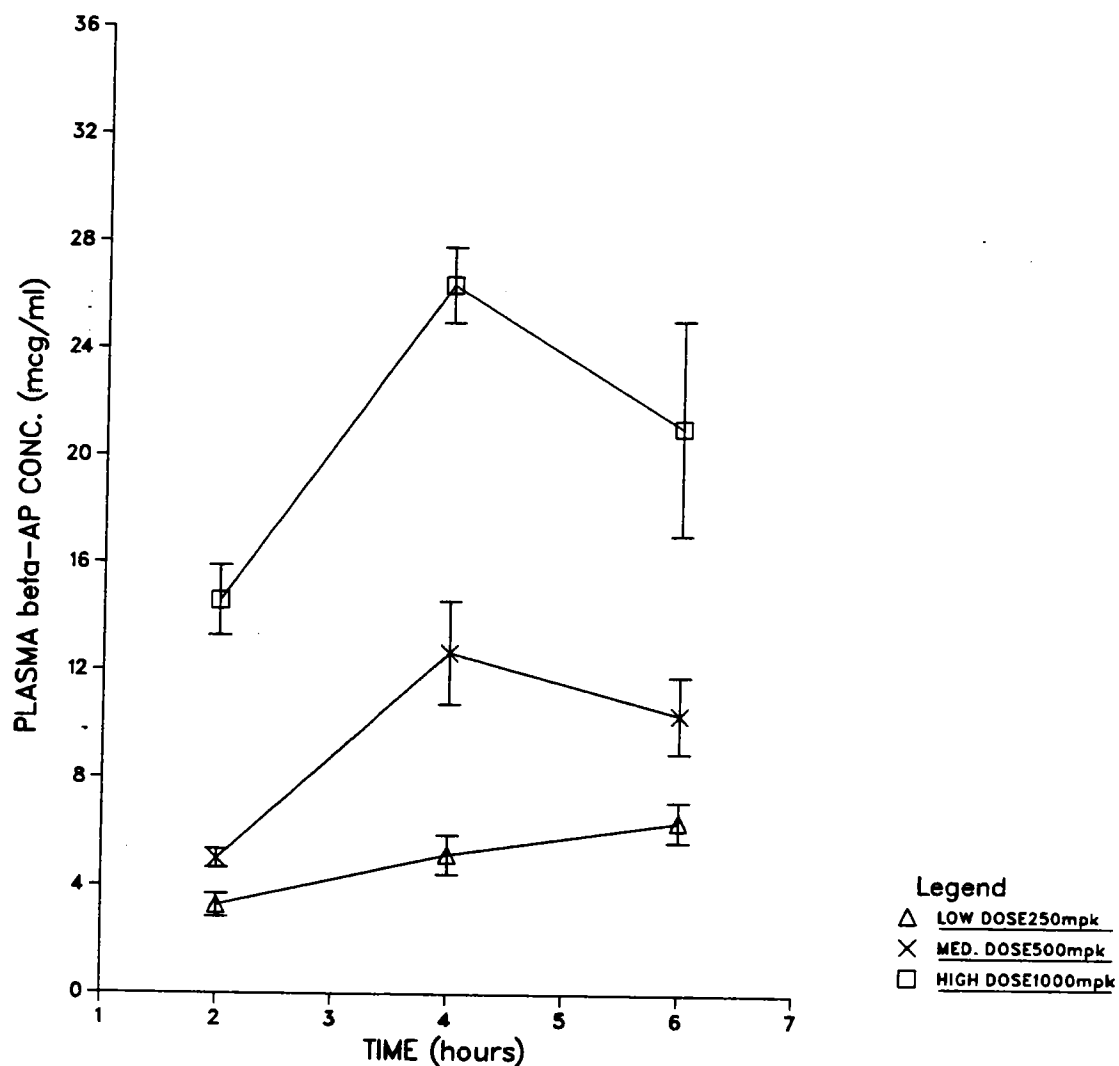


Figure 1. Mean Plasma Concentrations of β -AP for doses of 250 (Δ), 500 (\times) and 1000 (\square) mg of SC-19129 on day 1 of study S.A. 2449. Abscissa: time after initiation of dose administration (hours). Ordinate: concentration of β -AP in plasma (mcg/ml). The vertical bars indicate the standard errors of the means.

APPENDIX C

QUALITY ASSURANCE STATEMENT - SA- 2449

SC- 19129

The conduct of this study has been subjected to periodic inspections and this report has been audited by R&D Quality Assurance. The dates of inspection/audit are given below.

<u>Date of Inspec/Audit</u>	<u>Monitor</u>	<u>Date of Report to Mgmt.</u>
6/26 - 7/2/85 Audit of Draft Report Amendment #1	G. Herro	7/8/85

This report accurately described the methods used in the study and the reported results accurately reflect the raw data.

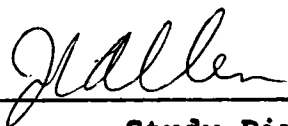
Donald V. Howard
Quality Assurance

7/15/85
Date

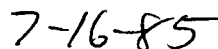
S.A. 2449

GLP COMPLIANCE STATEMENT

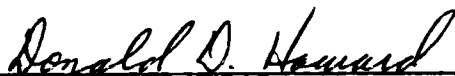
To our knowledge this study (SA-2449) (SC-19129) was conducted in compliance with the Good Laboratory Practices Regulations as set forth in part 58, 21 CFR.



Study Director

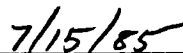


Date



Donald D. Howard

Dir., R&D Quality Assurance



Date