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FINAL REPORT

Tissue Distribution of ^{14}C -SC-19129 After Oral
Administration to Male Rats

Study No. 6127-113

for

G. D. Searle & Co.
Skokie, Illinois

by

Hazleton Laboratories America, Inc.
3301 Kinsman Boulevard
Madison, Wisconsin 53704

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Administration to Male Rats

Study No.	6127-113
Study Location	Hazleton Laboratories America, Inc. 3301 Kinsman Boulevard Madison, Wisconsin 53704
Test Material	^{14}C -SC-19129
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SUMMARY

[^{14}C]-SC-19129 was administered orally as an aqueous solution in a single dose to 24 male Crl:(LE)BR Long Evans Hooded rats at a dose level of 2 mg/kg body weight. In addition, there were three control (no dose) animals. Three rats per time point were sacrificed at pre-dose and at 1, 3, 6, 24, 48, 96, 168, and 240 hours after dosing. Urine and feces were collected at each consecutive 24-hour period from the three animals killed at 240 hours. A blood sample was collected by cardiac puncture at necropsy. Tissues for radiochemical analyses were dissected, weighed, and stored frozen until analysis. The total radioactivity in red blood cells, plasma, tissues, and excreta was measured by liquid scintillation counting.

The majority of the ^{14}C test material was excreted in the first 24 hours following dose administration (44% of the dose in urine and 21% in feces). The biological half-life for clearance of ^{14}C in the urine was 1.0 days and for plasma it was 4.6 days. The half-life for clearance of ^{14}C residues in tissues varied greatly from 1.4 days for large intestinal contents to too slow to measure within the 240 hour sampling period for brain, muscle, and red blood cells. Based on the urinary excretion of ^{14}C -residues remaining in the body after day two, the half-life for whole body clearance was 45.8 days. This suggested that a portion of the ^{14}C became associated with tissues in such a way that it cleared very slowly. Although this study did not determine the identity of the ^{14}C -residues, in other studies using [^{14}C]-phenylalanine and [^{14}C -phenylalanyl] aspartame, it has been shown that the ^{14}C -residues cleared slowly.

The highest tissue ^{14}C residues were found in the gastro-intestinal tract. Excluding this, the bladder, liver, and kidney had the highest ^{14}C residues with 4 to 38 $\mu\text{g/g}$ tissue at 3 and 6 hours. The brain, eye lens, and muscle had the lowest ^{14}C residues with 0.23 to 0.33 $\mu\text{g equivalents/g}$ tissue at 3 hours.

The highest radiation exposure doses in rat were found for brain, muscle, and red blood cells with greater than 6 rads/year. Plasma, eye, and bone had the lowest radiation doses with less than 0.4 rads/year.

When the ^{14}C residues from rat tissues were used to estimate radiation doses in humans after a 200 μCi dose, it was found that the highest radiation exposure dose would be for eye lens, testes and red blood cells with 0.41 to 0.93 rads/year and the lowest doses for plasma, bone and lung with less than 0.014 rads/year. The estimated whole body exposure was 0.147 rads/year.

INTRODUCTION

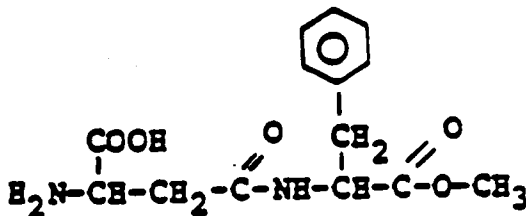
The objective of this study was to investigate the tissue disposition of [^{14}C]-SC-19129 in male rats following oral administration. The data will be used to provide estimates of the apparent whole body and selected tissue radiation exposures for doses of approximately 200 μCi of [^{14}C]-SC-19129 following oral administration to man. All phases of this study were conducted in compliance with the Nuclear Regulatory Commission Regulations (License No. 48-11805-02). All procedures were done according to Hazleton Laboratories America, Inc. (HLA) Standard Operating Procedures (SOPs).

TEST MATERIAL

Identification

Test Material:	[^{14}C]-SC-19129
Lot No.:	MRC 532-118-1
Molecular Formula:	$\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_5$
Molecular Weight:	294.3
Physical State:	Solid
Specific Activity:	Reported by Sponsor to be 32 $\mu\text{Ci}/\text{mg}$
Chemical Name:	N-L- β -aspartyl-L-phenylalanine, 1-methyl ester
Position of Radiolabel:	Uniformly ^{14}C labeled in phenylalanine subunit

Chemical Structure:



Storage

The test material was stored at room temperature and protected from light in a well closed container. The dose solution was prepared, stored at room temperature, and administered within 2 hours of preparation.

Radiochemical Purity

Radiolabeled test material was supplied by the Sponsor. Radiochemical purity of the dose solution was determined by thin layer chromatography (TLC).

Safety Precautions

When entering the test area, personnel wore disposable masks, caps, gloves, shoe covers, and jumpsuits. Before leaving the area, personnel discarded disposable items in containers double lined with plastic and properly marked

for radiolabeled waste. All work areas were marked with warning signs indicating the presence of radioactive material. These areas were isolated from other testing areas and locked when personnel were not present. Only personnel directly involved in this study had access to the test areas.

Disposal and Decontamination

The disposal of radiolabeled compound and any biological material that might contain radioisotopes was handled according to HLA SOPs. Burnable waste was disposed of in a high-temperature incinerator. When animals were sacrificed and tissues collected for analysis, the remaining carcasses were individually labeled (study number, animal number, sex, group, sacrifice interval, and isotope), placed in plastic bags, and stored frozen until analysis.

At least five separate swabbings of walls, floor, and basic equipment were used to demonstrate that the study room was free of radioactivity before the study began and after cleaning the room at termination of the study. The counts and the dates were recorded. Warm water and a detergent (Count-Off®) were used to clean the cages, racks, pans, and other equipment. At completion of the study, a solution of Count-Off was used to clean the walls and floor of the animal room.

TEST SYSTEM

Test Animal

Adult male Long Evans Hooded rats, Cr1:(LE)BR weighing 210.9 to 256.6 g at initiation were obtained from the facility of the Charles River Laboratories, Inc. and used as test animals. Upon receipt, the animals were taken to Room No. 336 where they were acclimated for 9 days before being placed on test.

During acclimation, the animals were examined for clinical abnormalities indicative of health problems (e.g., diarrhea, ectoparasites, rough hair coat, nasal or ocular discharge, evidence of injury, etc.).

The rat was selected as the test animal because it is a species routinely used for tissue distribution studies.

Identification

Each animal in the study was permanently identified by an ear tag. All data collected from an animal were recorded and filed under its identification number.

Housing and Maintenance

During acclimation, all rats were housed individually in suspended stainless steel wire-mesh cages (67 sq in.) equipped with automatic watering and with absorbent paper liners in the urine- and feces-collecting pans. The room was

maintained at 72°F +3°, 50% +20% relative humidity, and a minimum of 10 changes per hour of filtered, 100% outside air. The animal room was kept on a 12-hour light/12-hour dark cycle. During the test period, animals were housed individually in metabolism cages designed to collect urine and feces.

Animal husbandry and housing at HLA complied with the standards outlined in the "Guide for the Care and Use of Laboratory Animals."¹ Care was taken to ensure that animals were not disturbed for reasons other than routine maintenance and data collection.

Rats were fasted overnight prior to drug administration. Food was made available 6 hours after dosing. At all other times feed was available ad libitum from food containers designed to eliminate spillage and contamination. The diet for this study was pelleted Purina Certified Rodent Chow® No. 5002 (Lot Nos. 0612851A and 0702851A). This feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Tap water was available ad libitum and was provided fresh daily from glass water bottles fitted with rubber stoppers and stainless steel sipper tubes. Samples of the water are analyzed quarterly for total dissolved solids; conductivity; microbiological content; and selected elements, heavy metals, organophosphates, and chlorinated hydrocarbons.

There were no known contaminants present in the feed and water at levels sufficient to interfere with this study.

Route and Duration of Administration

The test material was administered to all treated animals as a single dose by oral gavage at a volume of 2 mL/kg body weight. This route was selected by the Sponsor because it is anticipated that humans will be exposed orally to the test materials.

Study Design

From a supply of 35 male rats, 27 animals were randomly assigned to the study with the following design:

<u>Group</u>	<u>Number of Males</u>	<u>Dose Level (mg/kg)</u>	<u>Dose Volume (mL/kg)</u>	<u>Time Points</u>
Treated	24	2.0	2.0*	1, 3, 6, 24, 48, 96, 168, and 240 Hours post-dose
Control	3	0.0	0.0	0 Hour

*The actual amount of material dosed is presented in Table 1. Each animal received a single oral dose.

¹DHEW Publication No. (NIH) 78-23 (1978).

EXPERIMENTAL PROCEDURES

Dose Preparation and Administration

The test material was prepared by dissolving 0.0254 g of [^{14}C]-SC-19129 in distilled water to give a final concentration of 1.0 mg/mL with a measured ^{14}C activity of 27.5 $\mu\text{Ci/mL}$. The test compound was administered within 2 hours of preparation by gavage at a rate of 2 mg/kg body weight in a volume of 2 mL/kg body weight.

Determination of Radiochemical Purity

Duplicate aliquots of excess dose solution were analyzed by thin layer chromatography using chloroform, methanol, water, formic acid (64:30:4:2 by volume) as a solvent system. The plates were developed within three hours of dose preparation. The developed plates were scanned with a linear analyzer.

Sample Collection

Urine and feces were collected at each consecutive 24-hour period after dosing from the three animals randomly assigned to the 240-hour sacrifice. These three rats were housed in metabolism cages from the day prior to dosing to allow separate collection of urine and feces. Urine samples were collected in containers surrounded by ice. Urine and fecal samples were weighed and stored frozen pending analysis.

The control rats were sacrificed without administration of test material. Three rats per time point were then sacrificed at 1, 3, 6, 24, 48, 96, 168, and 240 hours after test material administration. At the time of sacrifice, the animals were anesthetized with halothane and a blood sample was collected by cardiac puncture in a heparinized tube. The sample was centrifuged and the separated blood cells and plasma were stored at approximately -20°C pending analysis.

Following blood collection, the tissues listed below were dissected, weighed, and stored at approximately -20°C until analysis:

Stomach	Heart
Stomach contents	Lungs
Small intestine	Thymus
Small intestine contents	Submaxillary salivary glands
Large intestine	Skeletal muscle (leg sample)
Large intestine contents	Femurs
Liver	Eyes (minus lens)
Spleen	Eye lens
Kidneys	Brain
Adrenals	Skin (shaved samples from back)
Testes	Fat
	Bladder

Paired organs were weighed together.

All biological samples (blood, excreta, and tissues) were identified as to contents, amount, and dates of sampling. Samples were stored at approximately -20°C until analysis.

Equipment for Radioactivity Measurements

- o Combusto-Cones®, ash-free cellulose containers for sample oxidation, Packard Instrument Company
- o Combusto-Pads®, Packard Instrument Company
- o Combustaid®, Packard Instrument Company
- o Tissue homogenizer, Model 45, Virtis®
- o Tri-Carb® sample oxidizer, Model 306, Packard Instrument Company
- o Tri-Carb® liquid scintillation spectrometer, Models 460CD and 4640, Packard Instrument Company
- o TLC linear analyzer, Model LB2842, Berthold

Reagents for Radioactivity Measurements

- o Perma-Fluor V® liquid scintillation cocktail, Packard Instrument Company
- o Carbo-Sorb® carbon dioxide absorber, Packard Instrument Company
- o Spec-Chec®-¹⁴C radiocarbon standard, Packard Instrument Company
- o Insta-Gel® scintillation cocktail, Packard Instrument Company
- o Deionized water, filtered through a Milli-Q® water purification system, Millipore Corporation

Sample Preparation

Twenty-three different tissue matrices for each animal were prepared for radioactivity measurements after a rapid thaw by homogenizing each tissue with a Virtis homogenizer. Duplicate aliquots were combusted to determine total ¹⁴C content. Eye, eye lens and adrenals were combusted as single, whole samples for total ¹⁴C content.

Blood. Heparinized whole blood samples were centrifuged at 2,000 rpm for 10 minutes to separate red blood cells from plasma. Aliquots were taken from the red blood cells for combustion to determine total ¹⁴C content. Plasma samples were aliquoted (0.1 mL) and counted directly using Insta-Gel liquid scintillation cocktail in a liquid scintillation counter.

Urine. Total urine weights were recorded and duplicate 0.5-mL aliquots (sample size permitting) were removed, weighed, and analyzed directly for ¹⁴C content.

Feces. Total fecal weights were recorded. Each sample was diluted 1:2 with Milli-Q-filtered water. After homogenizing, duplicate aliquots were combusted to determine ^{14}C content.

Sample Oxidation

Aliquots (approximately 0.2 to 0.4 g) of prepared samples of tissues, red blood cells, and feces were weighed into tared Combusto-Cones containing a Combusto-pad. Three to four drops of Combust-Aid were added to each sample, which was then combusted in a sample oxidizer in a pure oxygen environment. The resulting carbon dioxide was absorbed by 10 mL of Carbo-Sorb, which was dispensed into a glass scintillation vial with 12 mL of Perma-Fluor V scintillation cocktail.

Control samples were assayed to establish background levels. Efficiency measurements were obtained by combustion of control tissue fortified with radiolabeled material.

Prior to each daily use and again at the end of each daily use, the performance of the oxidizer was evaluated for background levels, recovery of a known standard (Carbon-14 Spec-Chec®), and memory (sample carry-over).

Radioassay

All samples were analyzed by liquid scintillation counting for a maximum of 10 minutes or 100,000 counts. If the results differed by more than 10% from the mean value, the sample was remixed and the analysis repeated using fresh aliquots. This specification was met for all sample aliquots having radioactivity greater than 100 counts per minute (cpm).

The cpm were automatically converted to disintegrations per minute (dpm) using the external standardization technique and an instrument-stored quench curve. The curve was generated from a series of sealed quenched standards.

The minimum sensitivity for detecting ^{14}C residues in a tissue sample is shown in Appendix A.

Radiation Exposure Dose Calculation

Calculation of the radiation exposure dose was based on the area under the curve for $\mu\text{Ci/g}$ tissue versus time for the 10 days that data was collected and the estimated exposure that would be incurred after day 10 which was based on the $\mu\text{Ci/g}$ tissue on day 10 for each tissue and on the biological half-life for clearance of the ^{14}C residues in each tissue. The biological half-life varied considerably over the time points used in this study. To provide a worst-case estimate for radiation exposure, only the last 5 data points were used and the largest biological half-life value calculated at either the 168- or 240-hour time point was used except for brain, muscle, and red blood cells. For these matrices no clearance was observed and the radiation exposure was based on there being a constant amount of radioactivity present in the matrix. The formulas used for calculation of the area under the curve, the biological half-life and the radiation exposure dose are presented in Appendix B.

MAINTENANCE OF RAW DATA AND SPECIMENS

Original data or copies thereof are available at HLA to facilitate auditing the study during its progress and prior to acceptance of the final report. When the final report is completed, all original paper data generated by HLA as well as the final report will be retained in the archives of HLA. Upon acceptance of the final report, HLA will transfer all specimens and remaining test material to the Sponsor.

RESULTS AND DISCUSSION

Acclimation and Antemortem Observations

There were no abnormal observations during acclimation which necessitated removal of any animal from consideration for the study. Individual body weights are presented in Table 1.

Radiochemical Purity of Test Material

The radiolabeled material migrated as a single band during thin layer chromatography (Figure 1).

Excretion of ^{14}C Residues

All urine and feces were collected for the three rats that were sacrificed at the last time point (240 hours). The excretion pattern for these three animals is shown in Table 2 and individual values are shown in Tables 3 and 4. The majority of the dose was excreted during the first 24 hours with a total of approximately 46% excreted in the urine and 28% in the feces. A graph of the urinary excretion pattern is shown in Figure 2.

Uptake and Clearance of ^{14}C Residues in Blood

The ^{14}C content of both red blood cells and plasma peaked at 3 to 6 hours after dose administration. The ^{14}C residues in the red blood cells did not decline consistently, indicating a lack of clearance (Table 5 and Figure 3). The ^{14}C residues in the plasma declined steadily with a biological half-life of 4.6 days (Table 6).

Uptake and Clearance of ^{14}C Residues in Tissues

Tissue ^{14}C residues and calculated biological half-life data are presented in Tables 7 through 29. A summary of all the tissue residues is presented in Table 31. In general, the highest ^{14}C residues were found in the samples collected 3 to 6 hours post-dose. The ^{14}C was primarily found in samples from the gastro-intestinal tract. Excluding the gastro-intestinal tract, the bladder, liver, and kidney tissues had the highest ^{14}C residues.

The bladder ^{14}C residues peaked at 6 hours at 38.2 μg equivalents/g with a mean percent total dose of 7.76%, and decreased to 0.2 μg equivalents/g at 168 hours. The biological half-life calculated at 240 hours was 18.6 days (Table 8).

The highest ^{14}C residues in liver samples were found at 3 hours at 3.6 μg equivalents/g tissue with a mean percent total dose of 6.19%. This decreased to 0.6 μg equivalents/g tissue at 240 hours post-dose. The biological half-life calculated at 240 hours was 6.5 days (Table 18). A graph of the ^{14}C residues over time is shown in Figure 4.

The highest ^{14}C residues in kidney samples were found at 6 hours at 5.2 $\mu\text{g/g}$ tissue with a mean percent total dose of 2.27%. This decreased to 0.8 $\mu\text{g/g}$ tissue at 168 hours post-dose. The biological half-life calculated at 240 hours was 4.9 days (Table 15).

Tissues which contained the lowest ^{14}C residues were brain, eye lens, and muscle (see Table 30) which each contained maximum residues of $<0.01 \mu\text{Ci/g}$ tissue.

Although less than 1% of the dose was taken up by brain, eye lens, heart, or testes, the clearance rate for these tissues was slow with a biological half-life of greater than 24 days. This indicates the ^{14}C has become associated with some cell component which has a longer than average biological half-life; the average biological half-life for ^{14}C is 10 days.²

Determination of Radiation Exposure Dose in Rat Tissue

The calculated area under the curve for $\mu\text{Ci/g}$ tissue versus time and the radiation exposure dose are presented in Table 30. Again, the components of the gastro-intestinal tract had the highest calculated area under the curve and radiation exposure doses, primarily due to the high ^{14}C residues at the early time points. The large intestine contents had the highest exposure dose with 3.0 rads for one year. Excluding the gastro-intestinal tract, the bladder, liver, and kidney had the largest area under the curve determinations. The lowest exposures were found in the plasma, eye and bone (less than 0.4 rads for one year). The highest exposure doses were observed for brain, muscle and red blood cell. These had exposures ranging from 6.1 to 8.7 rads per year.

Estimation of Radiation Exposure Dose to Human Tissue

Using the data presented for rat tissues, an estimated radiation exposure dose for various human tissues was calculated and is shown in Table 32 (sample calculation is shown in Appendix B). These calculations are based on a dose of 200 $\mu\text{Ci}/70\text{kg}$ man. Eye lens, testes, and red blood cells had the highest doses with 0.41 to 0.93 rads/year and plasma, bone and lung had the lowest (excluding gastrointestinal tract) with less than 0.014 rads/year.

²Wang, Yen, Handbook of Radioactive Nuclides (1969).

Estimation of Whole Body Radiation Exposure

Using the data presented here for the excretion of ^{14}C in the rat, the amount of ^{14}C remaining in the rat was estimated. Assuming the same rate of excretion in a human given a dose of $200\mu\text{Ci}/70\text{ kg}$, the biological half life, area under the curve and the radiation exposure dose can be estimated. This is shown in Table 33. The whole body dose was estimated to be 0.147 rads/year .

CONCLUSIONS

Rats given an oral dose of ^{14}C -SC-19129 excreted the majority of the material in the first 24 hours post-dose. Most of the test material that was absorbed was readily excreted in the urine. Some of the absorbed ^{14}C became associated with tissues in such a way that it cleared very slowly (biological half-life greater than 10 days compared to 1.0 day for urine or 4.6 days for plasma). Although this study did not determine the identity of the ^{14}C -residues, in other studies using [^{14}C]-phenylalanine and [^{14}C -phenylalanyl] aspartame, it has been shown that the ^{14}C -residues cleared slowly.³

The highest tissue ^{14}C residues were found in the gastro-intestinal tract. Excluding this the bladder, liver, and kidney had the highest ^{14}C residues with 4 to $38\mu\text{g/g}$ tissue. The brain, eye lens, and muscle had the lowest ^{14}C residues with 0.23 to $0.32\mu\text{g/g}$ tissue.

The highest radiation exposure doses in rat were found for brain, muscle, and red blood cells with greater than 6 rads/year . Plasma, eye, and bone had the lowest radiation doses with less than 0.4 rads/year .

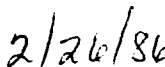
When the ^{14}C residues from rat tissues were used to estimate radiation doses in humans after a $200\mu\text{Ci}$ dose, it was found that the highest radiation exposure dose would be for eye lens, testes and red blood cells with greater than 0.4 rads/year and the lowest dose for plasma, bone and lung with less than $.014\text{ rads/year}$. The estimated whole body exposure was 0.147 rads/year .

³Stegink, L. D. and Filer, L. J., Jr., Aspartame Physiology and Biochemistry, Marcel Dekker, Inc., NY, pp. 141-159 (1984).

APPROVAL



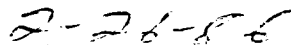
Anne Bösch, PhD
Metabolism



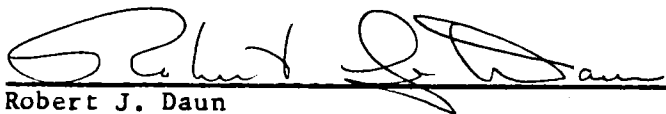
Date



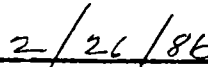
R. James Puhl, PhD
Manager, Metabolism and Environmental Fate



Date



Robert J. Daun
Director, Research Chemistry



Date

by and for Hazleton Laboratories America, Inc.

(2284F/jg)

Study No. 6127-113

Table 1

Individual Body Weights (g) and Dose Volumes (mL)

<u>Animal Number</u>	<u>Body Weight</u>	<u>Dose Volume</u>
C31373	230.0	Control
C31374	230.3	Control
C31375	248.0	Control
C31376	233.4	0.47
C31377	210.9	0.42
C31378	246.4	0.49
C31379	250.1	0.50
C31380	237.2	0.47
C31381	227.6	0.45
C37350 ^a	241.8	0.48
C31383	231.4	0.46
C31384	246.7	0.49
C31385	256.6	0.51
C31386	241.4	0.48
C31387	234.6	0.47
C31388	226.6	0.45
C31389	228.0	0.46
C31390	227.3	0.48
C31391	220.1	0.44
C31392	235.7	0.47
C31393	240.0	0.48
C31394	234.4	0.47
C31395	216.5	0.43
C31396	248.2	0.50
C31397	230.2	0.46
C31398	232.1	0.46
C31399	251.3	0.50

^aReplacement animal.

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TABLE 2

EXCRETION OF ¹⁴C RESIDUES

SUMMARY OF DOSE RECOVERED IN URINE AND FECES
AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

URINE	HOUR	AVERAGE*
		% DOSE
	24	44.00
	48	0.86
	72	0.31
	96	0.23
	120	0.13
	144	0.10
	168	0.09
	192	0.08
	216	0.07
	240	0.05
	TOTAL IN URINE	45.91
FECES	HOUR	AVERAGE
		% DOSE
	24	20.73
	48	3.89
	72	1.03
	96	0.42
	120	0.29
	144	0.19
	168	0.16
	192	0.13
	216	0.55
	240	0.45
	TOTAL IN FECES	27.84
	TOTAL EXCRETION	73.75

* Average from three rats. See Tables 3 and 4 for individual values for urine and feces respectively.

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TABLE 3

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT URINE AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g URINE	AVERAGE uCi/g URINE BY TIME	MICROGRAM EQUIVALENTS PER GRAM URINE	AVERAGE uG EQUIV./ g URINE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME
24	0.481	0.488	17.486	17.743	35.06	43.97
24	0.329		11.976		39.99	
24	0.654		23.767		56.87	
48	0.008	0.007	0.291	0.255	0.77	0.86
48	0.004		0.141		0.82	
48	0.009		0.334		0.98	
72	0.003	0.003	0.110	0.096	0.27	0.31
72	0.002		0.063		0.30	
72	0.003		0.116		0.37	
96	0.001	0.002	0.037	0.070	0.18	0.23
96	0.002		0.085		0.21	
96	0.002		0.088		0.30	
120	0.001	0.001	0.050	0.043	0.13	0.13
120	0.001		0.034		0.13	
120	0.001		0.043		0.13	
144	0.001	0.001	0.043	0.035	0.11	0.10
144	0.001		0.022		0.08	
144	0.001		0.040		0.10	
168	0.001	0.001	0.052	0.034	0.12	0.09
168	.000		0.017		0.07	
168	0.001		0.033		0.09	
192	0.001	0.001	0.034	0.026	0.09	0.08
192	.000		0.015		0.06	
192	0.001		0.030		0.08	
216	0.001	0.001	0.034	0.022	0.09	0.07
216	.000		0.012		0.06	
216	0.001		0.020		0.06	
240	0.001	.000	0.024	0.017	0.06	0.05
240	.000		0.012		0.05	
240	.000		0.014		0.03	

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TABLE 4

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT FECEs AFTER ORAL ADMINISTRATION OF (14C)-SC-1912

TIME HOUR	uCi/g FECEs	AVERAGE uCi/g FECEs BY TIME	MICROGRAM EQUIVALENTS PER GRAM FECEs	AVERAGE uCi EQUIV./ g FECEs BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME
24	0.065	0.092	2.366	3.339	16.63	20.73
24	0.097		3.517		20.59	
24	0.114		4.133		24.97	
48	0.021	0.020	0.775	0.722	3.36	3.89
48	0.012		0.451		2.88	
48	0.026		0.940		5.42	
72	0.007	0.006	0.246	0.230	1.13	1.03
72	0.006		0.223		0.99	
72	0.006		0.219		0.97	
96	0.003	0.002	0.108	0.088	0.38	0.42
96	0.002		0.078		0.42	
96	0.002		0.078		0.47	
120	0.001	0.002	0.051	0.055	0.26	0.29
120	0.001		0.050		0.27	
120	0.002		0.063		0.33	
144	0.001	0.001	0.043	0.039	0.18	0.19
144	0.001		0.038		0.19	
144	0.001		0.035		0.20	
168	0.001	0.001	0.026	0.031	0.17	0.16
168	0.001		0.037		0.15	
168	0.001		0.030		0.15	
192	0.001	0.001	0.025	0.027	0.13	0.13
192	0.001		0.023		0.13	
192	0.001		0.032		0.14	
216	0.001	0.003	0.022	0.105	0.12	0.55
216	0.001		0.025		0.12	
216	0.007		0.268		1.40	
240	0.001	0.001	0.021	0.025	0.10	0.10
240	0.001		0.036		0.11	
240	.000		0.018		0.10	

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TABLE 5

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT RED BLOOD CELLS AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g RED BLOOD CELL	AVERAGE uCi/g RBC BY TIME	MICROGRAM EQUIVALENTS PER GRAM RBC	AVERAGE uCi/g EQUIV./ g RBC BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.002	0.003	0.086	0.117	0.02	0.03	
1	0.002		0.091		0.03		
1	0.005		0.174		0.03		
3	0.014	0.013	0.516	0.474	0.10	0.10	
3	0.012		0.431		0.09		
3	0.013		0.476		0.10		
6	0.012	0.010	0.436	0.361	0.09	0.07	
6	0.010		0.358		0.08		
6	0.008		0.289		0.06		
24	0.007	0.008	0.256	0.303	0.05	0.06	
24	0.006		0.221		0.05		
24	0.012		0.432		0.09		
48	0.008	0.009	0.296	0.339	0.07	0.07	
48	0.011		0.417		0.09		
48	0.008		0.304		0.07		
96	0.007	0.009	0.259	0.346	0.06	0.07	
96	0.007		0.242		0.05		
96	0.015		0.538		0.11		
168	0.009	0.008	0.336	0.311	0.07	0.07	
168	0.009		0.320		0.07		
168	0.007		0.276		0.05		
240	0.015	0.013	0.562	0.484	0.11	0.10	N.C.*
240	0.011		0.418		0.09		
240	0.013		0.471		0.09		

* N.C. = No clearance, the biological half-life can not be calculated.

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TABLE 6

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT PLASMA AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/mL PLASMA CELL	AVERAGE uCi/mL PLASMA BY TIME	MICROGRAM EQUIVALENTS PER mL PLASMA	AVERAGE uG EQUIV./ mL PLASMA BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.007	0.009	0.244	0.321	0.05	0.07	
1	0.006		0.238		0.07		
1	0.013		0.480		0.09		
3	0.037	0.035	1.372	1.292	0.27	0.27	
3	0.032		1.165		0.24		
3	0.036		1.339		0.28		
6	0.033	0.030	1.230	1.090	0.25	0.23	
6	0.031		1.144		0.25		
6	0.024		0.896		0.18		
24	0.015	0.019	0.543	0.706	0.11	0.14	
24	0.014		0.512		0.11		
24	0.029		1.063		0.21		
48	0.012	0.014	0.447	0.507	0.10	0.11	4.19
48	0.017		0.641		0.14		
48	0.012		0.433		0.09		
96	0.006	0.008	0.237	0.281	0.05	0.06	3.01
96	0.006		0.206		0.04		
96	0.011		0.399		0.08		
168	0.005	0.005	0.183	0.172	0.04	0.04	3.43
168	0.006		0.205		0.05		
168	0.003		0.127		0.02		
240	0.005	0.004	0.168	0.155	0.03	0.03	4.57*
240	0.004		0.146		0.03		
240	0.004		0.149		0.03		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE

TABLE 7

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT ADRENALS AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.007	0.009	0.253	0.325	.00	.00	
1	0.007		0.273		.00		
1	0.012		0.448		.00		
3	0.053	0.049	1.964	1.800	0.02	0.02	
3	0.057		2.120		0.02		
3	0.036		1.317		0.01		
6	0.073	0.038	2.712	1.420	0.02	0.01	
6	0.008		0.306		0.01		
6	0.034		1.243		0.01		
24	0.030	0.042	1.121	1.561	0.01	0.01	
24	0.030		1.114		0.01		
24	0.066		2.447		0.02		
48	0.034	0.035	1.266	1.280	0.01	0.01	3.50
48	0.039		1.442		0.01		
48	0.031		1.131		0.01		
96	0.017	0.024	0.613	0.873	0.01	0.01	3.58
96	0.021		0.772		.00		
96	0.033		1.235		0.01		
168	0.014	0.014	0.514	0.516	.00	.00	3.76
168	0.018		0.682		.00		
168	0.010		0.351		.00		
240	0.016	0.013	0.577	0.467	0.01	.00	5.17*
240	0.014		0.512		.00		
240	0.008		0.310		.00		

* DENOTES THE BIOLOGICAL HALF-LIFE WHICH WAS USED TO CALCULATE THE EXPOSURE DOSE

TABLE 8

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT BLADDER AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.046	0.040	1.709	1.464	0.36	0.37	
1	0.056		2.077		0.64		
1	0.016		0.606		0.12		
3	0.311	0.169	11.505	6.246	2.29	1.27	
3	0.134		4.940		1.02		
3	0.062		2.294		0.49		
6	0.300	1.034	11.093	38.203	2.27	7.76	
6	0.606		22.370		4.84		
6	2.197		81.147		16.18		
24	0.015	0.016	0.537	0.596	0.11	0.12	
24	0.009		0.329		0.07		
24	0.025		0.921		0.18		
48	0.012	0.013	0.437	0.489	0.10	0.11	3.52
48	0.014		0.529		0.12		
48	0.014		0.500		0.11		
96	0.008	0.010	0.281	0.359	0.06	0.08	4.11
96	0.007		0.243		0.05		
96	0.015		0.553		0.11		
168	0.007	0.006	0.253	0.226	0.05	0.05	4.29
168	0.005		0.198		0.04		
168	0.006		0.226		0.04		
240	0.013	0.012	0.498	0.426	0.10	0.09	18.63*
240	0.011		0.412		0.09		
240	0.010		0.368		0.07		

* DENOTES THE BIOLOGICAL HALF-LIFE WHICH WAS USED TO CALCULATE THE EXPOSURE DOSE.

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TABLE 9

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT BONE AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uCi/g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.003	0.004	0.105	0.140	0.17	0.24	
1	0.003		0.093		0.22		
1	0.006		0.220		0.33		
3	0.028	0.020	1.050	0.744	1.58	1.17	
3	0.014		0.520		0.83		
3	0.018		0.664		1.09		
6	0.016	0.019	0.595	0.689	0.90	1.08	
6	0.023		0.840		1.38		
6	0.017		0.631		0.95		
24	0.012	0.016	0.442	0.579	0.67	0.87	
24	0.012		0.431		0.66		
24	0.023		0.865		1.29		
48	0.012	0.015	0.456	0.572	0.77	0.61	57.65
48	0.020		0.732		0.20		
48	0.014		0.530		0.87		
96	0.006	0.008	0.236	0.294	0.40	0.47	3.07
96	0.006		0.231		0.36		
96	0.011		0.416		0.63		
168	0.005	0.005	0.202	0.180	0.32	0.28	3.56
168	0.004		0.166		0.28		
168	0.005		0.172		0.26		
240	0.007	0.006	0.250	0.229	0.38	0.36	6.72
240	0.006		0.215		0.36		
240	0.006		0.221		0.33		

* DENOTES THE BIOLOGICAL HALF-LIFE WHICH WAS USED TO CALCULATE THE EXPOSURE DOSE.

TABLE 10

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT BRAIN AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.001	0.002	0.050	0.061	0.02	0.03	
1	0.001		0.046		0.03		
1	0.002		0.086		0.03		
3	0.011	0.009	0.409	0.325	0.14	0.11	
3	0.007		0.245		0.09		
3	0.009		0.321		0.12		
6	0.009	0.009	0.319	0.318	0.11	0.11	
6	0.010		0.368		0.14		
6	0.007		0.266		0.08		
24	0.006	0.008	0.234	0.305	0.09	0.11	
24	0.006		0.207		0.07		
24	0.013		0.475		0.16		
48	0.008	0.009	0.279	0.316	0.11	0.12	
48	0.010		0.364		0.15		
48	0.008		0.304		0.11		
96	0.005	0.006	0.189	0.235	0.07	0.09	
96	0.004		0.165		0.06		
96	0.009		0.351		0.13		
168	0.007	0.006	0.245	0.235	0.09	0.09	
168	0.007		0.271		0.11		
168	0.005		0.187		0.07		
240	0.008	0.008	0.303	0.285	0.11	0.10	N.C.
240	0.008		0.298		0.12		
240	0.007		0.255		0.09		

N.C. = No clearance, half-life can not be calculated

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TABLE 11

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT EYE AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.003	0.003	0.114	0.107	.00	.00	
1	0.002		0.062		.00		
1	0.004		0.145		.00		
3	0.013	0.012	0.495	0.438	0.01	0.01	
3	0.012		0.437		0.01		
3	0.010		0.382		0.01		
6	0.017	0.013	0.614	0.475	0.01	0.01	
6	0.013		0.468		0.01		
6	0.009		0.344		0.01		
24	0.009	0.013	0.319	0.468	0.01	0.01	
24	0.009		0.317		.00		
24	0.021		0.769		0.01		
48	0.010	0.010	0.361	0.359	0.01	0.01	2.61
48	0.009		0.346		0.01		
48	0.010		0.370		0.01		
96	0.005	0.006	0.174	0.234	.00	.00	3.00
96	0.004		0.129		.00		
96	0.011		0.400		0.01		
168	0.006	0.006	0.221	0.217	.00	.00	5.42*
168	0.007		0.254		0.01		
168	0.005		0.177		.00		
240	0.008	0.004	0.290	0.137	0.01	.00	5.09
240	0.001		0.043		.00		
240	0.002		0.079		.00		

* DENOTES THE BIOLOGICAL HALF-LIFE WHICH WAS USED TO CALCULATE THE EXPOSURE DOSE.

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TABLE 12

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT EYE LENS AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.001	0.001	0.035	0.051	.00	.00	
1	0.001		0.028		.00		
1	0.002		0.089		.00		
3	0.011	0.009	0.420	0.322	.00	.00	
3	0.006		0.215		.00		
3	0.009		0.331		.00		
6	0.006	0.006	0.217	0.234	.00	.00	
6	0.006		0.238		.00		
6	0.007		0.248		.00		
24	0.006	0.008	0.223	0.287	.00	.00	
24	0.005		0.183		.00		
24	0.012		0.453		.00		
48	0.005	0.005	0.199	0.173	.00	.00	1.38
48	0.004		0.159		.00		
48	0.004		0.162		.00		
96	0.005	0.006	0.202	0.216	.00	.00	9.89
96	0.003		0.095		.00		
96	0.010		0.352		.00		
168	0.008	0.007	0.309	0.245	.00	.00	26.31*
168	0.004		0.137		.00		
168	0.008		0.288		.00		
240	0.001	0.006	0.040	0.204	.00	.00	20.42
240	0.009		0.329		.00		
240	0.007		0.244		.00		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 13

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT FAT AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uCi/g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.002	0.002	0.063	0.089	0.42	0.72	
1	0.003		0.122		1.22		
1	0.002		0.082		0.52		
3	0.012	0.010	0.445	0.373	2.85	2.47	
3	0.007		0.276		1.84		
3	0.011		0.397		2.72		
6	0.011	0.013	0.395	0.482	2.60	3.22	
6	0.016		0.591		4.12		
6	0.012		0.459		2.95		
24	0.017	0.020	0.632	0.744	4.05	4.84	
24	0.019		0.694		4.65		
24	0.025		0.908		5.82		
48	0.018	0.017	0.682	0.614	4.85	4.35	3.60
48	0.015		0.541		3.83		
48	0.017		0.619		4.36		
96	0.009	0.012	0.337	0.448	2.43	3.02	4.09
96	0.007		0.246		1.66		
96	0.021		0.760		4.97		
168	0.009	0.010	0.349	0.378	2.34	2.58	6.13
168	0.014		0.520		3.74		
168	0.007		0.264		1.67		
240	0.012	0.013	0.453	0.477	2.93	3.15	14.01*
240	0.015		0.569		3.93		
240	0.011		0.408		2.57		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 14

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT HEART AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.004	0.004	0.141	0.161	0.03	0.03	
1	0.004		0.134		0.03		
1	0.006		0.208		0.04		
3	0.019	0.016	0.686	0.590	0.14	0.11	
3	0.013		0.481		0.09		
3	0.016		0.602		0.11		
6	0.015	0.015	0.568	0.561	0.10	0.11	
6	0.017		0.620		0.13		
6	0.013		0.493		0.10		
24	0.012	0.015	0.433	0.556	0.07	0.09	
24	0.009		0.348		0.06		
24	0.024		0.888		0.14		
48	0.013	0.015	0.474	0.556	0.24	0.15	
48	0.018		0.676		0.10		
48	0.014		0.519		0.09		
96	0.009	0.011	0.314	0.406	0.06	0.09	6.63
96	0.008		0.309		0.05		
96	0.016		0.596		0.15		
168	0.011	0.011	0.398	0.393	0.07	0.07	12.01
168	0.013		0.480		0.08		
168	0.008		0.302		0.06		
240	0.013	0.012	0.482	0.452	0.11	0.10	30.03*
240	0.012		0.435		0.10		
240	0.012		0.439		0.09		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 15

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT KIDNEY AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.035	0.044	1.302	1.611	0.55	0.68	
1	0.030		1.124		0.56		
1	0.065		2.408		0.92		
3	0.125	0.141	4.612	5.192	1.99	2.05	
3	0.132		4.883		1.94		
3	0.165		6.081		2.22		
6	0.146	0.141	5.378	5.206	2.58	2.27	
6	0.171		6.326		2.70		
6	0.106		3.914		1.54		
24	0.074	0.084	2.741	3.097	1.15	1.24	
24	0.048		1.760		0.65		
24	0.130		4.789		1.91		
48	0.067	0.080	2.479	2.966	1.08	1.31	16.10
48	0.094		3.478		1.52		
48	0.080		2.940		1.33		
96	0.029	0.043	1.089	1.574	0.49	0.68	3.08
96	0.029		1.080		0.45		
96	0.069		2.554		1.08		
168	0.019	0.021	0.690	0.771	0.34	0.34	3.00
168	0.026		0.944		0.37		
168	0.018		0.681		0.31		
240	0.024	0.023	0.887	0.861	0.36	0.38	4.88*
240	0.026		0.951		0.42		
240	0.020		0.745		0.37		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 16

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT LARGE INTESTINE AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE Z TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.016	0.014	0.605	0.530	0.26	0.27	
1	0.019		0.718		0.44		
1	0.007		0.266		0.10		
3	0.291	0.462	10.736	17.049	4.63	7.51	
3	0.608		22.444		10.15		
3	0.486		17.969		7.76		
6	0.448	0.385	16.564	14.207	8.48	5.99	
6	0.450		16.632		5.65		
6	0.255		9.425		3.84		
24	0.028	0.035	1.018	1.305	0.55	0.59	
24	0.031		1.138		0.49		
24	0.048		1.759		0.73		
48	0.023	0.021	0.855	0.766	0.43	0.42	1.30
48	0.023		0.849		0.45		
48	0.016		0.593		0.37		
96	0.008	0.011	0.301	0.389	0.17	0.16	1.72
96	0.008		0.283		0.13		
96	0.016		0.581		0.17		
168	0.007	0.007	0.265	0.243	0.14	0.13	2.47
168	0.007		0.250		0.15		
168	0.006		0.213		0.12		
240	0.006	0.007	0.237	0.253	0.14	0.15	3.81*
240	0.008		0.286		0.18		
240	0.006		0.238		0.13		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 17

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT LARGE INTESTINE CONTENTS AFTER ORAL ADMINISTRATION
OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.002	0.001	0.083	0.047	0.03	0.02	
1	0.001		0.049		0.03		
1	.000		0.008		.00		
3	1.609	3.563	59.422	131.638	20.10	40.51	
3	5.245		193.743		44.11		
3	3.837		141.749		57.31		
6	1.755	1.710	64.836	63.159	26.50	24.19	
6	2.005		74.052		20.84		
6	1.369		50.587		25.22		
24	0.047	0.059	1.737	2.172	2.39	3.42	
24	0.047		1.752		2.63		
24	0.082		3.027		5.24		
48	0.009	0.012	0.326	0.439	0.55	0.75	0.43
48	0.017		0.611		0.99		
48	0.010		0.379		0.71		
96	0.002	0.002	0.058	0.061	0.08	0.10	0.58
96	0.002		0.064		0.11		
96	0.002		0.061		0.09		
168	0.001	0.002	0.039	0.063	0.06	0.09	1.18
168	0.003		0.119		0.15		
168	0.001		0.031		0.07		
240	0.001	0.001	0.022	0.026	0.03	0.04	1.41*
240	0.001		0.033		0.05		
240	0.001		0.022		0.03		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 18

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT LIVER AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.024	0.030	0.880	1.105	1.57	1.97	
1	0.024		0.879		1.83		
1	0.042		1.556		2.51		
3	0.121	0.098	4.465	3.616	7.72	6.19	
3	0.077		2.835		4.54		
3	0.096		3.549		6.31		
6	0.066	0.068	2.434	2.490	4.14	3.90	
6	0.079		2.927		4.31		
6	0.057		2.109		3.26		
24	0.032	0.042	1.198	1.537	2.91	3.34	
24	0.026		0.971		2.39		
24	0.066		2.444		4.72		
48	0.033	0.036	1.225	1.313	2.97	3.43	4.39
48	0.041		1.505		3.93		
48	0.033		1.208		3.39		
96	0.018	0.022	0.677	0.824	1.66	2.17	3.34
96	0.017		0.637		1.74		
96	0.031		1.158		3.11		
168	0.018	0.017	0.655	0.610	1.59	1.48	4.50
168	0.020		0.721		1.59		
168	0.012		0.454		1.25		
240	0.017	0.016	0.629	0.585	1.74	1.66	6.46*
240	0.015		0.560		1.52		
240	0.015		0.566		1.73		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 19

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT LUNG AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uCi EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.005	0.005	0.174	0.193	0.05	0.05	
1	0.004		0.146		0.05		
1	0.007		0.260		0.05		
3	0.023	0.020	0.844	0.743	0.24	0.19	
3	0.016		0.606		0.13		
3	0.021		0.778		0.21		
6	0.018	0.019	0.654	0.716	0.17	0.19	
6	0.023		0.856		0.26		
6	0.017		0.637		0.15		
24	0.012	0.017	0.445	0.620	0.14	0.14	
24	0.012		0.447		0.09		
24	0.026		0.969		0.20		
48	0.015	0.016	0.543	0.602	0.14	0.15	45.49
48	0.018		0.666		0.17		
48	0.016		0.596		0.14		
96	0.009	0.012	0.341	0.432	0.09	0.10	7.66
96	0.009		0.331		0.06		
96	0.017		0.624		0.14		
168	0.009	0.009	0.338	0.330	0.10	0.09	7.69
168	0.011		0.395		0.09		
168	0.007		0.257		0.09		
240	0.010	0.010	0.359	0.351	0.09	0.09	12.19*
240	0.010		0.361		0.09		
240	0.009		0.334		0.08		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 20

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT MUSCLE AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE ug EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.002	0.002	0.074	0.071	1.40	1.43	
1	0.001		0.043		1.20		
1	0.003		0.095		1.68		
3	0.008	0.006	0.295	0.230	5.26	4.24	
3	0.005		0.184		3.42		
3	0.006		0.212		4.05		
6	0.006	0.005	0.224	0.200	4.11	3.73	
6	0.006		0.227		4.42		
6	0.004		0.149		2.66		
24	0.005	0.006	0.173	0.214	3.10	3.86	
24	0.004		0.153		2.86		
24	0.009		0.315		5.62		
48	0.007	0.007	0.248	0.274	4.91	5.41	
48	0.008		0.283		5.58		
48	0.008		0.291		5.72		
96	0.005	0.006	0.172	0.208	3.45	3.92	
96	0.005		0.172		3.23		
96	0.008		0.279		5.08		
168	0.006	0.006	0.231	0.235	4.31	4.44	
168	0.007		0.270		5.41		
168	0.006		0.205		3.61		
240	0.009	0.009	0.322	0.339	5.80	6.19	N.C.
240	0.009		0.333		6.41		
240	0.010		0.361		6.34		

N.C. = No Clearance, half-life can not be calculated

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TABLE 21

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT SUBMAXILLARY SALIVARY GLAND AFTER ORAL ADMINISTRATION
OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.006	0.009	0.240	0.345	0.03	0.04	
1	0.007		0.245		0.04		
1	0.015		0.550		0.05		
3	0.056	0.046	2.080	1.702	0.24	0.20	
3	0.039		1.438		0.18		
3	0.043		1.587		0.18		
6	0.042	0.043	1.567	1.594	0.17	0.18	
6	0.053		1.945		0.25		
6	0.034		1.269		0.11		
24	0.014	0.021	0.531	0.775	0.07	0.08	
24	0.014		0.528		0.05		
24	0.034		1.267		0.13		
48	0.019	0.020	0.684	0.723	0.11	0.09	19.75
48	0.020		0.748		0.08		
48	0.020		0.736		0.08		
96	0.010	0.015	0.387	0.560	0.05	0.07	8.54
96	0.010		0.370		0.04		
96	0.025		0.924		0.12		
168	0.010	0.010	0.368	0.372	0.13	0.08	6.61
168	0.012		0.450		0.05		
168	0.008		0.298		0.04		
240	0.011	0.010	0.418	0.364	0.05	0.05	9.16*
240	0.010		0.377		0.05		
240	0.008		0.295		0.05		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 22

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT SKIN AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.003	0.003	0.122	0.118	0.96	1.00	
1	0.002		0.083		0.96		
1	0.004		0.148		1.09		
3	0.016	0.013	0.579	0.481	4.30	3.69	
3	0.009		0.342		2.64		
3	0.014		0.522		4.14		
6	0.016	0.013	0.605	0.490	4.61	3.79	
6	0.013		0.492		3.97		
6	0.010		0.374		2.78		
24	0.013	0.013	0.489	0.480	3.63	3.60	
24	0.009		0.326		2.53		
24	0.017		0.626		4.65		
48	0.011	0.013	0.408	0.475	3.36	3.89	4.04
48	0.015		0.546		4.48		
48	0.013		0.469		3.83		
96	0.007	0.009	0.275	0.316	2.30	2.49	6.64
96	0.006		0.227		1.77		
96	0.012		0.447		3.39		
168	0.009	0.008	0.321	0.287	2.49	2.26	9.43
168	0.009		0.321		2.68		
168	0.006		0.219		1.61		
240	0.009	0.009	0.330	0.334	2.47	2.55	19.11*
240	0.010		0.356		2.85		
240	0.009		0.316		2.31		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 23

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT SMALL INTESTINE AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uCi/g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.523	1.129	19.318	41.702	25.97	49.69	
1	0.921		34.018		47.83		
1	1.943		71.771		75.26		
3	0.581	0.345	21.466	12.761	24.32	15.13	
3	0.142		5.230		6.06		
3	0.314		11.587		15.01		
6	0.087	0.088	3.210	3.239	3.40	3.24	
6	0.107		3.953		3.87		
6	0.069		2.553		2.46		
24	0.034	0.042	1.269	1.569	1.75	1.98	
24	0.026		0.968		1.33		
24	0.067		2.469		2.86		
48	0.024	0.025	0.886	0.905	0.99	1.12	2.52
48	0.027		0.996		1.29		
48	0.023		0.833		1.08		
96	0.008	0.010	0.295	0.360	0.34	0.42	1.88
96	0.007		0.248		0.33		
96	0.014		0.535		0.59		
168	0.007	0.007	0.277	0.243	0.31	0.29	2.60
168	0.007		0.249		0.32		
168	0.005		0.202		0.24		
240	0.007	0.006	0.248	0.237	0.40	0.36	3.67*
240	0.006		0.236		0.38		
240	0.006		0.226		0.30		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 24

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT SMALL INTESTINE CONTENTS AFTER ORAL ADMINISTRATION
OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uCi EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	9.595	6.137	354.436	226.704	82.25	48.15	
1	5.931		219.108		47.52		
1	2.885		106.568		14.70		
3	5.817	3.361	214.880	124.161	17.11	12.41	
3	1.595		58.919		1.22		
3	2.671		98.684		18.90		
6	0.084	0.125	3.087	4.620	0.32	0.55	
6	0.175		6.472		0.56		
6	0.116		4.301		0.77		
24	0.004	0.004	0.146	0.195	0.08	0.12	
24	NS		-		-		
24	0.007		0.244		0.16		
48	0.004	0.003	0.148	0.096	0.13	0.08	4.62
48	0.002		0.081		0.06		
48	0.002		0.059		0.04		
96	0.001	0.001	0.034	0.043	0.03	0.04	2.51
96	0.001		0.032		0.03		
96	0.002		0.063		0.06		
168	0.001	0.001	0.043	0.032	0.03	0.03	3.48
168	0.001		0.023		0.02		
168	0.001		0.030		0.04		
240	0.001	0.001	0.022	0.028	0.02	0.02	4.50*
240	0.001		0.027		0.02		
240	0.001		0.034		0.03		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

NS = No Sample

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TABLE 25

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT SPLEEN AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE ug EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.005	0.006	0.197	0.221	0.03	0.03	
1	0.005		0.172		0.03		
1	0.008		0.293		0.03		
3	0.042	0.032	1.538	1.169	0.15	0.13	
3	0.025		0.922		0.11		
3	0.028		1.046		0.13		
6	0.032	0.032	1.167	1.168	0.12	0.13	
6	0.037		1.353		0.17		
6	0.027		0.983		0.11		
24	0.024	0.030	0.895	1.124	0.09	0.11	
24	0.020		0.739		0.08		
24	0.047		1.738		0.16		
48	0.022	0.024	0.818	0.895	0.10	0.10	6.09
48	0.026		0.970		0.11		
48	0.024		0.897		0.10		
96	0.012	0.015	0.443	0.548	0.06	0.07	3.86
96	0.011		0.422		0.05		
96	0.021		0.779		0.12		
168	0.010	0.010	0.384	0.371	0.05	0.05	4.38
168	0.012		0.437		0.06		
168	0.008		0.290		0.04		
240	0.010	0.010	0.379	0.357	0.04	0.05	6.05*
240	0.009		0.349		0.05		
240	0.009		0.344		0.04		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 26

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT STOMACH AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.1773	0.110	6.549	4.066	1.57	1.21	
1	0.1204		4.446		1.74		
1	0.0325		1.202		0.34		
3	0.0802	0.057	2.961	2.122	0.77	0.58	
3	0.0456		1.684		0.53		
3	0.0466		1.723		0.45		
6	0.0433	0.044	1.600	1.637	0.45	0.47	
6	0.0555		2.050		0.64		
6	0.0341		1.259		0.31		
24	0.0186	0.025	0.686	0.923	0.22	0.29	
24	0.0178		0.658		0.21		
24	0.0385		1.424		0.44		
48	0.0216	0.020	0.798	0.744	0.26	0.25	6.44
48	0.0196		0.725		0.24		
48	0.0192		0.708		0.27		
96	0.0103	0.012	0.379	0.453	0.10	0.13	3.90
96	0.0087		0.321		0.10		
96	0.0178		0.659		0.19		
168	0.0100	0.009	0.369	0.315	0.10	0.10	4.52
168	0.0078		0.287		0.12		
168	0.0078		0.288		0.09		
240	0.0096	0.009	0.355	0.348	0.13	0.12	7.11*
240	0.0099		0.366		0.12		
240	0.0087		0.322		0.11		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 27

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT STOMACH CONTENTS AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE ug EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	1.7044	1.1189	62.962	41.335	1.33	1.04	
1	1.4347		53.000		1.64		
1	0.2178		8.044		0.16		
3	0.1236	0.1103	4.568	4.074	0.09	0.12	
3	0.0688		2.540		0.05		
3	0.1385		5.115		0.22		
6	0.0123	0.0417	0.453	1.539	0.02	0.02	
6	0.0593		2.189		0.00		
6	0.0535		1.975		0.04		
24	0.0004	0.0018	0.015	0.067	0.04	0.11	
24	NS		NA		NA		
24	0.0032		0.118		0.17		
48	0.0002	0.0003	0.008	0.012	0.01	0.02	0.88
48	0.0002		0.009		0.02		
48	0.0005		0.017		0.03		
96	0.0001	0.0002	0.004	0.006	0.01	0.01	1.26
96	0.0002		0.006		0.01		
96	0.0002		0.008		0.01		
168	0.0002	0.0002	0.009	0.006	.00	.00	1.88
168	0.0001		0.003		.00		
168	NS		NA		NA		
240	0.0001	0.0002	0.003	0.007	.00	0.01	3.25*
240	0.0003		0.010		0.01		
240	0.0002		0.007		0.01		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

N.S. = NO SAMPLE

N.A. = NOT APPLICABLE

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TABLE 28

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT TESTES AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.0017	0.002	0.061	0.072	0.03	0.05	
1	0.0014		0.053		0.04		
1	0.0028		0.102		0.06		
3	0.0121	0.009	0.445	0.348	0.21	0.19	
3	0.0069		0.254		0.15		
3	0.0093		0.343		0.20		
6	0.0111	0.010	0.411	0.375	0.22	0.21	
6	0.0115		0.424		0.25		
6	0.0079		0.291		0.15		
24	0.0076	0.010	0.280	0.364	0.13	0.18	
24	0.0068		0.252		0.13		
24	0.0152		0.561		0.29		
48	0.0084	0.010	0.311	0.363	0.19	0.22	289.74
48	0.0113		0.416		0.26		
48	0.0098		0.360		0.21		
96	0.0054	0.007	0.201	0.254	0.12	0.16	7.70
96	0.0054		0.200		0.11		
96	0.0098		0.362		0.24		
168	0.0069	0.006	0.254	0.236	0.15	0.14	11.20
168	0.0073		0.271		0.16		
168	0.0049		0.183		0.11		
240	0.0079	0.007	0.292	0.273	0.15	0.16	24.01*
240	0.0074		0.272		0.18		
240	0.0069		0.255		0.14		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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TABLE 29

(14C) RESIDUES AND CALCULATED BIOLOGICAL HALF-LIFE
IN RAT THYMUS AFTER ORAL ADMINISTRATION OF (14C)-SC-19129

TIME HOUR	uCi/g TISSUE	AVERAGE uCi/g TISSUE BY TIME	MICROGRAM EQUIVALENTS PER GRAM TISSUE	AVERAGE uG EQUIV./ g TISSUE BY TIME	PERCENT TOTAL DOSE	AVERAGE % TOTAL DOSE BY TIME	BIOLOGICAL HALF LIFE (DAYS)
1	0.0047	0.004	0.174	0.166	0.02	0.02	
1	0.0035		0.128		0.01		
1	0.0053		0.195		0.02		
3	0.0236	0.021	0.870	0.776	0.12	0.09	
3	0.0171		0.631		0.07		
3	0.0224		0.826		0.09		
6	0.0197	0.023	0.728	0.861	0.11	0.12	
6	0.0262		0.966		0.14		
6	0.0240		0.887		0.09		
24	0.0180	0.025	0.666	0.922	0.07	0.08	
24	0.0186		0.686		0.07		
24	0.0383		1.413		0.10		
48	0.0214	0.026	0.792	0.946	0.07	0.10	
48	0.0317		1.171		0.12		
48	0.0237		0.877		0.10		
96	0.0120	0.013	0.444	0.482	0.04	0.05	4.28
96	0.0087		0.321		0.03		
96	0.0184		0.680		0.09		
168	0.0093	0.008	0.344	0.308	0.04	0.04	4.43
168	0.0090		0.332		0.03		
168	0.0067		0.247		0.05		
240	0.0080	0.008	0.297	0.294	0.03	0.03	6.07*
240	0.0087		0.321		0.03		
240	0.0071		0.263		0.03		

* DENOTES THE BIOLOGICAL HALF-LIFE USED IN CALCULATING THE EXPOSURE DOSE.

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Table 30

Radiation Exposure Dose Determinations
Summary of ¹⁴C Residues and Calculated Radiation Exposure
Doses for Rat Tissues After Oral Administration of [¹⁴C]-SC-19129

Tissue	Maximum uCi/g Tissue*	uCi/g Tissue at 240 Hours*	Half-life (days)**	Area Under Curve***	Radiation Exposure Dose*** (1 year)	Total Radiation Exposure Dose***
Adrenals	0.049	0.013	5.17	0.192	0.716	0.716
Bladder	1.034	0.012	18.65	0.567	2.197	2.229
Bone/Marrow	0.020	0.006	6.72	0.091	0.229	0.379
Brain	0.009	0.008	N.C.	0.071	6.525	>10
Eye	0.013	0.004	5.42	0.066	0.237	0.243
Eye Lens	0.009	0.006	26.31	0.060	0.677	0.677
Fat	0.020	0.013	14.01	0.130	0.979	0.979
Heart	0.016	0.012	30.03	0.122	1.192	1.634
Kidney	0.141	0.023	4.88	0.478	1.608	1.608
Large Intestine	0.462	0.007	3.81	0.336	0.935	0.935
L. Int. Content	3.563	0.001	1.41	1.199	3.005	3.005
Liver	0.098	0.016	6.46	0.261	1.024	1.024
Lung	0.020	0.010	12.19	0.120	0.720	0.720
Muscle	0.009	0.009	N.C.	0.066	6.055	>10
Red Blood Cells	0.013	0.013	N.C.	0.095	8.692	>10
Salivary Gland	0.046	0.010	9.16	0.155	0.714	0.714
Skin	0.013	0.009	19.11	0.096	0.866	0.866
Small Intestine	1.129	0.006	3.67	0.296	0.827	0.827
S. Int. Content	6.137	0.001	4.50	0.932	2.345	2.345
Spleen	0.032	0.010	6.05	0.162	0.618	0.618
Stomach	0.110	0.009	7.11	0.157	0.633	0.635
Stomach Content	1.110	<0.001	3.25	0.127	0.319	0.319
Testes	0.010	0.007	24.01	0.076	0.833	0.833
Thymus	0.026	0.008	6.07	0.143	0.532	0.532
Plasma	0.035	0.004	4.57	0.094	0.304	0.304
Urine	0.488	0.001	0.99			
Feces	0.092	0.003	1.95			

N.C. = No clearance over 10 days.

*Average from three rats.

**Maximum calculated biological half-life value.

***See Appendix B for sample calculation.

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TABLE 31
SUMMARY OF 14C RESIDUES IN RAT TISSUES AFTER
ORAL ADMINISTRATION OF [14C]- SC-19129

TISSUE MATRIX	Average Tissue Microgram Equivalents/ g Tissue*							
	Hours Post-Dose							
	1	3	6	24	48	96	168	240
ADRENALS	0.325	1.900	1.420	1.561	1.280	0.873	0.516	0.467
BLADDER	1.464	6.246	38.203	0.596	0.489	0.359	0.226	0.426
RED BLOOD CELLS	0.117	0.474	0.361	0.303	0.339	0.346	0.311	0.484
BONE	0.140	0.744	0.689	0.579	0.572	0.294	0.180	0.229
BRAIN	0.061	0.325	0.318	0.305	0.316	0.235	0.235	0.285
EYE	0.107	0.438	0.475	0.468	0.359	0.234	0.217	0.137
EYE LENS	0.051	0.322	0.234	0.287	0.173	0.216	0.245	0.204
FAT	0.089	0.373	0.482	0.744	0.614	0.448	0.378	0.477
HEART	0.161	0.590	0.561	0.556	0.556	0.406	0.393	0.452
KIDNEYS	1.611	5.192	5.206	3.097	2.966	1.574	0.771	0.861
LARGE INTESTINE	0.530	17.049	14.207	1.305	0.766	0.389	0.243	0.253
LARGE INTESTINE CONTENTS	0.047	131.638	63.159	2.172	0.439	0.061	0.063	0.026
LIVER	1.105	3.616	2.490	1.537	1.313	0.824	0.610	0.585
LUNG	0.193	0.743	0.716	0.620	0.602	0.432	0.330	0.351
MUSCLE	0.071	0.230	0.200	0.214	0.274	0.208	0.235	0.339
SALIVARY GLAND	0.345	1.702	1.594	0.775	0.723	0.560	0.372	0.364
SKIN	0.118	0.481	0.490	0.480	0.475	0.316	0.287	0.334
SMALL INTESTINE	41.702	12.761	3.239	1.569	0.905	0.360	0.243	0.237
SMALL INTESTINE CONTENTS	226.704	124.161	4.620	0.195	0.096	0.043	0.032	0.028
SPLEEN	0.221	1.169	1.168	1.124	0.895	0.548	0.371	0.357
STOMACH	4.066	2.122	1.637	0.923	0.744	0.453	0.315	0.348
STOMACH CONTENTS	41.335	4.074	1.539	0.067	0.012	0.006	0.006	0.007
TESTES	0.072	0.348	0.375	0.364	0.363	0.254	0.236	0.273
THYMUS	0.166	0.776	0.861	0.922	0.946	0.482	0.308	0.294

*Average of values from three rats.

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Table 32

Estimation of Radiation Exposure Dose in Human Tissue

Tissue	Average Rat Tissue Weight*	Area Under Curve (Rat)	Radiation Exposure Dose (1yr) (Rat)	Half-life (days)**	Average Human Tissue Weight	Area Under Curve (Human)	Radiation Exposure Dose (1yr) (Man)
Adrenals	0.045	0.192	0.716	5.17	14	0.0006	0.0355
Bladder	0.118	0.567	2.197	18.65	45	0.0015	0.0980
Bone/Marrow	32.660	0.091	0.229	6.72	10000	0.0003	0.0114
Brain	1.742	0.071	6.525	N.C.	1400	0.0001	0.1240
Eye	0.084	0.066	0.237	5.42	15	0.0004	0.0203
Eye Lens	0.045	0.060	0.677	26.31	0.5	0.0054	0.9302
Fat	32.200	0.130	0.979	14.01	15000	0.0003	0.0321
Heart	0.957	0.122	1.192	30.03	300	0.0004	0.0580
Kidney	2.029	0.478	1.608	4.88	310	0.0031	0.1607
Large Intestine	2.317	0.336	0.935	3.81	250	0.0031	0.1323
Liver	10.328	0.261	1.024	6.46	1800	0.0015	0.0897
Lung	1.195	0.120	0.720	12.19	1000	0.0001	0.0131
Muscle	89.700	0.066	6.055	N.C.	28000	0.0002	0.2961
Red Blood Cells	7.115	0.095	8.692	N.C.	2300	0.0003	0.4105
Salivary Gland	0.616	0.155	0.714	9.16	85	0.0011	0.0790
Skin	37.260	0.096	0.866	19.11	4900	0.0007	0.1005
Small Intestine	5.841	0.296	0.827	3.67	1000	0.0017	0.0737
Spleen	0.569	0.162	0.618	6.05	180	0.0005	0.0298
Stomach	1.476	0.157	0.633	7.11	150	0.0015	0.0951
Testes	2.718	0.076	0.833	24.01	60	0.0034	0.5761
Thymus	0.539	0.143	0.532	6.07	20	0.0039	0.2188
Plasma	9.29	0.094	0.304	4.57	3200	0.0003	0.0135

N.C. = No clearance after 10 days

*Average from three rats.

**Maximum calculated biological half-life value.

***See Appendix B for sample calculation.

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Table 33

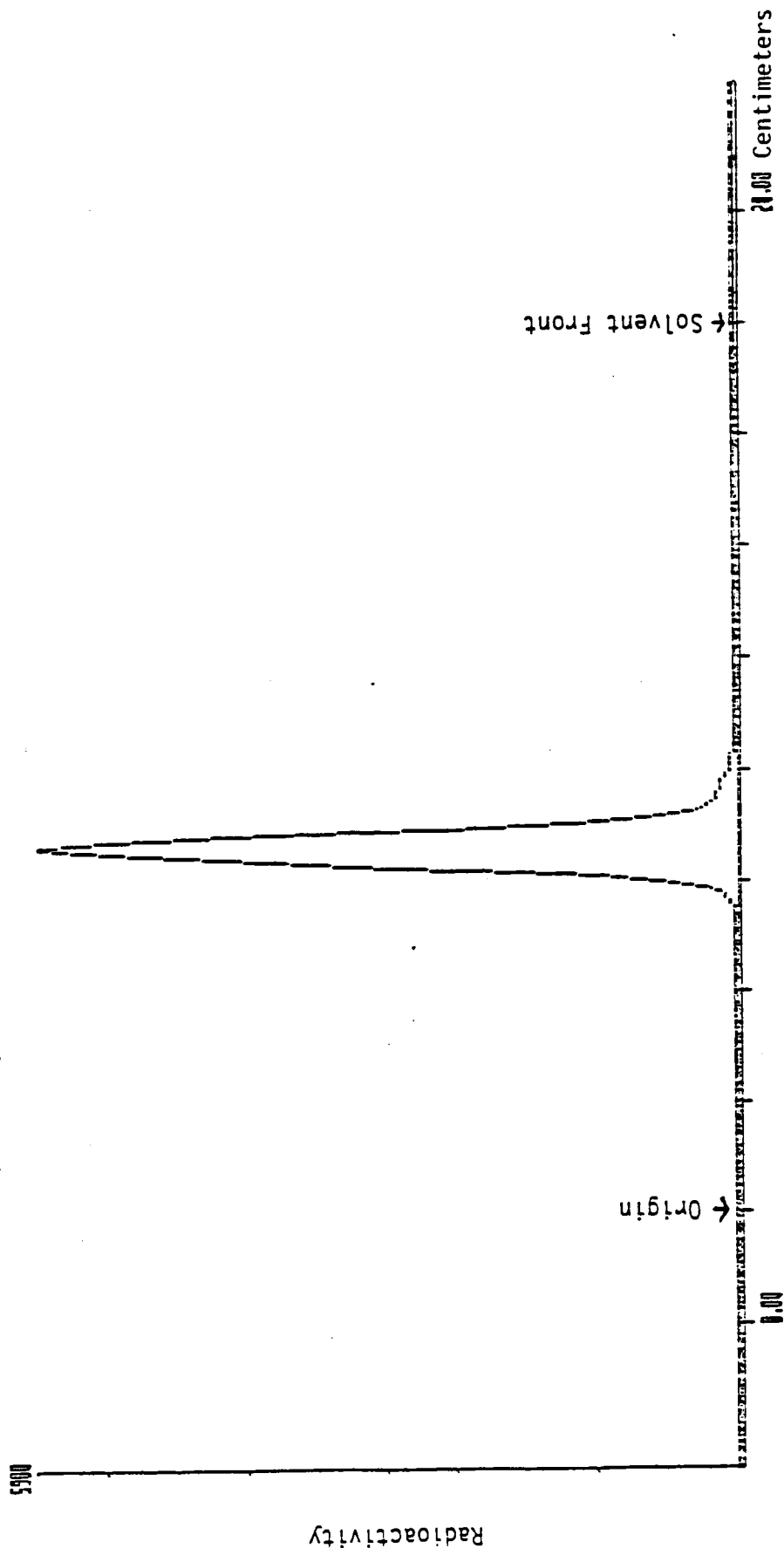
Estimation of Whole Body Radiation Exposure

Time (Day)	% Dose Excreted	% of Dose Remaining in Body	Biological Half Life (days)	Area Under The Curve (% X time)	Radiation Exposure Dose per 1 Year (RADS)	
					Rat	Man
0	0	100.00				
1	64.73	35.27		67.6		
2	4.75	30.52		32.9		
3	1.34	29.18	46.36	29.9		
4	0.65	28.53	41.16	28.9		
5	0.42	28.11	42.17	28.3		
6	0.29	27.82	44.94	28.0		
7	0.25	27.57	47.77	27.7		
8	0.21	27.36	50.78	27.5		
9	0.62	26.74	47.22	27.1		
10	0.50	26.24	45.92	26.5		
			average=	sum=	2.84	0.147
			45.79	324.22		

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FIGURE 1

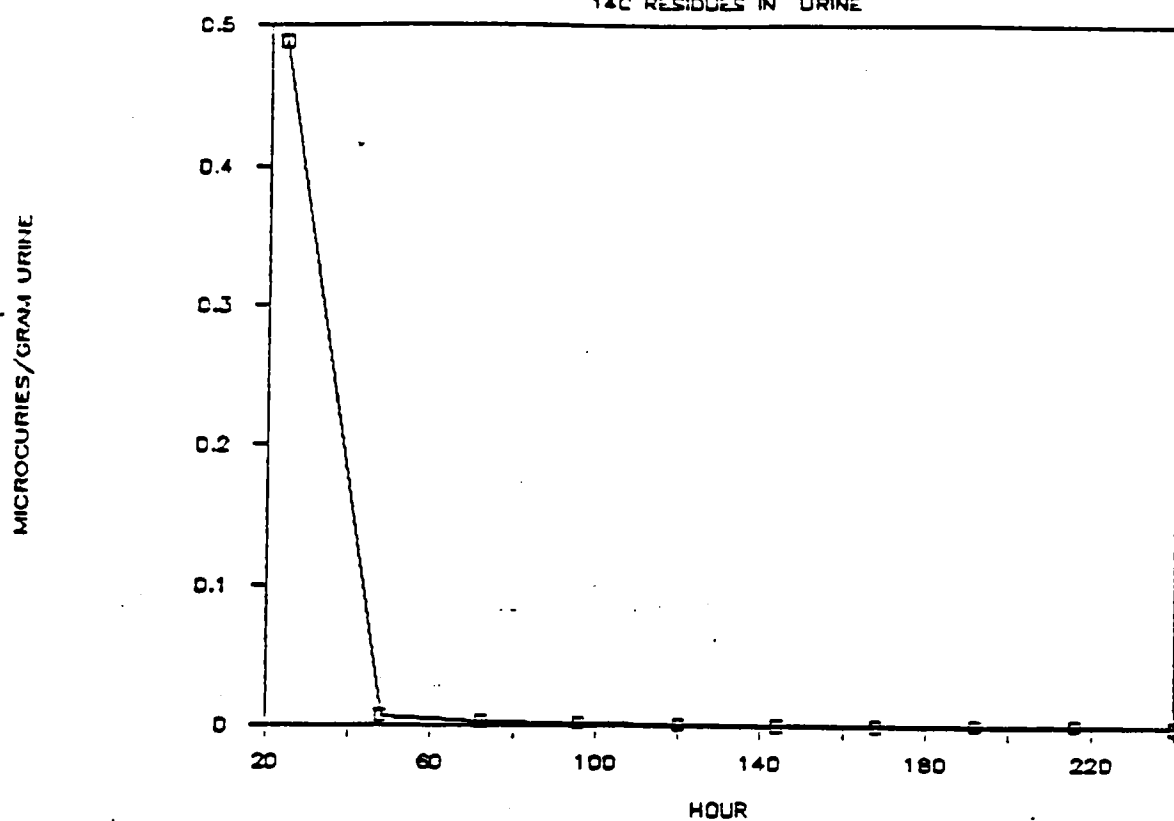
Analysis of [^{14}C]-SC-19129 by Thin Layer Chromatography



TLC analysis of dosing solution of 14C-SC-19129 using a chromatographic solvent consisting of chloroform, methanol, water and formic acid (64:30:4:2, by volume).

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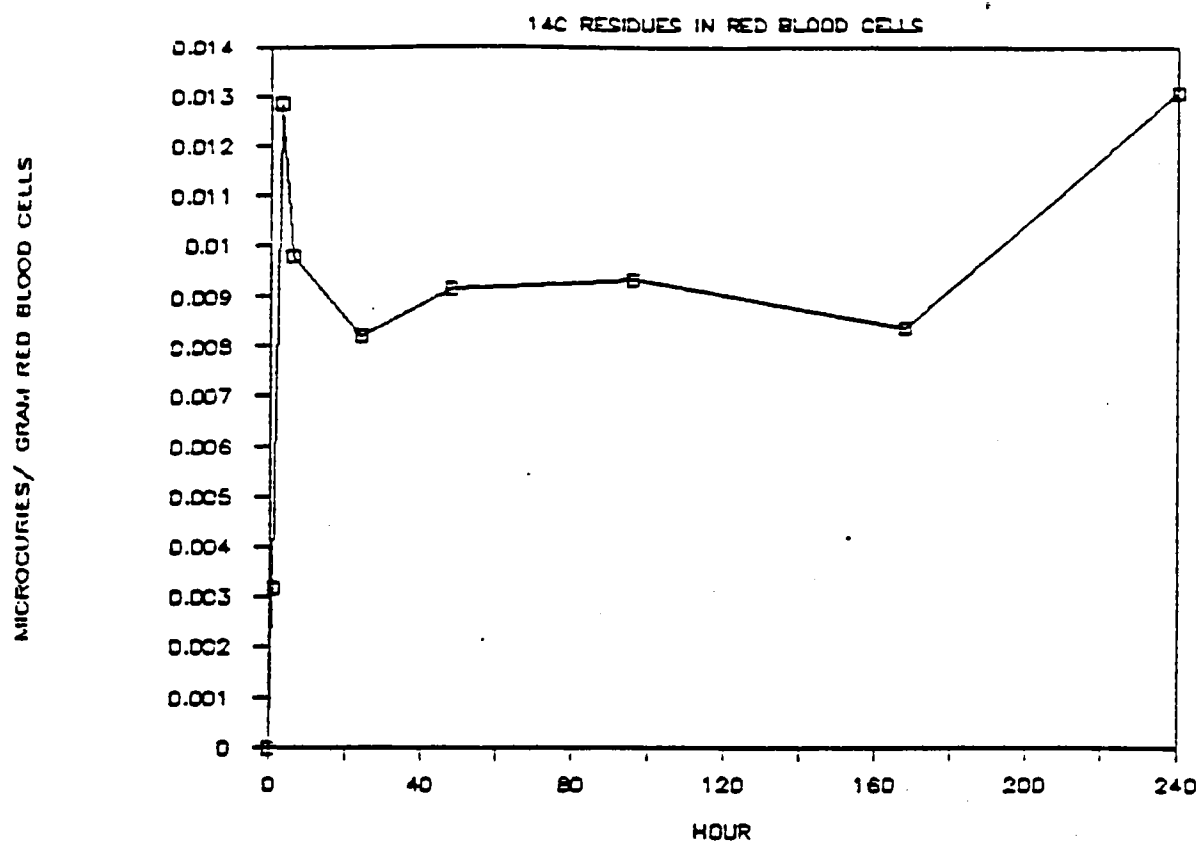
FIGURE 2

 ^{14}C RESIDUES IN URINE

Graph of the ^{14}C concentration in urine versus time after oral administration of ^{14}C -SC-19129 to rats.

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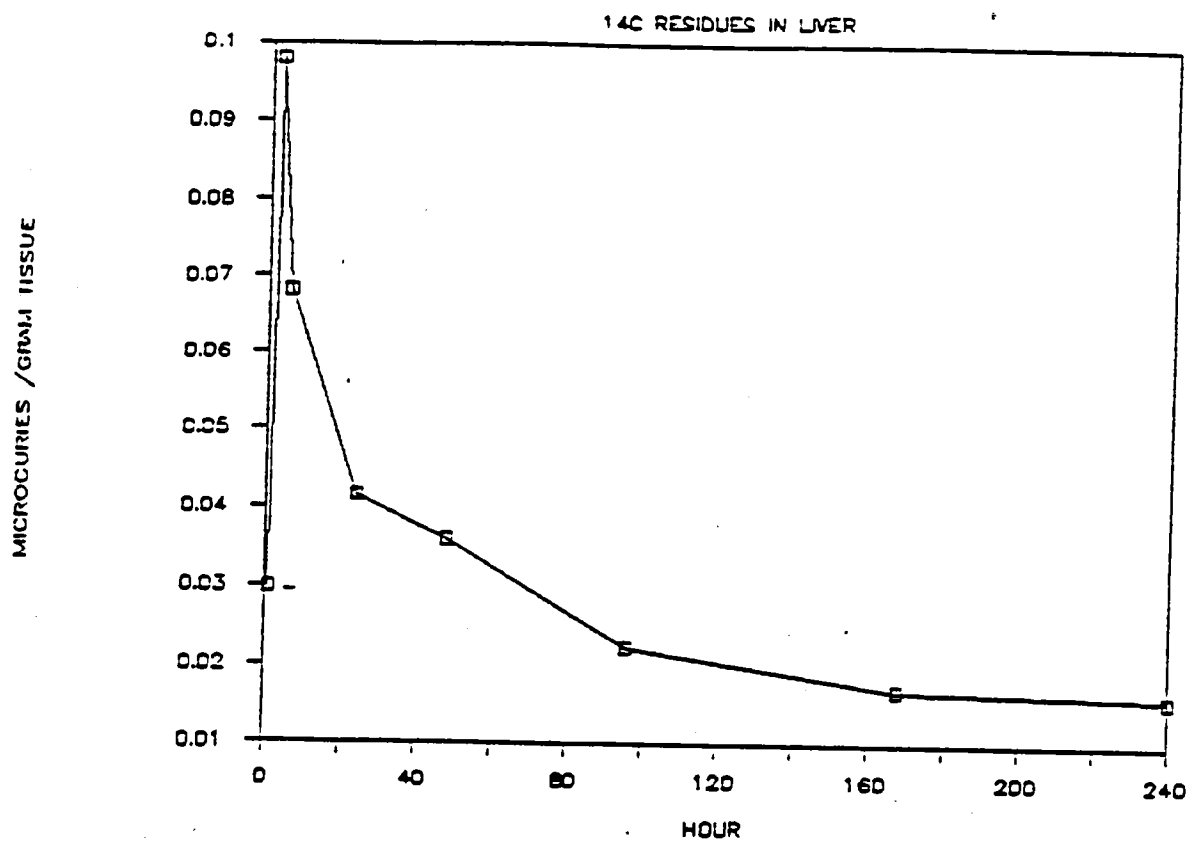
FIGURE 3



Graph of the ¹⁴C concentration in red blood cells versus time after oral administration of ¹⁴C-SC-19129 to rats.

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FIGURE 4



Graph of the 14C concentration in liver versus time after oral administration of 14C-SC-19129 to rats.

APPENDIX A

Sensitivity Calculations for Radiometric Analyses

Average Sample Size: 0.2 g
 Average Background: 30 cpm
 Sample Counting Time: 10 minutes
 Background Counting Time: 10 minutes
 Average Counting Efficiency: 77%
 Lowest Acceptable Gross Count Rate (LAGCR, 2X Background): 60 cpm
 Lowest Acceptable Net Count Rate (LANCR = LAGCR - Background): 30 cpm
 Specific Activity: 61,000 dpm/ μ g

$$\begin{aligned}
 \text{Greatest percent probable error} &= 0.6745 \left[\frac{\frac{\text{LAGCR}}{\text{Sample Count Time}} + \frac{\text{Background Count}}{\text{Background Count Time}}}{\text{LANCR}} \right]^{1/2} \times 100\% \\
 &= 6.7\%
 \end{aligned}$$

$$\begin{aligned}
 \text{Minimum Sensitivity} &= \frac{\text{LANCR}}{\text{Average Count Efficiency}} \times \frac{1}{\text{Specific Activity of Dose}} \times \frac{1}{\text{Average Sample Size (g)}} \\
 &= 0.003 \text{ ppm}
 \end{aligned}$$

APPENDIX B

Radiation Exposure Dose Calculation

Biological Half-Life

Equation: $t_{1/2} = 0.693 \times t / [2.3 \times \log (N_0/N)]$
 t = Time in days
 N_0 = the maximum ^{14}C residue (dpm/mL or g) observed
 N = dpm/mL or g at time t

Example used: liver matrix at 240-hour time point

$$t = 240 \text{ hours} \times 1 \text{ day} / 24 \text{ hours} = 9 \text{ days}$$

$$N_0 = 92,433 \text{ mean dpm/g}$$

$$N = 35,167 \text{ mean dpm/g}$$

$$t_{1/2} = 0.693 \times 9 \text{ days} / [2.3 \times \log (92,433 \text{ dpm/g} / 35,167 \text{ dpm/g})]$$

$$t_{1/2} = 6.46 \text{ days}$$

Area Under the Curve

Area = Sum of Trapezoids

$$= 1/2 (0.125C_1 + 0.208C_3 + 0.875C_6 + 1.75C_{24} + 3C_{48} + 5C_{96} + 6C_{168} + 3C_{240})$$

Where $C_1 - C_{240}$ = concentration of ^{14}C at the 1 - 240 hour time points

Example used: Liver Tissue

$$\text{Area} = 1/2 (0.125 \times 0.03 + 0.208 \times 0.098 + 0.875 \times 0.068 + 1.75 \times 0.042 + 3 \times 0.036 + 5 \times 0.022 + 6 \times 0.017 + 3 \times 0.016)$$

$$= 0.261 (\mu\text{g equivalents/g}) \times \text{day}$$

Radiation Exposure Dose*

Equation: beta-emitter dose

$$D = 73.8 E T_{\text{eff}} C (1 - e^{-\lambda_{\text{eff}} t}) + 51.1 E (\text{Area Under the Curve})$$

where D = dose (rads)

E = average energy of beta particle (MeV)

T_{eff} = effective half-life

C = concentration ($\mu\text{Ci/g}$) of radionuclide in tissue at 240 hours

λ_{eff} = effective decay constant (day^{-1})

t = time (day)

APPENDIX B (Continued)

Example used: liver tissue

$$E = 0.049 \text{ MeV for } ^{14}\text{C}$$

$$T_{\text{eff}} = \text{biological half-life} = 6.46 \text{ days}$$

$$C = 0.016 \text{ } \mu\text{Ci/g tissue}$$

$$\lambda_{\text{eff}} = 0.693/T_{\text{eff}} = 0.693/6.46 \text{ days}$$

$$t = 355 \text{ days}$$

$$D = 73.8 \times 0.049 \times 6.46 \times 0.016 \times [1 - e^{(-0.693/6.46 \times 365)}] + 51.1 \times 0.049 \times 0.261$$

$$D = 1.024 \text{ rads}$$

For tissues which show no clearance:

$$D = 51.1 E C t$$

Where C = average concentration of ^{14}C in $\mu\text{Ci/g}$ = area under the curve $\div 10$

$$t = 365 \text{ days}$$

Example: muscle tissue

$$D = 51.1 \times 0.049 \times 0.0066 \times 365 = 6.03 \text{ rads}$$

Calculation for Radiation Exposure in Human Tissue

Area Under the Curve

$$\text{Area (man)} = \text{Area (rat)} \times \frac{\text{average rat tissue weight}}{\text{average human tissue weight}^*}$$

Example: liver

$$\text{Area (man)} = 0.261 \times \frac{10.3}{1,800} = .0015$$

Estimation of Radiation Exposure Dose in Human Tissue

$$\text{Dose (man)} = \text{Dose (rat)} \times \frac{\text{rat tissue weight}}{\text{human tissue weight}} \times \frac{\text{dose to human}}{\text{dose to rat}}$$

Example used: Liver Tissue

$$\text{Dose (man)} = 1.024 \times \frac{10.328}{1,800} \times \frac{200}{13.1}$$

$$= 0.0897 \text{ rads/year}$$

*Radiological Health Handbook, U. S. Department HEW (1970).

APPENDIX B (Continued)

Estimation of Whole Body Radiation Exposure Dose

Using urine clearance for a biological half-life (Table 33):

$$\text{Dose (rat)} = [73.8 \times .049 \times 45.99 \times 26.24\% \times [(1-e^{(-.693/45.79)365})] + 51.1 \times .049 \times 324.2\%] \times \frac{13.1/238}{100\%}$$

$$= 2.84 \text{ rads/year}$$

$$\text{Dose (man)} = \text{Dose (rat)} \times \frac{\text{rat body weight}}{\text{human body weight}} \times \frac{\text{dose to human}}{\text{dose to rat}}$$

$$= 2.84 \times \frac{238}{70,000} \times \frac{200}{13.1}$$

$$= 0.147 \text{ rads/year}$$

Calculation of Percent of Total Dose

$$\% \text{ of Dose} = \frac{\text{DPM/g} \times \text{Total Sample Weight}}{\text{Total Dose (DPM)}} \times 100$$

Example: Liver rat C31376

$$\% \text{ of Dose} = \frac{52900 \times 8.449}{2.85 \times 10^7} \times 100$$

$$= 1.57\%$$

Study No. 6127-113

APPENDIX C

AVERAGE TISSUE WEIGHTS

TISSUE MATRIX *****	Average Tissue Weight at Time of Sacrifice (g)*									OVERALL AVERAGE *****
	Hours post-dose									
	0	1	3	6	24	48	96	168	240	
ADRENALS	0.039	0.046	0.045	0.097	0.033	0.041	0.028	0.035	0.045	0.045
BLADDER	0.111	0.139	0.126	0.147	0.103	0.099	0.113	0.116	0.107	0.118
BONE/MARROW	7.514	7.530	7.657	7.518	7.482	7.539	7.536	7.552	7.631	7.551
BRAIN	1.689	1.834	1.713	1.656	1.745	1.742	1.750	1.750	1.800	1.742
EYE	0.069	0.097	0.090	0.077	0.061	0.083	0.089	0.075	0.117	0.084
EYE LENS	0.036	0.045	0.042	0.044	0.051	0.041	0.049	0.049	0.049	0.045
FAT	0.289	0.304	0.293	0.207	0.316	0.409	0.392	0.476	0.598	0.365
HEART	0.857	0.894	0.925	0.924	0.821	1.274	0.981	0.871	1.061	0.957
KIDNEYS	2.005	1.852	1.934	2.098	1.966	2.009	2.036	2.153	2.205	2.029
LARGE INTESTINE	2.288	2.005	2.126	2.040	2.288	2.509	2.059	2.651	2.885	2.317
L. INT. CONTENT	2.2	2.0	1.6	1.9	7.6	7.9	7.4	8.1	7.1	5.1
LIVER	7.930	7.785	8.257	7.625	11.228	11.883	12.396	11.855	13.992	10.328
LUNG	1.086	1.157	1.242	1.275	1.183	1.139	1.067	1.365	1.238	1.195
MUSCLE	4.172	4.292	3.228	3.805	3.363	4.889	5.132	5.206	4.779	4.319
SALIVARY GLAND	0.554	0.538	0.568	0.516	0.546	0.571	0.575	1.001	0.677	0.616
SKIN	1.571	2.260	2.341	2.774	1.691	3.520	3.514	5.305	3.435	2.935
SMALL INTESTINE	5.640	5.411	5.793	4.842	6.451	5.624	5.642	5.742	7.423	5.841
S. INT. CONTENT	0.6	0.8	0.5	0.6	2.1	3.6	4.6	4.4	4.2	2.4
SPLEEN	0.538	0.552	0.555	0.535	0.493	0.516	0.624	0.679	0.629	0.569
STOMACH	1.562	1.271	1.349	1.351	1.570	1.552	1.375	1.578	1.677	1.476
STOMACH CONTENTS	0.0	0.1	0.1	0.1	16.6	8.0	7.0	3.6	6.3	4.6
TESTES	2.729	2.733	2.680	2.641	2.443	2.747	2.855	2.835	2.798	2.718
THYMUS	0.535	0.450	0.581	0.657	0.476	0.469	0.517	0.626	0.539	0.539
BLOOD	7.881	7.616	6.308	5.629	7.507	6.459	5.441	8.017	9.177	7.115
CARCASS	181.8	178.7	185.1	186.4	199.2	180.0	196.0	211.4	235.9	194.9

*Average of values from three rats.

APPENDIX D

Protocol Deviations

1. Protocol, Page 6. Rats were anesthetized with halothane at time of sacrifice.
2. Protocol, Page 6. In addition to the tissues listed, the following tissue matrices were analyzed: stomach contents, small intestine contents, and large intestine contents.
3. Protocol, Page 6. The femur was used instead of bone marrow.
4. Protocol, Page 6. The thymus was not oxidized as a single sample but was homogenized and aliquoted.
5. Protocol, Page 8. The radiation exposure for human tissues was calculated for a 200 μ Ci dose.
6. Protocol, Page 8. The radioactivity in each tissue was calculated as μ g equivalents per g of tissue.

APPENDIX E

Protocol

Protocol

1. Study Title:

Tissue Distribution of [^{14}C]-SC-19129 After Oral Administration to Male Rats

2. Study Sponsor:

G. D. Searle and Co.

3. Facility:

Hazelton Laboratories America, Inc. (HLA)
3301 Kinsman Blvd.
Madison, WI

4. Proposed Date:

First Dosing: August 20, 1985

5. Introduction:

SC-19129 has been identified as a conversion product of aspartame (SC-18862, N-L- β -aspartyl-L-phenylalanine methyl ester, APM) in sweetened soft drinks. Exploratory studies have indicated that up to 20% of APM may be converted to SC-19129 and SC-19200, the free acid of SC-19129 during prolonged storage at elevated temperature (40°C). A 12 ounce (354 ml) can of a soft drink sweetened with 0.05% APM (180 mg/12 ounces) could thus contain up to a total of 36 mg of the combination of SC-19129 and SC-19200. Consumption of three cans, each containing the above amount, would result in a dose of approximately 2 mg/kg to a 50 kg person.

In studies in the rhesus monkey and rat little or no SC-19129 reached the systemic circulation following oral administration but SC-19200, the product of ester hydrolysis, did reach the systemic circulation. Thus administration of SC-19129 appears to be equivalent to administration of a combination of SC-19129 and SC-19200.

6. Purpose:

The study is designed to provide estimates of the apparent whole body and selected tissue radiation exposures for doses of approximately 100 mCi [¹⁴C]-SC-19129 following oral administration to man.

7. Overview of Study Design:

[¹⁴C]-SC-19129 will be administered orally to 27 male Charles River rats at 2 mg/kg. Groups of three rats will be killed by diethyl ether anesthesia at each of 9 time points and selected tissues and organs will be dissected and weighed. The total radioactivity in plasma, tissues and organs will be measured by liquid scintillation counting, following suitable sample preparation. The total radioactivity data will be used to calculate the radiation exposure for specified doses of [¹⁴C]-SC-19129 administered to man.

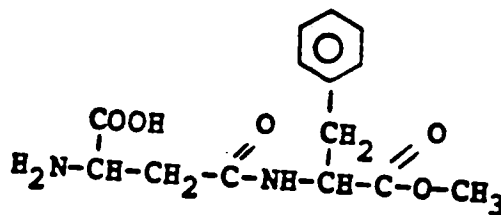
8. Laboratory Procedure:

This study is not within the scope of Good Laboratory Practice Regulations.

9. **Test Article:**

A. Chemical Name: SC-19129 (β-AP) is N-L-β-aspartyl-L-phenyl alanine, 1-methyl ester.

B. Chemical Structure:



SC-19129

C. Dosage Forms:

1. [U-¹⁴C-Phe]-SC-19129 with a specific activity of approximately 32 mCi/mg (approximately 9.6 mCi/mmol) and a radiochemical purity of approximately 98% will be supplied by the Radiochemistry Group, G.D.Searle & Co.
2. The oral (p.o.) dosage form will be prepared by dissolving the appropriate amount of [¹⁴C]-SC-19129 in distilled water to give a final concentration of 1.0 mg/ml.

MRC-851-0052

D. Administration:

- i Route: Test article will be given p.o. by gavage.
- ii Frequency: Each animal will receive the test article once.

- iii Volume and Dosage:

The [¹⁴C]-SC-19129 oral dose will consist of 2.0 ml/kg administered via a stomach tube attached to a syringe.

This is intended to provide a dose of 2 mg/kg.

E. Storage:

[¹⁴C]-SC-19129 will be stored at room temperature, protected from light, in a well closed container. The test article dose solution will be stored at room temperature and will be administered within two hours of its preparation.

F. Analyses:

The radiochemical purity of the test article in the dose solution will be determined by thin layer radiochromatography using aliquots of the excess remaining after dose administration. Duplicate thin layer plates will be spotted and their development initiated within 3 hours after dose preparation.

10. Test System, Housing and Diet:

A. Test System:

Male Charles River rats (Long-Evans Hooded rats, LE strain) will be used. The animals will weigh 200 to 300 g and will be individually identified. Twenty-seven animals will be used in this study.

B. Housing:

The rats will be kept in a room with a 12 hour light 12 hour dark cycle for at least three days prior to dosing.

Following drug administration the rats will be housed in individual mesh floored cages until killed. The three rats to be killed at 240 hours will be held in metabolism cages from the day prior to dosing to allow separate collection of urine and feces.

C. Diet:

1. Food: The rats will be fed standard laboratory rat diet (Purina Rodent Chow #5002, Ralston Purina, St. Louis, MO). They will be fasted overnight prior to drug administration. Food will be available from 6 hours after dosing.

2. Water: Tap water from the local supply will be available ad libitum.
3. Special analyses of food and water will not be performed since no contaminants known to be capable of interfering with the study are reasonably expected to be present.

11. Animal Observations:

Animals will be observed at the time of dosing and sample collection for any visible changes which might have an impact on the interpretation of results.

12. Sample Collection Times, and Storage:

1. The rats will be killed by diethyl ether anesthesia and blood samples will be taken by cardiac puncture. Each blood sample will be treated with heparin and centrifuged. The plasma and blood cells will be separated and stored frozen at approximately -20°C until analysis.
2. Three animals (randomly selected) will be sacrificed at each of the following times (hours after dose administration):
0 (control, no dose), 1,3,6,24,48,96,168, and 240.
3. The following tissues will be dissected, weighed and stored in labeled tubes at approximately -20°C until analyzed:
stomach, small intestine, large intestine, liver, spleen, kidneys, adrenals, testes, brown fat, bladder, heart, lungs, thymus, submaxillary salivary glands, skeletal muscle (sample from leg), bone marrow, eyes (minus lens), eye lens, brain, and skin (shaved samples from the back).

4. Urine and feces will be collected from the metabolism cages for each consecutive 24 hour period from 0 to 240 hours for the 3 animals killed at 240 hours. Samples will be stored frozen at approximately -20°C until analysis.

13. Sample Analysis:

1. Duplicate plasma and urine samples (0.1 and 0.5 ml, respectively) will be added to 5 ml of PCS[®] (Amersham Co., Arlington Heights, IL) for determination of ^{14}C concentrations.
2. Tissue and fecal samples will be oxidized using a Packard 306 sample oxidizer.
3. Weighed aliquots of blood cells will be oxidized using a Packard 306 sample oxidizer. Duplicate weighed aliquots will be processed for tissues except that the whole thymus will be oxidized as a single sample, and both adrenals, both eyes and both eye lenses from each animal will be oxidized as single samples.
4. Control and spiked control samples will be processed with the experimental samples to monitor the performance of the analytical procedures.
5. The radioactivity in the processed samples will be determined by scintillation counting with automatic quench correction and background subtraction.

14. Statistical Procedure:

1. The radioactivity in each tissue will be calculated as ng equivalents per g (or ml) of tissue and as a percentage of the administered radioactivity in each organ. The radioactivity excreted in urine and feces will be calculated as a percentage of the administered dose.
2. The area under the concentration-time curve for each tissue will be calculated for the 240 hour period.
3. The data will be used to estimate the radiation absorbed dose for various human tissues and the whole body for doses up to 100 mCi of [¹⁴C]-SC-19129.

15. Archiving of Materials:

The protocol and raw data will be archived by HLA. A final report will be submitted to the Study Coordinator by HLA.

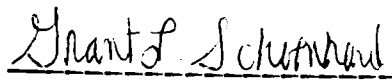
16. List of Study Participants:

Study Coordinator:

E. Burton

Drug administration,
Sample collection,
Sample analysis,

HLA

Statistical Procedures, and
Report:**17. Protocol Review Committee:**J. Oppermann
G. Schoenhard
C. Cook
A. MacKenthun
C. Tschanz**18. Protocol Apprival Committee:** 7/18/85
E. Burton Date 7/22/85
G. Schoenhard Date 7/23/85
J. Oppermann Date



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Protocol TP5129
Tissue Distribution of [^{14}C]-SC-19129
After Oral Administration to Male Rats

HLA Study No. 6127-113

Sponsor

Searle Research and Development
G. D. Searle & Co.
4901 Searle Parkway
Skokie IL 60077

Contractor

Hazleton Laboratories America, Inc.
Life Sciences Division
3301 Kinsman Boulevard
Madison WI 53704

Study Coordinator

Earl Burton, PhD

Study Director

R. James Puhl, PhD

Amendment No. 1
Effective August 5, 1985

This amendment changes the anesthetic used to kill the rats because diethyl ether is no longer routinely used in this facility.

- 1) Page 1, Proposed Date. To reflect the actual starting date, substitute the underlined for "August 12".

First Dosing: August 19, 1985

- 2) Page 2; 7. Overview of Study Design, sentence 2. Substitute the underlined for "diethyl ether".

Groups of three rats will be killed by halothane anesthesia at each of 9 time points and selected tissues and organs will be dissected and weighed.

- 3) Page 6; 12. Sample Collection Times, and Storage, 1., sentence 1. Substitute the underlined for "diethyl ether".

The rats will be killed by halothane anesthesia and blood samples will be taken by cardiac puncture.

AMENDMENT APPROVAL

Earl M. Burton
Earl Burton, PhD
Study Coordinator
Searle Research and Development
G. D. Searle & Co.

August 7, 1985
Date

Paul Miesler for
R. James Puhl, PhD
Study Director
Manager, Metabolism and Environmental Fate
Hazleton Laboratories America, Inc.

August 6, 1985
Date

Diane C. Bronson
Diane C. Bronson
Inspector, Quality Assurance Unit
Hazleton Laboratories America, Inc.

8/7/85
Date

(0845t/cja)