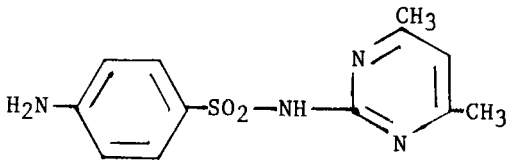
SULFADIMIDINE

IDENTITY

Chemical name: 4-amino-N-(4,6-dimethyl-2-pyrimydyl) sulphanilamide

Synonyms: Sulfamidine, Sulfamezathine

Structural formula:



Molecular formula: $C_{12}H_{14}N_4O_2S$

Molecular weight: 278.32

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient

Melting point: 176°C (depends on crystal structure)

RESIDUES IN ANIMALS AND THEIR EVALUATION

PHARMACOKINETICS

Pigs

The influence of sex on the pharmacokinetics of sulfadimidine (SD) was examined in male, female and castrated male pigs. Sex did not alter significantly elimination rates of SD and its metabolites into urine (Duffee et al, 1984).

SD was fed at the rate of 500 g per metric ton (5 times normal dose) for 30 days to pigs (18-43 kg). When the drug was withdrawn the bedding of the animals was not changed and thus the treated pigs and one group of non-medicated pigs were exposed to contaminated bedding. The contaminated bedding was found to contain SD in amounts from 42-117 ppm.

Mean plasma concentrations of SD were in a linear logarithmic depletion relationship with time with a short half life of 12.6 hours.

After withdrawal of the drug, the concentrations of SD in muscle and fat tissues depleted to <0.1 mg per kg in 4 days and to this level in liver and kidney within 8 - 10 days. Fat and muscle concentrations were 0.1 ppm or less within 4 days at which time the concentrations in the liver were 3.7 ppm and 2.2 ppm, respectively. It was concluded in this study that depletion of tissues and plasma of treated pigs had a linear relationship with time when the concentrations are plotted on a semilogarithmic graph. The values for the half life and time to deplete to 0.1 ppm can be calculated from the graph and are as follows:

Tissue	Half life (hours)	Time to reach 0.1 ppm (days - approx.)
Plasma	12.6	4
Muscle	16.5	4
Liver	31.5	8
Kidney	26.6	7
Fat	16.9	4

The semilogarithmic relationship was maintained over the early part of the withdrawal period but the recycling of the SD from the bedding and the limitations of the method to measure 0.1 ppm or less gave variable results towards the end of the experimental period (Samuelson et al, 1979).

The Food Safety and Inspection Service (FSIS), USDA, carried out a study using 70 pigs (90-113 kg) fed 110 grams SD per ton of feed for 30 days and reduced the level of SD from 1.1 to 13.9 grams per ton for an additional 15 days. The purpose was to determine the serum and tissue concentrations of swine at slaughter when withdrawal feeds were contaminated with various concentrations of SD, to compare serum/liver ratios and the usefulness of serum/tissue ratios in making regulatory decisions on tissue SD concentrations.

There was some difficulty in producing homogenious feeds, although the SD concentrations in all mixed feed batches was within the ± 25% analytical variation permitted. The basal or non-medicated feed fed to control groups was contaminated with a mean concentration of 1.1 gram SD per ton of mixed feed. Nevertheless the feed batches were claimed to be at least as good as those available commercially. Obviously it was not possible to obtain constant dietary intake because of the feed composition variation.

At the beginning of the withdrawal period the pigs were moved to clean pens and this was repeated 24 hours later. This should have reduced the major effect of recycling the excreted residues from the main 30 day treatment period. How this reflects normal pig management in the USA is not stated.

The correlation between serum and tissue concentrations was:

	Slope	Intercept	r (correlation)
Serum/liver	1.37	0.05	0.956
Serum/muscle	3.62	0.07	0.935

However there was large variation at the lower concentrations up to 0.2 ppm.

Concentrations of SD were <0.1 ppm in pigs fed <2 grams SD per ton and <0.1 ppm in muscle and pigs fed <8 grams per ton. When serum SD was <0.1 ppm all liver and muscle samples were also <0.1 ppm. Only when serum SD was >0.45 ppm was it certain that liver SD also exceeded 0.1 ppm. No measurements were made of SMZ in urine (Ashworth et al, 1986).

The excretion of SD into both urine and faeces was determined in a radiometric study using C14-SD administered orally to pigs. The results in table I show that the amount of radioactivity excreted reached plateau values of 72.2% in urine and 16.8% in faeces of the dose of C14 administered. The plateau values were reached at about 6 days after the drug was withdrawn (FDA 224-81-005 & USDA SEA-12-14-3001-064, 1984).

TABLE I. Cumulative excretion of carbon-14 in the urine and faeces (percentage of C14 given to that point in experiment) of pigs dosed with C14 SD

Hours after 1st dose of C14-SD	WT (days)	Urine %	Faeces %	Total %
0-24		37.5	2.4	39.9
0-48		41.5	5.2	46.7
0-96		50.4	8.2	58.6
0-144		54.3	9.8	64.1
0-168	0	59.2	10.5	69.7
0-192	1	66.8	13.6	80.4
0-216	2	69.7	14.6	84.3
0-240	3	70.8	15.6	86.4
0-264	4	71.7	16.2	87.9
0-288	5	72.0	16.4	88.4
0-312	6	72.1	16.6	88.7
0-360	8	72.2	16.7	88.9
0-396	9.5	72.2	16.8	89.0

WT is withdrawal time in the depletion study. Each value is the mean for three pigs.

Data from radiometric study FDA 224-81-005 & USDA SEA-12-14-3001-064. (1984).

Ruminants

Elimination in milk of dairy cattle

Five French Frisonne lactating cows were each administered 100 mg SD sodium salt per kg live weight by intravenous injection. Five similar cows were given three daily intramammary injections of 200 mg SD combined with 40 mg Trimethoprim into each quarter. The injections were carried out after the morning milking and milk was collected at 0800 hours and 1700 hours for a further 7 days. The residues of SD were determined in the milk samples and the results are shown in table II.

TABLE II. Residues of SD in the milk of cows treated parentally with either an intravenous injection of SD sodium salt (100 mg per kg) or after three administrations of 200 mg SD and 40 mg trimethoprim in each quarter

		Residues (ppm)			
		Intravenous treatment		Intramammary treatment	
Withdrawal time (days)	Time of milking	Mean	Maximum	Mean	Maximum
0.4	PM	24.6	31.5	9.97	20.6
1	AM	5.74	6.76	3.04	4.59
	PM	2.26	2.96	13.9	18.1
2	AM	0.55	0.82	0.46	1.0
	PM	0.22	0.36	0.17	0.79
3	AM	0.12	0.20	0.08	0.37
	PM	0.06	0.10	0.02	0.02
4	AM	0.04	0.07	<0.01	0.03
	PM	0.03	0.05	<0.01	0.01
5	AM	0.03	0.05	ND	ND
	PM	0.02	0.03	-	-
6	AM	<0.01	0.01	-	-
	PM	ND	ND		

The mean values are taken for five cows. ND is not detectable (<0.01 ppm). Residues measured by HPLC method.

After intravenous injection the concentration of SD was highest at the first milking and declined to less than the limit of detection 6 days after treatment. The elimination curve was biexponential.

After intramammary administration the concentrations of SD were highest at the first milking and declined rapidly thereafter to non-detectable levels 5 days after treatment.

In a further experiment on groups of five similar cows SD was administered by intravenous injection (4 and 8 mg per kg) or intramuscular injection (8 mg per kg) in a cocktail of sulfas containing the sodium salts of SD, sulfamerazine and sulfadiazine. The results are shown in table II. At these low doses the concentrations do not exceed 1 ppm for any of the three drugs. Residues of the drugs could be detected after the third milking. No calculations of the % dose excreted into the milk was recorded. (Boisseau, 1988).

Sheep

SD sodium salt was administered intravenously to 14 ewes and the concentrations of SD and its amino substituted metabolites determined by the classical diazotization reactions combined with TLC. The results are shown in table III. 71% original dose was excreted into the urine and excretion was essentially complete 60 hours after dosing. (Bevill et al., 1977a).

Table III: SD concentrations (ppm) in tissues and fluids of sheep after intravenous administration of 107.25 mg SD sodium salt per kg live weight

Hours after dosing	Muscle	Liver	Kidney	Fat	Plasma	Urine % dose accumulated
6	56.8	68.9	124.2	38.9	172	21.6
12	21.2	36.8	63.4	15.0	105	40.1
24	4.10	5.98	18.3	1.70	29	59.7
36	0.98	1.57	5.2	0.35	4	66.4
48	0.15	0.21	0.68	0.9	1	68.4
60	0.13	0.23	0.42	0.03	0	71.0
84	0.09	0.11	0.14	0.02	-	-

The value for tissue residues at 6 hours is for a single animal, all other values are the mean of two sheep.

Poultry

SD elimination in eggs

Two groups of six laying hens were treated with SD sodium salt at a dose of 1 g per L or 2 g per L in their drinking water for 5 consecutive days.

SD was measured by HPLC in both the yellow and white parts of the egg.

The elimination of SD was characterised by significant concentrations in both the white and yellow components. More SD was eliminated in the white which is the inverse of many antibiotics. In the white the concentrations after 1 day were >10 ppm and remained above this level for the duration of the treatment. In the yellow, the concentrations rose progressively but were always less than the levels in the white.

24 hours after drug withdrawal the concentrations in the eggs declined (see Tables IV and V). The elimination was slower in the yellow. About 50% of the dose is eliminated in eggs. (Boisseau, 1988).

TABLE IV: Concentrations of SD in eggs after oral administration for 5 days at the dose of 1 gram SD sodium salt per L in the drinking water

Time (days)	White (ppm) mean	Yellow (ppm) mean	Whole egg (ppm) mean	Whole egg (ppm) maxima
Treatment 1	15.5	3.2	11.6	15.5
2	41.8	14.2	33.0	47.0
3	47.1	25.7	40.1	47.0
4	50.9	28.4	46.0	53.6
5	51.5	34.1	46.0	52.9
Withdrawal 1	34.7	31.6	33.9	41.9
2	4.2	15.6	7.8	11.5
3	2.1	11.7	4.8	6.4
4	1.3	7.5	3.2	3.6
5	0.37	3.2	1.2	1.4
6	0.23	1.6	0.66	1.0
7	0.059	0.27	0.12	0.18
8	0.027	0.050	0.034	0.069
9	0.016	0.029	0.020	0.033
10	0.013	0.022	0.016	0.028
11	0.010	0.018	0.013	0.023
12	0.0051	0.015	0.0082	0.019
13	<0.0005	0.0099	0.0047	0.013
14	<0.0005	0.0050	0.0023	0.018
15	<0.0005	0.0055	0.0017	0.017
16	-	<0.0005	0.0004	0.0019
17	-	<0.0005	-	-

Each value is the mean or maxima of 6 birds which layed 3 - 6 eggs per day.

TABLE V. Concentration of SD in eggs after oral administration for 5 days at the dose of 2 g SD Sodium salt per l in the drinking water

Time (days)	White (ppm) mean	Yellow (ppm) mean	Whole egg (ppm) mean	Whole egg (ppm) maxima
Treatment 1	22.8	4.8	17.0	37.0
2	48.8	18.6	39.4	59.5
3	60.5	33.7	51.9	75.5
4	73.2	38.1	62.6	79.2
5	70.4	44.5	62.1	83.5
Withdrawal 1	43.2	43.8	43.4	54.0
2	7.8	25.3	13.0	17.4
3	2.2	17.3	6.6	7.4
4	1.3	11.3	4.2	4.5
5	1.1	7.6	3.0	4.7
6	0.43	4.1	1.5	1.6
7	0.14	1.0	0.42	0.92
8	0.058	0.35	0.12	0.24
9	0.026	0.025	0.025	0.038
11	0.017	0.012	0.015	0.087
13	0.014	0.0078	0.012	0.018
16	0.010	<0.005	0.0074	0.012
19	0.0061	<0.005	0.0043	0.011
23	<0.005	-	0.0017	0.0053
27	<0.005	-	0.0006	0.0037

Each value is the mean or maxima of 6 birds laying a total of 2 - 6 eggs per day.

RESIDUES

Introduction

Some data on residues was discussed in the section entitled Pharmacokinetics. This section expands the information on metabolism and discusses the information on residues reported in six studies.

Metabolism

In farm animals, rodents and humans, there is acetylation of the aromatic amino group in the reticuloendothelial cells of the liver and in other tissues to yeild N-acetyl SD, a major metabolite of SD. Two other metabolites of SD in pigs were identified in the radiometric study, namely, N-glucose SD and desamino SD. The production of desamino SD probably occurs in cattle, sheep and poultry but is not thought to be of importance in humans. A complication is that residues of SD in liver and muscle of pigs are converted either chemically or enzymatically to N-glucose-SD during storage at -20°C. Thus the ratio of SD to N-glucose-SD in pig meat will depend to some extent on how long the meat is stored before eating.

The small amounts (<5% of total residues) of polar metabolites have not been identified in most studies, but it is thought that they are produced by the hydroxylation of the aromatic ring which may be further conjugated with glucuronic acid. (FDA 224-81-005 USDA SEA-12-14-3001-064, 1984; Bevill et al., 1977a; Baggot, 1983; Wooley & Siegel, 1982; Kietzmann, 1981).

Residues in farm animals and tissues

The data from six studies are given in the tables as follows:

Table No.	Source	Species/ product	Route (dose)	Analytical method
II	Boisseau, France	milk	i.v. (100 mg/kg) or i.m. (200 mg/ quarter)	HPLC
III	Bevill et al, USA	sheep	i.v. (107.25 mg/kg)	Colorimetric
IV, V	Boisseau, France	eggs	oral in water (1-2G/L)	HPLC
VI	Ashworth, USA	pig	oral (110g/ton feed)	TLC
VII	Samuelson, USA	pig	oral (550 g/ton feed)	Colorimetric
VIII, IX	FDA, USDA, USA	pig	oral (110/ton feed)	C-14

Tables VI and VII indicate total residues of SD, measured by chemical means, in various tissues from pigs. In table VI the pigs were fed 110 g SD per ton of feed daily for 30 days and then placed on a ration containing 1-14 g SD per ton for 15 days before slaughter. In table VII the pigs were fed at 550 g SD per ton of feed daily for 30 days and then slaughtered after a withdrawal period varying from 0 to 12 days. At 12 days no detectable residue remained.

TABLE VI: Residues of SD in muscle and liver of five pigs fed 110 grams per ton feed daily for 30 days and then fed SD at different daily levels for 15 days before slaughter

SD in withdrawal feed (g per ton)	Residues (ppm) Muscle		Liver	
	mean	maximum	mean	maximum
1.1	0.008	0.014	0.04	0.06
2.03	0.015	0.026	0.10	0.19
2.36	0.014	0.030	0.13	0.18
5.74	0.074	0.10	0.34	0.46
13.5	0.14	0.16	0.60	0.74
13.9	0.16	0.22	0.68	0.79

Residues measured by TLC-fluorescence method of Thomas et al.; (1981).

TABLE VII: Residues of SD in tissues of pigs fed 550 grams per metric ton feed for 30 days

Withdrawal period (days)	Residues (ppm) muscle	liver	kidney	fat
0	5.77 (0.37)	18.27 (0.91)	16.07 (0.46)	4.90 (0.30)
2	0.67 (0.16)	2.81 80.40)	1.86 (0.46)	0.43 (0.12)
4	0.09 (0.02)	0.37 (0.1)	0.22 (0.07)	0.10 (0.02)
6	0.02 (0.00)	0.05 (0.03)	0.16 (0.06)	0.02 (0.01)
8	0.02 (0.01)	0.12 (0.08)	0.08 (0.05)	0.01 (0.01)
10	0.00	0.06 (0.02)	0.01 (0.01)	0.00
12	0.00	0.00	0.00	0.00

Each value is the mean value for 3 pigs; the values in parentheses are the SEM. Residues measured in plasma and feed by adaption of method of Annino, (1961), and in tissues by method of Tishler, (1968).

The radiometric study gives the only complete information on total residues because all of the other analytical methods miss one or more of the metabolites. The radiometric study will be discussed in detail because of its importance.

RADIOMETRIC STUDY IN PIGS

Summary

Pigs were administered feed containing 110 g SD per ton and 76 uCi Carbon-14 labelled SD (C14-SD) in two studies, a steady state residue experiment and a residue depletion experiment. The nature and quantity of residues in tissues and excreta were measured using combinations of radiometry with modern methods of separation and identification.

The results show that SD is converted in the live pig to three major metabolites, N-acetyl-SD, N-glucose-SD and desamino-SD. SD is also converted to N-glucose-SD in stored deep frozen liver and muscle tissues.

The major residues in all tissues were a mixture of parent drug and the three metabolites. The concentrations of residues were highest in the blood, GI tract plus contents, liver and kidney and depleted in all tissues to levels below 0.1ppm 10 days after drug withdrawal (see table VIII).

TABLE VIII: Concentration (ppm SD equivalents) of C14-residues in tissues of pigs dosed with C14-SD

Tissue	8 hr depletion animal number			2 day depletion animal number		
	10	11	12	13	14	15
Blood	11.36	10.01	13.85	2.61	4.67	4.59
Kidney	9.40	7.78	10.64	2.20	2.95	3.29
Skeletal muscle	3.24	2.82	3.40	0.74	0.98	1.07
Liver	6.52	6.29	8.11	1.59	2.82	2.81
Fat	1.16	1.10	1.34	0.26	0.37	0.38
Brain	2.62	2.39	3.11	0.65	0.86	0.93
Heart	4.84	4.78	5.94	1.23	1.81	1.82
Spleen	3.35	3.48	4.24	0.82	1.24	1.29
Lung	4.65	4.78	6.47	1.29	1.77	2.02
GI tract + contents	13.02	11.22	15.96	5.88	8.40	8.50

Tissue	5 day depletion animal number			10 day depletion animal number		
	16	17	18	19	20	21
Blood	0.44	0.10	0.28	0.027	0.037	0.019
Kidney	0.28	0.08	0.19	0.021	0.033	0.024
Skeletal muscle	0.10	0.02	0.05	0.004	0.005	0.003
Liver	0.32	0.15	0.21	0.048	0.071	0.066
Fat	0.04	0.01	0.02	0.003	0.004	0.002
Brain	0.09	0.02	0.04	0.003	0.005	0.003
Heart	0.23	0.03	0.09	0.011	0.014	0.013
Spleen	0.14	0.04	0.09	0.018	0.016	0.015
Lung	0.20	0.05	0.12	0.017	0.027	0.017
GI tract + contents	0.82	0.34	0.55	0.030	0.070	0.06

Note: All animals were dosed with C14-SD at 12 hour intervals for 7 consecutive days. The animals were sacrificed at 8 hours, 2 days, 5 days or 10 days after the last dose.

Animals and treatments

Steady state experiment - Five gilts and five barrows weighing 47-67 kg were fed at 12 hour intervals for 3, 5 or 7 days with a 1.5 kg ration containing 165 mg SD and 75.94 uCi C14-SD. Urine and faeces were collected separately at 24 hour intervals after the initial dose, 12 hours after the penultimate dose and 8 hours after the last dose. All the animals were sacrificed 8 hours after the last dose and tissue samples collected and stored at -20°C until analysis.

Residue Depletion Experiment - Twelve pigs were dosed orally with C14-SD for 7 consecutive days as described for the steady state experiment. The pigs were slaughtered in groups of three at 8 hours, 2, 5 and 10 days after withdrawal of the drug. Total urine and faeces were collected at 24 hour intervals throughout the dosing and depletion periods of the experiment. Tissue samples were collected and deep frozen at -20°C until analysed.

Methods

The total radioactivity of C14 was determined in aliquots of fluids, homogenised tissues and faeces. The activity in urine and fat was measured in solutions of the samples in liquid scintillator, whereas other tissues were measured after combustion of the C14-metabolites to C14-CO2. Only about 90% of the activity was recovered in the combustion method because the aromatic ring of SD limited total combustion.

The metabolic products of SD were isolated by a combination of solvent/solvent partition, XAD-2 column chromatography and finally HPLC. The products were divided essentially into those which were extracted into either methanol, hexane or water. More than 80% of the total C14-activity was extracted from muscle, liver and kidney samples into methanol in the steady state experiment or after 8 hours withdrawal time in the depletion experiment, however as withdrawal time increased through 2, 5 and 10 days there was a gradual rise (>70% in the liver) in the percentage of C14-activity that was not extracted into methanol. 39-59% of the activity was extracted into methanol from fat. The hexane extract always contained <22% of the total residues (see table IX).

The metabolites were identified from the HPLC fractions by using specific ion monitoring of GC-MS and electron-impact mass spectrometry of the N-Methyl derivatives. C14-labelled standards were prepared for the 3 metabolites. These were used for spiking control tissues and then confirming the methods.

TABLE IX: The distribution of carbon-14 in methanolic extracts of tissues of swine after withdrawal of C14-SD

Withdrawal time & tissue	C14 total ppm	C14 in XAD2/MeOH extract	% C14-metabolite in MeOH extract			
			SD%	Acetyl -SD %	Glucose -SD%	Desa-mino -SD%
Muscle						
8 hours	3.2	80.5	44.0	8.2	29.1	2.2
2 days	0.93	80.7	41.0	8.3	39.8	2.3
5 days	0.06	71.8	47.4	7.8	31.7	4.7
10 days	0.004	62.1	23.8	4.5	11.4	48.7
Liver						
8 hours	7.0	83.1	30.6	17.9	43.9	1.8
2 days	2.4	74.0	28.4	12.7	51.0	2.4
5 days	0.23	56.5	31.8	6.9	48.2	6.0
10 days	0.06	24.0	31.3	10.9	22.1	24.7
Kidney						
8 hours	9.3	91.2	50.5	30.4	5.5	6.7
2 days	2.8	89.2	53.8	28.1	5.2	4.2
5 days	0.18	73.5	54.8	25.1	5.0	7.4
10 days	0.03	35.3	26.6	13.3	6.7	42.4
Fat						
8 hours	1.2	58.5	41.1	18.6	15.4	11.1
2 days	0.38	50.6	45.2	17.9	7.2	13.2
5 days	0.02	39.1	30.3	14.5	10.3	22.0
10 days	0.003	40.6	11.9	3.7	0.1	75.1

Each value is the mean for three pigs.

The maximum mean concentrations for the metabolites was observed in the tissues collected at 8 hours withdrawal time. They were: SD, 4.3 ppm in kidney; Acetyl-SD, 26 ppm in kidney; N-Glucose-SD, 2.6 ppm in liver; Desamino-SD, 0.56 ppm in kidney.

Results

The results for the pigs fed for 7 days and slaughtered after 8 hours in the steady state experiment are similar to those found for the pigs slaughtered after 8 hours withdrawal time in the depletion experiment.

Metabolites

The four major compounds in the residues were identified as

1. Parent drug-SD
2. N-acetyl-SD
3. N-glucose-SD
4. Desamino-SD

SD was the major residue in blood, liver, muscle, kidney and fat from all animals in the steady state experiment. The major residues found in liver tissues were near equal amounts of SD and N-Glucose-SD. However it was proposed that SD is readily converted to N-Glucose-SD during storage of frozen tissues and so SD was probably the most abundant residue at the time of slaughter.

In the depletion kinetics study (table VII) there was a substantial increase in the percentage of the total C14-activity in all the tissues present as Desamino-SD as the withdrawal time increased through 2, 5 and 10 days. The percentage of total activity attributable to SD, N-acetyl-SD and N-glucose-SD decreased as the withdrawal time extended. However the total concentrations of residues at 10 days withdrawal time was <0.06 ppm and thus the actual amount of Desamino-SD was very low but it is the most persistant residue.

Total residues

The total residues of C14 expressed as ppm SD are shown in table IX. The highest concentration of total residues (16.0 ppm) was found in the GI tract and its contents, the maximum concentrations in blood (13.9 ppm), kidney (10.6 ppm) and liver (8.1 ppm) were also high whereas the maximum concentrations in muscle (3.4 ppm), brain (3.1 ppm) and fat (1.3 ppm) were the lowest in the tissues examined. The concentrations in the GI tract and its contents remained the highest at all withdrawal times but the maximum concentrations seen in any of the tissues was 4.6 ppm in blood after 2 days withdrawal, 0.44 ppm in blood after 5 days withdrawal time and 0.048 ppm in kidney after 10 days withdrawal time. Many of these very low residues at 5 and 10 days withdrawal time would have been too low to be measured by most of the non-radioisotopic analytical methods.

The total residues in four tissues and blood are plotted semilogarithmically against withdrawal time in Figure 1. This shows how the concentrations of residues in the tissues decrease. The pattern of depletion is not dissimilar from that observed in other studies. Certainly after 10 days the residues are very low. (FDA 224-81-005; USDA SEA-12-14-3001-064, 1984).

APPRAISAL

The depletion study provides the most important information on residues of SD fed the drug under conditions similar to the proposed use in pig production. N-glucose-SD and desamino-SD are two important metabolites which are not reported in the other studies.

The other two studies using oral feeding of SD to pigs (tables VI and VII) encountered problems with both coprophagia and cross-contamination of feeds with SD during the mixing and mill processing of the feeds.

The maximum residues in pigs fed SD are in the range 5-30 ppm and were found in blood, liver and kidney. The residues remain highest in these tissues throughout the first few days of a withdrawal period. This is well illustrated in the depletion curves shown in figure 1.

In all the studies where SD was dosed orally the residues decline to very low levels at some time during the second week of the withdrawal period. After intravenous injection or intramammary infusion of SD into lactating cows the concentrations of residues in milk declines very rapidly from maximum values of 21 and 32 ppm to <0.05 ppm after 5 days withdrawal.

Many nations have set tolerances for residues of SD with the most common being 0.1 ppm or zero. However, it is not always clear whether these tolerances are set for total residues or for the residue of the parent drug. In practice the residue of the parent drug is the compound normally monitored.

In the six studies presented, only the radiometric study gives information on total residues, threee studies report levels of parent drug and two studies report

concentrations of parent drug plus those metabolites which have the amino group attached to aromatic ring and can therefore give positive coupling reactions in the diazotization reaction. Only the radiometric study measures the residues of desamino-metabolites. The studies are summarised in table X.

TABLE X: Summary guide to residue studies using SD

Species	Tissue	Source Table no	Residue measured	Analysis
Cattle	milk	II	SD	HPLC
Sheep	M,L,K,F,P	III	SD + Ac-SD + other amine-derives	Diazo
Poultry	Eggs	IV, V	SD	HPLC
Pigs	M,L	VI	SD	TLC-fluor
Pigs	M,L,K,F	VII	SD + Ac-SD + other amine-derives	Diazo
Pigs	M,L,K,F,B + others	VIII	Total SD residues	C14
Pigs	M,L,K,F	IX	SD, Ac-SD, Glucose-SD Desamino-SD	C14

M is muscle, L is liver, K is kidney, F is fat, P is plasma, B is blood, U is urine. The methods are Diazo = Diazotization; TLC-Fluor = TLC and fluorescence. C14 is the radiometric assay after using C14-SD; HPLC is from study by Boisseau (1988).

The residues are vey high during and immediately after drug administration and a withdrawal time seems essential. Once a tolerance is decided the six studies provide a substantial amount of information which might be used to establish recommended withdrawal times.

The relationship between total concentrations of residues of SD and the concentration of parent drug is calculated from the data provided in the radiometric study and is shown in table XI. This data is a clear indication that, at least in the pig, residues of parent drug at levels of 0.1 ppm or higher are about one fifth to one half the total residues in edible tissues and at concentrations below 0.1 ppm the parent drug may account for as little as 5% total residues.

The pharmacokinetic studies show there is reasonable certainty that monitoring SD concentrations in body fluids can be used to indicate likely concentrations of SD in tissues. This method of control is practised in some countries and early reports show that is has been instrumental in reducing the number of violations in the USA pig industry.

FIGURE 1

RESIDUES OF C14-SD IN PIGS

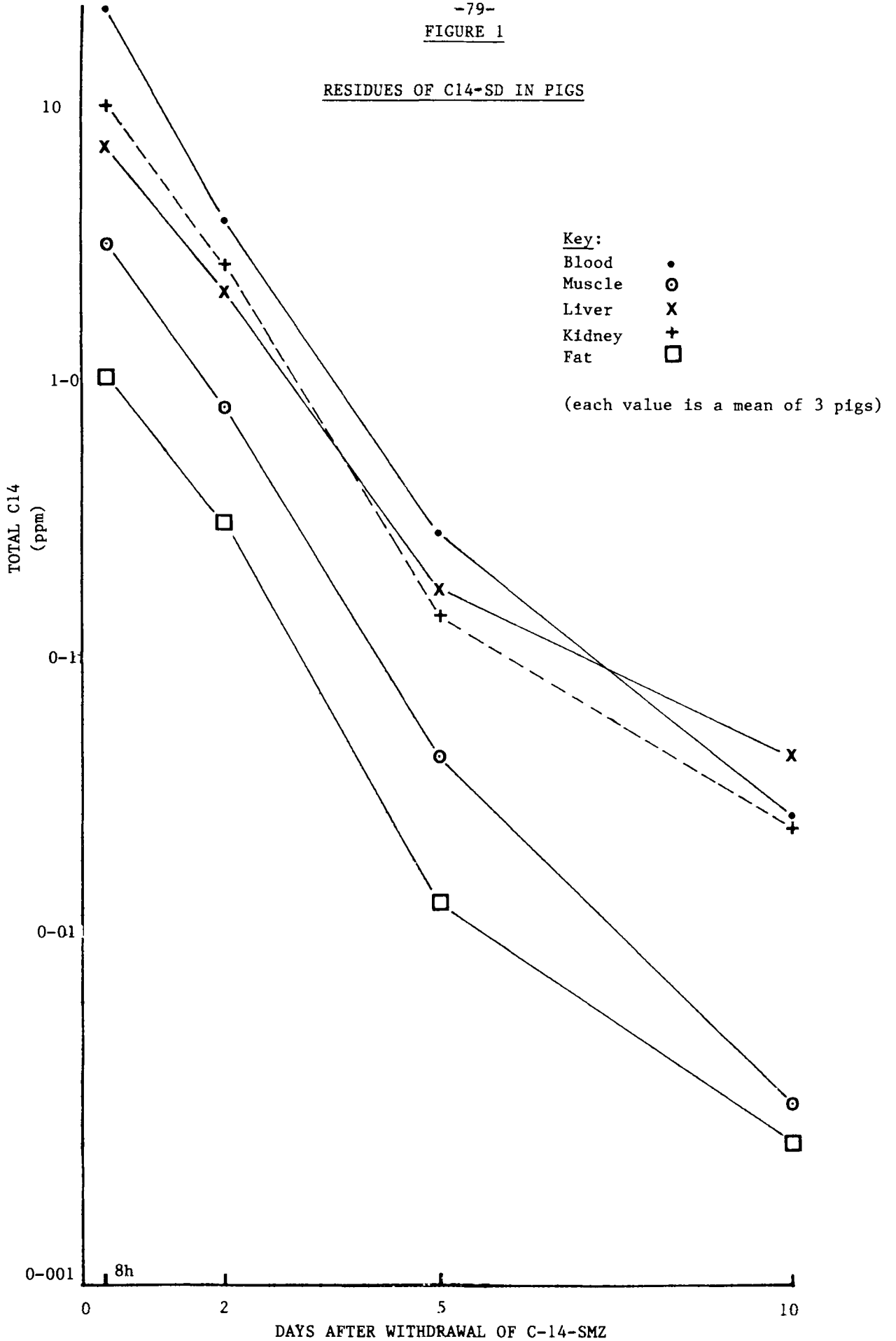


TABLE XI: Comparison of SD residues and total residues in pigs after withdrawal of feed containing C14-SD

Withdrawal time & tissue	C14 total ppm	SMZ ppm	SMZ % total
Muscle			
8 hours	3.2	1.13	35
2 days	0.93	0.31	33
5 days	0.06	0.02	34
10 days	0.004	0.0006	15
Liver			
8 hours	7.0	1.78	25
2 days	2.4	0.50	21
5 days	0.23	0.04	18
10 days	0.06	0.004	8
Kidney			
8 hours	9.3	4.38	46
2 days	2.8	1.34	48
5 days	0.18	0.07	40
10 days	0.03	0.003	10
Fat			
8 hours	1.2	0.29	24
2 days	0.38	0.09	23
5 days	0.02	0.002	12
10 days	0.003	0.0001	5

Each value is the mean for three pigs.

REFERENCES

Annino J.S., (1961), Sulphonamides, in Standard Methods of Clinical Chemistry, Ed by Sligson D.E., New York, Acad. press, vol. 3, pp 200-206.

Ashworth, R.B., Epstein, R.L., Thomas, M.H., and Frobish, L.T. (1986) Am. J. Vet. Res., 47, 2596-2603.

Baggot, (1983), "Systemic antimicrobial therapy in larger animals". In "Pharmacological Basis of Large Animal Medicine", Eds. Bogan, J.A., Lees, P. and Yoxall, A.T., Blackwell Scientific Publ. 45-69.

Bevill, R.F., Sharma, R.M., Meachum, S.H., Wozniak, S.C., Bourne, D.W.A. and Dittert, L.W. (1977a), Am. J. Vet. Res. 38, 973-977.

Boisseau, J., private communication (1988).

Duffee, N.E., Bevill, R.F., Thurmon, J.C., Luther, H.G., Nelson, D.E. and Hacker, F.E., (1984), J. Vet. Pharm. Ther. 7, 203-211.

FDA & USDA (1984), The Fate of Carbon-14 given to Swine as 14C-Sulfamethazine. USDA, SEA-12-14-3001-064, FDA-224-81-005.

Kietzmann, M. (1981), Arch. Geflugelkd. 45, 233-239.

Samuelson, G., Whipple, D.M., Showalter, D.H. Jacobson, W.C. and Heath, G.E. (1979) J. Am. Vet. Med. Ass, 175, 449-452.

Thomas, M.H., Soroka, K.E. and Simpson, R.M., (1981), J. Agric, Food Chem., 29, 621-628.

Tishler, F., Sutter, J.L., Bathish, J.N. and Hagman, H.E., (1968) J. Agr. Food Chem., 16, 50-53.

Wooley, J.L. and Siegel, C.W. (1982), Am J. Vet. Res. 43, 768-774.