COMPONENTS:	EVALUATOR:
(1) Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)-(sulfaethylthiadiazole); $C_{10}H_{12}N_4O_2S_2$; [94-19-9]	Anthony N. Paruta Department of Pharmaceutics University of Rhode Island Kingston, Rhode Island, USA and Ryszard Piekos Faculty of Pharmacy, University of Gdansk Gdansk, Poland 1986
(2) Aqueous phosphate buffers	

CRITICAL EVALUATION:

For the above compound, there were three reports (1-3) which determined the solubility in water at 293K and 310K at five pH levels as shown in Table I.

Table I: Solubility of Sulfaethylthiadiazole in water at various pH's and temperatures

		10^3 mol dm^{-3}	
Reference	pH	293K	310K
1	4.9[a]	1.48	-
3	5.0[b]	-	11.4
1	5.91[a]	2.95	4.64
2	5.9[a]	-	5.13
3	6.0[b]	-	26.7
1	7.0[a]	17.80	22.93
2	7.1[a]	-	21.45
3	7.0[b]	-	207.5
1	7.51[a]	44.91	-
3	7.5[b]	-	256.7
1	8.02[a]	32.64	-
3	8.0[b]	-	597.8

a = buffer concentration at 0.066 mol dm^{-3}
b = buffer concentration at 0.27 mol dm^{-3}

The data of Bandelin and Malesh (3) reported solubility over a pH range of 5-8 in phosphate buffers of 0.27 mol dm^{-3} concentration substantially greater than in the other data (1,2). The data, while showing the expected large increases in solubility with pH, refer only to initial pH values. At concentrations reported here, especially those about 0.1 mol dm^{-3} (~ pH 6.5), the dissolved amount should affect the final pH of the equilibrated solution. This would occur at pH values greater than about 5.5 (pK_a) by the production of highly soluble anionic species affecting the pH value through the ionic strength effect. The values given by Krüger-Thiemer (1) and Langecker (2) are for 0.066 mol dm^{-3} phosphate buffer. There are two sets of values that merit consideration, those at pH 5.9 and pH 7.0 (1,2). If it can be assumed that the solubility at 310K and a pH 5.5 ($\approx pK_a$) is about 2×10^{-3} mol dm^{-3} then at pH 5.9, about 2.5 times as many highly water solubble anions are formed leading to a value of about 5×10^{-3} mol dm^{-3}. The average of the two values (1,2) lead to a tentative solubility value at a pH = 5.9 in phosphate buffer of 4.88×10^{-3} mol dm^{-3}. At a pH of 7, there would be about 31 fold increase in anions, however, the values only indicate about a 10-11 fold increase. Although the values at a pH 7 (1,2) are reasonable in magnitude they could not be reconciled with each other and were not considered further. None of the data at 293K was duplicated by any two authors and are shown for completeness and data enhancement trend (except for pH 7.5) as a function of pH.

REFERENCES:

(1) Krüger-Thiemer, E. *Arch. Dermatol. Syphillis* 1942, *183*, 90-116.
(2) Langecker, H. *Arch. Exptl. Path. Pharmakol.* 1948, *205*, 291-301.
(3) Bandelin, F.J.; Malesh, W. *J. Am. Pharm. Assoc., Sci. Ed.* 1959, *48*, 177-81.

COMPONENTS:	ORIGINAL MEASUREMENTS:
(1) Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (sulfaethylthiadiazole); $C_{10}H_{12}N_4O_2S_2$; [94-19-9] (2) Water; H_2O; [7732-18-5]	Durel, M. P.; Allinne, M. *Bull. Soc. Med. Hop. Paris III* 1941, 251-9.
VARIABLES: One temperature: 37°C	**PREPARED BY:** R. Piekos

EXPERIMENTAL VALUES:

Solubility of sulfaethylthiadiazole in water at 37°C is 0.40 g/liter (1.41×10^{-3} mol dm^{-3}, compiler).

AUXILIARY INFORMATION

METHOD/APPARATUS/PROCEDURE:	SOURCE AND PURITY OF MATERIALS:
A mixture of sulfaethylthiadiazole and water was agitated for 24 hours at 37°C.	Source and purity of sulfaethylthiadiazole were not specified. Distilled water was used.
	ESTIMATED ERROR: Nothing specified.
	REFERENCES:

COMPONENTS:	ORIGINAL MEASUREMENTS:
(1) Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (sulfaethylthiadiazole); $C_{10}H_{12}N_4O_2S_2$; [94-19-9] (2) Water; H_2O; [7732-18-5]	Langecker, H. *Arch. Exptl. Path. Pharmakol.* 1948, *205*, 291-301.
VARIABLES: One temperature: 37°C	**PREPARED BY:** R. Piekos

EXPERIMENTAL VALUES:

Solubility of sulfaethylthiadiazole in water at 37°C is 60 mg%
(2.11×10^{-3} mol dm^{-3}, compiler).

AUXILIARY INFORMATION

METHOD/APPARATUS/PROCEDURE:	SOURCE AND PURITY OF MATERIALS:
An excess of sulfaethylthiadiazole in water was boiled and left for 24 h in a vessel protected from access of CO_2. The concn of the sulfonamide was detd colorimetrically by the method of Bratton and Marshall (1) using a Havemann colorimeter (2), as well as by microanal detn of the solid residue.	Source and purity of the materials were not specified.
	ESTIMATED ERROR: Nothing specified.
	REFERENCES: 1. Bratton, A. G.; Marshall, E. K., Jr. *J. Biol. Chem.* 1939, *128*, 537. 2. Havemann, R. *Klin. Wochenschr.* 1940, p. 503.

COMPONENTS:	ORIGINAL MEASUREMENTS:
(1) Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (sulfaethylthiadiazole); $C_{10}H_{12}N_4O_2S_2$; [94-19-9] (2) Sodium chloride; NaCl; [7647-14-5] (3) Water; H_2O; [7732-18-5]	Langecker, H. *Arch. Exptl. Path. Pharmakol.* 1948, *205*, 291-301.
VARIABLES: One temperature: 37°C	**PREPARED BY:** R. Piekos

EXPERIMENTAL VALUES:

Solubility of sulfaethylthiadiazole in a 0.9% w/w NaCl solution at 37°C is 62 mg% (2.2×10^{-3} mol dm^{-3}, compiler).

AUXILIARY INFORMATION

METHOD/APPARATUS/PROCEDURE:

An excess of sulfaethylthiadiazole in the 0.9% w/w NaCl soln was boiled for 1 h in a sealed ampul followed by keeping the ampul at 37°C. The concn of the sulfonamide was assayed colorimetrically by the method of Bratton and Marshall (1) using a Havemann colorimeter (2), as well as by microanal detn of the solid residue.

SOURCE AND PURITY OF MATERIALS:

Source and purity of the materials were not specified.

ESTIMATED ERROR:

Nothing specified.

REFERENCES:

1. Bratton, A. G.; Marshall, E. K., Jr. *J. Biol. Chem.* 1939, *128*, 537.
2. Havemann, R. *Klin. Wochenschr.* 1940, p. 503.

COMPONENTS:	ORIGINAL MEASUREMENTS:
(1) Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (sulfaethylthiadiazole); $C_{10}H_{12}N_4O_2S_2$; [94-19-9] (2) Phosphoric acid, disodium salt; Na_2HPO_4; [7558-94-4] (3) Water; H_2O; [7732-18-5]	Krüger-Thiemer, E. *Arch. Dermatol. Syphilis* 1942, *183*, 90-116.
VARIABLES: One temperature: ca 20°C; one pH: 8.74	**PREPARED BY:** R. Piekos

EXPERIMENTAL VALUES:

Solubility of sulfaethylthiadiazole in a 0.705M (10%) Na_2HPO_4 solution of pH 8.74 at room temperature (about 20°C) is 1.820 g% (6.400 x 10^{-2} mol dm^{-3} solution, compiler).

AUXILIARY INFORMATION

METHOD/APPARATUS/PROCEDURE:

Sulfaethylthiadiazole (0.5 g) was dissolved in 10 cm^3 of the 0.705M (10%) Na_2HPO_4 solution of pH 8.74, shaken for 2 h at room temp (about 20°C), and filtered. A 1-cm^3 aliquot of the filtrate was withdrawn, cooled, acidified with 1 cm^3 of 2N HCl, and the sulfonamide content was detd colorimetrically by the method of Marshall modified by Kimmig (1) using an Authenrieth colorimeter. The pH was detd on an ultraionograph using a glass electrode.

SOURCE AND PURITY OF MATERIALS:

Sulfaethylthiadiazole was the product manufd by Schering under the name Globucid. The source and purity of the remaining materials were not specified.

ESTIMATED ERROR:

Soly: precision ±5% (author).

Temp: not specified.

pH : ±0.05 pH unit (author).

REFERENCES:

1. Kimmig, J. *Arch. Dermatol.* 1938, *176*, 722; *Erg. Hyg.* 1941, *24*, 398.

COMPONENTS:	ORIGINAL MEASUREMENTS:
(1) Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (sulfaethylthiadiazole); $C_{10}H_{12}N_4O_2S_2$; [94-19-9] (2) Phosphoric acid, monopotassium salt; KH_2PO_4; [7778-77-0] (3) Water; H_2O; [7732-18-5]	Krüger-Thiemer, E. *Arch. Dermatol. Syphilis* 1942, *183*, 90-116.
VARIABLES: One temperature: ca 20°C; one pH: 4.37	**PREPARED BY:** R. Piekos

EXPERIMENTAL VALUES:

Solubility of sulfaethylthiadiazole in a 0.735M (10%) KH_2PO_4 solution of pH 4.37 at room temperature (about 20°C) is 0.0167 g% (5.87×10^{-4} mol dm^{-3} solution, compiler).

AUXILIARY INFORMATION

METHOD/APPARATUS/PROCEDURE:

Sulfaethylthiadiazole (0.5 g) was dissolved in 10 cm^3 of the 0.735M (10%) KH_2PO_4 soln of pH 4.37, shaken for 2 h at room temp (about 20°C), and filtered. A 1-cm^3 aliquot of the filtrate was withdrawn, cooled, acidified with 1 cm^3 of 2N HCl, and the sulfonamide content was detd colorimetrically by the method of Marshall modified by Kimmig (1) using an Authenrieth colorimeter. The pH was detd on an utraiongraph using a glass electrode.

SOURCE AND PURITY OF MATERIALS:

Sulfaethylthiadiazole was the product manufd by Schering under the name Globucid. The source and purity of the remaining materials were not specified.

ESTIMATED ERROR:

Soly: precision ±5% (author).
Temp: not specified.
pH : ±0.05 pH unit (author)

REFERENCES:

1. Kimmig, J. *Arch. Dermatol.* 1938, *176*, 722; *Erg. Hyg.* 1941, *24*, 398.

COMPONENTS:

(1) Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (sulfaethylthiadiazole); $C_{10}H_{12}N_4O_2S_2$; [94-19-9]

(2) Phosphoric acid, disodium salt; Na_2HPO_4; [7558-94-4]

(3) Phosphoric acid, monopotassium salt; KH_2PO_4; [7778-77-0]

(4) Water; H_2O; [7732-18-5]

VARIABLES:

Temperature; pH

ORIGINAL MEASUREMENTS:

Krüger-Thiemer, E.

Arch. Dermatol. Syphilis 1942, *183*, 90-116.

PREPARED BY:

R. Piekos

EXPERIMENTAL VALUES:

Composition of 1/15M phosphate buffer solution			pH	Solubility			
				Room temp (ca 20°C)		37°C	
Na_2HPO_4	KH_2PO_4	%Content		g%	10^2 mol dm^{-3} solution[a]	g%	10^2 mol dm^{-3} solution[a]
1.0	99.0	0.91	4.944	0.042	0.148	-	-
10.0	90.0	0.91	5.906	0.084	0.295	0.132	0.464
61.1	38.9	0.93	7.005	0.506	1.780	0.652	2.293
9.5	0.5	0.733[b]	7.51	1.277	4.491	-	-
94.7	5.3	0.95	8.018	0.928	3.264	-	-

[a]Calculated by compiler.

[b]Molar content; 10% buffer solution.

AUXILIARY INFORMATION

METHOD/APPARATUS/PROCEDURE:

Sulfaethylthiadiazole (0.5 g) was dissolved in 10 cm^3 of a buffer soln, shaken for 2 h at 20°C (or left for 48 h at 37°C), and filtered at respective temp. A 1-cm^3 aliquot of the filtrate was then withdrawn, cooled, (dild for expts at 37°C), acidified with 1 cm^3 of 2N HCl, and the sulfonamide content was detd colorimetrically by the method of Marshall modified by Kimmig (1) using an Authenrieth colorimeter. The pH was detd on an ultraionograph using a glass electrode.

SOURCE AND PURITY OF MATERIALS:

Sulfaethylthiadiazole was the product manufd by Schering under the name Globucid. The source and purity of the remaining materials were not specified.

ESTIMATED ERROR:

Soly: precision ±5 (author)

Temp: not specified

pH : ±0.05 pH unit (author)

REFERENCES:

1. Kimmig, J. *Arch. Dermatol.* 1938, *176*, 722; *Erg. Hyg.* 1941, *24*, 398.

COMPONENTS:	ORIGINAL MEASUREMENTS:
(1) Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (sulfaethylthiadiazole); $C_{10}H_{12}N_4O_2S_2$; [94-19-9] (2) Phosphoric acid, disodium salt; Na_2HPO_4; [7558-94-4] (3) Phosphoric acid, monopotassium salt; KH_2PO_4; [7778-77-0] (4) Water; H_2O; [7732-18-5]	Langecker, H. *Arch. Exptl. Path. Pharmakol.* 1948, *205*, 291-301.
VARIABLES: pH	PREPARED BY: R. Piekos

EXPERIMENTAL VALUES:

pH of the 1/15M phosphate buffer	Solubility at 37°C	
	mg%	10^3 mol dm^{-3} [a]
5.7	146	5.13
5.9	146[b]	5.13
6.6	500	17.58
7.1	610	21.45

[a] Calculated by compiler.

[b] Measured at 20°C.

AUXILIARY INFORMATION

METHOD/APPARATUS/PROCEDURE:

An excess of sulfaethylthiadiazole was added to a buffer soln and boiled for 1 h in a sealed ampul followed by keeping the ampul at 37°C. The concn of the sulfonamide was detd colorimetrically by the method of Bratton and Marshall (1) using a Havemann colorimeter (2), as well as by microanal detn of the solid residue.

SOURCE AND PURITY OF MATERIALS:

Source and purity of the materials were not specified.

ESTIMATED ERROR:

Nothing specified.

REFERENCES:

1. Bratton, A. G.; Marshall, E. K., Jr. *J. Biol. Chem.* 1939, *128*, 537.
2. Havemann, R. *Klin. Wochenschr.* 1940, p. 503.

COMPONENTS:	ORIGINAL MEASUREMENTS:
(1) Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazole-2-yl)- (sulfaethylthiadiazole); $C_{10}H_{12}N_4O_2S_2$; [94-19-9] (2) Phosphoric acid, disodium salt; Na_2HPO_4; [7558-94-4] (3) Phosphoric acid, monopotassium salt; KH_2PO_4; [7778-77-0] (4) Water; H_2O; [7732-18-5]	Bandelin, F. J.; Malesh, W. *J. Am. Pharm. Assoc., Sci. Ed.* 1959, *48*, 177-81.
VARIABLES: pH	PREPARED BY: R. Piekos

EXPERIMENTAL VALUES:

Solubility of sulfaethylthiadiazole in buffers of varying mixtures of $Na_2HPO_4 \cdot 7H_2O$ (71.6 g/l distilled water; 0.27 mol dm^{-3}, compiler) and KH_2PO_4 (36.3 g/l distilled water; 0.27 mol dm^{-3}, compiler) at 37°C.

Initial pH	Solubility	
	mg/100 ml	mol dm^{-3} [a]
5.0	325	0.0114
5.5	465	0.0163
6.0	760	0.0267
6.5	2250	0.0791
7.0	5900	0.2075
7.5	7300	0.2567
8.0	17,000	0.5978

[a]Calculated by compiler.

AUXILIARY INFORMATION

METHOD/APPARATUS/PROCEDURE:

Solns were prepd by adding an excess of sulfaethylthiadiazole to 10 ml of buffer soln at each pH level in 18 x 150-mm test tubes, stoppering the tubes and placing them in a water bath at 37°C with gentle agitation for 24 h. The mixt was then filtered and a 1-ml aliquot was accurately pipetted into a volumetric flask for diln and analysis. The balance was retained for pH detn to ascertain any change in pH value. The sulfonamide was assayed colorimetrically by the method of Bratton and Marshall as described in detail by Biamonte and Schneller (1). A standard curve was prepd using accurately prepd standard solutions.

SOURCE AND PURITY OF MATERIALS:

Neither source nor purity of the reagents were specified. Distilled water was used.

ESTIMATED ERROR:

Soly: av values of duplicate runs are reported (authors).

Temp and pH: not specified.

REFERENCES:

1. Biamonte, A. R.; Schneller, G. E. *J. Am. Pharm. Assoc., Sci. Ed.* 1952, *41*, 341.

COMPONENTS:	ORIGINAL MEASUREMENTS:
(1) Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (sulfaethylthiadiazole); $C_{10}H_{12}N_4O_2S_2$; [94-19-9] (2) Phosphoric acid, disodium salt; Na_2HPO_4; [7558-94-4] (3) Phosphoric acid, monopotassium salt; KH_2PO_4; [7778-77-0] (4) Water; H_2O; [7732-18-5]	Riess, W. *Intern. Congr. Chemotherapy, Proc. 3rd. Stuttgart* 1963, *1*, 627-32.
VARIABLES: One temperature: 20°C; one pH: 7.4	PREPARED BY: R. Piekos

EXPERIMENTAL VALUES:

Solubility of sulfaethylthiadiazole in M/15 phosphate buffer (pH 7.4) at 20°C is 1500 mg% (5.275×10^{-2} mol dm^{-3}, compiler).

AUXILIARY INFORMATION

METHOD/APPARATUS/PROCEDURE:	SOURCE AND PURITY OF MATERIALS:
Sörensen buffer solns of pH varying between 7 and 8 were prepd, satd with sulfaethylthiadiazole at 20°C, their pH was measured at equilibrium , and the sulfaethylthiadiazole was assayed colorimetrically. The measured pH values were plotted against concn, and the soly at pH 7.4 was detd by interpolation (personal communication).	Nothing specified.
	ESTIMATED ERROR: Nothing specified.
	REFERENCES:

COMPONENTS:

(1) Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (sulfaethylthiadiazole); $C_{10}H_{12}N_4O_2S_2$; [94-19-9]

(2) Phosphoric acid, disodium salt; Na_2HPO_4; [7558-94-4]

(3) Phosphoric acid, monopotassium salt; KH_2PO_4; [7778-77-0]

(4) Water; H_2O; [7732-18-8]

VARIABLES:

pH

ORIGINAL MEASUREMENTS:

Hekster, Ch. A.; Vree, T. B.

Antibiotics Chemother. 1982, *31*, 22-118.

PREPARED BY:

R. Piekos

EXPERIMENTAL VALUES:

pH	Solubility at 25°C	
	mg/l	10^3 mol dm^{-3} [a]
5.5	489	1.72
7.5[b]	7,110	25.00

AUXILIARY INFORMATION

METHOD/APPARATUS/PROCEDURE:

The earlier developed method (1) was used (personal communication). Satd solns of sulfaethylthiadiazole were prepd in phosphate buffers of pH 5.5 and 7.5 at 25°C. The concn of the solute was measured by means of a Spectra Physics 3500B high-performance liquid chromatograph equipped with a Model 748 column oven and a Pye-Unicam LC-UV spectrophotometric detector.

SOURCE AND PURITY OF MATERIALS:

Neither source nor the purity of the materials was specified.

ESTIMATED ERROR:

Soly: the detection limit of the solute by HPLC was 0.5 mg/l (authors).

The errors in temp and pH were not specified.

REFERENCES:

1. Hekster, Y. A.; Vree, T. B.; Damsma, J. E.; Friesen, W. T. *J. Antimicrob. Chemother.* 1981, *8*, 133.

COMPONENTS:	ORIGINAL MEASUREMENTS:
(1) Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (sulfaethylthiadiazole); $C_{10}H_{12}N_4O_2S_2$; [94-19-9] (2) Calcium chloride; $CaCl_2$; [10043-52-4] (3) Magnesium chloride; $MgCl_2$; [7786-30-3] (4) Phosphoric acid, monoammonium salt; $NH_4H_2PO_4$; [7722-76-1] (5) Potassium chloride; KCl; [7447-40-7] (6) Sodium chloride; NaCl; [7647-14-5] (7) Urea; CH_4N_2O; [57-13-6] (8) Water; H_2O; [7732-18-5]	Bandelin, F. J.; Malesh, W. *J. Am. Pharm. Assoc., Sci. Ed.* 1959, *48*, 177-81.
VARIABLES: pH at 37°C	PREPARED BY: R. Piekos

EXPERIMENTAL VALUES:

Solubility of sulfaethylthiadiazole in a solution containing $CaCl_2$ 0.143, $MgCl_2$ 0.121, $NH_4H_2PO_4$ 0.300, KCl 1.660, NaCl 2.950 and urea 20 g/dm^3 (synthetic urine, Mosher Vehicle) at 37°C.

Equilibrium pH	Solubility	
	mg/100 ml	10^2 mol/dm^3 [a]
4.4	360	1.27
4.7	380	1.34
5.2	440	1.55
5.6	480	1.69
6.35	600	2.11
6.7	1875	6.59

[a] Calculated by compiler.

AUXILIARY INFORMATION

METHOD/APPARATUS/PROCEDURE:	SOURCE AND PURITY OF MATERIALS:
Excess sulfaethylthiadiazole was added to aliquots of synthetic urine solns and 1% H_3PO_4 or 1% NaOH solns were used to adjust the pH to the required value. The solns were agitated for 24 h with addn of acid or base to keep them at the desired pH level until equilibrium was attained. Then the solns were filtered and in aliquots the sulfonamide was assayed spectrophotometrically by the method described by Biamonte and Schneller (1).	Nothing specified
	ESTIMATED ERROR: Soly: average values of 2 detns were given. Temp: not specified. pH : not specified.
	REFERENCES: 1. Biamonte, A. R.; Schneller, G. E. *J. Am. Pharm. Assoc., Sci. Ed.* 1952, *41*, 341.

COMPONENTS:	ORIGINAL MEASUREMENTS:
(1) Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (sulfaethylthiadiazole); $C_{10}H_{12}N_4O_2S_2$; [94-19-9] (2) Methane, trichloro- (chloroform); $CHCl_3$; [67-66-3]	Riess, W. *Intern. Congr. Chemotherapy, Proc., 3rd. Stuttgart* 1963, *1*, 627-32.
VARIABLES: One temperature: 20°C	**PREPARED BY:** R. Piekos

EXPERIMENTAL VALUES:

Solubility of sulfaethylthiadiazole in chloroform at 20°C is 109 mg%

(3.83×10^{-3} mol dm^{-3} solution, compiler).

AUXILIARY INFORMATION

METHOD/APPARATUS/PROCEDURE:	SOURCE AND PURITY OF MATERIALS:
Nothing specified.	Nothing specified.
	ESTIMATED ERROR: Nothing specified.
	REFERENCES: