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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

CASWELL FILE

MAY 7 1990

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Cyproconazole (SAN 619F): Review of Compound Stability Data and Sampling Techniques in Response to EPA Evaluation of a 2-Generation Rat Reproduction Study with SAN 619 F Technical.

FROM: Jess Rowland, Toxicologist 4/26/90
Section II, Toxicology Branch II (HFAS)
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THRU: K.Clark Swentzel, Section Head 5/3/90
Section II, Toxicology Branch II (HFAS)
Health Effects Division (H7509C)
and
Marcia van Gemert, Ph.D., Chief 5/3/90
Toxicology Branch II (HFAS)
Health Effects Division (H7509C)

STUDY IDENTIFICATION: SAN 619F, 2-Generation Reproduction Study (MRID No.406077-23); Tox.Chem.No.272 E; Current Submission MRID No.412945-00.

ACTION REQUESTED: Review Compound Stability Data. HED Project No.0-0264.

RESPONSE: The registrant submitted stability data and sampling techniques in response to Toxicology Branch II (TBII) review (Memorandum K.Swentzel, TBII, HED to L.Rossi, RD, 1/17/89)of a 2-generation rat reproduction study which was classified as core minimum. The current submission shows the compound to be stable in both the premix and the diet mix. In addition, appropriate analytical methods were used to determine the stability and the homogeneity of the test material in both the pre and the diet mixes. This information satisfies TB IIs concern regarding the stability of the compound in the reference study. This study is classified as core-minimum and satisfies the requirements for Guidelines 83-4.

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PRIMARY REVIEW: Jess Rowland, Toxicologist
Section II, Toxicology Branch II(H7509C)

SECONDARY REVIEW: K.Clark Swentzel, Section Head
Section II, Toxicology Branch II(H7509C)

STUDY TITLE: SAN 619F Characterization of Homogeneity of Mixing and Stability of Formulated Diet.

STUDY IDENTIFICATION: MRID No.412945; HED Project No.0-0264

TEST MATERIAL: SAN 619F; Cyproconazole Tox.Chem.No. 272E

SPONSOR: Sandoz Corporation

TESTING FACILITY: Sandoz Ltd., Agro Development, Basle, Switzerland.

AUTHORS: S.Warren, F.Muller, J.Karapally and R.Bourry.

REPORT DATE: March 7, 1988

MATERIALS AND METHODS:

Test Material: SAN 619 F; Lot No. 8507; Purity 96 ± 1%

Substrate Diet: Kliba powdered diet no.21-343-4

Mixing Procedure: A premix (at a concentration of 1%) was obtained by mixing 50 g of the test material with 4950 g of the rat diet in a Turbular radial mixer for a period of 1 hour. The low dose (4 ppm) diet was prepared weekly by mixing 2 g of the Premix with 4998 g of rat diet in a Turbular radial mixer for 1 hour.

Sampling Procedure: Two samples, each of 20 g, were taken from test and control diet mixtures as follows:
Premix - Stability: Stability of the premix under standard storage conditions(refrigerated) was monitored shortly after preparation and after 4 weeks storage.
Premix - Homogeneity: Homogeneity of the premix was assessed by checking accuracy of mixing of diets by direct dilution of the premix.
4-ppm diet - Stability and homogeneity was monitored on two occasions (April and July, 1986).

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RESULTS:

A shown in Table 1, the stability of 1% premix appears to be quite stable under normal storage conditions for a period of approximately 5 weeks.

As shown in Table 2, the homogeneity of the premix and the 20 ppm diet(formulated from the premix) showed adequate homogeneity except for marked variations during study weeks 24 (+ 25% above nominal concentration) and 32 (+ 28% above nominal). Since all other measurements approximated the accepted ± 15% of nominal, the increased concentrations at 2 intervals did not compromise the validity of the study.

The first trial (April, 1986) for homogeneity of the 4 ppm diet showed variations between top and bottom samples of 4.6 ppm (115% of nominal) and 2.7 ppm (68% of nominal), respectively (Table 3a). This data was considered sufficiently inhomogeneous to invalidate data for stability obtained from other samples of this batch. Consequently, minor modifications were made to the mixing procedures and a second trial was conducted.

As shown in Table 3b, the second trial (July, 1986), showed adequate homogeneity of diet with levels that were within the range considered acceptable.

As shown in Table 4, stability analyses showed adequate stability over 28 days. However, the 4 ppm diet should not be used at time periods greater than 28 days after formulations.

CONCLUSION:

The mixing procedures employed yields a homogeneous and stable 1% premix and diets at 4 ppm are adequately stable and homogeneous. However, this is considered to represent the lowest limit of acceptable mixing by this method.

Table 1. Stability of 1% Premix

	1 % Premix		20 ppm Diet		% Deviation
Week	Result	nominal	Result	nominal	Premix-nominal
0	1.02 %	102 %	21 ppm	105 %	+ 3 %
4	1.03 %	103 %	19 ppm	95 %	- 8 %
8	1.03 %	103 %	23 ppm	115 %	+ 12 %
12	1.06 %	106 %	20 ppm	100 %	- 6 %
16	0.94 %	94 %	20 ppm	100 %	+ 6 %
20	0.94 %	94 %	21 ppm	105 %	+ 9 %
24	1.10 %	110 %	27 ppm	135 %	+ 25 %
28	1.28 %	128 %	25 ppm	125 %	- 3 %
32	0.97 %	97 %	25 ppm	125 %	+ 28 %
36	0.95 %	95 %	21 ppm	105 %	+ 10 %
40	0.99 %	99 %	20 ppm	100 %	+ 1 %
44	1.00 %	100 %	20 ppm	100 %	0 %
48	1.03 %	103 %	22 ppm	110 %	+ 7 %
52	1.03 %	103 %	18 ppm	90 %	- 13 %

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Table 2. Homogeneity of 1% Premix.

Study Week	First analysis		Second analysis		Deviation, First to Second analysis
	Date	Mean result %	Date	Mean result %	
31	28 Oct. 85	1.02 %	2 Dec. 85	0.98 %	- 4 %
34	19 Nov. 85	0.97 %	19 Dec. 85	1.01 %	+ 4 %
37	11 Dec. 85	1.00 %	15 Jan. 86	1.01 %	+ 1 %
42	9 Jan. 86	1.00 %	13 Feb. 86	1.01 %	+ 1 %
45	30 Jan. 86	1.00 %	6 March 86	1.01 %	+ 1 %
50	4 March 86	1.02 %	8 April 86	1.06 %	+ 4 %
52	20 March 86	1.03 %	25 April 86	1.07 %	+ 4 %
55	10 April 86	1.01 %	15 May 86	1.01 %	0
59	12 May 86	0.99 %	16 June 86	1.03 %	+ 4 %

Table 3a. Homogeneity of 4 ppm Dietmix (First Trial).

Sample Numbers	Concen-tration	Location in container	Day of Samp-ling	Mean Result (ppm)	S. Rel.	Dev. from Nominal
1	4 ppm	Top	0	4.6	0 %	+ 15%
2	4 ppm	Top	0	2.9	[illegible].9 %	- 28%
3	4 ppm	Middle	0	4.2	1.7 %	+ 5%
4	4 ppm	Middle	0	4.3	1.6 %	+ 8%
5	4 ppm	Bottom	0	3.3	2.1 %	- 18%
6	4 ppm	Bottom	0	2.7	2.6 %	- 32%
7,8	control(0)	--	0	n.d.	--	

Table 3b. Homogeneity of 4 ppm Dietmix (Second trial).

Sample Numbers	Concen-tration	Location in container	Day of Samp-ling	Mean Result (ppm)	S. Rel.
1,2	4 ppm	Top	0	4.7	17.7 %
3,4	4 ppm	Middle	0	4.2	5.7 %
5,6	4 ppm	Bottom	0	5.1	16.6 %
7,8	control	--	0	0	--

S. Rel. = relative standard deviation

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Table 4. Stability of 4 ppm Dietmix.

Sample Numbers	Concen-tration	Day of Samp-ling	Mean Result (ppm)	S. Rel.	Deviation from Day 0
1 - 6	4 ppm	0	4.7 ppm	9.7 %	0
9, 10	4 ppm	7	4.3 ppm	25.0 %	- 9%
11, 12	4 ppm	14	3.6 ppm	10.4 %	-23%
13, 14	4 ppm	28	3.8 ppm	11.4 %	-19%
15, 16	0(control)	28	0	--	--

S. Rel. = relative standard deviation

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