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

MAY 7 1990

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Cyproconazole (SAN 619F): Request by Sandoz Crop Protection Corporation to Establish a NOEL in a 13-week Feeding Study in Rats and to Accept the Study for Regulatory Purposes.

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TO: Susan lewis/Carl Grable
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THRU: K.Clark Swentzel, Section Head K. Clark Swentzel 5/3/90
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and
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STUDY IDENTIFICATION: SAN 619F: 13-Week Feeding Study in Rats (MRID No.406077-18).HED Project No.0-0136

ACTION REQUESTED: Review and comment on response.

REGISTRANT'S REQUEST: Sandoz Crop Protection Corporation (via 10/18/89 letter from D.M.Hillebold to S.Lewis) requests establishment of a no-observed-effect level (NOEL) for SAN 619F in a 13-week feeding study in rats and reconsider the Agency's decision to not accept the study for regulatory purposes. The establishment of a NOEL is based on their argument that the changes seen in blood creatinine, sodium and calcium levels at the lowest dose tested (20 ppm) may have been fortuitous and not compound induced because similar changes in these parameters were not seen in male or female rats fed 20 or 50 ppm 619F diets in a chronic/oncogenic feeding study. Therefore, they concluded that a NOEL of 20 ppm was attained in the 13-week feeding study and consequently the study can be acceptable for regulatory purposes.

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BACKGROUND: In a subchronic toxicity study, SAN 619F was administered in the diet to groups of 15 male and 15 female HAN-Wistar rats at 0, 20, 80, or 320 ppm for 13 weeks. Toxicology Branch II (TBII) classified this study as core-minimum but not acceptable for regulatory purposes because a NOEL was not attained (Memorandum K.Swentzel, HED to L.Rossi, RD, January 19, 1989). TB II noted increased blood levels of creatine and sodium with a concomitant decrease in calcium levels in treated rats (Table 1) . The noted changes in creatinine and calcium levels were also consistently observed in rats fed the 20 and 320 ppm diets but not in those administered 80 ppm. However, since these changes were not seen in treated rats fed 320 ppm after a 4-week recovery period, these changes were considered treatment-related effects. Therefore, a NOEL was not attained and this study was classified as core-minimum but not acceptable for regulatory purposes.

RESPONSE: TB II concurs with the registrant in establishing a NOEL of 20 ppm for the 13-week study. The NOEL is established based on: 1) lack of a dose-response relationship; 2) lack of correlation with histopathological or organ weight changes; 3) because similar changes were not seen in male and female rats fed the same level (20 ppm) of SAN 619F in a chronic/oncogenicity study (MRID No.411647-01); and 4) because the creatinine, sodium, and calcium values observed in the 13-week study were within the range of baseline values for these parameters in several strains of rats of this age (Table 2). Since a NOEL was attained and a chronic/oncogenicity is available, the 13-week study can be used for regulatory purposes.

CONCLUSION: The 13-week feeding study is acceptable for regulatory purposes since a NOEL was attained.

CORE-CLASSIFICATION: Minimum; satisfies the data requirement for Guideline 82-1.

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Table 1. Creatinine, Sodium and Calcium Levels in the 13-Week Feeding Study with SAN 619F.

Creatinine(Mg/Dl) Mean/S.D.

Males	Treatment Period			Recovery Period	
Week--	4	8	13	14	18
Dose (ppm)					
0	0.872	0.700	0.795	0.732	0.846
	0.508	0.042	0.066	0.091	0.099
20	0.937†	1.016††	1.015††	--	--
	0.201	0.123	0.165		
80	0.741	0.718	0.835	--	--
	0.083	0.102	0.074		
320	0.854	0.904††	0.950†	0.847*	0.798
	0.080	0.133	0.104	0.105	0.078
Females					
0	0.785	0.711	0.809	1.131	1.212
	0.090	0.082	0.113	0.165	0.184
20	1.006**	0.935††	1.017**	--	--
	0.138	0.118	0.064		
80	0.842	0.761	0.842	--	--
	0.090	0.058	0.087		
320	1.035**	0.990††	1.063**	1.126	1.109
	0.056	0.150	0.142	0.088	0.149

Sodium (MMol/L) Mean/S.D.

Males	Treatment Period			Recovery Period	
Weeks--	4	8	13	14	18
Dose (ppm)					
0	140.2	144.4	144.9	143.4	145.5
	1.9	1.2	1.7	1.3	1.0
20	141.0	145.0	147.4**	--	--
	1.2	1.2	1.1		
80	138.4*	145.2	147.6**	--	--
	1.0	1.1	1.1		
320	138.7*	145.6	147.0**	149.2**	145.9
	0.9	1.8	1.4	1.5	1.1
Females					
0	145.1	143.9	142.1	143.7	145.1
	1.6	2.0	0.7	0.8	1.9
20	146.3	143.9	142.4	--	--
	2.1	1.8	1.5		
80	146.0	145.3	143.4	--	--
	1.5	0.7	0.8		
320	147.1	145.6	144.1*	151.9**	145.4
	1.5	2.1	2.2	1.7	1.2

Calcium(Mg/Dl)

Males					
0	9.46	9.33	10.71	9.07	8.39
	0.22	0.27	0.25	0.17	0.63
20	9.78	8.30**	10.12**	--	--
	0.24	0.52	0.40		
80	9.60	10.17**	10.87	--	--
	0.20	0.45	0.25		
320	9.41	9.13	10.33*	9.04	7.86*
	0.25	0.52	0.43	0.15	0.33
Females					
0	9.73	10.48	10.70	8.96	6.44
	0.19	0.17	0.31	0.29	0.68
20	9.25†	10.06*	10.44	--	--
	0.41	0.22	0.23		
80	9.44	10.47	10.30*	--	--
	0.36	0.33	0.27		
320	9.33†	10.48	10.23**	8.98	6.56
	0.38	0.43	0.36	0.25	0.94

*p<0.05; **p<0.01 (Dunnett's t test)

†p<0.05; ††p<0.01 (non-parametric--Kruskal-Wallis test)

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Table 2. Baseline Values for Creatinine, Sodium and Calcium in Several Strains of Male Rats (11 to 21 weeks of Age).[a]

Strain	Creatinine (mg/dl)		Sodium (mg/l)		Calcium (mg/l)	
	Mean	Range	Mean	Range	Mean	Range
Charles River	1.0	0.6-1.4	147	144-150	11	9.9-12.1
Harlan S-D	0.5	0.4-0.6	153	150-160	11.3	10.8-12.1
Fisher 344	0.5	0.4-0.5	150	147-153	11.2	10.5-11.7
Holtzman	0.5	0.4-0.6	152	151-155	10.4	9.7-11.7

[a] SOURCE: Charles River Breeding Laboratories. Baseline Hematology Clinical Chemistry Values for Charles River CD [Crl:CD(SD)BR] Rats as a Function of Sex and Age. Technical Bulletin. Volume 3, No.3, 1984.

Harlan Sprauge Dawley Inc. Serum Chemistry/Complete Blood Counts-Rats. Final Report. 1989.