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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT DIFENOCONAZOLE: Response to HED RfD Committee's Recommendations.

FROM: Jess Rowland, M.S, Acting Section Head *Jess Rowland*
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TO: George Ghali, Ph.D
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THRU: Marcia van Gemert, Ph.D., Chief *management 3/1/94*
Toxicology Branch II, Health Effects Division (7509C)

This memorandum addresses the recommendations made by the HED RfD/Quality Assurance Committee on 01/06/94 during the assessment of a Reference Dose for Difenconazole.

1. Cox, R.H [1989] Combined Chronic Toxicity and Oncogenicity Study of CGA-169374 Technical in Rats. MRID Nos. 42090019, 42090020, 42710010; HED Document # 009689 & 010588.

RfD Committee's Recommendations:

The Committee recommended the addition of summary tumor tables to the DER and referral of the carcinogenicity issue to the HED Carcinogenicity Peer Review Committee [CPRC] for a weight of the evidence evaluation.

Reviewer's Response:

- i. A Histopathology Incidence Summary of Neoplastic Findings [Table 11E] from the Study Report HLA 483-249 [pages 280 - 296] is attached.
- ii. The HED CPRC is scheduled to meet on April 27, 1994 to evaluate the weight of the evidence.



2. Cox. R.H [1989]. Oncogenicity Study in Mice. MRID Nos. 42090015, 42710006; HED Document # 009689 & 010588.

RfD Committee's Recommendations:

The Committee recommended the addition of summary tumor tables to the DER and referral of the carcinogenicity issue to the HED Carcinogenicity Peer Review Committee [CPRC] for a weight of the evidence evaluation.

Reviewer's Response:

- i. A Histopathology Incidence Summary of Neoplastic Findings [Table 11E] from the Study Report HLA 483-250 [pages 234 - 246] is attached.
- ii. The HED CPRC is scheduled to meet on April 27, 1994 to evaluate the weight of the evidence.

3. Rüdick et al. [1989]. CGA-169374 Technical: 52-Week Oral Toxicity Study in Dogs. MRID No. 42090014 & 42710005; HED Document # 009689, 010588.

RfD Committee's Recommendation:

The Committee questioned the NOEL establishment in this study and recommended further evaluation of the body weight data to ascertain this NOEL.

Reviewer's Response:

**GROUP MEAN PERCENT BODY WEIGHT GAIN (KG) FOR DOGS ADMINISTERED
CGA 169374 IN THE DIET FOR 52 WEEKS**

DAYS ON TEST	DDM =	Males					Females				
		0	20	100	500	1500	0	20	100	500	1500
7		2.84	3.10	3.78	2.93	1.25	4.58	1.49	1.16*	2.31	0.40*
14		3.48	4.05	4.20	4.51	2.60	4.81	2.53	2.02	2.77	2.48
21		8.39	7.45	8.54	7.80	6.98	8.47	9.78	7.28	7.47	6.98
28		11.15	9.35	12.83	10.07	9.86	14.09	13.45	8.86	10.49	10.24
35		15.32	10.58	16.33	13.52	12.50	16.29	14.24	11.31	12.43	13.24
42		17.18	12.83	19.21	17.11	15.15	20.57	17.44	15.06	14.64	16.09
49		19.45	14.37	22.54	19.76	19.29	22.30	19.97	16.28	16.09	18.82
56		21.54	17.50	24.19	20.70	19.65	23.91	23.23	17.80	17.77	21.34
63		24.10	19.40	27.86	23.84	23.12	26.53	25.01	20.32	20.08	22.56
70		25.63	20.73	30.55	26.48	24.02	29.43	27.60	22.60	22.05	24.67
77		26.32	22.23	31.17	27.13	24.39	28.62	27.30	24.49	21.59	24.27
84		28.53	23.46	33.23	28.53	27.02	32.49	28.54	25.57	23.73	25.93
91		28.94	25.06	34.88	30.59	27.91	33.30	29.21	29.45	25.24	27.23
105		27.64	27.23	36.29	31.97	28.43	32.94	32.73	27.87	22.38	25.80
133		28.79	33.19	41.83	38.41	32.94	39.54	39.84	35.65	25.20	31.05
161		28.13	35.66	43.11	39.63	33.62	40.88	41.31	39.68	24.54	29.73
189		30.27	38.43	45.42	40.77	36.30	42.35	40.66	41.47	27.58	32.36
217		27.87	38.43	46.02	39.71	38.55	40.77	37.45	37.45	26.08	29.76
245		34.35	44.13	49.98	43.38	41.70	46.01	42.25	44.27	32.50	33.34
273		35.86	46.08	51.68	45.44	43.34	44.21	45.55	47.21	30.17	34.55
301		35.57	45.76	51.26	45.46	41.30	40.91	44.53	47.51	25.95	31.28
329		36.22	47.66	53.66	43.89	41.60	41.87	46.65	45.22	25.36	31.28
357		35.14	48.63	54.30	42.56	40.94	41.68	44.93	43.49	24.87	28.94

The reevaluation of the NOEL was requested due to an error in the DER for this study. The Table on Page 5 of the DER showed identical mean body weight gain data for females at 20 ppm and 100 ppm dose groups between days 42 and 273. The table below shows the correct [hand written and boxed] mean body weight for the 100 ppm between days 42 and 273. Evaluation of the new data showed no meaningful decreases in mean body weight gain for the 100 ppm group. Consequently, the NOEL of 100 ppm [3.4 mg/kg/day in males and 3.7 mg/kg/day in females] and the LOEL of 500 ppm [16.4 mg/kg/day in males and 19.4 mg/kg/day in females] established in the initial evaluation remains status quo.

4. Gikinis, M.L.A. [1988]. A Two-Generation Reproductive Study in Albino Rats. MRID No. 009689; HED Document # 010588.

RfD Committee's Recommendation

The Committee recommended establishing a systemic/reproductive NOEL/LOEL.

Reviewer's Response:

The NOEL for systemic/reproductive effect is 1.25 mg/kg/day and the LOEL is 12.5 mg/kg/day based on decreases in mean body weight gains in the parental F₀ and F₁ generations.

5. Lochry, E.A. [1987]. Developmental Toxicity Study of CGA-169374 Technical [FL851406] Administered Orally Via Gavage to CrI:COBS [SD] BR Presumed Pregnant Rats. MRID No. 42090016; HED Document # 009689 & 010588.

RfD Committee's Recommendation

The Committee recommended that the actual dose levels need to be corrected to reflect the second evaluation of the chemical analysis of the test compound.

Reviewer's Response:

Although the Registrant provided the purity of the test article [95%], due to the high percent deviation of the actual doses tested, the NOELs/LOELs established [based on analytical results] remains status quo.