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

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SEP 23 1993

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Subject: EPA ID # 113201-007969; Vinclozolin; Expedited Review of an Interim Report of Supplementary Data to the Chronic Rat Study (428757-01) and an Interim Report of a Mouse Oncogenicity Study (428757-02).

PC No.: 113201. DP Barcode No.: D194268.
ToxChem No.: 323C. Submission No.: S446442.
Case No.: 816411. Action No.: 627 Generic Data Submission.

From: David G Anderson, PhD *David G Anderson 9/14/93*
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To: Bruce Sidwell/Alan Dixon PM 53
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Reregistration Division (H7505C)

Thru: Karen Hamernik, PhD.
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CC Karen Whitby

A. CONCLUSIONS: The interim report on the rat chronic study used 25 and 50 ppm dose levels and was designed to demonstrate a NOEL for a previously submitted chronic study. The study demonstrated no dose related effects after 24 months of dosing. The upper dose level is the interim NOEL for this study and MRID# 423551-01 and -02, reviewed in HED Doc # 009884. The RfD is not changed by the new NOEL or the other data.

The interim report on the mouse oncogenicity study reports no additional hazards over a 18 months dosing period. The previous 6(a)(2) data on the mouse oncogenicity study (MRID# 425766-01) is currently being reviewed by a contractor. A response to the 6(a)(2) data was presented in a memorandum from David G Anderson to Larry Schnaubelt/Brigid Lowery, PM 72, dated 3/2/93.

However, the oncogericity at 8000 ppm reported in the above mentioned letter may be mitigated by the reported excessive death at the 8000 ppm dose level reported in submission 428757-02. See the section on the bases of the conclusions.

The status of vinclozolin is unchanged by either interim study report, however, the final reports must be evaluated before

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any definitive conclusions can be made.

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B. REQUESTED ACTION:

The Reregistration Division requested an expedited review of the reports referenced below. An expedited review was requested because Vinclozolin was classified as a RfD exceeder by the Reregistration Division.

Mellert, W. Interim Report: Study of the Carcinogenicity of Reg. No. 83 258 (Vinclozolin) in Wistar Rats; Administration in the Diet for 24-Months, dated June 4, 1993, Project No. 71S0375/88109 - Supplementary Study to 71S0375/88026. BASF Reg. Doc. No. 92/10583, 209 pages. Performed at BASF Aktiengesellschaft, Dept. Toxicology, D-W6700 Ludwigshafen/Rhien, Germ. (MRID# 428757-01).

Mellert, W. Interim Report: Carcinogenicity Study of Reg. No. 83 258 (Vinclozolin) in C576BL/6N Mice; Administration for 78 Weeks, dated March 1, 1993, Project No. 80S375/88112, BASF Reg Doc. No. 93/10199, 257 pages. Performed at BASF Aktiengesellschaft, Dept. Toxicology, D-W6700 Ludwigshafen/Rhien, Germ. (MRID# 428757-02).

C. BASES FOR THE CONCLUSIONS:

Review of MRID# 428757-01 - Interim Report of a Chronic Study in Rats after Dosing for 24 Months:

The study is a supplementary study to a previously submitted chronic study in rats (MRID# 423551-01 and -02) and reviewed in HED Doc. #009884. The supplementary study was conducted in controls, 25 ppm (1.2 mg/kg/day in males and 1.6 mg/kg/day in females) or 50 ppm (2.4 mg/kg/day in males and 3.2 mg/kg/day in females) in 20 Wistar rats per sex per group for 24-months to determine a NOEL for chronic toxicity in rats. Body weight, food consumption and organ weight data (liver, kidney, testes and ovaries, epididymides, brain and adrenals) were submitted. In addition, gross necropsy data, but no individual animal data were submitted.

No dose related effects were seen in urinalysis, hematological or clinical chemical data.

No dose related effects occurred in the organ weights. The absolute testes, epididymides, ovaries and adrenal gland weights were variable with the coefficient of variation ranging as high as 256% for ovaries, 125% for adrenals, 108% for the testes and 22% for epididymides. Since the study is a chronic study, some of this variation may have been due to cysts and masses in these organs. Individual animal data, not submitted with this interim report, may aid in the evaluation of the organ weight data.

Although no effects were expected, the variation in the data prevents detecting possible dose response organ weight effects in these data. No dose related gross necropsy observations were reported in the necropsy data.

The ophthalmological examination of male rats indicated that opacities and cataracts in all groups were within historical control range. It seems unlikely that individual animal data from a final report would express different results. Therefore the interim NOEL from this study is 50 ppm or 2.4 mg/kg/day for opacities and cataracts. The LEL was 150 ppm for these and other effects from a previously submitted chronic study in rats (MRID# 423551-01 and -02).

Cataracts in historical control data ranged from 1/100 = 1% to 3/50 = 6% with an overall average of 22/1005 = 2.2%. A similar data base was not submitted for opacities but the incidence was generally higher, approximately 24% in the control data submitted with other studies on the Wistar rat for a comparable time period.

Table A: Summary of Ophthalmology Findings During the Chronic Study in Rats after 24 months of dosing.

Eye defect	Male 20 per group						Female 20 per group					
	0		25		50		0		25		50	
Dose level, ppm	LS	RS	LS	RS	LS	RS	LS	RS	LS	RS	LS	RS
Day -1 Opacities	0	0	0	0	0	0	0	0	0	0	0	0
Day -1 Cataracts	0	0	0	0	0	0	0	0	0	0	0	0
Day 363 Opacities	1	1	1	2	2	1	0	0	0	0	1	2
Day 363 Cataracts	0	0	0	0	0	1	0	0	0	0	0	0
Day 537 Opacities	2	1	1	4	4	4	2	0	2	2	2	4
Day 537 Cataracts	0	0	0	0	1	1	0	0	0	0	0	0
Day 722 Opacities	7	5	5	5	10	5	7	3	4	5	6	5
Day 722 Cataracts	1	0	1	0	1	2	0	0	0	0	0	0
Day 722 Opacities & cataracts	8	5	6	5	11	7	7	3	4	5	6	5

LS = Left side; RS = Right side.

Review of MRID# 428757-02 - Interim Report on an Oncogenicity Study in Mice after 18 Months of Dosing:

Vinclozolin was administered to 50 C57BL/6N Mice per group for 18-months at 0, 15, 150, 3000 or 8000 ppm (males: 2.1, 20.6, 432 or 1225 mg/kg/day; Females: 2.8, 28.5, 557 or 1411 mg/kg/day). This interim report included body weight, body weight gain, food consumption and efficiency of food utilization. Absolute and relative organ weights on the brain, liver, kidney, testis and adrenal were submitted. In addition, the report included mortality and gross necropsy data. Two control groups were used to increase the historical control data base. Ten additional rats per sex per group were sacrificed after 1-year as satellite animals.

Terminal body weights compared with control group 0 were statistically significantly depressed at 8000, 3000 and 150 ppm in males and females and at 15 ppm in males (Table B). Terminal body weights compared with control group 1 were statistically significantly depressed at 8000, 3000 in male and females and as low as 150 ppm in females (Table B). Food consumption was lower than control 0 or 1 in all treatment groups (Table C). There appears to be a decrease in the relative efficiency of food utilization in males and females at 8000 ppm (Table C) and possibly a lesser decrease in males at 3000 ppm.

Table B: Initial body weight, terminal body weight and body weight gain from day 0 to day 546 for males and females.

	Initial (g)	Terminal (g)	BWt. gain (g)	Initial (g)	Terminal (g)	BWt. gain (g)
Group	Male body weight (g)			Female body weight (g)		
Control 0	22.9	31.4	8.5	18.6	25.8	7.2
Control 1	22.8	29.7	6.9	18.5	25.7	7.2
15 ppm	23.0	28.7**	5.7	18.7	24.8	6.1
150 ppm	23.0	29.7	6.7	18.7	22.7**##	4.0
3000 ppm	23.0	27.8**	4.8	18.6	23.0**##	4.4
8000 ppm	22.8	24.4**##	1.6	18.5	20.9**##	2.4

** = Statistically significantly less than control 0, at $p \leq 0.01$; ## = Statistically significantly less than control 1, at $p \leq 0.01$.

Table C: Sum of relative food consumed from day 0 to 546, expressed as weekly daily average in g per animal per day for the given week per week; Relative efficiency of food utilization [(Body weight gain Day 0 to 546)/(relative food consumed over the same time period)].

	Males		Females	
	Accumulated food consumption (Σ daily av./week)	Relative Efficiency (Bwt. gain/food consumed)	Accumulated food consumption (Σ daily av./week)	Relative Efficiency (Bwt. gain/food consumed)
Control 0	128.5	0.0661	151.2	0.0476
Control 1	124.9	0.0552	151.0	0.0477
15 ppm	116.8	0.0488	136.9	0.0446
150 ppm	118.4	0.0566	134.9	0.0297
3000 ppm	116.6	0.0412	129.8	0.0339
8000 ppm	107.7	0.0149	113.8	0.0211

There were dose related increases in mortality and animals killed in extremis in males and females at 8000 ppm and possibly at 3000 ppm (Table D). Among males this values reached 60% in the main group of 50 animals at termination and 50% in the satellite group of 10 animals at day 364. Among females this values reached 48% in the main group of 50 animals at termination and 40% in the satellite group of 10 animals at day 364. Mortality was increased in males and females at 3000 ppm over control groups, but the increase was less than at 8000 ppm.

Previous data submissions on subchronic studies had not indicated toxicity other than endocrine toxicity and that body weight decreases had not been accompanied by a decrease in food efficiency at 3000 ppm. In addition, in a previously reviewed mouse oncogenicity study conducted for 26 months at a dose level as high as 4374 ppm, mortality in controls and the HDT were comparable (HED Doc #000244). Thus, BASF was advised that based on the data BASF had supplied, 3000 ppm may not be sufficient to adequately challenge the mouse with regard to carcinogenicity.

The findings with vinclozolin raise questions about setting dose levels for carcinogenicity studies with substances having antiandrogen effects. Perhaps the possibility of severe perturbations in test animal hormone levels should be considered in establishing appropriate dose levels for testing, especially for carcinogenicity studies.

Table D: Cumulative mortality from initial dosing to termination, Day 0 to day 546.

Males (%)							
Dose level	Day 0	Day 91	Day 182	Day 273	Day 364	Day 455	Day 546
Control 0	0	0	0	0	4	10	14
Control 1	0	0	0	0	4	4	6
Av. Control 0 & 1	0	0	0	0	4	7	10
15 ppm	0	0	2	4	12	18	20
150 ppm	0	2	2	2	8	18	22
3000 ppm	0	0	0	2	16	16	22
8000 ppm	0	6	12	14	44	58	60
Females (%)							
Dose level	Day 0	Day 91	Day 182	Day 273	Day 364	Day 455	Day 546
Control 0	0	0	0	4	4	6	12
Control 1	0	0	0	0	0	4	6
Av. control 0 & 1	0	0	0	2	2	5	9
15 ppm	0	4	4	4	6	6	8
150 ppm	0	0	2	4	6	6	6
3000 ppm	0	8	12	14	18	18	24
8000 ppm	0	14	14	22	30	34	48

Absolute and relative liver weights were increased at 8000 and 3000 ppm in males and females depending on which control group was used for comparison. Absolute and relative adrenal weights were increased at 8000 and 3000 ppm in males and females compared with either control group, but the effects were more sporadic at lower dose levels. Absolute and relative kidney weights in males were decreased at several dose levels depending on the control used for comparison. Brain weights were decreased at 8000 and 3000 ppm in males and females compared with either control group. Testes weights were increased and decreased, making it difficult to generalize.

Gross lesions were seen in male mice. These were glandular stomach focus and discoloration of gut contents, liver focus, prominent acinar pattern and liver enlargement. Reduced size was reported for the testes, seminal vesicles, prostate at 3000 and 8000 ppm. An decreased spleen size was noted at 8000 ppm. Enlarged adrenals were noted at 3000 and 8000 ppm. No Leydig cell hyperplasia was reported. In females, there was a dose related increase in glandular stomach focus and discoloration of gut contents at 3000 and 8000 ppm and liver focus and prominent acinar pattern at 8000 ppm. An increase in liver masses were

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reported at 8000 ppm. The ovaries were reported to be enlarged only at 8000 ppm.

The gross pathology report of seminal vesicle enlargement and reduction was not clear. A dose related decrease in enlargement as well as dose related reduction in organ size were reported in the seminal vesicles. The enlargement was 34 and 29 in the two control groups and zero enlargement in the 8000 ppm group, while reduced organ size was 0 and 1 in the two control groups and 42 in the 8000 ppm dose group.

Expedited review of interim reports on a rat chronic/428757-01 and a onco study/428757-02/D194268/A:\VINCL43.23C\MRCHRONC.MO /DANDERSON/8/31/93(Edited9/14/93)*.