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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Terbutryn - Amendment to Chronic Feeding Study in Rats; submitted by Ciba-Geigy Corporation on October 1, 1987 in Response to the Terbutryn Registration Standard. EPA ID No.: 100-540
Tox. Branch Project No.: 8-0182 Tox. Chem. No.: 125D

To: Robert Taylor/James Yowell
Product Manager No. 25
Registration Division (TS-767C)

From: Judith W. Hauswirth, Ph.D. Judith W. Hauswirth 12/11/87
Head, Section VI
Toxicology Branch/HED (TS-769C)

Thru: Theodore M. Farber, Ph.D., Chief
Toxicology Branch/HED (TS-769C)

Action Requested: Review additional statistical anaylysis submitted on the hematology data from the two year chronic toxicity study in rats on terbutryn.

Conclusions/Recommendations:

Based upon a statistical reevaluation of the hematology data from the two year rat chronic toxicity/oncogenicity study, a NOEL for systemic effects can be set at 2ppm. The LEL is 300 ppm based upon a statistically significant and dose-related decrease in hemoglogbin and erythrocytes in female rats at 18 months. This parameter was not measured for the mid dose group at term. At the HDT tested there was also statistically significant decrease in hematocrit in females at both 18 and 24 months.

This study is now considered to be acceptable for chronic toxicity.

Core Classification: Minimum

Background:

In the registration standard on terbutryn, the chronic toxicity/oncogenicity study was considered to be Core Supplementary for chronic toxicity since a NOEL for hematological paramenters was not determined. One of the flaws of the study that made it difficult to make this determination was that hematology parameters were not measured at every time point for the mid and low dose groups. These parameters were measured at 3, 6, 12, 18 and 24 months for the high dose and the control groups but only at 12 and 18 months for the low and mid dose groups.

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Discussion:

The registrant submitted the following in support of their position that this study does establish a NOEL for hemoatological effects in the rat due to terbutryn:

1. A statistical reevaluation of the data;

2. Historical control data from the performing laboratory and as well as from the open literature on the hematological parameters in question;

3. A discussion of their rationale for concluding that the NOEL for hematological effects is 300 ppm terbutryn in the diet.

Table 1 from the report containing the results of the statistical reevaluation and the historical control data from the performing laboratory is attached in Appendix 1. In the original report the 18 month values for both hemoglobin and erythrocyte values were statistically significantly reduced in female rats at the lowest dose tested of 2 ppm. In the reanalysis two females at the 18 month time point in the 2 ppm group were eliminated as outliers, thereby reducing the significance of the change at this dosage level. Since the effect at 2ppm was not dose related with these two animals included, we tend to concur with registrant on this point.

We agree with the registrant that the mean values for both hemoglobin and erythrocytes were for the most part within the historical control range of the performing laboratory for all dosage groups at 18 months and for the control and HDT groups at 24 months, this was not true for the values obtained at 12 months for the HDT. In addition, at the HDT the decrease in both of these parameters was seen consistently at 6, 12, 18 and 24 months and, therefore, is considered to be treatment related. At the mid dose the decrease was seen only at the 18 month time interval. However, for the mid dose these parameters were measured only at 12 and 18 months. Since we have data for only these two time points, we cannot make any conclusions about the consistency of this effect over time at the mid dose and furthermore, since there was a significant trend for both of these parameters at 18 months, we consider the effect to be treatment related and biologically significant.

With the limitations of the study, i.e. that hematology paramenters were not measured at every time point for the low and mid dose that they were for the high dose and control groups, we can conclude conservatively that NOEL for the effects of terbutryn on hemoglobin and erythrocyte values in female rats is 2 ppm and the LEL is 300 ppm. This study can be raised to a Core Minimum study.

Appendix 1

TABLE 1
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Comparisons Against Concurrent Control

Male Hgb	12 Months Mean	P	18 Months Mean	P
0 ppm	11.53		13.35	
2 ppm	14.26	0.0007** (+)	14.33	ANOVA P = 0.3261
300 ppm	14.52	<0.00005** (+)	14.21	Not significant
3000 ppm	11.65	0.9612 (-)	13.81	

Monotone Trend: None — None

Female Hgb	12 Months Mean	P	18 Months Mean	P
0 ppm	11.77		14.04	
2 ppm	14.02	<0.00005** (+)	12.95	0.1013 (-)
300 ppm	13.60	0.0001** (+)	12.43	0.0056** (-)
3000 ppm	10.50	0.0057** (-)	11.83	0.0002** (-)

Monotone Trend: None — P = 0.0001** (-)

Male Hct	12 Months Mean	P	18 Months Mean	P
0 ppm	31.40		37.00	
2 ppm	42.10	<0.00005** (+)	37.40	0.9944 (+)
300 ppm	36.50	0.0003** (+)	41.20	0.0891 (+)
3000 ppm	30.30	0.6720 (-)	36.50	0.9847 (-)

Monotone Trend: None — None

Female Hct	12 Months Mean	P	18 Months Mean	P
0 ppm	30.00		36.00	
2 ppm	35.60	0.0001** (+)	36.25	0.9965 (+)
300 ppm	35.50	0.0001** (+)	35.80	0.9979 (-)
3000 ppm	26.90	0.0106* (-)	30.00	0.0003** (-)

Monotone Trend: None — None

Male Erythrocytes	12 Months Mean	P	18 Months Mean	P
0 ppm	5.710		6.033	
2 ppm	7.409	<0.00005** (+)	6.651	ANOVA P = 0.1706
300 ppm	6.931	0.0011** (+)	6.530	Not significant
3000 ppm	5.714	1.0000 (+)	6.174	

Monotone Trend: None — None

Female Erythrocytes	12 Months Mean	P	18 Months Mean	P
0 ppm	5.066		5.999	
2 ppm	6.705	<0.00005** (+)	5.560	0.1410 (-)
300 ppm	6.361	0.0022** (+)	5.386	0.0170* (-)
3000 ppm	4.658	0.0776 (-)	4.914	<0.0005** (-)
				P = 0.0001** (-)

Monotone Trend: None

Note: Animal nos. 40132 and 40142, both female 2 ppm groups were excluded from statistical comparisons at 18 months as outliers.

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TABLE 2

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION
HISTORICAL CONTROL CLINICAL LABORATORY VALUES
2 Years Charles River CD Rat Studies
Means and Actual Ranges (1976-1980)

Males	12 Months	>13 Months
Erythrocytes x 10^6/ccm	7.24 (5.90-8.90)	6.62 (3.68-9.60)
Hemoglobin gm/dl	15.4 (13.4-17.8)	13.8 (8.0-19.6)
Hematocrit %	49 (41-61)	43 (21-66)
Females		
Erythrocytes x 10^6/ccm	6.69 (4.87-8.60)	5.92 (2.68-9.38)
Hemoglobin gm/dl	14.9 (11.6-17.5)	13.3 (8.0-18.0)
Hematocrit %	46 (39-50)	40 (21-53)

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