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9-29-86
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

9/29/86

MEMORANDUM

SUBJECT: Linuron - Evaluation of Rabbit Teratology Study

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Statistical evaluations were prepared on the following data that were submitted by Dr. Rowe. They consisted of information on skull malformations in rabbit fetuses of dams that were fed doses of linuron at 0, 13, and 100 mg/kg/day.

Table 1. Linuron - Rabbits, Dams with Fetuses with Skull Malformations

Dose (mg/kg/day)	0	5	25	100
# of Dams with malformed fetuses	1	5	3	6
			17	13
# Examined (percent)	20 (5.0)**	20 (25.0) ^B	(17.6)	(46.2)*

Table 2. Linuron - Rabbits, Fetuses with Skull Malformations

Dose (mg/kg/day)	0	5	25	100
# of Fetuses with malformed skulls	1	9	5	19
# Examined (percent)	135 (0.7)**	135 (6.7)*	121 (4.1) ^B	79 (24.1)*

* Significant ($p < .01$) by Fisher's Exact Test.

** Significant ($p < .01$) by Cochran-Armitage Trend Test.

^B Borderline Significance ($.05 < p < .10$) by Fisher's Exact Test.

The relationship between the number of skull malformations among fetuses with increasing doses of linuron was evaluated by the Cochran-Armitage Trend test; a significant ($p < .001$) trend was observed. The evaluation of this relationship for dams also resulted in a significant ($p < .01$) trend.

In making pairwise comparisons of the controls with the highest dose group by Fisher's Exact test, the differences related to fetuses or dams with fetuses with malformed skulls were highly significant ($p < .001$). However, in the pairwise comparisons of controls with the mid and then with the low dose group by Fisher's Exact test, the statistical results were less consistent. The comparisons for the dams with malformed fetuses were not significant ($p = .24$) and borderline ($p = .09$) for controls vs. mid dose and controls vs. low dose, respectively. These same comparisons for fetuses were of borderline significance ($p = .08$) and highly significant ($p = .01$), respectively.

Discussion

The interpretation of results should take into consideration that the statistical evaluation of dams with fetuses did not adjust for the number of fetuses per dam; while the evaluation of the fetuses did not consider the dependence of fetuses within the same litter. Thus, the measurement of the real effect of increasing doses of linuron on skull malformations lie somewhere in between these two extreme results.

At this time, there is no available statistical procedure which satisfactorily addresses the interdependence of fetuses and dams and the varying litter sizes.

However, another possible approach would be to suppose that this experiment was made up of twice as many dams, with the same proportions of defective fetuses. Then the comparison of controls with the low dose dams would be statistically significant ($p = .012$) by Fisher's Exact test.

In conclusion, the above evaluations suggest that there is no NOEL indicated in this study.