PO-1051
TR-1531

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

MEMORANDUM

001531 OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

DATE:

SUBJECT: Re-evaluation of Teratology Studies with Methoprene in the Light of New Data (EPA Reg. No. 20954-89 Acc. No. 246110, Caswell No. 28 AAA).

FROM: George Z. Ghali, Ph.D.
Review Section IV
Toxicology Branch, HED (TS-769)
G. Ghali 3/17/82

TO: Franklin Gee
Product Manager, No. 17
Registration Division (TS-767-C)

THRU: Christine F. Chaisson, Ph.D.
Review Section IV, Section Head
Toxicology Branch, HED (TS-769)
C. F. Chaisson 3/18/82

Registrant: Zoecon Corporation
California Avenue
Palo Alto, California

Action Requested:

Re-evaluation of mouse and rabbit teratology studies in the light of additional data.

Conclusions and Recommendations:

I. Rabbit Teratology:

The new data support our previous conclusion that this chemical is not teratogenic in the Japanese white rabbit. The NOEL is considered to be 200 mg/kg/day for maternal toxicity and embryo lethality in utero. The study is adequate to fullfil the requirement for teratology data in one mammalian species.

II. Mouse Teratology:

The new data support the initial conclusion that this chemical is not teratogenic in mice under the test conditions. However, the registrant or the testing laboratory is requested to address and rationalize the significant decrease in testes weight in the low and middle dose levels. The NOEL is considered to be 600 mg/kg/day (HDT). The study can be classified as Core-minimum data.

Background Information:

On November 4, 1980, two teratology studies with methoprene were reviewed by George Ghali (memo to Franklin Gee dated 11/4/80). Our conclusions from these two studies were as follows:

I. Rabbit Teratology:

This study does not show evidence of teratogenicity. However, this study is lacking a positive control to indicate the sensitivity of this particular strain of Japanese rabbits to any chemical teratogen.

The no effect level (NOEL) is considered to be 200 mg/kg/day, and the least effect level (LEL) is considered to be 2000 mg/kg/day for embryo lethality in utero.

This study is classified as Core-minimum. The registrant is requested to submit historical terata incidence for this strain of rabbit.

II. Mouse Teratology:

This study is classified as supplementary. The following additional data are required in order to allow proper review of the study for teratogenic and fetotoxic potential.

1. Absolute and relative internal organs weight for individual animals (tabulated).

2. Data on ossification and detail descriptions of vertebrae for individual animals (tabulated).

3. A statement from the registrant or testing laboratory addressing the possibility of a bimodal effect (or an effect at lower dose level) on the maturation of males and females as it is manifested by the delay in the descent of testes and the slowing of the opening of the vagina.

The registrant responded to our request by submitting the following:

1. Individual data in mice
2. Vehicle control data in mice.
3. Vehicle control data in rabbits.
4. A discussion of what seemed as possible bimodal effect.

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Evaluation of Data and Overall Comments:

In a previous review, Toxicology Branch expressed concern over the possible bimodal effect of this chemical as manifested by delay in the descent of testes and opening of the vagina.

The registrant has consulted a number of experts in the area of reproductive toxicology and teratology who could not see any possible biological significance of these effects and considered them within the normal range of variability. In addition the mean values and the standard deviations associated with this variability indicated overlap of the range among all groups including the control, i.e. the variability within the group is comparable in magnitude to that of the inter-group.

Furthermore, in a recent evaluation of the available toxicology data, including a 3-generation reproduction study in rats, no compound-related effects were observed with respect to reproduction.

We have also examined the individual data and the vehicle control data submitted and concluded that all the anomalies observed were within the normal range of spontaneous incidence in both species.