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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE:

SUBJECT: Vitavax, Registration No. 400-81 Accession No. 246323

FROM: Caswell #165A
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Registrant: Uniroyal Chemical

Request: Review of a teratology study in rabbits. Data submitted for the purpose of satisfying the requirements of the Registration Standard Guidance Package for Carboxin.

This review also contains the following:

- a) A brief review of The Historical Control Data. Appendix III-No. 399-042.
- b) A brief review of the Positive Control Data. Appendix V-No. 999-014.
- c) A brief review of a Range Finding Teratology Study in Rabbits. No. 399-029a.

Recommendations

The product did not produce teratogenicity as tested.

The study is classified as Core Guidelines data.

- a) The Summary of the Historical Control data submitted is acceptable to be used in conjunction with the teratology study. The figures and calculations are correct.
- b) The Positive Control Data Study is acceptable and suitable to be used in conjunction with the main teratology study.
- c) The Range-Finding Teratology Study in Rabbits is acceptable for the selection of the highest dose level used in the teratology study.

Study: Teratology Study in Rabbits

Laboratory: International Research and Development Corporation

Number: 399-043

Date: November 12, 1981

Sponsor: Uniroyal Chemical

Objective: Assay for Teratogenicity

Test Article: Vitavax Technical (99%)
D 6527--a white powder

Species: Dutch Belted Rabbits

Sex and Age: young virgin females

Number of Animals per dose level: 16 rabbits per dose level. Product
suspended in 0.5% carboxymethyl
cellulose.

Dose Levels: 0-control, received the vehicle only; 75, 375 and 750 mg/kg/day

Dosing: By gavage from the 6 through 27th day of gestation

Duration of Test: 27 days.

Observations: The highest dose produced maternal toxicity for mothers and
fetuses.

Mortality: yes

Signs of Toxicity: Appearance changes, behavior and clinical signs; daily.

Body Weight Changes: at intervals

Behavior and Appearance: Daily

Clinical Testing

<u>Test:</u>	Hematology	No
	Blood Chemistry	No
	Urine Analysis	No
	Other	No

Necropsy: Dead animals were examined for morphological changes. Fetuses were examined for external, skeletal and visceral defects.

Histopathology: Not performed

Other: On day 28, all surviving mothers were sacrificed and the uterus was examined, weighed; the number and location of viable or nonviable fetuses, early and late resorptions, number and location of implantations and corpora lutea were recorded. Other relevant parameters were also considered.

Fetal Observations

External malformations and variations;
Sex and Weight; visceral malformations and variations.

Results

Maternal

Mortality: Only due to intubation accidents. Otherwise no mortalities

Abortions: 1 in the 375 mg/kg and 3 in the 750 mg/kg group. The fetuses were externally normal.

Toxic Signs: Soft stool with greater incidence at the high dose level.

Body Weight Changes: Not considered treatment related.

Necropsy: Findings were considered to be not dose-related.

Cesarian Section Observations:

Body weights; changes not considered biologically significant.

Number of viable fetuses: No statistically significant difference. Post implantation loss, total implantation and corpora lutea - No meaningful differences when compared to the control group.

Fetal Observations: Frequency of genetic or developmental variation were within the range of the historical control data. Variations as malformation of the carpal or tarsal flexures noted in the 75 mg/kg dose did not occur at higher dose levels. Thus, such malformation cannot be attributed to the test material.

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Other variations in the vertebrae or in the ribs that were observed in the treated animals but not in the control animals were within the values of the historical control data. Thus, the difference was not considered biologically meaningful.

a) Brief Review of the Historical Control Data. Appendix III

International Research and Development Corporation No. 399-042. Historical Control Data

Species: Dutch Belted Rabbits

A summary of maternal and fetal observations is presented.

The summary data includes parameters related to pregnant mothers as deaths, abortions, resorptions, live fetuses, sex ratio, etc, percentage of malformations and developmental and genetic variations.

The summary is acceptable to be used in conjunction with the Teratology study. The figures submitted are correct.

b) Brief Review of the Positive Control Data. Appendix V.
International Research and Development Corporation No. 999-014
November 16, 1978

Procedure

Material: 6-aminonicotinamide 99+%

Species: Dutch Belted Rabbit

26 inseminated rabbits were divided into a control group of 14 rabbits and a test group of 12.

The control rabbits received carboxymethyl cellulose 3 ml/kg/day -- 1% aqueous, by gavage, from the 6th to the 18th day of gestation.

The test animals received a 2 mg/kg I.P. single injection on day 9 of gestation. Standard maternal fetal observations were performed.

Body Weight Changes: Recorded at 0, 6, 12, 18, 24 and at the 28th day.

Behavior and Appearance: Daily observations

Clinical Testing

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<u>Test</u>	Hematology	No
	Blood Chemistry	No
	Urine Analysis	No
	Other	No

Necropsy: Uterus and ovary, abdominal and thoracic cavities and organs.
Number and location of corpora lutea, total implantation,
resorptions, viable fetuses.

Histopathology: Maternal tissues saved for future examinations.

Other: Uteri for confirmation of pregnant status from non gravid
females were preserved and saved.

Results:

Mothers: Observations no different than the control rabbits.

Sex Ratio: No biologically meaningful differences.

Resorptions: Increase in the mean number when compared with controls.
Increase in number of nonviable fetuses.

Increased number of litters with malformations in the test
animals as compared with the control group.

The study is acceptable to establish a Positive Control to be
used in the main teratology study.

Study: Range-Finding Teratology Study in Rabbits

Laboratory: International Research and Development Corporation

Number: 399-029a Accession No. 246323

Date: October 8, 1981

Sponsor: Uniroyal Chemical

Objective: To establish dosage levels for a teratology study.

Test Article: Vitavax Technical (99%)
Carboxymethyl Cellulose (Control)

Species: Rabbit

Sex and Age: Virgin female Dutch Belted rabbits

Number of Animals per dose level: 5 per dose

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Dose Levels: Control 1 and Control 2 (8 and 10 ml/kg respectively).
Test: 300, 600, 900 and 1200 mg/kg

Dosing: Oral by gavage, 1 dose a day from the 6-27 day gestation

Duration of Test: 28 days.

Observations:

Mortality: Necropsy performed in found dead animals. Autopsies performed in all.

Signs of Toxicity: Daily appearance and behavior and other related indications.

Results

Maternal

Mortality: All animals died at the 1200 mg/kg dose level. 3 animals died at the 900 mg/kg dose level.

Signs of Toxicity: Hypothermia, lethargy, shallow breathing, dehydration, anogenital brown discharge.

Necropsy: Ulceration of the mucous membrane of the stomach 4 rabbits at the 1200 mg/kg dose level.

Abortions: 3 dams at the 900 mg/kg group and 2 at the 1,200 mg/kg group.

Body Weights: Changes at the high dose and the 900 mg/kg dose level

Uterine Examination: At the 1200 mg/kg dose level, a meaningful comparison was not possible due to the high mortality. There were no biologically meaningful differences at the 300 and 600 mg/kg dose level when compared to both control groups. Mean post implantation loss was increased in the 900 mg/kg dose level.

Based on the observations it was decided that a dose of 900 mg/kg would be considered excessive. Thus the higher dose used for the teratology study was 750 mg/kg.

Conclusion

The study is acceptable for a selection of a suitable high dose for the teratology study.