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11-16-85

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D C 20460

004772

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Vitavax Technical

Tox. Chemical No. 165A
Accession No. 258-933

FROM: Alex Arce
Toxicology Branch
Hazard Evaluation Division (TS-769C)

OCT 15-85

TO: Henry Jacoby, PM 21
Fungicide-Herbicide Branch
Registration Division (TS-767C)

THRU: Clint Skinner, Ph.D., Head, Section III
Toxicology Branch
Hazard Evaluation Division (TS-769C)

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and

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Theodore Farber, Ph.D., Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Compound: Vitavax (Carboxin)

Registrant Nos.: 400-152 and 400-81

Action Requested:

Review of submitted data; mutagenicity - four studies.

Recommendation and Conclusion:

Bone Marrow Chromosome Acute and Subacute:

The product did not produce clastogenic effects in rat bone marrow cell at the toxic and nontoxic levels tested - acute and subacute. These studies are acceptable.

1 of 1

Acute Oral LD_{50}

Males 3956 mg/kg - 95 percent CL (2577 to 6072 mg/kg).

Females 3107 - 95 percent CL (2229 to 4331).

Combined 3482 mg/kg - 95 percent CL (2678 to 4529 mg/kg).
Tox Cat. III, Core Minimum

Subacute Oral (Range-Finding)

The lowest dose tested of 1000 mg/kg showed overall marked toxicity. Thus the 800 mg/kg was chosen as the high dose for the in vivo bone marrow chromosome study.

Background Information

The experimental design follows the one suggested on June 29, by H. Jacoby.

Information Submitted

Acute and Subacute Toxicity Test. "In Vivo Bone Marrow Chromosome Study in Rats." Vitavax, Final Report.

Discussion

The tests have been accurately performed to satisfy the requirements as per EPA Health Effects Test Guidelines (560/6-82-001) and the three suggestions from H. Jacoby.

DATA EVALUATION RECORD 00172

Chemical: Vitavax

Test Material: Technical

Study Type: Mutagenicity

Title: "In Vivo Bone Marrow Chromosome Study in Rats - Vitavax"

Laboratory: Hazleton Laboratories

Location: Virginia Date: July 9, 1985

Lab No: 798-209

Sponsor: Uniroyal Chemical

EPA ID: 40C-81-152 MRID: None Acc. #258933

Reviewed by: Alex Acre Date: October 1985
Toxicologist
TOX/HED Phone: 557-1511

Approved By: Clint Skinner, Ph.D. Date: October 1985
Head
TOX/HED Phone: 557-1511

Organization: OPP-HED-TOX Branch

Conclusion:

No clastogenic effect was produced, by this method, using the rat bone marrow cell at toxic and nontoxic levels, acute and subacute tests.

The two studies acute and subacute were negative.

Protocol

Test Material And Methods

Material: Vitavax (Carboxin) Technical
Lot #MM 602 I.D. #BL12505-AC3418-CC0005
LH #21.954A

Animals: Rat Sprague-Dawley, CD

Sex, male and female; age, adult; weight, acceptable; source, Hazleton Labs

Dosage: Acute study 750 to 2000 and 4000 mg/kg. Number of animals per dose level 20 male and 20 females/dose (one administration).

Subacute: 100, 400, and 800 mg/kg to five male and five female (five administrations).

Description of the Study Design

The test material was administered to the rats at three dose levels (750, 2000, and 4000 mg/kg) single dose by gavage (acute) and three other dose levels (100, 400, and 800) five administrations by gavage (subacute). A positive control cyclophosphamide 40 mg/kg and a vehicle control were used.

Two tests were previously performed.

a. Acute Oral Toxicity, rat

b. In Vivo Bone Marrow Chromosome Subacute Dose Range-Finding Study (these two studies will be reviewed separately).

Observations During the Study

Signs of Toxicity: Observed daily (appearance)

Behavior: Daily

Body weights: "Once, prior administration for the 6- and 12-hour sacrifice."

"Twice, prior compound administration and prior to colchicine administration, for the 24- and 48-hour sacrifice."

Test Performed:

Bone Marrow Cell Harvest. The animals were sacrificed at specific time intervals and the bone marrow cells were collected as follows: acute study; five males and five females at the 6, 12, 24, and 48 hours for each dose tested. Subacute study (5-day) five males and five females per dose tested at the 6 hours. The controls, for the acute and subacute studies were sacrificed following the same schedule as the test animals.

Colchicine was administered to inhibit mitosis and arrest cells in metaphase (2 mg/kg body weight) to the acute and the subacute animals as follows: at the 4, 10, 22, and 46 hours after administration of substance for acutes and 4 hours after the last administration for the subacute.

Two hours after the colchicine, the animals were sacrificed.

Collection of Bone Marrow:

As per Evans (1976 and Kellian et al., 1977) Bone marrow cells were collected and processed for the preparation of slides; two to four per animal. The slides were prepared, coded, and examined).

Results

Mortality: None.

Signs of Toxicity: Acute administration:

Red stains on nose and eyes 10 animals in group 4, 6 animals in group 5. Subacute, one animal (800 mg/kg) moribund.

Body Weights:

Significant loss in groups 3, 4, and 5 (acute dose) and groups 7 (subacute).

Chromosomal aberrations:

The positive control, cyclophosphamide group showed a statistically significant increase in percent of aberrant cells. The treated groups were negative.

Chromosome Number and Mitotic Index Results:

No statistically significant difference between the treated animals and the controls.

Discussion

The report is complete, the study was well designed and conducted. The conclusions are accurate and acceptable.

The study is scientifically sound.

The biological meaning of the effects reported are that the product as tested did not produce clastogenic effects.

These effects mean that the material is safe as per this test.

Acute Oral Toxicity in Rats, Vitavax

Project # 798-208 Dated June 18-19, 1985 - Hazleton Laboratories

Protocol

Test Material And Methods

Material: Vitavax Technical, a white powder 98% pure.
Vehicle carboxymethyl cellulose.

Animals: Rats, Sprague-Dawley

Sex, male and female; age, adults; weight, acceptable (200 to 244 g) source; Charles River

Dosage; 0, 1000, 2000, 4000, and 6000 mg/kg. Number of animals per dose level - five males and five females.

Six males and six females were assigned to determine mitotic indices.

Description of the Study Design

The material was administered by oral gavage and responses were observed at regular intervals for 14 days.

Observations lasted for 1 day for the mitotic index study.

Reported Results

LD_{50} males = 3956 mg/kg (2577 to 6072).
LD_{50} females = 3107 mg/kg (2229 to 4331).
LD_{50} combined 3482 mg/kg (2678 to 4529) 95% confidence limits.
Tox Cat III.
The material did not cause bone marrow toxicity.
Core Minimum Data.

Observations during the study

Signs of Toxicity: At the 1, 2, and 4 hours; daily thereafter for 14 days.

Body weights: Prior to treatment and at the 7- and 14-day.

Food consumption: daily.

Termination of the Study

Necropsy: In survivors and animals found dead.

Gross Pathology: Organ weights: adrenals, heart, spleen, liver, kidneys, testes or ovaries.

Mitotic Indices:

The animals selected for this test received 2.0 mg/kg of colchicine 22 hours after dosing and were sacrificed 2 hours after.

The bone marrow was removed, processed, and placed on slides for mitotic index determination. The number of metaphase cells per 500 cells counted, expressed as a percentage, was used for the determination of the mitotic index.

Results

Mortality: Mortalities were dose related in groups 3, 4, and 5, males and females. No mortalities in the mitotic index study.

Signs of toxicity: Slight depression, rough coat.

Body weight: Survivor appeared to gain weight.

Necropsy: Liver appeared dark at the high dose level males; 4/5

Organ Weights: Liver and kidney showed weight variations.

Discussion

The report is complete, the study was well designed and conducted. The conclusions are accurate and acceptable.

The study is scientifically sound.

The biological meaning of the effects reported are that the product is mildly toxic as tested.

The mechanism of these effects are not known.

These effects mean that the material is safe for the intended purpose of finding a dose suitable for the mutagenicity study.

Pilot Study

"In Vivo Bone Marrow Chromosome Subacute Dose Range-Finding Study in Rats with Vitavex" Hazleton Laboratories #798-209, July 17, 1985.

Protocol

Test Material And Methods

Material: Vitavax Tech grade 98% pure, a white powder

Animals: Rats Sprague Dawley, albino.

Sex, male and female; age, 41 to 51 days; weight, acceptable; source, Charles River

Dosage; 1000, 2000, and 3000 mg/kg. Number of animals per dose level two males and two females.

Description of the Study Design

The material was administered by oral gavage for 5 days, once each day and the animals were observed for signs of toxicity as body weights. Four hours before sacrifice, 2.0 mg/kg of colchicine I.P. was administered in order to inhibit mitosis. Slides were prepared and examined.

Reported Results:

"No apparent effects on the mitotic indices of the animals that survived."

Observations During the Study

Signs of Toxicity: daily

Behavior: daily

Body weights: Prior to compound administration and to colchicine administration.

Termination of the Study:

Two hours after administration of colchicine, the animals were sacrificed and the bone marrow was collected.

Results

Mortality: One female at the 1000 mg/kg; one male and two females at the 2000 mg/kg and all animals at the 3000 mg/kg dose levels.

Signs of toxicity: Depression and rough coat

Body weight: All survivors lost weight. Mitotic indices. The results are based upon historical standards and other pilot work. No apparent affect on the mitotic indices was observed.

Discussion

The report is complete, the study was well designed and conducted. The conclusions are accurate and acceptable.

The study is scientifically sound.

The biological meaning of the effects reported are that administration of Vitavax does not affect the mitotic index.

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