

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

4-17-78
5

TOX REVIEW
000751

DATE: April 17, 1978

SUBJECT: VITAVAX Technical EPA Reg.#400-81 Caswell#165A

FROM: William Dykstra, Ph.D
Toxicology Branch

TO: Eugene Wilson
Product Manager #21

WWD 4/17/78

BEST DOCUMENT AVAILABLE

Registrant: Uniroyal Chemical

Action Type: Submission of new data for file.

Recommendations:

The enclosed five toxicological studies on Vitavax technical are acceptable as core-minimum data and can be added to the registrant's data file on this subject.

The following results were observed:

1. Inhalation LC₅₀ > 20 mg/L TOX Category IV: CAUTION
2. Intraperitoneal LD₅₀ = 680 mg/kg (males)
Intraperitoneal LD₅₀ = 460 mg/kg (females)
3. Vitavax technical was non-mutagenic in microbial assays with and without the addition of mammalian metabolic activation preparations.
4. Primary Skin Irritation Study TOX Category IV: CAUTION
5. Vitavax technical was non-teratogenic when administered orally to pregnant Sprague-Dawley rats from day 6 through day 15 of gestation at dose levels of 4, 20 or 40 mg/kg, BW/day.

*No RPAR Criteria have been exceeded in these studies.

Review:

Enclosed are five toxicological studies on Vitavax Technical.

1. Inhalation LC₅₀ - Rats - Vitavax Technical (J. Babish, Food and Drug Research Laboratories, Inc., Waverly, N.Y., Oct. 18, 1977)
2. Intraperitoneal LD₅₀ - Rats - Vitavax Technical (R. Sapiro, Product Safety Labs, New Brunswick, N.J., Nov. 17, 1977)
3. Mutagenicity Evaluation (Ames Test) Vitavax Technical (D. Brusick, Litton-Bionetics, Inc., Kensington, Maryland, May 1977)
4. Skin Irritation - Rabbits - Vitavax Technical (J. Babish, Food and Drug Research Lab, Inc., Waverly, N.Y., June 28, 1977)

60

Teratologic Evaluation - Rats - Vitavax Technical (K. Stevens, Food and Drug Research Laboratories, Inc., Waverly, N.Y., Sept. 14, 1977)

1. Inhalation LC₅₀

Test Material: white powder, Vitavax Technical, Lot 891.

One group of ten BLU: (LE) BR Long Evans descent rats (5M & 5F), 200-300 grams, were administered 20 mg/L of test material as a mist, for 1 hour, in a 75 L chamber equipped with an air supply of 10 liters per minute. Observation for 14 days.

Results: No deaths LC₅₀ > 20 mg/L

Toxic Signs: ataxia, urinary incontinence

Necropsy: not performed

Body weight: not reported

Classification: Core-Minimum Data

TOX Category IV: CAUTION

BEST DOCUMENT AVAILABLE

2. Intraperitoneal LD₅₀ - Rats - Vitavax Technical

Test Material: white powder, Vitavax technical, Lot BL8658

5 groups of 5 male and 5 female rats, 200-300 grams, received intraperitoneal injections of 600, 650, 700, 900 and 1100 mg/kg (males) and 300, 400, 475, 500 and 700 mg/kg (females). Observation for 14 days.

Results: LD₅₀ = 680 mg/kg (males)
LD₅₀ = 460 mg/kg (females)

Toxic Signs: not reported

Body weight: not reported

Necropsy: Evidence of internal hemorrhage general discoloration of liver, spleen and kidneys, bloated distended stomachs.

Classification: Core-Minimum Data

3. Mutagenicity evaluation of D735 Final Report

Test Material: white flake - like crystals

Indicator Microorganisms

Salmonella typhimurium, strains

- TA-1535
- TA-1537
- TA-1538
- TA-98
- TA-100

Saccharomyces cerevisial, strain: D4

2

61

Objective: to evaluate the test compound for genetic activity in microbial assays with and without the addition of mammalian metabolic activation preparations.

Postive control chemicals

<u>Assay</u>	<u>Chemical</u>	<u>Solvent</u>	<u>Mutagenic Specificity</u>
Non-Activation	methylnitroso - guanidine	water or saline	BPS
	2-nitrofluorene	DMSO	FS
	Quinacrine mustard	water or saline	FS
Activation	2-Anthramine	DMSO	BPS
	2-Acetylaminofluorene	DMSO	FS
	8-aminoquinoline	DMSO	FS

BPS = Base pair substitution
FS = frameshift

BEST DOCUMENT AVAILABLE

Results: A. Toxicity: The compound was tested over a series of concentrations such that there was either quantitative or qualitative evidence of some chemically - induced physiological effects at the high dose level. The low dose level in all cases was below a concentration that demonstrated any toxic effect. The dose range employed for the evaluation of this compound was from 0.1 μ g to 500 μ g per plate.

- B. Nonactivation Test Results: The results of the test conducted on the compound in the absence of a metabolic system were all ~~active~~ negative.
- C. Activation Test Results: The results of the test conducted on the compound in the presence of the rat liver activation system were all negative.

Conclusions: The test compound, D735 did not demonstrate mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions.

Classification: Core-Minimum Data

(Note): test compound D735 is Vitavax technical.

4. Primary Skin Irritation Study with Rabbits

Test Material: Vitavax technical, Lot 891

Six Adult Albino Rabbits received dermally 0.5 gm of test material on abraded and unabraded skin sites on the fur clipped trunks under an impervious cuff for 24 hours. Observation was at 24 and 72 hours after exposure.

Results: P.I. = 0 at 24 hours and 72 hours. No irritation.

Classification: Core-Minimum Data TOX Category IV: CAUTION

3

62

5. Teratologic evaluation of Vitavax Technical in Sprague-Dawley Rats

Test Material: Vitavax Technical BL8139, C-891, cream colored powder

Sexually mature BLU: (SD) BR female albino rats, 200-250, were mated 1:1 with sexually mature BLU: (SD) BR male albino rats, 300 grams. Beginning on Day 6 of gestation and continuing daily through day 15 of gestation, the appropriate test material was administered by gavage. Test materials were prepared fresh weekly and administered as a uniform mixture in corn oil on a 10 ml/kg basis. The dosage regimen was as follows.

<u>Group</u>	<u>No. of females</u>	<u>Treatment</u>
A	28	corn oil
B	28	250 mg/kg/day, Aspirin
C	29	4 mg/kg/day, Vitavax
D	28	20 mg/kg/day, Vitavax
E	28	40 mg/kg/day, Vitavax

Body weights for all females were recorded on days 0, 6, 11, 15 and 20 of gestation. All animals were observed daily for any changes in general appearance and behavior. On day 20 of gestation, all dams were sacrificed with an overdose of chloroform and subjected to Carsarean section. The following observations were recorded for each female. Numbers of implantation sites, resorption sites, live and dead fetuses, corpora lutea, sex of fetuses, and body weight of each live fetus.

The urogenital tract of each dam was examined in detail for normality. At the time of Carsarean section, all fetuses were examined grossly for the presence of external congenital abnormalities. Any and all external abnormalities were recorded. One third of the fetuses from each litter were randomly selected and fixed in Bouin's solution for detailed visceral examination employing the Wilson free-hand slicing technique. Any fetuses showing external abnormalities were fixed in Bouin's solution and examined in this manner.

The remaining two thirds of the fetuses were eviscerated, fixed in 70% isopropyl alcohol, macerated in 1 2% potassium hydroxide solution, stained with Alizarin - Red S dye, cleared in glycerin, and examined under low powder magnification for skeletal abnormalities. All observations of skeletal abnormalities were recorded. All animals were evaluated according to normally accepted degrees of development for a 20 day old fetuses.

Incidence of occurrence were expressed as percent and comparisons between treatment groups were performed using 99% confidence belts for proportions as preanted in standard statistical texts.

Results: There were no significant differences between the control rats and the Vitavac treated rats with respect to pregnancy rate, average implantation sites, live fetuses (M/F) or dead fetuses per dam between groups.

No significant difference was noted in skeletal anomalies. Similarly, hemorrhagic thoraces and abdomens occurred in all treatment groups without significant differences in incidence between control and treatment groups.

(continues on next page)

95

67

Thus, there were no soft tissue abnormalities ascribed to Vitavax treatment in this study.

Conclusion: Vitavax technical when administered orally to pregnant Sprague-Dawley rats from day 6 through day 15 of gestation at dose levels of 4, 20 or 40 mg/kg/day had no dose related effects on reproduction, gestation nor on skeletal or soft tissue anomalies of fetuses. Therefore, Vitavax technical is considered non-teratogenic under the conditions of this study.

Classification: Core-Minimum Data

Typists: TH

RD initial G.E.W. 4/17/78

F for G.E.W. 4/18/78

BEST DOCUMENT AVAILABLE

5