11/24/82

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Review of Submitted Data

Book III
Part I, II and III

PP# 2F2607, Registration No. 1023-36, Accession Nos. 070501, 070502, 070503

Application for amended registration of BOTRAN 75W Fungicide For Use in Peanuts.

Contents of Book III

Book III, Human Safety is composed of three parts:

* -Part I (also designated for another purpose as Book I), pages 1 to 661, contains the Botran toxicologic profile discussion, individual study summaries, and individual reports previously submitted by the Upjohn Company.

-Part II (also designated for other purposes as Book II), pages 662 to 1112, contains the remainder of individual reports previously submitted by the Upjohn Company.

-Part III (also designated for other purposes as Vol. I, Vol. II, Vol. III and Vol. IV) pages 1 to 1022, is a compilation of information submitted by the Boots Company, Ltd., Nottingham, England to WHO/FAO. Please note that several reports are identical studies found in Parts I and II.

STUDY TITLE: Primary Eye Irritation Evaluation in New Zealand White Rabbits with Botran Technical (U-2069)

LABORATORY: Agricultural Research and Development Laboratories - The Upjohn Company

STUDY #: 918-9610-80-001 DATE: February 29, 1980

SPONSOR: UpJohn Company, Acc. # 70501

OBJECTIVE: Evaluation of the product for eye irritation.

TEST MATERIAL: Botran Technical

SPECIES: Rabbit SEX: 4 males and 5 females AGE: Adults

NUMBER OF SUBJECTS/DOSE LEVEL: 9 rabbits - 100 mg in left eye

DOSE LEVELS USED: 100 mg to each left eye.
6 rabbits - washed eyes - 30 seconds after application.
3 unwashed -

DOSING METHOD: Placed into the conjunctival sac. Draize

DURATION OF TEST: 14 days. Observations at the 24, 48 and 72 hours and at 4, 7, 10 and 14 days.

Results

Injection of the conjunctival vasculature, edema of the nictating membrane. Score 3.3 for nonwashed eyes.

Toxicity Category: III

Core Classification: Core Guidelines

STUDY TITLE: Primary Dermal Irritation Study in New Zealand White Rabbits with Botran Technical (4-2069)

LABORATORY: Agricultural Research and Development Laboratories, The Upjohn Company

STUDY #: 218-9610-80-002 DATE: February 28, 1980

SPONSOR: The Upjohn Company, Acc. # 70501

OBJECTIVE: Test for dermal irritation potential of the product

TEST MATERIAL: Botran Technical (4-2069)

SPECIES: Rabbit SEX: Male, female AGE: Adults

NUMBER OF SUBJECTS: 6 males, 3 females

DOSE LEVELS USED: 500 mg to each animal in shaved areas

DOSING METHOD: Abraded and intact areas treated

DURATION OF THE TEST: 14 days test, examination at 24, 72 hours and daily till the 14th day.

Results, One animal (abraded) showed signs of erythema with a total remission by 48 hours.

Others - normal.

Toxicity Category: 4

Core Classification: Core Guidelines

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STUDY TITLE: Acute Dermal Toxicity Screen in New Zealand White Rabbits with Botran Technical

LABORATORY: Agricultural Research and Development Laboratories, The Upjohn Company

STUDY #: 218-9610-1-TJR-79-466 DATE: February 29, 1980

SPONSOR: The Upjohn Company, Acc. # 70501

OBJECTIVE: Test for potential dermal toxicity of the material

TEST MATERIAL: Botran Technical (V-2069)

SPECIES: Rabbit SEX: Male and female AGE: Adults - 7-12 weeks old

NUMBER OF SUBJECTS/DOSE LEVEL: 10/dose level

DOSE LEVELS USED: Only one (2.0 g/kg in abraded areas) only abraded

DOSING METHOD: Product moistened with saline, applied and covered.

DURATION OF THE TEST: 14 days - The material was in contact for 24 hours.

OBSERVATION

MORTALITY: Yes

SIGNS OF TOXICITY: Yes

BODY WEIGHT: Yes

BEHAVIOR AND APPEARANCE: Yes

RESULTS

MORTALITY: None LD_{50} >2.0 g/kg

SIGNS OF TOXICITY: None

BODY WEIGHT CHANGES: None

FOOD CONSUMPTION: Unremarkable

BEHAVIOR AND APPEARANCE: Unremarkable

DISCUSSION OF THE METHOD OR PROCEDURE USED: Although the method did not follow the Proposed Guidelines, the results are sufficient to assign a Toxicity Category to the product. 002624

NECROPSY: All animals survived

CONCLUSION: Toxicity Category III
Not a dermal irritant

CLASSIFICATION: CORE: Minimum

STUDY TITLE: U-2069 - 13 Week Interim Report and 104 Final Report. Safety Evaluation by Oral Administration to Rats and Dogs for 104 Weeks

LABORATORY: Woodard Research Corporation

DATE: May 14, 1962 and December 7, 1979 (Final)

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SPONSOR: The UpJohn Company, Acc. # 70501

RESULTS: The two above mentioned studies, 104-week rats and 104-week dogs, have been previously reviewed and found acceptable.

A discrepancy relating to the NOEL was solved as follows (from memo Frick to Fletcher, January 7, 1980).

Addendum as follows: "Upon the request of the reviewer the histological tissue preparations from the Botran studies were delivered to TE by the Woodard Research Corporation. This request was for the purpose of evaluating the significance of effect reported as 'slight' for the 100 ppm dogs and rats. It was the opinion of Drs. Davis and Gross (BSSE), veterinary pathologists, after examination of the tissue slides, that a diet level of 100 ppm in the dogs and rats was without effect."

On the basis of the above information, Toxicology Branch realizes that the problems in the original data package had been recognized and subsequently resolved. As a result of this information Toxicology Branch concurs with the 100 ppm NEL for setting the ADI for the pesticide chemical Botran. The gall bladder pathology is, in this case, of no concern (conversation Dr. Kasza 1/4/79). The information from FDA files has not been incorporated into the permanent Toxicology Branch files.

For future actions involving the use of Botran the following must be noted:

1. With the granting of PP #9E2268, 101.99% of the ADI of Botran has been utilized (see computer printout).

2. Only one species (2-year rat) has been tested for oncogenic potential.

3. No mutagenic studies have been submitted.

4. A second teratogenic study is lacking.

The two studies can be classified as "Core Minimum Data."

Dogs NOEL = 100 ppm

LEL = 3000 ppm

Rats NOEL = 100 ppm

LEL = 3000 ppm

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STUDY TITLE: Botran (U-2069): Effect of Oral Administration Final Report, Four Month Study

LABORATORY: The Upjohn Company

STUDY #: 543 and 544 DATE: December 23, 1963

SPONSOR: The Upjohn Company, Acc. # 70501

OBJECTIVE: "To see if Botran will induce any change in the hematopoietic system or has any effect on the blood platelet levels."

TEST MATERIAL: Botran (U-2069; 2,6-dichloro-4-nitroaniline

SPECIES: Rat SEX: Male and female AGE: Young

NUMBER OF SUBJECTS/DOSE LEVEL: 10 males and 10 females

DOSE LEVELS USED: Control 5, 20 and 100 mg/kg; (by intubation), 20 mg/kg (in diet). Untreated control.

DOSING METHOD: Intubation and incorporated in the diet.

DURATION OF THE TEST: 146 days - Carboxymethylcellulose and saline was used as vehicle for intubation

OBSERVATION

MORTALITY: Yes

SIGNS OF TOXICITY: Yes

BODY WEIGHT CHANGES: Yes

BEHAVIOR AND APPEARANCE: Yes

CLINICAL TESTING

HEMATOLOGY: Erythrocytes and leucocytes, hemoglobin

CLINICAL CHEMISTRY: Blood sugar

NECROPSY: In control and 100 mg/kg dose levels ORGANS: selected tissue (major organs)

HISTOLOGY: Yes, in major organs.

RESULTS

MORTALITY: None

Individual tissue studies are not reported.

SIGNS OF TOXICITY: None

BODY WEIGHT CHANGES: Normal

FOOD CONSUMPTION: Normal

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BEHAVIOR AND APPEARANCE: Normal

RESULTS OF CLINICAL TESTING

HEMATOLOGY: No indication of any effects in the blood-forming organs. RBC and WBC (normal platelet count). Histology study in organs showed no deleterious effects.

CLINICAL CHEMISTRY: Normal blood sugar values.

DISCUSSION OF THE METHOD OR PROCEDURE USED: Acceptable

NECROPSY: No significant gross changes

HISTOPATHOLOGY: No significant gross changes

CONCLUSION: The study is acceptable as an indication of the effects of Botran in the hematopoietic system

CLASSIFICATION: CORE Supplementary Data.

NOEL for hematopoietic activity = 100 ppm.

The specific organs were not mentioned, but they were examined by a pathologist, as per report.

PRIMARY DERMAL IRRITATION

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STUDY TITLE: Skin irritation in rabbits

LABORATORY: Upjohn Company

STUDY #: 4169RLJ-25-52 DATE: October 31, 1958

SPONSOR: The Upjohn Company, Acc. #70501

OBJECTIVE: Test for dermal irritation potential

TEST MATERIAL: U-2069 - Dry and as a 20% suspension in sodium chloride

SPECIES: Rabbits SEX: unknown AGE: unknown

NUMBER OF SUBJECTS: 2

DOSE: Liberal amounts

DOSING METHOD: Inunction

DURATION OF THE TEST: 4 days. Applied once a day to the clipped, abraded and intact skins of the rabbits. One week observation period.

RESULTS

IRRITATION INDEX: Mildly irritant to the abraded and intact areas

SIGNS OF TOXICITY: None reported

TOXICITY CATEGORY: N/A

CORE CLASSIFICATION: Supplementary Data

a) Unknown amounts of material used.
b) Not enough animals used.

DERMAL

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STUDY TITLE: Skin sensitization in guinea pigs

LABORATORY: Upjohn Company

STUDY #: 5567-64-RLJ-196B DATE: February 21, 1963

SPONSOR: The Upjohn Company, Acc. # 70501

OBJECTIVE: To evaluate the skin sensitization potential

TEST MATERIAL: U-2069 - Botran

SPECIES: Guinea Pigs SEX: male AGE: Not specified

NUMBER OF SUBJECTS: 10 males wt 300-500

DOSE: 0.1 ml of 1.0 mg U-2069 q.s. sodium chloride (0.1% suspension)

DOSING METHOD: 0.1% suspension. Amount of 0.10 ml intracutaneous injection every other day until a total of 10 had been made. First injection was of only 0.05 ml. The challenge injection of 0.05 ml was applied 2 weeks after.

RESULTS: The average sensitization result of the challenge injections was higher than the average of the induction injections. The product is a potential skin sensitizer.

TOXICITY CATEGORY: N/A

CORE CLASSIFICATION: Core Minimum

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SUBCHRONIC INHALATION

STUDY TITLE: Three week inhalation toxicity study of Botran in rats, rabbits, and dogs.

LABORATORY: The Upjohn Company, Acc. # 70501

REPORT #: 218-9610-80-004

STUDY #: 212-9610-69-MWG-15 DATE: May 28, 1969

SPONSOR: The Upjohn Company

OBJECTIVE: Evaluate toxicity through repeated exposure, via the respiratory system

TEST MATERIAL: U-2069 - Botran Technical grade

SPECIES: Rats, Dogs, Rabbits SEX: Rats male and female AGE: Not specified

NUMBER OF SUBJECTS: 10 male and 10 female rats; 2 dogs and 2 rabbits

DOSE: 2 ml/liter of air nominal concentration. Chamber capacity 322.9 liters.

DOSING METHOD: By gravity flow. Air exchange of 161.4 l/min.

DURATION OF THE TEST: 6 hrs day/5 days a week for 21 days exposure to dust aerosol.

OBSERVATION

MORTALITY: Yes

NOEL: Yes

SIGNS OF TOXICITY: Yes

BODY WEIGHT CHANGES: Yes

BEHAVIOR AND APPEARANCE: Yes

CLINICAL TESTING

HEMATOLOGY: In all animals

CLINICAL CHEMISTRY: In rabbits and dogs

NECROPSY: Yes ORGANS: Weight determined

HISTOLOGY: Yes

RESULTS: MORTALITY: 2 rats died after 3 days exposure; one rabbit after the 13th day

[redacted]

SIGNS OF TOXICITY: Not reported

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BODY WEIGHT CHANGES: Depressed

FOOD CONSUMPTION: Depressed

TOXICITY CATEGORY: N/A

CORE CLASSIFICATION: Core Minimum

BEHAVIOR AND APPEARANCE: Not reported

RESULTS OF THE CLINICAL TESTING

HEMATOLOGY: No consistent deviation observed, hemoconcentration in treated rabbits.

CLINICAL CHEMISTRY: Blood cholesterol significantly elevated in dogs and rabbits.

OTHER: Organ weights: Increment in weight in the liver as compared to controls.

DISCUSSION OF THE METHOD OR PROCEDURE USED:

Only 2 rabbits and 2 dogs were used in this test. One rabbit died.

Thus, the observation made in the only other rabbit cannot be considered as a typical results of the effects of the product.

NECROPSY: No significant changes

HISTOPATHOLOGY: No histopathological changes observed

CONCLUSION: The study gives an indication of the toxicity of the material. The material is toxic via respiratory system and induced hepatic toxicity.

Core Supplementary Data

STUDY TITLE: "Safety Evaluation by a Preliminary Dosage Range-finding Study in Dairy Cows for 5 Days"

LABORATORY: Woodward Research Corporation

STUDY #: None DATE: June 17, 1968

SPONSOR: The Upjohn Company, Acc. # 70501

OBJECTIVE: Toxicity potential of the material in cows

TEST MATERIAL: Botran Technical 99%

SPECIES: Cows SEX: females AGE: Young adults

NUMBER OF SUBJECTS: 3 for each dose level

DOSE LEVELS USED: 100 mg/kg (only one dose used)
50 mg/kg, 1 dose daily (total of 5) by balling gun in gelatin capsules.

DURATION OF THE TEST: 5 days for the 50 mg/kg

OBSERVATION

MORTALITY: Yes

SIGNS OF TOXICITY: Yes

BODY WEIGHT CHANGES: Yes

BEHAVIOR AND APPEARANCE: Yes

CLINICAL TESTING

HEMATOLOGY: In all animals

CLINICAL CHEMISTRY: Yes.

URINE ANALYSIS: Yes

OTHER: Milk production, heart rates, respiration rate, temperature

NECROPSY: Yes ORGANS: Yes

MORTALITY: The 3 cows at 100 mg/kg dose died within 48 hours.

SIGNS OF TOXICITY: Heavy mucoid vaginal secretion, free blood from rectum, depression, urination, and death at the 100 mg/kg dose. At 50 mg/kg dose level: restlessness, lacrimation, polyuria, tremors.

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BODY WEIGHT: Decreased for survivors

FOOD CONSUMPTION: Decreased

BEHAVIOR AND APPEARANCE: Aggressive and nervous behavior

RESULTS OF THE CLINICAL TESTING

HEMATOLOGY: At 100 mg/kg dose level, reduction in leucocytes.

CLINICAL CHEMISTRY: Marked reduction in blood glucose levels at 100 mg/kg. AT 50 mg/kg, 560T elevated.

URINE ANALYSIS: No unusual changes

DISCUSSION OF THE METHOD OR PROCEDURE USED: We do not have guidelines for this type of study, however it proves the toxicity of the material to cows.

NECROPSY: Hemorrhage in the intestines at 100 mg/kg dose level and antro lobular hepatic necrosis.

CONCLUSION: The product as tested was fatal at 100 mg/kg dose and induced toxic signs at 50 mg/kg with a revision after 6 days.

Classification: Core: Supplementary Data

STUDY TITLE: "Double Blind Botran 90-AA Study"

LABORATORY: By A. R. Stough, M.D.

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STUDY #: N/A DATE: 1962

SPONSOR: The Upjohn Company, Acc. # 7502

OBJECTIVE: To determine the effect of Botran on humans

TEST MATERIAL: Botran (U-2069)

SPECIES: Human SEX: "Male captives" AGE: Adults

NUMBER OF SUBJECTS/DOSE LEVEL: 20 and 10

DOSE LEVELS USED: 20 on Botran 10 mg/day, and 10 on Placebo

DOSING METHOD: By tablet

DURATION OF THE TEST: 90 days

OBSERVATIONS

BODY WEIGHT CHANGES: Yes

BEHAVIOR AND APPEARANCE: Yes

CLINICAL TESTING

HEMATOLOGY: Hgb. Hct. WBC as bone marrow.

CLINICAL CHEMISTRY: liver and kidney. S.G.O.T., ALK. PHS. B.S.P. retention and B.U.N.

URINE ANALYSIS: Yes

RESULTS

SIGNS OF TOXICITY: Only in a few subjects, and mild; dizziness, nausea, headache, sleepiness, insomnia and diarrhea (not chronic).

BODY WEIGHT CHANGES: Normal

FOOD CONSUMPTION: Increase in appetite

BEHAVIOR AND APPEARANCE: No major changes

RESULTS OF THE CLINICAL TESTING

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HEMATOLOGY: Normal

CLINICAL CHEMISTRY: Normal

URINE ANALYSIS: Normal

DISCUSSION OF THE METHOD OR PROCEDURE USED: Study conducted by medical doctors

CONCLUSION: The study indicates no or mild effects of Botran in humans while tested at 10 mg/kg/day - 90 days.

Classification: N/A or Supplementary Data

STUDY TITLE: "Medical Examination of a Man After Prolonged Exposure to 2,6-dichloro-4-nitroaniline"

DATE: February 7, 1963

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SPONSOR: By Bert W. Brooks, M.D.
The Upjohn Company
Director of Industrial Health Service

Subject: A man exposed to 2,6-dichloro-4-nitroaniline. The exposure was five times that of two other people doing similar work.

Exposure concentration: Range from 4% to 95% over a period of 3 years.

The subject was exposed to dust "about 6 days per year" with brief and frequent periods of inhalation exposure. The dermal contact was considerable.

Results: Dr. Brooks reported that the physical condition of the subject was found to be within normal limits.

The examination was performed on February 7, 1963 and the report includes a physical exam, chest X-ray, hematology, blood chemistry, urine analysis, and electrocardiogram.

STUDY TITLE: Excretion of Botran-C^{14} (2,6-dichloro-4-nitroaniline-4-C^{14}) by man.

DATE: August 26, 1964

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SPONSOR: The Upjohn Company, Acc. #70502

Subject: Oral Administration of Botran-C^{14} and excretion in man.

Procedure: 3 adult male human subjects received 50 mg of Botran containing 50 u.c. of Botran-C^{14} (2,6-dichloro-4-nitroaniline-4-C^{14}) in the form of dry crystals in a gelatin capsule. Urine and feces were collected and analyzed.

Results: Urine: mean excretion after 7 days - 75.2% (72.3 to 79.3)

Fecal: 31.6% (23.6 to 35.6)

Mean Total recovery 106.7% (102.9 to 109.5)

Discussion: Botran was excreted with a recovery of 107% of "Theory."

Botran is absorbed from the gastrointestinal tract but it will not accumulate in the body tissue.

NOTE: Refer to Chemistry Branch for further evaluation of methods used.

Supplementary Data

STUDY TITLE: U-2069. Effect on Reproductive Capacity Through Three Generations in the Rat

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LABORATORY: Woodard Research Corporation, Acc. # 70502

STUDY #: None DATE: December 21, 1964

SPONSOR: The Upjohn Company

OBJECTIVE: To evaluate the effect of the fungicide, U-2069 (Botran) on mammalian reproduction.

TEST MATERIAL: 2,6-dichloro-4-nitroaniline. Lot #13964

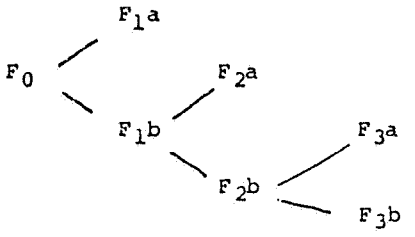
SPECIES: Rat SEX: Male and female AGE: Adult

NUMBER OF SUBJECTS/DOSE LEVEL: 20 males and 20 females

DOSE LEVELS USED: Control and 100 ppm

DOSING METHOD: Material incorporated in the diet.

DURATION OF THE TEST: 3 generations as follows:



F_0 generation: 2 groups; I, Control, 20 males and 20 females; II, 100 ppm, 20 males and 20 females, feeding continued until sacrifice of F_0 generation and weaning of the F_1b generation at about 100 days of age (75 days of feeding the material). Males and females of each group were paired for mating.

Observations performed

Birth date, number of live and stillbirths, mean weight at birth, general conditions of mothers and newborn; bone structure, head shape and appendages of the pups.

At weaning; the date, the number of survivors, body weights and physical conditions were recorded. The mating of each generation (as per diagram) was selected so that each litter was nearly equally represented. The selected weanlings were grouped, numbered and fed with 100 ppm of the material in their diet one week after weaning. Thus, the 3 generations, from the F_0 to the F_3a and F_3b, were selected, examined at birth and treated following similar procedures.

Results

The number of litters per group, total number of stillbirths, live births and the reproductive capabilities of the rats fed U-2069 in the diet were comparable to those of the control rats.

Slight differences were observed with respect to stillbirth, percent of survival, and mean body weight at weaning. This difference did not indicate a compound dependence. The means figures were comparable.

Summary and Conclusions

Feeding of 100 ppm of U-2069, in the diet, to rats, for 75 days, mating them, observing the young and saving 20 males and 20 females to continue the study for 3 generations, following the same routine as the first generation, did not produce impairment of reproductive functions in the animals. The young showed no abnormalities.

Core Classification: Core minimum data

STUDY TITLE: Metabolism of Botran by the Rat

LABORATORY: The Upjohn Company

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STUDY #: 26 DATE: September 23, 1963

SPONSOR: The Upjohn Company, Acc. # 70502

OBJECTIVE: To study the absorption, distribution, metabolic fate and excretion of the product.

TEST MATERIAL: Botran (Botran-4-C^{14})

SPECIES: Rat SEX: Male AGE: Adult

NUMBER OF SUBJECTS/DOSE LEVEL: 3 at 1.7 mg/kg; 3 at 8 mg/kg and 18 at 8 mg/kg

DOSING METHOD: Orally by intubation, one dose, C^{14}

DURATION OF THE TEST: 14 days

PROCEDURE: The animals were fasted for 16 hours prior to dosing, then were dosed and urine and feces collected (metabolic cages) for 24 hours and analyzed for radioactivity. Tissue was collected and analyzed for radioactivity content.

OBSERVATION

URINE ANALYSIS: Collected for liquid scintillation analysis.

OTHER: Feces collected for analysis to measure the amount of Botran-radioactive excretion.

NECROPSY: Tissue collected and weighed. ORGANS: Most organs and tissues collected and examined for measurable amounts of radioactivity.

RESULTS

MORTALITY: None

SIGNS OF TOXICITY: No

BODY WEIGHT CHANGES: None

FOOD CONSUMPTION: Normal

Botran U-C^{14} fed 1.7 mg/kg dose level was absorbed and metabolized. The recovery was 78% in one day and 82% in two weeks. Urinary excretion was 91% and fecal 9%.

When Botran was fed at 8 mg/kg dosed level the recovery was 90% in 24 hours (87% urine, 11% feces).

Botran was not stored in body tissues.

CLASSIFICATION: CORE: N/A

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STUDY TITLE: Somers test in the Albino Rabbit

LABORATORY: International Research and Development Corporation

STUDY #: 100-037 DATE: February 10, 1966

SPONSOR: The Upjohn Company

OBJECTIVE: The Somers test appears to be a test for teratology.

TEST MATERIAL: 2,6 Dichloro 4-Nitroaniline (Botran, lot #13,964)

SPECIES: Rabbit SEX: Females AGE: Adult

NUMBER OF SUBJECTS/DOSE LEVEL: 37

DOSING LEVELS USED: Control, 100 and 1000 ppm

DOSING METHOD: Incorporated in the diet

DURATION OF THE TEST: Dosing from the 8th to the 16th day of pregnancy

PROCEDURE: The female rabbits were mated during estrus. The day of mating was considered the first day of gestation. Pregnant females and the pups were sacrificed on the 21st day of weaning. Non-pregnant animals were sacrificed for examination of the uterus.

OBSERVATION

MORTALITY: Yes

NOEL: Yes

SIGNS OF TOXICITY: For abnormalities and teratogenesis

BODY WEIGHT CHANGES: At weekly intervals, parental females were observed for fertility, fetal resorption, abortion, delivery, length of gestation period, and lactation performance.

Newborn observations: Live births, size of litters, sex ratio, viability, survival, growth, weight at 21 days and congenital external and internal abnormalities using alazarin red staining of the skeleton.

NECROPSY: At termination of the nursing period. ORGANS: Yes

RESULTS

MORTALITY: No mortality - mothers. Pups' mortality was due to other unrelated causes.

SIGNS OF TOXICITY: None reported

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BODY WEIGHT CHANGES: Comparable to controls

FOOD CONSUMPTION: Comparable to controls

BEHAVIOR AND APPEARANCE: Normal observations for the mothers. Breeding cycle, litter size, sex ratio viability, growth and weight of pups were similar to the values for the control animals.

DISCUSSION OF THE METHOD OR PROCEDURE USED: Acceptable

NECROPSY: No gross pathology attributable to administration of Botran was observed.

PATHOLOGY: No gross morphological anomalies in offsprings of control and treated animals were observed.

CONCLUSION: No compound or dosage anomalies were detected in mothers or offspring dosed at 100 and 1000 ppm of Botran.

CLASSIFICATION: CORE: Minimum

NOTE: The investigator did not state if the NOEL was 100 or 1000 ppm.

The NOEL is = 1000ppm.

STUDY TITLE: Tissue Distribution of [^{14}C]-Dicloran in Rats, Dogs and Pigs Following Repeated Oral Dosing at 100 mg/kg/day. 002624

LABORATORY: Boots Pure Drug Company, Ltd.

STUDY #: NONE DATE: July 27, 1977

SPONSOR: The Upjohn Company

PURPOSE: To measure the distribution of radiolabeled residues in the tissue following a short repeated dose with [^{14}C]-dicloran in rats, dogs and pigs. In other studies, dogs developed eye lesions in the cornea and lens after administration of the product at dose levels between 25 and 50 mg/kg per day.

This study has the purpose of proving that the oculotoxicity of dicloran is specie specific or confined to the dog only.

PROCEDURE: Rats, dogs, and pigs were dosed with [^{14}C]-dicloran for five days, housed in metabolism cages, and sacrificed 24 hours after the administration of the final dose.

SUBJECT	DOSE mg/kg/day	DAYS	VIA	SAMPLES COLLECTED	TISSUE
Rats	100	5	Oral intubation	Urine Feces	Major for* radioassay
Dogs 2 pairs	100	5	Capsules	Urine Feces Blood from one pair at 45 minutes and at 1-1/2, 3, 6, and 24 hours, and at 24 hours after other doses.	Major for* radioassay
Pigs 4 females	100	5	Capsules	Urine Feces Blood at 1, 3, 6, and 24 hours, and at 24 hours after other doses.	Major for* radioassay

* Emphasis on eye tissue.

Eyes, liver, kidney, lungs, gonads, small and large intestine, fat, muscle, brain, skin, adrenal, thyroid, plasma, heart, etc.

RESULTS: Accumulation of material in tissue.

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Subject	Organs With Highest Residue ppm	Eye ppm	Highest Plasma ppm
Rats	Liver 10.1 and 9.2	0.1 (male) 0.2 (female) whole eye	1.1 (male) 1.6 (female)
Dogs	Liver 43.7 (male) 31.0 (female)	Iris Retina Choroid 100.9 and 89.7 (male) and 121.8 and 63.5 (female)	16.3 (male) 16.9 (Female)
Pig	Liver 24.3	Iris 27.6 Retina Choroid 59.8	12.2

The accumulation in tissue in dogs and pigs was higher than the one in the rats. This study is classified as supplementary data.

Dosing schedule may not have been long enough. Too few animals per group were used.

STUDY TITLE: "Tissue Residues and Safety Evaluation in Calves Fed This Material in the Diet for 28 to 30 Days"

LABORATORY: Woodard Research Corporation

STUDY #: DATE: June 29, 1968

SPONSOR: The Upjohn Company

TEST MATERIAL: Botran Technical 99% Lot #4575

PROCEDURE: 9 calves were divided into 3 groups of 3 calves per group and fed the material, incorporated into the daily diet at dose levels of 0 (control), 80 and 20 ppm for 28 or 30 days.

WEIGHT: At 0, 14, and 28 days.

OBSERVATIONS: Daily for physical condition, food consumption, urinary excretion, and stool consistency.

PHYSICAL EXAMINATION: Eye, heart, and respiration rate, temperature, conditions of observable mucous membranes, skin, hair, coat, and locomotor activity. Hematology, blood chemistries, and urinalysis were performed initially and on the 28th day.

NECROPSY: After 28 or 30 days the animals were sacrificed and necropsied. The organs were weighed and representative samples were sent to the Upjohn Company.

RESULTS: During the study, all the physiological parameters were observed as being normal. Behavior and appearance appeared to be normal. Hematology, blood chemistry, and urinalysis results were normal. The tissue and organs examination at necropsy appeared normal. No histopathological changes were observed.

CONCLUSIONS: Feeding to calves 20 and 80 ppm of Botran for $\pm$ 30 days did not induce deleterious observable effects.

CORE CLASSIFICATION: Supplementary data

a) Not enough time in study. Only 30 days, not enough time to evaluate the effects.

b) The method of sacrifice is not standard.

Shot in the head: The product produced lesions in the eyes of dogs in a previous study; thus the eyes of the calves should have been analyzed for accumulation of the material in the eyes and effects on the cornea and the choroid as in the study with other species, mainly the dog.

Mutagenicity Testing in Bacteria *in vitro* Systems

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The information submitted does not qualify as protocol. There is not sufficient evidence as to where the study was conducted; the date and other pertinent information have not been submitted. Although the result of the study showed that the product is not mutagenic, the information can be used only as supplementary data.

Salmonella/Microsome Test
Bacterial Mutagenicity

Incomplete information submitted.

Not acceptable

HED/TOX:ARCE/CARLETTA:DCR-07874:RAVEN-479-2013:FILE-0650B:04/12/82

REVISED:Alex Arce:DCR-26424:WANG-0650B:ert:Raven:479-2013:11/21/82

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Nov 24-82

Tox Chem No. 311 Botran File Last Updated Current Date

Study/Lab/Study/Date	Material	EPA Accession No.	LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Studies done by Agricultural Research and Development Labs Eye Irritation- rabbit # 218-9610-80-001 Feb 28, 1980	Tech	070501	Conjunctivitis Score 3.3	III	Guidelines
#218-9610-80-002 2-28, 1980	Tech	070501	Erythema on abraded area.	IV	Guidelines
Acute dermal LD50 #218-9610-1-TJR 79-466 2-29, 1980	Tech	070501	LD50 >2.0 g/kg negative for irritation	III	Minimum
2-year chronic rat Woxlard Research Corporation 12-7-29	U2069	70501	Rats NOEL = 100 ppm Next Highest dose level was 3000 ppm LEL = 3000 ppm?		Guidelines

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2-year chronic dog Woodard Research Corporation 12-7-29	U2069	70501	Dog NOEL = 100 ppm NOEL = LEL = 3000 ppm (Highest dose)		Guidelines
4-month-rat The Upjohn Co. #543-544 Dec. 23, 1963	U2069	70501	NOEL for hematopoietic activity = 100 ppm highest dose tested		Supplementary
Skin irritation rabbit Upjohn Company Oct. 31, 1958	U2069 Dry and as 20%	Acc. 70501	Mild irritant	N/A	Supplementary
Skin sensitization Guinea pigs Upjohn Company Feb. 21, 1983	U2069 Tech	"	Potential sensitizer	N/A	Minimum

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Three week inhalation Rats, dog, rabbits	Tech	"	At 2 ml/liter of air Elevated cholesterol levels Increment in liver wieght LC50 - not established		Supplementary Data
Dose range finding 5 days Cows	Tech	"	At 100 mg/kg, 1 dose fatal to the 3 cows treated, liver necropsies at the 50 mg/kg - Elevated SGOT Polyuria, Tremors, no deaths	N/A	Supplementary
Effects of Botran on humans Double blind Botran 90-AA study-man 1972	W2069	70502	At 10 mg/kg dose for 90 day, 20 humans-mild temporary effects.	N/A	Supplementary
Medical Examination to a man after exposure Feb. 7, 1967	Botran	70502	At exposure range of 4 to 95% over 3 years Reported normal	N/A	Supplementary

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Metabolism Excretion of Botran - C^{14}-man Upjohn Aug. 26, 1964	C^{11}-Botran	70502	106.7% excretion	N/A	Supplementary
3 generation reproduction - rat, Woodard Dec. 21, 1964	U2069	70502	NOEL = 100 ppm Highest dose	N/A	Minimum
Metabolism of Botran by the rat Upjohn-Sept. 23, 1963	C^{14} Botran	70502	Dose of 8 mg/kg was recovered 87% urine 11% feces	N/A	N/A
Teratology	Tech	70502	NOEL = 1000ppm		
Somers test-rabbit International Research and Development Corp. #100-037 Feb. 10, 1966			Negative for Teratogenicity fetal toxicity or maternal toxicity	N/A	Minimum

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Tissue Distribution Rats, dog-pig. Boots Pure Drug Co. July 27, 1977	C^{14} Botran	70502	Highest accumulation in the liver. Eyes of dogs high accumulation		N/A
28-day Tissue residue calves Woodard Research June 29, 1968	Tech	70502	No deleterious effects		Supplementary

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