July 92 Update
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

009075

JAN 29 1992

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Iprodione - 21-Day Dermal Toxicity Study in Rabbits

TO: Kathryn Davis/Barbara Briscoe PM 51
SRRD (H7508W)

FROM: K. Clark Swentzel 1/29/92
Section Head, Section 2
Toxicology Branch II
HED (H7509C)

THROUGH: Marcia van Gemert, Ph.D. m van Gemert 1/29/92
Branch Chief
Toxicology Branch II
HED (H7509C)

ID NO.	109801-000264
CASE	816345
BARCODE:	D170595
MRID	420232-01
PROJECT NO.	2-0388
CASWELL NO.	470A
REGISTRANT:	Rhone-Poulenc Co.

Requested Action

Review reregistration data

Conclusion

Iprodione was evaluated in a 21-day dermal toxicity study in rabbits at dosages of 0, 100, 500 and 1000 mg/kg/day.

There were no mortalities or clinical signs of toxicity during the study. No adverse effects were apparent based on body weight, body weight gain, food consumption, clinical pathology parameters or organ weights. Histopathologic evaluations of the kidneys and liver from high-dose rabbits did not reveal any treatment-related effects.

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The LOEL for systemic toxicity was > 1000 mg/kg/day (highest dose tested) and the NOEL was 1000 mg/kg/day under the conditions of this study.

Stability data for the test material under the conditions of this study, which was tested only a few weeks before the expiration date, were not provided in the report, therefore, the study is currently unacceptable. This study may be upgraded pending the review of acceptable stability data.

Core classification: supplementary. This study currently does not satisfy guideline requirements for a 21-day dermal toxicity (82-2).

K. Clark Swentzel 1/29/92

Reviewed by: K. Clark Swentzel
Tox. Branch II, Section II (H7509C)
Secondary Reviewer
Marcia van Gemert, Ph.D. M van Gemert 1/29/92
Tox. Branch II (H7509C)

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DATA EVALUATION REPORT

STUDY TYPE: 21-Day Dermal Toxicity in Rabbits Tox. Chem. No. 470A

MRID NO. 420232-01

TEST MATERIAL: 3-(3,5-dichlorophenyl)-N-isopropyl-2,4-dioxoimidazolodine-1-carboxamide

SYNONYMS: Iprodione

STUDY NO. 3147.101

SPONSOR: Rhone Poulenc Ag Co.

TESTING FACILITY: Springborn Laboratories Inc.

TITLE OF REPORT: 21-Day Dermal Toxicity Study in Rabbits with Iprodione Technical

AUTHOR: Joseph Siglin

REPORT ISSUED: August 29, 1991

COMPLIANCE STATEMENTS: Signed and dated Quality Assurance and GLP Compliance Statements were included on pages 4 and 3 of the report, respectively.

CONCLUSIONS

Iprodione was evaluated in a 21-day dermal toxicity study in rabbits at dosages of 0, 100, 500 and 1000 mg/kg/day.

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TEST MATERIAL

Description:

Iprodione technical (96.2%, w/w), described as an off-white granular solid. Lot No. 89062 01.

Stability:

No information provided in the report.

Preparation for administration:

The test material was ground to a fine powder with a mortar and pestle. The ground material was moistened with water before administration.

TEST ANIMALS

Housing and acclimation:

Male and female New Zealand white rabbits from Hazleton Research Products, Denver, PA. Each animal was identified with numbered ear tag. Body weights were 2.2-2.9 kg at the initiation of the study.The animals were housed individually during acclimation as well as the study in stainless steel cages. The rabbits were acclimated to the laboratory environment for 9 days prior to study initiation. The rabbits were also acclimated to Elizabethan collars during the final 7 days of the acclimation period.

Diet and drinking water:

Purina Certified Rabbit Chow #5322 and municipal tap water were provided to each animal ad libitum.

Environmental conditions:

The rabbits were housed in a room with a 12-hour light cycle, a temperature of 61-70°F and a relative humidity of 40-60%.

EXPERIMENTAL PROCEDURES

Randomization and group assignment:

Five animals per sex were randomly assigned to each of the following groups: sham-treated control, 100, 500 or 1000 mg/kg/day.

Treatment:

The fur was clipped from the dorsal trunk area ("10% of the total body surface area") of each rabbit on the day preceding the first dose. The exposure sites were kept free of fur throughout the

study.

A 4 x 8 inch 8-ply gauze dressing was taped onto a layer of 4-inch wide Coban self-adherent wrap. Ten ml of sterile water, USP, was applied to saturate the gauze dressing on which the test material was subsequently spread. After applying the treated gauze, the Coban was wrapped around the torso and secured in place with athletic tape. A plastic Elizabethan collar was then fitted on the rabbit. Control animals were wrapped in a similar manner, but received water-saturated gauze only.

The animals received 21 consecutive daily doses for 6 hours/day. After each daily exposure period, the wraps and collars were removed and any residual test material was wiped from the skin with gauze pads moistened with sterile water. Dosages were adjusted according to weekly body weight data.

Clinical observations:

The rabbits were observed at least once daily for outward signs of toxicity while mortality checks were made twice daily.

Dermal observations:

The application site on each animal was examined daily prior to dosing as well as on the day of sacrifice for signs of erythema, edema, desquamation and other adverse skin reactions.

Body weight and food consumption:

Individual body weights were measured weekly and food consumption was measured daily. Terminal body weight was determined on the day of scheduled sacrifice for calculation of organ-to-body weight ratios.

Clinical pathology:

Blood was collected from each rabbit once during the pretest period (day -7) and on the day of scheduled sacrifice (day 22) for evaluation of selected hematology and clinical chemistry parameters. The animals were fasted overnight prior to blood sample collection. Blood samples were obtained via the marginal ear vein. The following parameters were evaluated:

Hematology

Erythrocyte count	Hematocrit
Hemoglobin concentration	Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)	Mean corpuscular hemoglobin concentration (MCHC)
Platelet count	Reticulocyte count
Total and differential leukocyte counts	

Clinical chemistry

Albumin	Albumin/globulin ratio
Alkaline phosphatase	Blood creatinine
Calcium	Chloride
Cholesterol	Fasting glucose
Globulin (calculated)	Phosphorous
Potassium	Serum glutamic-oxaloacetic transaminase (aspartate aminotransferase) (AST)
Sodium	Serum glutamic-pyruvic transaminase (alanine aminotransferase) (ALT)
Total bilirubin	Total serum protein
Triglycerides	Urea nitrogen

Necropsy:

A gross necropsy on day 22 included the following: all orifices, carcass, cervical tissues and organs, cranial cavity, external and cut surface of the brain and spinal cord, external surface, nasal cavity and paranasal sinuses and thoracic, abdominal and pelvic cavities and their viscera.

Organ weights were obtained for the brain, kidneys, liver with drained gallbladder, thyroid (including parathyroid), testes with epididymides and ovaries of all animals; paired organs were weighed together.

The following organs and tissues from each animal were preserved in 10% neutral buffered formalin: gross lesions, kidneys, liver, treated skin (mid-back) and untreated skin (hip area).

Histopathology:

The liver and kidneys from control and high-dose animals and the treated skin, untreated skin and gross lesions from rabbits in all groups were examined microscopically.

Statistical analysis:

Continuous data such as body weight, weight gain, food consumption and organ weight data were analyzed by One-Way Analysis of Variance (ANOVA). When significance was observed with ANOVA, control to treatment group comparisons were performed using Dunnett's Test. The tests were two-tailed.

RESULTS

Mortality:

There were no unscheduled deaths in the study.

Clinical observations:

The investigator indicated that no clinical signs of toxicity were noted in the treated rabbits and that findings were limited to occasional observations of abnormal excreta (mucoid and/or soft stools).

Dermal observations:

Slight desquamation of the dorsal surface was observed in two 500 mg/kg/day females, one 1000 mg/kg/day female and three 1000 mg/kg/day males. Also, slight desquamation of the later surface was seen in one 500 and one 1000 mg/kg/day female. These effects were transient, typically occurring within the first two weeks, and all treatment sites appeared to be normal at termination. No signs of dermal irritation were observed in 100 and 500 mg/kg/day males or 100 mg/kg/day females.

Body weight gain:

Body weight gain was lowest among high-dose males and highest among high-dose females relative to other groups of the same sex. No differences in body weight gain were statistically significant; none appeared to be treatment-related.

Food consumption:

No treatment-related differences in food consumption were evident.

Clinical pathology:

Hematology:

Differences in hematology values were sporadic, of low magnitude, not dose-related and apparently untreated to treatment. Statistically significant different values at day 22 included increased reticulocytes and decreased basophils in 100 and 1000 mg/kg/day males, decreased MCHC in 1000 mg/kg/day males and decreased lymphocytes in 500 mg/kg/day females.

Clinical chemistry:

Statistically significant differences in day 22 clinical chemistry data included decreased sodium in 500 mg/kg/day females, increased cholesterol in 500 and 1000 mg/kg/day females and increased globulin and total bilirubin in 1000 mg/kg/day females. Although statistically significant, all of these values, with the exception of globulin in high-dose females, were comparable to pre-test values. There were no histopathologic observations related to any of these changes, therefore, they are not considered to be related to treatment.

Gross necropsy:

Gross observations at necropsy consisted of subcutaneous edema in one 1000 mg/kg/day male, reddened thyroid/parathyroid in one 100 mg/kg/day female and two 500 mg/kg/day females and enlarged cervical lymph node in one 1000 mg/kg/day female.

Organ weights:

Neither the absolute nor relative organ weight data showed a treatment-related effect.

Histopathology:

The only noteworthy microscopic effects were observed in the skin. These effects, seen predominantly in high-dose animals, were moderate degeneration in 1 male, minimal acute dermatitis in 1 male, edema in 2 males (1 mild and 1 moderate) and myositis in 1 male. The only other effect seen in skin was mild edema in 1 low-dose female.

DISCUSSION AND CONCLUSION

Iprodione was evaluated in a 21-day dermal toxicity study in rabbits at dosages of 0, 100, 500 and 1000 mg/kg/day.

There were no mortalities or clinical signs of toxicity during the study. No adverse effects were apparent based on body weight, body weight gain, food consumption, clinical pathology parameters or organ weights. Histopathologic evaluations of the kidneys and liver from high-dose rabbits did not reveal any treatment-related effects.

Slight effects in treated skin, predominantly in a small number of high-dose animals, included transient desquamation, moderate degeneration, minimal acute dermatitis, edema (mild to moderate) and myositis.

The treated skin areas were less than 10% (approximately 3, 5 and 7% for the low-, mid- and high-doses, respectively), however, the study will not be rejected on this basis since the limit dose was administered over an area which approximated 7% of the total surface area.

The LOEL for systemic toxicity was > 1000 mg/kg/day (highest dose tested) and the NOEL was 1000 mg/kg/day under the conditions of this study.

Stability data for the test material under the conditions of this study, which was tested only a few weeks before the expiration date, were not provided in the report, therefore, the study is currently unacceptable. This study may be upgraded pending the review of acceptable stability data.

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