



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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MEMORANDUM:

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA ID Number: 061601; EPA Registration No. 239-2460
Paraquat: Evaluation of 21-Day Dermal Toxicity Study
in Albino Rabbits.

Accession No. 260988
Record No. 166482

Tox. Chem. No. 634
Project No. 1155

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1-30-86

TO: Walter Waldrop
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THRU: Edwin R. Budd, Section Head
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Ed R. Budd
1/31/86
1/11/86
1/13/86

Toxicology Branch/HED has completed an evaluation of the following study:

1. Twenty-One Day Dermal Toxicity Study in Albino Rabbits with Paraquat Technical [SX-1465].
Hazleton Laboratories America, Inc.;
Report No. 2107-132; January 21, 1986

This study was performed to fulfill the May 3, 1985 Data Call-In requirement in support of registration for Ortho Paraquat Concentrate 3 (EPA Reg. No. 239-2460). Pursuant to an agreement with the EPA (December 3, 1985) that the results of the study be made available prior to the Agency's final toxicology reviews for the Paraquat Registration Standard, the Registrant submitted an "Unaudited Draft Report" and an "Unaudited Draft Final Report" (ref. Memoranda - John Whalan, 11-22-85 and 1-15-86). Due to the numerous reporting deficiencies, these reports were classified as Core Supplementary.

The Final Report with Quality Assurance Review was received as promised in late January, 1986. Based on the Final Report, this study was classified as Core Minimum.

There were few indications of compound-related toxicity at the doses tested. The NOEL was defined as 1.15 mg cation/kg/day. The LEL was defined as 2.60 mg cation/kg/day at which dose there

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was dosing site scabbing, chronic active inflammation, erosion/ulceration, surface exudate, and acanthosis. At the 6.00 mg cation/kg/day dose, there was slight to well-defined erythema and scabbing which began on day 11 and worsening during the study.

cc Robert J. Taylor
Registration Division (TS-767c)

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Study Type: Subacute Dermal Toxicity

Study Title: Twenty-One Day Dermal Toxicity Study in Albino Rabbits with Paraquat Technical [SX-1465];
Report No. 2107-132

Accession No.: 260988

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Sponsor: Chevron Chemical Company
Richmond, California

Testing Laboratory: Hazleton Laboratories America, Inc.,
Vienna, Virginia

Test Material: Paraquat Technical, 43.5% (Lot/Batch No. SX-1465)

Date of Final Report: January 21, 1986

PROTOCOL:

Randomized groups of six male (1918-2383 g) and six female (1881-2318 g) New Zealand White rabbits (8-10 weeks of age) were dermally dosed with Paraquat (43% pure) for 6 hours/day over 21 consecutive days at cation dose levels of 0 (vehicle control), 0.50, 1.15, 2.60, and 6.00 mg/kg/day (Paraquat technical doses of 0, 1.5, 3.4, 7.8, and 17.9 mg/kg). The test formulations were prepared weekly by dissolving the test article in distilled water. Samples of each dose formulation were retained, but there was no mention in the report of dose concentration analyses.

The rabbits were dosed on the shaved dorsal skin of their trunks with a dose volume of 1.0 ml/kg. The dosing sites were occluded with rubber damming, cloth wrapping, and tape. The rabbits also wore plastic collars to prevent ingesting the doses. After each six hour exposure period, the wrappings were removed and the dosing sites cleaned with wet paper towels.

The rabbits were observed twice daily for clinical signs, and weekly for food consumption. Dermal irritation was graded by the method of Draize prior to dosing on days 1, 2, 4, 8, 11, 15, 18, and 21. Body weights were measured on days -7, -4, 1, 4, 8, 11, 15, 18, and terminally. Food and water were available ad libitum. Clinical pathology studies were performed by drawing blood samples from the medial ear arteries prior to dosing (days -5 and -6) and from the abdominal aorta at study termination (day 22). The following parameters were measured:

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Hematology

Erythrocytes
Reticulocytes
Hemoglobin
Hematocrit

Total leukocytes
*Differential leukocytes.
Platelets

Clinical Chemistry

Bilirubin, total
Bilirubin, direct
BUN
Creatinine
BUN/Creatinine ratio
Total protein
Albumin
Globulin
Glucose
AST
ALT

Total cholesterol
Alkaline phosphatase
Creatinine phosphokinase
LDH
Triglycerides
Uric acid
Sodium
Potassium
*Chloride
Calcium
Phosphorus

At the termination of the study, all rabbits were necropsied, and urine was collected from their bladders but was not evaluated. They were examined grossly, and the following tissues were examined histopathologically (weights were measured for asterisked organs):

*Brain (with brainstem)	*Kidneys
*Adrenals	*Testes
*Lungs	*Ovaries
Heart	Treated skin
Spleen	Untreated skin
*Liver (with gallbladder)	Gross lesions

RESULTS:

Rabbits dosed with <1.15 mg cation/kg/day of the test article were free of dermal irritation. There were no findings of erythema or edema in any rabbits at the 2.60 mg cation/kg/day dose, but scabbing was seen in two males (days 18 and 21) and 1 female (days 15, 18, and 21). All rabbits dosed with 6.00 mg cation/kg/day had very slight to well-defined erythema and scabbing which began on day 11 and worsened during the study.

No clinical signs of toxicity were reported during the course of the study at any dose. Body weights and food consumption were similar for all groups throughout the study. There were no compound-related clinical pathology anomalies for any group. The only dose-related gross lesions were skin lesions at the treated skin sites. These included scabs at the 2.60 and 6.00 mg cation/kg/day dose, and redness, thickening and prominent subcutaneous vessels at the 6.00 mg cation/kg/day dose. The gross findings in these groups were confirmed by histopatho-

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logic lesions in treated skin. These lesions included minimal to moderately severe chronic active inflammation, slight to severe erosion/ulceration, slight to severe surface exudate, minimal to moderately severe acanthosis, and minimal to moderately severe hyperkeratosis (high-dose females only). No dose-related lesions were found in any other tissues examined.

Absolute and relative organ weights were similar for all groups, except for testicle weights which were reduced 18% for absolute weights and 17% to 22% for testes to body weight and testes to brain weight ratios in the 6.00 mg cation/kg/day group. This finding is probably not biologically significant, given the small group sizes, variability within the groups, and the lack of corroborating histopathologic lesions. The principle target organ for paraquat is the lungs, yet no lung lesions were found in this study.

Defined doses:

NOEL = 1.15 mg cation/kg/day

LEL = 2.60 mg cation/kg/day (dosing site scabbing, chronic active inflammation, erosion/ulceration, surface exudate, and acanthosis).

Core Classification: MINIMUM. Although samples of all dose formulations were taken, no dose concentration analyses were performed.