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1-15-86

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

004886

MEMORANDUM:

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA ID Number: 061601; EPA Registration No. 239-2186
Paraquat: Evaluation of 21-Day Dermal Toxicity Study in Albino Rabbits.

Accession No. 260635
Record No. 164396

Tox. Chem. No. 634
Project No. 1056

FROM: John E. Whalan, Toxicologist
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1-10-86

TO: Walter Waldrop
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THRU: Edwin R. Budd, Section Head
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Budd 1/15/86
1/15/86

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; December 16, 1985

The submitted report is an "Unaudited Draft Final Report." It was submitted pursuant to an agreement with the EPA (December 3, 1985) that it be made available prior to the Agency's final toxicology reviews for the Paraquat Registration Standard. The final report with Quality Assurance Review is expected to be available in late January, 1986. Based on the unaudited draft final report, this study was classified as Core Supplementary.

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 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.

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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

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Sponsor: Chevron Chemical Company
Richmond, California

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

Test Material: Paraquat Technical (Lot/Batch No. SX-1465)
[NOT OTHERWISE SPECIFIED]

Date of Final Report: December 16, 1985

PROTOCOL:

Randomized groups of six male (1918-2383 g) and six female (1881-2318 g) New Zealand White rabbits were dermally dosed with Paraquat 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 formulation was 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:

2

2

Hematology

Erythrocytes	Total leukocytes
Reticulocytes	Differential leukocytes.
Hemoglobin	Platelets
Hematocrit	

Clinical Chemistry

Bilirubin, total	Total cholesterol
Bilirubin, direct	Alkaline phosphatase
BUN	Creatinine phosphokinase
Creatinine	LDH
BUN/Creatinine ratio	Triglycerides
Total protein	Uric acid
Albumin	Sodium
Globulin	Potassium
Glucose	Chloride
AST	Calcium
ALT	Phosphorus

At the termination of the study, all rabbits were necropsied, and urine was collected from their bladders but was not evaluated. 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:

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 histopathologic lesions in treated skin. These lesions included minimal to moderately severe chronic active inflammation, slight to

3

severe erosion/ulceration, slight to severe surface exudate, minimal to moderately severe acanthosis, and minimal to moderately severe hyperkeratosis (high-dose females only).

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.

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: SUPPLEMENTARY. The age of the rabbits, and the purity of the test article were not reported. The severities of the histopathologic lesions were not given in the summary table. This made interpretation of the data difficult, since severities were only presented in the individual animal data sheets. Histopathologic lesions were scored on the basis of five degrees of severity; this was not explained in the report. The core classification for this study can be upgraded once these deficiencies have been addressed, and the final report is signed by the principle scientists and reviewed for GLP compliance. Any changes from the "Unaudited Draft Final Report" must be itemized in a letter to the EPA if the core classification is to be changed.

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

4