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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: January 29, 1982

SUBJECT: Review of a Four-Week Study of Naled in Rats. Action No. 239-1633. EPA Accession No. 246496. Caswell No. 586.

FROM: Roger Gardner, Toxicologist
Toxicology Branch, HED (TS-769) *Roger Gardner CFC*

TO: William H. Miller, Product Manager (16)
Registration Division (TS-767) *W.H.M.*

THRU: Christine F. Chaisson, Section Head
Review Section IV
Toxicology Branch, HED (TS-769)

Action Requested

Review of a four-week oral toxicity study of naled in rats.

Background

Naled (Dibrom R; 1,2-dibromo-2,2-dichloroethyl dimethyl phosphate) is an organophosphate insecticide which is manufactured by Chevron Chemical (Canada) Limited. The study was submitted by Chevron to replace an Industrial Bio-Test study. The stated objective of the study is to establish dosages to be administered in a two-year oral (gavage) study in rats.

Review

Citation: Lough, R. L., P. Batham, C. Bier, B. Legg, P. Arango, J. W. Hooper, B. Broxup, B. E. Osborne, and B. G. Procter. 1981. DIBROM R: Four week subchronic oral toxicity study in rats. Conducted by Bio-Research Laboratories, Ltd., 87 Senneville Rd, Senneville, Quebec H9X 3R3, Canada, for Chevron Chemical (Canada) Ltd., 3228 South Service Rd., Burlington, Ontario L7N 3H8, Canada. Unpublished report. EPA Accession No. 246496. *(date?)*

MATERIALS AND METHODS

Test substance: Dibrom R (1,2-dibromo-2,2-dichloroethyl dimethyl phosphate), a yellow viscous liquid (Lot No. SX1278) of unspecified purity was used. Before administration of the test chemical, it was suspended in 0.5% aqueous sodium carboxymethyl cellulose at concentrations of 0.0025, 0.01, 0.1, or 1% (by weight). A set of samples from these solutions were set aside (stored at -15°C) for analysis one day of each of the first two weeks of the study. Such samples of the solutions taken during the third and fourth weeks of the study were analyzed immediately. *(1)*

Test species: Twenty-eight day old male and female Sprague-Dawley rats were acclimatized to the laboratory conditions for 18 days. They were housed individually and received Purina Rodent Chow No. 5002 and water ad libitum.

Experimental procedures: Groups of 10 male and 10 female rats were given by gavage dosages of 100, 10, 1, 0.25, or 0 mg Dibrom^R per kg body weight, and the chemical was administered for 28 days.

The animals were checked twice each day for mortality and clinical signs. Dosages were administered at about the same time early each day, and frequent observations of treated animals were made subsequent to dosing in order to determine time of onset for clinical signs or recovery.

During the fourth week blood was drawn from the orbital sinus of 2 male and 2 female rats on each group on each of 5 consecutive days. Plasma and red blood cell cholinesterase activities were measured in these samples.

Beginning on the first day of the next week 2 males and 2 females from each group were anesthetized with sodium phenobarbital and exanguinated. Brain cholinesterase activity was determined and the animals were grossly examined for external and internal lesions. The terminal body weight as well as brain, heart, kidney, liver, and gonad weights were determined. Tissues were preserved but not examined microscopically.

Group means and standard deviations for body weight, food consumption, food consumption to body weight gain ratios, cholinesterase determinations, and absolute and relative body weights were calculated. Student's t test was used to test for significance of differences between control and treated groups.

Reported results: Clinical signs reported in animals receiving the 100 mg/kg/day dosages were muscular tremors, salivation, ocular discharge, increased urination, and soft moist feces. The authors stated that all females and 3 males had muscular tremors 10 to 30 minutes after administration of the first dose. Six other males were reported to have noted muscular effects after the second dose, while the remaining male had tremors after the third dose. Recovery was noted three hours after dosing. According to the investigators, the rats of this group were generally in poor condition with weakness, pallor lethargy, hypothermia and respiratory distress. Ocular discharges were reported to be reddish brown to clear in color and were noted an hour after treatment. The investigators observed these discharges intermittantly during the first two weeks of the experiment and more frequently during the remaining two weeks. Salivation was also noted from dosing to an hour afterward. Five of 10 male and 5 of 10 female rats died during the first week of treatment. Two males died during the fourth week. Deaths were seen to occur 5 to 25 minutes after treatment in the first week and 30 to 45 minutes after dosing in the fourth week.

The authors reported that none of the other animals receiving 100 mg/kg/day died during the study.

In the 10 mg/kg/day dosage group one male was reported to have muscular tremors after the sixth dose. Another male and 4 females were reported to be slightly lethargic after the sixth dose. The authors stated that one female died because of a dosing error as indicated by a punctured esophagus and blood in the thoracic cavity.

No clinical signs or mortality were noted in the other two treatment groups and the untreated controls group.

The only statistically significant differences reported in group mean body weight between control and treated groups was for males receiving the 100 mg/kg/day group. The percentage of mean body weight decrease in these animals was 13 for the first two weeks, 15 for the third week, and 10% for the fourth of the experiment.

The authors reported that mean body weight gain was not affected during the four week test period. However, results for male rats in the 100 mg/kg group showed that they gained an average of 13.6 g during the first week of the study compared with an average gain of 48 g for untreated males in the same period. No significant differences were between treated and control groups of female rats.

The authors reported mean food consumption in males getting the 100 mg/kg dose during the first week of treatment to be 20.5 g and that of the third week to be 23.4 g. The respective control values for the first and third weeks were reported as 26.6 and 28.7 g. There were no significant differences noted between control and treated females for food consumption.

The authors used the ratio of food consumption (g) to body weight gain (g) as an estimate of food conversion efficiency. The only significant finding was noted for males receiving 100 mg/kg during the first week. The ratio for that group was 11.7 compared with a ratio of 4 in untreated controls.

Cholinesterase activity in treated animals (expressed as a percentage of control values) are as follows:

Males

<u>Dose (mg/kg/day)</u>	<u>Plasma</u>	<u>Erythrocyte</u>	<u>Brain</u>
0.25	93	100	100
1.0	91	98	98
10	63	74	47
100	48	76	26

Females

0.25	99	103	99
1.0	85	94	94
10	52	72	48
100	26	70	27

The authors states that gross examination at necropsy revealed varying degrees of lung congestion in those rats that died. The only statistically significant organ weight changes reported were those of the liver in 100 mg/kg/day group and the kidneys in females receiving 10 mg/kg/day. The absolute liver weights in males were on considered reported significantly different from control group weights, by the investigators, but the relative weight was higher as the result of decreased body weight. In the females of the highest dose group the mean absolute liver weight was 8.845 g compared with 7.116g in untreated controls. Reported results showed that the relative liver weights for the 100 mg/kg group of females and the untreated control were 3.932 and 3.453, respectively. The differences were reported to be statistically significant at $p < 0.01$ (absolute weight) and $p < 0.001$ (relative weight). The higher relative kidney weight females receiving the 10 mg/kg/day dose was not considered to be treatment related because it was not observed at higher doses, and the absolute weight was not significantly different from controls.

No microscopic examinations of tissues were done.

Discussion:

The authors concluded that the lethality of the 100 mg/kg/day dose makes it too high for use in a long-term study. Based on cholinesterase determinations, the lowest effect dose is between 10 and 1 mg/kg/day. The no-observed-effect level based on the same effect is 1 mg/kg/day. The study provides adequate information to support these conclusions.

Core Classification:

This is a range-finding study which is supplementary to a long-term study to be submitted at a later date. It is designed to provide rational for dose selection.