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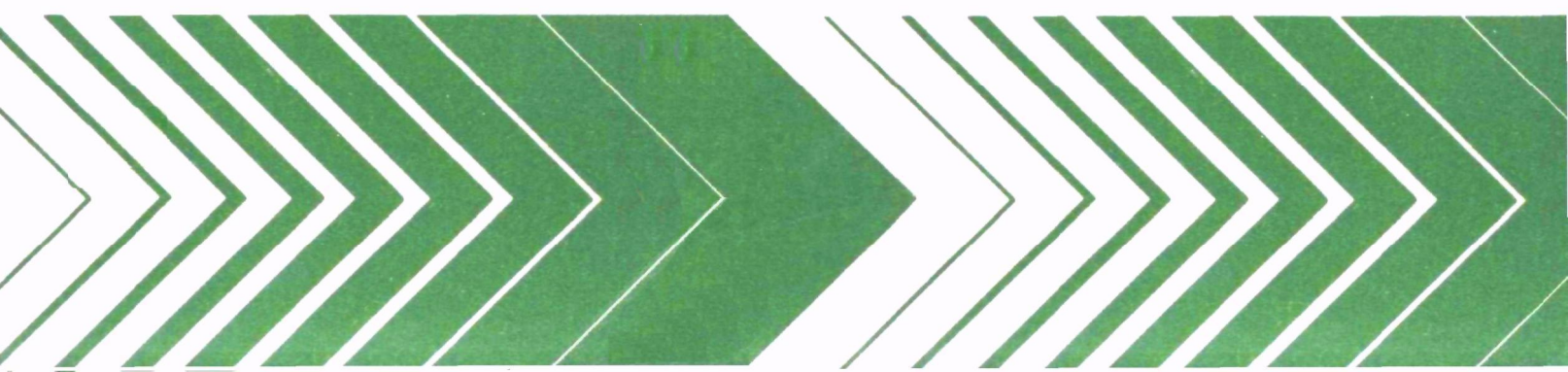
Study of the Chemical and Behavioral Toxicology of Substitute Chemicals in Microtine Rodents



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STUDY OF THE CHEMICAL AND BEHAVIORAL TOXICOLOGY OF SUBSTITUTE CHEMICALS IN MICROTINE RODENTS

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FOREWORD

Effective regulatory and enforcement actions by the Environmental Protection Agency would be virtually impossible without sound scientific data on pollutants and their impact on environmental stability and human health. Responsibility for building this data base has been assigned to EPA's Office of Research and Development and its 15 major field installations, one of which is the Corvallis Environmental Research Laboratory (CERL).

The primary mission of the Corvallis Laboratory is research on the effects of environmental pollutants on terrestrial, freshwater, and marine ecosystems; the behavior, effects and control of pollutants in lake systems; and the development of predictive models on the movement of pollutants in the biosphere.

This report provides significant new data on the toxicological response of microtine rodents to selected agricultural chemicals.

A. F. Bartsch
Director, CERL

ABSTRACT

Ten pesticides were evaluated in acute LD_{50} and 30-day subacute LC_{50} studies using microtine rodents (voles). The order of pesticide toxicity based on the acute studies was: parathion > methyl parathion > dieldrin > 2, 4-D > 2,4,5-T > simazine > propanil = PCNB = HCB = trifluralin. It was demonstrated in both the acute and the 30-day subacute studies that Microtus canicaudus voles are approximately twice as sensitive to these pesticides as Microtus ochrogaster. When pesticides were compared by LD_{50} values in all four species, the general order of species sensitivity was as follows: Microtus canicaudus > Microtus pennsylvanicus ≥ Microtus ochrogaster ≥ Microtus montanus.

No apparent sex differences were observed in LD_{50} values except for methyl parathion in Microtus canicaudus, wherein the female appears to be two- to three-fold more sensitive to this pesticide than the male.

Based on the 30-day subacute LC_{50} values, the order of pesticide toxicity was: dieldrin > parathion > methyl parathion > HCB > 2,4,5-T > PCNB ≥ propanil.

In the 30-day subacute feeding studies, Microtus canicaudus was more sensitive than Microtus ochrogaster by a factor similar to that in the acute oral studies. Toxicological signs observed throughout this study were classically similar to general pesticide intoxication observed in laboratory animals, and no gross pathology attributable to pesticide treatment was observed in the animals.

A comparison of the LD_{50} values in laboratory rodents with the most sensitive vole species, Microtus canicaudus, revealed that the rat and mouse are more susceptible to the lethal effects of 2,4-D, dieldrin, methyl parathion, parathion, propanil, and 2,4,5-T. Equal susceptibility to pesticides for both Microtus canicaudus and laboratory rodents is evident for HCB, PCNB, and trifluralin. The only exception noted in this study was that the Microtus canicaudus appears to be more susceptible to simazine than the laboratory rat and mouse.

This report was submitted in fulfillment of EPA Contract Number 68-01-4195 by Midwest Research Institute under the sponsorship of the U.S. Environmental Protection Agency. This report covers a period from September 16, 1976 to May 1, 1978, and work was completed as of March 10, 1978.

CONTENTS

ACKNOWLEDGMENTS

The research was conducted in the Biological Sciences Division under the direction of Dr. H. M. Hubbard, Acting Director, with the assistance of Dr. Cheng-Chun Lee, Associate Director. Dr. Paul J. Peters was the Principal Investigator up to August 8, 1977, and technical assistance was provided by Mr. Andrew Heinemann during the interval. Dr. Michael T. Koeferl became Principal Investigator after August 8, 1977, with technical assistance from Mr. Michael J. McKee. Drs. James M. Cholakis and Laurence C. K. Wong provided administrative and technical expertise after November 15, 1977, and Mr. Jan L. Minor assisted in computations and statistics throughout the entire project.

SECTION 1

INTRODUCTION

The large scale, worldwide use of insecticides, herbicides, and defoliants has prompted the U.S. Environmental Protection Agency to undertake studies to evaluate the global implications of general pesticide use.

As particularly toxic or persistent pesticides are identified, efforts are made to find replacements for them. Not wishing to allow equally hazardous chemicals to be used as replacements for condemned pesticides, the U.S. Legislature passed Public Law 93-135 on October 24, 1973. This law established the Substitute Chemicals Program which is directed at testing new pesticides before they are adopted for wide usage.

Most toxicity testing is done with laboratory animals; however, while these results can be used to compare the toxicity of different chemicals, as determined in laboratories anywhere, the animal models cannot be directly applied to the actual native fauna at risk. Thus, for more reliable comparison with the results in laboratory animals, it would be advantageous to test pesticides in representative native species.

As an approach to some aspects of this problem, this study subjected four species of vole (Microtus spp.) to toxicologic evaluation. The vole represents a wild animal type with extensive U.S. geographic distribution; these toxicologic data were compared to data obtained from laboratory rodents.

The habitats of the four Microtus species chosen for toxicologic study cover most of the United States (1). M. pennsylvanicus, the meadow vole, is found throughout the eastern and northern United States, Canada, and Alaska. M. ochrogaster, the prairie vole, is found throughout the Midwest and part of central Canada. M. montanus, the montane vole, is found in the West and Northwest, while M. canicaudus, gray-tailed vole, is found only in northwest Oregon.

The overall objective of this work was to study the acute oral toxicity (LD_{50}) and 30-day subacute toxicity (LC_{50}) of 10 selected pesticides in microtine rodents.

SECTION 2

MATERIALS AND METHODS

TEST ANIMALS

All voles were laboratory-reared from live trapped stocks. Microtus ochrogaster were supplied by Dr. Orin B. Mock, Associate Professor of Anatomy, Kirkville College of Osteopathic Medicine, Kirksville, Missouri 63501. M. canicaudus, M. montanus, and M. pennsylvanicus were supplied by Dr. Larry G. Forslund, Assistant Professor of Biology, Oregon State University, Corvallis, Oregon 97331. The M. pennsylvanicus originated from a colony that was lab-reared for about 14 years by Dr. Fred Elliot, Michigan State University, East Lansing, Michigan.

Voles were shipped to MRI when they were approximately 6 to 7 weeks of age, and acclimated to controlled animal room environment (temperature 72°F ± 5°, humidity 50% ± 10% and a 16-hour light, 8-hour night cycle) for a minimum of 1 week. Voles placed on tests were approximately 60 to 120 days of age. Animals were handled according to standardized procedures (2-5).

TEST COMPOUNDS

All pesticides were supplied by the USEPA. Most were either obtained in analytical grade from the manufacturer, or were recrystallized in the laboratories of the EPA:

1. 2,4-D acid damp (2,4-dichlorophenoxyacetic acid), lot No. 093826, Dow Chemical Company, Midland, Michigan;

2. HCB (hexachlorobenzene), lot No. HX160P2719, Matheson, Coleman and Bell, Norwood, Ohio;

3. Simazine (2-chloro-4,6-bis-ethylamino-S-triazine), lot No. FL-750033 and FL-751091, CIBA-GEIGY, Agricultural Division, McIntosh, Alabama;

4. Methyl parathion (0,0-dimethyl O-p-nitrophenyl phosphorothioate), no lot number, Monsanto Agricultural Products, St. Louis, Missouri;

5. Parathion (0,0-diethyl 0-p-nitrophenyl phosphorothioate), no lot number, Monsanto Agricultural Products, St. Louis, Missouri;

6. PCNB (pentachloronitrobenzene), lot No. 2J-13-76, Olin Corporation, Industrial Products and Service Division, McIntosh, Alabama;

7. Propanil (3',4'-dichloropropionanilide), no lot No., Rohm and Haas Company, Philadelphia, Pennsylvania;

8. 2,4,5-T (2,4,5-trichlorophenoxyacetic acid, iso-octyl ester), lot No. LF-5362, Thompson-Hayward Company, Kansas City, Missouri;

9. Trifluralin (α,α,α-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine), no lot No., Eli Lilly and Company, Tippecanoe Laboratories, Lafayette, Indiana; and

10. Dieldrin (1,2,3,4,10,10-hexachloro-exo-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo, exo-5,8-dimethanonaphthalene), lot No. 12 PCD-38, Shell Chemical Company, Houston, Texas.

EXPERIMENTAL PROCEDURES

Acute LD_{50}

The LD_{50} or medium lethal dose is defined as the statistical estimate of the dosage of a pesticide (in mg/kg body weight) which kills 50% of the voles within 14 days after a single oral administration of the compound.

Pesticides were administered by gavage to voles which had been food-deprived overnight. Most pesticides were pulverized and then sifted through a 300 μ screen prior to weighing. All pesticides were administered at dosing volumes of either 10 ml/kg or 20 ml/kg body weight. After experimentation with various vegetable oils, agars, etc., we found that an aqueous solution of 1% methyl cellulose (Methocel, lot No. 7412X, grade 60HG, Dow Chemical Company) with or without 0.4% Tween 80 was a very satisfactory suspending agent. All drug suspensions were agitated for uniformity using a Polytron, Model No. PT 10/35, Brinkman Instruments Company, Westbury, Connecticut. Both untreated and treated control animals were maintained throughout the study.

Dose-range (DR) studies were initially performed with five voles/dose group and later changed to three voles/dose group. Animals were housed five per cage while on test. The DR study was run for 3 to 7 days. Once limits of mortality were established in the DR study for each chemical, then appropriate log dosage intervals were selected for the full scale study (0.2, 0.1, or 0.05 log units depending on the defined limits). The full-scale studies

for acute LD_{50} evaluation utilized 10 voles/dosage level with a minimum of five test groups. More test groups were added, as needed, in order to more accurately define mathematically the acute LD_{50} or subacute LC_{50}. If the DR study revealed that less than one-half of the animals would die at 5,000 mg/kg, then only 10 voles were dosed at 5,000 mg/kg. No attempt was made to define any mortality above 5,000 mg/kg for the acute study or 50,000 ppm for the subacute studies.

Animals were observed immediately after dosing and daily for 28 days for toxicologic and other behavioral signs. Daily observations of clinical signs were of a semi-quantitative nature (i.e., severe depression, moderate exophthalmos, etc.).

After 28 days, a gross necropsy was performed on a representative number of surviving animals ($\cong$50% from each dosage group). Necropsy of animals that died while on study was not successful because the dead animal was usually cannibalized by its cage-mates.

30-Day Subacute LC_{50}

The LC_{50} (median lethal concentration) is defined as that concentration (in parts per million or ppm) of pesticide which kills 50% of the animals within 30 days when the compound is administered daily in the diet.

Thirty-day subacute feeding studies were performed after an initial 7-day DR study was performed with 3 to 5 voles/group utilizing 3 to 5 groups/pesticide. The full-scale study was accomplished with 10 voles/group and five groups/test compound utilizing appropriate log dosage intervals. The pesticide was divided into small portions and mixed with equal parts of the feed (lab chow and alfalfa) in a mortar and pestle and then added to the bulk feed in a cement mixer and/or ball mill. Lower dietary concentrations were made by dilution of the main stock.

To determine the amount of pesticide to be incorporated into the feed mixture, control body weights and food consumption were determined in 10 voles in each of four groups: M. ochrogaster, male; M. ochrogaster, female; M. canicaudus, male; and M. canicaudus, female. This allowed the conversion of parts per million (ppm) in diet to mg/kg/day and vice-versa:

Animal	Body weight g[a/]	Food consumption per day, g[a/]	1 ppm in Diet equals, in mg/kg/day[b/]	1 mg/kg/day equals, in ppm of diet[b/]
M. ochrogaster, Male	46.0	5.62	0.122	8.2
M. ochrogaster, Female	35.3	4.62	0.131	7.6
M. canicaudus, Male	37.9	7.01	0.185	5.4
M. canicaudus, Female	27.7	6.70	0.242	4.1

a/ Recorded data.
b/ Computed data.

Animals were observed daily for 30 days for toxicologic and other behavioral signs. Daily observations of clinical signs were of a semiquantitative basis (i.e., severe depression, moderate ataxia, etc.).

After 30 days of observations, a gross necropsy was performed on a representative number of surviving animals ($\cong$50% from each dosage group). Necropsy of animals that died while on study was not successful because the dead animal was usually cannibalized by its cage-mates.

Feed Preparation

The control and stock vole diet consisted of a mixture of rat chow mash and alfalfa: Wayne Lab-Blox Mash, lot No. 8600-00, Allied Mills, Inc., Chicago, Illinois; 17% dehydrated alfalfa meal, Western Alfalfa Corporation, Shawnee Mission, Kansas. After mixing three parts Wayne Mash to two parts alfalfa meal in a cement mixer (Sears, Roebuck and Company), the mixture was further formulated with 1 liter of tap water to 10 kg of mixture and pelleted. A model No. 2298-4A pellet mill, California Pellet Mill Company, San Francisco, California, was used for this purpose.

Special Procedures

Cross inhalation contamination or room pesticide odor was avoided by a unique holding system: special holding racks capable of housing 30 large cages (five voles/cage) were utilized for the 30-day subacute feeding studies. Each set of two cages had its own reverse flow-exhaust system such that no pesticide odors could enter the room or other cages within this holding rack.

DATA ANALYSIS

All data from both the acute and subacute studies were evaluated by a computer technique using the probit analysis method of Finney (6). The percent mortality, the dosage, and the number of animals dosed were used for

computation. The program generated the LD_{50} (LC_{50}), the LD_{10} (LC_{10}), the LD_{90} (LC_{90}), the slope, the standard errors, and the 95% confidence limits (see Appendix II for computer printouts). If Finney's g factor $\geqq 1$, the 95% confidence limits are not validly computed. Only one 100% mortality and only one 0% mortality dosage groups were entered into the probit program, even though in some situations more than one 100% or 0% mortality group was obtained.

The acute oral LD_{50} was computed based on a 14-day observation period, even through observation continued through day 28, and the subacute dietary LC_{50} was computer based on a 30-day feeding period.

SECTION 3

RESULTS

The results of the acute and subacute studies in microtine voles are presented by pesticide. Table 1 is a summary tabulation of all LD_{50} and LC_{50} (95% confidence limits) determinations performed in this study. Appendix I contains detailed tables of every study performed and includes dosage group, % mortality, day of death of each animal, mean day of death/dosage group, LD_{50}, and 95% confidence limits. Appendix II contains computer sheets for each study with results as described in the Materials and Methods section.

2,4-D

The acute oral LD_{50}'s in male and female M. ochrogaster voles were 2,106 and 2,104 mg/kg, respectively; and in the male and female M. canicaudus voles were 1,205 and 1,314 mg/kg, respectively. In M. ochrogaster no remarkable toxicologic signs were noted at lower dosages; however, some lethargy, palpebral closure, and convulsion before death were noted at high dosages of 2,4-D. Most deaths were noted within 72 hours of dosing. In M. canicaudus some loss of righting reflex was noted with hind-limb paralysis, and labored breathing at high doses. Most deaths occurred within 24 hours of dosing.

DIELDRIN

The acute oral LD_{50}'s in male and female M. ochrogaster were 201 and 216 mg/kg, respectively; for male and female M. canicaudus were 94 and 101 mg/kg, respectively; for male and female M. montanus were 229 and 182 mg/kg, respectively; and for male and female M. pennsylvanicus were 179 and 173 mg/kg, respectively. No toxic signs were observed at low doses; however, tremor, hind-limb paralysis, depression, and convulsions in some animals were noted at high doses of dieldrin. Most deaths occurred within 72 hours post dosing.

In the 30-day subacute feeding studies, the LC_{50}'s in male and female M. ochrogaster were 129 and 82 ppm, respectively; and in the male and female M. canicaudus were 43 and 39 ppm, respectively. No toxic signs were noted at low doses; however, sporadic breathing, piloerection, increased spontaneous

TABLE 1. THE LD_{50} AND LC_{50} VALUES OF PESTICIDES IN VOLES.

Pesticide		Acute Studies				Subacute Studies	
		M. ochrogaster LD_{50} (mg/kg)	*M. canicaudus* LD_{50} (mg/kg)	*M. montanus* LD_{50} (mg/kg)	*M. pennsylvanicus* LD_{50} (mg/kg)	*M. ochrogaster* LC_{50} (ppm)	*M. canicaudus* LC_{50} (ppm)
2,4-D	♂ [a/]	2,106(1,803-2,572)	1,205(955-1,513)				
	♀ [b/]	2,104(1,895-2,388)	1,314(1,013-1,791)				
Dieldrin	♂	201(163-261)	94(73-124)	229(177-616)	179(118-271)	129(36-459)	43(36-50)
	♀	216(177-294)	101(64-201)	182(159-219)	173(145-213)	82(58-102)	39(15-101)
HCB	♂	> 5,000	> 5,000			3,553(2,654-5,007)	1,280(857-1,919)
	♀	> 5,000	> 5,000			3,450(g ≥ 1)	1,047(533-1,940)
Methyl-parathion	♂	311(223-480)	137(104-183)	--	--	--	--
	♀	253(75-974)	57(40-79)	379(325-512)	371(304-426)	912(345-1,136)	613(g ≥ 1)
Parathion	♂	87(76-102)	55(49-67)			--	--
	♀	96(61-151)	49(43-57)			699(605-787)	192(170-228)
PCNB	♂	> 5,000	> 5,000	4,194(2,870-17,110)	> 5,000	42,840(32,790-82,830)	11,290(5,728-15,750)
	♀	> 5,000	> 5,000	3,717(2,981-5,048)	> 5,000	37,270(28,250-65,400)	23,780(18,660-30,140)
Propanil	♂	> 5,000	2,758(2,258-3,366)			> 50,000	15,660(g ≥ 1)
	♀	> 5,000	2,527(2,070-3,095)			> 32,000 < 50,000	20,250(g ≥ 1)
Simazine	♂	3,925(3,437-4,568)	2,014(1,401-2,896)				
	♀	3,251(2,636-3,979)	2,363(2,090-2,686)				
2,4,5-T (ester)	♂	4,963(4,227-5,940)	2,071(1,653-2,682)	--	2,066(1,382-3,501)	--	--
	♀	3,889(3,298-4,623)	2,123(1,097-4,109)	2,057(1,645-2,860)	--	19,670(17,100-22,750)	10,810(9,605-11,920)
Trifluralin	♂	> 5,000	> 5,000				
	♀	> 5,000	> 5,000				

Values are expressed as the LD_{50} or LC_{50} (95% confidence limits); if g ≥ 1, confidence limits not computed.

a/ ♂ = male.

b/ ♀ = female.

activity, decreased activity with slight tremors, convulsions and hind-limb extension at death were noted in higher dosage groups. No gross pathology attributable to the compound was seen in the animals.

HCB

The acute oral LD_{50} in the male and female of both M. ochrogaster and M. canicaudus were greater than 5,000 mg/kg. Some animals at 5,000 mg/kg exhibited depression, decreased spontaneous activity, and palpebral closure; however, all animals recovered within 24 hours after dosing.

In the 30-day subacute feeding studies, the LC_{50}'s in male and female M. ochrogaster were 3,553 and 3,450 ppm, respectively; and in the male and female M. canicaudus were 1,280 and 1,047 ppm, respectively. Toxicological signs noted at high doses of HCB were: shivering, lethargy, body tremors, and hind-limb extension at death for one animal. Necropsy performed on surviving animals after 30 days revealed no significant findings attributable to compound administration.

METHYL PARATHION

The acute oral LD_{50}'s in male and female M. ochrogaster were 311 and 253 mg/kg, respectively; for male and female M. canicaudus were 137 and 57 mg/kg, respectively; and for female M. montanus and female M. pennsylvanicus were 379 and 371 mg/kg, respectively. After dosing with methyl parathion, the following toxic signs were common to most voles: ataxia, lacrimation, body tremors, muscle fasciculations, depression, labored breathing, palpebral closure, piloerection, hind-limb extension, complete paralysis, convulsions, and death within 15 minutes in some voles at the higher dosage levels.

In the 30-day subacute feeding studies, the LC_{50}'s in the female species of both M. ochrogaster and M. canicaudus were 912 and 613 ppm, respectively. At low concentrations of methyl parathion, some labored breathing and body tremors were noted. At higher concentrations of pesticide piloerection, lethargy, lacrimation, piloerection, body tremors, palpebral closure, and hunched or arched back were noted in some voles.

PARATHION

The acute oral LD_{50}'s in male and female M. ochrogaster were 87 and 96 mg/kg, respectively; and for male and female M. canicaudus were 55 and 49 mg/kg, respectively. Animals treated at high dosages exhibited ataxia, tremors, piloerection, palpebral closure, hind-limb extension, and convulsions prior

to death. Most voles died within 24 hours of dosing with several dying within 1 or 2 hours after dosing with parathion.

In the 30-day subacute feeding studies, the LC_{50}'s in both female species of M. ochrogaster and M. canicaudus were 699 and 192 ppm, respectively. Toxicological observations were piloerection, ataxia, depression, body tremors, loss of forearm coordination, and abdominal muscle contractions or fasciculations. The death pattern was variable, but most animals died after about 7 to 14 days on test. No gross pathology attributable to pesticide treatment was noted at the 30-day necropsy.

PCNB

The acute oral LD_{50} was greater than 5,000 mg/kg in both sexes of M. ochrogaster, M. canicaudus and M. pennsylvanicus. No toxicological signs were noted except for some piloerection, loss of righting reflex, lacrimation, and decreased activity in a few voles. Most of these signs disappeared after 24 hours of dosing. The acute oral LD_{50}'s in male and female M. montanus were 4,194 and 3,717 mg/kg, respectively. Most deaths occurred between 2 and 6 days of dosing. No other toxic signs were noted in this study.

In the 30-day subacute studies, the LC_{50}'s in male and female M. ochrogaster were 42,840 and 37,270 ppm, respectively; and for male and female M. canicaudus were 11,290 and 23,780 ppm, respectively. Animals exhibited toxicological signs of lacrimation, piloerection, irregular breathing, lethargy, and body tremors at high concentrations of PCNB. Alopecia was noted, but this was not considered to be drug-related. No gross pathology attributable to pesticide treatment was seen in the animals at the 30-day necropsy.

PROPANIL

The acute oral LD_{50}'s in both male and female M. ochrogaster were greater than 5,000 mg/kg. The acute oral LD_{50}'s in male and female M. canicaudus were 2,758 and 2,527 mg/kg, respectively. The toxic signs observed at high doses were difficulty in breathing, lethargy, loss of righting reflexes and paralysis. Most animals died within 48 hours of dosing.

In the 30-day subacute studies, the LC_{50} in male and female M. ochrogaster was greater than 50,000 ppm in the male and greater than 32,000 ppm, but less than 50,000 ppm for the female. The LC_{50}'s in male and female M. canicaudus were 15,660 and 20,250 ppm, respectively. The toxic signs were piloerection, palpebral closure, depression and loss of motor control in one vole. No gross pathology attributable to pesticide treatment was seen in the animals at the 30-day necropsy.

SIMAZINE

The acute oral LD_{50}'s in male and female M. ochrogaster were 3,925 and 3,251 mg/kg, respectively; and for male and female M. canicaudus were 2,014 and 2,363 mg/kg, respectively. The toxic signs noted were hind-limb extension, piloerection, loss of anal sphinter control, lethargy, muscle spasms, lacrimation, and depression. Most animals died after 4 to 5 days of dosing with simazine.

2,4,5-T

The acute oral LD_{50}'s in male and female M. ochrogaster were 4,963 and 3,889 mg/kg, respectively; for male and female M. canicaudus were 2,071 and 2,123 mg/kg, respectively; for female M. montanus the LD_{50} was 2,057 mg/kg, and for male M. pennsylvanicus was 2,066 mg/kg. The toxic signs noted were lethargy, palpebral closure, ataxia, and decreased spontaneous activity.

In the 30-day subacute studies, the LC_{50}'s in female M. ochrogaster and female M. canicaudus were 19,670 and 10,810 ppm, respectively. The toxic signs noted were piloerection, palpebral closure, lethargy, decreased spontaneous activity, and depression. Most animals died after 10 days on test. No gross pathology attributable to pesticide treatment was seen in the animals.

TRIFLURALIN

The acute oral LD_{50} was greater than 5,000 mg/kg for both sexes of M. ochrogaster and M. canicaudus. No toxic signs were noted except for some voles with depression, which disappeared within 24 hours of dosing.

SECTION 4

DISCUSSION

In the acute oral studies, voles were treated with the vehicle (1% methyl cellulose) in the same dosing volume as the experimental test group. A high incidence of deaths in the vehicle-treated group of the M. pennsylvanicus male (14.7%) was attributed to rupturing of the esophagus during intubation. This problem was encountered early in the study and corrected after some experimentation with dosing needles and different dosing techniques.

In the acute oral toxicity studies, M. canicaudus was generally more susceptible to 2,4-D, dieldrin, parathion, propanil, simazine, 2,4,5-T and methyl parathion (male) than M. ochrogaster, M. montanus and M. pennsylvanicus by a factor of about 2:1. Since the LD_{50} was greater than 5,000 mg/kg for PCNB, HCB and trifluralin in both sexes of these species, no conclusion could be made with regard to species sensitivity. In the acute oral LD_{50} study, the female M. canicaudus was four to five times more susceptible to methyl parathion than the female M. ochrogaster.

In the feeding studies, early experimentation with a closed feeder food system revealed that the voles on the subacute studies could not adapt to this feeding method. Thereafter, an open jar feeder was used in all subacute studies, a system which proved more satisfactory. However, one problem with this technique was a slightly higher food consumption than reported in the literature (literature: 3.0-3.5 gm/day/vole (2); this study: 5.6-7.0 gm/day/vole). This higher food consumption was generally due to spillage. Other sources of problem areas in collecting food consumption data were: voles had a tendency to fill the feeder jars with bedding material and the voles would deposit fecal material in the feeders.

In the 30-day subacute studies, M. canicaudus was more susceptible to pesticides (dieldrin, parathion, methyl parathion, HCB, 2,4,5-T, PCNB and propanil) than the M. ochrogaster by a factor of about 2:1. This is the similar relationship seen in the acute studies, i.e., 2:1 relationship. However, if we examine the relationship developed in the subacute study between ppm in diet and convert this to mg/kg/day of pesticide consumed, the 2:1 relationship between the M. ochrogaster and M. canicaudus is not nearly so evident:

Animal	1 ppm in Diet Equals in mg/kg/day[a/]
M. ochrogaster, male	0.122
M. ochrogaster, female	0.131
M. canicaudus, male	0.185
M. canicaudus, female	0.242

a/ See Materials and Methods section.

It appears that M. canicaudus consume about twice as much food as the M. ochrogaster. Table 2 presents the LC_{50} data as ppm recomputed to mg/kg/day from the control food consumption-body weight data (see Methods section). An examination of this recomputed data now reveals clear species differences of LC_{50} values only with parathion and PCNB (male only). Comparison of data on the basis of mg/kg/day minimizes the differences in species susceptibility for dieldrin, HCB, propanil, 2,4,5-T and even methyl parathion. Even though M. canicaudus voles consume about twice as much food as the M. ochrogaster, parathion and PCNB (male) are still twice as toxic to the M. canicaudus as to the M. ochrogaster species.

The overall rank order of pesticide toxicity based on the 30-day subacute (LC_{50}) values (ppm) is as follows: dieldrin > parathion > methyl parathion > HCB > 2,4,5-T > PCNB $\geq$ propanil (simazine, 2,4-D and trifluralin were not studied). In the acute oral studies (LD_{50}), the order of toxicity of the first three pesticides was parathion > methyl parathion > dieldrin, etc.

Some tentative explanations of these differences are as follows:

1. Parathion, methyl parathion but not dieldrin, could have stimulated (induced) the liver drug metabolizing enzyme systems to increase the detoxication of these pesticides (7,8).

2. Dieldrin could have been acting in a cumulative manner (9,10). It can be shown that the dieldrin acute LD_{50} values are approximately equal to the subacute LC_{50} values (on a mg/kg/day basis):

M. canicaudus

		LC_{50}	x	Mean Day of Death	=	"Total" LC_{50}	LD_{50}	Ratio	"Total" $\frac{LC_{50}}{LD_{50}}$
Dieldrin	♂	9	x	10	=	90	94	$\cong$	1
	♀	9	x	12	=	108	101	$\cong$	1

TABLE 2. THE LC_{50} VALUES OF PESTICIDES IN VOLES (SUBACUTE).
(ppm vs. mg/kg/day)

		M. ochrogaster LC_{50} (ppm)	M. canicaudus LC_{50} (ppm)	M. ochrogaster LC_{50} (mg/kg/day)[a]	M. canicaudus LC_{50} (mg/kg/day)[a]
Dieldrin	♂[b]	129(36-459)	43(36-50)	16(4-56)	9(8-10)
	♀[c]	82(58-102)	39(15-101)	11(8-13)	9(4-24)
HCB	♂	3,553(2,654-5,007)	1,280(857-1,919)	433(324-611)	268(179-401)
	♀	3,450(g ≧ 1)	1,047(533-1,940)	452(g ≧ 1)	253(129-469)
Methyl parathion	♀	912(345-1,136)	613(g ≧ 1)	119(45-149)	148(g ≧ 1)
Parathion	♀	699(605-787)	192(170-228)	92(79-103)	46(41-55)
PCNB	♂	42,840(32,790-82,830)	11,290(5,728-15,750)	5,226(4,000-10,105)	2,360(1,197-3,292)
	♀	37,270(28,250-65,400)	23,780(18,660-30,140)	4,882(3,700-8,567)	5,755(4,516-7,294)
Propanil	♂	> 50,000	15,669(g ≧ 1)	> 6,100	3,273(g ≧ 1)
	♀	> 32,000 < 50,000	20,250(g ≧ 1)	> 4,192 < 6,550	4,900(g ≧ 1)
2,4,5-T (ester)	♂	--	--	--	--
	♀	19,670(17,100-22,750)	10,810(9,605-11,920)	2,577(2,240-2,980)	2,259(2,007-2,491)

Values are expressed as LC_{50} (95% confidence limits); if Finney's g ≧ 1, confidence limits not validly computed.

a/ LC_{50} in mg/kg/day (computed from control food consumption data - see Material and Methods and Discussion section).

b/ ♂ = male

c/ ♀ = female

	LC_{50}	x	Mean Day of Death	=	"Total" LC_{50}	LD_{50}	Ratio	"Total" $\frac{LC_{50}}{LD_{50}}$
Parathion ♀	46	x	6.2	=	285	57	≅	5

This data interpretation suggests that dieldrin is cumulative in its effects and that parathion can be tolerated by M. canicaudus in amounts much higher than the single lethal dose. However, more detailed studies should be performed before final conclusions can be made about these differences (i.e., bioavailability, distribution, excretion experiments, etc.).

To determine if the vole represents a more or less sensitive species than the laboratory rat or mouse, an extensive review of the literature was undertaken to tabulate rat and mice LD_{50}'s. Table 3 provides a comparison of the acute LD_{50}'s of M. ochrogaster, M. canicaudus, the laboratory rat and the mouse. Generally, it appears that both the laboratory rat and mouse are more sensitive than (2:1) or about equal to M. canicaudus with respect to acute toxicity of these pesticides. However, species variability, strain differences among rats and mice, laboratory condition, dosing techniques, vehicle variables, chemical formulation variations, etc., make any strict comparative evaluation subject to reasonable criticism. Some outstanding exceptions should be noted: (1) the four- to ten-fold difference between the laboratory animal and vole LD_{50} values with 2,4,5-T (i.e., $LD_{50} \cong$ 300-551 mg/kg for laboratory animals (12,16,17) vs. $LD_{50} \cong$ 2,000-5,000 mg/kg for voles). A reasonable explanation of this finding is that earlier study with 2,4,5-T showed that it was contaminated with high concentrations of TCDD or 2,3,7,8-tetrachlorodibenzodioxin. These earlier studies probably reflected TCDD toxicity and not necessarily 2,4,5-T ester formulations studies (20,21); however, more careful manufacturing processes have decreased this dioxin product to less than 0.1 ppm. (2) Similarly large order of magnitude differences between the laboratory species and voles with respect to parathion, methyl parathion, and dieldrin. It would appear that the laboratory animal is more sensitive to these three pesticides than the vole. (3) The only example in this entire report that suggests the vole is more sensitive than the laboratory rat or mice is with simazine, i.e., $LD_{50} >$ 5,000 mg/kg for lab animals vs. $LD_{50} \cong$ 2,000 mg/kg for M. canicaudus.

The overall order of pesticide toxicity for the laboratory rat and mouse is as follows: parathion > methyl parathion > dieldrin > 2,4,5-T ≥ 2,4-D ≥ propanil ≥ PCNB ≥ HCB ≥ trifluralin ≥ simazine (see Table 3). This order is quite similar to that established in the voles, and except for the sensitivity difference between voles and laboratory rodents, the similar pesticide toxicity order suggests a common mechanism of pesticide action.

TABLE 3. COMPARISON OF THE LD_{50} VALUES OF TEN PESTICIDES IN VOLES, RATS, AND MICE.

		M. ochrogaster LD_{50} (mg/kg)	*M. canicaudus* LD_{50} (mg/kg)	Laboratory Rat LD_{50} Ranges[a]	Laboratory Mouse LD_{50} Ranges[a]
2,4-D	♂[b]	2,106(1,803-2,572)	1,205(955-1,513)	300 to 666	368 to 375
	♀[c]	2,104(1,895-2,388)	1,314(1,013-1,791)		
Dieldrin	♂	201(163-261)	94(73-124)	46 to 87	114
	♀	216(177-294)	101(64-201)		
HCB	♂	>5,000	>5,000	3,500 to 10,000	4,000
	♀	>5,000	>5,000		
Methyl parathion	♂	311(223-480)	137(104-183)	14 ♂	23
	♀	253(75-974)	57(40-79)	24 ♀	
Parathion	♂	87(76-102)	55(49-67)	7.6 to 13 ♂	6 to 25
	♀	96(61-151)	49(43-57)	3.6 ♀	
PCNB	♂	>5,000	>5,000	1,650 to 12,000	LD_{50} not found
	♀	>5,000	>5,000		
Propanil	♂	>5,000	2,758(2,258-3,366)	560 to 1,400	LD_{50} not found
	♀	>5,000	2,527(2,070-3,095)		
Simazine	♂	3,925(3,437-4,568)	2,014(1,401-2,896)	>5,000	5,000
	♀	3,251(2,636-3,979)	2,363(2,090-2,686)		
2,4,5-T (ester)	♂	4,963(4,227-5,940)	2,071(1,653-2,682)	300 to 495	551
	♀	3,889(3,298-4,623)	2,123(1,097-4,109)		
Trifluralin	♂	5,000	>5,000	3,700 to 10,000	5,000
	♀	5,000	>5,000		

Values are expressed as LD_{50} or LC_{50} (95% confidence limits).

a/ LD_{50} values (mg/kg) tabulated from literature. See references 11 to 19.

b/ ♂ = male

c/ ♀ = female

SECTION 5

CONCLUSIONS

The acute oral toxicity (LD_{50}) and 30-day feeding effects (LC_{50}) were performed in adult microtus voles with selected pesticides. Conclusions are as follows: (1) Based on the acute oral toxicity (LD_{50}) studies, the overall order of pesticide toxicity is as follows: parathion > methyl parathion > dieldrin > 2,4-D > 2,4,5-T > simazine > propanil = PCNB = HCB = trifluralin; (2) the general order of species sensitivity to pesticides is as follows: *M. canicaudus* > *M. pennsylvanicus* ≥ *M. ochrogaster* ≥ *M. montanus*; (3) *M. canicaudus* are approximately twice as sensitive to pesticide treatment as *M. ochrogaster* in both the acute and 30-day subacute studies (on a ppm basis); (4) No apparent sex differences were observed in LD_{50} values except for methyl parathion in *M. canicaudus* (female twice as sensitive as male); (5) Based on the 30-day subacute toxicity (LC_{50}) study, the overall order of pesticide toxicity is as follows: dieldrin > parathion > methyl parathion > HCB > 2,4,5-T > PCNB ≥ propanil (simazine, 2,4-D and trifluralin not tested); (6) No apparent sex difference was observed in LC_{50} values except for PCNB in *M. canicaudus* (male twice as sensitive as female); and (7) Laboratory rodents are generally more sensitive to pesticides than the most sensitive vole species, *M. canicaudus*.

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APPENDIX A

ACUTE AND SUBACUTE ORAL TOXICITY (LD_{50}) DATA

TABLE A-1. ACUTE ORAL LD_{50} OF 2,4-D IN *M. OCHROGASTER*

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days
		Male	
4,000	10/10	1,1,1,1,1,3,3,3,3,3	2.0
2,500	10/15	1,1,1,1,1,2,3,3,6,7	2.6
1,995	1/10	3	-
1,585	5/15	1,1,1,3,3	1.8
1,260	2/10	3,3	3.0
1,000	1/10	4	-
790	0/10		-
		Female	
4,000	10/10	1,1,1,1,2,3,3,3,3,3	2.1
2,500	13/15	1,1,1,1,1,2,2,2,3,3,3,3,6	2.2
1,995	2/10	1,6,(27)	3.5
1,585	1/15	3	-
1,260	1/10	1	-
1,000	0/10	(26)	-

LD_{50} (95% confidence limits) Male: 2,106 (1,803-2,572) mg/kg
Female: 2,104 (1,895-2,388) mg/kg

TABLE A-2. ACUTE ORAL LD_{50} OF 2,4-D IN *M. CANICAUDUS*

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
2,500	10/10	1,1,1,1,1,4,4,4,4,4	2.5
1,585	6/10	1,1,1,1,4,4	2.0
1,000	5/10	1,1,4,4,4	2.8
630	0/10		-
		Female	
2,500	10/10	1,1,1,1,1,1,1,4,4,4	1.9
1,585	4/10	1,1,1,4,(19)	1.8
1,000	3/10	4,4,4,(19)	4.0
630	2/10	1,11	6.0
400	0/10		

LD_{50} (95% confidence limits)	Male:	1,205 (955-1,513) mg/kg
	Female:	1,314 (1,013-1,791) mg/kg

TABLE A-3. ACUTE ORAL LD_{50} OF DIELDRIN IN M. OCHROGASTER

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
398	9/10	2,2,2,2,2,2,4,4,7	3.0
320	9/10	1,1,1,2,5,5,5,5,6	3.4
250	4/10	2,3,3,3	2.8
200	5/10	1,1,1,5,5	2.6
150	3/10	3,7,8	6.0
126	1/10	1	-
100	2/7	7,8	7.5
79	1/10	1	-
63	1/10	1	-
		Female	
315	8/10	2,2,3,3,7,7,7,8	4.9
250	6/10	3,4,4,4,4,7,(25)	4.3
200	4/10	5,5,5,6	5.3
150	2/10	3,3	3.0
126	1/10	5	-
100	2/5	3,8	5.5
79	0/10	(28)	-

LD_{50} (95% confidence limits)	Male:	201 (163-261) mg/kg
	Female:	216 (177-294) mg/kg

TABLE A-4. ACUTE ORAL LD_{50} OF DIELDRIN IN M. CANICAUDUS

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
240	10/10	1,1,4,4,4,4,4,4,4,4	3.4
150	8/10	1,1,4,4,5	3.0
96	4/10	1,4,4,4	3.3
60	1/10	4	
40	2/10	4,4	4.0
25	0/10		
		Female	
250	6/10	1,2,3,3,4,4	2.8
150	8/10	1,4,4	3.0
96	5/10	1,1,4,4,4	2.8
60	3/10	4	
40	4/10	4,4,5,5	4.5
25	0/10		

LD_{50} (95% confidence limits)	Male:	94 (73-124) mg/kg
	Female:	101 (64-201) mg/kg

TABLE A-5. ACUTE ORAL LD_{50} OF HCB IN M. OCHROGASTER

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
5,000	0/10		
		Female	
5,000	0/10		

LD_{50} (95% confidence limits) Male: >5,000 mg/kg
Female: >5,000 mg/kg

TABLE A-6. ACUTE ORAL LD_{50} OF HCB IN M. CANICAUDUS

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
5,000	0/10		
3,160	0/5		
1,995	0/5		
		Female	
5,000	0/9		
3,160	1/5	1	
1,995	0/5		

LD_{50} (95% confidence limits) Male: >5,000 mg/kg
Female: >5,000 mg/kg

TABLE A-7. ACUTE ORAL LD_{50} OF METHYL PARATHION IN *M. OCHROGASTER*

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
790	7/10	1,1,3,3,3,3,4	2.6
500	7/10	1,1,1,3,3,3,3	2.1
355	7/10	1,1,1,1,1,1,8,(22)	2.0
250	5/10	1,1,1,1,1,(29)	1.0
178	2/10	1,1	1.0
126	2/10	1,1	1.0
89	1/10	1	
50	0/5		
		Female	
790	7/10	1,2,3,3,3,3,3	2.6
500	8/9	1,1,1,1,3,3,3,3	2.0
355	7/10	1,1,1,1,1,1,1	1.0
250	8/10	1,1,1,1,1,1,1,1	1.0
178	4/10	1,1,1,1	1.0
126	1/10	1	
89	0/10		

LD_{50} (95% confidence limits) Male: 311 (223-480) mg/kg
Female: 253 (75-974) mg/kg

TABLE A-8. ACUTE ORAL LD_{50} OF METHYL PARATHION IN M. CANICAUDUS

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
400	10/10	1,1,1,1,1,1,1,1,1,1	1.0
250	8/10	1,1,1,1,1,1,1,1	1.0
160	5/10	1,1,1,1,2	1.2
100	3/10	1,1,1	1.0
63	2/10	1,1	1.0
40	0/10	(27)	
		Female	
250	10/10	1,1,1,1,1,1,1,1,1,5	1.4
160	9/10	1,1,1,1,1,1,1,2,2	1.2
100	6/10	1,1,1,1,1,1	1.0
63	5/10	1,1,1,1,2	1.0
40	3/10	1,1,1	1.0
25	4/10	1,1,1,1	1.0
16	0/10	(18,18,18)	

LD_{50} (95% confidence limits)	Male:	137 (104-183) mg/kg
	Female:	57 (40-79) mg/kg

TABLE A-9. ACUTE ORAL LD_{50} OF PARATHION IN M. OCHROGASTER

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
126	10/10	1,1,1,1,1,1,1,1,1,1	1.0
100	5/10	1,1,1,1,2	1.2
80	4/10	1,1,1,1	1.0
63	1/10	3	
50	1/10	2	
40	0/10		
		Female	
160	10/10	1,1,1,1,1,3,3,3,3,3	2.0
126	9/10	1,1,1,1,1,1,1,1,1	1.0
100	7/10	1,1,1,1,1,1,1	1.0
80	7/10	1,1,1,1,1,1,1	1.0
63	2/10	1,1	1.0
50	0/10		

LD_{50} (95% confidence limits)	Male:	87 (76-102) mg/kg
	Female:	96 (61-151) mg/kg

TABLE A-10. ACUTE ORAL LD_{50} OF PARATHION IN M. CANICAUDUS

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
100	10/10	1,1,1,1,1,1,1,1,1,2	1.1
60	4/10	1,1,5,6	3.2
50	6/10	1,1,1,1,1,3	1.3
40	1/10	6	
32	0/10		
25	0/10		
		Female	
60	8/10	1,1,1,1,1,1,1,2	1.1
50	5/10	1,1,1,1,1	1.0
40	3/10	2,11,14	9.0
32	0/10		
25	0/10		

LD_{50} (95% confidence limits) Male: 55 (49-67) mg/kg
Female: 49 (43-57) mg/kg

TABLE A-11. ACUTE ORAL LD_{50} OF PCNB IN M. OCHROGASTER

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
5,000	0/10		
		Female	
5,000	0/10		

LD_{50} (95% confidence limits) Male: > 5,000 mg/kg
Female: > 5,000 mg/kg

TABLE A-12. ACUTE ORAL LD_{50} OF PCNB IN M. CANICAUDUS

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
5,000	2/10	1,3	2.0
		Female	
5,000	3/10	2,3,8	4.3

LD_{50} (95% confidence limits) Male: > 5,000 mg/kg
Female: > 5,000 mg/kg

TABLE A-13. ACUTE ORAL LD_{50} OF PROPANIL IN M. OCHROGASTER

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
5,000	6/20	1,3,4,4,4,7	3.8
2,510	0/10		
1,260	1/10	3	
		Female	
5,000	8/20	1,1,1,1,3,3,4,7	2.6
2,510	6/10	1,1,7,7,9,10	5.8
1,260	1/10	4,(17,25)	

LD_{50} (95% confidence limits) Male: > 5,000 mg/kg
Female: > 5,000 mg/kg

TABLE A-14. ACUTE ORAL LD_{50} OF PROPANIL IN M. CANICAUDUS

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
6,310	9/10	1,1,1,1,1,1,1,1,2	1.1
5,010	8/10	1,1,1,1,1,1,2,4	1.5
4,000	7/10	2,2,3,3,3,4,4	3.0
3,160	8/10	2,2,2,2,2,3,3,3	2.4
2,510	4/10	2,2,2,4	2.5
1,995	3/10	2,2,2	2.0
1,585	1/10	2,(21)	
1,230	1/10	12	
630	0/5		
		Female	
6,310	10/10	1,1,1,1,1,1,1,1,1,2	1.1
5,010	7/9	1,1,1,2,2,2,3	1.7
4,000	7/10	2,2,2,2,2,3,5	2.6
3,160	6/10	2,2,2,2,2,2	2.0
2,510	5/10	2,2,2,2,3	2.2
1,995	5/10	2,2,2,2,3	2.2
1,585	3/10	2,2,5	3.0
1,230	1/10	1	
1,000	0/10		

LD_{50} (95% confidence limits)	Male:	2,758 (2,258-3,366) mg/kg
	Female:	2,527 (2,070-3,095) mg/kg

TABLE A-15. ACUTE ORAL LD_{50} OF SIMAZINE IN M. OCHROGASTER

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
6,310	8/10	3,3,3,3,3,6,6,6	4.1
5,000	8/10	3,3,3,3,4,4,10,10	5.0
4,000	11/20	2,3,3,3,3,3,5,6,7,10,14	5.4
3,160	4/10	3,3,4,4	3.5
2,820	2/10	3,3	3.0
2,500	0/10		
		Female	
6,310	9/10	3,3,3,3,3,3,3,6,7	3.8
5,000	9/10	3,3,4,4,7,7,7,10,10	5.0
4,000	11/20	1,1,3,3,6,6,7,7,7,9,12	5.6
3,160	5/10	1,3,3,3,7	3.4
2,500	2/10	3,7	
1,995	1/10	4	
1,585	3/10	3,3,12	6.0

LD_{50} (95% confidence limits)	Male:	3,925 (3,437-4,568)	mg/kg
	Female:	3,251 (2,636-3,979)	mg/kg

TABLE A-16. ACUTE ORAL LD_{50} OF SIMAZINE IN M. CANICAUDUS

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
3,548	8/10	2,2,2,4,4,4,5,6	3.6
2,818	6/10	2,2,2,4,4,4	3.0
2,240	4/10	2,4,4,10	5.0
1,780	5/10	1,1,1,2,5	2.0
1,412	4/10	1,1,1,10	3.2
		Female	
3,548	9/10	1,2,2,2,2,2,4,5,5	2.8
2,818	8/10	1,1,2,2,4,4,4,4	2.8
2,240	5/10	1,1,2,2,4	2.0
1,780	1/10	1	
1,412	0/10		

LD_{50} (95% confidence limits)	Male:	2,014 (1,401-2,896) mg/kg
	Female:	2,363 (2,090-2,686) mg/kg

TABLE A-17. ACUTE ORAL TOXICITY (LD_{50}) OF 2,4,5-T IN M. OCHROGASTER

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
7,433	9/10	1,1,2,2,2,4,4,4,4	2.7
5,935	5/10	1,2,2,4,4	2.6
4,688	6/10	2,2,2,4,4,4	3.0
3,724	3/10	5,5,5	5.0
2,960	0/10		
		Female	
7,433	10/10	1,3,3,3,3,3,3,4,4,4	3.1
5,935	13/15	3,3,3,3,3,4,4,4,5,6,6,6,7	4.4
4,688	5/10	3,3,3,4,4	3.4
3,724	3/14	4,4,5	4.3
2,960	3/10	3,3,11	5.7
2,352	1/5	6	
2,255	4/10	3,4,11,12	7.5
1,484	0/15		

LD_{50} (95% confidence limits) Male: 4,963 (4,227-5,940) mg/kg
Female: 3,889 (3,298-4,623) mg/kg

TABLE A-18. ACUTE ORAL LD_{50} OF 2,4,5-T IN *M. CANICAUDUS*

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
3,160	7/10	1,1,2,2,2,2,2	1.7
2,510	7/10	1,1,1,1,1,1,1	1.0
1,995	5/10	1,1,1,1,1	1.0
1,585	5/10	1,1,1,1,9	2.6
1,260	0/10		
		Female	
2,510	6/10	2,2,2,2,2,2	2.0
1,995	5/9	2,2,2,2,5,5	3.0
1,585	2/9	2,2	2.0
1,260	3/10	2,3,9	4.7
1,000	4/10	2,2,2,5	2.7

LD_{50} (95% confidence limits) Male: 2,071 (1,653-2,682) mg/kg
Female: 2,123 (1,097-4,109) mg/kg

TABLE A-19. ACUTE ORAL LD_{50} OF TRIFLURALIN IN *M. OCHROGASTER*

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
5,000	0/10		
		Female	
5,000	1/10	1	

LD_{50} (95% confidence limits) Male: >5,000 mg/kg
Female: >5,000 mg/kg

TABLE A-20. ACUTE ORAL LD_{50} OF TRIFLURALIN IN M. CANICAUDUS

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
5,000	1/10	2	
		Female	
5,000	2/10	3,9,(>14)	5.5

LD_{50} (95% confidence limits) Male: >5,000 mg/kg
Female: >5,000 mg/kg

TABLE A-21. ACUTE ORAL LD_{50} OF DIELDRIN IN M. PENNSYLVANICUS

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
250	10/100	1,1,1,1,1,1,2,4,4,9	2.3
200	2/10	2,13,(25,25)	7.5
150	6/10	1,1,2,3,3,3	2.2
126	1/10	2	
100	1/12	3	
63	0/5		
		Female	
400	5/5	1,1,1,1,2	1.2
250	9/10	1,1,1,2,3,3,7,7,8	3.7
200	5/10	1,3,3,6,9,(> 14)	4.4
150	4/10	1,1,1,3	1.5
126	0/10	(20)	
100	3/10	3,3,3	3.0
63	0/5		

LD_{50} (95% confidence limits) Male: 179 (118-271) mg/kg
Female: 173 (145-213) mg/kg

TABLE A-22. ACUTE ORAL LD_{50} OF DIELDRIN IN *M. MONTANUS*

Dose (mg/kg)	Mortality d.(1-14)	Time of Death (days)	Mean (days)
		Male	
316	5/5	1,2,2,5,5	3.0
250	6/10	1,1,1,3,4,5	2.5
200	2/15	1,5,(16)	3.0
150	6/15	1,2,6,11,11,13	7.3
125	3/14	1,1,13	5.0
100	3/14	1,4,6	3.7
		Female	
250	10/10	1,1,1,1,2,2,2,3,3,4	2.0
200	6/15	1,1,1,2,2,5,(16)	2.0
150	5/15	1,2,6,8,11	5.6
125	2/14	8,8	8.0
100	1/10	1	

LD_{50} (95% confidence limits)	Male:	229 (177-616)	mg/kg
	Female:	182 (159-219)	mg/kg

TABLE A-23. ACUTE ORAL LD_{50} OF METHYL PARATHION IN M. PENNSYLVANICUS

Dose (mg/kg)	Mortality d.(1-14)	Time of Death (days)	Mean (days)
		Female	
793	10/10	1,1,1,1,1,1,1,1,1,2	1.1
630	10/10	1,1,1,1,1,1,1,1,1,1	1.0
500	9/10	1,1,1,1,1,1,1,1,2	1.1
397	5/10	1,1,1,1,1	1.0
250	1/10	1,(18)	

LD_{50} (95% confidence limits) Female: 371 (304-426) mg/kg

TABLE A-24. ACUTE ORAL LD_{50} OF METHYL PARATHION IN M. MONTANUS

Dose (mg/kg)	Mortality d.(1-14)	Time of Death (days)	Mean (days)
		Female	
562	9/10	1,1,1,1,1,1,1,2,2	1.2
355	3/10	1,1,2	1.3
316	3/10	1,2,2	1.7
280	2/10	1,2	1.5
250	2/10	2,2	2.0
224	2/10	1,1,(21,23)	1.0

LD_{50} (95% confidence limits) Female: 379 (325-512) mg/kg

TABLE A-25. ACUTE ORAL LD_{50} OF PCNB IN M. PENNSYLVANICUS

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
5,000	1/15	2,(23,23)	
		Female	
5,000	1/15	4	

LD_{50} (95% confidence limits) Male: > 5,000 mg/kg
Female: > 5,000 mg/kg

TABLE A-26. ACUTE ORAL LD_{50} OF PCNB IN M. MONTANUS

Dose (mg/kg)	Mortality d.(1-14)	Time of death (days)	Mean (days)
		Male	
5,000	8/15	1,2,2,5,6,6,6,6,(26)	4.3
3,160	3/5	5,5,5,(20)	5.0
2,000	2/10	1,1	1.0
1,585	1/10	2	
		Female	
5,000	11/15	2,2,2,2,5,5,6,6,6,6,14	5.1
3,160	4/10	1,5,5,6	4.3
2,000	0/10		
1,585	1/10	(< 14)	

LD_{50} (95% confidence limits) Male: 4,194 (2,870-17,110) mg/kg
Female: 3,717 (2,981-5,048) mg/kg

TABLE A-27. ACUTE ORAL LD_{50} OF 2,4,5-T IN M. PENNSYLVANICUS

Dose (mg/kg)	Mortality d.(1-14)	Time of Death (days)	Mean (days)
		Male	
3,162	9/10	1,1,1,2,2,3,3,4,13	3.3
2,512	4/10	1,1,1,2	1.3
1,995	5/10	1,1,1,2,14	3.8
1,585	2/10	2,3	2.5
1,260	4/10	2,2,2,3	2.3

LD_{50} (95% confidence limits) Male: 2,066 (1,382-3,501) mg/kg

TABLE A-28. ACUTE ORAL TOXICITY (LD_{50}) OF 2,4,5-T IN M. MONTANUS

Dose (mg/kg)	Mortality d.(1-14)	Time of Death (days)	Mean (days)
		Female	
3,722	10/10	1,1,1,1,1,1,1,1,1,2	1.1
2,352	4/10	2,3,3,5	3.3
1,869	3/10	1,2,3	2.0
1,484	3/10	1,2,9	4.0
1,178	2/10	1,1,(29)	1.0
935	2/10	3,3,(29,29)	3.0

LD_{50} (95% confidence limits) Female: 2,057 (1,645-2,860) mg/kg

TABLE A-29. SUBACUTE DIETARY LC_{50} OF DIELDRIN IN M. OCHROGASTER

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Male	
400	10/10	7,7,7,8,8,8,9,9,11,13	8.7
250	10/10	3,7,7,7,8,9,11,13,13,14	9.2
160	10/10	8,8,9,13,13,14,15,18,19,20	13.7
126	1/10	13	
100	2/10	17,19	18.0
63	2/11	11,15	13.0
		Female	
400	10/10	3,4,8,8,8,9,9,11,13,15	8.8
250	10/10	7,7,9,9,9,10,11,13,13,13	10.1
160	10/10	8,8,9,10,11,13,14,14,18,18	12.3
100	6/10	10,11,13,13,19,20	14.3
63	3/10	13,13,14	13.3

LC_{50} (95% confidence limits)	Male:	129 (36-459) ppm
	Female:	82 (58-102) ppm

TABLE A-30. SUBACUTE DIETARY LC_{50} OF DIELDRIN IN M. CANICAUDUS

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Male	
100	10/10	2,3,3,3,4,7,7,7,7,10	5.3
63	10/10	4,4,7,7,7,8,8,9,10,14	7.8
40	3/10	2,21,22	15.0
25	0/10		
16	0/10		
		Female	
160	10/10	7,7,7,7,7,7,8,8,9,10	7.0
63	9/10	7,7,7,7,7,8,10,13,17	9.2
40	0/10		
25	3/9	16,17,17	16.7
16	3/10	2,17,17	12.0
10	1/10	23	

LC_{50} (95% confidence limits) Male: 43 (36-50) ppm
Female: 39 (15-101) ppm

TABLE A-31. SUBACUTE DIETARY LC_{50} OF HCB IN M. OCHROGASTER

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Male	
5,000	8/10	9,19,21,25,27,29,29,30	23.6
2,500	2/10	22,29	25.5
1,250	0/10		
625	0/10		
313	0/10		
		Female	
5,000	9/10	10,19,20,20,21,23,25,25,26	21.0
3,890	9/10	18,20,21,21,24,25,25,28,29	23.4
2,500	0/10		
1,250	0/10		
625	0/10		
313	1/10	29	

LC_{50} (95% confidence limits)	Male:	3,553 (2,654-5,007) ppm
	Female:	3,450 ($g \geqq 1$) ppm

TABLE A-32. SUBACUTE DIETARY LC_{50} OF HCB IN M. CANICAUDUS

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Male	
5,000	9/10	10,11,11,11,13,16,26,29,29	17.3
2,500	8/10	19,21,22,23,23,24,27,29	23.5
1,250	6/10	5,9,27,27,29,29	21.0
625	2/10	10,10	10.0
313	0/10		
		Female	
5,000	5/5	17,17,20,20,22	19.2
2,500	3/5	12,14,29	18.3
1,250	5/5	16,16,27,30,30	23.8
625	1/5	3	
313	0/5		

LC_{50} (95% confidence limits)	Male:	1,280 (857-1,919)	ppm
	Female:	1,047 (533-1,940)	ppm

TABLE A-33. SUBACUTE DIETARY LC_{50} OF METHYL PARATHION IN M. OCHROGASTER

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Female	
2,000	10/10	8,11,11,11,11,12,13,14,15,15	12.1
1,780	9/10	6,8,8,9,11,12,14,15,22	11.7
1,585	9/10	11,12,12,14,14,15,16,18,22	14.9
1,412	6/10	12,15,16,25,26,27	20.2
1,259	8/9	5,5,7,15,16,16,17,20	12.6
891	5/10	5,8,10,14,18	11.0

LC_{50} (95% confidence limits) Female: 912 (345-1,136) ppm

TABLE A-34. SUBACUTE DIETARY LC_{50} OF METHYL PARATHION IN M. CANICAUDUS

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Female	
1,096	7/10	5,5,7,9,9,15,16	9.4
875	8/10	5,5,7,8,9,11,13	7.3
692	2/9	5,19	12.0
550	2/10	11,13	12.0
436	7/10	9,9,11,11,12,22,25	14.1

LC_{50} (95% confidence limits) Female: 613 ($g \geq 1$) ppm

TABLE A-35. SUBACUTE DIETARY LC_{50} OF PARATHION IN M. OCHROGASTER

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Female	
1,750	10/10	7,7,7,8,9,9,11,12,17,19	10.5
1,380	10/10	4,5,7,7,8,9,11,15,16,19	10.1
1,096	10/10	4,5,7,8,9,12,12,12,13,16	9.8
871	7/10	6,8,11,11,14,14,21	12.1
692	7/10	6,11,17,17,20,26	13.8
500	0/10		

LC_{50} (95% confidence limits) Female: 699 (605-787) ppm

TABLE A-36. SUBACUTE DIETARY LC_{50} OF PARATHION IN M. CANICAUDUS

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Female	
251	9/10	3,3,4,4,5,5,6,7,8	5.0
200	3/10	4,5,5	4.7
158	5/10	5,5,6,6,9	6.2
141	1/10	9	
112	0/10		

LC_{50} (95% confidence limits) Female: 192 (170-228)

TABLE A-37. SUBACUTE DIETARY LC_{50} OF PCNB IN M. OCHROGASTER

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Male	
50,000	6/10	12,12,17,18,18,20	16.2
32,000	3/10	17,22,30	23.0
20,000	1/10	30	
12,600	0/10		
7,900	0/10		
		Female	
50,000	6/9	9,11,12,17,21,30	16.7
32,000	4/10	12,19,20,25	19.0
20,000	2/10	14,14	14.0
12,600	0/10		
7,900	0/10		

LC_{50} (95% confidence limits)	Male:	42,840 (32,790-82,830)	ppm
	Female:	37,270 (28,250-65,400)	ppm

TABLE A-38. SUBACUTE DIETARY LC_{50} OF PCNB IN M. CANICAUDUS

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Male	
50,000	10/10	2,2,4,4,4,5,6,11,11,14	6.3
32,000	9/10	2,3,4,4,6,6,19,20,29	10.3
20,000	7/10	6,6,6,6,8,22,22	10.9
12,600	5/10	2,3,5,6,6	4.4
7,900	4/10	6,8,8,9	4.8
		Female	
50,000	9/9	4,5,5,6,6,8,11,11,14	7.8
32,000	6/9	5,6,6,13,14,29	12.2
20,000	4/8	3,3,17,30	13.3
12,600	0/10		
7,900	0/10		

LC_{50} (95% confidence limits)	Male:	11,290 (5,728-15,750) ppm
	Female:	23,780 (18,660-30,140) ppm

TABLE A-39. SUBACUTE DIETARY LC_{50} OF PROPANIL IN M. OCHROGASTER

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Male	
50,000	2/11	15,15	15.0
32,000	0/10		
20,000	0/10		
12,600	1/10	2	
7,900	1/10	3	
		Female	
50,000	6/9	3,4,10,15,16,30	13.0
32,000	0/10		
20,000	0/10		
12,600	0/10		
7,900	1/10	30	

LC_{50} (95% confidence limits) Male: > 50,000 ppm
Female: > 32,000 < 50,000 ppm

TABLE A-40. SUBACUTE DIETARY LC_{50} OF PROPANIL IN M. CANICAUDUS

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Male	
20,000	9/10	2,2,4,5,5,10,12,13,27	8.9
12,600	0/10		
7,900	1/10	3	3.5
5,000	4/10	1,3,4,6	
3,160	0/10		
		Female	
20,000	4/10	2,3,3,5	3.3
12,600	4/10	6,6,16,24	13.0
7,900	0/10		
5,000	0/10		
3,160	1/10	3	

LC_{50} (95% confidence limits) Male: 15,660 ($g \geq 1$) ppm
Female: 20,250 ($g \geq 1$) ppm

TABLE A-41. SUBACUTE DIETARY LC_{50} OF 2,4,5-T IN M. OCHROGASTER

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Female	
29,674	10/10	4,5,5,6,7,9,10,11,11,14	8.2
23,739	7/10	13,18,18,22,24,26,30	21.6
14,837	2/10	15,27	21.0
13,220	0/10		
11,780	1/10	27	
9,362	0/10		

LC_{50} (95% confidence limits) Female: 19,670 (17,100-22,750) ppm

TABLE A-42. SUBACUTE DIETARY LC_{50} OF 2,4,5-T IN M. CANICAUDUS

Concentration (ppm)	Mortality d.(1-30)	Time of Death (days)	Mean (days)
		Female	
14,837	10/10	2,4,5,6,6,6,12,14,17,20	9.2
13,220	7/10	2,2,3,6,7,11,29	8.6
11,780	6/10	3,4,5,7,11,27	9.5
9,362	4/10	2,3,6,9	5.0
7,418	0/10		

LC_{50} (95% confidence limits) Female: 10,810 (9,605-11,920) ppm

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
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16. ABSTRACT Acute oral LD_{50} and 30-day dietary subacute LC_{50} studies of 10 selected pesticides were evaluated in microtine rodents. As a means to developing new animal model systems, four species of microtine rodents including Microtus ochrogaster (MO), Microtus canicaudus (MC), Microtus pennsylvanicus (MP) and Microtus montanus (MM) voles were used. The acute LD_{50} (median lethal dose in mg/kg) in all four species and the subacute LC_{50} (median lethal concentration in ppm) in MO and MC voles were computed using probit analysis. The data from both the acute and the 30-day subacute studies revealed that MC voles were approximately twice as sensitive to these pesticides as MO voles. Based on the acute studies, the overall order of pesticide toxicity was as follows: parathion > methyl parathion > dieldrin > 2,4-D > 2,4,5-T > simazine propanil = PCNB = HCB = trifluralin. The general order of species sensitivity was as follows: MC > MP ≥ MO ≥ MM. No apparent sex differences were observed in MP, MO or MM voles. In MC voles, the female appeared to be two- to threefolds more sensitive to methyl parathion than the male. Based on the 30-day subacute LC_{50} studies, the overall order of pesticide toxicity is as follows: dieldrin > parathion > methyl parathion > HCB > 2,4,5-T > PCNB > propanil. Based on LD_{50} values the laboratory rodents appear to be more susceptible to 2,4-D, dieldrin, methyl parathion, parathion, propanil, and 2,4,5-T, equally susceptible to HCB, PCNB, and trifluralin, and less susceptible to simazine than the MC voles.

17. KEY WORDS AND DOCUMENT ANALYSIS

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Animals *Pesticides *Toxicology	Acute LD_{50} Subacute LC_{50}	6T

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