



Estimation of Median Lethal Dose of Fenpropathrin in Wistar Rat

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Abstract

Background: Fenpropathrin, a synthetic pyrethroid (Type I/II) is commonly used as an insecticide in homes and in agriculture. The present study was planned to determine the median lethal dose (LD₅₀) of Fenpropathrin in adult Wistar rats, both male and female. Statistically, LD₅₀ is a first screening step to assess and evaluate the toxicity for a chemical that causes death of 50% population of test animals when given by a specified route as a single dose for a specific time period. **Methods:** The experimental rats were divided into 10 groups (5 of male and 5 of female rats) and ten rats were divided into each group. For each group of animals, a single oral dose of Fenpropathrin dissolved in corn oil was administered orally at 15, 30, 45, 60 and 75 mg/kg body weight (bw) concentrations. The animals were monitored up to 96 hours to assess the signs of toxicity and to calculate the LD₅₀ as per the graphical method procedure suggested by Miller and Tainter (1944)¹⁰. **Result:** Estimated LD₅₀ of Fenpropathrin was found to be 52.72±8.61mg/kg body weight in male rats and 48.08±8.13 mg/kg body weight in female rats. There were no toxic signs or behavioural changes in the single oral dose of Fenpropathrin at 10mg/kg body weight, thus it can be considered as No Observed Adverse Effect Level (NOAEL). **Conclusion:** It can be concluded from the study that Fenpropathrin is highly toxic pyrethroid due to its low LD₅₀ value in Wistar rats. The result of this study may serve as a basis for dose administration for further research on Fenpropathrin toxicity.

Keywords: Fenpropathrin, Pyrethroid, Lethal Dose (LD₅₀), Wistar Rat

1. Introduction

Pyrethroids are natural known toxins produced by flowers of pyrethrum (*Chrysanthemum cinerariaefolium* and *C. coccineum*) and are currently the most extensively used class of pesticides. Usage of pyrethroids as insecticides has increased in recent years for agriculture and domestic applications resulting in greater exposure of human beings, as a result many questions arise concerning their adverse side effects and action mechanism in non-target species¹. Based on the chemical structure and toxicity signs, pyrethroids fall into 2 distinct groups: Type I and Type II²⁻⁴. Those that lack cyano group on the phenoxybenzyl moiety are Type I pyrethroids and they are characterized by the T-syndrome (tremors) affecting sodium channels in nerve membranes and cause vigorous sparring, high responsiveness external stimuli, fine tremors progressing to entire body tremors and prostration. Type II pyrethroids in the alcohol moiety

have an alpha-cyano group and produce a longer delay in inactivation of sodium channel^{4,5}. These are characterized by CS syndrome (choreoathetosis and salivation). A few pyrethroids can induce tremors and also salivation and were graded as accordingly Type I/II pyrethroids^{2,4}.

Fenpropathrin [(RS) α-cyano-3-phenoxybenzyl 2,2,3,3-tetramethylcyclopropanecarboxylate] is a highly toxic synthetic pyrethroid insecticide which is included in Type I/II pyrethroid as it causes tremors as well as salivation in animal models⁶. Commonly, it is used to control a wide range of insect pests to enhance the production of crops. Fenpropathrin acts on the nervous system of insects, and disturbs the function of neurons as it binds to NaV (voltage-sensitive sodium) channels and modifies their gating kinetics. Being lipophilic in nature, Fenpropathrin crosses the blood brain barrier and has been found to accumulate in brain and induce neurotoxicity⁷. Therefore, misapplication

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or accidental exposure to Fenpropathrin may cause severe toxic effects on human beings and non-target organism.

To find out the Acceptable Daily Intake (ADI) and other adverse effects of Fenpropathrin, we need to perform toxicity test. To assess potential hazards to humans, acute, sub-chronic and chronic toxicity tests are conducted on laboratory animals.

Acute toxicity tests evaluate toxic effects when a chemical substance is absorbed from a single or multiple exposures into the body, through mouth, skin or lungs over a short period of time (usually within 24 hours). It is one of the most common way to quantify a chemical substance's potential to trigger ill effects "relatively soon"⁸. Median lethal dose (LD₅₀) figures of a substance's acute toxicity measured by any accepted method such as given by Bliss (1934)⁹, Miller and Tainter (1944)¹⁰, Litchfield and Wilcoxon (1949)¹¹, Thompson (1947)¹², Weil (1952)¹³ and Finney (1971)¹⁴ under controlled and standardized laboratory conditions. This information can be used to deal with cases of accidental ingestion of material and provides data in sub-chronic and chronic studies to create a dosage regimen. Generally, toxicity tests are conducted in rats and other animal models and are used to set standards for human toxicity.

Commonly, acute toxicity expressed as LD₅₀, where LD means a lethal dose and subscript 50 means that the dose is acutely lethal to 50% of the animals. Therefore, this evaluates the relation between the dosage and the severe response i.e. death. The chemical is highly toxic when its LD₅₀ value is low. An attempt was made here to determine Fenpropathrin's oral LD₅₀ (corn oil as a vehicle) in Wistar rats.

2. Materials and Methods

2.1 Experiment Chemical

Fenpropathrin PESTANAL®, analytical standard (CAS No. 39515-41-8) was purchased with 99.8% purity from Sigma-Aldrich, Germany.

2.2 Procurement of Animals and Ethics

Approval

Adult Wistar rats (male and female) were randomly selected for present study. They were kept in an air-cooled room at 25 ± 3 °C with a light and dark cycle (12–12 h) under regular laboratory conditions. Prior to the initiation of the experiment, they were acclimatized to the basal diet for three days. Throughout the experiment, Animals were maintained on regular pellet diet purchased from Ashirwad Industries, Chandigarh, India and water *ad libitum*. The investigational procedure was approved by DAEC (Departmental Animal Ethical Committee) and animal care committee, and handling was conforms to the

guidelines set by CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals), New Delhi, India.

2.3 Dose Preparation and Administration

Adult Wistar rats aged sixty days and weighing 150±5g were chosen for the experiment. Prior to dosing, animals were fasted for eighteen hours because feeding tends to increase the metabolic activities such as rates of respiration, excretion or production of other waste products, which affect the toxicity. In the present study, the doses of Fenpropathrin dissolved in 0.5ml of corn oil and administered once orally to the rats as a single dose by intubation cannula.

2.4 Approximation of Dose Range and Mortality Percentage

Initially, Approximate LD₅₀ was calculated by a pilot study named "up and down" using two animals with gradually increasing doses of Fenpropathrin. Six doses were picked *viz.* 5, 10, 20, 40, 80 and 160 mg/kgbw for determination of approximate LD₅₀. The results of this pilot study indicated approximate LD₅₀ for male and female rats at 50 mg/kgbw and 40 mg/kg bw respectively. Fenpropathrin did not produce any toxic effects at 5 mg/kg bw and 10 mg/kg bw dose levels, hence 10 mg/kg may be considered as NOAEL (No Observed Adverse Effect Level). Doses from 20 mg/kg bw to 160 mg/kg bw showed signs of toxicity *viz.* salivation, choreoathetosis, seizures, aggressive sparring, whole body tremors and prostration in the treated animals of both sexes.

We conducted confirmatory experiments in accordance with the method provided by Miller and Tainter (1944), based on the results of our pilot study¹⁰. Total 10 groups (5 groups of male and 5 groups of female rats) were selected, each containing 10 animals. For both the sexes, 5 doses of Fenpropathrin *viz.* 15, 30, 45, 60 and 75mg/kg bw were chosen. Simultaneously two groups (one of male and one of female) of control animals were received 0.5ml of corn oil through the same route of administration. Mortality was then calculated from 0% to 100%¹⁵. For the toxic signs and symptoms the rats were observed for 2 hours and then for 4, 6, 24, 48, 72 and 96 hours. Any change in behaviour pattern and other responses were carefully noted. After 96 hours, the number of deceased rats in every single group was counted. The mortality % was estimated as per the graphical method procedure proposed by Miller and Tainter (1944)¹⁰.

3. Results

3.1 Toxicity Symptoms

Initially, Fenpropathrin did not produce any significant effect on central nervous system (CNS) up to 10 mg/kg bw dose level. However, when the doses of 20 mg/kg bw to 160 mg/kg bw were administered, the animals of both sexes showed

signs of toxicity viz. salivation, choreoathetosis, seizures, aggressive sparring, whole body tremors and prostration. The animals exhibited writhing and twisting movement of the neck and tail due to choreoathetosis, followed by

laboured breathing, gasping, and death. The parameters observed for toxicity study after the administration of the Fenpropathrin in selected doses groups compared with control groups are presented in Table 1.

Table 1. Observations of overall health and behaviour in control and treated groups

Observation	Sex	Control group	15 mg/kg bw	30 mg/kg bw	45 mg/kg bw	60 mg/kg bw	75 mg/kg bw
Body weight	M	☺	☹	☹	☹	☹	☹
	F	☺	☹	☹	☹	☹	☹
Temperature	M	☺	☺	☺	♦	▲	▲
	F	☺	☺	♦	♦	▲	▲
Salivation	M	☹	☹	▲	▲	▲	▲
	F	☹	☹	▲	▲	▲	▲
Lethargy	M	-	-	-	+	+	+
	F	-	-	+	+	+	+
Tremors	M	-	-	-	+	+	+
	F	-	-	-	+	+	+
Seizures	M	-	-	+	+	+	+
	F	-	-	+	+	+	+
Choreoathetosis	M	-	+	+	+	+	+
	F	-	+	+	+	+	+
Drowsiness	M	-	-	+	+	+	+
	F	-	+	-	+	+	+
Sedation	M	☹	☹	☹	■	■	■
	F	☹	☹	■	■	■	■
Blinking of eyes	M	☺	☺	♦	▲	▲	▲
	F	☺	♦	▲	▲	▲	▲
Scratching	M	-	-	+	+	+	+
	F	-	+	+	+	+	+
Aggression	M	-	-	▲▲	▲▲▲	▲▲▲	▲▲▲
	F	-	-	♦	▲▲▲	▲▲▲	▲▲▲
Excitation	M	☺	+	+	+	+	+
	F	☺	+	+	+	+	+
Thirst	M	☺	▲	▲	▲	▲	▲
	F	☺	▲	▲	▲	▲	▲
Food intake	M	☺	☺	▼	▼	▼	▼
	F	☺	▼	▼	▼	▼	▼
Urination	M	☺	☺	□	□	□	□
	F	☺	□	□	□	□	□
Rate of respiration	M	☺	☺	▲ (LB)	▲ (LB,g)	▲ (LB,g)	▲ (LB,g)
	F	☺	▲ (LB)	▲ (LB)	▲ (LB,g)	▲ (LB,g)	▲ (LB,g)
Mortality	M	0% (Alive)	0%	10%	40%	60%	80%
	F	0% (Alive)	0%	20%	50%	70%	90%

Abbreviations/signs: (M), male; (F), female; (☺), Normal; (☹), No effect; (-), Not present; (+), Present; (▲), Increased; (♦), Slightly increased; (▲▲), Moderately Increased; (▲▲▲), Highly Increased; (■), Observed; (□), Frequent; (LB), Laboured breathing; (g), gasping (▼), Decreased.

3.2 Transformation of %Mortalities to Probits and Calculation of LD₅₀

At each Fenpropathrin dose level, the number of deceased male and female rats was recorded (Tables 2 and 3). By

Finney’s method, the % (percentage) of animals that died at each dose level was converted to probit (Table 4)¹⁴. In the present study, for male rats Log LD₅₀ is 1.722 (Figure 1) and calculated LD₅₀ is 52.72 mg/kg bw and for the female rats Log LD₅₀ is 1.682 (Figure 2) and LD₅₀ is 48.08 mg/kg bw were obtained.

Table 2. Results of Fenpropathrin lethal doses for LD₅₀ calculation in male Wistar rats

Group	Dose (mg/kg bw)	Log Dose	% Dead	Probits
1	15	1.176	0	0
2	30	1.477	10	3.72
3	45	1.653	40	4.75
4	60	1.778	60	5.25
5	75	1.875	80	5.84

Table 3. Results of Fenpropathrin lethal doses for LD₅₀ calculation in female Wistar rats

Group	Dose (mg/kg bw)	Log Dose	% Dead	Probits
1	15	1.176	0	0
2	30	1.477	20	4.16
3	45	1.653	50	5.00
4	60	1.778	70	5.52
5	75	1.875	90	6.28

Table 4. Conversion of % mortalities to probit

%	0	1	2	3	4	5	6	7	8	9
0	-	2.67	2.95	3.12	3.25	3.36	3.45	3.52	3.59	3.66
10	3.72	3.77	3.82	3.87	3.92	3.96	4.01	4.05	4.08	4.12
20	4.16	4.19	4.23	4.26	4.29	4.33	4.36	4.39	4.42	4.45
30	4.48	4.50	4.53	4.56	4.59	4.61	4.64	4.67	4.69	4.72
40	4.75	4.77	4.80	4.82	4.85	4.87	4.90	4.92	4.95	4.97
50	5.00	5.03	5.05	5.08	5.10	5.13	5.15	5.18	5.20	5.23
60	5.25	5.28	5.31	5.33	5.36	5.39	5.41	5.44	5.47	5.50
70	5.52	5.55	5.58	5.61	5.64	5.67	5.71	5.74	5.77	5.81
80	5.84	5.88	5.92	5.95	5.99	6.04	6.08	6.13	6.18	6.23
90	6.28	6.34	6.41	6.48	6.55	6.64	6.75	6.88	7.05	7.33

3.2 Standard Error Calculation of LD₅₀

With the following formula given by Ghosh (1984)¹⁶, SE of the LD₅₀ was determined. (N = Number of animals in each group)

$$\text{Approximate Standard Error of LD}_{50} = (\text{Log LD}_{84} - \text{Log LD}_{16}) / \sqrt{2N}$$

The Probits of 84 and 16 are calculated from Table (4) and found to be 5.99 and 4.01 (approximately 6 and 4), respectively. In case of male rats, the log LD values for the probits 6 and 4 are 1.844 and 1.602 (obtained from the line

on the graph in Figure 1) and their antilogs are 69.82 and 39.99 respectively. In case of female rats, the log LD values for the probits 6 and 4 are 1.801 and 1.561 (obtained from the line on the graph in Figure 2) and their antilogs are 64.56 and 36.39 respectively. After putting these values in formula (1), the Standard Error of LD₅₀ is 8.61 for male rat and 8.13 for female rat. Therefore, LD₅₀ Fenpropathrin in corn oil for male rat is 52.72±8.61 and 48.08±8.13 when given orally, with 95% confidence interval.

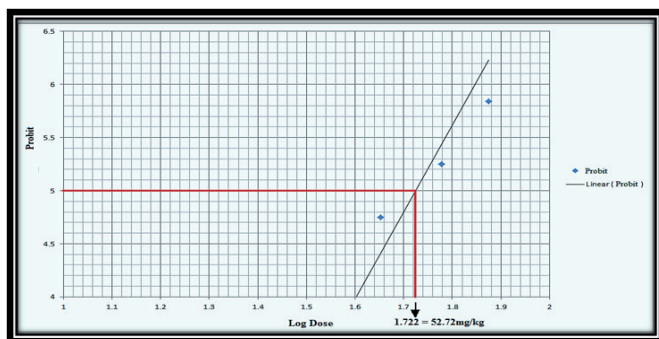


Figure 1. Graph plot showing Log doses versus probit from Table 4 for the calculation of oral LD_{50} of Fenpropathrin in male Wistar rats.

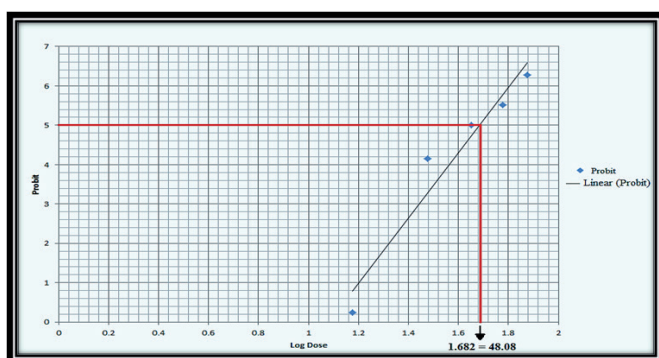


Figure 2. Graph plot showing Log doses versus probit from Table 4 for the calculation of oral LD_{50} of Fenpropathrin in female Wistar rats.

4. Discussion

Synthetic pyrethroids are available in wide variety of insecticide formulations and extensively used in indoor and outdoor environments, including agriculture, horticulture, public health initiatives and veterinary use for pest control because of their high bio-efficacy¹⁷. In recent years, excessive production and application of pyrethroid pesticides has raised potential environmental hazards to animals and humans as they accumulate in the food chain¹⁸. Biological testing and monitoring assessed the presence of pesticide residues in fresh or cooked fruits and vegetables and in processed food products¹⁹. Consumption of these food products has been linked to high levels of exposure to pesticide. Epidemiological evidence, medical reports and research laboratory studies suggest that pyrethroid exposure contributes to immunotoxic, neurotoxic, reproductive toxicity effects, developmental defects and behavioural disorders in humans and animals, despite being considered reasonably safe for humans^{20–26}. Thus, it becomes important to know the LD_{50} of the pyrethroid pesticides before using them.

The current research was conducted to investigate, the Fenpropathrin's acute oral toxicity in both sexes of Wistar rats. The pesticide dissolved in corn oil and administered once orally to rats at different dose levels (15, 30, 45, 60 and 75 mg/kg bw) as recommended in OECD/OECD Guidelines (2001)²⁷. The male and female experimental rats exhibited common symptoms of pyrethroid toxicity i.e. salivation, choreoathetosis, seizures, aggressive sparring, whole body tremors and prostration at dose levels of 20 to 160 mg/kg bw. However, as observed in pilot study, the single oral dose of Fenpropathrin did not show any toxic effect at the 5 and 10 mg/kg bw dose levels. Hence, 10 mg/kg bw may be considered as NOAEL dose. The outcomes of this analysis show that Fenpropathrin's oral LD_{50} was found to be 52.72 ± 8.61 in male Wistar rats and 48.08 ± 8.13 mg/kg bw in female Wistar rats.

Earlier studies with Fenpropathrin demonstrated that the vehicle and the sex of test animal could affect LD_{50} value. The oral LD_{50} of Fenpropathrin was reported to be 77.4 mg/kg bw (corn oil as vehicle) and 164 mg/kg bw (gum arabic as vehicle) in male Sprague-Dawley rats, where as in female Sprague-Dawley rats the reported oral LD_{50} was 66.7 mg/kg bw and 104 mg/kg bw with corn oil and gum arabic respectively^{28,29}. Kohda (1979)³⁰ found dermal LD_{50} of Fenpropathrin (with corn oil as vehicle) to be 1600 mg/kg bw and 870 mg/kg bw for male and female Sprague-Dawley rats respectively. For Japanese albino rabbits, the oral LD_{50} of Fenpropathrin with corn oil as vehicle was 675 mg/kg bw and 510 mg/kg bw for male and female animals respectively³¹.

In our investigation the oral LD_{50} of the Fenpropathrin using corn oil as vehicle is 52.72 ± 8.61 mg/kg bw in male and 48.08 ± 8.13 mg/kg bw in female Wistar rats.

5. Conclusion

For forensic toxicologists, the determination of LD_{50} is very significant for correlating or defining a chemical substance or other poison and for the evaluation of acute drug toxicity, food poisoning and cases of accidental domestic poisoning. According to standard protocols, Fenpropathrin was investigated, which revealed it to be a highly toxic pyrethroid since its LD_{50} value is low. It was observed that LD_{50} value for female rats was lower than that for male rats. The outcome of this study clearly shows that the oral LD_{50} of Fenpropathrin with corn oil as a vehicle is 52.72 ± 8.61 mg/kg bw in males and 48.0 ± 8.13 mg/kg bw in Wistar rats and NOAEL is 10 mg/kg bw in both sexes. The result of this study may serve as a basis for dose administration for further research on Fenpropathrin toxicity.

6. Conflict of Interest

None

7. Acknowledgement

This work was supported by University Grants Commission.

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