Original Article

Assessment of chlorpyrifos induced toxicity against *Acetyl cholinesterase* and investigation of various biochemical parameters

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DOI: 10.47750/pnr.2022.13.S08.115

Abstract

Chlorpyrifos pesticide is widely used to control harmful pesticides and insecticides. This well-known organophosphorus pesticidepossesses toxicity to its users. In the current study, we have evaluated the toxic effect of repeated exposure tochlorpyrifos in Wistar rats. The toxic effect of the chlorpyrifos at different dose levels *i.e.* low dose (10 mg/kg b.wt.), intermediate dose (30 mg/kg b.wt.), and high dose groups (60 mg/kg b.wt.) have been investigated. Various biochemical parameterssuch as glucose, total protein, ALT, AST, ALP, AChE, urea, creatinine, sodium, potassium, and chloride have been assessed. No toxic sign was observed in the treated group animals when compared with the control group animals. Under the condition of this study, the high dose animal body weight was found slightly reduce as compared with the control and other treated animal group. The study showed the various changes in the biochemical parameters in rats after repeated exposure to chlorpyrifos by the oral route. Under the condition of this study, the repeated oral administration of Chlorpyrifos in Wistar rats at the dose level of 60 mg/kg. b.wt. for 28 consecutive days, showed an alteration in the biochemical enzyme like ALT, AST, and AChe when compared with the control group respectively. The level of ALT and AST were found to increase and the level of AChe was found to decrease as compared with the control, low dose, and intermediate-dose group animals. Other parameters which were estimated, were found comparative with the control group. The use of chlorpyrifos in domestic and agricultural platforms provides a great help in minimizing the damages caused by insects, but on the other hand, its long-term exposure is harmful tothe animal as well as the human population.

Keywords: Chlorpyrifos, Organophosphorus Pesticide, Wistar Rats, Biochemical Parameter, 28 days exposure.

Introduction

Crops are routinely protected with chlorpyrifos, which is also approved for use in the control of termites, mosquitoes, cockroaches, fly ants, and lice[1,2]. Due to its potential toxicity against a variety of insect species and the fact that it is both affordable and leaves minimal residue on food grains, it is frequently employed in impoverished nations for effective crop protection. It also does not alter the activity of seeds. Along with target species, Chlorpyrifos is commonly used throughout India in large amounts as per official data of the directorate of plant protection, quarantine, and storage Govt. of India 2009-10 listed Chlorpyrifos as the ninth most consumed pesticide

in the country. Anemia and other alteration in hematology and biochemical parameter have been recorded during the repeated exposure[3]. As a lipophilic molecule, CPF easily passes through the cell into the cytoplasm[4]. When it entered into the cell it induces damage to the cellular molecules[5]. Several organophosphorus pesticides including Malathion, methyl parathion, and trichlorphon have displayed immunotoxicity during the various toxicological studies[6]. Chlorpyrifos causes deleterious effects through acetylcholinesterase inhibition at the synapse of central and peripheral nervous system[7] and cause vomiting, nausea, diarrhea, salivation tremor and convulsion-like symptoms. Sub-acute toxicological studies of chlorpyrifos have been reported in rats showing reduced weight and *Ache* inhibition[8].

Chlorpyrifos is a natural organic non-volatile poison and it is derived from thiophosphoric acid, its chemical name is o,o-diethyl o-3,5,6-trichloro-2-2pyridyl phosphorothioate. Chlorpyrifosis formulated in liquid form as spraying material,granular wettable powder, soluble concentrate pellets. Chlorpyrifos is insoluble in water but soluble in most organic solvents such as acetone, xylene, and methylene chloride. Chlorpyrifos is stable in acidic aqueous solution and its stability decrease with increased pH.

Comparing Chlorpyrifos to another organophosphorus pesticide, the chlorine group on Chlorpyrifos makes the molecule more lipid-soluble and has a longer half-life in the body, which lowers cholinesterase (ChE) levels more persistently and in granules.

When it comes to both target and non-target organisms, chlorpyrifos poisoning is comparable. Direct ingestion, oral administration during suicide attempts or unintentional inhalation, dermal route during spraying, and the toxic effects of chlorpyrifos on both humans and animals include effects on the central nervous system, cardiovascular system, and respiratory system. Exposure to chlorpyrifos can result in poisoning. After consumption, it has a variety of effects on mammals, including the suppression of the acetylcholinesterase (AChE) enzyme and other biochemical indicators[9].

Acetylcholinesterase is inhibited by chlorpyrifos poisoning by attaching to the enzyme's active site, which renders the enzyme inactive. In the liver, chlorpyrifos is converted to chlorpyrifos-oxon, a substance that is more powerful than chlorpyrifos alone and exhibits more activity toward serine-dependent ester hydrolases such AChE[10,11].

The main objective of thecurrent study was to evaluate the toxic effect of repeated exposure to chlorpyrifos in Wistar rats. Toxic effects of the chlorpyrifos at different dose levels *i.e*. low dose(10 mg/kg b.wt.), intermediate dose(30 mg/kg b.wt.), and high dose groups (60 mg/kg b.wt.) have been investigated. Further various biochemical parameters such as Glucose, Total protein, ALT, AST, ALP, AChE, urea, creatinine, sodium, potassium and chloride have been assessed.

Materials and method

Animal selection

Animals ranging from a body weight of 190-240g of age between 8-12 weeks were selected for the study as per the protocol specified.

Acclimatization and identification of animals

Before accepting animals for the experiment, the Animal house In-charge declared Wistar rats to be healthy and then released the animals for the experiment. The Wistar rats were received and kept for 5 days for acclimatization in the experimental room. Veterinary examination of all the animals was recorded on the day of receipt and during the acclimatization period. All the animals were housed in a group of three in polypropylene rat cages fitted with wire mesh tops. A tag hung on the cage hook mentioning the details of study number, animal number, sex, dose, group, experiment

start date, date of dosing, and date of completion of the experiment, Each animal within the cage was identified with tail marking. 12. (OECD Guideline No 423)

Environmental Conditions and maintenance of animals

All the rats were maintained in an environment controlled (Centrally Air-Conditioned room at a temperature of 20 ± 3 ºC, relative humidity of 55-60 %, 15-20 air changes/hour, a light intensity of 250–300 lux, and a 12 h light/dark cycle and noise intensity of <85 db.

Animals were housed in a group of three, in solid floored polypropylene rat cages. Each cage was fitted with a stainless-steel top grill having provision for keeping pellet feed and a water bottle. The bottom of the cage was layered with sterilized corn cob. Samples of bedding material were analyzed for specified microbiological and chemical contaminants on a routine basis. 13. Sterilized rat pellet diet (Krishna Valley Agrotech LLP, Pune.), was offered *adlibitum* to the rats throughout the experimental period. There were no known contaminants in the feed and water at levels that would have potentially influenced the outcome of this study. (a sample of bedding material was analyzed for microbiological and chemical contaminants a routine basis. 8.)

Animal Welfare

All animals were handled with due regard for animal welfare. Care of animals complied with the regulations of the Committee for Control and Supervision of Experiments on Animals (CPCSEA) Govt. of India and followed the standard operating procedures. 14

Acute oral toxicity study

In the assessment and evaluation of the toxic characteristics of a Test Item, determination of 'Acute Oral Toxicity in Wistar rats' is usually an initial step. This study was hence, performed to assess the acute oral toxicity with 'Chlorpyrifos technical' in Wistar rats.

The Procedure was followed as per OECD Guideline for Testing of Chemicals; Acute Oral Toxicity- Acute Toxic Class Method (No. 423, Section 4: Health Effects)

This study was conducted by taking 3 female rats. "Chlorpyrifos technical" as a single oral gavage dose (60 mg/kg b.wt.) was administered to rats after overnight fasting, using an intubation cannula

Dose preparation

Three doses were prepared in distilled water in the calibrated volumetric flask at the dose levels of 10 mg/kg b.wt.,30 mg/kg b.wt.and 60 mg/kg b.wt.For low, intermediate, and high dose groups respectively,and 60 mg/kg b.wt. for recovery high dose group. The doses were prepared freshly before dosing. 10 ml/kg b.wt. dose was administered to maintain each rat. The dosing was done via a metallic cannula attached to a syringe. the doses has been selected on the bases of available literature. 15. '"The Pesticide Manual, Editor: Dr. J. A. Turner, 18th Edition (2018)"

Table . 1 Groups, Dose level and Animal Used

Group	Dose level (mg/kg b.wt.)	Animal used	Sacrifice (after 28 days)	Recovery group-(Sacrifice after 14 days
Control (G1)	**0. 0**	**10**	**10**	**-**
Low Dose(G2)	**10**	**10**	**10**	**-**
Intermediate Dose(G3)	**30**	**10**	**10**	**-**

High Dose(G4)	**60**	**10**	**10**	**-**
Recovery control (G5)	**0. 0**	**10**	**-**	**10**
Recovery High Dose(G6)	**60**	**10**	**-**	**10**

Sub-Acute (Repeated) oral toxicity study

The experimental procedure followed was as per OECD guideline No. 407. 16.

The main study was conducted with 60 (30 male and 30 female) Wistar rats which were randomly distributed into six groups. Three groups of 10 rats each (5 male and 5 female) were administered "Chlorpyrifos Technical" orally at the dose levels of 10 mg/kg b.wt. (low dose), 30 mg/kg b.wt. (intermediate dose), and 60 mg/kg b.wt. (high dose) respectively for seven days a week for 28 days. Similarly, a control group of 10 rats (5 male and 5 female) was orally administered with distilled water (vehicle) for 28 days and was designated as a control group.

Two additional recovery groups i. e. 'recovery Control' and 'recovery High dose' each comprised of 10 rats (5 male and 5 female) were also administered with distilled water and test item i. e. Chlorpyrifos technical at the dose level of 60 mg/kg b.wt. respectively for 28 days. The body weight of the animals was recorded during the acclimatization period and on the I^{st} day of dosing, 7th, 14th, 21st, and 28^{th} days as per the OECD (409) protocol.

After 28 days, the treatment and control group of animals were sacrificed and blood was collected for biochemical investigations. Recovery animals were sacrificed after 14 days post-treatment to check the reversibility of biochemical parameters *e.g.* glucose (mg/dl), alanine aminotransferase (ALT) (U/L), aspartateaminotransferase (AST) (U/L), cholinesterase (U/L), Serum, alkaline, phosphatase (SAP) (U/L), phosphorus (mg/dl), triglycerides (mg/dl), urea (mg/dl), creatinine (mg/dl), total cholesterol (mg/dl), sodium (mEq/L), potassium (mEq/L), chloride (mEq/L) were estimated by using "Beckman Coulter AU480" Clinical chemistry autoanalyzer.

Statistical analysis

The data obtained were statistically analyzed using Minitab 16. 0. Standard errors and one-way ANOVA.

Results

Clinical signs

No toxic sign was observed in the treated group animals when compared with the control group animals.

Body weight

Under the condition of this study the high dose animal body weight was found slightly reduce as compared with the control and other treated animal group.

Table-1: Mean body weight data of male rats

Week Group	1	2	3	4	5
Control	185.2 ± 5.25	201.84 ± 5.97	217.94 ± 6.57	233.62 ± 6.46	249.88 ± 6.12
High Dose	189.84 ± 5.88	195.98 ± 6.27	203.76 ± 5.59	211.34 ± 6.16	218.56 ± 5.43
Low Dose	190.76 ± 3.43	205.38 ± 4.15	220.5 ± 4.49	236.36 ± 4.60	252.46 ± 4.95
Intermediate Dose	181.5 ± 5.21	196.7 ± 4.75	212.04 ± 3.95	228.08 ± 3.99	245.4 ± 3.87

Table-2 Mean body weight data of female rats

Week Group	1	2	3	4	5
Control	185.58 ± 8.91	196.06 ± 9.94	207.1 ± 9.80	217.72 ± 10.11	229.24 ± 10.28
High Dose	187.74 ± 6.56	195.6 ± 6.76	203.48 ± 6.91	211.18 ± 7.80	218.14 ± 7.80
Low Dose	184.56 ± 4.38	194.7 ± 4.83	205.8 ± 4.43	217.12 ± 4.73	228.94 ± 5.22
Intermediate Dose	181.2 ± 10.54	192.72 ± 9.99	204.22 ± 9.13	215.38 ± 10.22	226.82 ± 10.64

Table: 3: Body weight of male and female rats of Vehicle control at 0.0 mg/kg b.wt.

Animal No.	Sex	Before dosing	Day 7	Day 14	Day 21	Day 28	Animal No.	Sex	Before dosing	Day 7	Day 14	Day 21	Day 28
1	M	184.3	200.3	217.8	235.8	252.1	6	F	181.5	191.6	203.3	214.6	226.5
2	M	189.6	208.5	225.6	241.2	256.2	7	F	195.2	206.5	216.5	225.4	235.4
3	M	190.4	206.8	222.4	237	254.3	8	F	175.3	184.3	194.5	203.6	214.2
4	M	184.4	200	215.3	228.9	244.3	9	F	194.7	206.4	217.6	229.4	241.5
5	M	177.3	193.6	208.6	225.2	242.5	10	F	181.2	191.5	203.6	215.6	228.6
Mean ± S.D		185.2 ± 5.25	201.84 ± 5.97	217.94 ± 6.57	233.62 ± 6.46	249.88 ± 6.12			185.58 ± 8.91	196.06 ± 9.94	207.1 ± 9.80	217.72 ± 10.11	229.24 ± 10.28

Table: 4: Body weight of male and female rats of low dose groups (10 mg/kg b.wt.)

Animal No.	Sex	Before dosing	Day 7	Day 14	Day 21	Day 28	Animal No.	Sex	Before dosing	Day 7	Day 14	Day 21	Day 28
21	M	188.1	202.4	216.8	231.8	246.1	26	F	177.4	186.9	198.6	209.3	220.3
22	M	192.4	210.5	225.9	241.3	256.1	27	F	189.3	200.1	210.5	221.6	233.6
23	M	195.3	208.9	224.8	241.3	258.6	28	F	186.1	196.4	207.6	218.8	231.1
24	M	186.7	200.9	216.7	233.1	251.3	29	F	185.4	194.8	206.9	219.4	231.6
25	M	191.3	204.2	218.3	234.3	250.2	30	F	184.6	195.3	205.4	216.5	228.1
Mean ± S.D		190.76 ± 3.43	205.38 ± 4.15	220.5 ± 4.49	236.36 ± 4.60	252.46 ± 4.95	Mean ± S.D		184.56 ± 4.38	194.7 ± 4.83	205.8 ± 4.43	217.12 ± 4.73	228.94 ± 5.22

Table-5 Body weight of male and female rats of intermediate dose groups (30 mg/kg b.wt.)

Animal No.	Sex	Before dosing	Day 7	Day 14	Day 21	Day 28	Animal No.	Sex	Before dosing	Day 7	Day 14	Day 21	Day 28
31	M	184.3	200.4	215.4	231.7	247.6	36	F	176.1	189.9	201.8	212.3	223.3
32	M	177.9	193.4	211.2	228.4	248.3	37	F	172.3	182.6	195.4	206.5	218.4
33	M	189.4	203.1	216.8	231.9	248.1	38	F	181.6	192.8	203.7	214.5	225.4
34	M	178.3	194.2	209.2	225.9	243.6	39	F	199.1	209.3	219.6	232.9	245.3
35	M	177.6	192.4	207.6	222.5	239.4	40	F	176.9	189	200.6	210.7	221.7
Mean ± S.D		181.5 ± 5.21	196.7 ± 4.75	212.04 ± 3.95	228.08 ± 3.99	245.4 ± 3.87	Mean ± S.D		181.2 ± 10.54	192.72 ± 9.99	204.22 ± 9.13	215.38 ± 10.22	226.82 ± 10.64

Table 6: Body weight of male and female rats of high dose groups (60 mg/kg b.wt.)

Animal No.	Sex	Before dosing	Day 7	Day 14	Day 21	Day 28	Animal No.	Sex	Before dosing	Day 7	Day 14	Day 21	Day 28
11	M	194.1	200.5	205.5	216.4	222.8	16	F	176.9	184.9	191.2	197.5	204.8
12	M	188.4	195.1	207.3	214.0	220.6	17	F	194.1	201.8	206.8	212.2	218.4
13	M	189.1	195.3	201.3	207.4	215.8	18	F	191.2	200.5	207.5	214.5	220.6
14	M	181.2	186.4	195.3	202.5	210.4	19	F	189.2	197.1	205.4	215.2	221.5
15	M	196.4	202.6	209.4	216.4	223.2	20	F	187.3	193.7	206.5	216.5	225.4

Mean ± S.D	189.84 ± 5.88	195.98 ± 6.27	203.76 ± 5.59	211.34 ± 6.16	218.56 ± 5.43	Mean ± S.D	187.74 ± 6.56	195.6 ± 6.76	203.48 ± 6.91	211.18 ± 7.80	218.14 ± 7.80

Biochemical investigation

The level of ALT, and AST were found to increase and the level of Ache was found to decrease as compared with the control, low dose, and intermediate-dose group animals.Other parameters which were estimated, were found comparative with the control group.(Tables: 7 and 8)

Glucose: After the Chlorpyrifostreatmenti.e.at the end of the study the blood glucose level was found normal as compared to the pesticide control group.

Total protein: After the Chlorpyrifostreatmenti.e.at the end of the study the serum protein level was found to decrease as compared to the pesticide control group

ALT: After the Chlorpyrifostreatmenti.e.at the end of the study a dose-dependent increase in the serum ALT level was observed.On Day 29 serum ALT level was significantly increased in the high dose groups animals as compared to the pesticide control group.The

AST: After the Chlorpyrifos treatment i.e.at the end of the study a dose-dependent increase in the serum AST level was observed.On Day 29 serum ALT level was significantly increased in the high dose groups animals as compared to the pesticide control group.The

ALP: After the Chlorpyrifostreatmenti.e.at the end of the study the blood ALP level was found normal as compared to the pesticide control group

ACHE After the Chlorpyrifostreatmenti.e.at the end of the study a dose-dependent decrease in the serum Ache level was observed.On Day 29 serum Ache level was a significant decrease in the high dose groups animals as compared to the pesticide control group.

UreaAfter the Chlorpyrifostreatmenti.e.at the end of the study the blood urea level was found normal as compared to the pesticide control group

Creatinine After the Chlorpyrifostreatmenti.e.at the end of the study the serum creatinine level was found normal as compared to the pesticide control group

Sodium After the Chlorpyrifostreatmenti.e.at the end of the study the sodium level was found normal as compared to the pesticide control group

Potassium After the Chlorpyrifostreatmenti.e.at the end of the study the potassium level was found normal as compared to the pesticide control group

Chloride After the Chlorpyrifostreatmenti.e.at the end of the study the chloride level was found normal as compared to the pesticide control group

Table-7: Effects of Low, intermediate, and high doses of Chlorpyrifos on biochemical parameters of Male rats

Parameters	**Glu (mg/dl)**	**TP (g/dl)**	**SGOT (U/L)**	**SGPT (U/L)**	**SAP (U/L)**	**ACHE (U/L)**	**UREA(mg/dl)**	**CRET (mg/dl)**	**NA^+mEq/L**	**K^+ mEq/L**	**CL^-mEq/L**
Control(0.0 mg/kg b.wt.)	99.80 ±	7.62 ±	50.40 ±	48.20 ±	113.20	629.0 ±	53.40 ±	0.78 ±	143.20 ±	4.30 ±	102.80 ±

	1.62	0.09	2.88	4.32	± 7.85	33.99	3.05	0.07	1.30	0.13	1.48
Low dose (10.mg/kg b.wt.)	101.80 ± 5.26	7.67 ± 0.20	50.8 ± 1.30	53.00 ± 4.06	113.40 ± 3.85	630.4 ± 12.97	56.20 ± 3.63	0.74 ± 0.08	142.60 ± 1.95	4.20 ± 1.95	102.00 ± 2.00
Intermediate dose (30.mg/kg b.wt.)	101.00 ± 5.15	7.48 ↑1 0.33	66.0 ± 13.02	48.60 ± 17.78	115.20 ± 5.07	346.0 ± 28.15	51.60 ± 3.51	0.80 ± 0.09	143.00 ± 2.55	4.35 ± 0.18	104.20 ± 0.84
High dose (60.mg/kg b.wt.)	102.00 ± 4.53	7.71 ± 0.14	107.00 ± 26.40	107.2 ± 8.17	112.60 ± 5.22	284.40 ± 19.73	56.20 ± 2.17	0.80 ± 0.12	143.40 ± 1.14	4.41 ± 0.20	103.80 ± 1.64
Recovery control (0.0.mg/kg b.wt.)	101.60 ± 4.83	7.51 ± 0.38	50.6 ± 3.36	50.20 ± 11.48	126.20 ± 12.50	616.8 ± 12.21	56.20 ± 8.67	0.72 ± 0.24	142.00 ± 2.12	4.22 ± 0.22	103.80 ± 2.39
Recovery High dose(60.mg/kg b.wt.)	104.00 ± 5.96	7.39 ± 0.26	50.2 ± 1.48	52.00 ± 2.74	128.80 ± 16.08	307.40 ± 24.63	51.20 ± 8.07	0.75 ± 0.09	141.20 ± 1.30	4.19 ± 0.08	103.20 ± 1.64

Table-7: Effects of Low, intermediate, and high dose of Chlorpyrifos on biochemical parameters of female rats

Parameters	**Glu (mg/dl)**	**TP (g/dl)**	**SGOT (U/L)**	**SGPT (U/L)**	**SAP (U/L)**	**ACHE (U/L)**	**UREA(mg/dl)**	**CRET (mg/dl)**	**NA^+ mEq/L**	**K^+ mEq/L**	**CL^-mEq/L**
Control(0.0 mg/kg b.wt.)	101.80 ± 4.66	7.68 ± 0.18	53.6 ± 2.97	43.00 ± 11.58	115.60 ± 3.65	625.6 ± 24.21	57.60 ± 12.20	0.75 ± 0.07	144.60 ± 1.67	4.48 ± 0.21	104.40 ± 2.07
Low dose (10.mg/kg b.wt.)	102.80 ± 5.07	7.60 ± 0.15	48.6 ± 3.65	49.00 ± 5.52	115.80 ± 11.52	639.6 ± 17.27	53.20 ± 10.47	0.77 ± 0.11	142.80 ± 2.39	4.34 ± 0.23	103.60 ± 1.52
Intermediate dose (30.mg/kg b.wt.)	104.00 ± 4.30	7.46 ± 0.38	69.2 ± 4.76	49.40 ± 5.86	118.16 ± 8.45	342.6 ± 11.55	50.20 ± 10.71	0.78 ± 0.10	140.80 ± 0.45	4.22 ± 0.14	101.80 ± 1.48
High dose (60.mg/kg b.wt.)	101.60 ±	7.73 ±	112.40 ±	106.8 ±	122.60	196.00	154.40	0.83 ±	143.60	4.24 ±	102.00 ±

	4.83	0.19	8.65	3.83	± 6.27	± 10.98	± 7.50	0.11	± 2.51	0.19	0.71
Recovery control (0.0.mg/kg b.wt.)	101.00 ± 3.39	7.33 ± 0.52	47.6 ± 3.65	59.40 ± 11.46	113.40 ± 5.32	619.2 ± 3.19	44.40 ± 7.83	0.86 ± 0.09	142.80 ± 1.92	4.36 ± 0.27	103.60 ± 2.30
Recovery High dose(60.mg/kg b.wt.)	104.60 ± 9.24	7.26 ± 0.26	48.8 ± 2.59	56.60 ± 11.74	114.40 ± 19.89	598.6 ± 10.95	46.60 ± 7.99	0.82 ± 0.08	141.20 ± 1.64	4.30 ± 0.16	103.60 ± 1.14

Conclusion

The organophosphorus insecticide chlorpyrifos has gained popularity in India during the past year for controlling insects in a variety of places, mostly for agricultural, home, and industrial purposes.The WHO has classified chlorpyrifos as a moderately hazardous pesticide, providing clear evidence of its toxicity and potentially fatal effects on users and the population who are exposed to it directly or indirectly.The growing use of chlorpyrifos in India may also increase the risk to public health.The use of CPF in domestic and agricultural platforms provides a great help in minimizing the damages caused by insects, but on the other hand its long term exposure is harmful for animal as well as human population.Under the condition of this study, it observed that Chlorpyrifos is responsible for the alteration in liver enzyme like ALT, AST and neurological enzyme like Ache and also responsible for the body weight reduction .

Acknowledgement

The authors are thankful to the Shri Ram Institute of Industrial Research, Delhi, India for providing the facility for this research work.

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