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Full Length Article

Use of Clodinafop-Propargyl as a Rodenticide against Black Rat (*Rattus rattus*)

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Abstract

This study aims to assess the impact of clodinafop-propargyl herbicide on black rat (*Rattus rattus* L.). It was tested as bait using non- and free choice feeding method. Serial concentrations of the tested compound as bait were offered to rats through non-choice feeding technique during different periods to detect the most effective bait concentration gives high mortality percent. The results depicted that the best bait concentration which gave 100% mortality was 0.98% and the time of death ranged between 5–15 days with 6.2 days mean. The acceptance of tested bait was examined by free choice feeding technique and it was 45.83% with 100% mortality and the time of death ranged between 10–16 days with 6.7 days mean. The clinical symptoms were a reduce in body weight, loss of water through the skin, slow movement and loss of appetite of rats as well as increase in heart and lung weights. Additionally, cardiac hypertrophy and pulmonary hemorrhage as a result of treatment has been observed. Studying toxic action revealed that, 1/4 LD_{50} (348 mg/kg b. wt.) oral administration of clodinafop-propargyl after seven days caused remarkable increase in serum levels of lactate dehydrogenase (LDH) and malondialdhyde (MDA), but it caused marked decrease in total protein, total lipids and glutathione (GSH) contents. This disruptive effect is supported by histopathological changes in heart and lung tissues. Furthermore, application of the tested bait 0.98% of clodinafop-propargyl in poultry farm conditions achieved 87.77% reduction in rat population. So, it is taken into regard that clodinafop-propargyl bait has a strong effect against rats as it caused destruction of heart and lung tissue and motivation of oxidative stress leading to death.

Keywords: Clodinafop-propargyl; *Rattus rattus*; Free-choice feeding; Oxidative stress; Histopathology; Field application

Introduction

Rodents induce a serious problem for food security. Rodents cause extensive damage including loss of crop production, disease transmittance, damage to irrigation and water storage infrastructure (Gebhardt *et al.* 2011; Ordeñana *et al.* 2012; Kilonzo *et al.* 2013; Baldwin *et al.* 2014). Current rodenticides have some limitations. Firstly, rodents can produce a resistance to some rodenticides making them ineffective. Secondly, some rodenticides have secondary toxicity risks (Eason *et al.* 2010; Crowell *et al.* 2013). Aryloxyphenoxy-propionate herbicides (ArOPP) revealed neurotoxic, genotoxic, cytotoxic, and immunosuppressive in experimental rats (Barenekow *et al.* 2000; Charles *et al.* 2001; Pistl *et al.* 2003; Bortolozi *et al.* 2004). Clodinafop-propargyl is a systemic herbicide with aryloxyphenoxy propionic acid groups and used in wheat fields to control narrow-leaf weeds (Noshadi *et al.* 2017). It interferes with the production of fatty acids needed for plant growth in susceptible grassy weeds *via* inhibition of the enzyme acetyl coenzyme-A-carboxylase which is necessary for lipid biosynthesis (Hammami *et al.* 2011). Many studies have revealed that clodinafop-propargyl and its derivatives are toxic for various living organisms (Gui *et al.* 2011; Yin *et al.* 2011; Mir *et al.* 2014; Zaka *et al.* 2019). The oral LD_{50} was 1392 mg/kg b.wt in rats (EFSA Scientific Report 2005). The treatment of male and female albino rat (*Rattus norvegicus*) with glyphosate herbicide bait in both non- and free choice feeding methods caused 70 and 60% mortality, respectively (El-Abd 2015). Atrazine herbicide caused decrease in body and sex organs weight of rats after 7 days of treatment (Abarikwu *et al.* 2010; Khozimy *et al.* 2022). Transepidermal water loss (TEWL) represents a significant portion of insensible water loss for mice (Dmitrieva and Burg 2011). Fluazifop-p-butyl, an aryloxyphenoxypropionate herbicide, caused disturbance in antioxidant enzymes in animals (Olayinka and Ore 2015; Ore and Olayinka 2017). Clodinafop- propargyl cause decrease in body weight of male mice (EFSA 2020). Recent researches have been directed to assess other products for rodent control instead of the currently used rodenticides. Clodinafop-propargyl is available in low price and has wide

prevalence among farmers. Therefore, the purpose of this research was to evaluate the extent of effects resulting from clodinafop-propargyl usage on black rats, through laboratory and field implementation. Additionally, some biochemical parameters and pathological changes following treatment in heart and lung tissue were also assessed.

Materials and Methods

Compound

Common name: Clodinafop-propargyl.
Trade name: Topik (15% WP), herbicide, The LD_{50} value for rats is 1392 mg/kg b. wt. (EFSA Scientific Report 2005). It was purchased from Syngenta Co., Egypt.

Tested animals

Adult black rats (*Rattus rattus* L.) were caught by rat traps (30 × 15 × 20 cm) every day for one month from fields and stores located in Kerdasa, Giza, Egypt, then transferred to the Harmful Animals Research laboratory, Plant Protection Research Institute, Agriculture Research Center (ARC), Dokki, Giza, Egypt. Rats were adapted individually in cages of size (50 × 30 × 30 cm) and fed on crushed maize and water at 20–25°C and 12 h daily light/dark cycles for 15 days before the beginning of the experiments. Healthy rats were selected and divided into 18 groups (including 15 groups for bait concentrations and 3 groups for control, ten rats for each group) for non-choice test. Two groups of rats were used for choice test (one treated and one untreated, ten rats for each group). Other two groups were used for biochemical and histological examinations. The weight of rats ranged about (180 – 200 g).

Non-choice feeding test

Serial concentrations of clodinafop-propargyl bait (0.45, 0.57, 0.68, 0.82 and 0.98% by constant factor of 1.2) were tested using non-choice feeding technique. It was used as bait mixed with crushed maize. Each rat was fed on treated bait 50 g for different periods (3, 7 and 10 days) to assess the best concentration that gives the high mortality percent. The bait replenished daily through treatment period and the consumed amount of bait was daily weighted. The treated bait was removed, and survivor animals were fed on standard diet and observed up to 28 days. The mortality percentages were recorded during these periods (Shefte *et al.* 1982).

Free choice feeding test

Free choice feeding test is a serious method for assessment of the acceptability of clodinafop-propargyl bait (0.98%) comparing with challenge diet (65% crushed maize + 25% ground wheat + 5% sugar + 5% corn oil) according to (Palmateer 1974). The treated bait (0.98%) and challenge diet were offered to each rat (50 g of each) in small separate tureen for ten successive days. Their position was daily changed to a void feeding preference for certain location. The mortality percent and consumed amount of bait and diet were recorded daily. Bait acceptance was calculated using the following equation (Mason *et al*. 1989).

$$\text{Acceptance\%} = \frac{\text{Consumed amount of treatment bait (g)}}{\text{Consumed amount of treatment bait (g) + challenge diet (g)}} \times 100$$

Biochemical and histopathological studies

Samples preparation: Rats were orally administered with ¼ LD_{50} (348 mg/kg b. wt.) of clodinafop-propargyl according to (EFSA Scientific Report 2005). Animals were sacrificed with diethyl ether anesthesia after seven days of treatment. Blood samples were collected from cervical vein and left to coagulant at room temperature. Some samples were centrifuged at 4000 rpm for 15 min for determination of malondialdhyde MDA level, and the other at 3000 rpm for 10 min to determine lactate dehydrogenase (LDH) activity, total protein, total lipids and glutathione (GSH) contents. The clear supernatant serum was removed and kept in deep freezer at -20°C until used (Henry 1979). The same process was occurred with untreated rats.

Biochemical analysis

Serum LDH and total protein were assayed by enzymatic colorimetric method according to the method of Pesce (1984) and Titez (1994) using kits from Spectrum Co. Serum total lipids, GSH content and MDA level were assessed utilizing reagent kit bought from Biodiagnostic Co. (Egypt) according to methods of (Zöllner and Kirsch 1962); (Beulter *et al*. 1963) and (Ohkawa *et al.* 1979), respectively.

Histopathological studies

After dissection, heart and lung from each treated and untreated rat were rapidly removed. Pieces from these organs of each rat were rapidly fixed in 10% neutral buffered formalin for 24 h. Then, they were washed in running tap water and serial dilutions of ethanol were used for dehydration process, cleared in xylene then embedded in paraffin at 56°C in hot air oven for 24 h. The paraffin wax tissue blocks were prepared for sectioning by microtome at 4 µm thickness. Freshly prepared sections, floating on a 40°C water bath containing distilled water, were collected on glass slides, deparaffinized and stained with hematoxylin and eosin (H&E) stains according to the method of (Banchroft *et al.* 1996).

Field experiment

Field evaluation of clodinafop-propargyl bait (0.98%) was carried out under poultry farm conditions of Kafour Belshay Village, Kafr El-Zayat district, El-Gharbiya Governorate which infected with *R. rattus*. The area of 1800 m^2 was

divided into three regions for treatment and three as a check control. The population density of rats was estimated pre and post treatment using the food consumption method according to (Dubock 1984). Pre-treated with diet 3000 g (small plastic sacks 250 g of each) was put inside bait station (Fig. 1) and distributed in and out the farm. The consumed amount was weighted daily for five days and removed. The daily consumption was estimated from the average consumption of the fourth and fifth days only. After that, clodinafop-propargyl treated bait was applied and changed every 3 days until consumption stopped. The bait stations were left empty for one a week. Then untreated crushed maize was placed inside each bait station for one week. The consumed amount was recorded, and the population reduction of rats was calculated as follows:

Statistical Analysis

$$\text{Population reduction\%} = \frac{\text{Pre-treatment consumption (g) - Post-treatment consumption (g)}}{\text{Pre-treatment consumption (g)}} \times 100$$

Experimental design was completely randomized with different replicate. The obtained data were statistically analyzed by one way ANOVA and Least Significant Difference (LSD) at ($P \leq 0.05$) using Costat program (Cohort Software 2005).

Results

Impact of clodinafop-propargyl bait against *R. rattus* in laboratory

Table 1 shows the effect of serial concentrations of clodinafop-propargyl bait against *R. rattus* using non-choice feeding technique to achieve the highest mortality rate. A gradual increase in mortality percentage was observed with increasing tested compound concentration and increasing time of feeding. Regarding feeding for 3 days, the tested concentrations (0.45, 0.57, 0.68, 0.82 and 0.98%) induced morality rates of (0, 0, 20, 30 and 40%, respectively). Increasing feeding time with bait to 7 days increased the mortality percent to be (10, 20, 40, 50 and 70% respectively). While rats treated with bait for 10 days caused marked increase in mortality rate. The high concentration of bait (0.98%) induced most potent morality percent (100%) with average consumption of bait 6.12 g compared with the average consumption of control 10.66 g. So, the most effective bait concentration was 0.98% that produced 100% mortality and the time of death ranged between 5–15 days with 6.2 days mean. There was significant decrease in treated bait consumption compared to untreated rats feeding. Concerning the free-choice feeding test with clodinafop-propargyl bait (0.98%) in Table 2, the average consumption of challenge diet was 3.08 g, while it was 4.14 g for treated bait compared with the average consumption of control rats was 10.66 g. There was significant decrease in treated bait and challenge diet comparing with control rats. The treated bait induced high acceptance percent (45.83%) causing 100% mortality and the time of death ranged between 10–16 days with 6.7 days mean.

Fig. 1: Bait station for field application

Clinical symptoms and pathological changes

Clodinafop-propargyl bait (0.98%) caused clinical symptoms and pathological changes on *R. rattus* as noticed in Table 3. Body weights of rats were decreased obviously after treatment recording 160 g compared with control 200 g. In addition to that, treatment caused excessive loss of water through the skin, slow movement and loss of appetite of rats. Heart and lung weights increased to be 4.48 and 4.50 g in treated rats comparing with 3.26 and 2.13 g in untreated rats, respectively. Additionally, dissection of treated rats showed cardiac hypertrophy and pulmonary hemorrhage.

Effect of clodinafop-propargyl on biochemical parameters

Data in Table 4 depicted that oral administration of ¼ LD_{50} of clodinafop-propargyl (348 mg/kg b. wt.) after seven days of treatment. Administration motivated significant decrease in serum total protein, total lipids and GSH content with difference percent of -41.58, -43.47 and -48.61%, respectively compared with control rats. Regarding LDH and MDA activities, treatment induced elevations persuading difference percent of 62.45 and 42.30%, respectively comparing with untreated rats.

Histopathological studies

The histopathological impacts of oral administration of ¼ LD_{50} (348 mg/kg b. wt.) clodinafop-propargyl on heart and lung tissues were very obvious and declared as follows. Normal myocytes were observed in untreated rats in Fig. 2. On the other hand, administration prompted disorganization of myocarial bundles of heart section associated with congestion of blood vessels in Fig. 3. The normal structure of lung tissue of control rats was depicted in Fig. 4. While

Table 1: Response of black rat, *R. rattus*, to different concentrations of clodinafop-propargyl bait using non- choice feeding technique

Feeding periods / Bait concentration	3 days						7 days						10 days					
	Average consumption (g) (Mean ± SE)		LSD	Mortality%	Time of death (day)		Average consumption (g) (Mean ± SE)		LSD	Mortality %	Time of death (day)		Average consumption (g) (Mean ± SE)		LSD	Mortality %	Time of death (day)	
	Treatments	Control			Range	Mean	Treatments	Control			Range	Mean	Treatments	Control			Range	Mean
0.45	10.34^{a} ±0.28			0	.....	.....	9.74^{b} ± 0.22			10	10	10	7.22^{bc} ±0.21	10.66^{a} ±		30	9.15	12.0
0.57	9.42^{b} ± 0.19			0	.....	.....	9.2^{b} ± 0.29			20	9-12	10.5	7.68^{b}±0.07	0.45		50	8-17	10.4
0.68	8.86^{c} ± 0.13	10.54^{a} ±0.13	0.56	20	8-12	10.5	8.24^{c} ± 0.13	10.28^{a} ±0.15	0.52	40	8-16	9.3	7.53^{b} ±0.16		0.88	60	8-16	6.0
0.82	8.62^{c} ± 0.21			30	7-14	7	7.82^{cd} ±0.10			50	7-16	6.8	7.73^{b} ±0.07			60	7-14	8.5
0.98	8.36^{c} ± 0.19			40	6-14	7.5	7.38^{d} ± 0.15			70	6-16	6.6	6.12^{c} ±0.43			100	5-15	6.2

Values are expressed as means ± standard error

^{abcd} values in column with different letters are significantly different at ($P \leq 0.05$).

LSD: Least Significant Difference

Table 2: Effect of clodinafop-propargyl bait (0.98%) against *R. rattus* using free- choice feeding method

Average consumption (g) (Mean ± SE)		Mortality (%)	LSD	Acceptance (%)	Time to death (day)	
					Range	Mean
Treated bait	4.14^{b} ± 0.51					
Challenge diet	3.08^{b} ± 0.23	100%	1.595	45.83	10–16	6.7
Control	10.66^{a} ± 0.45					

Values are expressed as means ± standard error

^{ab} values in column with different letters are significantly different at ($P \leq 0.05$).

LSD: Least Significant Difference

Table 3: Clinical symptoms caused by clodinafop-propargyl bait (0.98%) on the body, heart and lung of *R. rattus*

Organ	Average weight (g)		LSD	Clinical symptoms
	Untreated	Treated		
Body	200^{a} ± 5.78	160^{b} ± 3.26	18.44	Reduction in body weight, loss of water through the skin, slow movement and loss of appetite
Heart	3.26^{b} ± 0.12	4.48^{a} ± 0.16	0.64	hypertrophy
Lung	2.13^{b} ± 0.18	4.50^{a} ± 0.12	0.585	hemorrhage and congestion

Values are expressed as means± standard error

^{ab} values in column with different letters are significantly different at ($P \leq 0.05$).

LSD: Least Significant Difference

Table 4: Effect of ¼ LD_{50} (348 mg/kg) of clodinafop-propargyl on some biochemical parameters of *R. rattus*

Groups-parameters	Control	Treatment	Difference %	LSD
Total protein (mg/dL)	12.53^{a} ± 0.82	7.32^{a} ± 0.60	-41.58	2.81
Total lipids (mg/dL)	1068.28^{a} ± 64.65	603.91^{b} ± 35.08	-43.47	203.95
GSH mmol/L	0.32^{a} ± 0.02	0.17^{b} ± 0.01	-48.61	0.069
LDH (U/L)	81.67^{b} ± 1.77	132.67^{a} ± 2.91	62.45	9.437
MDA nmol/L	4.90^{b} ± 0.15	6.63^{a} ± 0.22	42.30	0.744

Values are expressed as means± standard error

^{ab} values in column with different letters are significantly different at ($P \leq 0.05$).

LSD: Least Significant Difference

oral treatment of ¼ LD_{50} of the tested compound caused various lesions in lung tissue including presence of hemorrhagic pneumonia in form of RBCs infiltration within the alveolar lumen in Fig. 5, interstitial pneumonia in form of inter-alveolar inflammatory cells infiltration with thickening of the alveolar wall associated with rupture the walls of other alveoli leading to emphysematous alveoli in Fig. 6 and also massive infiltration of lymphocytes leading to larges size peri-bronchial lymphocytic nodule in Fig. 7.

Field assessment

Impact of clodinafop-propargyl bait (0.98%) against *R. rattus* was estimated under poultry farm condition. Data in Table 5 pointed that the average consumption of crushed maize in pre-treatment was 1051.25 g from 3000 g, while it was 661.25g during treatment period. Additionally, the average consumption in the post-treatment period was 133.33 g compared with 1293.37 g of control. The results revealed that clodinafop-propargyl bait (0.98%) achieved 87.31% reduction in rat population. There was significant difference at ($P \leq 0.05$) between average rat consumptions during the experiment.

Discussion

In the current study, treatments of *R. rattus* with serial concentrations of clodinafop-propargyl through non-choice technique produced lethal action. Where, the mortality percent increased with increasing the concentration of the treated bait and period of feeding. Thereby the most functional concentration of clodinafop-propargyl bait is 0.98% producing high mortality percent. This action may be

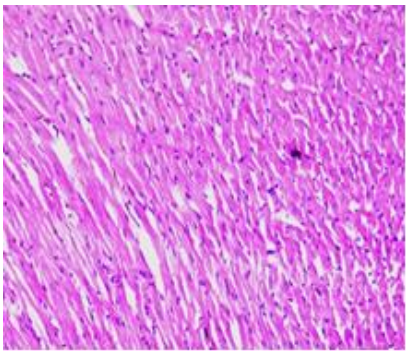

Fig. 2: Photomicrograph of H&E stained heart section of untreated rats showing normal structure of heart containing normal myocytes of heart. 400x

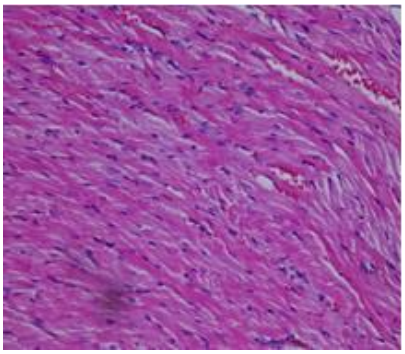

Fig. 3: Photomicrograph of H&E stained heart section of clodinafop-propargyl treated rat shows disorganization of myocarial bundles associated with congestion of blood vessels. 400x

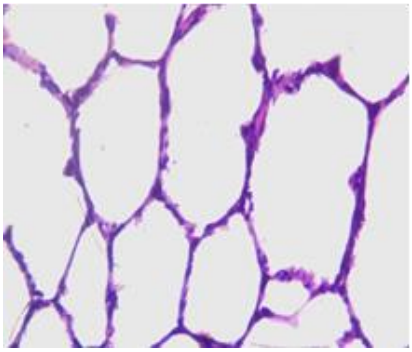

Fig. 4: Photomicrograph of H&E stained lung sections of untreated rats showing normal alveoli. 400x

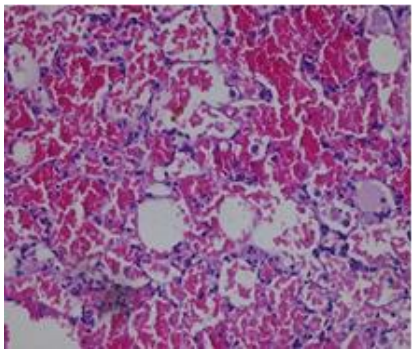

Fig. 5: Photomicrograph of H&E stained lung sections of clodinafop-propargyl treated rat showing hemorrhagic pneumonia in form of RBCs infiltration within the alveolar lumen. 400x

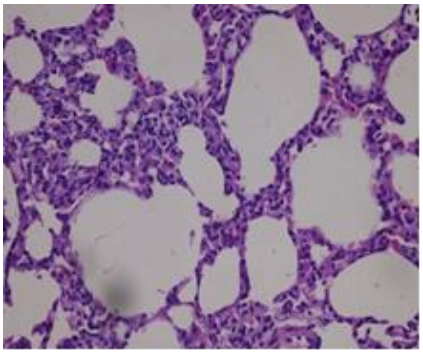

Fig. 6: Photomicrograph of H&E stained lung sections of clodinafop-propargyl treated rat showing interstitial pneumonia in form of inter-alveolar inflammatory cells infiltration with thickening of the alveolar wall associated with rupture the walls of other alveoli leading to emphysematous alveoli. 400x

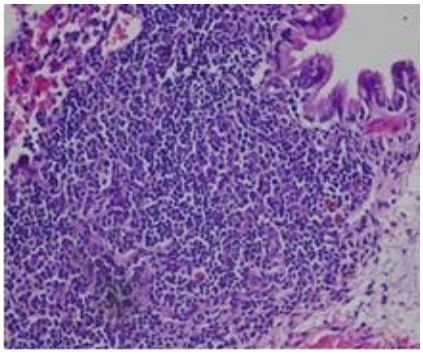

Fig. 7: Photomicrograph of H&E stained lung sections of clodinafop-propargyl treated rat showing massive infiltration of lymphocytes leading to larges size peri-bronchial lymphocytic nodule. 400x

Table 5: Effect of Clodinafop-propargyl bait (0.98%) against *Rattus rattus* under poultry farm conditions

Average consumption of bait (g) Mean ± SE				Population reduction %	LSD
Pre-Treatment	Treatment	Post-Treatment	Control	87.31	239.77
$1051.25^{b} \pm 10.87$	$661.25^{c} \pm 23.9$	$133.33^{d} \pm 3.19$	$1293.75^{a} \pm 10.68$		

Values are expressed as means (consumptions) ± standard error

^{abcd}values in column with different letters are significantly different at ($P \leq 0.05$).

LSD: Least Significant Difference

due to the toxic impact of clodinafop-propargyl bait on the organ functions inducing disturbance in body function. So, rat body becomes unable to resist the tested compound and causing death. In free-choice method in our study, rats developed acceptance without any additives. This may be related to high palatability to the clodinafop-propargyl bait. Previous study depicted that treatment of *R. norvegicus* with glyphosate herbicide bait *via* both non- and free choice feeding induced rat mortality (El-Abd 2015). Clodinafop-propargyl bait (0.98%) caused reduction in body weight of the tested rats. This decrease may be return to bodies lost large quantities of water during treatment as well as inhibition of acetyl coenzyme-A-carboxylase as indicated by (Tong 2005). It is concluded by (EFSA 2020) that clodinafop-propargyl cause decrease body weight in male mice. Atrazine herbicide caused decrease in body weight of rats after 7 days of treatment as a result of harmful impacts of atrazine (Abarikwu *et al.* 2010; Khozimy *et al*. 2022).

Protein is essential for building muscle, skin, enzymes, hormones, and all body tissues. As observed in this study, administration of clodinafop-propargyl produced disturbance in total protein. This interruption may be as a result of generation of free radicals by the tested compound affecting amino acids. This impact on proteins is supported by the histopathological effects on heart tissue. Where, treatment caused disorganization of myocarial bundles and congestion of blood vessels. This result agrees with (Nagra and Dang 2022) who proved that protein loss due to cardiac diseases can present with symptoms of heart failure like pitting edema, pleural effusion and shortness of breath. It was reported by (Mobarak *et al*. 2021) that clodinafop-propargyl caused noticeable decrease in total protein content in animals. Lipids play an important role in the body's storage of energy, the formation of cell membranes, intracellular signaling, dissolves some vitamins (A, D, E, and K) and hormonal regulation. In the present study, decrease in total lipid level may be due to the action of clodinafop-propargyl bait in inhibition of the enzyme acetyl coenzyme-A-carboxylase involved in lipid synthesis. Decrease of fatty acid leads to heart diseases, colon cancer, vitamin deficiency diseases, weaker immune system, hormonal imbalance, essential fatty acid deficiency diseases, and dermatitis (Jones and Rideout 2014). Administration of clodinafop-propargyl produced remarkable increase in serum LDH level causing disruption in heart function as supported by obvious lesions in heart section. LDH is a cytoplasmic enzyme that is exceedingly expressed in tissues. LDH is a biomarker widely used in toxicology and in clinical chemistry to diagnose cell, tissue and organ damage (Nathan *et al.* 2006). As the elevation in LDH activity is considered a marker for heart function disturbance. So this elevation can induce damage in the heart tissue. Regarding the toxic effects on lung tissue, treatment with the tested compound caused various injuries involving hemorrhagic pneumonia and interstitial pneumonia. The present lesions in lung tissue may be related to the toxic action of the tested compound through induction of oxidative stress.

The toxicity mechanism of various compounds is linked to formation of reactive oxygen species (ROS) which are able to react with proteins, nucleic acids, lipids and/ or molecules leading to changes in the structure and cell damage (Mates 2000). A majority of cells has defense mechanisms against the toxic effects of ROS *via* extra- and intracellular antioxidants that could inhibit overproduction of free radicals and make protection against propagation of peroxidative reactions (Kulikowska-Karpinska and Moniuszko-Jakoniuk 2004). The level of MDA, an indicator of lipid peroxidation, is a marker of oxidative stress and damage in *vivo* (Aitken and Roman 2008). Previous studies concluded that ArOPP herbicides generate free radicals and ROS, causing oxidative stress in susceptible plants and animal species (Luo *et al.* 2004; Olayinka and Ore 2015). GSH plays important role in cellular redox balance, so it is a vital line of protection against oxidation status in body (Aprioku 2013). In the current study, oral administration of clodinafop-propargyl caused significant increase in serum MDA activity and marked depletion in GSH content. This action may return to overproduction of ROS after treatment. These results are in line with those of (Ore and Olayinka 2017) who studied the effects of fluazifop-p-butyl, an ArOPP herbicide, on albino rats revealing increase in MDA level and decrease in GSH level. Our results are boosted by previous studies that concluded the toxic action of ArOPP herbicides *via* induction of oxidative stress (Yea *et al.* 2014; Olayinka and Ore 2015; Ore and Olayinka 2017).

Concerning the application in poultry farm, clodinafop-propargyl bait caused 87.31% reduction in rat population. This reduction may be due to the high efficiency of the used herbicide as it can withstand temperature, humidity, light and the palatability and also preference of rats for the tested bait. This field application is similar with (Kandil *et al*. 2022) who found reduction in *R. rattus* population in crops store was 71.34%.

Conclusion

Clodinafop-propargyl bait had a strong effect on extermination of rats through direct effect on oxidative enzymes, depletion in total protein, total lipids and destroying lung and heart tissues leading to death of rats in laboratory and field application. We recommend further studies to clarify the importance of the herbicide clodinafop-propargyl for rodent control.

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Author Contributions

Nema M. El-Abd and Randa A. Kandil proposed the research plan. Nema M. El-Abd, Randa A. Kandil and Heba Y. Ahmed processed the laboratory and field experiments and shared in writing the manuscript. Heba Y. Ahmed contributed in the biochemical and histological investigations. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no competing interests.

Ethics Approval

None.

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