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Research Article

Acute Toxicity Test Study of Tricyclazole Original Drug

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Abstract

Objective: In this study, the acute toxicity of 95% tricyclazole was observed through four acute toxicity tests of pesticides.

Methods: The acute oral toxicity test of rats was carried out by Horn's method, and the weight change, clinical manifestations and mortality of animals were observed, and 95% acute oral LD_{50} of tricyclazole was calculated. The acute percutaneous toxicity test of rats was carried out by the limited method, and the death was observed, and the acute percutaneous LD_{50} was calculated. The eye irritation test and skin irritation test of rabbits were investigated.

Results: During the observation period of acute oral percutaneous, rabbit eye irritation and skin irritation of 95% of female rats, the weight of all surviving animals increased, there were no abnormalities in the gross anatomy of all rats. The mortality rate of the 100mg/kg dose group was 0%, the mortality rate of 215mg/kg was 40%, and the mortality rate of 464mg/kg and 1000mg/kg dose group was 100%. The remaining trials showed no dead and dying animals. The oral test LD_{50} was 233mg/kg; Acute percutaneous LD_{50} >2000mg/kg. Without irrigation, 95% of tricyclazole has moderate irritation to the eyes and no irritation to the skin.

Conclusion: 95% of the original tricyclazole drugs were graded as moderate toxicity in rats and low in acute percutaneous toxicity, and non-rinsing after infection had moderate irritation to the eyes and no irritation to the skin.

Keywords: Tricyclazole, Acute oral toxicity, Acute percutaneous toxicity, Eye irritation, Skin irritation

Introduction

Tricyclazole is a kind of special bactericide for rice blast control with good safety and low toxicity, belonging to thiazole compounds. Current scientific research has confirmed that the drug is less toxic to humans, livestock, fish, shellfish, silkworms and birds, and does not change the microbial diversity of the environment, and the drug damage to different crops is relatively small, and good stability; However, it should not be ignored that the application of tricyclazole fungicide not only interferes with the population composition and biological composition of microorganisms in soil, but also causes the increase of genotoxic activity in rice crop water [1-4]. In recent years, many scholars have conducted studies in related aspects, although tricyclazole has no significant acute toxicity, and dietary risk assessment studies have found that tricyclazole has a low risk of being ingested by crabs, and it has also been confirmed that tricyclazole lacks genotoxicity to human lymphocytes and has no mutagenicity in related systems. However, the current research on its molecular physiological effects is not sufficient for the time being. Therefore, when people use tricyclazole-related products, they cannot ignore the possible chronic toxicity of such low-toxicity fungicides to earthworms and their impact on ecology, nor can they ignore the effects of tricyclazole on the development and function of vertebrate liver [5-7]. The study of tricyclazole has become a hot spot at home and abroad in recent years.

The acute toxicity test of 95% tricyclazole was carried out to observe its acute toxicity and provide theoretical basis for its research, production, and use. This study included acute oral percutaneous toxicity test in rats, acute eye irritation and skin irritation test in rabbits, etc, [8].

Materials and Methods

Test Instruments and Materials

Test Main Instruments and Equipment: 1% and 1‰ Electronic balance, purchased from Sartorius Scientific Instruments (Beijing) Co., Ltd; ULUPURE Ultrapure equipment, purchased from Sichuan ULUPURE Ultrapure Technology Co., Ltd; Handheld slit lamp microscope, purchased from Suzhou Kangjie Medical Co., Ltd.

Test Materials: The subject matter of this study was 95% tricyclazole (the actual measured pH is 7.8), which was provided by Guangdong Zhongke Yinghai Technology Co., LTD.

Normal saline: Weigh 0.9g sodium chloride, dissolve in a small amount of pure water, dilute to 100 mL. 2% sodium fluorescein saline solution: Weigh 0.2 g sodium fluorescein in a suitable container, then add 10 mL normal saline, fully dissolved, and filtered to obtain 2% sodium fluorescein saline solution.

Experimental Animals: A total of 45 SPF SD rats, 35 female (non-pregnant and undelivered) and 10 males, were purchased from Guangdong Weitong Lihua Laboratory Animal Technology Co., LTD. The animals were 8-10 weeks old at the beginning of exposure. The weight of the animals in the acute oral test ranged from 183.45 g to 234.43 g. The weight of the females and males in the acute percutaneous toxicity test ranged from 205.93 g to 251.41 g and 248.63 g to 280.72 g.

There were 6 ordinary New Zealand rabbits (2 ♀, no pregnancy and no birth; 4), purchased from Hunan Taiping Biotechnology Co., LTD. The animals were 3~4 months old at the beginning of exposure. The weight ranges from 2.021kg to 2.704kg. Animals were quarantined/acclimated after receiving them. The adaptation period was at least 3 days, during which no abnormality was observed in the animals.

Acute Oral Toxicity Test in Rats

Pretest results: The experimental subjects of SD rats were poisoned orally, and the animals died at the dose of 464mg/kg. In this experiment, Horn's method was used, and the dose series of 95% tricyclazole were 0mg/kg, 100 mg/kg, 215mg/kg, 464mg/kg, and 1000mg/kg. The stratified random method was used to divide the subjects, 5 animals in each group, different doses of test preparations were given at a single time, fasting overnight before infection, observation for 14 days after infection, and the first day of infection was set as D1.

Clinical observation was carried out once a day about 30min, 4h and D2~D15 after infection, and the poisoning reaction and death of each animal were recorded. Animals were weighed once at D1 (before poisoning), D8 and D15. Animals that died during the trial period and were still alive at the end of the observation period (D15) were euthanized and grossly dissected.

Acute Percutaneous Toxicity Test in Rats

This experiment refers to the guiding principles [8], and 2000mg/kg dose is selected for limited test. At the same time, a parallel control group is set up. In this experiment, 20 SD rats were used, half male and half female; The test object was applied to the marked area on the back of the animal for about 24h, and then the test object was removed with purified water, and the day of poisoning was set as D1. Animals were observed for 14 days after being poisoned.

After poisoning (D1) to D15, the animals were clinically observed once a day, and the poisoning reaction and death of each animal were recorded. Animals were weighed once at D1 (before poisoning), D8 and D15. Gross dissection was performed on animals that were still alive at the end of the observation period (D15). According to the mortality and mortality of the animals, the LD_{50} was calculated, and the toxicity of the test objects was graded.

Acute Eye Irritation Test in Rabbits

In this experiment, 3 rabbits were used for the test, and the rabbits were examined for ophthalmology one day before the poisoning, and the rabbits with healthy eyes were selected, and the test object was given to the right eye, and the left eye was not treated as a control. When the poison is infected, gently lift the lower eyelid of the animal's right eye and put 0.1 g of the test object directly into the conjunctival sac, so that the upper and lower eyelids are passively closed for 1 s to prevent the test object from being lost, and the eyes are not rinsed for 24 h. The day of the poison infection is set at D0. Clinical observation was performed on the day before (D-1) and about 1 h, 24 h, 48 h, and 72 h after poisoning, and eye examination and ocular damage score were performed at about 1 h, 24 h, 48 h, and 72 h after poisoning. Animals were weighed 1 time at D0 and on the day of the end of the test.

Acute Skin Irritation Test in Rabbits

For reference to the guiding principle [8], In this test, three rabbits were used to remove hair from both sides of the spine on the animal's back the day before infection. When contaminating the poison, put 0.5 g of the test object on cellophane, moisten it with an appropriate amount of pure water, apply it slowly and evenly on the cellophane, first cover the skin in the marked area on the left side of the cellophane upside down, then cover it with two layers of gauze, and then fix it with breathable pressure-sensitive tape for about 4 h. The right skin was used as a control, and the other treatments were the same as those of the left skin except for the test substance. The first day of infection is set as D1. Clinical observation was performed on D-1 (the day before infection), and clinical observation and skin irritation response scores were performed about 1 h, 24 h, 48 h, and 72 h after the test object was removed. Animals were weighed 1 time on D1 and the day of the end of the test.

Results

Acute Oral Toxicity Test in Rats

It can be seen that 95% tricyclazole was orally infected with 100mg/kg, 215mg/kg, 464mg/kg and 1000mg/kg, and the corresponding number of dead animals in rats was 0, 2, 5 and 5. Accordingly, it is found in Table A.1 of Appendix A of GB/T15670.2-2017 that the corresponding LD_{50}=233mg/kg, 95% confidence interval: 160~399mg/kg.

In 0mg/kg dose group, no abnormal clinical symptoms were found. Two animals in the 100mg/kg dose group showed symptoms of back arch after being poisoned and returned to normal one after another (no more than D3), and the other three animals showed no abnormal clinical symptoms after being poisoned. Two animals in the 215mg/kg dose group were found to die one after another (no more than D2) after being poisoned, and all of them had symptoms of back arch and reduced activity before death, and the other three animals showed back arch or reduced activity after being poisoned, and all of them completely returned to normal on D3. All animals in the 464mg/kg dose group were found to die successively (no more than D3) after being poisoned, and some or all of the following symptoms appeared before death: arched back, prone and reduced activity. All animals in the 1000mg/kg dose group were found to die on D2, and there were back arch and reduced activity or prone symptoms before death. During the 14-day observation period, all the surviving animals showed an increase in body weight. No abnormality was found in gross autopsy of animals in all dose groups, and no histopathological examination was performed.

Acute Percutaneous Toxicity Test in Rats

During the experiment, no abnormality was found in all the animals after being poisoned, and no dead or dying animals appeared. During the 14-day observation period, the mean weight of both male and female animals showed an increasing trend. No abnormality was found in gross anatomy of all animals and no histopathological examination was performed.

Acute Eye Irritation Test in Rabbits

At the beginning and end of the experiment, the weight of all animals showed an overall increase trend, and no abnormalities were found. No abnormal clinical symptoms were found in all animals.

There were no abnormalities in the eye examination of the control eye (left eye) of all animals, and the results of the eye examination of the infected eye (right eye) were as follows:

1. At 1h after exposure, all animals developed conjunctival vasocongestion with bright red color (score 1) and significant edema, accompanied by partial eyelid ectropion (score 2).

2. 24h after exposure, all animals developed conjunctival vasocongestion bright red (score 1) and slight edema (including nictitating membranes) (score 1).

3. 48h after exposure, eye irritation returned to normal in all animals.

4. No eye irritation was found in all animals 72h after exposure.

Acute Skin Irritation Test in Rabbits

At the beginning and end of the experiment, the weight of all animals showed an overall increase trend, and no abnormalities were found. No abnormal clinical symptoms were found in all animals. The results of skin stimulation response were as follows: no erythema, eschar formation, or edema formation occurred on the skin of the control side at each time point, and the average score was 0.

The results of the skin examination on the infected side are as follows:

1. 1 h after removal of the subjects, all the animals showed mild erythema skin irritation reaction symptoms, and the mean score was 1 point.

2. 24 h after the removal of subjects, the skin irritation reaction symptoms of all animals returned to normal, and the mean score was 0.

3. No skin irritation reaction was found in all animals 48 h and 72 h after removal of subjects, and the mean score was 0.

Discussion

In this paper, 95% of tricyclazole was non-irritating and low toxic to the skin of rats and rabbits after being poisoned, and it was safe for skin contact. However, the half lethal dose (LD_{50}) = 233mg/kg (95% confidence interval: 160~399mg/kg) for acute oral poisoning in female rats, and the safety was reduced compared with the data obtained from domestic studies. Although according to the pesticide toxicity rating standard, the current test results are still medium toxicity standards, but there is an obvious difference with the data, and it is also necessary to attract the attention of manufacturers, consider whether it is the cause of the production process, and then improve the process to make it safer and more effective. In addition, tricyclazole is moderately irritating to rabbit eyes if it is not rinsed after being poisoned, so it is necessary to pay more attention to prevent accidental ingestion, strengthen self-protection, and reduce contact as much as possible during daily use. If it comes into contact with it, it should be rinsed with clean water in time to shorten the contact time as much as possible. In addition, in places where pesticides are used and stored, warning slogans and emergency rescue tools and facilities should be installed.

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Conflict of Interest

None.

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