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Cytotoxicity, Acute and Sub-Acute Study of Aluminium Phosphide in Rats, Toad and Rabbit

[1]Manamêdè Adédé Assima, [1]Essotolom Badjabaïssi, [2]Yawo Apélété Agbobli, [1]Aboudoulatif Diallo, [1]Komlan Mawubédjro Dossou-Yovo, [3]Mindédé Assih, [4]Sabrina Sanvee, [5]Povi Lawson-Evi, [4]Batomayena Bakoma and [6]Tchin Darre

[1]Laboratory of Toxicology, Faculty of Health Sciences, University of Lomé, Lomé, Togo
[2]Laboratory of Occupational Medicine, Faculty of Health Sciences, Lomé, Togo
[3]Laboratory of Pharmacology, Faculty of Health Sciences, University of Lomé, Lomé, Togo
[4]Laboratory of Chemistry and Natural Substances, Faculty of Health Sciences, University of Lomé, Lomé, Togo
[5]Laboratory of Animal Physiology and Pharmacology, Faculty of Sciences, University of Lomé, Lomé, Togo
[6]Laboratory of anatomic pathology, Faculty of Health Sciences, University of Lomé, Lomé, Togo

ABSTRACT

Background and Objective: Aluminium phosphide is a pesticide widely used in our countries, particularly for the preservation of foodstuffs. The phosphine released in contact causes harmful and fatal toxic effects. In this study, the low-dose toxicity induced by aluminium phosphide was evaluated. **Materials and Methods:** Cytotoxicity was studied on *Artemia salina* larvae. The acute toxicity test was carried out at doses of 1.5; 3; 5 and 10 mg/kg. The 10 day repeat dose toxicity was performed at doses of 0.312; 0.625 and 1.25 mg/kg. The cardiotoxicity study was carried out on toad hearts with concentrations between 0.01 and 4 mg/mL. Studies on the isolated intestine were carried out in rabbits. Cardiac toxicity has also been reported in toad hearts. **Results:** The aluminium phosphide was very toxic with an LC_{50} equal to 3.70 µg/mL and an LD_{50} less than 5 mg/kg. During repeated dose toxicity, aluminium phosphide induced deaths at administered doses. It did not cause any variation in average body weight and relative organ weight after 10 days of administration. However, it significantly caused an increase in ALP and a decrease in AST at doses of 0.312; 0.625 mg/kg. At a dose of 0.625 mg/kg it significantly increased the number of platelets and reduced CPK. Acetylcholine did not contract the intestine after exposure to aluminium phosphide. **Conclusion:** The demonstrated that even at low doses, aluminium phosphide remains very dangerous and deadly. The lack of an antidote must lead to strict measures being taken on the marketing and control of this pesticide and the search for an effective treatment.

KEYWORDS

Aluminium phosphide, pesticide, acute toxicity, subacute toxicity, cardiotoxicity, intestinal motility

INTRODUCTION

Pesticides are natural or synthetic chemicals used against harmful organisms for the protection of crops and the preservation of stored foodstuffs but also in the fight against disease vectors[1]. As a result, the fight against pests has been identified as a challenge for humans due to crop losses[2,3]. Several harmful

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organisms constitute a major problem for agriculture, hygiene and industry, like animals and insects[4]. It is difficult to quantify the exact cost of damage caused by these pests. The most effective and almost systematic way to improve crop yields is unfortunately the use of pesticides[5-7].

These pesticides are the cause of numerous accidental or criminal poisonings[8,9], most often due to non-compliance with protective measures and guidelines for use by the population[7]. It is estimated in 2022 that they are the cause of nearly 385 million annual cases of accidental poisoning, to which are added around 11,000 deaths[10].

Among the insecticides most used in agriculture for the protection of stored foodstuffs, we have aluminium phosphide, a fumigant widely used throughout the world. Its application is increasing rapidly due to its wide availability, high effectiveness against different pests, easy use and affordable price[11,12]. However, its free marketing in underdeveloped countries and it represents a real danger insofar as the product is proven to be toxic to humans and animals but also a common means of intoxication in suicide attempts and criminal acts[13,14].

Aluminium phosphide is most commonly available in the form of tablets, lozenges or granules and contains phosphide in combination with ammonium carbonate. In contact with water or humidity, it releases phosphine or hydrogen phosphide, a foul-smelling gas from rotting fish[15-17]. Acute poisoning is caused either by direct ingestion or by inhalation of the phosphine released during its use[17,18].

In Togo, aluminium phosphide is widely used for seed preservation by large companies but also by farmers and traders. After use, certain cereals are not, or are not, washed well, which could lead to the presence of aluminium phosphide residues in these products. Therefore, we initiated this study with the aim to evaluate the toxicity of low doses of aluminium phosphide in animals.

MATERIALS AND METHODS

Study area: It was an experimental study that took place at the University of Lome (Togo); in the Laboratory of Pharmaco-Toxicology of the Department of Pharmaceutical Sciences of the Faculty of Health Sciences. The study was carried out from October, 2020 to December, 2021.

Chemical product: The product used was aluminium phosphide formulated in the form of tablets, purchased in Lomé at an approved point of sale of phytosanitary products and seeds. The tablets, gray in color, had a garlic odor.

Animals: Male and female Wistar rats (*Rattus norvegicus*) weighing between 105 and 200 g were used for toxicity. They were provided by the pharmaceutical sciences department of and were acclimated at least one week prior the beginning of the manipulations (Faculty of Health Sciences). Animals were fed standard rodent chow and water ad libitum. They were maintained before and during the study at a temperature of 22±2°C with a relative humidity of 40% and with a period was 12 hrs of light and 12 hrs of darkness. Animal handling complied with accepted standards[19,20].

Ethical consideration: Ethical approval was obtained from the Institutional Ethics Committee for Teaching and Research under number (Ref. CNCB-CEER 2801/2010).

Rabbits (*Oryctolagus cuniculus*), purchased from a breeder in the city of Lomé (Togo) were used to evaluate the effect of aluminum phosphide on the isolated intestine. Toads (*Bufo regularis*), collected on the campus of the University of Lome (Togo), to study the effect on cardiac activity *in situ* and then of *Artemia salina* eggs (crustacean larvae), obtained from the department of pharmaceutical sciences for the study of cytotoxicity.

Cytotoxicity on *Artemia salina* larvae: The toxicity of aluminium phosphide was monitored by the shrimp lethality test. The protocol of Meyer *et al.*[21] described in 1982 and modified by Diallo *et al.*[22] was used. For this test, the eggs of *Artemia salina* (500 mg) were introduced into a pot containing 500 mL of previously filtered sea water. The bottle was placed under automatic shaking for 48 hrs. After hatching, the live larvae were distributed into 11 test tubes at a rate of 16 larvae per tube in 1 mL of seawater. In the first 10 tubes, aluminum phosphide was added at a dilution of order 2 from a stock extract solution at 6 mg/mL. The last tube served as a control. The tubes were then incubated for 24 hrs. After this incubation period, the tubes were analyzed and the number of dead larvae counted. A larva was considered dead if it showed no movement for at least 30 seconds of observation. The number of dead larvae in the control tube made it possible to validate the test in the case where the mortality rate in the latter is less than 15%.

Acute toxicity in rat: The test was carried out according to Dossou-Yovo *et al.*[23] on female Wistar rats. Four batches of five female rats were selected for this test. We administered orally, sequentially and at 48 hrs intervals, doses of 10, 5, 3 and 1.5 mg/kg b.wt., of the aluminium phosphide solution to each rat at a rate of 1 mL/100 g. The rats were observed for 12 hrs following administration of the solution and then every day for 14 days. Parameters such as mortality, neurological signs (convulsions, tremors), changes in alertness were noted during the observation period.

Repeated dose toxicity in rats: For this study, Eliassou *et al.*[24] protocol was used. Doses were chosen based on acute toxicity findings. Due to the death of the rats, the study was carried out for 10 days. The 4 batches of 6 male rats were used.

Batch 1 received distilled water at a rate of 1 mL/100 g (control batch). Batches 2, 3 and 4 received doses of 0.312 mg/kg, respectively; 0.625 and 1.25 mg/kg, at a rate of 1 mL/100 g of body weight. Rats were weighed daily before each gavage.

On the 11th day, after 12 hrs of fasting, the rats were anesthetized with ether and blood was collected from the retro-orbital sinus in tubes containing EDTA and in dry tubes, in order to determine hematological and biochemical parameters. For biochemical analyses, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (ASAT), alkaline phosphatase (PAL), creatine phosphokinase (CPK) were measured and blood sugar measured. The ionogram was carried out to determine the concentration of ions such as calcium (Ca^{2+}), potassium (K^{+}), sodium (Na^{+}) and chloride ions (Cl^{-}). The hematological parameters determined were: The number of red blood cells (RBC), the mean corpuscular volume (MCV), the hemoglobin level (Hb), the hematocrit (Hte), the mean hemoglobin content (TMH), the concentration mean corpuscular hemoglobin (CCMH), white blood cell count (WBC) and platelet count (PLQ).

After exsanguination, each rat was euthanized again with ether and then dissected for macroscopic examination. The liver, kidneys, testes, heart and spleen were isolated and weighed. Relative organ weight was calculated.

***In vivo* cardiac activity of the toad heart:** The test for evaluating cardiac activity modified by Diallo *et al.*[22] was used. The toad was decerebrated and demedulated then placed in dorsal recumbency. The heart was exposed by successively cutting, using scissors and forceps, the skin, the musculoskeletal wall and the pericardium. The apex of the heart was attached to a thin wire linked to the force transducer. Recording of heart rate and amplitude was done with the LabChart 8 application software. The heart was exposed to 500 µL of aluminium phosphide at concentrations of: 0.01, 0.1, 1, 2 and 4 mg/mL. Each test was repeated 5 times.

Evaluation of the effects of aluminium phosphide on the isolated rabbit intestine

Effect on the basal tract: After anesthetizing the rabbits, they were sacrificed by cervical rupture and their abdominal cavity was opened. A small 1 cm fragment was taken and immersed in a 25 mL insulated organ tank which was connected to a thermostatically controlled water bath whose temperature was set at 37°C. The intestine was subjected to cumulative doses of aluminium phosphide (20, 40, 80 and 100 µg) and the different modifications in contraction were recorded using LabChart 8 software.

Action of acetylcholine on the intestine under the effect of aluminium phosphide: This test was carried out to check for possible interference between aluminium phosphide and the cholinergic system. After a single dose of aluminium phosphide 80 µg/mL causing a visual decrease in the amplitude of contractions, we introduced 10 µL of acetylcholine of normality 10^{-2} N into the tank.

Statistical analysis: The results were expressed as a mean carried out by Analysis of Variance (ANOVA) with the Tukey's test to assess the difference between two groups. While, $p<0.05$ were considered significant. GraphPad Prism 8.4.3 was used to perform all statistical analyses.

RESULTS

Cytotoxicity: The number of dead larvae in each tube allowed us to plot a logarithmic trend curve (Fig. 1) expressing the number of dead larvae as a function of the concentration of the solutions. From this trend curve, we determined the LC_{50} which was 3.70 µg/mL.

Acute toxicity: The data on mortality at the different doses were presented in Table 1. All of the rats died at doses of 5 and 10 mg/kg in less than 24 hrs. Apathy and inability to move were also recorded before the rats died. No deaths were observed at doses of 3 and 1.5 mg/kg. Then the LD_{50} in wistar rat is between 3 and 5 mg/kg.

Study of the 10 day repeated dose toxicity of aluminium phosphide on rats: At a dose of 1.25 mg/kg, all rats were dead after 4 days of administration. Two and one death were recorded, respectively at the dose of 0.312 and 0.625 mg/kg.

Table 1: Mortality rate collected after acute administration of aluminium phosphide in rats

Doses (mg/kg)	Number of rats tested	Mortality rate (%)	Survival time
10	5	100	6 hrs
5	5	100	10 hrs
3	5	0	14 days
1.5	5	0	14 days

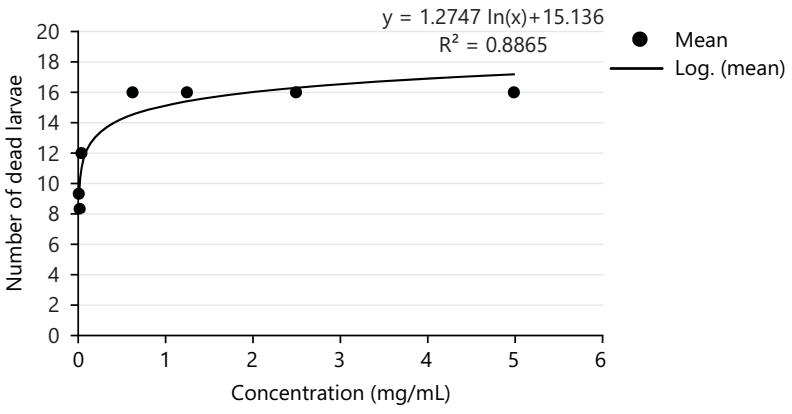

Fig. 1: Cytotoxicity curve of aluminium phosphide on the larvae of *Artemia salina*

Table 2: Effect of aluminium phosphide on rat body weight after 10 days of experiment

		Aluminium phosphide	
Days	Control	0.312 mg/kg	0.625 mg/kg
J-0	125.3±8.5	123.3±9.2	125.0±8.1
J-5	133.5±8.3	133.7±10.1	125.0±8.2
J-10	135.7±10.7	137.0±13.9	123.7±12.0

Each value is expressed as Mean±SEM and ANOVA followed by Tuckey's test and n = 6

Table 3: Effect of aluminium phosphide on rat's organ relative weight after 10 days of experiment

		Aluminium phosphide	
Organs	Control (%)	0.312 mg/kg (%)	0.625 mg/kg (%)
Heart	0.4±0.0	0.4±0.1	0.5±0.0
Spleen	0.3±0.1	0.3±0.0	0.4±0.1
Liver	3.4±0.2	3.4±0.1	3.6±0.2
Kidney	0.7±0.1	0.7±0.1	0.7±0.1
Testicles	1.8±0.0	1.7±0.0	1.8±0.7

Each value is expressed as Mean±SEM, ANOVA followed by Tuckey's test and n = 6

Table 4: Effect of aluminium phosphide on biochemical parameters after 10 days of experiment

		Aluminium phosphide	
Parameter (Units)	Control	0.312 mg/kg	0.625 mg/kg
SGOT (UI/L)	165.5±12.5	136.7±12.9***	110.7±11.3***
SGPT (UI/L)	44.7±5.6	53.3±8.4	42.5±4.4
ALP (UI/L)	146.7±38.3	264.0±41.0***	234.3±35.8***
Urea (mg/L)	0.2±0.0	0.3±0.1	0.3±0.0
Creatinine (mg/L)	5.3±0.3	5.0±0.6	5.3±0.3
Glycemia (g/L)	1.0±0.1	0.9±0.1	1.1±0.0
Calcemia (mg/L)	94.7±2.3	99.3±6.4	97.5±2.4
Chloremia (mEq/L)	139.3±3.5	136.6±2.8	144.5±3.0
Kaliemia (mEq/L)	5.4±0.3	6.3±0.2	5.3±0.2
CPK (UI/L)	353.7±36.1	309.3±35.0	217.5±37.8****

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, ALP: Alkaline phosphatase, CPK: Creatine phosphokinase. Each value is expressed as Mean±SEM, ANOVA followed by Tuckey's test, ***p 0.001, ****p 0.0001 and n = 6

Effect of aluminium phosphide on body weight of rats: The aluminium phosphide did not cause any significant changes in the body weight of rats during the entire 10-day administration period (Table 2).

Effect of aluminium phosphide on rat's organ relative weight: After 10 days of administration of aluminium phosphide, no significant difference was observed in the relative weight of the organs between the two treated batches and compared to the controls (Table 3).

Effect of aluminium phosphide on biochemical parameters: The results presented in Table 4 indicate that after 10 days of administration, aluminium phosphide caused a significant increase in alkaline phosphatase compared to controls. On the other hand, a significant decrease in CPK and AST was observed.

Effect of aluminium phosphide on haematological parameters: Apart from a significant increase in the number of platelets at the dose of 0.625 mg/kg, no significant variation in hematological parameters was observed (Table 5).

Effect of aluminium phosphide on cardiac activity: The results in Table 6 indicate a significant decrease in frequency from the concentration of 1 mg/mL aluminium phosphide.

Table 5: Effect of aluminium phosphide on haematological parameters after 10 days of experiment

		Aluminium phosphide	
Parameter (Unit)	Control	0.312 mg/kg	0.625 mg/kg
WBC (10^9/L)	5.4±0.9	6.2±1.1	5.0±0.7
RBC (10^{12}/L)	7.4±0.7	8.0±0.2	7.9±0.1
HB (g/dL)	12.1±1.1	13.1±0.2	13.1±0.2
HCT (%)	34.6±2.6	37.8±0.4	37.6±0.3
VGM (fl)	47.1±1.3	47.5±0.7	47.8±0.6
CMH (pg)	16.4±0.2	16.5±0.4	16.7±0.1
CCMH (g/dL)	34.8±0.6	35.1±0.4	34.8±0.3
PLT (10^9/L)	519.0±56.0	586.7±58.2	796.8±57.4***

WBCs: White blood cells, RBCs: Red blood cells, HB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration, MCH: Mean corpuscular hemoglobin and PLT: Platelets. Each value is expressed as Mean±SEM, ANOVA followed by Tuckey's test, ***p 0.001 and n = 6

Table 6: Effect of aluminium phosphide on isolated toad hearts

Concentration (mg/mL)	Amplitude (g)	Frequency (bpm)
Control	0.8±0.0	102.1±9.5
0.01	0.8±0.0	89.2±7.9
0.1	0.8±0.0	82.3±7.7
1.0	0.8±0.0	74.6±7.6*
2.0	0.8±0.0	60.8±6.4***
4.0	0.7±0.0	58.5±6.9***

Each value represents the Mean±SEM, n = 6. *p<0.05, ***p<0.001, significant difference compared to the control and bpm: Beats per minute

Table 7: Effect of aluminium phosphide on the isolated rabbit intestine

Concentration (µg/mL)	Amplitude (g)	Frequency (bpm)
0	0.9±0.1	11.6±1.3
20	1.5±0.2	11.4±1.3
40	1.7±0.2	9.6±1.1
80	1.3±0.1	5.9±1.0***
100	1.0±0.1	5.2±1.2****

Each value represents the Mean±SEM, n = 6. *p<0.05, ***p<0.001, significant difference compared to the control and bpm: Beats per minute

Table 8: Action of acetylcholine on the intestine under the single dose effect of aluminium phosphide

Concentration (µg/mL)	Amplitude (g)	Frequency (bpm)
0	1.0±0.1	11.6±1.3
20	1.5±0.2	11.4±1.3
40	1.7±0.2	9.6±1.1
80	1.3±0.1	5.9±1.0***
100	0.1±0.1	5.2±1.2****

Each value represents the Mean±SEM, n = 6. *p<0.05, ***p<0.001, significant difference compared to the control and bpm: Beats per minute

Effects of aluminium phosphide on the isolated rabbit intestine

Effect of aluminium phosphide on the basal tract: Aluminium phosphide caused a significant decrease in contraction frequency compared to control (Table 7). On the other hand, no significant variation in the amplitude of contraction is observed.

Action of acetylcholine on the intestine under the effect of aluminium phosphide: The values provided in Table 8 indicate a significant increase in the amplitude of intestinal contraction after the introduction of acetylcholine. On the other hand, no significant variation in contraction frequency was observed.

DISCUSSION

In this study, we showed the toxic effects of aluminium phosphide. The larval toxicity test carried out mentioned an LC_{50} equal to 3.70 µg/mL, aluminium phosphide is therefore very cytotoxic according to the Mousseux scale[25-27]. A highly reactive radical, phosphine, when released after hydrolysis, diffuses into intracellular compartments, causing cell injury through oxidative damage[28,29].

An LC_{50} of less than 5 mg/kg was reported by our study, making aluminium phosphide a substance classified as very toxic if ingested according to the OECD. Acute phosphide poisoning is a real emergency requiring early and adequate treatment[16]. The lack of antidote makes its poisoning very dangerous and responsible for high mortality rates[16,30]. Jafari *et al.*[31] and Baeeri *et al.*[32] used an LC_{50} of 12 mg/kg in their studies.

Aluminium phosphide is still dangerous at low and repeated doses. The biochemical results reported a significant difference between the different batches. Indeed, the results show a significant increase in alkaline phosphatase at doses of 0.312 and 0.625 mg/kg of phosphide compared to controls (p 0.001). This increase could indicate the presence of cholestasis of toxic origin[33,34]. Okolie *et al.*[35] reported in a study a notable dose-related increase in serum alkaline phosphatase activity in rats after sub-chronic exposure to phosphine.

The inhibition of cytochrome-c oxidase and oxidative phosphorylation by phosphine would thus lead to a strong mobilization of CPK available in the production of energy at the cell level by the anaerobic pathway[36,37]. This mechanism would thus be responsible for the reduction in CPK at the dose of 0.625 mg/kg ($p>0.001$). Amand *et al.*[38] observed ultrastructural changes indicative of mitochondrial injury in heart, liver and kidney tissues. They had also reported a marked reduction in cytochrome-c immunostaining compared to controls. These mitochondrial lesions in liver tissues would explain the decrease in AST reported by our study at the dose of 0.625 mg/kg ($p>0.001$).

The hematopoietic system is one of the most sensitive targets for toxic substances. It represents an important marker of the physiological and pathological state of humans and animals[39]. Current results reported a significant increase in the number of platelets in rats treated with the dose of 0.625 mg/kg (p 0.001). This increase in platelet levels is a risk of thrombosis in rats[39,40]. Afolabi *et al.*[41], on the other hand, reported thrombocytopenia induced by exposure to aluminium phosphide. Previous studies have reported cases of blood congestion in the intestine after autopsy as well as cardiorespiratory disorders in cases of aluminium phosphide poisoning[40,42].

The study of the effect of aluminium phosphide on toad cardiac activity *"in situ"* revealed a significant decrease in frequency from the concentration of 1 up to 4 mg/mL. The decrease in heart rate reflects a negative chronotropic effect indicating the cardiotoxicity of aluminium phosphide marked by bradycardia or a slowing of electrical conduction[26,33]. This is undoubtedly linked to phosphine which is responsible for cardiac toxicity through a corrosive action or the inhibition of cytochrome-c oxidase and the formation of highly reactive hydroxyl radicals[43]. This cardiac toxicity was demonstrated in the study by Abdolghaffari *et al.*[44], with changes in ECG patterns such as decreased heart rate, blood pressure and abnormal QRS complexes, QTc and of height ST. Cardiac dysfunction is the main cause of mortality and morbidity in aluminium phosphide poisoning[44].

Once ingested, metal phosphides generate highly toxic phosphine gas through the action of dilute hydrochloric acid in the stomach. Both of these mechanisms play a role in the occurrence of extensive hemorrhage and ulceration in the gastrointestinal tract[45]. This would explain the decrease in the frequency of contraction of the isolated intestine reported in our study. Furthermore, inhibition of cytochrome-c

oxidase by phosphine leads to cellular hypoxia and cell death[39,46] which could explain the decrease in this frequency. Indeed, aluminium phosphide would cause activation of peroxide radicals, inhibition of catalase and depletion of glutathione thus leading to an increase in free radicals[40,47]. Cases of acute damage to the esophageal mucosa in the form of ulcers, leading to upper gastrointestinal bleeding in the acute phase have been reported in the literature[48].

With acetylcholine, the aim was to check whether an interference exists between aluminium phosphide and acetylcholine receptors. Acetylcholine did not contract the intestine after exposure to aluminium phosphide. This result would thus confirmed the cytotoxic effect of aluminium phosphide on intestinal cells.

CONCLUSION

The present study allowed us to evaluate the toxicity of aluminium phosphide at low doses. Aluminium phosphide is a very toxic substance following the results of cytotoxicity, acute and sub-acute toxicity, reported by this study. With repeated administration of low doses, aluminium phosphide has induced an increase in alkaline phosphatase and platelets, then a decrease in AST, creatine phosphokinase and heart rate. Due to the presence of aluminum phosphide residues in certain poorly washed foodstuffs, it would be good for further work to quantify these residues and identify the mechanisms responsible for the toxic effects observed

SIGNIFICANCE STATEMENT

This work was carried out to elucidate the toxic effects of low doses of aluminum phosphide on *Artemia salina* larvae, rats, toads and rabbits. The study results indicated that even at low doses, aluminum phosphide is toxic with adverse effects on the heart, liver, digestive tract and blood of animals.

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