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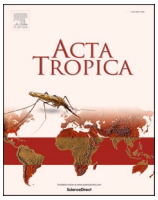

# Acute toxicity of two insecticides on two species of Chagas disease vectors

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ABSTRACT

The control of triatomine vectors of Chagas disease is mainly based on the use of pyrethroid insecticides. Because chemical control is the primary method for managing these insects, it is crucial to diversify the range of products utilized to mitigate the risk of resistance development. This study evaluated the toxicity of two insecticides with different modes of action on *Triatoma dimidiata* Latreille and *T. pallidipennis* Stal first and third instar nymphs. Our study focused on the effects of two insecticides, buprofezin (a growth regulator) and flunocamid (an anti-feeder), on the mortality rate of triatomine bugs in a laboratory setting. Moreover, we investigated how direct and indirect (film method) exposure to these insecticides impacted the survival of the insects. Flonicamid emerged as a promising insecticide for triatomine control since it caused 100% mortality in first-instar nymphs 48 h after direct exposure. While, in third instar nymphs, the maximum mortality was 88% at 72 h after exposure. Our result can be used as a basis for future triatomine control plans.

## 1. Introduction

Chagas disease is caused by the protozoan *Trypanosoma cruzi*, which is transmitted to humans mainly via blood-sucking bugs (Hemiptera) of the Reduviidae family, Triatominae subfamily (Vos et al., 2015). Two Triatominae of epidemiological importance are *Triatoma dimidiata* and *T. pallidipennis* (de Fuentes-Vicente et al., 2018). *Triatoma dimidiata* is distributed from Mexico to Peru, while *T. pallidipennis* occurs only in Mexico (Guzmán-Bracho, 2001; Gorla and Noireau, 2017). Both species have a strong dispersal capacity and can be found in various environments, including domestic, peridomestic, and sylvatic habitats (Dumonteil et al., 2007). Moreover, these species can colonize both rural and urban environments (Enger et al., 2004; Ramsey et al., 2005).

While Chagas disease is a parasitic infection that affects millions of people worldwide, there is currently no effective medicine or vaccine to prevent the disease, despite efforts to mitigate its impact (Camargo et al., 2022). Synthetic insecticides with long residual duration (e.g., pyrethroids) are the most widely used in programs for vector control and elimination (OPS, 2002; WHO, 2017; Wilson et al., 2020; Gonçalves et al., 2021). These insecticides are favored for their long residual duration and effectiveness in reducing disease transmission.

Because triatomines are controlled mostly through chemical means (WHO, 2017), it is crucial to explore new molecules with different modes of action to prevent the development of resistance to existing insecticides. By expanding the availability of products that effectively control these vectors, we can minimize the risk of resistance and maintain the effectiveness of insecticide-based control measures. In this regard, two competent insecticides are buprofezin and flonicamide. Buprofezin is a highly effective thiadiazine that acts on several sucking insect pests (Sohrabi et al., 2011; Ali et al., 2017), and its primary mode of action is a disruption of the molting process by being an inhibitor of Type 1 chitin biosynthesis (Dhadialla et al., 1998; Schneider et al., 2003). Flonicamide is a selective insecticide against Hemiptera and belongs to the pyridinecarboxamide group (IRAC, 2021). It acts by altering the function of the rhodotonal stretch receptor organs, which are critical to the senses of hearing, gravity, balance, acceleration, proprioception, and kinesthesia. Altering the senses causes feeding inhibition and alters other behaviors in insect individuals (Koo et al., 2014; IRAC, 2021).

We believe that chemical formulations intended to combat agricultural pests, specifically, insecticides that kill plant sap-sucking insects, may be effective in controlling kissing bugs. Therefore, in this work, we aimed to evaluate the toxic effect of the commercial formulation of buprofezin and flonicamid, on first and third-instar nymphs of

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*T. dimidiata* and *T. pallidipennis* under laboratory conditions. This is the first time these compounds have been tested in triatomines vectors of Chagas disease.

## 2. Materials and methods

### 2.1. Insects

First and third instar nymphs of *T. dimidiata* and *T. pallidipennis* were obtained from a colony maintained by the National Institute of Public Health, México (Cuernavaca, Morelos). Both species were maintained in controlled conditions of temperature (25 ± 3 °C) and humidity (60 ±10% RH) with a 12:12 h photoperiod. *Triatoma dimidiata* was initially collected from Chiapas, México, while the founders of *T. pallidipennis* colony originated from the southern region of Morelos state, México. The two species were maintained in the laboratory for more than five generations without the contribution of external material, making them susceptible to insecticides according to WHO (1994) provisions. All the individuals used in this study were ten days old after molting.

### 2.2. Insecticides

We evaluated two commercial formulations of insecticides from different toxicological groups: Bruprofezin 400 g/L (Thiadiazine -APPLAUD 40 SC, ANASAC) and Flonicamid 500 g/L (pyridinecarboxamides -BELEAF GS, FMC Agroquímica de México S. de RL de CV). We used the highest dose recommended by the manufacturer for plant sapsucking Hemiptera (buprofezin: 6.25 mL/L of water, and flonicamid: 1.75 g/L of water). The treatments comprised the insecticides diluted in distilled water and a control group, which consisted only of distilled water.

### 2.3. Lethal effect by film method

The experimental unit consisted of glass Petri dishes (θ= 10 cm, 1.5 cm high). The assay was carried out according to Birah's et al. (2008) method, with minor modifications. We added 1 mL of the insecticidal solution to each box. The boxes were allowed to dry at room temperature for 30 min. Subsequently, ten first or third-instar nymphs of each evaluated species were placed inside each box. The boxes were covered with parafilm®, which included ten ventilation holes made with an entomological needle. The insects were exposed to contaminated surfaces for 24 h. After exposure, they were removed and placed in containers free of insecticide. The Petri dishes of the control group were treated with distilled water.

### 2.4. Lethal effect of direct exposure

To immobilize the first and third instar nymphs of *T. dimidiata* and *T. pallidipennis*, they were subjected to 3 °C for five minutes. Immobilization was necessary to ensure the consistent application of the insecticides. After immobilization, the insects were placed in groups of ten individuals inside glass Petri dish (θ=10 cm), adding a filter paper disk at the bottom of each box. The insecticides were applied using a pump-top spray bottle (Sunnimix) 20 cm from the target. The application volume was 2 mL of insecticidal solution. The control group received only distilled water (Wang et al., 2016). After direct exposure to the insecticides, the insects were transferred to clean Petri dishes (θ=10 cm) free of insecticide and covered with organza fabric to allow ventilation.

We maintained the evaluated specimens in both trials at a controlled temperature of 25 °C ± 3 and relative humidity of 60.0 ± 10%. Mortality was recorded at 24, 48, and 72 h after insecticide exposure. We considered individuals that were immobile or had difficulty moving when stimulated with a fine-bristled brush (000) to be dead, following the criteria established by WHO (1994) and Pessoa et al. (2015). Five repetitions were conducted for each treatment. The individuals were fed rabbit blood 24 h before the tests (Coelho et al., 2006). We aimed to determine the maximum penetration rate of insecticides, as this is influenced by the nutritional status of insects. Cuticular distension produced by blood ingestion can facilitate higher product penetration through the intersegmental membrane of the insect cuticle (Carvajal et al., 2012). By assessing the maximum penetration rate of the insecticides, we can better understand the potential effects of these products on insects and develop more effective pest control strategies.

### 2.5. Data analysis

All models and test statistics were performed in R statistical environment (R Core Team, 2021). We used the betareg package in R (Zeileis et al. 2022) to construct beta regression models to determine the effect of insecticide types (Buprofezin and Flonicamide) on the mortality rate of first and third-instar nymphs of *Triatoma dimidiata* and *T. pallidipennis* individuals over three time periods (24, 48, and 72 h), and two different exposure types to the insecticides (exposure to treated surfaces and direct exposure). A beta distribution was employed since our response variable, i.e., the mortality rate of Triatominae individuals, was constrained between 0 and 1 (Douma and Weedon 2019). Differences between mortality rates by type of insecticide and hours of application were evaluated with Tukey's multiple comparison tests with Bonferroni correction at 95% confidence using the eemeans package in R (Lenth 2022).

## 3. Results

We found significant differences in the mortality rate of both triatomine species based on the insecticide types and time since exposure, as well as a significant interaction between these variables (Table 1). The mortality rate of *T. dimidiata* and *T. pallidipennis* was higher when exposed to flonicamide compared to buprofezin (Fig. 1). Furthermore, we observed progressive mortality in first-instar nymphs 24 h after indirect exposure (film method) to flonicamide (Fig. 1A, E). Conversely, third-instar nymphs of both species showed a high insecticide tolerance as we observed no mortality in the tested individuals (Fig. 1C, G). Direct exposure to flonicamid caused 100% mortality in first-instar nymphs within 48 h hours after exposure (Fig. 1B, F), whereas the mortality of first-instar nymphs exposed directly to buprofezin did not exceed 60%. Finally, the mortality rate of third-instar nymphs was significant only with flonicamid, 48 h after exposure (Fig. 1D, H).

## 4. Discussion

The misuse of insecticides can lead to the development of resistance in target insects. For instance, in the countries of the Southern Cone of America, *Triatoma infestans* (Klug 1834), the primary vector of *T. cruzi*, has been reported to have resistance to pyrethroids in several studies (Picollo et al., 2005; Germano et al., 2010; Fronza et al., 2019). Consequently, molecules with different modes of action from pyrethroids have been explored as potential alternatives for controlling triatomines. In this regard, insecticides such as fipronil (Rojas de Arias et al., 2002; Santo Orihuela et al., 2008; Germano et al., 2010; Roca Acevedo et al., 2011), imidacloprid (Carvajal et al., 2014), ivermectin (Dias et al., 2005), and fenitrothion (Santo Orihuela et al., 2008; Germano et al., 2010) have shown effectiveness against *T. infestans* and *Rhodnius prolixus* Stal. In addition to these insecticides, our study demonstrates the potential of buprofezin and flonicamid in controlling *T. dimidiata* and *T. pallidipennis*.

Our results revealed a marked difference in the susceptibility of first and third-instar nymphs to the evaluated insecticides, with first-instar nymphs being more susceptible than third-instar nymphs in both exposure methods. Age-related physiological and biochemical changes could contribute to this disparity (Remon et al., 2017). For instance, cuticle sclerotization varies during ontogeny, with the cuticle being

**Table 1**
Beta regression model results according to triatomine species, nymphal instar and exposure type. Non-significant: N.S.

| Species | Instar | Exposure type | Parameter | df1 | F.ratio | p.value | Pseudo R |
|---|---|---|---|---|---|---|---|
| *T. dimidiata* | 1 | Film | Insecticide | 2 | 133.65 | <0.001 | 0.88 |
| | | | Hour | 2 | 66.01 | <0.001 | |
| | | | Insecticide * Hour | 4 | 29.41 | <0.001 | |
| *T. dimidiata* | 1 | Direct | Insecticide | 2 | 1584.74 | <0.001 | 0.95 |
| | | | Hour | 2 | 41.61 | <0.001 | |
| | | | Insecticide * Hour | 4 | 22.24 | <0.001 | |
| *T. dimidiata* | 3 | Film | Insecticide | 2 | – | N.S. | 0.00 |
| | | | Hour | 2 | – | N.S. | |
| | | | Insecticide * Hour | 4 | – | N.S. | |
| *T. dimidiata* | 3 | Direct | Insecticide | 2 | 128.91 | <0.001 | 0.82 |
| | | | Hour | 2 | 77.11 | <0.001 | |
| | | | Insecticide * Hour | 4 | 47.03 | <0.001 | |
| *T. pallidipennis* | 1 | Film | Insecticide | 2 | 199.63 | <0.001 | 0.89 |
| | | | Hour | 2 | 30.22 | <0.001 | |
| | | | Insecticide * Hour | 4 | 13.77 | <0.001 | |
| *T. pallidipennis* | 1 | Direct | Insecticide | 2 | 2808.00 | <0.001 | 0.97 |
| | | | Hour | 2 | 34.61 | <0.001 | |
| | | | Insecticide * Hour | 4 | 18.88 | <0.001 | |
| *T. pallidipennis* | 3 | Film | Insecticide | 2 | – | N.S. | 0.00 |
| | | | Hour | 2 | – | N.S. | |
| | | | Insecticide * Hour | 4 | – | N.S. | |
| *T. pallidipennis* | 3 | Direct | Insecticide | 2 | 159.36 | <0.001 | 0.81 |
| | | | Hour | 2 | 71.45 | <0.001 | |
| | | | Insecticide * Hour | 4 | 45.49 | <0.001 | |

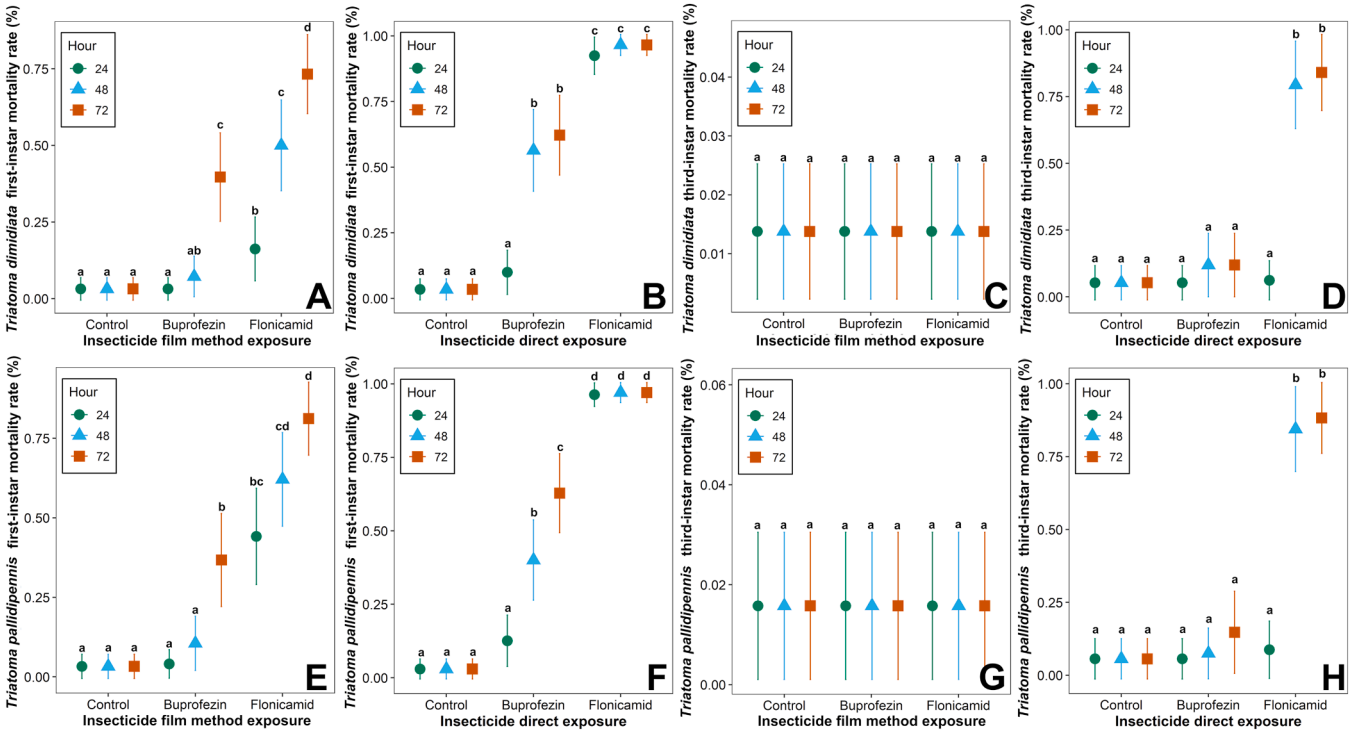


**Fig. 1.** Mortality values (means and STD errors) of *T. dimidiata* (A-D) and *T. pallidipennis* (E-H) according to instar (1 and 3), exposure method (direct and film) and time after exposure to two different insecticides. Different letters above each bar and within each panel imply significant differences. The complete test results of the pair-wise can be found in the supplementary material section.

more sclerotized in older nymphs (Wood et al., 1986; Casabé and Wood, 1998). Balabanidou et al. (2018) suggested that the thickening of the cuticle and changes in its composition could make it harder for insecticidal molecules to penetrate. Furthermore, the variation in toxicological susceptibility among different developmental stages may be attributed to 1) size difference, where larger insects have more surface area exposed to the insecticide and, therefore, greater product absorption, and 2) surface/volume relationship, where a amount of absorbed product affects small insects more than larger ones because larger insects have more body volume for the insecticide to distribute, resulting in a lower concentration of the toxicant at the site of action. Thus, smaller insects are more susceptible (Remon et al., 2017). Based on these findings, we suggest that the size difference between first and third-instar nymphs could be a key factor contributing to their varying susceptibility to the insecticides used in our study.

Our study is the first to demonstrate the efficacy of buprofezin and flonicamid against hematophagous triatomines under laboratory conditions. Regarding acute toxicity, flonicamid was more effective, causing

100% mortality in first-instar nymphs. Flonicamid is a selective insecticide for sucking insects of the order Hemiptera, including bugs, aphids, whiteflies, leafhoppers, and psyllids (Morita et al., 2014; Kodandaram et al., 2017). According to the Insecticide Resistance Action Committee (IRAC), flonicamid belongs to group 29, classified as having an undefined target site of action (Sparks and Nauen, 2015). The positive aspect of using flonicamid for Chagas Disease vector control is that it has not shown cross-resistance to carbamates, organophosphates, or pyrethroids and has been demonstrated to have no negative impact on beneficial arthropods (Morita et al., 2014). Thus, flonicamid may represent a promising tool for controlling triatomines

The efficacy of buprofezin as a growth/development disruptor (De Cock and Degheele, 1998) is dependent on the developmental stages of the insect. Greater control has been observed for first and second-instar nymphs compared to the following instars (Prabhaker and Toscano, 2007). While our study subjects tolerated this insecticide, buprofezin has demonstrated effectiveness against other hemipterans, such as aphids and mealybugs, having a noticeable effect between three to seven days after application (Dutta et al., 2016; Ather et al., 2022). The differential effectiveness between buprofezin and flonicamid may be related to the cuticular properties of the susceptible and non-susceptible species since the penetration rate of the product depends on the integument properties with which it comes into contact (Fontan and Zerba, 1987). Buprofezin inhibits molting, and insect growth regulators are known to disrupt normal insect growth and development processes, leading to eventual death. However, the kill rate of the target insects is slow, resulting in a long time to kill the pests (Prabhaker and Toscano, 2007). This may explain why the mortality of nymphs of the studied species did not exceed 60%.

In conclusion, our study highlights the need for new chemical molecules to control triatomine vectors of Chagas Disease. Flonicamid, which has not been previously studied in hematophagous triatomines, shows promising efficacy based on our laboratory results. Further experiments, both in the laboratory and in field conditions, are needed to confirm its potential as a tool for triatomine control.

## Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.actatropica.2023.106906.

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