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CHEMICAL SCIENCES

Insecticidal activity of the organotellurium 2-Phenylethynyl-Butyltellurium on the *Drosophila melanogaster* model

KARINA C. BITTENCOURT & RAFAEL R. DE SOUZA

Abstract: 2-Phenylethynyl-Butyltellurium (PEBT) is a synthetic organotellurium compound that has shown various pharmacological properties on mammals without any signs of toxicity, but its effects on insects have not been reported before. Therefore, the aim of this study was to assess whether acute exposure to PEBT would promote an insecticidal effect against *Drosophila melanogaster*. The flies were exposed to three concentrations of PEBT (0.325 µmol L^{-1}, 1.300 µmol L^{-1}, and 5.200 µmol L^{-1}) and a control solution (vehicle), using 450 flies per treatment (three repetitions of 150 flies), for 48 hours. Negative geotaxis and open field tests were performed (*in vivo*) after 24 and 48h, and acetylcholinesterase (AChE) activity was assessed (*ex vivo*) after 48h. Also, the mortality rate, 50% Lethal Concentration (LC_{50}), 80% Lethal Concentration (LC_{80}), and 95% Lethal Concentration (LC_{95}) were calculated. Our results show that PEBT presented insecticidal activity against *Drosophila melanogaster* at all tested concentrations, which caused locomotor impairment and increased acetylcholinesterase activity in the flies' heads.

Key words: Fruit fly, insecticides, locomotor activity, pest management, toxicology.

INTRODUCTION

Pest insect management is practiced, mainly, through chemical control, that is, the use of different types of insecticides (Perry et al. 2021). However, although this has been the most effective way to prevent and reduce yield losses (Schreinemachers et al. 2017, Rani et al. 2020), most insecticides have presented several harmful effects on human health (Hirano et al. 2015, Kataria et al. 2016, Ye & Liu 2019, Sun et al. 2020), which concerns not only consumers because of toxic residues in food, but also, agricultural workers and producers that are exposed to those risks (Hassaan & El Nemr 2020, Fatunsin et al. 2020). On this basis, the search for products with insecticidal activity that are not toxic to humans and mammals, in general, becomes ever more important, making 2-Phenylethynyl-Butyltellurium (PEBT) an interesting target for investigation, once this compound has demonstrated several beneficial effects to vertebrate animals before, without showing any sign of toxicity (Souza et al. 2012, 2013a, b, Quines et al. 2015).

PEBT is a synthetic organotellurium compound, classified as a telluroacetylene (Avila et al. 2017), which was synthesized for the first time based on the methodology proposed by Comasseto et al. (1996), as reported by Souza et al. (2009), along with other telluroacetylenes that were used for pharmacology assays on mice. Organotellurium compounds have shown many pharmacological effects on the human organism over the years and, notably, telluroacetylenes, have not only proven to be harmless to mammals but have also presented interesting properties,

such as immunomodulatory, chemoprotective, antidepressant, anti-epileptogenic, and antioxidant (Ba et al. 2010, Sredni 2012, Tiekink 2012). PEBT, in particular, has demonstrated memory and learning improvement in mice, as well as an anxiolytic-like effect, without causing locomotor alterations (Souza et al. 2009, 2012, 2013a, b, Quines et al. 2015). However, the effects of tellurium organic compounds can variate according to the species and concentration tested (Nogueira & Rocha 2011). An example of this is the antimicrobial activity of PEBT against the bacteria species *Escherichia coli* which was verified by Pinheiro et al. (2018). Thus, a question that arises is how different living beings, such as insects, would respond to this compound.

Drosophila melanogaster, known as the common fruit fly, represents an advantageous biological model for scientific research due to its easy and low-cost laboratory maintenance (Scott & Buchon 2019). These organisms are considered a useful tool for insect toxicology studies (Scott & Buchon 2019) and have been used for assessing the insecticidal activity and toxicological effects of several substances over the last few years (Alarcon et al. 2013, Vargas-Soto et al. 2017, Chowański et al. 2018, Kissoum et al. 2020, Rima et al. 2021). Therefore, the aim of this study was to assess whether acute exposure to the PEBT compound would promote an insecticidal effect against *D. melanogaster*.

MATERIALS AND METHODS

Drosophila melanogaster stock culture and reagents

The fruit flies used in the experiment (*D. melanogaster* - wild-type - Harwich strain) were obtained from the Oxidative Stress and Cellular Signaling (GPOSCEL), UNIPAMPA, São Gabriel, Brazil. Stock cultures were kept under controlled conditions (12 hours light/dark cycle, 25 ± 1°C temperature, and 60% humidity) and fed with a standard diet (76.59% cornmeal, 8.51% wheat germ, 7.53% sugar, 7.23% milk powder, 0.05% salt, and 0.09% methylparaben).

PEBT was prepared according to the method proposed by Comasseto et al. (1996) by the Laboratory of Organic Clean Synthesis – LASOL, CCQFA, Federal University of Pelotas, RS, Brazil. All the other reagents were of analytical grade and purchased from standard commercial suppliers.

Experimental conduction

The experiments were carried out in the Laboratory of Pharmacological and Toxicological Evaluations applied to Bioactive Molecules (LaftamBio Pampa) at the Federal University of Pampa, Itaqui Campus, RS, Brazil. Flies of both sexes, 2 days old, were divided into four treatments of 450 flies each (three repetitions of 150 flies, equalling three independent experiments, subdivided into three containers of 50 flies each): [1] Control (vehicle), [2] PEBT (0.325 µmol L^{-1}), [3] PEBT (1.300 µmol L^{-1}), [4] PEBT (5.200 µmol L^{-1}), totaling 1.800 flies. The exposure protocol lasted 48 hours (h).

Preparation of the diet and experimental design

To prepare the diet, the value corresponding to the highest concentration of PEBT was weighed (0.02808 g) using a precision scale (0.0001 g) and an adjustable automatic micropipette, and the product was fully dissolved in 200 µL 0.0001% dimethyl sulfoxide (DMSO - vehicle) prepared in water, to obtain the first stock solution (0.5200 mol L^{-1}). The two less-concentrated stock solutions were obtained by dilution.

Next, to achieve the final concentrations used in the treatments (5.200 µmol L^{-1}, 1.300 µmol L^{-1}, and 0.325 µmol L^{-1}), 10 µL from each respective stock solution were pipetted and

990 µL saccharose (1%) were added. Such concentrations were selected based on range-finder preliminary tests for mortality assessment. For the control, a solution of 10 µL DMSO (0.0001%) plus 990 µL saccharose (1%) was prepared. Finally, three glass containers (11.0 cm high and 5.5 cm diameter) were set per repetition, introducing paper cut-outs to the base and fifty flies in each. Each respective 1000 µL solution was carefully pipetted on the paper cut-outs into the containers, which were sealed with sponges.

Mortality rate and determination of the LC_{50}, LC_{80} and LC_{95}

Mortality was assessed after 24 and 48h, and the percentage of dead flies in each treatment was calculated from the mean of the three repetitions. Next, the mortality rate was fitted as a function of the PEBT concentration via a log-logistic nonlinear model with 4 parameters (Ritz et al. 2015). This model was chosen for presenting a better fitting quality for the dataset in comparison to nonlinear regression models, which were previously tested. Thus, the following mathematical model was parameterized using the *drm()* function from the R software (R Development Core Team 2021):

where MR_i is the mortality rate at the concentrations of 0 µmol L^{-1}, 0.325 µmol L^{-1}, 1.300 µmol L^{-1}, and 5.200 µmol L^{-1} PEBT, C represents each of those concentrations, c and d are asymptotic parameters, b is an adjustment of the sigmoidal curve, e represents the mortality rate, and ε_i is the error of random effect. After generating the models, LC_{50} was estimated for the mortality rate in 24h, and LC_{50}, LC_{80}, and LC_{95} in 48h, through the *ED*() function of the drc package (Ritz et al. 2015).

Negative Geotaxis test

The negative geotaxis test was performed as described by Coulom & Birman (2004), with modifications by Araujo et al. (2015). Six flies from each repetition (18 flies per treatment) were randomly selected among the live flies, and after being immobilized on ice, each one was transferred to a falcon tube (15.0 cm in length and 1.5 cm in diameter) individually. After a 10-minute recovery period, the flies were gently tapped to the bottom of the tube, and the time each fly spent climbing to the height of 8 cm, marked on the wall of the tube, was recorded in seconds (s). The test was repeated six times for each fly in each tube, and the mean of those six attempts was calculated for the individual flies. For each treatment, the mean of the three resultant means of each repetition was then calculated.

Open field test

The open field test was performed as described by Connolly (1966), with modifications by Musachio et al. (2020). Six flies from each repetition (18 flies per treatment) were randomly selected among the live flies, and after being immobilized on ice, each one was placed on a Petri dish divided into squares measuring 1 cm^2. After a 5-minute recovery period, the number of squares each fly crossed in 60 seconds (crossing number) was counted. The test was repeated twice for each fly in each Petri dish, calculating the mean of those two attempts for the individual flies and the mean of the three repetitions for each treatment.

Acetylcholinesterase activity

After 48h of exposure to PEBT, 10 live flies remaining from each repetition were euthanatized on ice and had their heads and bodies carefully separated, which were homogenized separately in a buffer solution of HEPES (4- (2-hidroxietil)

-1-piperazinoethanesulfonic acid – 20 mM, pH 7.0) for 2 minutes (min) using a motorised homogeniser. The samples were centrifuged at 1000 rpm for 10 min at 4°C and the supernatant was removed to be used in the biochemical assays. Protein concentration was colorimetrically measured through the method by Bradford (1976), using bovine serum albumin as standard, in order to normalize enzymatic activity.

Acetylcholinesterase (AChE) activity was determined according to Ellmann et al. (1961), with modifications by (Araújo et al. 2015). The reaction medium contained 0.25 mol L^{-1} KPi of the buffer solution, 5.50 mol L^{-1} KPi dithiobis-2-nitrobenzoic acid (DTNB 5 µmol L^{-1}), and 7.25 µmol L^{-1} (2.1 mg mL-1) of acetylthiocholine, which was added to the supernatant. Background activity was removed by using a control blank (supernatant + DTNB + buffer without substrate) for each supernatant. Readings were performed for 2 min at 412 nm. Enzymatic activities were expressed as nm hydrolyzed substrate/min/mg protein.

Statistical analyses

Results are expressed as mean ± standard deviation. The statistical analyses were performed through the analysis of variance (one-way ANOVA), after 24 and 48h for the mortality rate, negative geotaxis and open field separately, and head and body for AChE activity. The following mathematical model was applied:

where Y_i is the mean value observed of the response variable (mortality rate, behavioral tests, and AChE activity), m is the overall mean, C_i is the fixed effect of the PEBT concentration factor, where i = 0 µmol L^{-1} (control), 0.325 µmol L^{-1}, 1.300 µmol L^{-1}, and 5.200 µmol L^{-1}, and ε_i is the experimental error. The error normality and homogeneity of variance assumptions were verified through Shapiro-Wilk and Bartlett tests at 5%, respectively. When the effects of the factor under study (PEBT concentration) were significant, the Scott-Knott test (Scott & Knott 1974) was applied for the comparison of means between treatments. Differences were considered significant when $p<0.05$. Next, Pearson's correlation coefficient was estimated by combining data from eight characteristics (Cruz et al. 2014). All statistical analyses were performed using R software (R Development Core Team 2021) and Microsoft Office Excel.

RESULTS

The one-way ANOVA assumptions were met

An approximately normal distribution of errors and homogeneous variances were obtained. Shapiro-Wilk test p-value oscillated from ≥0.0975 to ≤0.9560 and the Bartlett test varied from ≥0.0613 to ≤0.9827 for the mortality rate and all behavioral and biochemical assays. These results are desirable, indicating that the assumptions of the one-way ANOVA model were not violated, for presenting values of $p>0.05$, thus enabling the estimate of variance components without the need for data transformation nor the use of nonparametric methodologies.

Acute exposure to PEBT promoted an insecticidal effect against *D. melanogaster* with high mortality rates

The statistical analyses (one-way ANOVA and Scott-Knott test) revealed a significantly higher mortality rate (Fig. 1) for the flies that were exposed to PEBT, at all concentrations tested, compared with the control after 24h (Concentration Degrees of Freedom = 3; F = 9.54; p-value = 0.0097) and 48h (Concentration Degrees of Freedom = 3; F = 15.33; p-value = 0.0016). The highest mortality corresponded to the highest PEBT concentration (5.200 µmol L^{-1}) at both 24 and 48h (70.22% and 97.33% respectively), while the second-highest mortality

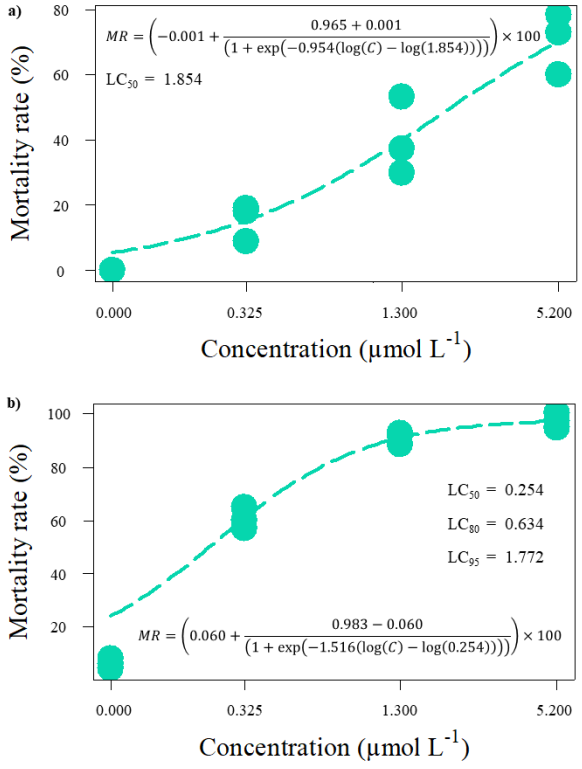

Figure 1. Response-curve of Mortality rate (%) as a function 2-Phenylethynyl-Butyltellurium (PEBT) Concentration (µmol L^{-1}) via log-logistic nonlinear model, in 24h (a) and 48h (b). ^{MR} Mortality Rate. ^{C} Concentration of PEBT. $^{R^2}$ Coefficient of determination. $^{LC}_{50}$ 50% Lethal Concentration. $^{LC}_{80}$ 80% Lethal Concentration. $^{LC}_{95}$ 95% Lethal Concentration.

rates corresponded to the concentration of 1.300 µmol L^{-1} (40.11% and 91.11%), and the third highest, to the concentration of 0.325 µmol L^{-1} (15.33% and 60.66%).

Furthermore, the majority of the flies died within 24h at the highest concentration, and within 48h at the two lower concentrations. The LC_{50} values found were 1.854 and 0.254 µmol L^{-1} after 24 and 48h of exposure to PEBT, respectively, whereas LC_{80} and LC_{95} values were only obtained after 48h, corresponding to the concentrations of 0.634 and 1.772 µmol L^{-1}.

Acute exposure to PEBT decreased fly locomotor behavior

The statistical analyses revealed a significant decrease in locomotor behavior, assessed through the negative geotaxis and open field tests. The negative geotaxis test showed that the flies moved more slowly after 24h (Concentration Degrees of Freedom = 3; F = 6.16; *p*-value = 0.0178) of exposure to PEBT at the concentrations of 1.300 and 5.200 µmol L^{-1}, and at all concentrations tested after 48h (Concentration Degrees of Freedom = 3; F = 35.65; *p*-value = 0.0003), when compared with the control (Fig. 2). PEBT increased fly climbing time compared to the control (6.67 s after 24h and 6.00 s after 48h), with averages of 49.00 and 59.33 s (1.300 and 5.200 µmol L^{-1} respectively) after 24h, and values varying from 48.00 to 51.33 s, after 48h.

For the open field test (Fig. 3), the statistical analyses showed that, after 24h of exposure (Concentration Degrees of Freedom = 3; F = 24.68; *p*-value = 0.0009), the number of quadrants the flies crossed in 60 s decreased as the concentration was increased, with averages varying from 8.13 to 25.67 squares crossed, in comparison to the control (32.17 crossed squares). Moreover, after 48h (Concentration Degrees of Freedom = 3; F = 36.25; *p*-value = 0.0001), although all concentrations decreased the crossing number compared with the control (31.50 crossed squares), no significant differences were observed between concentrations, with averages varying from 5.16 to 8.55 crossed squares.

Acute exposure to PEBT increased AChE activity in the flies' heads

No significant differences were observed for AChE activity in the body of the flies between the control and the PEBT concentrations (Concentration Degrees of Freedom = 3; F = 1.09; *p*-value = 0.4061). On the other hand,

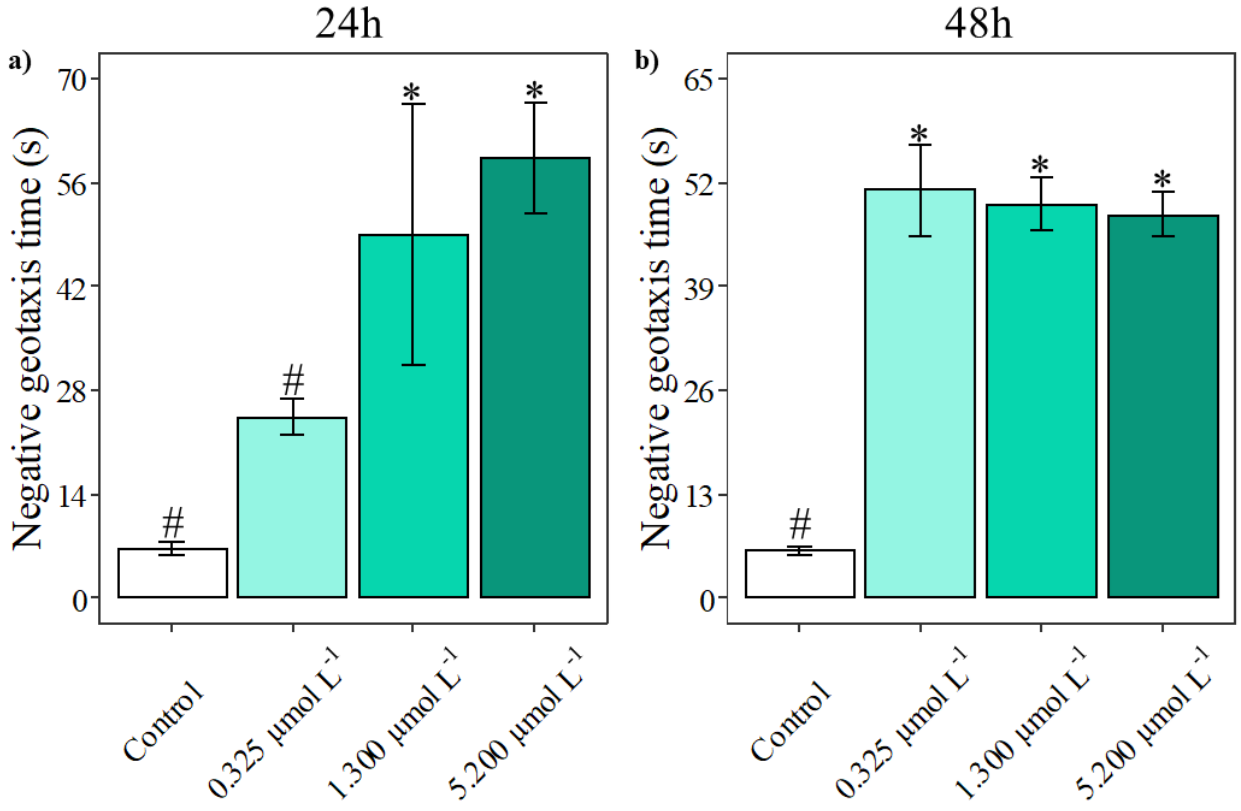

Figure 2. Locomotor behavior of *Drosophila melanogaster* exposed to three concentrations of 2-Phenylethynyl-Butyltellurium (PEBT) verified through the negative geotaxis test, in 24h (a) and 48h (b). * Significant difference compared with #. # Significant difference compared with *.

PEBT increased AChE activity in the head at all tested concentrations (Concentration Degrees of Freedom = 3; F = 7.54; *p*-value = 0.0102) (Fig. 4) where, although no statistical differences were observed between concentrations (average values varied from 120.37 to 154.14 mU/mg protein), the results found for the flies exposed to PEBT were much higher than the average value obtained for the control group (83.12 mU/mg protein).

Pearson's correlation matrix

Pearson's correlation matrix expressed 21.43% positive high-magnitude correlations (r > 0.70) and 25.00% inversely proportional correlations (r < -0.70) (Fig. 5). Correlations fluctuated from 0.87 to -0.96, so the highest positive correlation was observed between negative geotaxis in 48h and mortality rate in 48h, and the highest negative correlation, between open field in 24h and mortality rate in 24h. The mortality rate in 24h was also highly correlated with negative geotaxis in 24h (r = 0.84).

The mortality rate in 48h was significantly correlated with all characteristics, except for AChE activity in the body of the flies, which was the only characteristic that was not highly correlated with any other. Furthermore, high inverse correlations were also verified between the negative geotaxis in 24h and open field in 24h (r = -0.80), and the negative geotaxis in 48h and open field in 48h (r = -0.94). As for AChE activity in the flies' heads, the most relevant correlations were verified with negative geotaxis in 48h (r = 0.66), open field in 48h (r = -0.70), and mortality rate in 48h (r = 0.70).

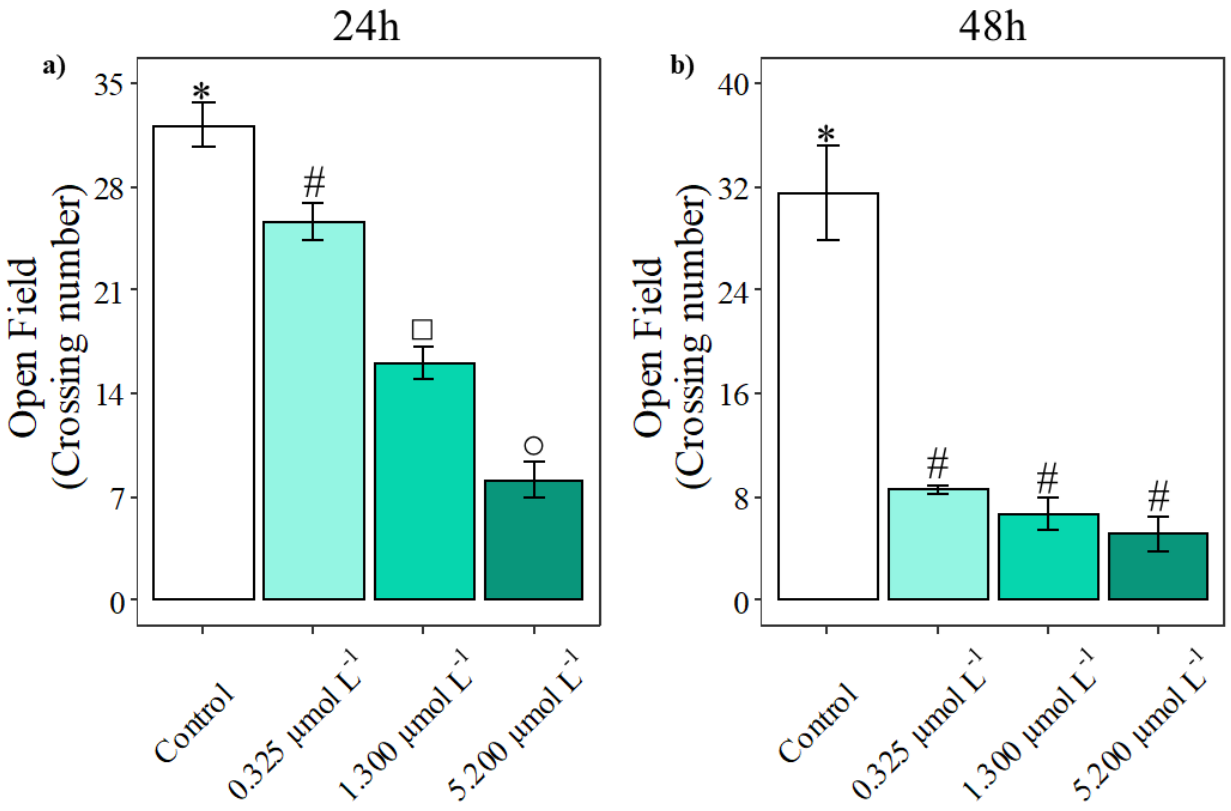

Figure 3. Locomotor behavior of *Drosophila melanogaster* exposed to three concentrations of 2-Phenylethynyl-Butyltellurium (PEBT) verified through the open field test, in 24h (a) and 48h (b). * Significant difference compared with #, □ and ○. # Significant difference compared with *, □ and ○. □ Significant difference compared with *, # and ○. ○ Significant difference compared with *, #, and □.

DISCUSSION

In this study, we assessed the insecticidal activity of PEBT against *D. melanogaster*, a species that has been demonstrated to be an effective biological model for insect toxicology studies (Scott & Buchon 2019). This work intended to contribute to the search for insecticidal potential in substances that do not represent a risk to human health and vertebrate animals, based on previous studies on this compound that have shown it is not toxic to mammalians (Souza et al. 2012, 2013a, b, Quines et al. 2015) and others that suggest PEBT toxicity depends on the target organism and concentration (Nogueira & Rocha 2011, Souza et al. 2012, Quines et al. 2015, Pinheiro et al. 2018).

Our results show that PEBT caused the death of *D. melanogaster* at all concentrations tested within 48h of acute exposure, evidencing, for the first time, the insecticidal potential of this compound. This finding represents the first step towards the study of the insecticidal properties present in PEBT, which emerges as an interesting alternative in view of the several neurological disorders that have been associated with pesticide exposure, including diseases of the central and peripheral nervous systems and neurobehavioral changes (Tulchinsky & Varavikova 2014, Mrema et al. 2014), and considering that PEBT has been tested on mammals before, presenting many pharmacological properties without any sign of

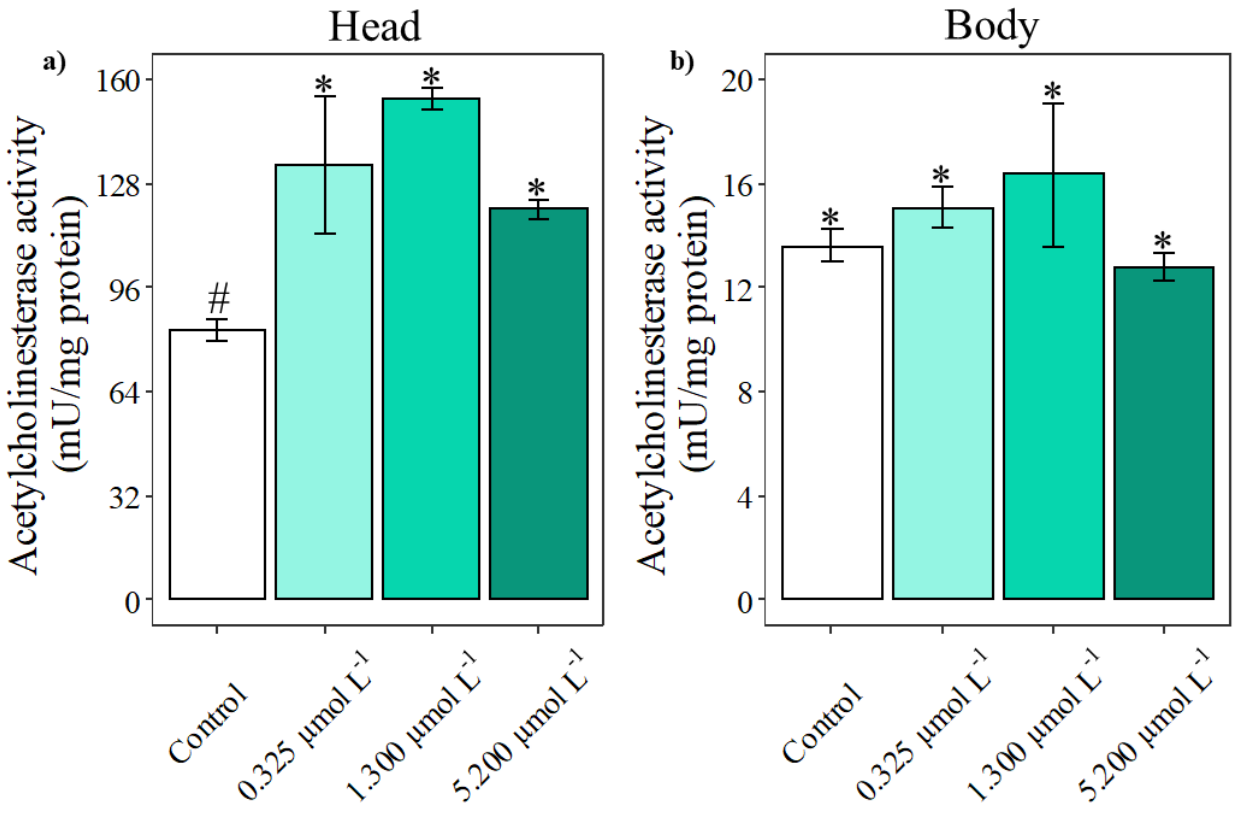

Figure 4. Acetylcholinesterase (AChE) activity of *Drosophila melanogaster* exposed to three concentrations of 2-Phenylethynyl-Butyltellurium (PEBT) in the head (a) and body (b), after 48h of exposure. * Significant difference compared with #. # Significant difference compared with *.

toxicity (Souza et al. 2012, 2013a, b, Quines et al. 2015).

When analyzing the mortality-concentration response curve, fly mortality showed a fast initial increase as PEBT concentration increased, until it reached a point beyond which the increases in mortality became lower and lower. To better understand this response, the definition of LC_{50} has been evermore used in insecticidal activity studies (Wu et al. 2021) along with points of higher concentrations, such as LC_{80} and LC_{95} (Schutze et al. 2018, Hematpoor et al. 2017), since these points can help extract important information from the curve. After 24h of exposure to PEBT, as the maximum mortality rate was 70.22%, the determination of LC_{80} and LC_{95} values was hindered, obtaining only LC_{50}, which corresponds to the concentration capable of causing 50% of the death of a population (Gad 2014). However, although after 48h mortality reached 97.33% at the maximum PEBT concentration (5.200 µmol L^{-1}), LC_{95} was equal to 1.772 µmol L^{-1}, which corresponds to less than half of that concentration, meaning that an increase in concentration up from that value would not generate much higher responses, since doubling it would only increase mortality in only almost 2%. Moreover, when comparing those values to LC_{80} (0.634 µmol L^{-1}), although the latter is much lower, it still represents a useful piece of information, considering Brazilian legislation requires at least 80% pest mortality for an insecticide to be considered efficient (Araújo et al. 2017). Interestingly, the maximum dose administered on a mammalian model by Souza et al. (2012) and Souza et al. (2013a) was 10

Figure 5. Pearson's correlation matrix with Pearson's correlation coefficients between Mortality Rate in 24h (MR 24h), Mortality Rate in 48h (MR 48h), Negative Geotaxis in 24h (NG 24h), Negative Geotaxis in 48h (NG 48h), Open Field in 24h (OF 24h), Open Field in 48h (OF 48h), Acetylcholinesterase activity in the head in 48h (AChE head) and Acetylcholinesterase activity in the body in 48h (AChE body) of *Drosophila melanogaster*.

mg kg^{-1}, which had no toxic effects and is much higher than the LC values here found.

Behavioral tests are also extremely important tools for assessing the toxicological potential of compounds (Araujo et al. 2015, Musachio et al. 2020). This is because behaviors serve as a guide to understanding the mechanisms behind the results found (Belovicova et al. 2017, Hånell & Marklund 2014). PEBT exposure resulted in behavioral alterations for the flies, with a decrease in locomotor activity, as observed through the negative geotaxis test. Negative geotaxis behavior refers to the natural tendency of the flies to migrate upward against gravity (Ajjuri et al. 2015), indicating an innate escape response (Musachio et al. 2020). The flies exposed to PEBT performed slow movements showing impaired motor coordination and muscle tone (Chen et al. 2014) with an increase in climbing time.

As expected, similar alterations were observed through the open field test, as it verifies the spontaneous locomotor capacity of the flies (Musachio et al. 2020), detecting changes in their exploratory behavior (Soibam et al. 2012). Accordingly, both characteristics presented high inverse correlations, since one considers increases in climbing time and the other, decreases in the number of crossings as diminished locomotor activity. Also, both were highly correlated to the mortality rate in 24 and 48h, indicating such locomotor alterations probably occurred in response to PEBT toxicity.

Impaired locomotor performance is often related to cholinergic impairment, which is frequently linked to AChE regulation (Oboh et al. 2021), especially when it comes to tellurium toxicity (Pinton et al. 2010, Klichkhanov et al. 2019, Khuwaja et al. 2020). Although, impaired locomotion induced by AChE regulation is frequently linked to AChE decrease (Čolović et al. 2013), on some occasions, tellurium compounds, including diphenyl ditelluride, another organotellurium, have also shown increased AChE activity involving locomotor alterations (Pinton et al. 2010, Khuwaja et al. 2020), which is also the case of PEBT. This leads to an interesting hypothesis since, as proposed

by Halmenschelager & Rocha (2019), either a decrease or an increase in AChE activity can disrupt locomotion of adult *D. melanogaster*. That is because AChE is a key enzyme in the cholinergic system that has as its main role the termination of nerve impulse transmission at cholinergic synapses through the rapid hydrolysis of ACh (Barnard 1974). When its activity is inhibited, such as by carbamate and organophosphorus insecticides, ACh breakdown is interrupted, causing continuous impulse transmission and consequently leading to hyperexcitability and neuronal death (Čolović et al. 2013). However, when AChE activity is increased, as observed in the head of *D. melanogaster* exposed to PEBT, the opposite might occur, which means a consequent decrease in ACh levels (Pinton et al. 2010), eventually resulting in the stop of nerve impulse transmission, which logically would affect locomotion and may even contribute to the neuronal death of the flies (Oboh et al. 2021).

Similarly, Oyetayo et al. (2020) observed reduced survival rates of *D. melanogaster* related to AChE activity increase that also caused locomotor impairment. Thus, the behavioral alterations caused by PEBT may have reflected the consequences of this process, suggesting AChE activity increase is involved in PEBT toxicity. Also, this corroborates the positive correlations between behaviors and AChE activity in the head, especially since the behaviors assessed after 48 hours of acute exposure and AChE activity in the head did not show any significant differences between concentrations, establishing a strong connection between these characteristics. On the other hand, in the body of the flies, no alterations in the activity of this enzyme were observed. A possible explanation for this is that AChE activity regulation can variate according to the fly region, and also, this could mean PEBT acts mainly in the fly Central Nervous System (Halmenschelager & Rocha 2019). Thus, the results here obtained can serve as a basis for future studies on PEBT's insecticidal properties, highly encouraging further investigation regarding its effects on plants and pest insects, as well as the mechanisms behind its toxicity and AChE regulation involvement.

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KARINA CHERTOK BITTENCOURT[1]
https://orcid.org/0000-0002-4127-0715

RAFAEL RODRIGUES DE SOUZA[2]
https://orcid.org/0000-0002-7068-4079

[1]Federal University of Santa Maria (UFSM), Department of Agronomic and Environmental Sciences, Linha 7 de Setembro, s/n, BR 386, Km 40, 98400-000 Frederico Westphalen, RS, Brazil

[2]Federal University of Santa Maria (UFSM), Department of Plant Science, Avenida Roraima, 1000, 97105-900, Santa Maria, RS, Brazil

Correspondence to: **Karina Chertok Bittencourt**
E-mail: kari.cher.bitt@gmail.com

Author contributions

Karina Chertok Bittencourt: Conceptualization (lead); writing – original draft (lead); writing – review and editing (equal); methodology (equal); data curation (lead). Rafael Rodrigues de Souza: Formal analysis (lead); software (lead); methodology (equal); writing – original draft (supporting); writing – review and editing (equal).