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Use of inhibitors and protectors in the tolerance of white oat cultivars to the penoxsulam herbicide

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Abstract: Background: Crop tolerance to herbicides and the effectiveness of weed control are key considerations of a chemical management program. Crop tolerance levels and the mechanism involved is of great importance in ensuring the safe use of an herbicide.

Objective: This study aims to evaluate the effect of mefenpyr-diethyl as a safener and metabolic inhibitor (organophosphorus insecticides) on the penoxsulam tolerance of white oat cultivars.

Methods: We determined the relative tolerance (%) of URS Guará and URS Guria white oat cultivars to different doses of penoxsulam with and without prior application of organophosphorus metabolic inhibitors (malathion + chlorpyrifos). We then determined the relative tolerance (%) of the white oat cultivar URS Guria with and without prior application of a protective metabolization stimulator (mefenpyr-diethyl).

Results: Increased penoxsulam doses resulted in lower relative tolerance of both cultivars. The application of organophosphorus insecticides reduced the penoxsulam tolerance of white oat cultivars, with a 14.4 and 4.8 fold reduction of C_{50} in the URS Guará and URS Guria cultivars, respectively. The use of mefenpyr-diethyl increased the penoxsulam tolerance of URS Guria by a factor of 2.62.

Conclusions: The penoxsulam tolerance of white oat cultivars was reduced by organophosphorus insecticides and increased by mefenpyr-diethyl. Metabolization is the likely mechanism of tolerance of white oats to this herbicide.

Keywords: *Avena sativa* L.; Organophosphorus insecticide; Safener; Detoxification

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1. Introduction

The cultivation of white oat (*Avena sativa* L.) for a variety of purposes, such as grain production and grazing is important for the sustainability of several agricultural production systems in Brazil (Castro et al., 2012), in the 2020/2021 crop, a cultivated area in Brazil of 503.4 thousand ha, productivity of 2,259 kg ha^{-1} and production of 1,137.3 thousand tons (Companhia Nacional de Abastecimento, 2022). However, adequate weed management is necessary to maximize yield (Nunes et al., 2007).

Herbicides are important tools for controlling weeds in agricultural areas. However, they must at the same time result in effective weed control and be selective for crops, including those cultivated plants that are taxonomically like weeds (Duhoux et al., 2017). Herbicide selectivity is defined as the ability of an herbicide molecule to control or suppress weeds while not harming other plants of commercial interest (Azania, Azania, 2014). Selectivity depends on several factors related to herbicide type, application, and environmental conditions, as well as plant characteristics (Abu-Qare, Duncan, 2002).

To study the basis of herbicide resistance or tolerance, mechanisms of plant resistance or tolerance must be considered. These mechanisms can be classified as mechanisms related to the target-site mechanisms, such as overexpression of proteins linked to the target enzyme, multiple copies of the target enzyme and alteration of the enzyme, which makes it insensitive to herbicides of different chemical groups (Gaines et al., 2010; Cruz-Hipolito et al., 2013). In addition mechanisms not related to the target site, such as reduced absorption, translocation, metabolism and compartmentalization of herbicides, among others (Beckie et al., 2012; Dalazen et al., 2015; Ghanizadeh, Harrington, 2017).

Among the characteristics of plants that explain herbicide tolerance, the metabolism or detoxification of herbicides is particularly important (Délye, 2013). Herbicide metabolism or detoxification is the ability to break down or metabolize the herbicide molecule, making it less active or inactive in the plant (Vargas, Fleck, 1999). Resistance or tolerance by metabolization or detoxification of the herbicide occurs due to the presence of the group of cytochrome P450 enzymes (monooxygenases),

glutathione S-transferase (GST), glucosyltransferases, esterases, hydrolases, oxidases, peroxidases and carrier proteins (ABC) (Pan et al., 2016; Nandula et al., 2019), which cause the herbicide molecule to undergo oxidation, conjugation and transport reactions in the first, second and third phases of metabolization (Vidal, 2002; Scarponi et al., 2006; Jugulam, Shyam, 2019).

To increase crop selectivity, some herbicides are sprayed in association with compounds called safeners. These compounds strengthen herbicide degradation pathways in crop plants (Duhoux et al., 2017), without affecting the level of weed control (Hatzios, Burgos, 2004). Safeners have a high degree of botanical and chemical specificity and protecting from herbicide damage without reversing the process (Galon et al., 2011). Mefenpyr-diethyl is the first safener that can be used in chemically different herbicides with different modes of action (Hacker et al., 2000).

The safeners used for white oat cultivation are naphthalic anhydride, isoxadifen, and mefenpyr-diethyl (Galon et al., 2011). In general, safeners have a specific effect and are only effective for a limited spectrum of action and application conditions for specific cultivars (Galon et al., 2011). Mefenpyr-diethyl is applied to increase the tolerance of white oats to the herbicide iodosulfuron-methyl (Queiroz et al., 2017). Rizzardi and Serafini (2001) observed that the protective ability of naphthalic anhydride was limited in white oats due to high sensitivity to the dosage, the herbicide used, and the cultivar.

The level of herbicides resistance or tolerance caused by metabolism can be influenced with metabolic inhibitors associated with the herbicide. These include organophosphorus insecticides, which can inhibit the cytochrome P450 enzymes group (Tardif, Powles, 1999). Studies report a negative interaction between acetolactate synthase (ALS)-inhibiting herbicides and organophosphorus insecticides in maize (Diehl et al., 1995; Nicolai et al., 2006), tomatoes (Buker et al., 2004), and cotton (Minton et al., 2005), resulting in reduced herbicide tolerance.

Herbicides and insecticides are commonly applied simultaneously or within a very short period to agricultural areas (Nicolai et al., 2006). A lack of awareness of compatibility issues between herbicides and insecticides may lead to a reduction in the herbicide selectivity, with undesirable consequences (Carvalho et al., 2009). Crop herbicide tolerance mechanism studies are crucial since they can help test for compatibility between herbicides and insecticides.

The use of selective herbicides to reduce weed interference in autumn and winter crops is limited due to the reduced number of herbicides registered for this crop. The herbicide penoxsulam has no registered for these crops, but other studies have shown selectivity for white oat cultivars (Queiroz et al., 2017). Complementary studies on selectivity, which include elucidating the mechanism of tolerance of white oats to penoxsulam, would assist in supporting the registration process having the potential to increase the number of active ingredients to be used in this crop and the spectrum of weeds to be controlled. This can result in information for farmers regarding herbicide/ insecticide interactions that do not lower crop herbicide tolerance. Therefore, this study aims to evaluate the effect of mefenpyr-diethyl and organophosphorus insecticides on the penoxsulam tolerance of white oat cultivars.

2. Material and Methods

This study consists of two greenhouse experiments conducted from May to August 2017 at the Agronomy Experimental Station of Federal Technological University of Paraná (PR), located in Pato Branco, RS, Brazil (26°07'S and 52°41'W). Both experiments were conducted in a completely randomized design. For each treatment used, in the experiments, three repetitions per treatment were used, which were three pots of 5 dm^3 containing three plants per pot, filled with soil from the place of the experiment, of the Red Latosol type.

The first experiment evaluated the interaction between the penoxsulam and metabolic inhibitors (malathion and chlorpyrifos, two organophosphorus insecticides). The first experiment was performed in a tri-factorial arrangement. Factor A consisted of white oat cultivars with high (URS Guará) and low (URS Guria) penoxsulam tolerance, according to the selectivity test carried out previously. Both cultivars were made available by the Oat Genetic Improvement Program (PMGA) at Federal University of Rio Grande do Sul (UFRGS). Factor B was composed of five doses of penoxsulam, 0, 60, 120, 240 and 360 g a.e. ha^{-1}, corresponding to the doses of 0x, 1x, 2x, 4x and 6x, respectively. Depending on the dose of the herbicide label for rice crop. Factor C was the application of the metabolism-inhibiting insecticides malathion (1.000 g a.e.ha^{-1}) and chlorpyrifos (1.125 g a.e.ha^{-1}), applied three hours before penoxsulam. The three-hour period between applications and dosages of insecticides was used according to the methodology proposed by Queiroz et al. (2017).

The second experiment evaluated the interaction of the penoxsulam with the mefenpyr-diethyl, was conducted in a bi-factorial arrangement using the URS Guria cultivar, which is less tolerant to penoxsulam, according to previous experiments. Factor A was composed of the same concentrations of penoxsulam used in the first experiment (0, 60, 120, 240 and 360 g a.e.ha^{-1}). Factor B was the application of mefenpyr-diethyl, at a dose equivalent to 18 g a.e.ha^{-1}, performed three hours before applying penoxsulam. For both experiments, previous tests were performed, considering two replicates over time.

Treatments were applied at four to five leaf stage. An adjuvant based on ethoxylated alkyl ester of phosphoric acid at a dose of 1 L ha^{-1} was added to penoxsulam. Mineral oil at

0.5% v/v was added to the metabolic inhibitors (malathion + chlorpyrifos) and mefenpyr-diethyl. The herbicides and other compounds were applied in a pressurized CO_2 sprayer at constant pressure at 200 kPa, with three fan nozzles 110.02, spaced 0.50 m between each nozzle and carrier volume of 200 L ha^{-1}. The environmental conditions at the beginning and end of the applications of all treatments were as follows: air temperature = 12 to 17 °C; relative air humidity = 85 to 70%.

For both experiments, herbicide tolerance was determined at 28 days after treatment (DAT) using a visual scale adapted from Frans et al. (1986), where 0% represents plant death and 100% absence of symptoms, compared to control plants without application of the herbicide. Above ground biomass was harvested, and the samples were packed in a dryer with forced air circulation at a temperature of 60 °C . The shoot dry weight (SDW) was converted into percentage values in relation to the control without the application of the herbicide.

For both experiments, the data obtained were analyzed for normality by the Shapiro-Wilk test and homogeneity by the Bartlett test and submitted to analysis of variance, by the F test ($p < 0.05$), using the Winstat software. When the interaction of the factors was detected, the data were subjected to regressions between the dependent variables and the herbicide doses, which were adjusted by non-linear models using a three-parameter logistic model (Equation 1), according to Streibig (1988), using SigmaPlot® version 10.0 (Systat Software Inc, 2006):

$$y = a / (1+(x / x_0)^b) \text{ (Equation 1)}$$

Where: y = dependent variable; a = maximum asymptote; x = concentration of the herbicide; x_0 = concentration that provides 50% control or dry mass reduction; b = slope of the curve.

The mean standard error was calculated by the quotient of the standard deviation and the square root of the sample size (n = 3). The logistic equation parameters used were C_{50} (dose at 50% control) and GR_{50} (dose at 50% reduction in SDW). We calculated the tolerance factor (TF) based on the quotient between the C_{50} and GR_{50} of the tolerant and the herbicide-sensitive cultivars.

3. Results and Discussion

For the first experiment, the interaction between cultivars x doses x metabolism- inhibiting was significant and for the second experiment, the interaction dose x safener was significant. In the first experiment at 28 DAT, the increased dosage of penoxsulam reduced cultivar tolerance. Prior application of metabolism inhibitors reduced herbicide tolerance in both tested cultivars (Figure 1). At the commercial dose of penoxsulam (60 g a.e. ha^{-1}), URS Guará with no metabolic inhibitor had the highest relative tolerance at 87%, while the lowest relative tolerance, 52%, was obtained with the URS Guria cultivar with metabolic inhibitor. To achieve 50% control of URS Guará was required 2,177.4 g a.e. from penoxsulam, but this value was reduced to 151.2 g a.e. with prior application of metabolic inhibitors, a 14.4-fold reduction in herbicide tolerance (Table 1). The application of metabolic inhibitors before the application of penoxsulam should be avoided, due to the reduction in the tolerance level in plants.

The results of SDW (% in relation to the control) (Figure 2) and GR_{50} of SDW (Table 1), further support the relative tolerance data and highlight the reduction in

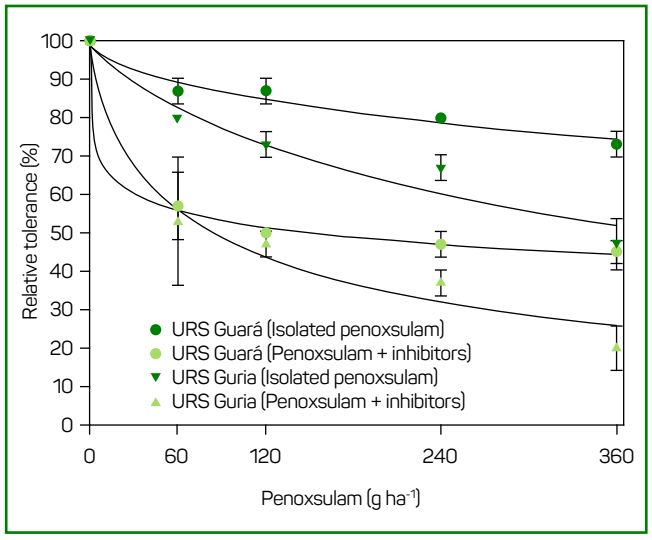

Figure 1 - Relative tolerance (%) at 28 days after treatment of penoxsulam with and without metabolic inhibitors (malathion+chlorpyrifos), in URS Guará and URS Guria cultivars. Vertical bars represent the standard error of the mean for each treatment

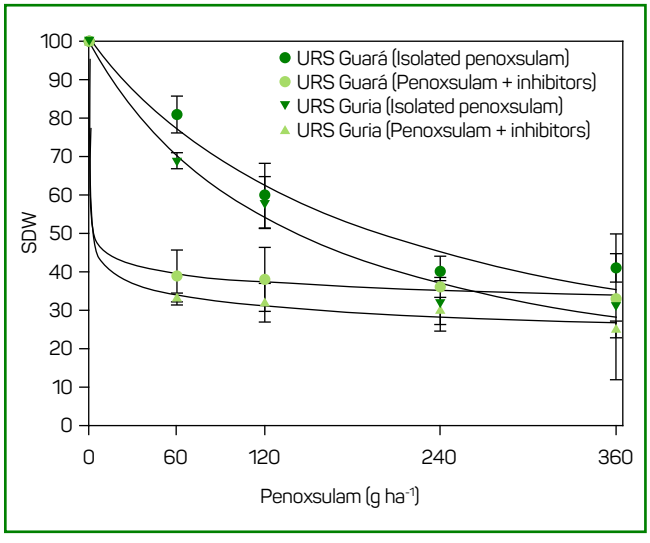

Figure 2 - Shoot dry weight (SDW) (% in relation to the control) of URS Guará and URS Guria white oat cultivars when applying penoxsulam, with and without metabolic inhibitors (malathion+chlorpyrifos). Vertical bars represent the standard error of the mean of each treatment

Table 1 - Estimation of parameters in the equation[1] describing the effect of doses of penoxsulam with and without metabolic inhibitors (malathion+chlorpyrifos) on the relative tolerance and the shoot dry weight in the cultivars URS Guará and URS Guria at 28 days after treatment.

Treatments	Parameters[1]					
	Relative tolerance					
	a	B	X_0(C_{50} or GR_{50})[6]	R^2[4]	p[5]	TF
URS Guará (Isolated penoxsulam)	99.69(2.64)[2]*[3]	0.6 (0.17)*	2,177.4 (1343.79)*	0.98*	0.035	25.7
URS Guará (Penoxsulam + inhibitors)	100 (1.35)*	0.26(0.04)*	151.2 (22.45)*	0.99*	0.002	1.8
URS Guria (Isolated penoxsulam)	100 (6.18)*	0.84 (0.28)*	400 (119.53)*	0.97*	0.050	4.8
URS Guria (Penoxsulam + inhibitors)	99.78 (6.38)*	0.72 (0.21)*	84.6(25.84)*	0.99*	0.022	-
Treatments	Shoot dry weight (SDW)					
URS Guará (Isolated penoxsulam)	100 (6.27)*	1.00(0.24)*	196.2 (38.65)*	0.99*	0.029	109
URS Guará (Penoxsulam + inhibitors)	100 (1.07)*	0.14 (0.03)*	2.4 (2.75)*	0.99*	<0.01	1.3
URS Guria (Isolated penoxsulam)	100 (4.99)*	1.00 (0.18)*	142.2 (22.44)*	0.99*	0.015	79
URS Guria (Penoxsulam + inhibitors)	100 (1.97)*	0.19(0.06)ns	1.8 (2.88)*	0.99*	0.002	-

[1] Three-parameter logistic equation Y= a/(1+(x/X_0)^b): a = Maximum asymptote, b = Slope of the curve [2] Numbers in parentheses correspond to standard error of the parameter estimates. [3] *: Significant t-test value (p-value < 0.05); ns: Non-significant (p-value < 0.05). [4] Coefficient of determination of the model. [5] Probability of the significance of the equation by the t test. [6] C_{50} or GR_{50}= Dose (g a.e.ha^{-1}) providing 50% control or providing 50% reduction in the shoot dry weight. TF (tolerance factor) = C_{50} tolerant/ C_{50} susceptible or GR_{50} tolerant/ GR_{50} susceptible

tolerance due to the increasing the herbicide dose and the prior application of metabolism inhibitor. The URS Guará cultivar was more tolerant of penoxsulam than the URS Guria cultivar (Figure 2). The application of metabolic inhibitors reduced the GR_{50} of both cultivars, from 2,177.4 to 151.2 in URS Guará and from 400 to 84.6 in URS Guria (Table 1).

In the study using mefenpyr-diethyl, the relative tolerance values at 28 DAT were 90% with mefenpyr-diethyl and 80% without the safener (Figure 3). At the highest application of penoxsulam 360 g ha^{-1} (6x), mefenpyr-diethyl application raised the relative tolerance from 46% to 70%, in relation to the application of only the herbicide (Figure 3). The C_{50} and TF values support the findings of increased herbicide tolerance following mefenpyr-diethyl application (Table 2). The application of the safener resulted in a 2.62-fold increase in the C_{50} value (Table 2).

Although increased dosages of penoxsulam resulted in reduced SDW, prior application of mefenpyr-diethyl resulted in a lower reduction in SDW at all penoxsulam doses (Figure 4). The higher GR_{50} values corroborated the higher tolerance of the URS Guria cultivar with the application of mefenpyr-diethyl. In the presence of the safener, the GR_{50} values were 1.67 times higher than in plants that were not sprayed with the safener, an observation similar to the relative C_{50} values (Table 2).

The reduction in penoxsulam tolerance among white oat cultivars due to the prior application of metabolic inhibitors (malathion + chlorpyrifos) suggests that the mechanism of selectivity in white oat plants is, at least in part, due herbicide metabolism. This conclusion is supported by the increased penoxsulam tolerance due to the mefenpyr-diethyl application. This finding is consistent with an earlier study by Queiroz et al. (2017) who found reduced tolerance

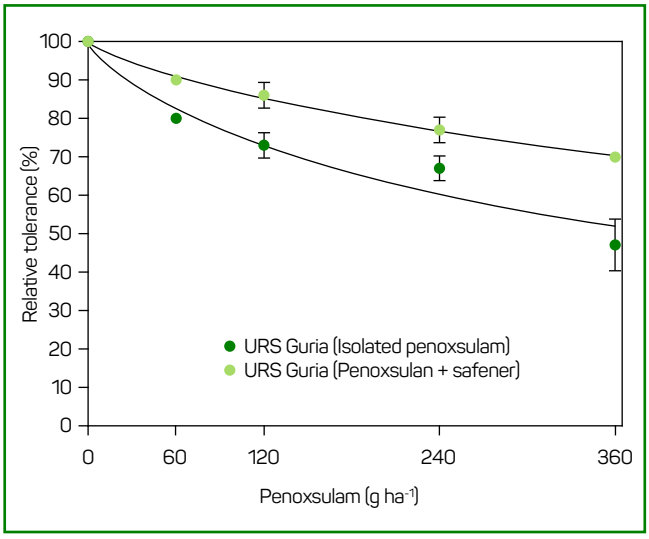

Figure 3 - Relative tolerance (%) at 28 days after treatment of the URS Guria cultivar to penoxsulam, with and without safener (mefenpyr-diethyl). Vertical bars represent the standard error of the mean of each treatment

among white oats to iodosulfuron-methyl (another ALS-inhibiting herbicide) when the plants were treated with metabolic inhibitors (malathion + chlorpiryphos), as well as increased tolerance of the herbicide when plants were sprayed with the mefenpyr-diethyl. These findings support the hypothesis of herbicide metabolism in white oat plants of an herbicide similar to penoxsulam.

Reductions of plant tolerance to ALS-inhibiting herbicides, caused by the previous application of organophosphate insecticides, have also been observed in

Table 2 - Estimation of parameters in the equation[1] describing the effect of doses of penoxsulam with and without safener (mefenpyr-diethyl) on the relative tolerance and the shoot dry weight in the URS Guria cultivar at 28 days after treatment.

Treatments	Parameters[1]					
	Relative tolerance					
	a	B	$X_0(C_{50}$ or $GR_{50})$[6]	R^2[4]	p[5]	TF
URS Guria (Isolated penoxsulam)	99.3(6.18)[2]*[3]	0.84 (0.28)*	402(119.5)*	0.97*	0.005	-
URS Guria (Penoxsulam + safener)	99.8(0.92)*	0.81(0.06)*	1,055.20 (118.94)*	0.99*	0.003	2.62
Treatments	Shoot dry weight (SRW)					
URS Guria (Isolated penoxsulam)	100 (4.99)*	1.00(0.18)*	142.2(22.44)*	0.99*	0.015	-
URS Guria (Penoxsulam + safener)	100 (5.04)*	1.08 (0.22)*	237.6 (36.3)*	0.99*	0.021	1.67

[1] Three-parameter logistic equation $Y= a/(1+(x/X_0)^b)$: a = Maximum asymptote, b = Slope of the curve [2] Numbers in parentheses correspond to standard error of the parameter estimates. [3] *: Significant t-test value (p-value < 0.05); ns: Non-significant (p-value > 0.05). [4] Coefficient of determination of the model. [5] Probability of the significance of the equation by the t test. [6] C_{50} or GR_{50}= Dose (g a.e.ha^{-1}) providing 50% control or providing 50% reduction in the shoot dry weight. TF (tolerance factor) = C_{50} tolerant/ C_{50} susceptible or GR_{50} tolerant/ GR_{50} susceptible

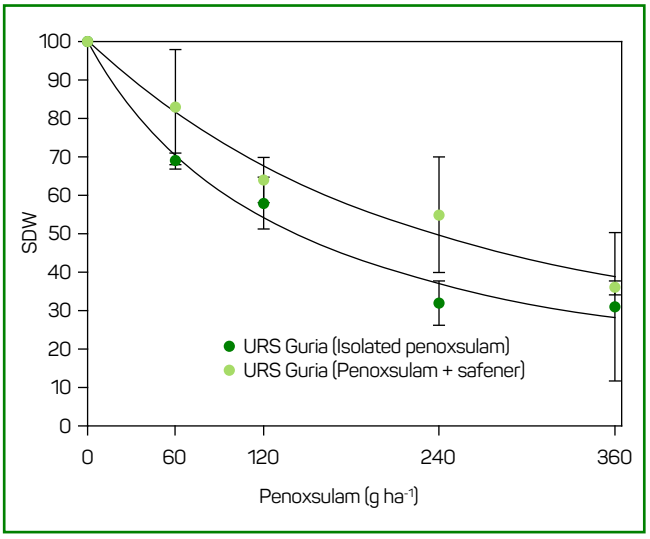

Figure 4 - Shoot dry weight (% in relation to the control) of the URS Guria cultivar by the application of penoxsulam, with and without safener (mefenpyr-diethyl). Vertical bars represent the standard error of the mean of each treatment

other crops. Tolerance of maize cultivars to nicosulfuron was reduced when the herbicide was applied after the use of the terbufos (Diehl et al., 1995) and chlorpyrifos (Nicolai et al., 2006), two organophosphorus insecticides. *Avena fatua* L. resistant to ALS-inhibitors became susceptible to the herbicides following the application of malathion, an organophosphorus insecticide (Beckie et al., 2012). The pretreatment of *A. fatua* plants with malathion, a cytochrome P450 inhibitor, allowed to reverse resistance to ALS-inhibiting herbicides and target site mutations that are known to confer resistance to ALS-inhibitors were not found, suggesting the involvement of non-target site resistance mechanisms (Keith et al., 2015; Burns et al., 2018). The application of malathion to sunflowers (*Helianthus annuus* L.) reduced their tolerance to ALS-inhibiting herbicides (Kaspar et al., 2011).

Reduction of selectivity of ALS-inhibiting herbicides by organophosphate insecticides occurs when the oxygenated insecticide releases a sulfur atom that inhibits the activity of the cytochrome P450 enzyme group, which are involved in the metabolic mechanisms of herbicide resistance in plants (Hinz et al., 1997; Werck-Reichhart et al., 2000; Busi et al., 2017). Furthermore, organophosphorus insecticides reduce the epicuticular wax layer on the leaves, which increases the absorption of ALS-inhibiting herbicides (Diehl et al., 1995).

The use of mefenpyr-diethyl increases the tolerance of crops to herbicides. It was used in conjunction with fenoxaprop-p-ethyl and iodosulfuron-methyl herbicides to increase crop resistance and conferred higher selectivity to herbicides (Hacker et al., 2000; Queiroz et al., 2017). The co-application of mefenpyr-diethyl with pyroxsulam, iodosulfuron, and mesosulfuron resulted in reduced herbicide sensitivity of perennial ryegrass populations (Duhoux et al., 2017). The safeners generally have a very specific action, which depends on the species tested and the herbicide used. This helps explain the less strong protective effect of mefenpyr-diethyl in white oats to the penoxsulam, reflected in a TF value of 2.62 in our study.

The mechanisms of herbicide resistance and tolerance in plants should be studied before using herbicides in conjunction with organophosphorus and protective insecticides since this can result in unfavorable consequences, such as reducing the tolerance of the crop and increasing the tolerance of unwanted (non-target) plants. Thus, crop selectivity should be preserved to ensure safety in the use of herbicides following the best agricultural practices. Additional recommendations include using the correct combinations of products, applying safeners whenever recommended, and planting genetically modified herbicide-tolerant crops whenever possible (Carvalho et al., 2009).

The application of malathion and chlorpyrifos reduced the penoxsulam tolerance in white oat cultivars. The safener mefenpyr-diethyl increased the tolerance of white oats to this herbicide. Both results suggest that the metabolization

process of penoxsulam is the mechanism involved in the tolerance of white oat plants to this herbicide.

Authors' contributions

EX: conducted the study and wrote the text. MMT: designed the project and the study, assisted in writing. MCO: designed the project, assisted in writing. RAV: designed the project and the study.

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