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Chapter

Joint Action of Herbicides on Weeds and Their Risk Assessment on Earthworm (*Eisenia fetida* L.)

Mohammad Taghi Alebrahim, Elham Samadi Kalkhoran and Te-Ming Paul Tseng

Abstract

Frequent and intensive use of similar modes of action herbicides increases selection pressure resulting in nature adapt and a number of herbicide-resistant weeds. The most effective methods to prevent and delay herbicide-resistant weeds are herbicide tank mixture and adjuvant mixed herbicides. This chapter intends to explain the advantages of herbicide tank mixture and adjuvant mixed herbicides. In addition, the models of estimated herbicide mixture interaction response have been explained. Although herbicide mixtures have benefits, they may present risks leading to soil pollution and affecting soil fauna such as earthworms. Therefore, we discussed the negative effect of mixture herbicides on *Eisenia fetida*. On the other hand, various models to calculate mixture herbicide toxicity on earthworms will be present in this chapter.

Keywords: adjuvant, chemical control, earthworm, estimated model herbicide mixture

1. Introduction

Heavy reliance on herbicides has increasingly raised environmental concerns [1–3]. The selection pressure of herbicides resulted in nature adapting and eventually developing herbicide-resistant and tolerant weeds biotype [4–7]. The most effective tool to inhibit, delay, or control herbicide-resistant weeds is to substitute herbicides with different modes of action [8, 9]. But numerous studies have been conducted that simple switches do not delay the evolution of resistant weeds [10, 11]. Previous studies have shown that combining multiple herbicide modes of action in tank mixtures is more efficient in managing weeds [10, 12]. Mixing various modes of action in the mixture can control resistant weeds via broadening the selection pressure by targeting multiple metabolic pathways and delaying the evolution of herbicide-resistant weeds [13]. Ideal herbicide mixtures have proven beneficial over using a single herbicide in improving control and broadening the weed control spectrum [14, 15]. It contains active components with the same persistence and spectrum of controlled weeds but through a different mode of action [16]. Tank mixing increases

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in a spectrum of controlled weeds or an extension of weed control over a more extended period, which reduces production cost by saving time and labor, reduces the number of machine entrances into the production area, fuel consumption, water use to prepare the solution, and hours spent. This leads to lower soil compaction by eliminating multiple field operations. Crop safety is improved by adopting a combination of selected herbicides with minimum doses rather than a single high amount of one herbicide. The soil residues of persistent herbicides were decreased following the application of the minimum levels of such herbicides [17]. It is presupposed that herbicide tank mixtures with two or more herbicide partners behave and act independently so that the presence of each one does not affect the activity of another or may significantly modify the biological behavior of every herbicide in the mixture. Regarding the herbicide tank mixtures, the activity of the applied combination can be easily predicted as the sum of the activities related to each herbicide when applied separately.

In some cases, the interactions often result in declining or enhancing the activity of the combined herbicides compared with the sum. Practically, the herbicide combinations exhibit more activity on target weed species and less on crops (higher selectivity). However, the prediction of this issue is difficult since the behavior of each herbicide in the mixture is mainly influenced by the presence of the other(s), and the mixture activity may significantly vary depending on plant species, growth stage, and environmental conditions. Multiple herbicides applied in the mixture have three types of herbicide interaction: additive/neutral, synergistic, or antagonistic [18–20] (**Figure 1**). Synergism is favorable when two or more herbicide mixtures perform rather than the herbicides applied alone. It allows a lower application rate or frequency of herbicide treatment [22], but finding a new synergy remains challenging. In contrast, an antagonistic response is an interaction of two or more herbicides such that the effect, when combined, is less than the predicted effect based on the activity of each chemical applied separately. Antagonism is 2–3 times more common than synergy, especially when herbicides from different chemical families are combined [21]. Sometimes, synergism can be hypothesized based on mechanistic assumptions, as was done by [23], who predicted the synergism between glufosinate and protoporphyrinogen oxidase inhibitors and confirmed it experimentally; but generally,

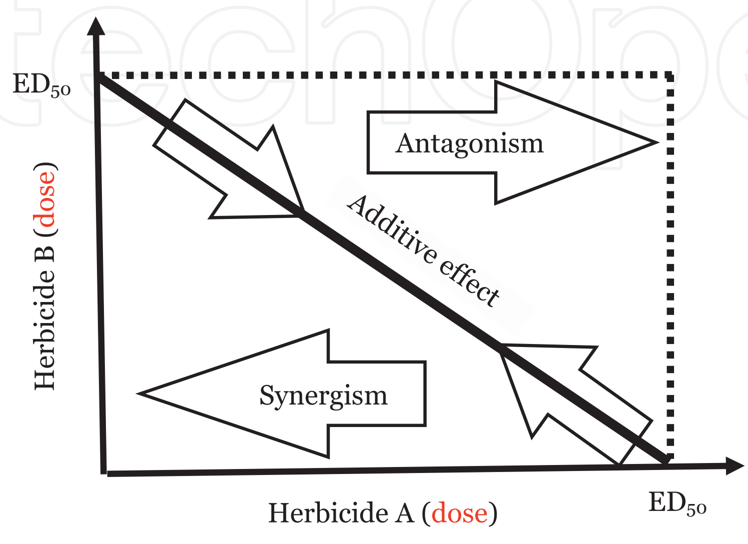

Figure 1.
Schematic isobologram for additive, synergism, and antagonism response of herbicide interaction (ED_{50} = herbicides doses, applied singly or in the mixture for 50% weed control) (modified from [21]).

synergies are not predictable. A synergistic herbicide mixture for one species can also be antagonistic or additive for another species [24]. Thus, herbicide synergies appear to be rare and unpredictable. An additive/neutral response occurs when the observed response of two jointly applied herbicides is statistically similar to the expected value of the mixture. The interactions in herbicide mixtures can occur before, during, or after utilizing the mixture, the mechanisms of which can be broadly grouped into biochemical, competitive, physiological, and chemical categories [25]. This chapter aims to explain the importance of herbicide mixtures for weed control and to clarify the models to estimate combined herbicides' effects. Meanwhile, discusses the risk assessment of herbicide mixtures on the earthworm population.

1.1 Models used to estimate mixture herbicide interaction

The use of isobologram could determine the synergism and antagonism response of the mixtures [26]. Isobologram is a two-dimensional graph. There are two dose axes, x and y, in the mixtures. Herbicide A is the dose on the x-axis, and herbicide B is the dose on the y-axis. The mixtures follow the additive response when mixtures do not interact and present straight lines, and the analysis of this mixture is based on the additive dose model (ADM) [27]. The mixtures may interact, and the performance of combined herbicides is greater than that of herbicides applied alone. So, herbicides are more effective than expected and followed synergism. It means using a lower dose of combined herbicides to provide the same effect as herbicides applied alone. In contrast, if the efficacy of the herbicide mixture is less than that applied alone, then they show antagonism [26].

The reference model uses to determine synergism, antagonism, and additive response in the mixtures. Any consistent model must relate biological response to the doses of two or more herbicides. Choice of the reference model is crucial as the different models may produce different conclusions. The two most frequently referenced models in the study of joint action will be referred to as the additive dose model (ADM) and the multiplicative survival model (MSM) [28]. ADM assumes additivity of doses, i.e., that one herbicide can be replaced, wholly or partly, by another herbicide at equivalent doses. In contrast, MSM assumes that the expected efficacy of herbicide mixtures can be calculated by multiplying the percent survivals of the individual herbicides. Hence, a fundamental difference between the two models is that ADM considers dose rates, whereas MSM considers effects. Both dose addition and independent action should be helpful to approximations for defining the predicted response in the absence of herbicide interactions. A widely known characteristic of the ADM is that, for mixtures of two components, when the response surface predicted by the model is plotted against arithmetic scales of the component doses, the contours of equal response (i.e., isobols) are straight lines. At any particular level of response, the relative potency of the components when acting alone establishes scales of equivalent doses. In terms of this effective-dose (ED) scale, if one component of the mixture is replaced, wholly or in part, by the other, the predicted response is unchanged. By contrast, the MSM does not generally give straight-line isobols. The distinction between the ADM and MSM has not consistently been recognized, and different analysis methods have been confused with other models.

A third reference effect, effect addition, has been proposed, although it predicts implausible effects under certain realistic conditions [29, 30]. Therefore, it is unlikely to be helpful in practice. Likewise, the evaluation of adjuvants does not elicit any antagonistic or synergistic effects since there is no comparison with a reference effect, and it is the only so-called enhancement or potentiation effect [30]. There are various types of herbicide mixtures, experimental designs, and used models. A single-dose factorial design and multiple-dose factorial design are two main groups.

1.1.1 A single-dose factorial design

Two factors are involved in fixed-dose or single-dose experimental design. The first factor is several herbicides (two herbicides), and the second factor is dose with two levels (dose 0 and a nonzero dose). Overall, four treatments result in this design: control (dose 0 of both A and B) (E_0), a nonzero dose of A and dose 0 of B (E_A), dose 0 of A and a nonzero dose of B (E_B), and a single mixture dose corresponding to nonzero doses of both A and B (E_{AB}) [31].

Two nonzero doses justify certain model assumptions despite playing no role in the subsequent derivation. Thus, the doses should be carefully selected since any claim about an antagonistic or synergistic effect is only valid for the chosen doses. Synergism or antagonism can influence dose selection so that the use of a full recommended dose of each pesticide may mask potential synergism when trying to detect synergism for two highly effective herbicides. In this case, pesticide dose reduction (e.g., by 50%) is a common solution. The statistical analysis of 2×2 factorial design is based on the ordinary or linear mixed two-way Analysis of Variance (ANOVA) model depending on the experimental design [32]. It is assumed that fitting the two-way ANOVA model leads to the four estimates of E_0, E_A, E_B, and E_{AB}. In this regard, the subscript 0 refers to the control, A and B are considered as the separate effects of A and B, respectively, and AB indicates their combined effect. Regarding the ordinary two-way ANOVA, the estimates are simple treatment means for each group, while the weighted mean for the linear mixed one. Comparing E_0, E_A, E_B, and E_{AB} through pairwise comparisons does not demonstrate any antagonistic or synergistic effects after fitting a two-way ANOVA model. An antagonistic or synergistic effect may be reported where there is none. Further, the estimates can be used to derive the predicted effect under the assumptions of dose addition and independent action.

1.1.1.1 Dose addition

The reference effect (E_{add}) under the assumption of dose addition is defined as follows [33]:

$$E_{add} = (E_A - E_0) + (E_B - E_0) \tag{1}$$

The definition in Eq. (1) may be justified as reflecting dose addition (even though effects and not doses are added up) by supposing linear dose-response relationships for the two pesticides [32]. Given the availability of only a single nonzero dose for the two pesticides, it is not meant to assume any nonlinear dose-response relationships. However, a linear dose-response relationship may often be assumed as a local approximation to the true nonlinear relationship. This assumption can be justifiable if amounts were chosen as the effective doses, which are not too extreme since the dose-response relationship within a restricted dose range may be supposed to be approximately linear. Particularly, let $y_A = a_0 + b_A x_A$ and $y_B = a_0 + b_B x_B$ denote the simple linear regression equations for the two pesticides with the response values of y_A and y_B, as well as the doses of x_A and x_B, respectively. Then, the reference effect E_{add} is as follows:

$$\mathrm{E_{add}} = (\mathrm{a_0} + \mathrm{b_A x_A} – \mathrm{a_0}) + (\mathrm{a_0} + \mathrm{b_B x_B} – \mathrm{a_0}) = \mathrm{b_A x_A} + \mathrm{b_B x_B} \tag{2}$$

representing that the sum of effects is equal to that of doses after appropriate scaling [34]. Each antagonistic or synergistic effect can be defined as the difference (D_{DA}) between the observed response (expressed as the difference from the control) and predicted effect (Eq. (1)). Especially, the difference is considered as follows:

$$\mathrm{D_{DA}} = \mathrm{E_{AB}} - \mathrm{E_0} - \mathrm{E_{add}} = \mathrm{E_{AB}} - \mathrm{E_0} - (\mathrm{E_A} - \mathrm{E_0} + \mathrm{E_B} - \mathrm{E_0}) = \mathrm{E_{AB}} - \mathrm{E_A} - \mathrm{E_B} + \mathrm{E_0} \tag{3}$$

Based on the definition of difference D_{DA} in Eq. (3), the values significantly larger and smaller than zero exhibit a synergistic and an antagonistic effect, respectively. Testing the null hypothesis of no antagonistic or synergistic effect corresponds to testing for no interaction in a standard two-way ANOVA model. Regarding reporting, the difference must be accompanied by the corresponding standard error or 95% confidence interval to allow for the uncertainty attached to the estimate.

1.1.1.2 Independent action

The reference effect (E_{ind}) under the assumption of independent action is defined as follows:

$$\mathrm{E_{ind}} = \mathrm{E_0}\left(1 - \frac{E_0 - E_A}{E_0}\right)\left(1 - \frac{E_0 - E_B}{E_0}\right) = \mathrm{E_0}\left(\frac{E_A.E_B}{E_0.E_0}\right) = \frac{E_A.E_B}{E_0} \tag{4}$$

as rephrasing in terms of the parameters in the two-way ANOVA model [35]. Similar to the dose addition, the reference effect only involves the three estimates corresponding to the control group (E_0) and the two separate effects of pesticides A and B (E_A and E_B, respectively). In contrast to the definition of dose addition in Eq. (4), which only includes contrasts (i.e., the differences relative to the control), the definition in Eq. (3) relies heavily on the absolute level of the control group (E_0). Furthermore, any antagonistic or synergistic effect may be expressed as the discrepancy between the observed and reference effect under the assumption of independent action in the same way as for dose addition. The difference (D_{IA}) is defined as follows:

$$\mathrm{D_{IA}} = \mathrm{E_{AB}} - \mathrm{E_{ind}} = \mathrm{E_{AB}} - \left(\frac{E_A.E_B}{E_0}\right) \tag{5}$$

The difference D_{IA} significantly below or above zero demonstrates an antagonistic or synergistic effect, respectively. The difference should be reported with the corresponding standard error or 95% confidence interval, which can be obtained by using the delta method. The delta approach is a statistical technique for estimating the standard errors of derived parameter estimates (i.e., the parameters that do not explicitly feature the model parameterization) [18].

1.1.2 Multidose factorial designs

The multidose design is similar to the single-dose one except that a dose range is selected for one or both pesticides, and mixture doses are obtained based on a complete or incomplete two-way factorial design (**Figure 2**). The statistical modeling

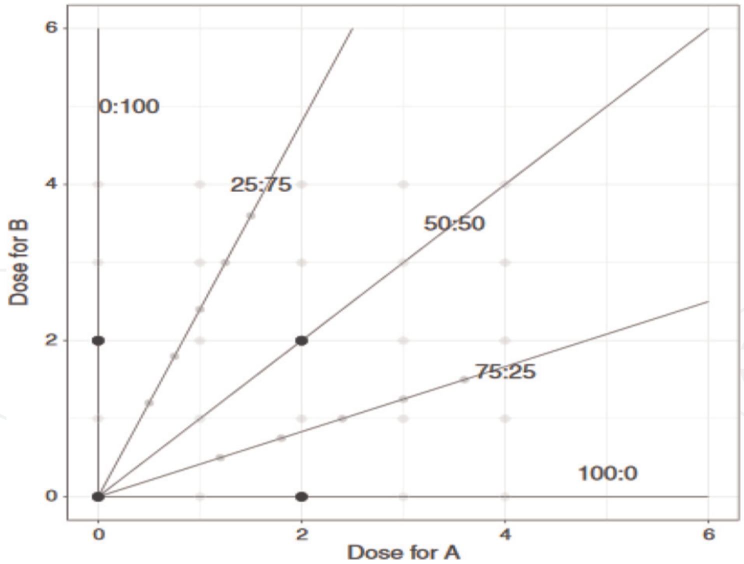

Figure 2.
Factorial and fixed-ratio designs for binary mixture experiments (black and light-gray points illustrate fixed-/single-dose and multidose factorial designs, respectively. The dark-gray lines reflect the rays in a fixed-ratio design with five rays. In addition, three mixtures (virtual proportions of 25:75, 50:50, and 75:25) and two degenerate mixture rays are observed for the individual pure pesticides (virtual proportions of 100:0 and 0:100). The dark-gray points represent the amounts selected along the rays. The doses for the factorial and fixed-ratio designs hardly overlap [33].

approach outlined for single-dose designs can be simply applied in multidose designs by analyzing one mixture dose at a time in the separate statistical analyses corresponding to fitting two-way ANOVA models. A multidose design can be considered as a collection of single-dose designs, and a design involving multiple mixtures in single doses can be analyzed in the same way. However, this method may or may not imply the suboptimal use of data depending on the type of response and experimental design. Fitting a simultaneous model and borrowing strength across mixture doses may improve the analysis in some cases [36].

1.1.3 Single-ray fixed-ratio designs

The single-ray mixture fixed-ratio design consists of several mixture doses so that the two individual herbicides contribute to doses in a constant ratio (in a single ray), which may be specified in terms of so-called actual or virtual proportions. Further, the design involves the two rays corresponding to the individual, pure pesticides, utilized in several doses. Determining total mixture doses is an important preliminary step in planning a fixed-ratio mixture experiment. These doses can be used for subsequent dose-response modeling. Ideally, this step requires prior knowledge about effective doses. Therefore, it is assumed that ED_{50A} and ED_{50B} are available from the previous experiment. The resulting relative potency of pesticide B relative to A is denoted ρ ($=ED_{50B}/ED_{50A}$). For a given mixture fraction $f \in [0, 1]$, which is respectively related to virtual (mixture) proportions f and $1 - f$, the corresponding actual mixture proportions f_A and f_B (the relative potency of the pesticides A and B) can be calculated as:

$$f_A = f ED_{50A} / (f\ ED_{50A} + (1 - f)(ED_{50B}) \tag{6}$$

$f_B = 1 - f_A$. This approach for extracting the actual mixture proportions is referred to as Hewlett's criterion, which is optimal compared with the other methods [31]. For instance, if the ED_{50} values of herbicides metribuzin and flumioxazin are respectively equal to 17 and 153 μg cm^{-2} in a preliminary experiment, then, a virtual 50:50 mixture (f = 0.50) corresponds to an actual 10:90 mixture by using Eq. (6) (with the actual mixture proportions of 0.10 and 0.90 for metribuzin and flumioxazin, respectively). The ED_{50} value under the assumption of dose addition, ED_{50add} (expressed as a total dose), can be obtained by using either actual or virtual mixture proportions as $ED_{50A}/(f_A + f\rho) = fED_{50A} + (1-f)\,ED_{50B}$ [34]. Based on the actual proportions f_A and f_B, the doses of A and B in the mixture can be respectively recovered as $f_A ED_{50add}$ and $f_B ED_{50add}$ (they are needed for the practical application of the mixture). The resulting ED_{50add} and corresponding doses A and B are typically used to derive a dose series through repeated twofold decreases and increases [37]. The number of doses should be guided by the same considerations utilized for the ordinary dose-response curves of single pesticides. Additionally, no preliminary experiments are carried out in some cases. As an approximation, the relative potency can be estimated from the dose-response data for pesticides A and B, obtained as a part of the ongoing mixture experiment. However, it should be noted that the resulting doses for the mixture are partly based on the estimates (which are based on the response data). The uncertainty in these estimates is ignored in a standard statistical analysis. The data of three dose-response curves can be used to assess synergistic and antagonistic effects on the dose scale [38]. The presence of a shared control group (for dose 0) in dose-response curves is an important prerequisite. This assumption is usually ensured by the experimental design. It implies an indirect standardization relative to the control, which is not unlike the use of differences relative to the control in the case of factorial designs. A joint dose-response model should be fitted for continuous response data, while dose-response models may be separately fitted for each ray concerning binomial and count response data.

1.1.3.1 Dose addition for fixed-ratio designs

Three scenarios are distinguished depending on how similar or dissimilar the dose-response curves are assumed. The assumptions have profound implications on how to evaluate antagonistic and synergistic effects.

1.1.3.2 Identical lower limits and slopes: dose-response models

That imposing shared lower and upper limits and slopes for all three dose-response curves often referred to as parallelism have been used for a long time. These models involve only a single parameter for the common lower and upper limits, slope, and three parameters for the ED_{50} (one for each curve). Accordingly, there are a total of six model parameters. Under the assumption of dose addition, the estimated mixture ED_{50} (ED_{50add}) can be calculated by the linear combination of the ED_{50} values estimated for individual pesticides as [33]:

$$ED_{50add} = f\ ED_{50A} + (1-f)ED_{50B} \tag{7}$$

by using the virtual proportions f and $1-f$ [39]. It is important to realize that ED_{50add} is a derived estimate and consequently is determined with uncertainty like other estimates. Further, Eq. (7) is equivalent to the commonly shown but less intuitive equation for dose addition in terms of so-called toxic units [33]:

$$\frac{f_A ED_{50add}}{ED_{50A}} + \frac{f_B ED_{50add}}{ED_{50B}} = \frac{x_A}{ED_{50A}} + \frac{x_B}{ED_{50B}} = 1 \quad (8)$$

where $x_A = f_A ED_{50add}$ and $x_B = f_B ED_{50add}$ are respectively considered as the total doses of pesticides A and B in proportions f_A and f_B, leading to an effect corresponding to $ED50_{add}$. In the following, Eq. (8) is only utilized because of offering a much more direct interpretation of dose addition [39].

Fitting the dose-response model(s) results in estimating ED_{50A}, ED_{50B}, and ED_{50mix} (expressed as total doses). Furthermore, both a difference and a ratio may be used to examine departures from the assumption of dose addition. In any case, the corresponding standard error or 95% confidence interval should be reported, the first of which can be computed by employing the delta method. Particularly, the definition of the difference is as follows [33]:

$$D_{DA} = ED_{50mix} - ED_{50add} \quad (9)$$

An estimated difference significantly more or less than zero reflects an antagonistic or synergistic effect. It is worth noting that ED_{50add} and ED_{50mix}, which do not incorporate the uncertainty of both estimates, should not be compared [40]. The ratio, combination, or interaction index is defined as follows [32]:

$$R_{DA} = \frac{ED_{50mix}}{ED_{50add}} \quad (10)$$

where a value significantly larger than 1 illustrates an antagonistic effect, while a synergistic effect is detected when a value is significantly lower than 1. The use of arbitrary cutoffs such as $R_{DA} < 0.8$ and > 1.2 is not enough for declaring synergism or antagonism, respectively, since the variation in R_{DA} is ignored entirely. The utilization of a difference in terms of logarithm-transformed estimated ED_{50} values corresponds to the application of ratio R_{DA}. These difference and ratio respectively expressed by Eqs. (9) and (10) need not lead to the same results because of using various approximations while calculating the corresponding standard errors based on the delta approach.

1.1.3.3 Identical lower limits but varying slopes

In log-logistic and Weibull dose-response models, the approximations of estimates for the slope parameter b and parameter e (ED_{50} in the log-logistic one) have recently been established by supposing dose addition [41]. The approximations can be compared with the parameters estimated for the fitted dose-response curve of the mixture. Regarding the log-logistic model, this approach provides a framework for comparing the observed ED_{50} for the mixture with the predicted ED_{50} under this assumption. The approximation of ED_{50} coincides with Eq. (7) for the identical slope scenario. In addition, a slight difference is observed in the approximations for the identical and varying slope scenarios [42]. Thus, varying slopes may not warrant a different analysis than for the earlier case of identical slopes and lower limits when interest lies in ED_{50}. In other words, Eqs. (7), (9), and (10) may still be applied for assessing synergistic and antagonistic effects. However, a different definition of reference effect under the assumption of dose addition may be required for varying slope scenario if interest is in other effective doses [42].

1.1.3.4 Varying slopes and varying lower limits

The varying lower limits may be caused by the lack of absorption or solubility, complicating the evaluation of synergistic and antagonistic effects. For example, the assumption of dose addition needs to no longer correspond to the linear relationships between effective doses (Eq. (7)) [43]. A crude approximation is obtained by supposing identical limits, which should be flagged during use. The literature has proposed several approaches for handling varying lower limits or relevant varying upper limit scenario. Further, many generalizations of existing dose-response models have been suggested [44], often involving highly nonlinear regression models or additional assumptions to present suitable predictions. However, the generalizations are not yet readily available to practitioners. The estimation and quantification of departure from the reference effect remain difficult. The utilization of an absolute effect level, which is separately reached for both pesticides, can be addressed as an alternative. The corresponding (relative) effective doses need not correspond to (relative) ED_{50}, although they are defined independently of the lower limit (as if the lower limit is zero for both pesticides). This approach can provide a viable solution in pesticide science since the control (dose 0) mostly corresponds to the highest response level. Differing lower limits often occur for relatively high doses. The procedure previously described for the case with identical slopes and lower limits can be employed in the case of selecting the appropriate absolute effect level. However, the definition of the effective dose under the assumption of dose addition may not be straightforward for the varying slope scenario.

1.1.4 Independent action for fixed-ratio designs

In analogy with Eq. (4), the dose-response function for the mixture f_{ind} under the assumption of independent action is defined from the dose-response functions f_A and f_B for individual pesticides as f_{ind}:

$$f_{\text{ind}}(\mathrm{x}) = \frac{f_{A(x)} \cdot f_{B(x)}}{f_{A(0)}} \tag{11}$$

for any dose x. The denominator can be the mean response level at dose zero for each of the two individual pesticides, which should have the same upper limit by the assumption. In many applications, in which the response values are pre-standardized against the control [45], Eq. (11) reduces to simply being the product (e.g., standardization means $f_A(0) = f_B(0) = 1$ in Eq. (11) f_{ind}:

$$f_{\text{ind}}(\mathrm{x}) = f_A(\mathrm{x}) \cdot f_B(\mathrm{x}) \tag{12}$$

With respect to mathematical form, the function f_{ind} expressed by Eqs. (11) or Eqs. (12) is not the same as the model functions f_A and f_B for individual pesticides. Accordingly, log-logistic models for individual pesticides do not imply a log-logistic model under the assumption of independent action. However, the upper limits of function f_{ind} and two individual functions are identical [41]. Furthermore, the lower limit of find equals zero if one of the model functions f_A and f_B has a lower limit of zero. The entire estimated dose-response curve for the mixture. The entire estimated dose-response curve for the mixture can be compared with the predicted dose-response curve under the assumption of independent action obtained from Eqs. (11) or Eqs. (12)

through visual inspection or statistical tests such as two-sample t-tests or nonparametric equivalents (comparing fitted and predicted values dose by dose) [46]. The statistical methods suppose the independence between fitted and predicted values, so they are not entirely appropriate. In other words, the assumption of independent action is amenable for predicting, not for quantifying antagonistic or synergistic effects in terms of mean departures from the reference effect in the fixed-ratio ray design.

1.1.5 Multi ray fixed-ratio designs

In the case of an experimental design with multiple mixture rays (**Figure 2**), the earlier methods for the identical and varying slope scenarios for ED50 may still be implemented, repeating the analysis for each mixture ray. Since these separate analyses share the same control group, some overlaps are detected in the used data, although they may be acceptable [47].

1.2 Review of research on the effects of herbicides mixtures on weeds

We note in this section several research results that concluded additivity, antagonism, and synergism effects on weeds.

One of the most common herbicide mixtures is different graminicides with broadleaf herbicides mixture to broaden the weed control spectrum. The postemergence application of various graminicides in a mixture with one or more broadleaf herbicides often results in reduced efficacy of graminicides [48]. Antagonistic interactions are probably due to morphological and physiological differences between grasses and broadleaf weeds. Broadleaf weeds have meristems at the top of the plant, whereas grasses have them at the base. On the other hand, this difference affects absorption and mainly translocation of the foliar-applied herbicides, particularly the systemic ones that are translocated and accumulated at the meristematic tissues of the plant where they act. The herbicide amount translocated to its site of action can be declined by the presence or concomitant translocation of another herbicide into the plant [48]. Increasing the ratio of graminicide to broadleaf herbicide in a mixture can alleviate the antagonism of the graminicide [49]. Historically, ACCase inhibiting herbicide antagonism has been observed when applied in a mixture with broadleaf or sedge herbicides, such as ALS inhibiting herbicides and photosystem II inhibiting herbicides [19, 50]. Research by [19] showed that quizalofop (120 g ha^{-1}) mixed with the full labeled rate of halosulfuron at 53 g ha^{-1} could result in an antagonistic interaction for weedy rice and barnyardgrass control. The interaction of herbicides in-tank mixing depended on weed species. Noticeably, the highest dose of halosulfuron (53 g ha^{-1}) mixed with quizalofop followed an additive response on red rice (*Oryza punctata*) 28 days after treatment [51, 52]. Glufosinate antagonized the activity of clethodim on a mixed population of annual grass species: large crabgrass and fall panicum (*Panicum dichotomiflorum* Michx.), goosegrass (*Eleusine indica* L.) [53], and giant foxtail (*Setaria faberi* Herrm.) [51]. However, [54] did not identify antagonism of glufosinate + clethodim on barnyardgrass. Weed's different responses to herbicide interactions may be due to genetic, physiological, or morphological differences [25]. Antagonism of an ACCase inhibiting herbicide can be reduced by increasing the rate of the ACCase inhibitor to broadleaf herbicide in a mixture. The antagonism between bentazon and quizalofop for control of barnyardgrass (*Echinochloa crus-galli*) can be overcome by doubling the rate of quizalofop [55]. Antagonistic interactions may be attributed to the increased metabolism of an herbicide in the presence of another. Based on the study results [56], the less efficacy of diclofop on various species following application with hormone herbicides such as 2,4-D is ascribed to an enhancement in its metabolism (complex formation) carboxylic group)) due to the presence of 2,4-D. The previous studies revealed that the members of aryloxyphenoxypropionate and cyclohexanedione herbicides are more affected when mixing with systemic broadleaf herbicides than the contact ones. The interaction of herbicide mixtures depends on dose and growth stages. Glufosinate at 451 g ha^{-1} + clethodim at 76 g ha^{-1}, an improvement in control was observed over the individual herbicides for barnyardgrass and Johnson grass (*Sorghum halepense*) control. In contrast, a reduction was observed for large crabgrass (*Digitaria sanguinalis*) and no difference for broadleaf signalgrass [57]. Additionally, the extent of the interactions between combined herbicides is mostly influenced by the growth stage of weeds. The post-emergence use of chlorsulfuron and diclofop diminishes the efficacy of diclofop on Italian ryegrass (*Lolium multiflorum*), the effect of which is more severe when the application is performed at the three-leaf growth stage than the two-leaf one [58]. This issue may be related to a reduction in detoxification ability compared with the younger plants, as well as their thinner cuticle, which probably allows to retain, absorb, and translocate the greater amounts of the utilized herbicides. In the research of [59], the antagonism effect was observed when 28.5% nicosulfuron mixed mesotrione by ADM model on canola at 10, 17, and 40 days after treatment. An increased level of Reactive Oxygen Species (ROS), produced by the mesotrione, may block the inhibitory effect of nicosulfuron on ALS [55]. Clomazone at 760 g ha^{-1} + 1540 g ha^{-1} pendimethalin mixed with 1120 or 2240 g ha^{-1} propanil followed an antagonistic effect on yellow nutsedge (*Cyperus esculentus*) at 28 days after treatment; however, the mixture of clomazone + pendimethalin at 1145 g ha^{-1} with 4485 g ha^{-1} propanil showed a neutral response [60]. An antagonistic response occurred in yellow nutsedge used as a control when treated with 760 and 1540 g ha^{-1} of clomazone plus pendimethalin mixed with 1120 or 2240 g ha^{-1} of propanil at 28 DAT; however, 1145 g ha^{-1} of clomazone plus pendimethalin mixed with 4485 g ha^{-1} of propanil resulted in a neutral interaction [61]. Unlike yellow nutsedge, a synergistic response occurred when barnyardgrass was treated with all rates of clomazone plus pendimethalin mixed with either rate of propanil evaluated at 56 days after treatment.

An antagonistic effect of metribuzin with halosulfuron and metribuzin with flumioxazin at the different dose and mixture ratios was observed on common lambsquarters (*Chenopodium album*) and redroot pigweed (*Amaranthus retroflexus*) and in potato biomass. On the other hand, the effect of metribuzin with flumioxazin mixtures was antagonistic on potato maximum quantum efficiency (Fv/Fm) while metribuzin with halosulfuron mixtures followed the additive model on Fv/Fm [62]. The mixture of chloridazon and clopyralid followed additive model on *Portulaca oleracea* L., *Solanum nigrum* L., *Amaranthus retroflexus* L., and *Chenopodium album* L. In contrast, desmedipham, phenmedipham, ethofumesate, and clopyralid mixtures showed a synergistic effect on all species except *P. oleracea* at 80 and 90% response levels. The binary mixture of desmedipham+ phenmedipham+ ethofumesate and chloridazon represented additive effect on *S. nigrum* and *A. retroflexus* and followed an antagonism effect on *C. album* and *P. oleracea* [63]. The greenhouse research investigated by [64] showed the mixtures of mesosulfuron+ iodosulfuron + pinoxaden followed synergism effect on wild oat (*Avena fatua)* and *Phalaris minor.* If oxadiargyl + rimsulfuron and metribuzin + rimsulfuron mixed with (25:75)% mixture ratio, a high reduction of common lambsquarters (*Chenopodium album*) and redroot pigweed (*Amaranthus retroflexus*) provided at potato emergence stage in the field [65].

2. Herbicides with adjuvants

Historically, adjuvants are essential components for herbicide-resistant weeds control. To improve herbicides' performance or application objective, adjuvants are used in the spray tank. These adjuvants are commonly added to the spray tank to improve herbicidal activity or application characteristics [66]. According to the [67] "adjuvants are the substances used with a herbicide to improve its performance." In the last definition, "adjuvants are already included in the formulations of some herbicides available for sale. They may be purchased separately and added into a tank mix before use" [68]. Generally, adjuvants have been developed to assist herbicides. They allow mix and handle with herbicide active ingredients better, contact to target weed, increase droplet coverage, and spray retention and droplet drying [66]. Adjuvants diminish or even eliminate spray application problems [69] (e.g., drift reduction) [70], enhance herbicide cuticle penetration and cellular accumulation [71], and decline herbicide amount and total weed control costs. Furthermore, they lead to a significantly greater herbicide efficacy [72] and consequently a lower total herbicide concentration to achieve a given effect [73], as well as promoting the formulation's ability to kill the targeted species without harming other plants [74]. In terms of environmental aspects, they can decrease herbicide leaching through soil profile [75]. However, adjuvant addition does not significantly improve control in some circumstances. Adjuvants can sometimes exhibit adverse effects such as declined herbicide activity (antagonistic effects) [76], enhanced formulation ability to spread or persist in the unwanted environment [77], and increased harmful effects on nontarget plants and aquatic species [78]. Adjuvants are divided into activators, spray modifiers, and utility modifiers [79]. Activators are components that change characteristic herbicides such as viscosity and particle size, evaporation, etc. They improved herbicide activity, spread, absorption into a tissue, rainfastness, and reduced herbicide photodegradation. There are three categories of activators: surfactants, wetting agents, and oils [79].

Surfactants are the most widely used and probably the most essential adjuvants [80]. Surfactants can be classified into nonionic, cationic, anionic, and ampholytic based on their ability to ionize the aqueous solution. Organosilicone and silicone surfactants are two types of nonionic surfactants. Cationic surfactants, which have a positive charge, often are not applied with herbicides, and anionic ones are rarely utilized with herbicides. Ampholytic (amphoteric) have both positive and negative charges, that is, in aqueous solution are capable of forming cations or anions. Wetting agents increase solution spread on the leaves [79]. Oils increase herbicide uptake by increasing the time of retention. They mixed with water via emulsifiers. Oils have uniform droplet size (reduction of drift), decreasing spray evaporation and rainfastness time, and increasing penetration into waxy leaves. They can be classified as: crop oils, dormant oils, crop oil concentrates, vegetable oils, vegetable oil concentrate, modified vegetable oil, and modified vegetable oil concentrate. In addition, spray modifiers are among the most important adjuvants, which influence the delivery and placement of spray solution [81]. They limit or alter the physicochemical characteristics of spray solution, make herbicide spray easier to aim, reduce herbicide drift in the air, and cause the spray to adhere to plants more readily. Spray modifiers include thickening agents (i.e., invert emulsions and polymers), stickers, spreaders, spreader stickers, foaming agents, humectants, and UV absorbents. Utility modifiers are the third group of adjuvants, which help minimize handling and application problems. They do not directly improve efficacy, although they widen the conditions in which an herbicide can be used or maintain the integrity of the spray solution. For instance, utility modifiers diminish foaming, promote solubility, modify pH, or decrease spray drift. Emulsifiers, dispersants, cosolvents, ammonium fertilizers, and stabilizing, coupling, compatibility, buffering, and antifoam agents can be addressed as the types of modifiers.

2.1 Review of research on the positive effects of adjuvants mixture herbicides on weeds

Adjuvants can be especially effective in increasing the biological activity of many herbicides [82]. Previous studies reported that density, viscosity, surface tension, contact angle, droplet size, and droplet evaporation of the spray solution could change with the addition of adjuvants to the spray solution [83]. The activity of tribenuron-methyl significantly enhances following the use of NIS (20% isodecyl alcohol ethoxylate + 0.7% silicone surfactants), an anionic surfactant (25.5% alkyl ether sulfate sodium salt), and vegetable oil (95% natural rapeseed oil with 5% compound emulsifiers) on *Sinapis arvensis*, *Tripleurospermum inodorum*, *Papaver rhoeas*, and *C. album*. Further, only minor differences are observed among the tested adjuvant [84]. The character of foliar surfaces such as cuticle, stomata and trichomes number, leaf position, angle, and leafage is different in various weed species that affect retention and deposition of herbicides [85]. COC (crop oil concentrate), NIS, MSO (methylated soybean oil), and COC-DRA (crop oil concentrate-drift retardant adjuvant) with lactofen increased the spray solution viscosity by 4.3, 2.6, 3.6, 7.5, respectively. Lactofen containing COC, NIS, MSO (methylated soybean oil), and COC-DRA increased viscosity by 4.3%, 2.6%, 3.6%, and 5.7%, respectively, compared with lactofen alone [86]. Methylated seed oil (MSO) and NIS promote the foliar absorption and efficacy of many herbicides such as primisulfuron, rimsulfuron, imazethapyr, quinclorac, and several graminicides for grass weed control [87]. Nonionic surfactants improve glyphosate absorption by 20 times greater, and spray drop is spread 200-fold more than when no adjuvant is added [88]. Furthermore, some researchers reported the strong effect of mineral and vegetable oil on clodinafop-propargyl and diclofop-methyl + fenoxaprop-p-ethyl on *Lolium multiflorum*, *Avena ludoviciana*, and *Phalaris minor* [89]. Seed-oil-based crop oils and organosilicone adjuvants combined with halosulfuron lead to 100% control of *Cyperus rotundus* L. at 8 weeks after treatment (WAT) compared with a combination of halosulfuron with the nonionic or paraffin-based crop oil adjuvants (<90% control) [90]. The measurement of ED_{50} and ED_{90} showed that Citogate (0.1 and 0.2%) increased sulfosulfuron efficacy [91].

Generally, environmental agents affect the efficacy of the mixture of herbicides with adjuvants. In the mixture, rain shortly after utilizing herbicides is among the most detrimental issues for performance. Given that the rainfastness of herbicides increases by applying adjuvants, the effect should be considered when selecting an adjuvant [92]. A study [93] represented a shorter critical rain-free period following the addition of an OSL adjuvant to glyphosate. This decline can be attributed to the lower liquid surface tension of glyphosate caused by the OSL (Organosilicone) adjuvant and the subsequent promotion of the stomatal infiltration of glyphosate into the plant. The conventional adjuvants produced slower absorption of the 14C-glyphosate, as the maximum absorption was not achieved until at least 24 h in redroot pigweed, remaining similar until 72 h [88]. The effect of the vegetable oil on tribenuron-methyl's rainfastness was significantly lower than that of the surfactants with rain at

1 h, while no significant differences among the three adjuvants were observed when rain occurred at 2 and 4 h [84].

2.2 No or negative interaction between herbicides and adjuvants

Adjuvants can significantly enhance the effect of an herbicide, while they fail to increase control and cause harmful effects on nontarget plants in some circumstances (antagonistic effect). Several studies have revealed that *A. theophrasti* is more controlled by adding AMS (ammonium sulfate) into herbicides; however, the control of other species such as *C. album* is not always improved [94]. The combination of sethoxydim and halosulfuron with COC or MSO is antagonistic to smooth crabgrass (*Digitaria ischaemum* (Schreb.) ex Muhl.) [76]. Flumioxazin does not damage wheat or cabbage except after adding silicone adjuvant, which enhances the retention of the spray solution [95]. Adjuvant addition slows down degradation and elevates the level of phenmedipham residue in the soil [77]. The addition of nonionic surfactants to dicamba plus glyphosate tank mixture not only decreased contact angle and surface tension but also droplet size [96].

3. Risk assessment of mixture herbicides on soil: emphasis on earthworm (*Eisenia fetida* L.)

Continuous application of herbicides may lead to soil pollution and affect soil fauna [97]. Generally, herbicides applied alone and in mixture negatively influenced nottargeted animals [98]. As soil inhabitant animals, earthworms might be affected, although the site of action herbicides is not targeted toward animals. They are bioindicators for determining herbicide and heavy metals pollution in soil due to their high sensitivity to soil pollution [99, 100]. The *Eisenia fetida* is currently used as test species in ecotoxicology [101]. There are many methods of testing the toxicity of chemicals to earthworms. Tests include two kinds: a paper contact toxicity and an artificial soil test. A simple paper contact toxicity test is described as an optional initial screen to indicate those substances likely to be toxic to earthworms in soil and which will require further more detailed testing in artificial soil. The artificial soil test gives toxicity data more representative of the natural exposure of earthworms to chemicals [102]. On the base of LC_{50}, for the contact test, the concentration of the test substance is expressed in mg cm^{-2}. For the artificial soil test, it is expressed in mg kg^{-1} (dry weight). The LC_{50} of a reference substance should be occasionally determined to ensure that the laboratory test conditions are adequate and have not changed significantly. Only contact filter paper and artificial soil tests adopt mortality (LC_{50}) as the toxic endpoint in all acute toxicity test methods and have received the most attention. The screening test (filter paper contact test) involves exposing earthworms to test substances on moist filter paper to identify potentially toxic chemicals to earthworms in the soil. The artificial soil test involves keeping earthworms in samples of precisely defined artificial soil to which a range of concentrations of the test substance has been applied. Mortality is assessed 7 and 14 days after application. One concentration resulting in no mortality and one resulting in total mortality should be used. The mortality in the controls should not exceed 10% at the end of either test. Only contact filter paper and artificial soil tests exposure protocols using mortality (LC_{50}) as the toxic endpoint and *E. fetida* as the test species have received the most attention, with the latter being adopted by both [101] and European Economic Community [102] in Europe and the United States Environmental Protection Agency in the United States.

As mentioned before, additive, synergism, and antagonism are three types of herbicide interactions. Concentration addition (CA) and independent action (IA) are two common reference models for determining mixture toxicity.

3.1 Concentration addition (CA)

The toxicity of herbicide mixtures with a similar mode of action is estimated by concentration addition (CA) [103], which has extensively been used for herbicides, and is most straightforward [104]. Generally, CA assumes additivity of toxicity that components will not interact with each other in the mixtures, and the relative potency is equal to the sum of singly potencies [105].

3.2 Independent action

The independent action model (IA) is used for components with the dissimilar mode of action on the organism. They act independently. The toxicity of the total mixture is calculated by the expected effects of each component [106].

3.3 Interaction models

Physical, chemical, and biological interactions of herbicides do not account for by CA and IA models. MIXTOX is an empirical model that determines how much mixture toxicity results deviate from CA and IA model predictions [107]. MIXTOX considered a difference between synergism and antagonism based on concentration and mixture ratios along with deviations [108]. Therefore, experimental design for MIXTOX is considerable due to covering all concentration and mixture ratios [109]; to date, MIXTOX has been used with binary mixture toxicity [110]. The median-effect/combination index (CI) is a method used by [111] to expound chemical interactions. It quantitatively determines the mixtures interactions at various concentrations and mixtures ratios. Pollution interaction is developed by [112].

The response to toxic exposure of *E. fetida* in artificial soil and filter paper tests was estimated using the median-effect equation, as described by [112]:

$$\frac{f_a}{f_u} = \left(\frac{D}{D_m}\right)^m \tag{13}$$

where D is the concentration, Dm is the concentration for 50% effect (50% mortality rate), f_a is the fraction affected by concentration D, f_u is the unaffected fraction (f_a = 1 -f_u), and m is the coefficient of the sigmoidicity of the dose-response curve: m = 1, $m > 1$, and $m < 1$ indicate hyperbolic, sigmoidal, and negative sigmoidal dose-response curves, respectively. Therefore, the method considers both the potency (D_m) and shape (m) parameters. If Eq. (14) is rearranged, then:

$$\mathrm{D} = D_m\left(f_a\left(1 - f_a\right)\right)]^{1/m} \tag{14}$$

The D_m and m values for each pesticide are easily determined by the median-effect plot: x = log (D) versus y = log (f_a/f_u) which is based on the logarithmic form of

Eq. (14). The median effect plot, m is the slope, and log (D_m) is the x-intercept. The conformity of the data to the median-response principle can be readily manifested by the linear correlation coefficient (r) of the data to the logarithmic form of Eq. (14).

These parameters were then used to calculate concentrations of the pesticides and their combinations required to produce various effect levels according to Eq. (14); combination index (CI) values were then calculated according to the general combination index equation for n chemical combination at 10%, 50%, and 90% mortality rate:

$$(CI)_X = \sum_{j=1}^{n} \frac{(D)_j}{(D_x)_j} = \sum_{j=1}^{n} \frac{(D_x)_{1-n}\{ \frac{[D]_j}{\sum_1^n [D]}}{(D_x)_j \{ \frac{(f_{ax})_j}{1-(f_{ax})_j}} \qquad (15)$$

where $^n(CI)_x$ is the combination index for n chemicals at x% effect level; (Dx)1_n is the sum of the concentration of n pesticides causing x% mortality rate of the earthworms in the mixture, $\frac{[D]_j}{\sum_1^n [D]}$ is the proportionality of the concentration of each of n pesticides causing x% mortality rate in combination; and $(D_x)_j \{ \frac{(f_{ax})_j}{1-(f_{ax})_j}$ is the concentration of each pesticide causing x% mortality rate. From Eq. (15), CI < 1, CI = 1, and CI > 1 indicate synergism, concentration addition, and antagonism, respectively. Where c_{mix} and E (c_{mix}) are the total concentration and total effect of the mixture, respectively. E (ci) denotes the effect of the ith component with the concentration of ci in the mixture.

$$(EC)_{X,mix} = (\sum_{i=1}^{n} \frac{p_i}{EC_{x,i \times CI_{x\ comp}}} \qquad (16)$$

CIx comp is the computed combination index value for the mixture at the x level of effect (x%) from the experimental toxicity curve of the mixture [113].

3.4 Review of research on the effect of mixtures of herbicides on *Eisenia fetida*

The study of herbicide mixtures on *Eisenia fetida* is rare. The (50:50) and (25:75)% mixture ratios of metribuzin plus halosulfuron and metribuzin plus flumioxazin provided higher toxicity than the other mixture ratios (100:0) and (0:100)% on earthworm biomass, respectively. Isobologram demonstrated metribuzin plus halosulfuron and metribuzin plus flumioxazin followed an antagonistic effect meaning that the mixtures retracted the action of the herbicide in the earthworms relative to a concentration addition (CA) reference model. Earthworms exposed to a mixture of metribuzin plus halosulfuron and metribuzin plus flumioxazin showed that increased exposure time decreased the LC_{50} in filter paper and artificial soil tests on *Eisenia fetida* mortality. The binary mixture experiments demonstrated for both experiments an apparent antagonistic effect on two types of tests [114]. Antagonistic effects are detected from many mixtures because the compounds in the mixture may stimulate the metabolism of each other, leading to affected absorption in the organism [115]. Synergistic effects become significantly dangerous to soil organisms once the mixture toxicity is much greater than its predicted level [116]. Principles of concentration addition model to assess the impact of triazine herbicides on organophosphate insecticide toxicity to the earthworm *Eisenia fetida*. Atrazine and cyanazine also increased the toxicity of chlorpyrifos 7.9- and 2.2-fold, respectively. However, simazine caused no toxicity to the worms and did not affect chlorpyrifos toxicity in binary mixture experiments. The uptake of chlorpyrifos into the worms was reduced when found in binary mixtures with atrazine, so an increased uptake cannot be considered an explanation. The synergistic effects might be linked to increased biotransformation of the original phosphorus-sulfur bond into a phosphorus-oxygen bond characteristic of oxon derivatives [117]. Atrazine disrupts photosynthesis, which may induce cytochrome P_{450} and general esterase activities in *E. fetida* [117]. Cytochrome P_{450} has an essential role in metabolism [5, 118]. These enzymes break down pesticides by either increasing or decreasing the toxicity of other pesticides depending on whether the resulting metabolites are more or less toxic than their parent compounds [119].

Several herbicides (acetochlor, anilofos, flutamone, pretilachlor, S-metolachlor, and terbutryn) were very toxic in contact toxicity but were low in soil toxicity testing [120]. The mixture of tribenuron methyl (TBM) plus tebuconazole (TEB) showed an antagonistic effect on the earthworms in filter paper and artificial soil tests. In the chronic toxicity experiment, both high concentrations of TBM and TEB, single or combined, induced oxidant stress in the earthworms, and the cellulase activity was inhibited in the earthworm exposed to high concentrations of TBM at the early 35 exposure period. However, both pesticides did not damage the DNA of earthworms in all treatments [99]. Both acute and chronic toxicity tests play an essential role in the risk evaluation of pesticides to earthworms. They are considered valuable for predicting the responses of soil organisms to pesticides [121]. An antagonistic effect was observed the binary mixture of butachlor plus λ-cyhalothrin at all effect levels in artificial soil test, while it shows synergism effect in filter paper test [122]. In the research of Chen et al., [122], the binary mixture of butachlor plus atrazin showed moderate synergism at the highest effect levels. An additive and slightly synergism were observed at $<0.2\,f$a in artificial soil test. The mixtures of atrazine plus exhibited a synergism response in filter paper and artificial soil tests on *Eisenia fetida* mortality. Yang et al. [123] reported the combination of acetochlor plus chlorpyrifos followed a synergism response at 4:1 and 3:2 combination. An antagonistic response was observed the combination of 2:3 and 1:4 of clothianidin plus acetochlor, while a dual additive/antagonist response showed at 4:1, 1:1, and 3:2 combination on *Eisenia fetida* mortality. The most strongly synergistic reported at phoxim plus butachlor plus λ-cyhalothrin combination at the all range. The mixture of atrazin plus butachlor plus cadmium exhibited a slight synergism on *Eisenia fetid* mortality [124].

4. Conclusion

Herbicide resistance is a pervasive challenge in intensive agriculture. Applying multiple modes of action can help to manage herbicide-resistant weeds. Herbicide mixture is a powerful tool to prevent, delay, and control herbicide-resistant weeds. The choice of the most appropriate mixture is crucial and is based on herbicide components, formulation, and weed species. The reference models used to determine the interaction of herbicide and the use of isobologram can illustrate the synergism, additive, and antagonism responses by the ED scale. Another method to manage herbicide-resistant weeds is utilizing adjuvant. Adjuvants are the best tool for improving herbicide performance and optimizing herbicide application. In addition, the adjuvant can overcome antagonist response in the tank mixture. Despite the positive effect, the synergism response in high doses can influence the soil animals such as earthworms. Therefore, growers need knowledge of the management strategies to maximize the long-term benefits of herbicide mixture and reduce weed shifts to difficult-to-control and herbicide-resistant weeds.

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Conflicts of interest

The authors declare no conflict of interest.

Author details

Mohammad Taghi Alebrahim[1]*, Elham Samadi Kalkhoran[1] and Te-Ming Paul Tseng[2]

1 Faculty of Agriculture and Natural Resources, Department of Plant production and Genetics, University of Mohaghegh Ardabili, Ardabil, Iran

2 Department of Plant and Soil Sciences, Mississippi State University, Mississippi State, MS, USA

*Address all correspondence to: m_ebrahim@uma.ac.ir

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