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Resistance or tolerance: distinction without a difference

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My View

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Introduction

The serious threat of herbicide resistance for modern agriculture has raised awareness of the importance of understanding the biochemical mechanisms and evolutionary processes that explain its pervasiveness in agroecosystems. Like any other scientific issue, nomenclature is key to properly describing and studying this phenomenon. Although herbicide resistance has been researched for many years, more in-depth knowledge of its biochemical mechanisms and awareness of the historical context have made it necessary to better define herbicide resistance and tolerance. In fact, important organizations such as the Weed Science Society of America and the Herbicide Resistance Action Committee (WSSA 1998; https://hracglobal.com/herbicide-resistance/confirming-resistance, accessed December 15, 2023) have provided definitions for those terms:

> Herbicide resistance is the inherited ability of a plant to survive and reproduce following exposure to a dose of herbicide normally lethal to the wild type. In a plant, resistance may be naturally occurring or induced by such techniques as genetic engineering or selection of variants produced by tissue culture or mutagenesis.
>
> Herbicide tolerance is the inherent ability of a species to survive and reproduce after herbicide treatment. This implies that there was no selection or genetic manipulation to make the plant tolerant: it is naturally tolerant.

There are several problems with those definitions. First, in practical terms, the only difference is whether we know if the population was originally susceptible. This criterion ignores the fact that resistance genes move across populations. Therefore, individuals from a population that was selected for resistance can transfer the resistance alleles to a new population never exposed to the herbicide. If we then treat the new population with a commonly lethal dose and most of the individuals survive, should this population be considered tolerant? Or because the resistance evolved via herbicide selection in the source population, is the recipient population resistant? The opposite is also plausible: gene flow from a tolerant population transfers the so-called tolerance trait to a susceptible population, and via selection, the latter now survives the lethal dose. Without knowing the history of the population, which is the norm where there is gene flow, there is no way to distinguish resistance from tolerance. Also, demonstrating selection under those circumstances is not a trivial task and requires elaborate molecular genetic studies.

A second problem is that both terms require the trait to be genetically controlled (i.e., inherently controlled). There could be a distinction if the mechanisms were controlled by different genes (see "Microbiology and Antibiotics"), but this is not specified. Third, both definitions are relative to a reference population. In other words, there is no "absolute" resistance or tolerance. Because this nomenclature is relative, it can only be applied if we agree on a universal ideotype or always describe in detail (e.g., dose–response curves) the sensitivity of the reference and test populations and then explain the rationale for choosing the discriminatory dose. There is also variation in herbicide sensitivity among susceptible individuals. Thus, one can easily manipulate experiments to report a large sensitivity reduction in the putative resistant population by choosing the most sensitive individuals as reference. For more examples of the challenges distinguishing between herbicide resistance and tolerance, see Thum et al. (2023).

The difficulty of biochemically and physiologically differentiating resistance from tolerance has been a persistent challenge over many years and in many disciplines. When addressing pesticide resistance issues, most articles do not define or provide an operational framework for the use of the term. In general, authors make the implicit assumption that resistance is a widely known and clear term. This might be true within a small scientific group, but across disciplines, the lack of agreement on the terminology has resulted in confusion and contradictions. Furthermore, it is not uncommon to see resistance and tolerance being used as synonyms or as descriptors of different levels of sensitivity to the pesticide (Alyokhin and Chen 2017).

The goals of the present commentary are (1) to provide a brief historical overview of the factors that led to the current use and distinction between the terms "herbicide resistance" and "herbicide tolerance," (2) to discuss how the use of that terminology is no longer appropriate based on our current knowledge of the mechanisms controlling plant sensitivity to herbicides,

and (3) to call attention to the importance of considering gene flow when making inferences about the evolutionary processes explaining changes in herbicide sensitivity.

Historical Context

Part of the problem we have in weed science is the insistence on using nomenclature that was created when there was no knowledge of the mechanisms responsible for the survival of the pest after pesticide exposure. Understanding the origin and modifications over time of the meaning of resistance and tolerance is critical to assess the validity of those terms in the current scientific context.

The first report of pesticide resistance is attributed to Melander, who identified populations of San Jose scales (*Quadraspidiotus perniciosus*, Hemiptera: Diaspididade) that presumably evolved resistance to sulfur-lime (Melander 1914). The author used the terms "resistance" and "immunity" as synonyms and did the same for "susceptibility" and "non-resistance." An important detail of his article is that Melander recognized the difficulty of clearly defining those categories, stating: "The data at present at hand do not permit us to determine whether resistance and susceptibility are differences of degree and not of kind, or whether they behave as allelomorphs" (p. 171). Melander's comment was not given the importance that it merited, otherwise the pesticide literature would have been more careful in considering sensitivity as a continuum (i.e., quantitative trait).

In the 1950s to 1960s, resistance to fungicides started to be regarded as a problem for agriculture. At that time, the nomenclature was still inconsistent, and resistance and tolerance were used indistinctly (Georgopoulos 1969). However, there was more awareness of the quantitative nature of the problem, and it was not uncommon for researchers to talk about "level" or "intensity" of resistance and tolerance (Dekker 1977).

In the case of synthetic herbicides, resistance was first reported by Switzer (1957) in wild carrot (*Daucus carota* L.) surviving 2,4-D applications. This researcher talked of resistance and susceptibility, but the former term was associated with 0% to 25% control and the latter with 85% to 99% control. Such large and non-overlapping differences made it easier and convenient for the author to adopt those two categories. The same year, Hilton reported a spreading dayflower (*Commelina diffusa* Burm. f.) biotype also surviving 2,4-D, but he referred to them as "tolerant" (Hilton 1957). During the following 20 years, reports predominantly used the term "resistance" to describe weed populations shifting from adequate to poor control after repeated herbicide use (Bandeen and McLaren 1976; Ryan 1970).

As knowledge about the mechanisms of resistance increased, more specific descriptions and definitions of the factors involved were generated, but the difference between tolerance and resistance was still elusive. Other factors such as the level of sensitivity and the stability of the trait were taken into consideration, adding complexity to how the terms were interpreted (Dekker 1976).

Uses in Other Disciplines

Microbiology and Antibiotics

In the case of bacteria, microbiologists use quantitative variables such as differences in the minimum inhibitory concentration (MIC) to separate antibiotic-susceptible from antibiotic-resistant strains. However, tolerance is determined with a different quantitative indicator, which is the minimum duration for killing (MDK). Thus, tolerant strains have a longer MDK than susceptible strains, even though they may have the same MIC (Brauner et al. 2016). The distinction between resistance and tolerance using these criteria has a biochemical basis, because the genes conferring resistance are different from those that confer tolerance (Liu et al. 2020). From the antibiotic nomenclature, weed science incorporated the meaning of resistance but not of tolerance.

Entomology and Insecticides

In the entomological literature, it is frequent to find authors designating insect populations as insecticide susceptible, tolerant, and resistant, depending on arbitrarily established levels of mortality (i.e., high, medium, and low, respectively) (Scott et al. 2015). In these cases, it is implied that the mechanism responsible for the reduced sensitivity is the same for resistance and tolerance, and the expression of this mechanism is what determines the variation in survival. In the absence of clear differences in the biochemical pathways responsible for resistance and tolerance, some authors have based the distinction on the origin of the toxic molecule. For example, resistance is used when referring to synthetic insecticides and tolerance to natural toxins affecting the insect (e.g., plant defense chemicals). In both cases, researchers ascribed the detoxification to cytochrome P450s (Scott et al. 1998).

Similarly to entomologists, many weed scientists assume that the mechanisms responsible for resistance and tolerance are the same, especially for non–target site (NTS), and the difference resides in whether the trait was predominant within the population before the first application or was rare and increased due to selection by repeated herbicide applications.

Plant Pathology and Fungicides

Plant pathologists have a variety of terms to describe differences in pathogen survival in response to fungicides, but resistance is the most common and consistently used term. For example, the sensitivity spectrum is divided into sensitive, naturally resistant, or inherently resistant for those populations that survive the fungicide without previous exposure (Brent and Hollomon 2007). Furthermore, resistance or acquired resistance is the reduced sensitivity in response to the repeated use of the fungicide. This latter case is equivalent to evolved resistance. There are only a few exceptions in which plant pathologists use insensitivity, loss sensitivity, and tolerance as synonyms of resistance. All these are very similar definitions to the ones found in the weed science literature. For this reason, the limitations associated with the "before and after first fungicide exposure" criterion will likely create confusion for plant pathologist as done for weed scientists.

Plant Ecology

In the plant ecological literature, there are studies that use the terms "innate tolerance" or "constitutive tolerance" to refer to low sensitivity for which there is no known selection and "induced tolerance" to refer to a selection-driven process, which is similar to the use given to resistance in pesticide research (Hua et al. 2014, 2015). Again, this is the "before and after selection" concept.

Plant ecologists distinguish resistance from tolerance based on the presence of injury symptoms and impact on fitness (e.g., reproductive output or biomass production). This approach has frequently been applied to the effect of pathogen infection and disease development on plant growth. Thus, if two genotypes show similar levels of disease but one produces more biomass or seed

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than the other, the former is considered tolerant and the latter susceptible. Resistant genotypes will exhibit minor infection and limited injury symptoms (Simms and Triplett 1996).

These classifications have been proposed under the assumption that resistance and tolerance are controlled by different physiological and genetic mechanisms. This approach conflicts with the body of research explaining the biochemical mechanisms responsible for changes in herbicide sensitivity.

There were attempts to adapt the ecological nomenclature of resistance and tolerance to herbicides by studying common morningglory [*Ipomoea purpurea* (L.) Roth] responses to glyphosate (Baucom 2009; Baucom and Mauricio 2008). Those researchers tried to apply herbivory criteria for defining resistance and tolerance to glyphosate with the limitation that insects cause injury in ways that are not equivalent to herbicides. Thus, with those systems, resistance is usually conferred by genes and chemicals that prevent/limit insect feeding. In the case of tolerance, the insect causes damage (e.g., defoliation), but the plant is capable of minimizing the negative effects on growth and reproduction (i.e., fitness).

To apply such classification to herbicides, the correct analogy must consider the plant's spatial and morphological factors in order to differentiate between resistance and tolerance. Thus, resistant plants should have reduced uptake and translocation, so the herbicides do not move through the plant to reach their target sites and cause damage. Whereas tolerance would be when the herbicide reaches the target site, causing damage, and the plant maintains, at least partially, fitness. From physiological and biochemical perspectives, such classification is erroneous, because uptake and translocation reductions tend to result in highly variable symptomatology and survival. Conversely, reductions in target-site (TS) affinity cause a more defined and dramatic change in survival and symptom reduction, so it is not surprising that this mechanism was designated as resistance.

One could argue that only the tolerance aspect of the ecological terms can be applied to herbicides, and this trait should be assessed in plants in which the herbicide reaches the TS and initiates the chain of biochemical reactions that result in tissue death. The problem with this approach is that this phenomenon is almost impossible to prove. If injury is high and growth and reproduction are ultimately not affected, the question is whether there is actual tolerance or the dose was sublethal. Also, if sublethal doses are tested, resistance cannot be easily proven. For these reasons, it is biologically and experimentally incorrect to use the ecological insect-pathogen classification system. It seems that the ecological term of "tolerance" is what in the pesticide literature has been denominated NTS resistance.

Mechanisms

In weed science, our current use of "resistance" and "tolerance" is based on a historical series of events and not on the mechanisms that explain them. Once weed populations exhibited reduced sensitivity and increased survival, this shift in herbicide response became evident because there was a known adequate control at herbicide introduction and reduced mortality after repeated herbicide use. The ability to witness and document such shifts in a population gave researchers confidence to describe this as resistance evolution. This was indeed a direct application of the terminology used for antibiotic, insecticide, and fungicide resistance in the second half of the twentieth century.

The mechanisms of the first cases of herbicide resistance were later described as TS, which explained the clear and rapid change in herbicide sensitivity. Little attention was paid to NTS mechanisms, perhaps because of their complexity and difficulty in detecting and studying them. Although not explicitly stated, in many studies, tolerance has been associated with NTS mechanisms. It is important to highlight that NTS is the main mechanism for crop and weed survival in populations that have not been under selection (Beffa et al. 2019).

Adopting a Definition

Today, widespread single and multiple resistance and high levels of resistance gene flow among populations challenge the use of a clear "before and after" criterion. Furthermore, we now better understand NTS mechanisms and their presence in most species in varying degrees, which makes it difficult to draw a distinct line between resistance and tolerance using physiological criteria.

The survival of a population is partially dependent on the sensitivity variation among individuals and the frequency of individuals with similar sensitivity. In the case of TS mechanisms, the mortality rate of the population is given mainly by the frequency of the individuals carrying the mutation that confers survival. In contrast, population mortality due to NTS mechanisms is determined by the range of sensitivity levels in addition to their frequency in the population (i.e., weighted average).

The definition of resistance or tolerance must be based on the genetic, biochemical, and physiological factors that determine the sensitivity to herbicides. This approach has two important experimental advantages. First, it can be studied biochemically at the individual level. Second, it can be described at the population level by quantifying the frequency of resistant individuals. Third, there is no need for "before and after" data, because modern genome-sequencing tools can help determine the genetic context favoring the presence and selection of the trait (e.g., in situ mutations, gene flow, directional selection, genetic bottlenecks).

Because of the intrinsic quantitative nature of how we study herbicide sensitivity, "resistance" is a term that from practical and scientific perspectives cannot be distinguished from tolerance unless one creates arbitrary divisions or evidence is generated proving the existence of distinct biochemical mechanisms. In other words, resistance versus tolerance is a distinction without a difference. Maintaining both terms in the weed science jargon will only prolong the confusion. Historically and across disciplines, resistance is the most consistent term used to indicate the existence of reduced sensitivity to a pesticide or xenobiotic. Also, it has been clearly associated with the loss of control in commercial production. Unlike tolerance, resistance unambiguously refers to the condition of individuals or populations that confers reduced sensitivity to a herbicide compared with a reference group. This definition should be used regardless of whether the predominance of the trait in the population was due to selection.

I hope that this commentary encourages colleagues to review and update the nomenclature considering the information accumulated during the last 30 years and the potential that new technologies offer for better understanding weed adaptations. Along these lines, this is my proposal: we can eliminate tolerance and maintain resistance, defining the latter as "the heritable reduced herbicide sensitivity resulting in higher plant survival when compared with a reference population or an initial sensitivity baseline." This definition has the advantage that it can be used for

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natural, experimental, and commercial production situations and only depends on measurable quantitative parameters.

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