Review

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Insecticide-induced hormesis and arthropod pest management

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Abstract

Ecological backlashes such as insecticide resistance, resurgence and secondary pest outbreaks are frequent problems associated with insecticide use against arthropod pest species. The last two have been particularly important in sparking interest in the phenomenon of insecticide-induced hormesis within entomology and acarology. Hormesis describes a biphasic dose–response relationship that is characterized by a reversal of response between low and high doses of a stressor (e.g. insecticides). Although the concept of insecticide-induced hormesis often does not receive sufficient attention, or has been subject to semantic confusion, it has been reported in many arthropod pest species and natural enemies, and has been linked to pest outbreaks and potential problems with insecticide resistance. The study of hormesis remains largely neglected in entomology and acarology. Here, we examined the concept of insecticide-induced hormesis in arthropods, its functional basis and potential fitness consequences, and its importance in arthropod pest management and other areas.

Keywords: biphasic concentration–response; hormoligosis; insecticidal stress; insecticide ecotoxicology; pesticide-mediated homeostatic regulation; sublethal effects

1 HORMESIS: ANCIENT ADAGES, OLD LAWS AND CURRENT THEORY

Friedrich Nietzsche in his *Twilight of the Idols* (1888) expressed the maxim that what does not destroy you, makes you stronger. Although not everything that does not kill will make you stronger, Nietzsche's idea is well known in human society and emulates the concept of hormesis, which describes a dose–response phenomenon characterized by a reversal of the response between low and high doses of a stressor, such as an insecticide.

The concept of hormesis may have been developed from the dose–response relationship illustrated by the ancient Greek and Latin adages 'nothing too much' and 'the virtue is in the middle', respectively.[1,2] In the 16th century, the monophasic dose–response concept was applied to the discipline of toxicology by Paracelsus, who recognized that the dose makes the poison,[3] meaning that toxic substances are nonpoisonous at low enough doses, and what are generally innocuous substances can be toxic at high enough doses. The sigmoid or linear (on a log-logit or a log-probit scale), or also monophasic dose–response relationship was initially challenged in the late 19th century by Hugo Schulz, who demonstrated stimulation by substances at low (sublethal) concentrations that are toxic at high concentrations.[4] This (nonlinear) biphasic relationship described by Schulz was referred as the Arndt–Schulz law. This law was co-opted by the homeopathic community as its scientific principle, which, in part, led to its marginalization. It was later re-established by Ferdinand Hueppe and has become known as Hueppe's rule.[2,5–7]

The term 'hormesis' has its beginning in the early 1940s when Chester M Southam and John Ehrlich observed a biphasic dose–response to red cedar extracts in different fungal strains, and they referred to the phenomenon as 'hormesis', from the Greek 'to excite'.[8] More recently, Edward J Calabrese and his group recognized the general nature of the phenomenon in a succession of meta-analyses.[9–13] They suggested that the hormetic dose–response model is more common in toxicology than the threshold model (Fig. 1), which is widely viewed as the most dominant model in toxicology.[9–13] The common definition of hormesis as the stimulatory effect associated with low (sublethal) doses of compounds that are toxic at higher doses has been refined to avoid referring to the response as 'beneficial', which may not always be the case. Hormesis, therefore, can be defined as a dose–response relationship characterized by a reversal in response between low and high doses of a stressor (e.g. an insecticide), thus characterizing a biphasic relationship.[2,14] Doses that cause hormetic responses are limited in range and typically below the No Observable Effects Concentration (Fig. 1), although this is not always the case for arthropods in their response to pesticides.[15]

2 CONCEPTUAL CONUNDRUM IN ENTOMOLOGY AND ACAROLOGY

The concept of hormesis is now widely recognized and accepted as a general stress response phenomenon.[2,13–16] Semantically, however, insecticide-induced hormesis remains subject to

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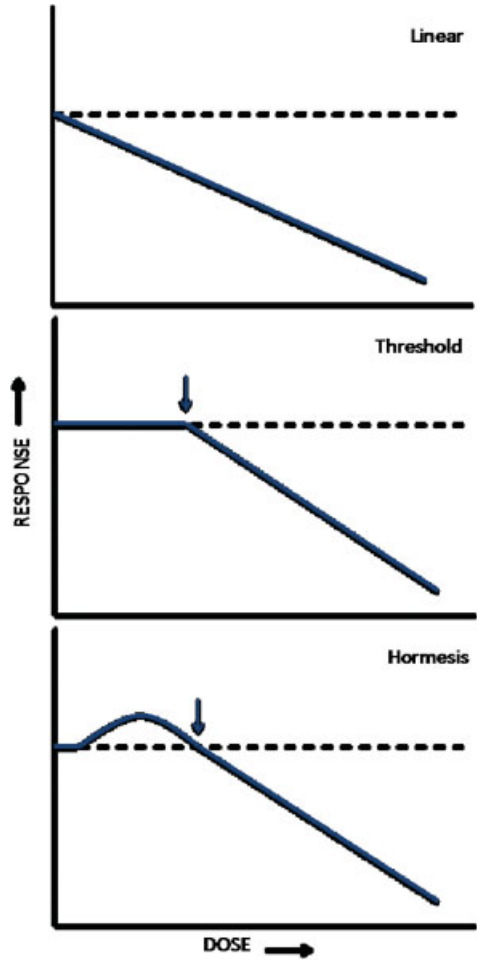

Figure 1. Depiction of the linear, threshold and hormesis dose–response models (solid line) generally used in toxicology (a log-logit or log-probit scale was assumed allowing for a linear relationship). Arrows indicate the No Observable Effects Concentration. The black dashed line indicates the (control) expected response without insecticide exposure.

confusion in entomology and acarology. In these fields, two additional terms, 'insecticide hormoligosis' and 'pesticide-mediated homeostatic modulation', have been used synonymously, analogously or complementary to the concept of hormesis. The historical precedence of the term 'hormesis' and the generality of this concept make this semantic confusion unnecessary and difficult to justify. In addition, there are misunderstandings (or misconceptions) about the original definitions of hormoligosis and pesticide-mediated homeostatic modulation.

2.1 Insecticide hormoligosis

The term 'hormoligosis', or more precisely 'insecticide hormoligosis', was coined by Thomas D Luckey in his influential 1968 paper. Luckey developed the term from the Greek hormo (= to excite) and oligo (= small quantities) and defined it as a phenomenon in which '. . . subharmful quantities of many stress agents may be helpful when presented to organisms in suboptimal environments . . . '.[17] This original definition emphasizes situations in which stimulation under sublethal exposure of a given compound will occur when the organism is already under stress (i.e. due to suboptimal conditions or a second stress agent). This concept is distinct from that of hormesis, although the later encompasses the former; therefore, insecticide hormoligosis is basically a special case of hormesis in which a biphasic dose–response for an insecticidal compound is observed when the organism is already under stress due to another environmental factor or agent.

The distinction between hormesis and hormoligosis has been previously recognized.[15,18,19] Nonetheless, most entomological and acarological studies neglect the distinction between the terms, particularly regarding the suboptimal environment in which insecticide hormoligosis is referred to take place. Indeed, hormesis and hormoligosis have been equivocally redefined and are treated synonymously in the insecticide and acaricide literature,[20,21] likely contributing to the semantic confusion. However, a shift favoring the proper recognition of the hormesis phenomenon within insecticide toxicology seems to be taking place,[18,19,22] which should reduce the misuse of the term 'hormoligosis' (Fig. 2). The term insecticide hormoligosis, if used, should be restricted to cases of insecticide-induced hormesis where the biphasic dose–response takes place when the organism in already under stress due to another environmental factor.

2.2 Pesticide-mediated homeostatic modulation

The concepts of hormesis and insecticide hormoligosis as they related to arthropods and insecticides in certain situations were recently questioned by Cohen,[18] and have received some support (e.g. Yu *et al*).[23] Cohen readily recognizes the conceptual distinction between hormesis and hormoligosis, and the general misuse of the latter when referring to the former in insecticide studies with insects and mites. The concept of hormesis was, however, challenged by Cohen in favor of 'pesticide-mediated homeostatic modulation' in arthropods in two circumstances: (1) hormesis is not applicable to situations in which stimulatory effects are observed in a nontarget pest species not controlled by the pesticide under consideration; and (2) one can only quantitatively measure lethal doses of a given pesticide in target pests.[18] However, the hormesis concept is not species- or target-driven and the homeostatic modulation notion is management-based (i.e. determined by the field use of registered recommendations) rather than the toxicological dose–response.[15] Furthermore, the suggestion that the quantification of dose–response relationships and determination of lethal doses as toxicological endpoints are only possible in target species is incorrect.

3 FUNCTIONAL BASIS AND POTENTIAL FITNESS CONSEQUENCES

The mechanisms underlying insecticide-induced hormesis in arthropods remain largely unknown, despite a few recent advances.[14,23,24] Recognition of the mechanisms underlying hormesis is crucial to understand the process and its relevance and consequences.[14,25,26] In a general sense, different hormetic agents, chemicals, radiation, temperature, etc. likely change gene expression in components of physiological response pathways, including hormones, heat shock proteins and antioxidant enzymes,[23,27–29] ultimately affecting fitness-related traits.[14,16,30,31] Two main overall alternative hypotheses currently prevail in providing a mechanistic explanation for hormesis: the growth hormesis theory of Stebbing (also referred to as growth control, the Maia hypothesis and 'overcompensation' theory),[30,32–34] and the principle of physiological resource allocation as applied to hormesis.[14,31,35,36]

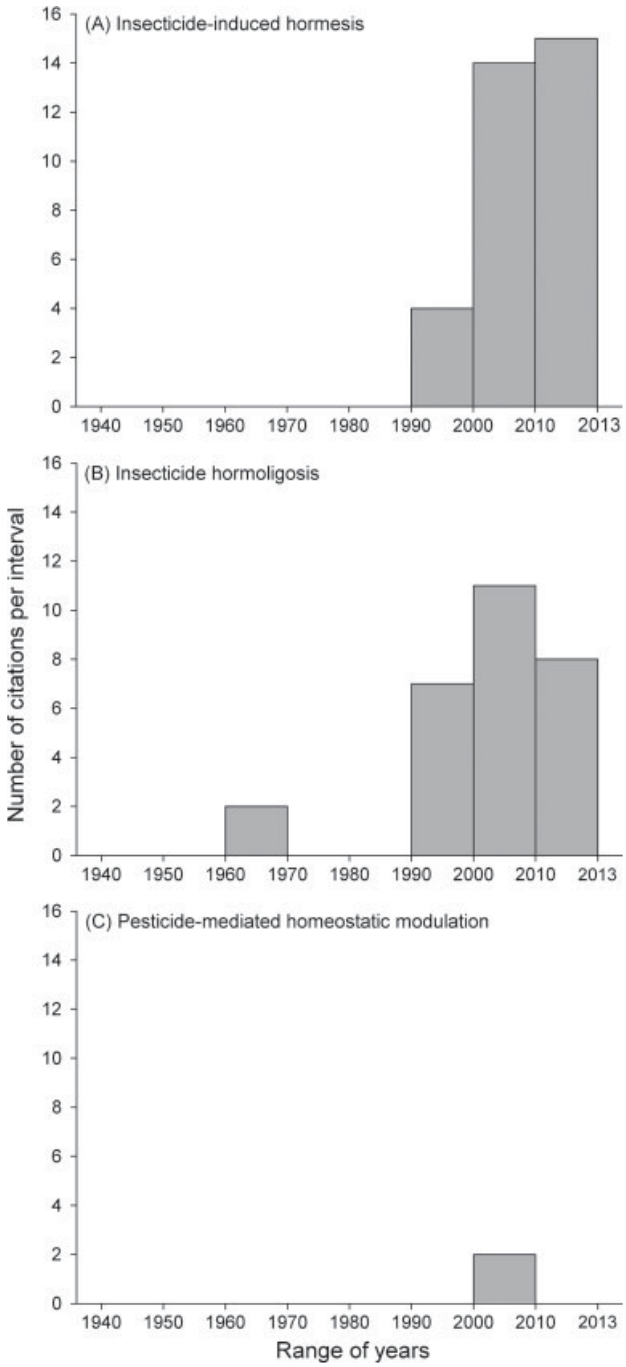

Figure 2. Citations of insecticide-induced hormesis (A), insecticide hormoligosis (B) and pesticide-mediated homeostatic regulation (C) registered over 10-year periods since the 1940s, when the concept of hormesis was initially proposed. Data were obtained from the Web of Science database (accessed 20 August 2013).

3.1 Growth hormesis theory

According to the growth theory, hormesis is a byproduct of homeostasis overcompensation.[33,34] This idea has proven popular and is based on control systems and growth analysis.[30,33] The assumption is that self-regulated processes (e.g. growth) and thus organism self-regulation require control systems with feedback responses.[33,37] The control mechanisms that regulate growth counteract the perturbing or inhibitory effects of toxic agents. Hormesis is the alleged result of both transient and sustained overcorrection (or overcompensation) by the control system to low levels of inhibition by the toxic compound.[30,32–34,38] Although interesting, this hypothesis remains highly speculative and is mainly focused on growth as a life-history trait lacking a general mechanistic underpinning.[14,25,26]

3.2 Principle of resource allocation

The principle of resource allocation is the general basis of physiological energetic models that predict trade-offs in resource allocation among different physiological processes.[31,35] Based on this principle and energy conservation laws, Jager *et al*[14] suggest three broad categories of energy/mass management underlying hormesis: acquisition, medication and allocation. This view holds two fundamental assumptions: the functional link between physiology and fitness, and the existence of physiological costs associated with a toxic challenge. There is ample evidence to support these assumptions and this theory.[35,39–45]

Hormesis by acquisition reflects the increased performance of a stress-exposed individual and is explained by an unlimited increase in energy uptake from the environment, when such a resource is not limited.[14] This increased energy uptake favors growth rate, and possibly maximizes size, which increase reproduction and population growth rate. This is exemplified by findings with insecticide-exposed spined soldier bugs and aphids.[19,45] By contrast, hormesis by medication may occur when the toxicant is, or contains, an essential element in which the individual is deficient. This second view is more limited in scope.[14]

Hormesis by resource allocation is a more traditional and widely accepted notion in which the stress-exposed individual shifts the balance between potentially energy-conflicting physiological trade-offs, favoring one (e.g. reproduction) at the expense of another (e.g. longevity).[14,31] Cadmium-exposed springtails and azadirachtin-exposed bean beetles (bruchids) both exhibited trade-off shifts, the first favoring longevity at the expense of growth and reproduction, and the latter favoring reproduction at the expense of longevity.[46,47] In both situations, improved performance of one trait impairs the performance of the other. This may have either positive or negative fitness consequences for the individual depending on the traits involved and may exhibit trans-generational effects.[14] In other cases, there may be no evidence of trade-offs within a generation of insects exposed to low doses of insecticide, but trade-offs across generations may occur, without any evidence of overall biological fitness being compromised.[45] Similarly, evolution of insecticide resistance during exposure to low doses of insect growth regulators may induce evolutionary changes in metabolism or signaling that may mediate evolution of a longer life span without trade-offs with fecundity.[48]

The fitness consequences of hormesis likely depend on the underlying mechanism involved. The initial suspicion that hormesis in individual traits may not translate into improved fitness has been challenged of late by reports of enhanced population fitness due to insecticide-induced hormesis in insects and mites.[31,45,47,49,50] These recent findings suggest that insecticide-induced hormesis in arthropods may indeed be adaptive, as suspected and reported with other stress agents for other taxa,[14,51–54] with potential consequences for arthropod pest management.

4 HORMESIS IN ARTHROPODS

Hormesis has been a subject of growing attention in the scientific literature with over 1700 published papers

according to the Thomson Reuters database Web of Science (http://thomsonreuters.com/web-of-science/). However, only 82 (4.82%) of those papers explore insecticide-induced hormesis (including hormoligosis) and only 50 (2.94%) are devoted to insects and mites. Comprehensive lists of these studies were reported by Cohen,[18] and more recently by Cutler.[15] Here, we focus on trends and deficiencies in how the subject has been explored thus far in insect and mite studies. The past focus on lethality as the toxicological endpoint in insecticide studies with arthropods has likely been one of the barriers to recognizing both the occurrence and importance of hormesis in insects and mites, which is a sublethal phenomenon. In the past decade, the significance of the sublethal effects of insecticides on arthropods has become more accepted.[55] This is important because exposure to low insecticide doses often occurs in the field due to insecticide degradation and the lower exposure of nontargeted arthropods (i.e. beneficials and nontargeted pests) that are usually less exposed or more tolerant to the compound than the target species.

4.1 Hormesis in arthropod pest species

Insecticide-induced hormesis in arthropod pest species has received only modest attention compared with hormesis studies in other disciplines (e.g. biomedical sciences). This is surprising because the phenomenon and its importance have been recognized since the 1950s.[16,56] The fruit fly *Drosophila melanogaster*, house fly *Musca domestica*, granary weevil *Sitophilus granarius* and house cricket *Acheta domesticus* were early subjects of study, particularly with exposure to sublethal doses of organochlorine insecticides.[17,57–62] Insecticide-induced population stimulation in mites has been observed since the 1970s and has sparked concerns of insecticide-induced pest outbreaks among at least two mite species: the citrus red mite, *Panonychus citri*, and the two-spotted spider mite, *Tetranychus urticae*.[18,63,64] More recently, pyrethroid-induced outbreaks of the southern red mite, *Oligonychus ilicis*, were examined.[50] Thus, there is awareness of the hormesis phenomenon in insects and mites, but interest remains relatively modest, despite the increase in attention in the last decade.[15]

Insecticide-induced hormesis in arthropod pests has been studied for different biological traits, but its impact on reproductive traits and potential fitness consequences are most commonly reported.[15,18] This provides support for the perception that insecticide-induced hormesis in arthropod pest species is adaptive, with potential consequences for pest management.[14,15,18,50,56] More long-term laboratory and field studies are necessary to confirm this perception.

4.2 Hormesis in natural enemies

Interest in insecticide-induced hormesis in nontarget arthropods, particularly predators, started in the 1950s and 1960s with the lacewing *Chrysopa californica*, the ladybird beetle *Coleomegilla maculata* and the braconid parasitoid wasp *Bracon hebetor*.[65–67] The big-eyed bug *Geocoris* spp. and the spined soldier bugs *Podisus distinctus and Supputius cinceticeps* were subsequently studied.[19,68–71] Hormesis studies on natural enemies are more common with insect predators than parasitoids. We are aware of no study to date dealing with hormesis in entomopathogens.

There are few reports of insecticide-induced hormesis in natural enemies compared with arthropod pests, which may be due to the lack of preliminary evidence of occurrence. Although insecticide-induced pest population outbreaks have been reported for decades, no such observations with natural enemies appear in the literature. It is also likely that the long-standing emphasis and experimental bias toward the deleterious effects of insecticides on natural enemies have meant that researchers have remained naïve about potential stimulatory effects of chemicals on these taxa. Although natural enemies may be subject to hormesis, Morse[20] suggests that there is less potential for hormesis in natural enemies in the field because they are generally more susceptible to insecticides compared with pest species,[72] and because of the density-dependence of natural enemies on their prey or host species. Both may have an effect, but the overall lower susceptibility of natural enemies to current insecticides is disputable for more modern insecticides,[73–76] and neither factor seems to play a direct role in the expression of hormesis in natural enemies.

4.3 Plant-mediated hormesis?

The possibility that insecticide applications may induce hormesis in arthropods indirectly via changes in plant physiology, is an intriguing concept. For example, imidacloprid-treated boxwoods (*Buxus sempervirens* L.) led to higher egg-laying activity by the boxwood mite *Eurytetranychus buxi*.[74,75] Although no direct evidence of hormesis was provided in these studies (i.e. no concentration–response relationship was established nor were changes in plant physiology assessed), their findings, and the reported herbicide-induced performance improvement of plant species of economic value,[22,77,78] suggest potential indirect impacts of insecticide hormesis in arthropods and their management, possibility that have been largely neglected.

5 PEST MANAGEMENT, INSECTICIDE-INDUCED HORMESIS AND ECOLOGICAL BACKLASHES

More than 50 years after the publication of Rachel Carson's *Silent Spring*, insecticides remain a major component of insect pest management and are still surrounded by controversy.[79,80] However, changes in attitudes and policy over the use of pesticides against pest species have led to the development and use of insecticides with improved safety profiles towards human health and the environment.[81,82]

Insecticide applications leading to outbreaks of pest species were recognized as early as the early 1950s, following the onset of the large-scale use of organochlorine insecticides for arthropod pest control.[56,83] Since then, these outbreaks have been relatively frequent, particularly for broad-spectrum insecticides.[56,84,85] This form of ecological backlash was frequently dealt with by increasing insecticide use, which often leads to the 'pesticide treadmill' or 'pesticide syndrome'.[84,86–88] Frequent or improper insecticide use is often associated with two ecological backlashes that can lead to pest control failures: insecticide resistance and pest resurgence or outbreaks, both of which have some common causes and are ecological consequences of insecticide applications.[56,84,85,89,90] Insecticide-induced hormesis is potentially important in both cases.

5.1 Insecticide-induced hormesis in insecticide-resistant populations

Since the 1950s, the evolution of insecticide resistance in arthropod pests has been a major concern in agricultural and medical arthropod pest management.[91–93] Insecticide-induced hormesis is potentially a complicating factor for arthropod pesticide

resistance management because of the prevailing exposure of resistant insects to sublethal doses of insecticides in the field. The subject has been largely neglected and there are few studies that have explored this scenario.

Evidence of a hormesis-like stimulatory egg-laying response to the pyrethroid fenvalerate and the carbamate methomyl was detected in a Japanese strain of the diamondback moth, *Plutella xylostella*, selected for resistance to each respective insecticide.[94] However, the stimulatory effect was observed at a relatively high dose range exhibiting significant mortality (LD_{25}), and may have been an artifact of selection, which allowed the fitter individuals to survive and reproduce. Insecticide-induced hormesis was also reported in a strain of maize weevil, *Sitophilus zeamais*, resistant to the pyrethroid insecticide deltamethrin.[49] Maize weevil fitness was significantly affected with increased population growth of the insecticide-resistant strain following sublethal insecticide exposure.[49] This finding suggests a potential problem for managing insecticide-resistant populations because field doses of the insecticide may not control these insects and may actually boost their population growth (Fig. 3). There is preliminary evidence of higher insecticide-induced hormetic effect on the most resistant populations.[95]

Mechanistically, there are reasons to suspect that adaptive hormetic responses to low doses of insecticide might augment the development of resistance or increased tolerance to these compounds. Exposure of insects to sublethal doses of pesticides or plant allelochemicals can induce production of enzymes that are important in detoxification processes,[96,97] and induction of esterases (hydrolases), which are important in pesticide metabolism, as observed during insecticide-induced hormesis in insects.[98] If the propensity to express such detoxification enzymes during the hormetic response was a heritable epigenetic process without fitness costs,[16,45,99] one could reasonably predict that the coupling of the hormetic response with detoxification gene induction could assist in insecticide resistance development. This hypothesis should be explored further.

5.2 Insecticide-induced hormesis and arthropod pest outbreaks

Pest resurgence and secondary pest outbreaks, although important and frequently reported, have received far less attention than insecticide resistance. Resurgence is an increase in abundance of the arthropod pest species targeted by the insecticide application to levels higher than those of the uncontrolled populations.[56,85] By contrast, secondary pest outbreaks – also called pest replacement or type II resurgence – are an increase in the abundance of a nontargeted arthropod pest species after insecticide application.[84,85] Both phenomena have common causes, including reduction in the number of natural enemies, increase of the pest population, and removal of competitors.[56]

The reduction of natural enemies is commonly thought to be the cause of the phenomenon, although it has seldom been tested, particularly at the population level.[50,85] Insecticide-induced hormesis is a possible cause of outbreaks in some pest species. Evidence of insecticide applications directly stimulating arthropod populations outbreaks has been reported in mites,[64] planthoppers,[100] aphids[101] and thrips.[102] The southern red mite, *Olygonychus ilicis*, often exhibits outbreaks in coffee plantations after pyrethroid applications against the coffee leafminer, *Leucopetera coffeella*. Mite predators of the red mite are not compromised by the pyrethroid deltamethrin, which is more toxic to the red mite.[50] In addition, deltamethrin did not lead to behavioral avoidance by the predatory mites but did induce hormesis in the red mite (Fig. 4).[50]

6 BEYOND INSECTICIDE-INDUCED HORMESIS

Hormesis is a general phenomenon and insecticide-induced hormesis may occur in arthropod pest species and their natural enemies. Pesticide-induced hormesis in crop plants may lead to yield increase, but it may also mediate arthropod pest outbreaks.[74,75,103,104] In addition, insecticide-induced hormesis may lead to arthropod pest outbreaks, and may impair the management of insecticide-resistant populations or augment resistance development in insects, illustrating the importance of this phenomenon to pest management.

The hormesis phenomenon is not, however, restricted to insecticides (or pesticides) as stress agents.[9–13,15] Other environmental stress factors such as temperature, diet and UV

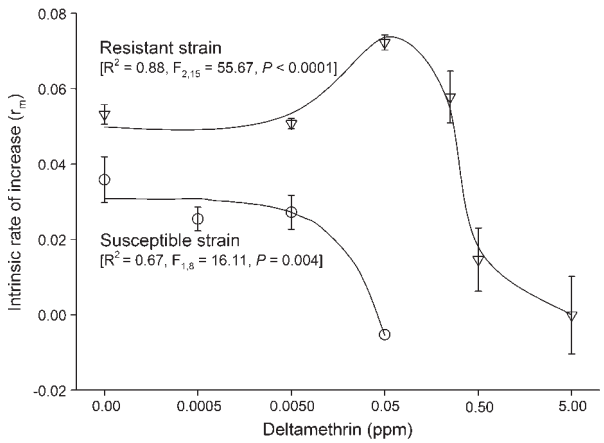

Figure 3. Intrinsic rate of population growth ($r_m \pm$ SEM) of a susceptible and a pyrethroid-resistant strain of the maize weevil (*Sitophilus zeamais*) exposed to sublethal doses of the pyrethroid insecticide deltamethrin ($n = 3$) (modified from Guedes *et al*,[49] with added data from the susceptible strain).

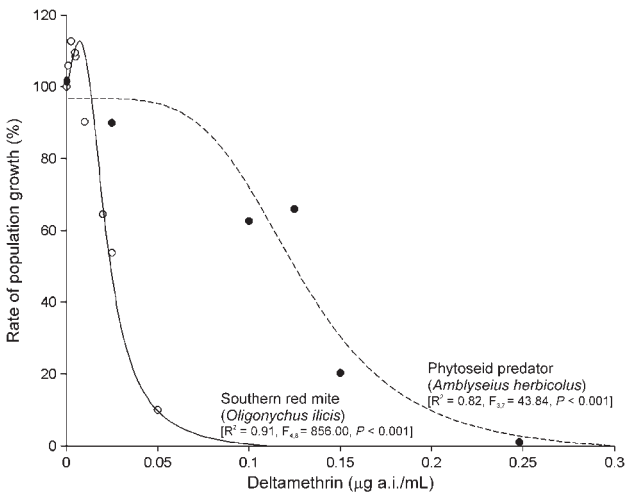

Figure 4. Observed concentration–response values and curve (Brain–Cousen model) based on the intrinsic rate of population growth (r_m) of the southern red mite (*Oligonychus ilicis*; ○) and its phytoseid predator (*Amblyseius herbicolus*; ●) exposed to the pyrethroid insecticide deltamethrin (modified from Cordeiro *et al*[50]).

radiation, may also induce hormesis, which may have fitness implications relevant to evolutionary processes and with practical consequences.[28,105–109] Combinations of these stressors may have important consequences for the concurrent expression of traits directly related to biological fitness, such as growth and resistance to pesticides, and hormesis may manifest in different ways depending on the combinations of stressors.[103–109]

Low (sublethal) levels of pesticide, heat or nutritional stress may also have potential uses in enhancing the productivity and/or efficacy of natural enemies, such as predators, parasitoids or insect pathogens. Utilization of the hormetic response might result in economic and performance benefits in culturing beneficial insects, mirroring the observed increases in productivity of plants exposed to low levels of stress.[22] Thus, insecticide-induced hormesis is not only a potentially important phenomenon for the occurrence of arthropod pest resurgence and insecticide resistance development, but also for the development and improvement of techniques to reduce impacts of these pests.

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