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Sublethal exposure, insecticide resistance, and community stress

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Sublethal exposure, insecticide resistance, and community stress

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Insecticides are an invaluable pest management tool and anthropogenic stressors of widespread environmental occurrence that are subject to biased perceptions based on the targeted application, market value of use, and regulatory requirements. As a result, short-term and simplistic efforts focusing on lethal effects toward individual species and populations prevail. Holistic and comprehensive studies exploring rather common sublethal insecticide exposures are rare, particularly considering their potential role in structuring populations and communities in diverse environmental settings and potentially interfering in a range of ecological interactions. Studies on insecticide resistance, for example, do not go beyond population-based studies, disregarding temporal and spatial effects in the associated community, and rarely considering the whole of sublethal exposure. Some of these knowledge gaps are here recognized and explored.

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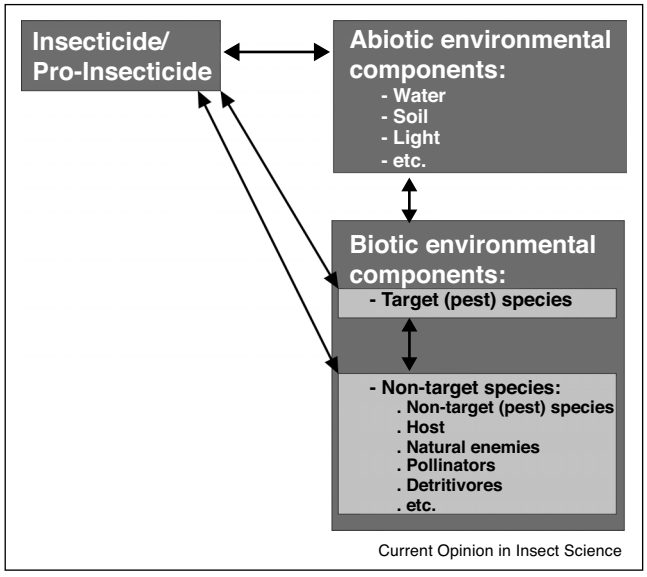
Insecticides, sublethal exposure, and stress response

Popular concepts and their perception have far-reaching consequences. Such seems to be the case with insecticides, which are popularly defined as a substance or chemical that kills insects. Curiously, this prevailing notion is at odds with the technical definition of an insecticide used by regulatory agencies as "any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any insect pest" (*e.g.*, US Federal Insecticide, Fungicide, and Rodenticide Act). The latter tends to be overshadowed by the former even within professional circles [1,2]. The subliminal message and appeal of the popular notion of insecticides is an overemphasis on the *killing* of insects leading to a relative neglect in recognizing the importance of sublethal effects of these compounds [3–5,6••]. This shortcoming exists not only for conventional (synthetic) insecticides, but also for bioinsecticides, reduced-risk insecticides, and insecticidal proteins.

Although frequently intended to cause the quick mortality of a targeted pest species, insecticide residue degrades over time reducing the initial (lethal) deposit to a (sublethal) residue, and/or may generate new structurally-derived residues exhibiting biological activity. Furthermore, the initial application is aimed at a particular target or limited number of target species, but non-target species will be subjected to sublethal doses and/or exposure at the onset of the application (Figure 1). This (sublethal) insecticide exposure can lead to adverse consequences to the exposed organisms, but not necessarily so. Responses to such a stress are bound to vary in a dose/concentration-dependent manner between lower and upper thresholds (*i.e.*, the basic dose/concentration–response relationship of toxicology), outside of which the organism is unaffected by the exposure, or too much affected reaching around 100% response. However, within the said thresholds and apart from the expected detrimental effects, an inverted response trend may occur, potentially benefiting either the exposed organism or its progeny, depending on the physiological trade-off involved [8,9].

A hierarchical view of insecticide stress response is helpful in recognizing the potential consequences of insecticide exposure, and particularly of sublethal exposure [6••]. Upon reaching and penetrating an organism, the insecticide will likely affect its physiology or that of associated symbiont(s) [6••,9]. Interacting conspecifics are also likely to be affected, eliciting a population-level response (*e.g.*, insecticide resistance and control failure), that can eventually be translated into a community-level consequence via direct or indirect effects of insecticide exposure [6••] (Figure 2). The recently conceived conceptual construct of *the adverse outcome pathway* reflects the concern of linking a direct molecular initiating event

Figure 1



The nature of insecticide stress arising from the potential interactions between an insecticide and environmental components, as well as the potential interactions among environmental components under the direct influence of the insecticide.

to an adverse outcome at a higher biological level of organization relevant to risk assessment [10,11]. This promising construct, which recognizes the progress of toxicity events across hierarchical scales of biological organization, does have its limitations including its overly (unrealistic) simplicity and reductionism (*e.g.*, ignoring parallel cascades and intercrossing pathways) [10,11]. An additional shortcoming of this conceptual construct is that it neglects to recognize that a stress response does not necessarily lead to an adverse outcome, but may also hierarchically elicit non-toxic (and non-adverse) responses [7,8,10–12]. The stress response will vary with the individual and its susceptibility, the insecticide and its dose/concentration, and the environmental context in which exposure takes place. Insecticide resistance provides an illustrative context worthy of exploring.

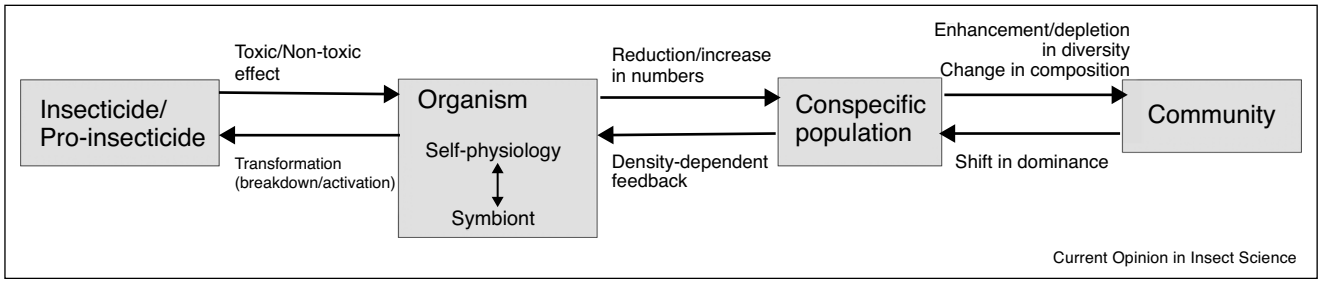
Insecticide resistance under sublethal exposure

Insecticide resistance is essentially a genetic change in response to selection by a toxicant, the insecticide, among individuals of a given species, the potential consequence of which is impaired chemical control in the field [13]. Although selection for insecticide resistance is frequently associated with differential mortality among individuals, the phenomenon refers to differential survival and reproduction. Therefore, insecticide resistance can be achieved not only by the use of lethal insecticide concentrations eliminating susceptible individuals, but also by sublethal exposure favoring survival and reproduction of the resistant individuals.

The role and potential consequences of sublethal insecticide exposure for insecticide resistance are frequently neglected, but their relevance may be recognized on three fronts. First, sublethal exposure may delay selection for major single gene resistance while favoring multifactorial or polygenic resistance [14]. This is the likely consequence of the accumulation of low-level resistance genes and mechanisms (*e.g.*, reduced penetration, behavioral avoidance, *etc.*) allowing small increases in the magnitude of insecticide resistance distinct from the selection of a major mutation (*e.g.*, altered target site sensitivity) leading to a high resistance [14,15]. Furthermore, sublethal stress may also contribute to resistance by promoting increased mutation rates of genes involved in DNA repair, as observed in bacteria and weeds [14,16•,17]. Insecticides involved in oxidative stress, such as the fumigant phosphine, seem like good candidates for investigation as they may directly or indirectly compete for energy from NAD(P)H and nucleotide triphosphates necessary for performance of DNA repair enzymes [14,18,19].

Sublethal insecticide exposure may influence insecticide resistance beyond selection of resistant individuals via two additional phenomena: insecticide-induced hormesis, and induction/cross-induction of detoxification enzymes. Neither is usually considered in studies of

Figure 2



The chain of potential hierarchical interactions and responses sparked by an insecticide.

insecticide resistance, but both have management and environmental implications. Insecticide-induced hormesis is a biphasic dose–response relationship characterized by a reversal in response between low and high doses of a stressor, such as an insecticide [6••,8,9]. The direct relevance of hormesis to insecticide resistance is its occurrence in insecticide-resistant populations, as demonstrated by pyrethroid-resistant weevils [20]. This may take place upon failure of the insecticide to suppress the insecticide-resistant population, with the sublethal exposure falling in the range of hormesis for that population. The end result is the field application rate not only leading to control failure, but actually boosting the growth of the resistant population.

The possibility of induction and cross-induction of detoxification enzymes is also of interest. These are broadly recognized as important insecticide resistance mechanisms upregulated (and overexpressed) in several resistant populations and prevailing against certain insecticides like neonicotinoids [21]. However, these detoxification enzymes are inducible, and the induction may still take place in insecticide-resistant populations sublethally exposed to insecticide, priming the insects against further exposure to the same or even other compounds, a phenomenon also referred to as hormetic priming or conditioning [22,23•,24]. Imidacloprid priming was recently recognized in the green peach aphid with the involvement of esterases (E4) and cytochrome P450 (CYP6CY3) [23•]. The priming may take place between distinct stressors following a cross-induction pattern and may occur in non-resistant populations as well, allowing enhanced insecticide tolerance [23•,24,25]. This risk is already an expressed concern for mosquito control where prior exposure to urban pollutants and agriculture pesticides can shape the response to insecticide exposure and eventual selection for resistance [26–28]. As in hormetic priming, forewarned is forearmed. The implications of the phenomenon deserve attention as it may contribute to and even shape inadvertent selection for insecticide resistance in non-targeted pest species, as observed in indoxacarb-resistant maize weevils and Bt-resistant fall armyworm [29,30], apart from potentially leading to cross-tolerance in insecticide-resistant populations.

Dual species interactions

Insecticide resistance is a broadly recognized ecological backlash resulting from intensive insecticide use and overuse/misuse. Therefore its study is a priority, where the proactive role of the Insecticide Resistance Action Committee is but an industry response to the challenge [31]. Curiously though, the investigative effort on insecticide resistance focuses solely on the target species neglecting its interactive context and the chemical landscape in which it takes place. This reductionist approach is understandable from an experimental perspective, since it is simpler and cheaper. However, it is wholly unrealistic, because single isolated species and/or chemicals do not exist alone in nature, and sublethal exposure to chemicals prevails.

Among co-occurring species, heterospecific interactions may be affected by insecticides. Host–parasite interactions allow for good examples, as does interspecific competition between arthropod pest species. Although examples of insecticides affecting arthropod-natural enemy interactions are frequent, the potential insecticide effects on host plant-arthropod pest interactions and plant-pest-natural enemy tri-trophic interactions are also potentially important [6••]. For example, there is only preliminary evidence that insecticides may interfere with volatile emission by host plants either enhancing or compromising arthropod pest foraging [32–34], a growing concern with anthropogenic compounds in general [35,36•]. The potential pesticide induction of (and *de novo*) extrusion of linear furanocoumarins to the leaf surface of host plants is but an example deserving of attention [37]. Furthermore, insecticides can of course impair stimuli reception and/or processing by insects, compromising such interactions [6••,38], the specifics of which will vary with the level of insecticide resistance and underlying mechanism involved.

Shifts in species dominance may also be mediated by sublethal insecticide exposure due to differences in tolerance, and resistance, between insect species and populations. Insecticides, as agents of disturbance or stress, may alter ecological relationships leading to shifts in dominance of competing species, as reported among mosquitoes and grain beetles [39,40•]. Such direct evidence is rare, but gives credence to the intermediate disturbance hypothesis: intermediate levels of environmental disturbance are predicted to result in increased species diversity while compromising the previously dominant species [6••,40•]. The rationale is the same if insecticide-resistant populations of different species are involved.

Insecticide resistance and sublethal exposure may also contribute to secondary pest outbreaks, which is the increase in abundance of a non-targeted pest species after insecticide application against the targeted species. Pyrethroid-induced hormesis for instance seems to favor outbreaks of the southern red mite in coffee plantations upon pyrethroid use against the coffee leafminer [41]. In addition, insecticide application against a targeted species will also likely lead to sublethal insecticide exposure of an already resistant population of another co-existing pest species, promoting its outbreak. Current use of *Bacillus thuringiensis* toxins (Bt toxins; or Bt for short) in transgenic soybean in Brazil, for instance, might be favoring further increase in stink bug outbreaks in the country, a non-targeted group of pest species. Past use of Bt maize expressing Cry1A toxins against budworms likely allowed

inadvertent cross-selection to Cry1F in the fall armyworm. Both circunstances likely aggravated recent outbreaks of stink bugs and armyworm in the country since the introduction of this technology justifying the stated concern.

Community stress

Anthropogenic stress agents, particularly insecticides, are rather frequent components of urban and agricultural ecosystems, combining to form a complex chemical landscape where an assemblage of species populations coexist. If these populations do interact with one another, they integrate as a community that is subject to the landscape and its (biologically-active) chemical components. Thus, these biologically-active chemicals are potential contributors to shaping community structure. The underlying mechanisms involved in this process are a focus of debate in ecotoxicology, besides constituting an unplanned evolutionary experiment based on the adaptive mismatch between undisturbed and anthropogenically disturbed environments [42]. Research with bacterial communities and aquatic ecosystems has been intensive, giving credence to this notion [42–46], in sharp contrast with the attention paid to pesticides and arthropods in urban and agricultural ecosystems [6••].

Sublethal (insecticide) exposure and insecticide resistance are important components in shaping community stress through inadvertent selection, hormesis, hormetic priming, induced shift in dominance, impairment of species interactions, and eventual pest outbreaks, as already discussed. Most research on insecticide-induced community stress carried out with terrestrial arthropods has focused on natural enemies of arthropod pest species, frequently even neglecting their associated host complex [6••,47,48]. Besides non-targeted pest species, insecticides are also likely to affect direct and indirect competitors, their host organisms, detritivorous species, and pollinators, organisms potentially important to agricultural yield and disease transmission. The few available studies on terrestrial arthropod communities are relatively short-term, encompassing no more than two or three seasons, and thus less likely to detect community-wide effects since such effects usually take longer to express. Among these studies, the impact of Bt toxins in transgenic crops have received the bulk of recent attention.

Pre-market assessments of the risk associated with Bt crops are a current regulatory requirement in several countries, which encourages assessment of community stress. However, their community effects tend to be negligible, and the short-term assessment is a likely reason for that [45,49–52]. Nonetheless, post-marketing 5–10 year assessments of community effects are also required in some countries, and such data sets still must be duly explored. As with any modification in cultivation system, community changes are expected, but they may be negligible. Nonetheless, considering the intended negative impact on at least one key arthropod pest species targeted by the transgenic Bt plants, changes in this targeted species and associated food-web are expected and should be evident, particularly in long-term assessments. Curiously, we are aware of only a single study exploring food web analysis in community stress by Bt crops [53••]. This laudable effort was a short-term study focusing on broad trophic groups and taxa, compromising the potential resolution of the analyses for detecting species-associated food-web effects, while understandably favoring the search for broader patterns across Central Europe. Nevertheless, the approach is most welcome and merits further use.

Knowledge gaps & future perspectives

The prevailing negative perception of insects in human society [54,55] and use of insecticides as killing agents arguably contribute to the insecticide debate, as well as research biased towards oversimplified lethal assessments and short-term studies focusing on individual organisms and populations of arthropod pests, some of their natural enemies, and pollinators. The market value of insecticides as the dominant pest management tool in use for the last 70+ years, the associated agrochemical industry and user interests, together with regulatory demands, have largely reinforced and shaped insecticide research along the current lines.

The inherent conflict of interest existing in insecticide research, where the agrochemical companies are the main research sponsors, and a user-oriented focus favor short-term studies on efficacy and on immediate localized (and suspected) impacts directly influencing pest control or yield production. This scenario neglects the prevalence of sublethal exposure in nature, and the complex environmental context in which this exposure takes place among a myriad of co-occurring species and biologically active chemicals. Thus, the role of sublethal exposure in insecticide resistance remains largely unexplored. Furthermore, sublethal insecticide stress is bound to interfere with environmental context and ecological interactions, particularly when long-term exposure, or more precisely persistent short-term exposure, is considered.

An overhaul of the current methods and approaches used in insecticide research should be considered exploring a more holistic and comprehensive theoretical framework. The experimental methods necessary for this approach necessarily require expertise that goes beyond the current focus on proximate mechanisms at the biochemical and physiological levels, which are a common emphasis in current Insecticide Toxicology courses within Entomology (Post-)Graduate Programs. The ultimate consequences of pesticide exposure, particularly sublethal exposure, are paramount but require knowledge of

life-history trade-offs, behavioral ecology, and population and community ecology; the mediating role of natural and engineered environmental chemistries also should not be neglected, as they are critical to arthropod–arthropod and arthropod–host interactions.

The simultaneous assessment of sublethal toxicological endpoints, such as effective median concentrations for population growth rate and the balance among the life-history traits involved, is labor intensive. They usually require the use of life tables, but are pivotal for studies on insecticide-induced hormesis, among others. However, these methods have been greatly simplified and surrogates exist making then more cost-effective [6••,7]. Studies on insect assemblages and communities are also labor intensive and require high-level taxonomic expertise because identification at genus and species level is important for high resolution detection of responses. Multivariate statistical methods are required for such studies with multiple species, multiple chemical compounds, and their interactions. Furthermore, more recent approaches such as food-web and social network analyses are under current development exhibiting unrealized potential for future endeavors in understanding pesticide–arthropod interactions.

The proposed theoretical framework should expand the notion of adverse outcome pathways to explore stress response pathways linking molecular (primary and secondary) events taking place within co-occurring species, their potentially intercrossing and parallel pathways, and their intertwined hierarchical consequences beyond the population level. The notion is bold, the challenges and expertise required may be daunting at first, but rewards greatly surpass the challenges. The relevance of the subject goes well beyond pest management. Anthropogenic compounds, particularly pesticides, are a prevalent landscape feature, whose potential eco-evolutionary consequences have yet to be comprehended. Thus, let there be light!

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