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Interactions between pesticides and pathogen susceptibility in honey bees

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There exist a variety of factors that negatively impact the health and survival of managed honey bee colonies, including the spread of parasites and pathogens, loss of habitat, reduced availability or quality of food resources, climate change, poor queen quality, changing cultural and commercial beekeeping practices, as well as exposure to agricultural and apicultural pesticides both in the field and in the hive. These factors are often closely intertwined, and it is unlikely that a single stressor is driving colony losses. There is a growing consensus, however, that increasing prevalence of parasites and pathogens are among the most significant threats to manage bee colonies. Unfortunately, improper management of hives by beekeepers may exacerbate parasite populations and disease transmission. Furthermore, research continues to accumulate that describes the complex and largely harmful interactions that exist between pesticide exposure and bee immunity. This brief review summarizes our progress in understanding the impact of pesticide exposure on bees at the individual, colony, and community level.

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Introduction

Bees are important pollinators of many crops and native plants, contributing about one-third of the human diet globally and providing immeasurable ecosystem services [1–3]. There are ca. 4000 species of bees across North America, but a number of species have exhibited population declines [4,5•], including several bumble bee species that have decreased in both abundance (up to 96%) and geographical range (23–87%) [6]. Similar declines have also been reported in solitary species, particularly with bees that are habitat and flower specialists [7]. Additionally, beekeepers have reported economically unsustainable, annual honey bee colony losses of ca. 31–46% since 2010 [8]. Research efforts are focused on the relationship between current agricultural practices and consistent losses of honey bee colonies. This includes large-scale conversion of natural landscapes into productive crop fields, which has led to a reduction in forage availability and malnutrition, as well as increased pesticide exposures to bees [4,8–18,19•,20–22]. Other factors that affect honey bee health can include parasites and pathogens, with increased infestations and infections, respectively, in colonies with reduced immunocompetence caused by poor nutrition and exposure to pesticides [23–26,27••].

There are multiple interacting stressors that affect honey bee colonies. For example, the ectoparasitic mite *Varroa destructor* feeds on the hemolymph of bees, resulting in physiological deficiencies that reduce overwintering success for the colony [28]. Moreover, physical damage to the bee cuticle caused by mite feeding can introduce several viruses into host bees [29,30]. If unmanaged, *Varroa* mite infestations can increase the mortality of bees in the colony within one season [31,32]. The lack of, or improper, *Varroa* mite management is a significant driver for losses among beginning and hobbyist beekeepers [33]. However, *Varroa* mites continue to be the major reason for the use of beekeeper-applied miticides or varroacides since their introduction to the U.S. [34,35]. These apicultural pesticides, along with agricultural pesticides (insecticides, fungicides, herbicides) transported to the hive by foraging bees, may result in synergistic interactions that cause higher toxicity than compounds acting alone [36–40,41•]. Pesticides may also accumulate in the hive, affect brood development, and increase selection pressure for varroacide-resistant mites [42–44]. Laboratory studies often examine individual stressors for direct evidence of their adverse effects on bees; however, complex stressor interactions and the ability for bees to socially or behaviorally defend themselves have made it difficult to understand the causes and effects of stressor interaction in the field [25,41•,45,46]. This review examines the current literature focusing on pesticide exposure and pathogen impacts on honey bees, with emphasis on the interface between these stressors at different levels of biological organization (i.e., individual to colony to apiary).

Individual-level effects

Laboratory studies have demonstrated that exposure to sublethal doses of pesticides can negatively affect honey

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bee behavior [47,48], foraging [49], longevity [43], and olfactory learning and memory [50–53]. Pesticide exposure can also impair honey bee detoxification pathways [54], and the harmful effects of interactions between multiple pesticides in bees appear to be nearly as complex as the drug interactions observed in mammals [39,55]. More pertinent to concerns related to the increasing role of pathogens in colony decline is the impact of pesticide exposure on the immune response of honey bees and their ability to resist or tolerate pathogen infection. The pathogen most commonly used in laboratory studies has been the microsporidium *Nosema ceranae*, which has proven the most tractable in controlled infection studies. Significant effects on honey bee immune responsiveness to infection with *Nosema* have been observed with exposure to neonicotinoid pesticides [23,24,56–58,59••,60••], fipronil [23,57,61], as well as fungicides [62], in addition to altered queen physiology and survival [59••] and reduced sperm viability and gene expression [60••]. More noteworthy, given the widespread prevalence of agricultural and apicultural pesticide residues in the hive environment [42], is the finding that bees exposed to these residues in the hive also have increased susceptibility to *Nosema* [62,63]. With regards to other honey bee pathogens, harmful interactions have been demonstrated between viral pathogenicity and exposure to the neonicotinoid pesticide clothianidin [26], as well as the pyrethroid miticide *tau*-fluvalinate [64]. Recent work has also employed a model insect virus [65••] to reveal that exposure to the formamidine miticide amitraz increases mortality associated with viral infections [66•]. In addition to pesticide exposure, there is also mounting evidence that organosilicone spray adjuvants used in various pesticide formulations may pose a more serious threat than previously realized, as they have been demonstrated to both impair olfactory learning [67] and increase viral pathogenicity in bees [68•]. Another exciting recent study shows a synergistic interaction when bee larvae are exposed to clothianidin or the organophosphate dimethoate in combination with *Paenibacillus larvae*, the causative agent of American foulbrood [69]. Finally, gene expression studies have also suggested that thymol, formic acid, and the phosphorothioate miticide coumaphos may suppress expression of genes related to bee immunity [70]. A number of recent reviews address in greater detail the links between pesticides and bee diseases [71••] and provide some discussion of improvements and future directions for this research [72••]. Although there exist ample correlative studies to suggest a link between pesticide exposure and the ability of bees to resist or tolerate pathogen infection, there is very little known about the mechanisms of such a connection. One outlier is a study describing a negative modulator of NF-κB activation (NF-κB function reviewed here [73]) that reduces honey bee immunocompetence when exposed to clothianidin and another neonicotinoid, imidacloprid, but not when exposed to the organophosphate chlorpyrifos [26]. Two recent studies also described an important role for the evolutionarily conserved ATP-sensitive inwardly rectifying potassium (K_{ATP}) channel in the regulation of honey bee cardiac function [65••] and antiviral immunity [74••]. This supports earlier findings that K_{ATP} channels play a role in mediating fruit fly survival during viral infections similar to that observed in mammals [75]. Although the exact mechanism has yet to be elucidated, evidence suggests that K_{ATP} channels have a function in modulating antiviral RNAi by facilitating tissue-specific regulation of innate immune response mechanisms by the cellular environment of the heart [76]. Taken together, these studies also support the hypothesis that disruption of cardiac function and subsequent inability to maintain homeostasis may reduce the ability of bees to tolerate infection by pathogens [66•], providing another possible mechanism by which cardioactive pesticides could reduce honey bee immunocompetence.

Colony-level effects

Pesticide effects on honey bee colonies are typically studied in the field; however, the number of interacting biotic and abiotic stressors that can affect these colonies presents variables that are difficult to manage with these studies. Additionally, social bee behaviors, such as age-based divisions of labor, can cause disparities in the evaluation of pesticide exposures, toxicities, and risks to the different castes and their roles in the colony [38,77,78]. For example, older forager bees are more likely to be exposed to pesticides via contact or oral exposure to contaminated nectar and water sources than younger nurse bees, and these older bees are reported to be more sensitive to these pesticide exposures [79,80••,81•,82•]. By contrast, nurse bees are more likely to be exposed to pesticide-contaminated pollen than forager bees, since the nurse bees consume pollen to produce glandular secretions to feed brood and queen bees. Nurse bees infected by *Varroa* mites and feeding on pesticide-contaminated pollen may have higher virus titers compared to those feeding on uncontaminated pollen and, in turn, can increase the risk of transmitting viruses to the brood and queen during feeding [78,83–85]. Additionally, young adult bees emerging from parasitized pupae may be disproportionately impacted by *Varroa* mites as multiple mites reproduce and feed within the developing pupal cell. Heavy parasitism alters physiological features critical for winter survival in host bees and may lead to developmental abnormalities such as malformed wings caused by *Varroa*-vectored deformed wing virus [86,87]. In addition, the exposure of bees to pesticides can not only adversely affect brood care and production, but can affect other caste behaviors such as mating, egg laying, and other routine tasks that support healthy colony numbers. Forager bees exposed to certain pesticides are reported to exhibit impaired foraging behaviors and cognitive functions that not only lead to reduced food stores, lower brood production, and higher pathogen

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