

Insecticide resistance in social insects: assumptions, realities, and possibilities[☆]

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Insecticide resistance is an evolved ability to survive insecticide exposure. Compared with nonsocial insects, eusocial insects have lower numbers of documented cases of resistance.

Eusocial insects include beneficial and pest species that can be incidentally or purposely targeted with insecticides. The central goal of this review is to explore factors that either limit resistance or the ability to detect it in eusocial insects. We surveyed the literature and found that resistance has been documented in bees, but in other pest groups such as ants and termites, the evidence is more sparse. We suggest the path forward for better understanding eusocial resistance should include more tractable experimental models, comprehensive geographic sampling, and targeted testing of the impacts of social, symbiont, genetic, and ecological factors.

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Introduction

The goals of this review are to explore potential factors that either limit insecticide resistance or the ability to detect it in eusocial insects and to synthesize potential paths forward for a better understanding of eusocial resistance phenomena. Eusocial insects mainly include bees, wasps, ants, and termites. These insects live in groups that display overlapping generations, cooperative care of the young, and a division of labor among castes. The three general eusocial castes are workers,

reproductives, and defenders (i.e. soldiers, guards), each with distinct morphological and behavioral phenotypes. Both eusociality and these castes evolved independently in the orders Hymenoptera (bees, wasps, and ants) and Blattodea (termites) that are mainly considered here.

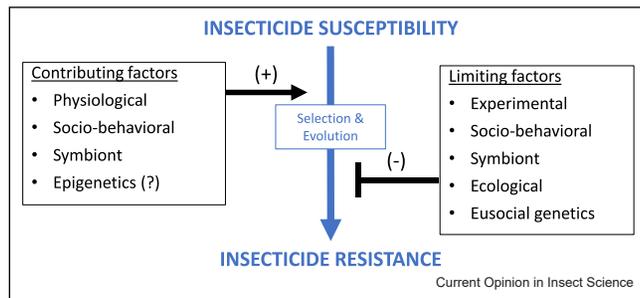
Insecticide resistance is the evolved ability of insects to survive in the presence of insecticides. From an operational perspective, the Insecticide Resistance Action Committee defines resistance as “a heritable change in the sensitivity of a pest population that is reflected in the repeated failure of a product to achieve the expected level of control when used according to the label recommendation for that pest species” [1]. Resistance is caused by pest adaptations that confer a selective advantage in the presence of insecticides (Figure 1), leading to increased survival in subsequent generations. Insecticide resistance evolves in populations following Darwinian principles [2]. Centrally important to this review, there are thousands of examples of insecticide resistance in nonsocial insects, but comparatively minimal evidence in eusocial insects [3,4].

Most individuals within eusocial insect colonies are nonreproductives or ‘hopeful reproductives’ that retain the potential to reproduce. Primary reproductives comprise smaller proportions of colonies and are long-lived individuals whose lifespan mirrors their host colony [5,6]. In the absence of primary reproductives, however, supplementary reproduction usually becomes possible [7]. Thus, most individuals in eusocial insect colonies are not capable of passing resistance genes to future generations. Also, nonreproductives are expendable and can buffer colonies from insecticidal effects [8]. For these reasons, it has been argued that insecticide resistance evolution in eusocial insects should be impossible or at least rare [9].

Below, we explore the topic of insecticide resistance in social insects. We consider multiple perspectives, including experimental constraints that may obscure an ability to observe resistance, documented cases of resistance in eusocial insects and affiliated resistance mechanisms, and testable theories relating to social, symbiont, genetic, and ecological factors. We also suggest several approaches for consideration

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Figure 1



Overview of potential factors that impact insecticide resistance evolution, and its perception, in eusocial insects. The blue arrow in the center represents the evolutionary transition from insecticide-susceptible to insecticide-resistant states. The various contributing (+) and limiting (-) factors listed are discussed in this review.

by researchers to better document and understand the potential for resistance in eusocial insect species.

Experimental constraints limiting the ability to study resistance in eusocial insects

There are constraints to working with eusocial insects that impact the ability to study resistance. Nonsocial insects can be reared continuously to study resistance in small genetically distinct groups, usually having one or fewer generations per year (e.g. German cockroaches; [10–12]). However, eusocial insects must be reared as entire colonies that might require years or decades to reach testable numbers. Eusocial species that produce neotenic or supplementary reproductives might offer more tractable model systems (e.g. termites *Reticulitermes* or ants *Monomorium pharaonis* (L.) or *Solenopsis invicta* Buren), particularly for studying early phases of resistance evolution under different socio-environmental conditions. Bees, alternatively, are a tractable model system with excellent molecular and genetic resources that have yielded clear outcomes.

Examples from bees

Honeybees have reduced numbers of detoxification genes relative to nonsocial insects, which often is cited as a cause of increased susceptibility, but in reality, honeybees are well-adapted to thrive in the presence of environmental toxins [13–15]. Widespread use of DDT through the 1950s–1960s selected for DDT-resistant populations of honeybees in California [16,17]. Owing to their exposure to pesticides that target hive parasites and other diseases, honeybees have further adapted to tolerate numerous pesticides [13,17–20]. Regarding the insecticide imidacloprid, honey bee colonies produce two seasonal susceptibility phenotypes where winter workers are significantly more tolerant than summer workers [21]. Investigating larval chronic exposure to a pesticide mixture revealed that

different stocks had different susceptibilities [22]; specifically, Old World/progenitor and feral stocks were the most pesticide-tolerant.

Conversely, another study found that insecticides negatively affect honey bee growth, development, foraging activity, and pollination by influencing olfaction, memory, navigation, flight, and dance circuits [23]. Even at low pesticide concentrations below “no-observed-adverse-effect concentrations (NOAEC),” transcriptional impacts seen in honey bee larvae are indicative of physiological stress [24]. However, honeybees can resist these harmful effects by coordinating the expression of immunity, metabolism, and detoxification genes [23]. Nutritional resources also modulate pesticide tolerance and titers of developmental hormones [25,26]. It is clear from the above examples that bees can develop resistance and possess tolerance mechanisms that can overcome the deleterious effects of insecticides, including the relatively newer neonicotinoids [27–29].

Case studies from ants and termites

Ants

Initial studies to select for sodium arsenate resistance in Pharaoh’s ants, *M. pharaonis*, found only increased susceptibility, suggesting that sodium arsenate resistance is impossible due to the “protection mechanism of the social food chain” [30]. In more recent work with the insecticide fipronil, dark rover ants (*Brachymyrmex patagonicus* Mayr) and white-footed ants (*Technomyrmex difficilis* Forel) showed significant species-wide tolerance [31,32]. In a survey of 12 urban ant pests tested with bifenthrin, fipronil, and chlorfenapyr, odorous house ants (*Tapinoma sessile* [Say]) were consistently the most tolerant species, which agrees with their invasiveness and difficulty to control [33]. Another finding was that tolerance levels in *T. sessile* were independent of body mass, indicating the involvement of specific physiological resistance mechanisms.

Termites

Several studies have identified significant reductions in toxicity for soil termiticides in the Formosan subterranean termite *Coptotermes formosanus* Shiraki. This included a range of soil termiticides from the chlorinated hydrocarbon, pyrethroid, organophosphate, carbamate, and phenylpyrazole classes [34–36]. The above studies also included the native sympatric termite *Reticulitermes virginicus* (Banks), but susceptibility differences were generally insignificant. Other studies revealed ~twofold permethrin resistance between two populations of *Reticulitermes flavipes* (Kollar), 11–660-fold pyrethroid resistance among three populations of the sand termite *Psammodermes hypostoma* Desneux, and 20–27-fold chlorpyrifos resistance among two *Microcerotermes diversus* populations [36–38].

Resistance mechanisms

The two types of resistance in insects are behavioral and physiological (Table 1). Behavioral resistance is less common, and physiology underlies behavior [39,40]. However, eusocial behaviors may provide a degree of innate tolerance. For example, the social food chain of ants in which carbohydrate or protein insecticide baits would cycle first through workers or larvae effectively

protects reproductives [8]. Also, decreased tunneling into insecticide-treated substrates was noted in *C. formosanus* termites [34], and ants express ‘particle covering’ and necrophoresis behaviors that can protect colonies from insecticide exposure [41,42].

Physiological resistance includes detoxification, target site, and penetration/transport mechanisms [3,43–45], and an

Table 1

Potential mechanisms for overcoming and avoiding insecticide impacts in social insects.

| Mechanism | Insect (species) | Insecticides affected | References |
|---|--|--|---|
| Physiological resistance | | | |
| Metabolic detoxification | | | |
| P450 | Black garden ant (<i>Lasius niger</i>) | Azadirachtin, β -cypermethrin, and λ -cyhalothrin | Konorov and Nitikin [50] |
| | Red imported fire ant (<i>Solenopsis invicta</i>) | Sulfuramid, triflumuron, fipronil, β -cypermethrin, and indoxacarb | Zhang et al. [51], Siddiqui et al. [45] |
| | Honey bee (<i>Apis mellifera</i>) | Cyfluthrin, λ -cyhalothrin, T-fluvalinate, imidacloprid, thiamethoxam, and thiacloprid | Johnson et al. [18], Manjon et al. [27] |
| | Bumble bee (<i>Bombus terrestris</i>) (<i>A. mellifera</i> , <i>B. terrestris</i>) | Thiacloprid, acetamiprid, imidacloprid, thiamethoxam, and thiacloprid | Trocza et al. [28], Manjon et al. [27] |
| | Sand termite (<i>Psammotermes hypostoma</i>) | Deltamethrin, α -cypermethrin, and λ -cyhalothrin | Toughan et al. [37] |
| Adrin epoxidase | Formosan subterranean termite (<i>C. formosanus</i>) | Aldrin, chlorpyrifos, and cypermethrin | Valles and Woodson [35] |
| | Dark Southern subterranean termite (<i>Reticulitermes virginicus</i>) | Aldrin | Valles et al. [55] |
| Esterases | Eastern subterranean termite (<i>Reticulitermes flavipes</i>) | T-Permethrin | Valles et al. [36,54] |
| | Formosan subterranean termite (<i>C. formosanus</i>) | | Valles and Woodson [35] |
| | Sand termite (<i>P. hypostoma</i>) | Deltamethrin, α -cypermethrin, and λ -cyhalothrin | Toughan et al. [37] |
| | Honeybee (<i>A. mellifera</i>) | Chlorpyrifos, coumaphos, coumaphos-oxon, fluvalinate, and propargite | Milone et al. [22] |
| Glutathione S-transferase | (<i>Microcerotermes diversus</i>) | Chlorpyrifos | Ravanshadi et al. [38] |
| Symbiont-mediated metabolism | Eastern subterranean termite (<i>R. flavipes</i>) | Imidacloprid | Blanton et al. [68] |
| Target site insensitivity | (<i>Microcerotermes diversus</i>) | Chlorpyrifos | Ravanshadi et al. [38] |
| Altered AChE | | | |
| Cuticular changes | Formosan subterranean termite (<i>C. formosanus</i>) | N/A | Richardson et al. [56] |
| Behavioral (social and ecological) resistance | | | |
| Nutrient flow | Pharaoh ant (<i>Monomorium pharaonis</i>) | Sodium arsenate | Berndt [30] |
| | Ants (in general) | N/A | Csata and Dussutour [64], Gutierrez et al. [66] |
| Reproduction (haplodiploidy, asexual) | Social insects (in general) | N/A | Kato et al. [72], Martellosi [73] |
| Particle-covering behavior | Red imported fire ant (<i>S. invicta</i>) | Fipronil, rotenone, and avermectin | Wen et al. [41] |
| Necrophoresis | Argentine ant (<i>Linepithema humile</i>) | N/A | Choe et al. [42] |
| Saturating birth rates | Social insects (in general) | N/A | Field and Toyozumi [7] |
| Group size-dependent helping decisions | Social insects (in general) | N/A | Field and Toyozumi [7] |
| Urban versus natural habitats | Odorous house ant (<i>Tapinoma sessile</i>) | N/A | Blumenfeld et al. [78] |

emerging concept is microbe or symbiont-mediated metabolism [46,47]. Regarding detoxification, an analysis of 65 insect genomes revealed that ants and termites have comparable numbers of detox-encoding genes to more resistance-prone insects [48]. Chronic exposure studies on black garden ant colonies, *Lasius niger* (L.), with the neonicotinoid thiamethoxam, revealed differences in the internal ratio of thiamethoxam to its metabolite clothianidin between queens and workers, suggesting queens have superior detoxification capabilities [49]. P450 detoxification genes have elevated expression in urban-adapted *L. niger*, and the most elevated (*CYP9*) is capable of docking with mycotoxins and xenobiotics [50]. In work with *S. invicta* fire ants, knockdown of another P450 gene, *CYP6AS160*, supports its role in fipronil detoxification [51].

No detox genes were induced in *C. formosanus* termites after exposure to chitin synthesis inhibitor insecticides [52], but numerous termite gut detox genes are inducible by wood-feeding [53]. No differences in P450 or GST detox activity were found among *C. formosanus* populations tolerant to chlordane, chlorpyrifos, and cypermethrin, but differences in esterase activity were found [35]. Permethrin-hydrolyzing esterases were identified from permethrin-tolerant *R. flavipes* [36,54] and a functional P450 system documented in *R. virginicus* [55]. Also, elevated P450 content and esterase activity occurred in pyrethroid-resistant *P. hypostoma* [37], and differences in AChE and GST activity were found in chlorpyrifos-resistant *Microcerotermes diversus* [38]. Regarding cuticular penetration, desiccation stress increases cuticular hydrocarbon production in *C. formosanus* [56]. In other insects, such changes have been associated with P450 genes that have potential overlapping roles in insecticide detoxification and climate change adaptation [57–59]. It is also noteworthy that, other than the AChE insensitivity example noted above, no target site resistance has yet been identified in eusocial insects. Two possible explanations for the lack of target site resistance are genetic factors discussed later and the many detoxification examples noted above.

Testable theories

Intercolony susceptibility

Sampling across multiple populations/species can reveal susceptibility differences that are indicative of resistance or evolving resistance. Comparisons of urban versus natural ant colonies revealed urban colonies were more tolerant of the neonicotinoid dinotefuran; queens were more tolerant than workers toward dinotefuran, fipronil, and lambda-cyhalothrin; and *T. sessile* was the most tolerant ant species overall [33]. Studies examining insecticide susceptibility across termite colonies revealed differential susceptibility that generally agreed with insecticide treatment history [34–38].

Social factors

A meta-analysis comparing eradication efforts between eusocial versus nonsocial invasive species found that efforts were 79% less successful for eusocial than nonsocial species [60], suggesting natural recalcitrance to insecticides by eusocial insects and/or that reproductives are not being impacted by insecticides [7,61]. Alternatively, eusocial species may be more susceptible to some kinds of toxicants because of horizontal transfer [62,63]. Thus, present-day insecticides and delivery strategies may be so well-engineered that they achieve ‘high dose’ delivery that effectively limits resistance evolution.

Another factor limiting resistance evolution (through protection of reproductives) may relate to colony nutrient flow. Nutrition is important in the evolution/maintenance of sociality and caste determination, and food collection relies on foraging workers whose nutritional requirements may differ from the rest of a colony [64]. Selective protein digestion by ant larvae can protect reproductive castes from insecticides, that is, protein preferentially flows into larvae and increases the carbohydrate:protein ratio in foraging workers [65].

Nutrient intake targets in ants may further serve a protective function [64]. Larvae can improve worker immunity to pathogens and parasites via this role in nutritional regulation [65], which may suggest a broader protective mechanism by larvae extending to insecticides. For example, in ants, a trade-off was found between growth and survival for high-protein versus high-carbohydrate diets, where protein diets caused larger workers and carbohydrate diets caused higher lipid content [66]. In contrast, wood-feeding termites receive high-carbohydrate and low-protein diets that additionally present xenobiotic challenges and induce physiological defenses [53]. These examples might suggest that eusocial factors broadly favor colony fitness and induced tolerance over constitutively expressed resistance.

Symbiont factors

Eusocial insects are hosts to gut bacterial communities that serve a variety of functions [67]. Termite reproductives can live for decades, leading to slow genetic turnover [5]; however, gut symbiont generation times are much faster, creating the potential for symbiont-mediated insecticide resistance [9,68]. Conversely, insecticides can cause a loss of termite social immunity and/or a loss of symbiont-mediated immunity to pathogens [69,70], which may increase insecticide susceptibility and contribute to the lack of resistance identified in termites.

Genetic and ecological factors

Eusocial insects express higher degrees of genetic relatedness than solitary insects, which is a primary driver in the evolution and maintenance of sociality [71]. Also, haplodiploidy in hymenopterans [72] and asexual queen succession in termites [73•] further increase genetic homogeneity within colonies. Such factors could limit the genetic variation necessary for resistance evolution. On the topic of epigenetics, while different social phenotypes expressed by eusocial insects can be linked to specific epigenetic landscapes [74], thus far, no links between epigenetics and cases of eusocial resistance have been documented.

Ecological factors may further limit the evolution of eusocial resistance. Two risk-limiting socio-ecological factors are saturating birth rates and group size-dependent helping decisions [7]. Another possibility with pest ants and termites is the existence of large untreated natural refuges that provide reservoirs for susceptible genotypes that dilute resistant genotypes during random outbreeding [75,76]. Another ecological factor is differential insecticide selection pressures and other xenobiotic challenges between urban and natural habitats [31,77,78••].

Conclusion

This review considered insecticide resistance in eusocial insects, exploring potential factors that limit resistance in eusocial species and/or our ability to detect it. Bees clearly have the capacity to develop resistance, but examples from other eusocial pest species such as ants and termites are more limited due to apparent experimental and biological constraints. From an experimental perspective, eusocial insects must be reared as entire colonies that might require years or decades to reach testable numbers. Thus, we propose species with supplementary reproductives as the most tractable experimental models. Based on our literature survey, conventional physiological resistance mechanisms have been documented in bees, ants, and termites that appear equally represented between eusocial and nonsocial insects.

Additionally, social behaviors such as nonreproductive foraging and social food chains likely provide reproductive castes with innate levels of insecticide tolerance that might supersede a need for all colony members to evolve more conventional mechanisms. Furthermore, based on our synthesis from the available literature, we propose approaches and testable theories that include continued testing for variation in insecticide susceptibility across colonies or populations and testing of the impacts of social, symbiotic, genetic, and ecological factors on eusocial resistance evolution. We propose that considering these factors from systems biology and/or holobiont perspectives will provide novel insights that lead to new abilities to document resistance in eusocial

insects, manage invasive eusocial species, protect beneficial species, and achieve sustainable pest management.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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- of special interest
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