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Review

Enhancing knowledge of chemical exposures and fate in honey bee hives: Insights from colony structure and interactions

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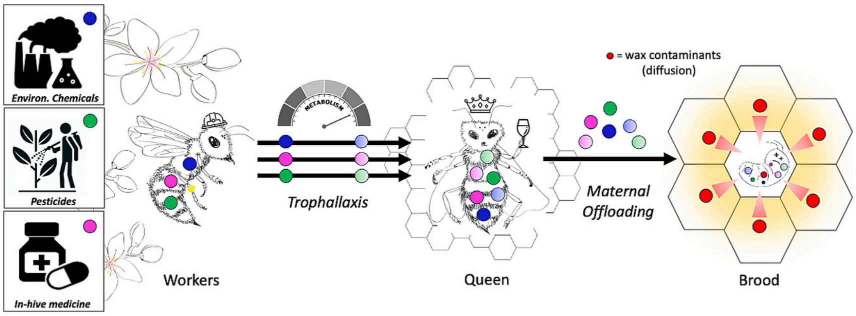
HIGHLIGHTS

- Honey bees are unintentionally exposed to various chemicals in their environment.
- Social structure and food sharing facilitates chemical transfer between members.
- Limited sensitive analytical techniques restrict studying cumulative impacts.
- New tracing and AI can track chemical transfers in hives to identify exposures.

GRAPHICAL ABSTRACT



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ABSTRACT

Honey bees are unintentionally exposed to a wide range of chemicals through various routes in their natural environment, yet research on the cumulative effects of multi-chemical and sublethal exposures on important caste members, including the queen bee and brood, is still in its infancy. The hive's social structure and food-sharing (trophallaxis) practices are important aspects to consider when identifying primary and secondary exposure pathways for residential hive members and possible chemical reservoirs within the colony. Secondary exposures may also occur through chemical transfer (maternal offloading) to the brood and by contact through possible chemical diffusion from wax cells to all hive members. The lack of research on peer-to-peer exposures to contaminants and their metabolites may be in part due to the limitations in sensitive analytical techniques for monitoring chemical fate and dispersion. Combined application of automated honey bee monitoring and modern chemical trace analysis techniques could offer rapid progress in quantifying chemical transfer and accumulation within the hive environment and developing effective mitigation strategies for toxic chemical co-exposures. To enhance the understanding of chemical fate and toxicity within the entire colony, it is crucial to consider both the intricate interactions among hive members and the potential synergistic effects arising from combinations of chemical and their metabolites.

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1. Introduction

1.1. Economic importance of managed bees

Honey bees (*Apis mellifera*) are one of the best monitored and most widely used commercial crop pollinators worldwide. The practice of managing honey bees has been developing for millennia to obtain commercial products such as honey, wax, and propolis (Kritsky, 2017). It was not until 1851 that the invention of the movable frame hive gave rise to the existence of modern beekeeping practices and the extension of the use of honey bee colonies for commercial agriculture (Oxley and Oldroyd, 2010). Pollination services increase essential crop production by up to 90 % while also providing an annual income source for beekeepers (Porto et al., 2020). According to the 2022 USDA Annual Strategic Pollinator Priorities Report, honey bees pollinate over 100 commercially grown crops in the U.S. and increase their total value by tens of billions of dollars annually (USDA, 2022a). While there are increasing efforts to identify additional wild insect species with the potential to be managed for crop production (Klein et al., 2018; Osterman et al., 2021), honey bees still remain the most economically valuable pollinators for global crop monocultures (Khalifa et al., 2021; Klein et al., 2018). However, the continuous expansion and geographic concentration of pollinator-dependent crop cultivation, such as the almond industry in California, has demanded an increase in the honey bee colony movements across states, ultimately exposing bees to multiple agrochemicals within a short period of time (Bond et al., 2021; USDA, 2022b).

1.2. Multi-chemical and chemical mixture exposure as emerging threats to colony health

Multiple categories of stressors, including biological (parasites, pathogens), dietary (poor nutrition), climate (warmer, dryer), and manmade factors (pesticides, miticides, biocides) (Daisley et al., 2020), can have negative effects on the populations of both commercial and wild bee species, compromising their productivity and survival. The issue of pesticide exposure is particularly complex in commercial beekeeping operations, as they are often migratory (Alger et al., 2018; Simone-Finstrom et al., 2016; Traynor et al., 2016). Colonies are moved regionally and even nationally during massive monoculture pollination events in the U.S. (Bond et al., 2021). This constant annual migration exposes bee colonies to different types of crop pesticides, hive medications, and environmental chemicals within the span of only a few months (Sanchez-Bayo et al., 2016; Traynor et al., 2016). Managed honey bees live in a well-coordinated colony environment with their hives acting as superorganisms with intricate communication and food-sharing mechanisms. This makes chemical exposures a community problem, rather than an individual one, with hive-wide health implication. To begin to understand the dynamic nature and effects of multichemical co-exposures on colony health, it is important to first develop sensitive chemical analysis techniques to detect and monitor chemical residue levels and their possible metabolites within the hive environment.

1.3. Technical challenges to study chemical pathways and fate within the colony

Most studies on detection of trace chemicals in the hive environment have focused on quantifying pesticides in products of human use and consumption, such as wax, honey, and pollen (Calatayud-Vernich et al., 2018; Murcia-Morales et al., 2022). However, only a few studies have focused on identifying levels of pesticide residues as they are processed, transferred, and stored within different organismal and physical checkpoints of the honey bee colony (Murcia Morales et al., 2020). A major limitation when analyzing chemical residues in hive members and matrices is the fact that standard analytical methodologies, such as liquid chromatography (LC-) or gas chromatography (GC-) coupled with mass spectrometry (MS), are often not sensitive enough to detect trace levels of chemicals and their metabolites as they are moved and transformed within the hive environment (Charlton and Jones, 2007; Wu et al., 2021). Furthermore, chemical compounds need to be isolated through optimized extraction techniques, such as Quick Easy Cheap Effective Rugged Safe (QuEChERs) and solid-liquid extraction protocols (Barganska et al., 2018; Barganska et al., 2014; Calatayud-Vernich et al., 2016), which are in turn limited to sample size or amount. When evaluating small samples such as eggs (∼0.0001 g) or larvae (∼0.002–0.2 g) (Taber and Roberts, 1963; Zoltowska et al., 2011), sample sizes can be prohibitively small. Yet bees are highly sensitive to pesticides even at sublethal concentrations and exposure to low-dose mixtures of these chemicals could promote synergistic effects on honey bee behavior and toxicity when acting the same molecular targets (Nicklisch et al., 2016; Nicklisch and Hamdoun, 2020; Taenzler et al., 2023; Wade et al., 2019). To develop a more holistic understanding of multichemical stressors in honey bees, it is important to apply modern tracking and quantification techniques to better elucidate the single and multi-chemical fate pathways, to identify chemical sinks within the honey bee hive environment, and to monitor and quantify how social interactions and caste structure can influence chemical exposures.

In this review, we synthesize current knowledge on sources and types of multi-chemical exposure experienced by commercial honey bees, the observed toxic effects on individual members and the impacts on colony health. We provide updates on the emerging information on possible chemical contaminant sinks and transfer from within-hive structures and food. We further shed light on how caste and developmental stage of the hive members can influence both chemical exposure and elimination pathways. We additionally highlight the importance of two unique but understudied features of the honey bee superorganism that can determine chemical fate within the colony, trophallaxis and maternal offloading. The overall goal of this review is to emphasize the need to consider social structure and colony interactions to advance our understanding of chemical fate in bee hives and for mitigating the impacts of multi-chemical stressor to honey bees.

2. Discussion

2.1. Routes of honey bee exposures to chemical mixtures

2.1.1. Primary routes of exposure

Direct exposure of honey bees to pesticides and environmental chemicals can occur outside or within the hive (Fig. 1). Forager bees, that collect food and material for hive maintenance and colony food supply, are regularly exposed to multiple chemicals in their environment (Johnson, 2015; Vannette et al., 2015). Thereby, exposure can typically occur via three different routes: i) orally through consumption of contaminated food (pollen, nectar) or water; ii) via direct contact (e.g., cuticle, antenna) with pesticides applied to plants or other surfaces or sequestered in wax comb; and iii) via air exposure when pesticides are applied as aerial sprays and drift onto bees or through active and passive air influx into colonies from nearby treated agricultural areas (Benuszak et al., 2017; Calatayud-Vernich et al., 2018; Johnson, 2015; Krupke et al., 2012; Murcia Morales et al., 2020; Peters et al., 2019; Southwick and Moritz, 1987; Zhu et al., 2015).

Within the hive, physical hotspots and reservoirs of chemical contaminants primarily include stored contaminated food and various hive matrices, such as propolis or wax. The systemic transfer of pesticides to pollen, nectar, beebread, and wax has been widely reported in the literature and poses a significant threat to honey bees (Alder et al., 2006; Benuszak et al., 2017; Calatayud-Vernich et al., 2018; Chauzat and Faucon, 2007; Dively and Kamel, 2012; Gunes et al., 2021; Mullin et al., 2010; Ostiguy et al., 2019; Sanchez-Bayo and Goka, 2014; Stoner and Eitzer, 2012; Stoner and Eitzer, 2013; Traynor et al., 2016; Traynor et al., 2021). This is particularly important for developing larvae, which, as one of the most vulnerable members in the hive, cannot relocate from contaminated wax cells and rely on the food produced by the nurse bees (Murcia Morales et al., 2020). The levels of pesticides detected in royal jelly are often relatively low, and there appears to be minimal transfer from worker bee diet to the glandular secretions they produce to feed to larvae. For instance, worker bees exposed in the field to a pollen-honey diet fortified with a cocktail of 13 commonly used pesticides produced royal jelly with the majority of the detected concentrations of each active ingredient below 1 μg/kg (Böhme et al., 2017). However, in recent field studies, it was observed that pesticide residues are higher in royal jelly collected from natural comb compared to artificial queen cups, suggesting that there is some diffusion of pesticide residues from wax into the larval diet (Alkassab et al., 2022). Wu and coworkers showed that worker bees reared in pesticide-contaminated wax have shorter lifespans, which may be partly due to this diffusion and direct contact with the pesticide-laden wax (Wu et al., 2011). This highlights the importance of rotating comb to reduce pesticide contamination in wax and the need to assess long-term exposure and sublethal effects of pesticides on caste differentiation and queen bee development, which are still not fully understood (Böhme et al., 2017; Calatayud-Vernich et al., 2018; Payne et al., 2019; Schmuck et al., 2001).

2.1.2. *Secondary and tertiary routes of exposure*

The complex dynamics within honey bee castes foster numerous biological intersections, creating various points where hive inhabitants engage in the processing and exchange of food. As such, food contaminant transfer and accumulation should be studied in the context of a colony “superorganism” that collectively absorbs, distributes, metabolizes, and eliminates (ADME) these chemicals. Indeed, pesticide residues have been detected in several hive members, such as foragers and larvae (Calatayud-Vernich et al., 2018; Kasiotis et al., 2014; Murcia Morales et al., 2020). These studies revealed that food sources consumed by all hive members (such as bee bread and nectar) were contaminated with a cocktail of pesticides (Table S1).

2.1.2.1. Trophallaxis. The unique process of food exchange through mouth-to-mouth regurgitation is a significant route of secondary exposure to pesticides for in-hive bees, including foragers, nurses, MABs, and drones. The queen bee and brood are likely to experience tertiary exposure since their food is first processed by nurse bees. As primary consumers of contaminated food, worker bees may dilute ingested pesticides across hive members involved in food handling (depending on the number of organisms in the food-sharing chain) (Böhme et al., 2017; Sponsler and Johnson, 2017). Moreover, the vectorial transport of contaminated food toward the queen bee creates a potential avenue for pesticide bioaccumulation in this vital individual.

While the impacts of peer-to-peer trophallaxis on viral transmission and spread have been well-documented (Chen et al., 2006; de Miranda et al., 2015; Dolezal et al., 2016; Posada-Florez et al., 2021; Ullah et al., 2021), studies on chemical residue levels across all hive members and on possible chemical transfer between bees are patchy and often do not consider continuous biomonitoring of chemical and/or metabolite pathways from the flower (via worker bees) to the reproductive hive members (i.e., queen, drone) and bee products for human consumption (i.e., honey). For instance, to our knowledge, almost no studies have been conducted to determine pesticide, hive medicine, and other chemical residues in queen or drone bees (nor the manner of their transfer). Furthermore, the levels of ubiquitous environmental chemicals, such as the ICES-7 PCB compounds and other persistent, bioaccumulative, and toxic (PBT) chemicals, have so far only been studied in bee products of human consumption, including pollen, propolis and honey (Table S1) (Tang, 2013; Webster et al., 2013; Weisbrod et al., 2007).

Such a holistic approach toward sensitive multi-chemical tracing within a colony would allow for discriminating the extent to which interindividual trophallaxes of contaminated food and contact exposures could provide a biological pathway to mix and distribute toxic chemicals and their metabolites throughout the colony. Likewise, queen bee retinue behavior in worker bees, including grooming and trophallaxis, could facilitate toxic chemical and metabolite bioaccumulation in this longest-living hive member and have detrimental impacts on brood development and survival.

2.1.2.2. Maternal offloading. Another aspect of superorganism ADME is the possibility of maternal offloading via the rapid elimination of accumulated contaminants from the queen bee. This process has been extensively characterized in marine fish and birds and involves the passive transfer of xenobiotic chemicals (including pesticides) through lipids from the fat storages of the reproductive female to nourish and support offspring development (Chynel et al., 2021; Jouanneau et al.,

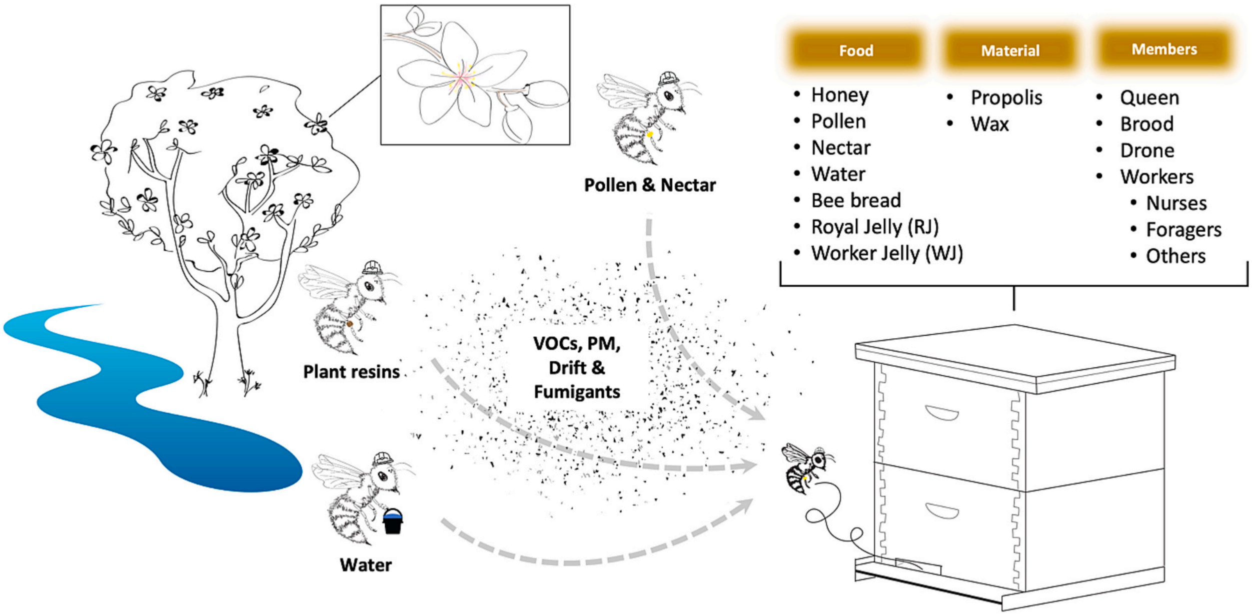
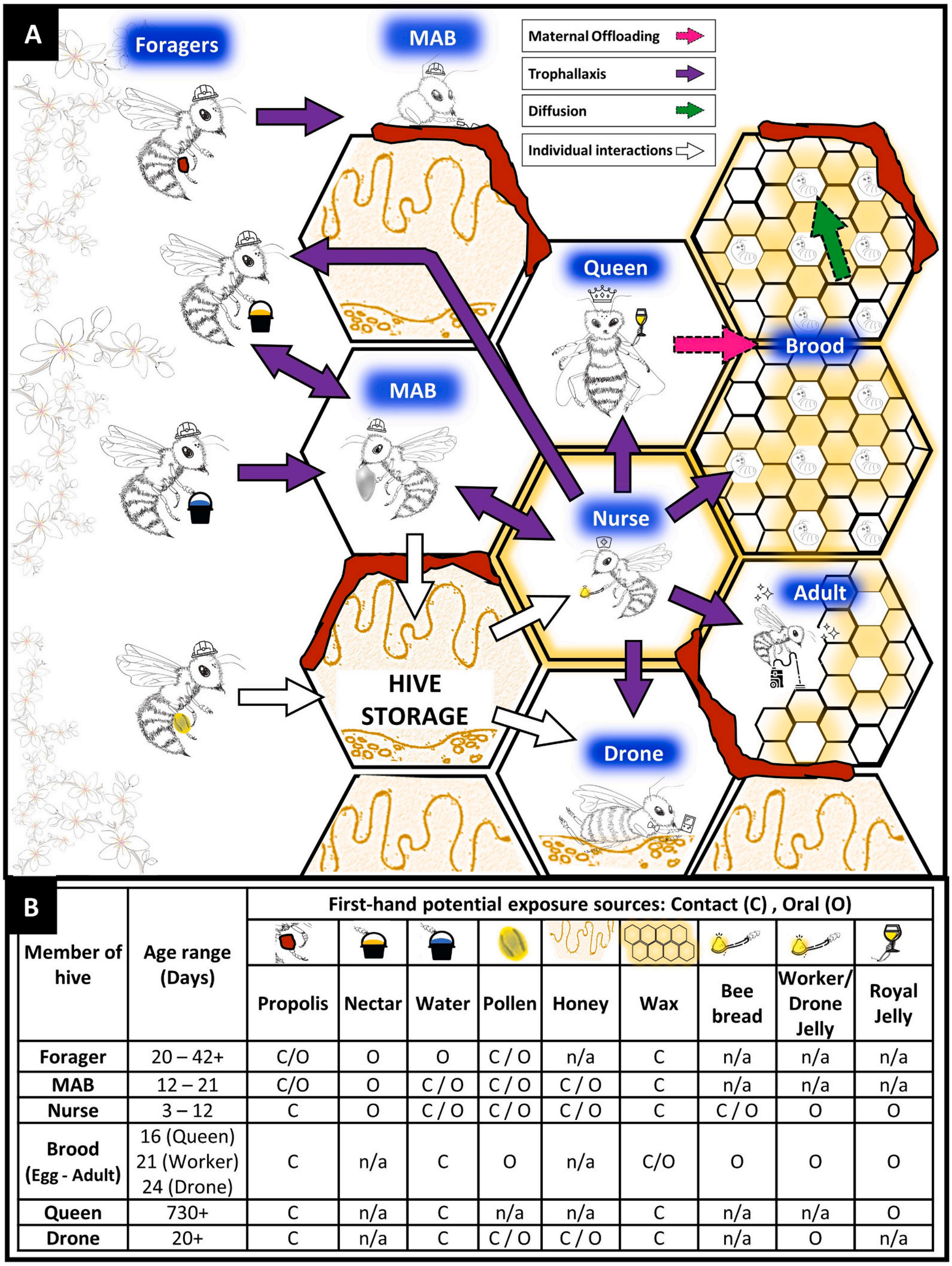


Fig. 1. Routes of honey bee exposure to mixtures of pesticides and environmental chemicals. VOCs = Volatile organic compounds; PM = particulate matter.

2022; Lyons and Adams, 2015; Lyons et al., 2013a; Lyons et al., 2013b; Mull et al., 2013). Honey bee larvae, consisting mostly of fat tissue, could serve as an ideal deposition site for hydrophobic chemicals originating from the queen bee's body (Bishop, 1961). Maternal environment influences traits in insects, including honey bees, such as the onset of diapause, egg production and size, and pupal and adult weight (Amiri et al., 2020; Fox, 1993; Mousseau and Dingle, 1991; Rossiter, 1991). However, the effects of maternal pesticide exposure on metrics such as disease susceptibility, behavior, and longevity of adult worker offspring are not known. Most evidence of maternal offloading in insects exists in the form of egg and immature insect toxicity data generated by exposing reproductive adults (Fine, 2020; Fine et al., 2017b; Hodgson et al., 2011; Joseph, 2019; Medina et al., 2010; Trostanetsky and Kostyukovsky, 2008). Information pertaining directly to the amount of a pesticide that deposits in embryos is scarce, likely owing to the difficulty of performing quantitative assessments on small samples such as insect eggs. However, one study, using isotopically labeled pesticides, demonstrated that the insect growth disruptors pyriproxyfen and diflubenzuron are deposited into the eggs of the predatory lacewing bug (*Chrysoperla carnea*) following maternal exposure (Medina et al., 2002). This work generated precise quantitative data relating exposure scenarios to tissue-specific residue concentrations and physiological outcomes. Similar



Member of hive	Age range (Days)	First-hand potential exposure sources: Contact (C) , Oral (O)								
		Propolis	Nectar	Water	Pollen	Honey	Wax	Bee bread	Worker/ Drone Jelly	Royal Jelly
Forager	20 – 42+	C/O	O	O	C / O	n/a	C	n/a	n/a	n/a
MAB	12 – 21	C/O	O	C / O	C / O	C / O	C	n/a	n/a	n/a
Nurse	3 – 12	C	O	C / O	C / O	C / O	C	C / O	O	O
Brood (Egg - Adult)	16 (Queen) 21 (Worker) 24 (Drone)	C	n/a	C	O	n/a	C/O	O	O	O
Queen	730+	C	n/a	C	n/a	n/a	C	n/a	n/a	O
Drone	20+	C	n/a	C	C / O	C / O	C	n/a	O	n/a

Fig. 2. Hive member interactions determine chemical movement and fate within the honey bee superorganism. (A) Honey bee hive members and possible pathways of chemical contaminant deposition: Individual bee food deposition or consumption (white arrow), interindividual transfer across castes (purple arrows), passive absorption by the brood (green arrow), and active elimination by the queen (pink arrow). (B) List of possible first-hand oral (O), contact (C), and unknown (U) exposure routes for each hive member and bee product or food source. MAB = middle-aged bees.

information about chemical residue levels in honey bees could be valuable, where the outcome and fate of an entire colony is dependent on a single reproductive queen.

2.2. Hive structure and interactions determine chemical exposure risk

The colony structure of honey bees is characterized by a close-knit eusocial community where individuals share food, labor, and information (Fig. 2 and Table S2). This complex and coordinated behavior evolved through a caste system, typically formed by a single queen bee, multiple worker bees (i.e., nurse, forager, and middle-aged bees (MAB)), drones, and brood (including egg, larvae, and pupa) (Johnson, 2010). Acknowledging the unique social structures and food-sharing practices within the bee hive is important to comprehensively track chemical exposure pathways and identify biological and physical reservoirs of chemical contaminants. This requires considering factors such as caste-specific routes of exposure, differences in metabolic enzymes among bees, physical contacts and feeding behavior within the hive, and the storage sites of contaminated food and bee products (Barascou et al., 2022; Medrzycki et al., 2015). These factors can significantly influence the movement, degradation, and potential accumulation of pesticides and other chemicals within the hive, ultimately impacting the overall health and well-being of the colony.

2.2.1. Honey bee development and hive member interactions

Forager honey bees are the oldest of all worker bees (Fig. 2 and Table S2). Depending on the time of the year, foragers can live from 20 days (summer) to up to three months (winter) (Johnson, 2010). Forager honey bees venture outside of the hive and collect goods such as nectar, pollen, propolis, and water, which will serve the hive mainly as food sources. When forager bees return to the hive, they pass the collected goods to middle-aged bees (MABs), another type of worker bee, whose age ranges from 12 to 21 days old. At the entrance of the hive, MABs take nectar and pollen for storage, water for hive temperature control, and propolis for fixing gaps within the hive combs. MABs can also be in charge of handling comb building and hive defense. Deeper inside the hive at the brood comb region, nurse bees perform queen retinue behaviors and brood care. The life span of nurse bees ranges between 4 and 12 days, during which time they utilize gland secretions and hive-stored goods such as pollen, nectar, honey, and water to produce *brood* and *queen bee* food (Berenbaum and Liao, 2019) and share processed food via trophallaxis, the hive's main food-sharing mechanism. It is thought that queen bees are fed with royal jelly (though the full composition and extent of the queen bee's diet has not been well studied), while the worker brood are fed a mixture of primarily gland secretions, bee bread, and honey (though again, the specifics of these mixtures have not been established) (Berenbaum and Liao, 2019; Free, 1959; Haydak, 1943; von Planta, 1888; Wueppenhorst et al., 2022). The brood consist of eggs laid by the queen (~1500 per day), larvae (at different stages), and pupae (Remolina and Hughes, 2008). Brood are the youngest hive members and are taken care of by nurse bees until they become adult bees and replace them in their role. Finally, drones, or male bees are produced only to mate with virgin queens from other colonies to spread the colony's genes. During the summer, drones feed on stored goods and attempt to mate until they die. By winter any remaining drone will be removed from the colony to reduce the burden to the hive resources. Depending on the developmental stage and caste differentiation, each hive member can be exposed to multiple natural and synthetic chemicals in their foraging environment or within the hive.

2.3. Effects of multi-chemical exposure on colony health and survival

2.3.1. Synergistic toxicity of chemical mixtures

Managed and wild bees are continuously exposed to a wide-ranging mixture of natural compounds as well as man-made in-hive medicine, pesticides, and environmental chemicals. Once entering the organism, these complex mixtures of chemicals can interact with cells and biomolecules to directly exert harmful effects. These chemicals further interact with one another, creating a complex web of interactions that indirectly contribute to their overall impact on bee health. If the chemicals act on the same molecular target, such as receptors, transporters or enzymes, the interactions can be antagonistic (combined effect is less than the sum of its individual effects), additive (combined effect is the sum of its individual effects), or synergistic (combined effect is greater than the sum of its individual effect) (Nicklisch and Hamdoun, 2020). In a recent literature review on the effects of binary mixtures of pesticides on honey bee, wild bee, and solitary bee toxicity, it was noted that additive and synergistic toxicity were the most common interactions, representing 17 % and 72 % of reported data, respectively (Carnesecchi et al., 2019). One historical example of the synergistic toxicity observed in laboratory and field studies is the interaction between ergosterol biosynthesis inhibiting (EBI) fungicides and neonicotinoids or pyrethroids caused by the fungicide's inhibition of the cytochrome P450 monooxygenase system (Meled et al., 1998; Pilling et al., 1995; Pilling and Jepson, 1993; Tosi and Nieh, 2019). While enhanced toxicity of multi-pesticide combinations toward bees has been thoroughly described and tested in field and laboratory assays (Berenbaum and Johnson, 2015; Carnesecchi et al., 2019; Pal et al., 2022; Siviter et al., 2021; Wade et al., 2019; Wang et al., 2021b; Zhu et al., 2017a; Zhu et al., 2017b), intended and unintended co-exposures to mixtures of pesticide-adjuvant, pesticide-in-hive medicine, and pesticide-environmental chemicals have been less appreciated.

2.3.1.1. Intended chemical mixtures

2.3.1.1.1. Tank mixing of pesticides and adjuvants. Pesticides are often applied in mixtures (known as tank mixing) to control multiple pests and diseases (e.g., an aphid infestation alongside a fungal infection) while reducing the number of trips over a field (Holloway and Western, 2003). Although intentional tank mixing of agrochemicals can be controlled and monitored by applicators, the possible synergistic toxicities of these chemical mixtures on non-target pollinators are not well understood. Toxicity to bees can also increase when pesticides are combined with adjuvants, a common agricultural practice of adding additional compounds like surfactants and oils to boost pesticide absorption and distribution with an eye toward improving their efficacy (Green, 2000; Hazen, 2000; Mullin et al., 2016). In a comparative study of over 1300 wax, pollen, and bee samples from hives across the US and Canada, Mullin and coworkers revealed a notable finding: only 70 % of the targeted pesticide active ingredients were detected in the beehive samples, whereas 100 % of the other sought-after formulation ingredients were present (Mullin et al., 2015). The ubiquitous and concurrent detection of pesticide contaminants and formulation ingredients in the hive environment could facilitate toxic pesticide bioaccumulation and toxicity in bees. Indeed, a 2015 field and laboratory study showed that the broad-spectrum insecticide Fipronil with the added spray surfactant and adjuvant, Sylgard, increased honey bee mortality up to 100 % within 24 h of application (Mayer and Lunden, 2015). Similar adjuvants typically considered biologically inert have also been shown in laboratory studies to promote viral pathogenicity in chronically exposed honey bee larvae (Fine et al., 2017a), enhance viral replication in adults, and impair queen oviposition rates (Fine et al., 2023). More recently, laboratory tests on 30 tank mixtures of different pesticide-adjuvant combinations showed that 50 % of the combinations increased honey bee mortality (Wernecke et al., 2021). In another study, Walker et al. demonstrated that the adjuvant *Dyne-Acmin*, when combined with the fungicide tilt and the insecticide altacor, can result in elevated toxicity levels, attributed to increases in overall toxicity of the pesticide mixture (Walker et al., 2022).

Adjuvants can be added to the pesticide formulation as “inert” ingredients, in which case they are classified as formulation adjuvants, or they can be added separately on top of other formulated products in a tank mix, in which case they are classified as spray adjuvants. Each adjuvant can add a specific characteristic to the formulation or tank mix, therefore multiple adjuvants can be used in the same application to achieve several different functions (reduce drift, increase penetration, increase solubility, increase attachment, increase stability) (Hock, 2022; Wu et al., 2023). Adjuvants are thought to lack inherent pesticidal properties, and federal law exempts spray adjuvants from EPA pesticide registration, leaving them largely unregulated. However, this rule varies by state, and in California the CDPR does require spray adjuvants to be registered as pesticides prior to sale and use (Cox and Zeiss, 2022). Unlike in the EU, where toxicity testing of active ingredients and adjuvants is required to have a 'representative formulation', in the US toxicity testing of pesticide products does not involve inert ingredients such as adjuvants and mainly focuses on active ingredients (Straw et al., 2022). In addition, given the lack of scrutiny and toxicological testing of these "inert" formulation ingredients for lethal and sublethal effects on the reproductive Queen and vulnerable hive members, such as the bee brood, more research is needed to better predict the effects of various pesticide-adjuvant interactions on colony health and survival.

2.3.1.1.2. In-hive medicine. There is a growing body of evidence that in-hive medications applied to treat bee infections and hive infestations can be detrimental to bee health when bees are pre-exposed to other agrochemicals (Mullin et al., 2010; Rangel and Tarpy, 2016; Traver et al., 2018; Traynor et al., 2016). It has been suggested that such unintended co-exposures of agricultural pesticides affect bee colony health directly (by causing acute additive or synergistic toxicity in bees) or indirectly (by sensitizing bees to other xenobiotics). For instance, in a laboratory assay, bees pre-treated with oxytetracycline (OTC), an antibiotic treatment for foulbrood diseases, and sequentially exposed to the acaricide coumaphos, a therapy for mite infestation, experienced a 44 % increase in mean mortality (Hawthorne and Dively, 2011). Likewise, bees fed with OTC and the acaricide tau-fluvalinate exhibited a 33 % increase in mortality. In another laboratory study, researchers found that orally administering fumagillin (an antibiotic used to treat Nosema within hives) together with tau-fluvalinate (an acaricide used to treat varroa mite infestations) can decrease the median LD_{50} by 2-fold compared to sucrose syrup control treatment in exposed honey bees (Johnson et al., 2013).

As such, a precautionary approach accounting for potential synergies between in-hive medications and agrochemicals is prudent to ensure thriving honey bee colonies. Ongoing monitoring of pesticides exposures and a carefully timed application of in-hive medications to avoid simultaneous pesticide exposure may help mitigate interactive toxicity.

2.3.1.2. Unintended chemicals mixtures

2.3.1.2.1. Foodborne toxicities. Arguably the primary route of honey bee exposure to toxic xenobiotics is through ingestion of contaminated pollen and nectar, typically a result of the widespread application, systemic distribution, and environmental persistence of modern insecticides such as neonicotinoids applied to growing crops (Bonmatin et al., 2015; Stoner and Eitzer, 2012; Tosi et al., 2018). Exposures to multiple pesticides at lethal and sublethal concentrations may cause synergistic toxicity across hive members and contribute to colony loss (Biddinger et al., 2013; Farooqui, 2013; Iwasa et al., 2004; Johnson et al., 2010; Levine and Borgert, 2018; Lu et al., 2014; Magal et al., 2019; Magal et al., 2020; Pilling et al., 1995; Pilling and Jepson, 1993; Spurgeon et al., 2016; Thompson et al., 2014; Williamson et al., 2013; Williamson and Wright, 2013). For instance, Zhu and coworkers showed in two separate laboratory studies that when honey bees were exposed to eight different insecticides (imidacloprid, acephate, λ-cyhalothrin, oxamyl, tetraconazole, glyphosate, sulfoxaflor, and clothianidin) in binary combinations, the mixtures showed synergistic toxicity that increased mortality between 15 and 26 % (Zhu et al., 2017a; Zhu et al., 2017b). Notably, when bees were exposed to a mixture of all eight pesticides, the mortality increased to 100 % (Zhu et al., 2017b). Johnson and coworkers performed a similar laboratory study using pairwise combinations of six different acaricides, eight fungicides, three antimicrobials, and three detoxification enzyme inhibitors (Johnson et al., 2013). The group reported synergistic toxicity as median lethal dose (LD_{50}) and observed the highest toxicities for the acaricide tau-fluvalinate in combination with the fungicide prochloraz (LD_{50} = 0.01 mg/bee), the model CYP450 inhibitor piperonyl butoxide or PBO (LD_{50} = 0.01 mg/bee), and the acaricide coumaphos (LD_{50} = 0.78 mg/bee). Tau-fluvalinate also increased toxicity in honey bees pre-treated with different EBI fungicides, including myclobutanil (LD_{50} = 0.121 mg/bee) and metconazole (LD_{50} = 0.452 mg/bee).

2.3.1.2.2. Waterborne contaminants. Unintended co-exposures to water-soluble environmental chemicals, such as *Per*- and polyfluoroalkyl substances (PFAS), is another understudied research area and possible threat to honey bee health. PFAS are a group of persistent organic pollutants (POP) that are ubiquitously found in the environment and are recognized by the EPA as contaminant of emerging concern (CEC) in surface waters (Gluge et al., 2020; Miner et al., 2021; Podder et al., 2021). PFAS are regularly detected in aquatic environments, including wastewater, agricultural runoff waters, rainwater, groundwater, and receiving waters such as rivers, ponds, and lakes (Dauchy et al., 2019; Lin et al., 2014). These forever chemicals have also been shown to move from irrigated soil through roots into plants, including flowering crop plants known to be pollinated by commercial and solitary bees (Navarro et al., 2017; Xu et al., 2022). Honey bees need water as a dietary salt source, as a thinner to prevent honey crystallization, and for thermal homeostasis of the hive during the warm summer months (Butler, 1940; Lau and Nieh, 2016; Nicolson, 2009; Stabentheiner et al., 2021). As such, water consumption could be a significant route of PFAS exposure to honey bees. Indeed, PFAS compounds have been shown to bioaccumulate in different aquatic and terrestrial insects and can be transferred to their predators (Koch et al., 2021; Lan et al., 2020). Recently, Sonter and coworkers showed in a laboratory assay that the major water contaminant perfluorooctanesulfonic acid (PFOS) can accumulate in honey bees and increase mortality, reduce colony defense and maintenance behaviors, and even halt brood development (Sonter et al., 2021). Furthermore, Surma and coworkers showed the presence of perfluoroalkyl substance in honey from various European countries, indicating that bees who undergo the intricate process of producing and storing this natural product within the hive, come into contact with PFAS (da Silva et al., 2016; Surma et al., 2016).

2.3.1.2.3. Airborne toxicities. Bees can also be unintentionally exposed to airborne pesticides, heavy metals, micro- and nano-plastics (also present in water) (Alma et al., 2023; Buteler et al., 2022; Edo et al., 2021), and air pollutant mixtures due to wind drift or when bees are foraging on neighboring crop fields with varying foliar spray applications (Botias et al., 2015; Davis and Williams, 1990; Krupke et al., 2012; Macri et al., 2021; Marzaro et al., 2011; Moffett et al., 1972; Thimmegowda et al., 2020; Ucar and Hall, 2001; Zaric et al., 2018; Zhu et al., 2015). It has been suggested that both airborne particles such as respirable suspended particulate matter (RSPM) and volatile agrochemicals interfere with pest insect and pollinator sensory physiology, chemical and pheromone signaling, and behavior (Gate et al., 1995; Jacobson, 1966; McFrederick et al., 2009). Smoke has been traditionally used by beekeepers to reversibly interfere with the bee's sense of smell and subdue the alarm response (Gage et al., 2018; Visscher et al., 1995). But chemical air pollutant mixtures, such as agriculture and horticulture pesticides, diesel exhaust, and other volatile organic compounds (VOCs) have been shown in field studies to sensitize pollinators to additional stressors and affect crucial pollinator foraging behavior and reproduction (Reitmayer et al., 2019; Samuelson et al., 2018).

2.3.1.2.4. Micro- and nanoplastics. Bees can also incorporate ubiquitous micro- and nanoplastics (MNPs) from a variety of media in the environment and deliver it to multiple hive matrices and members (Alma et al., 2023; Edo et al., 2021). MNP toxicity depends not only the particle size, but also on the type of polymer, and the presence of other chemicals (Al Naggar et al., 2021). For instance, in recent laboratory assays, micro particles of polystyrene have been shown to accumulate in honey bee tissues, and to promote adverse health effects (i.e., decrease gut microbiome diversity, changes in oxidative damage, impaired detoxification and immunity, and reduced lipid metabolism gene expression) when in combination with other pollutants or existing diseases (Alma et al., 2023; Buteler et al., 2022; Deng et al., 2021; Wang et al., 2021a). Further research is needed to better characterize the effects of MNP exposure on a colony level and to elucidate possible synergistic effects with MNP-adsorbed or co-exposed chemicals in the hive environment.

2.4. Sublethal pesticide exposures

The effects of repeated exposures of commercial and wild bee species to low levels of pesticides have traditionally been underestimated. Sublethal exposure has been shown to interfere with the colony's survival, performance, winterization, behavior, development, and physiology (Barron, 2015; Bryden et al., 2013; Dively et al., 2015; El Hassani et al., 2008; Fine, 2020; Hatjina et al., 2013; Ingram et al., 2015; Lu et al., 2014; Negi et al., 2022; Williamson et al., 2014; Wu et al., 2011; Wu et al., 2022; Xavier et al., 2015). Specifically, delayed larval development and adult emergence, downregulation of detoxification enzymes, and shortened worker bee longevity have been identified as added stressors that impact a colony's fitness and survival (Fisher et al., 2021; Glass et al., 2021; Smodis Skerl et al., 2009; Tome et al., 2020; Wu et al., 2011).

2.4.1. Learning and memory impairment

Low-dose exposures have also been shown to cause direct neurological effects in bees, including decreased memory and learning performance. For instance, honey bee exposure to sublethal concentrations of the neonicotinoids thiamethoxam and thiacloprid in field studies caused an increase in mortality and affected the ability of forager bees to navigate home (Henry et al., 2012; Tison et al., 2016). Thiamethoxam was also shown in two other field studies to alter honey bee and bumble bee feeding rates, motor skills, and visual learning (Laycock et al., 2014; Ludicke and Nieh, 2020). As a result, sublethal studies triggered a re-evaluation of thiamethoxam which led to its eventual banning in Europe for application to flowering plants (Stokstad, 2018). Acute laboratory exposure of bees to sub-lethal doses of the organophosphate in-hive acaricide coumaphos impaired short-term (10 min) and long-term (24 h) memory in response to a conditioned olfactory stimulus (Williamson et al., 2013), while environmentally-relevant subchronic treatment of bees over four days with either coumaphos or the neonicotinoid imidacloprid resulted in degraded olfactory learning and memory (Williamson et al., 2014). Using the proboscis extension response (PER) assay, Decourtye and coworkers found that worker bees exposed in the laboratory to sublethal concentrations of fipronil, deltamethrin, endosulfan, and prochloraz showed reduced learning performance (Decourtye et al., 2005). Since associative learning of odor, color, and shape of flowers with essential food sources such as pollen and nectar is an important behavior of foraging bees (Hammer and Menzel, 1995), the disruption of this vital sense through chronic exposure to sublethal concentrations of pesticides could both threaten colony survival and disturb the pollination services in the ecosystem.

2.4.2. Disruption of chemical communication

Laboratory assays examining low-level pesticide exposure have also demonstrated that chronic exposure can interfere with the production and quality of queen mandibular pheromone (QMP), thereby impacting communication between the hive and queen bee, affecting labor, queen-rearing suppression, and colony cohesion (Bortolotti and Costa, 2014; Milone and Tarpy, 2021; Rangel and Tarpy, 2016; Walsh et al., 2020). Laboratory pesticide exposures also affect chemically guided worker bee retinue behaviors toward the queen, which usually promotes attenuating, grooming, and trophallaxis (Litsey et al., 2021). Indirect effects of low-level pesticide exposures in the laboratory have also been shown to cause glandular degeneration and impact the nutritional quality and quantity of royal jelly produced by nurse bees (Milone et al., 2021), which can have dire consequences for adequate provisioning of queen bees and healthy colony maintenance.

2.4.3. Disturbance of gut microbiome

Exposure to low levels and mixtures of agricultural pesticides have also been shown to affect gut bacterial colonization of larval, newly emerged, and adult honey bees (Almasri et al., 2022; Motta and Moran, 2020; Motta et al., 2018; Vazquez et al., 2023). Furthermore, exposure to commonly used in-hive medicine has been shown to affect honey bee microbiome structure and function (Kakumanu et al., 2016). Altering the bee gut microbiota, including core species like *Snodgrassella alvi*, *Gilliamella apicola*, *Lactobacillus Firm-4*, *Lactobacillus Firm-5*, and *Bifidobacterium asteroids*, can have detrimental effects on bee development, metabolism, immunity, and behavior (Daisley et al., 2020; Kwong and Moran, 2016; Motta and Moran, 2023). However, to date only a few pesticides have been tested for their effects on honey bee and wild bee microbiomes at either sub-lethal or environmentally relevant concentrations, and more research is needed to better understand the impacts on the host's immune system and overall health (Hotchkiss et al., 2022).

2.4.4. Cumulative multi-stressor effects

Finally, sublethal pesticide exposure to larval and adult bees already battling pathogens may also have synergistic detrimental effects. For instance, Doublet and coworkers found in laboratory assays that honey bee larvae exposed to sublethal doses of the neonicotinoid thiacloprid in conjunction with Black Queen Cell Virus (BQCV) have a lower survival rate (65 %) than the control (90 %) or exposure to just thiacloprid (80 %) or the virus (85 %) (Doublet et al., 2015). In a similar way, Pettis and coworkers showed in field studies with three brood generations that sublethal exposure to the pesticide imidacloprid sensitized honey bee colonies toward increased infections with the *Nosema* gut pathogen (Pettis et al., 2012).

Chronic exposure to multiple agricultural chemicals, even at low sublethal doses, can negatively impact honey bee health. At the colony level, these sublethal effects can reduce productivity and increase susceptibility to disease and parasites, ultimately leading to higher mortality. While testing myriad potential mixtures of real-world residues in a laboratory setting poses challenges related to scope and analytical detection limits, the integration of innovative computer-aided approaches for individual bee monitoring, coupled with sensitive trace chemical analysis techniques will be essential for developing a holistic understanding of sublethal and toxic effects resulting from chemical mixtures within bee hives.

2.5. Toward improved understanding of chemical fate and toxicity in bee colonies

Pesticides in the U.S. are regulated by the Environmental Protection Agency (EPA) to ensure the safety of humans, pollinators, and other non-target organisms (EPA, 2014; EPA, 2016a, 2016b). A plethora of pesticides have been approved for U.S. agricultural crops, often applied in mixtures to combat several pests at once. Globally, according to the FAOSTAT statistics (https://www.fao.org/faostat) of the Food and Agriculture Organization (FAO) of the United Nations, between 1990 and 2021 herbicides were the largest applied pesticide class (by tons), followed by fungicides in second place, and insecticides in third. In contrast to Europe, where in 2021 fungicides were the most applied pesticide class, in the US herbicides continue to dominate the market for agricultural use. The pesticide classes most associated with honey bee and other pollinator toxicity are neonicotinoids, pyrethroids, carbamates, organophosphates, and the phenylpyrazole Fipronil (Cressey, 2017; Johnson et al., 2010; Pisa et al., 2015; Sanchez-Bayo, 2014;

Sanchez-Bayo and Goka, 2014).

Historically, most evaluations of pesticide toxicity toward bees are based only on tests evaluating the effects of direct contact and oral exposures of adult bees or larvae to a single compound (Maus et al., 2022). Furthermore, assessments of pesticide hazards toward honey bee colonies by calculating a Hazard Quotient (HQ) or Risk Quotient (RQ) from pesticide application rate divided by the acute adult bee LD_{50} values often produce poor correlation results between field application rates and actual pesticide residues reaching the individual colony members (Carlson et al., 2022; Drummond et al., 2018; Mu et al., 2022; Thompson, 2021). These methods were initially developed for foliar spray applications and assume that the combined total bee exposure from all routes (oral, contact, air) is directly related to the pesticide application rate. Due to a lack of residue-level validation studies, predicting effects of agrochemical exposure using these methods is hampered by the fact that dietary and contact exposure pathways during bee developmental stages are different (i.e., capped brood versus roaming adult bees).

The eusocial system within a honey bee hive forms another underexplored dimension of developmental and caste-specific exposure risks and interindividual chemical transfer and mixing that needs to be considered when evaluating effects of agrochemicals. Furthermore, within the hive, wax functions as the structural foundation for both present and future hive occupants, serving not only as their habitat but also as a repository for stored food. Its hydrophobic nature makes it an ideal sink for lipophilic environmental pollutants. However, there is a limited body of research exploring wax as a possible route of developmental exposure and the toxicity of contaminated wax across the diverse members of the hive. A major limitation to performing these studies is the fact that chemical concentrations in small samples such as eggs and larvae are typically below the detection limit of standard analytical methods. In addition, it is technically still challenging to determine the chemical-specific diffusion or transfer rates from the wax into larvae and other hive members to develop estimates of exposure (Alkassab et al., 2022; Kast and Kilchenmann, 2022; Murcia Morales et al., 2020; Wilmart et al., 2021).

Modern isotope tracing analysis techniques, such as accelerated mass spectrometry (AMS), that use stable radiolabeled chemicals to detect trace levels of multiple chemical compounds and their metabolites, can lower the detection capabilities to quintillion levels (10^{-18} mol) and sample size to milligrams (Enright et al., 2016; Kutschera, 2016; Nnane and Tao, 2005). This technique has shown its capability to do accurate quantification of parent pesticide and metabolite distribution in Argentinian ant colonies (Hooper-Bui et al., 2015). However, to our knowledge, to date no AMS studies have been performed on honey bees. An additional challenge to track chemical contaminant flow between hive members is the need to clearly identify and monitor individual bees and their interactions.

Artificial intelligence (AI)-based automated monitoring of insects using computer vision systems (Bjerge et al., 2021; Gernat et al., 2023; van Klink et al., 2022) is a promising, emerging technology in the field of animal behavior studies and could provide a new avenue to study parent compound and metabolite transfers within and across honey bee hive members. Such AI-guided systems could facilitate monitoring the interactivity of individual bees, including trophallaxis and behavior, and – in combination with the sensitive AMS technology – could aide in the prediction of contaminated food flow, deposition, and the effects on colony survival.

3. Conclusions

Honey bees are exposed to complex chemical mixtures in their natural habitat that can significantly threaten colony health and survival. Although this article focuses on the honey bee hive superorganism and its interactions with chemicals, it is worth remembering that chemical exposure is not exclusive of commercial pollinators and more research needs to be done in unmanaged pollinator species, such as wild bumble bees and solitary bees, where the species survival can be entirely dependent on one individual. Levels and composition of these chemical mixtures may vary during the year and over time due to crop-specific pesticide application schedules and chemical degradation rates. Identifying levels and the metabolic fate of trace amounts of chemicals as they are processed, transferred, and stored within different organismal and physical checkpoints of the hive will be necessary to identify and apply appropriate mitigation strategies such as comb replacement (for physical sinks) or requeening (for biological sinks).

Based on the available literature, sublethal impacts on factors such as learning, immunity, and colony productivity can have substantial consequences for bee health at the colony level. Additionally, synergistic interactions between the multiple active and inert ingredients in commercial pesticide formulations and tank mixes may alter toxicity but are not fully captured in single active ingredient assays. To enhance protection of bees from pesticide-related harm, more research investigating sublethal endpoints across exposure scenarios at the individual and colony levels is needed. Continuing development of field-realistic chronic toxicity protocols, evaluation of pesticide mixtures, and increased use of semi-field and field studies can help ensure the intricate effects of toxicants are fully considered.

A fundamental understanding of the combined effects of the chemical mixtures on bees is crucial for addressing the complex and evolving challenges posed by multiple chemical exposures in their natural environment. This will require adopting modern tracing analysis techniques and artificial intelligence-based monitoring to better understand possible cumulative and synergistic effects of chemical mixtures, especially within the hive's social structure at field realistic concentrations. This comprehensive approach aims to achieve a fundamental understanding of chemical fate in hives for safeguarding honey bee health and colony survival in the face of diverse and changing chemical threats.

CRediT authorship contribution statement

Angela M. Encerrado-Manriquez: Writing – review & editing, Writing – original draft, Visualization, Methodology, Data curation, Conceptualization. **Amara K. Pouv:** Writing – review & editing, Writing – original draft, Conceptualization. **Julia D. Fine:** Writing – review & editing, Writing – original draft, Validation, Resources, Investigation, Funding acquisition, Conceptualization. **Sascha C.T. Nicklisch:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declared no competing interests in this work.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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