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Neurotoxic Effects of Agrochemicals on Honeybee Nervous System

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Abstract
Honeybees (Apis mellifera) are chronically exposed to complex mixtures of agrochemicals that can impair brain function at levels much lower than those that kill them rapidly. Neonicotinoid and sulfoximine insecticides act on the nicotinic acetylcholine receptor. Organophosphates, carbamates and pyrethroids however act on acetylcholinesterase or voltage-gated ion channels. The chemicals interfere with the balance between excitatory and inhibitory signalling, calcium homeostasis, and energy metabolism in the bee brain. These molecular modifications affect synaptic remodelling and signalling in specific brain regions such as the antennal lobes, mushroom bodies and the central complex. This makes learning, remembering, navigating, processing visual information, sleeping and your body's natural rhythms harder. Contaminated pollen, nectar and wax can lead to sublethal exposure, altering neuropeptide profiles, immunity and stress responses. This makes people more susceptible to pathogens and increases neurotoxicity. At the colony level, these problems at the individual level manifest themselves in less efficient feeding, loss of brood, queen failure, increased cannibalism among larvae, and slower colony growth and overwinter survival. But most pesticide risk assessments today don't consider the long-term neurobehavioral effects from mixtures, focusing instead on the immediate lethality of single compounds. This review summarises mechanistic and colony scale information regarding the deleterious effects of agrochemicals on honeybee brains. It also identifies key knowledge gaps that need to be addressed for pollinator-safe pest management.

Keywords: *Apis mellifera, Voltage-Gated Ion Channels, Neurotoxicity, Neurobehavioral Effects, Effects of Agrochemicals etc.*

I. Introduction

Honeybees (Apis mellifera) are also important pollinators supporting natural ecosystems and world food production. Many flowering plants and major crops are helped to reproduce by them. However, over the last 20 years, beekeepers and researchers have observed large declines in colony numbers and performance, especially in areas of intensive agriculture [1]. We now know that these losses are driven by multiple interacting factors, including parasites, pathogens, poor nutrition, habitat loss and chronic exposure to agrochemicals. In modern agriculture, pesticides and other crop-protection products are used everywhere, and they are particularly dangerous because they are designed to attack the nervous systems of insects.

Field and laboratory studies have demonstrated that honeybees are commonly exposed to a wide variety of insecticides, fungicides, herbicides and adjuvants through contaminated nectar, pollen, honey, water, wax and dust. They are often exposed to concentrations that are "sublethal" on an individual basis, but may still alter their behaviour and physiology. Neonicotinoids and other insecticides target nicotinic acetylcholine receptors, whereas organophosphates, carbamates and pyrethroids target acetylcholinesterase or voltage-gated ion channels [2]. These chemicals have a huge effect on the brains of insects by changing the way that neurones fire and send signals to each other. There is growing evidence that these neuroactive agrochemicals impair bees' ability to learn, remember, navigate, communicate and organise their social lives. This can affect not only individual workers but the dynamics of the colony as a whole and the long-term survival of the population.

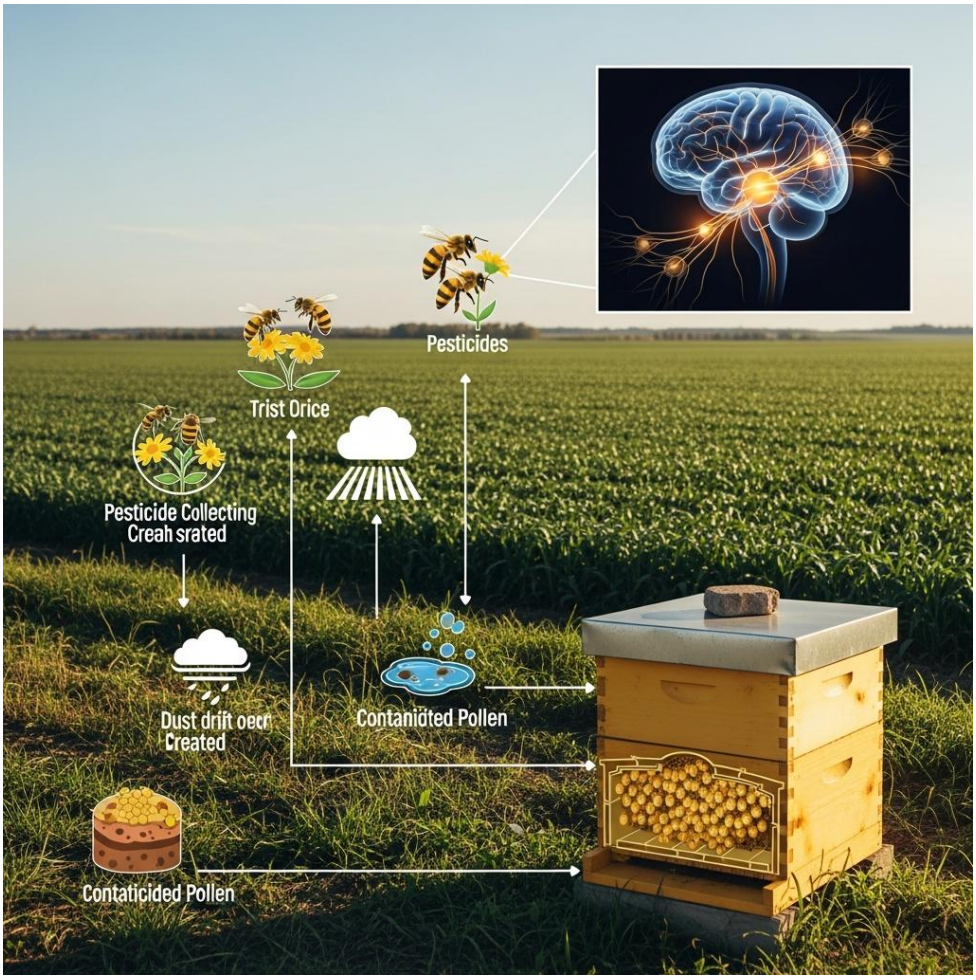

Figure 1: Honeybee Landscape Concept, Source: Canva Generated

This paper addresses the neurotoxic effects of major classes of agrochemicals on the honeybee nervous system. It connects the molecular mechanisms with the behavioural and colony-level effects that matter for pollinator-safe farming.

II. The honeybee nervous system: main regions Neurotoxicity Important

The honeybee nervous system consists of a small brain in the head and a ventral nerve cord with segmental ganglia that control motor skills, senses and social habits. The brain is organised into main nerve bundles. These are the antennal lobes (primary olfactory centres), the visual lobes (lamina, medulla, lobula) for vision, the gnathal ganglion for taste, and higher order integration centers like the mushroom bodies and central complex [3]. The antennal lobes contain some 160 glomeruli. These are sites where olfactory receptor neurones synapse on to projection neurones and local interneurons. This is the first level of smell coding that happens here before the information is sent to the mushroom bodies and the lateral horn.

The sense and associative areas of the honeybee brain contain nicotinic and muscarinic acetylcholine receptors. Acetylcholine is the principal fast excitatory transmitter. Histochemical localisation of acetylcholinesterase shows that there are many cholinergic synapses in the antennal and optic lobes, the gnathal ganglion, the mushroom bodies and the central complex. That is a measure of how important cholinergic signalling is for smelling, seeing, learning and controlling movement [4]. The Kenyon cells of the mushroom bodies, which receive cholinergic input from the antennal lobe projection neurones, are very important for learning and remembering smells.

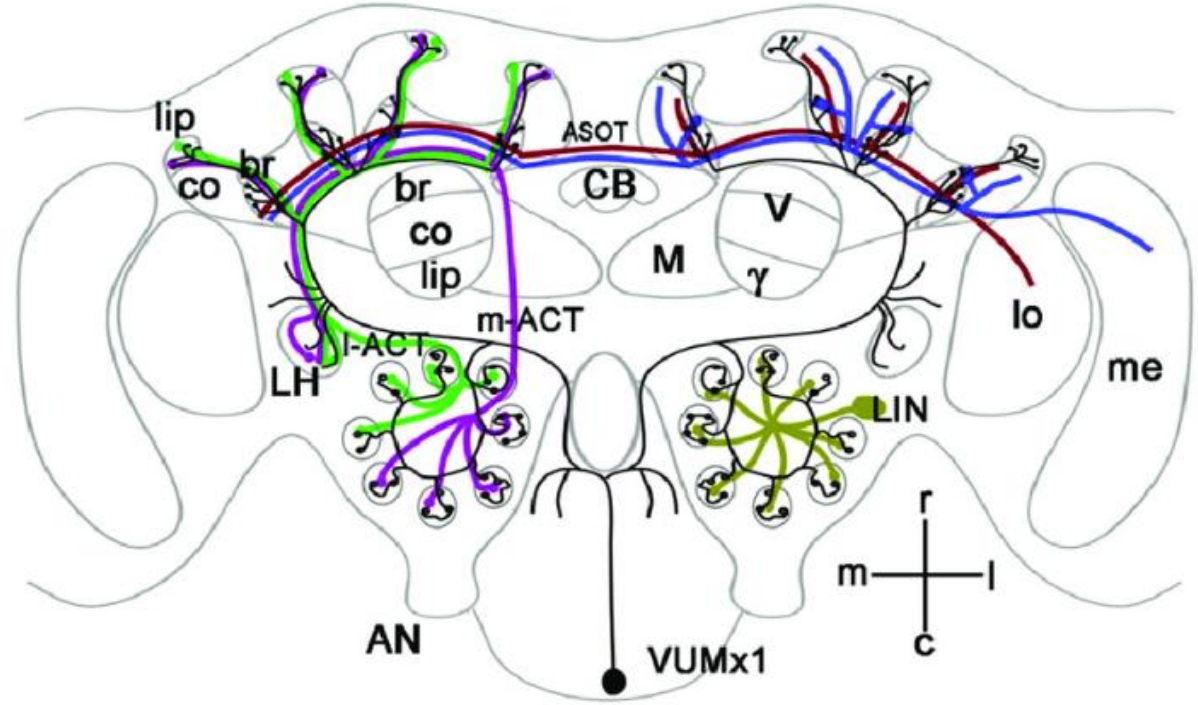

Figure 2: Dorsal and Lateral Views, Source: https://www.researchgate.net/figure/Schematic-view-of-the-visual-and-olfactory-pathways-in-the-honey-bee-mushroom-body-calyx_fig12_49785514

In contrast, the central complex combines visual and mechanosensory cues to help the bird during flight to navigate and maintain balance. "Neonicotinoids, organophosphates, carbamates and other agrochemicals act specifically on nicotinic receptors or on acetylcholinesterase [5]. These cholinergic circuits are the most likely targets for honeybee brains to be harmed by pesticides.

III. Main types of agrochemicals and the molecules act

Many of the pesticides that are used today to protect crops have direct effects on important parts of the honeybee nervous system, mainly cholinergic receptors, acetylcholinesterase and voltage-gated ion channels [6]. Neonicotinoids and related compounds act on and activate nicotinic acetylcholine receptors (nAChRs), while organophosphates and carbamates inhibit acetylcholinesterase (AChE), the enzyme that terminates cholinergic transmission. Pyrethroids keep voltage-gated sodium and, in some bee neurones, calcium channels open for longer. Some fungicides can make them much more poisonous by blocking the enzymes which detoxify them. Fungicides and pesticides are not generally designed to be neurotoxins, but some of them work together very well to make insecticides more neurotoxic to bees that are exposed to them.

Class	**Representative compounds**	**Primary molecular target in bees**	**Key neural/behavioural effects reported**
Neonicotinoids / sulfoximines	Imidacloprid, clothianidin, thiamethoxam, sulfoxaflor	Agonists at nicotinic acetylcholine receptors	Persistent depolarisation, altered Ca^{2+} signalling, impaired learning, navigation and sucrose
Organophosphates	Chlorpyrifos, coumaphos, dimethoate	Irreversible inhibition of acetylcholinesterase	ACh accumulation, tremors, abdominal spasms, impaired motor function and righting
Carbamates	Aldicarb and metabolites	Reversible AChE inhibition	Sublethal motor impairment, altered grooming and behaviour, AChE up-regulation as compensatory
Pyrethroids	Deltamethrin, lambda-cyhalothrin	Prolonged opening of voltage-gated Na^+ (and Ca^{2+}) channels	Neuronal hyperexcitability, cardiotoxicity, paralysis, acute worker
Fungicides (EBI group)	Propiconazole, prochloraz, tebuconazole	Inhibit cytochrome P450 monooxygenases (detox pathways)	Strongly increase toxicity of pyrethroids and some insecticides to beespmc.
Herbicides / others	Glyphosate, various adjuvants	Diverse: metabolic, gut microbiota and indirect neural effects	Subtle alterations in navigation, microbiome, stress tolerance

Table 1: *Main agrochemical classes, targets and key neurotoxic effects in honeybees, Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC7246883/*

3.1 Neonicotinoid Compounds and Similar Bug Killers

Neonicotinoids like imidacloprid, clothianidin, thiamethoxam, and thiacloprid, and the sulfoximine pesticide sulfoxaflor are very efficient at binding to nAChRs located in insect antennal lobes, mushroom bodies and optic lobes. Patch-clamp and calcium imaging experiments demonstrate that imidacloprid and clothianidin depolarise Kenyon cells and increase intracellular calcium, sometimes producing even larger currents than natural acetylcholine [7]. Chronic exposure to field-realistic amounts alters expression of nAChR subunit genes and stress-response pathways in brains of bees. This is associated with olfactory learning deficits, reduced response to sucrose, navigational deficits and higher mortality especially in winter bees [17].

3.2 Carbamates and Organophosphates

Chlorpyrifos, coumaphos (organophosphates) and aldicarb (carbamate) are harmful since they inhibit the activity of AChE. Thus, acetylcholine can accumulate in synapses and nAChRs and muscarinic receptors remain active for longer. Biochemical assays of honeybee head and gut tissues demonstrate that active oxon metabolites of chlorpyrifos and coumaphos are potent inhibitors of AChE. These chemicals also cause an increase in AChE-2 transcripts in bees exposed to these chemicals. Sublethal exposure to the AChE inhibitor alters behaviour by increasing the number of grooming sessions, abdominal spasms, regurgitation and decreasing the righting response and general motor performance [8]. Even if the animal does not die straight away, these changes could make it harder to find food and less likely to survive.

3.3 Voltage-Gated Ion Channel Modulators and Pyrethroids

Pyrethroids, which mainly act on voltage-gated sodium channels, include deltamethrin and lambda-cyhalothrin. These are kept open, making the action potentials last longer and causing insect neurones to fire again and again. Experiments on isolated honeybee brain cells show that deltamethrin also impacts T-type voltage-gated calcium channels. This results in sustained increases in intracellular calcium, which can lead to excitotoxic damage and loss of function [9]. At the organismal level, pyrethroids cause knockdown, tremors, cardiotoxic effects and rapid worker mortality upon contact with treated crops. They also cause sudden poisonings occurring in agricultural settings.

3.4 Fungicides, herbicides and synergism

EBI fungicides, including propiconazole, prochloraz, difenoconazole and tebuconazole, inhibit the cytochrome P450-dependent monooxygenases that normally detoxify insecticides, making pyrethroids much more toxic to honeybees. Lab and semi-field tests indicate that lambda-cyhalothrin mixed with EBI fungicides can reduce the LD_{90} for bees by >10-fold. For example, propiconazole lowered the LD_{90} of lambda-cyhalothrin from 68.0 nanograms per bee to 4.2 nanograms, a 16.2:1 synergistic ratio [10]. Herbicides like glyphosate are not primarily targeting neural targets, however chronic exposure has been associated with small alterations in navigation, gut bacteria and stress tolerance which may interact with neuroactive pesticides to adversely affect colony health [18].

Insecticide	Co-applied fungicide(s)	Mechanistic basis of synergy	Observed outcome in bees
Lambda-cyhalothrin	Propiconazole (EBI fungicide)	Inhibition of P450-mediated detoxification of pyrethroid	LD_{50} reduced from 68.0 to 4.2 ng per bee (synergy ratio ≈16.2)
Lambda-cyhalothrin	Prochloraz, tebuconazole, others (EBI group)	Broad P450 inhibition, impaired metabolism	Strong increase in acute mortality, cardiotoxic effects in semi-field
Various insecticides	Multiple fungicides in mixtures	Combined metabolic and physiological stress	Elevated worker losses and higher risk of poisoning incidents near treated

Table 2: Examples of synergistic interactions relevant to bee neurotoxicity, Source: https://www.semanticscholar.org/paper/Synergism-between-EBI-fungicides-and-a-pyrethroid-Pilling-Jepson/f8008d95d218f4907aa07889a10121ed836a1936

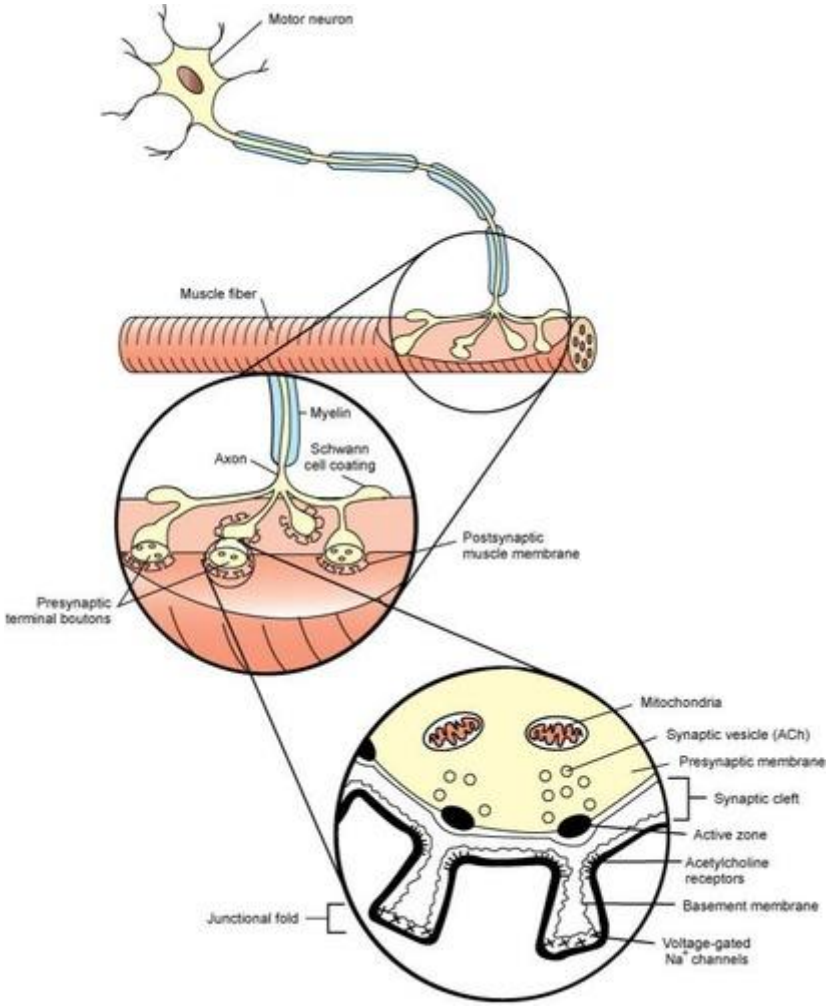

Figure 3: Multi‑panel mechanistic figure, Source:https://quizlet.com/ca/375436894/neuroscience-exploring-the-brain-4th-ed-chapter-3-the-neuronal-membrane-at-rest-diagram/

IV. Neurophysiological and behavioural effects: non-lethal

Even at doses below the levels that would kill them, agrochemicals can have serious effects on the brains and behaviour of honeybees, often in ways that are difficult to detect in normal toxicity tests. Neonicotinoids and other cholinergic poisons interfere with the excitatory-inhibitory balance, calcium homeostasis, and energy metabolism of the bee brain [16]. This makes it harder for the bees to learn, remember, navigate, keep track of time, and communicate with other bees. Other chemicals and mixtures change neuropeptides, immunity and stress response pathways which in turn affects how neurones function and how well they are equipped to cope with challenges that they encounter in their environment [19, 20].

4.1 Memory, Learning, and Mushroom Plasticity

Associative smell learning and memory mainly take place in mushroom bodies. Mushroom bodies are rich in nicotinic acetylcholine receptors, which facilitate synaptic changes during foraging related experiences [21]. Sublethal neonicotinoid exposure overstimulates these receptors, resulting in excess calcium entering Kenyon cells, less activation of memory-related transcription factors such as CREB and CaMKII, and synapse problems or neural death over time. Immunolabelling and morphometric studies indicate that low doses of imidacloprid can reduce the number of microglomeruli in the mushroom body calyces in a time-dependent manner. This means that synaptogenesis is slower and structure is less flexible [11].

Bees exposed to field-realistic doses of neonicotinoids or sulfoxaflor take more training trials to learn smell-reward associations in the proboscis-extension response paradigm. They also have worse memory recall at 24 hours [22]. When bees are treated, they don't always select the flowers that smell good to them. Instead, they visit a wider variety of flowers, which don't produce as much nectar, limiting the colony's ability to find food and eat pollen and nectar. These learning and memory deficits are therefore a major way in which neurotoxic agrochemicals harm colony performance, without causing overt mortality [12].

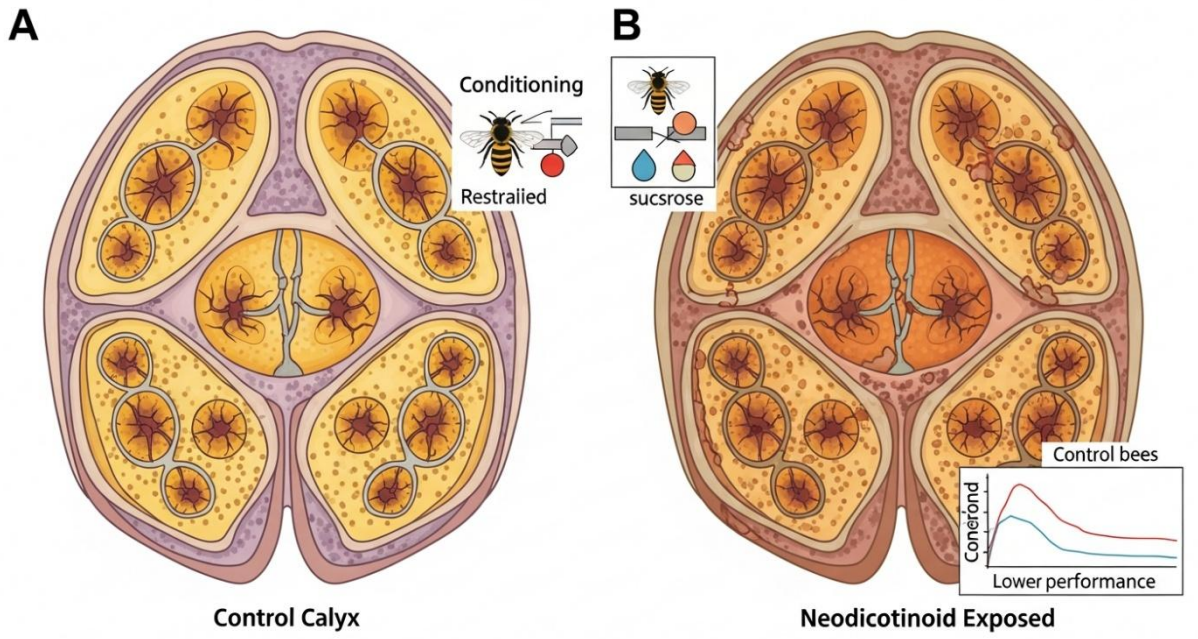

Figure 4: Side‑by‑side schematic of mushroom bodies from control versus neonicotinoid‑exposed honeybees, Source: Canva Generated

4.2 Sleep, Circadian Rhythms and Clock Neurones

The circadian clocks in honeybees regulate their food searching behaviour, amount of sleep and the way they communicate. Clock neurones are light sensitive via cholinergic pathways that are sensitive to neonicotinoids. Bees eating thiamethoxam or clothianidin at levels found in their environment accumulate the chemicals in their brains. This disrupts the circadian rhythms of many foragers and advances the phase of bees whose locomotor rhythms remain rhythmic. In bees, light exposure causes a delay of activity offset after the lights are turned off and an increase of activity during the night. This indicates that the wake-promoting clock neurones are hyperactive and that the internal clocks of the bees are out of synchrony with the light–dark cycle [13].

Neonicotinoid-treated beetles also slept less and for shorter periods of time. This is a form of chronic sleep deprivation that is known to affect learning, memory and accurate navigation. Circadian rhythm and sleep problems are expected to decrease the effectiveness of time compensated sun-compass tracking and temporal precision of waggle dance communication. This reduces the probability of foraging success and the probability that foragers will not return to the hive. Risk assessments of traditional pesticides only consider measures of acute mortality and therefore easily overlook these effects, which occur at doses that do not kill immediately.

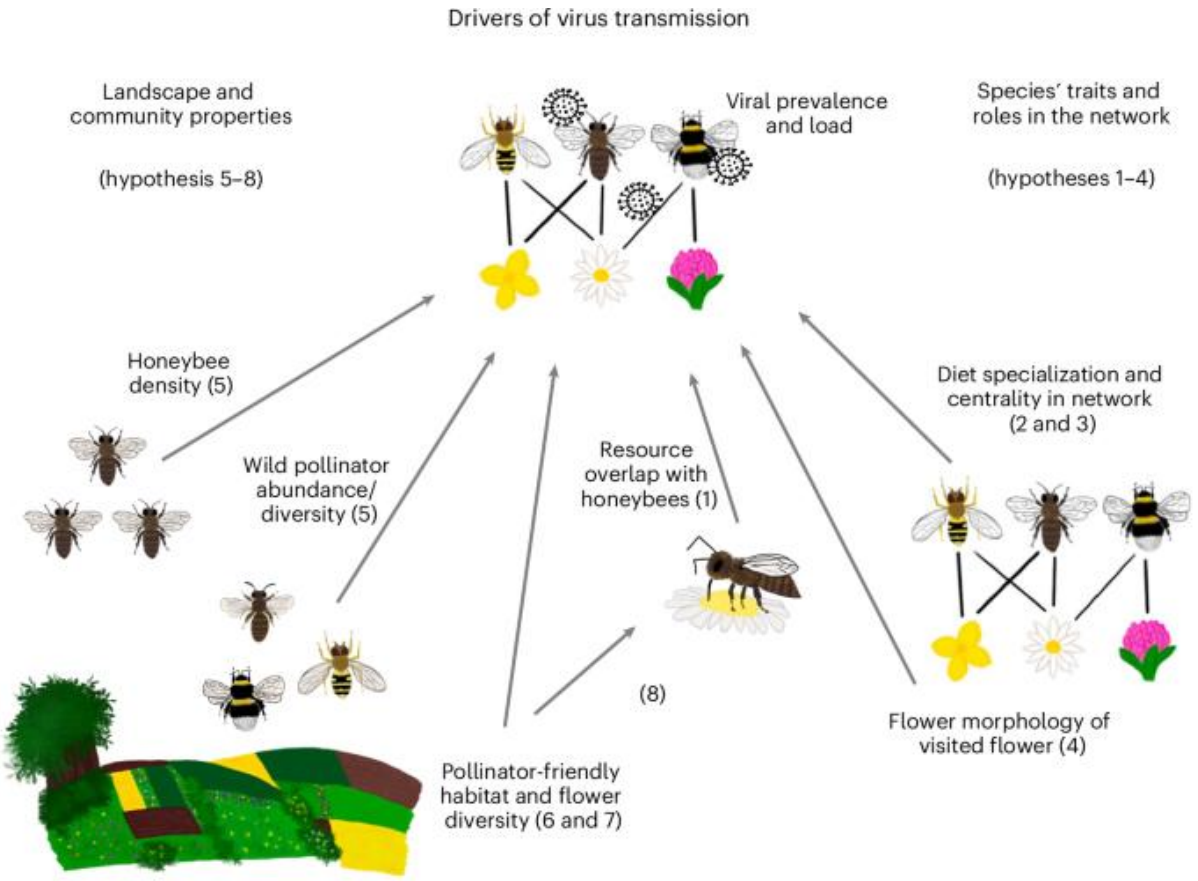

Figure 5: Conceptual figure of the honeybee circadian system,
*Source:*https://www.nature.com/articles/s41559-024-02555-w

4.3 Stress and Neuropeptides, Immune-Neural Crosstalk and Weight Loss

Pesticides can alter more than the levels of hormones in the brain. They can also change the levels of neuromodulators and neuropeptides that control things like eating, how we respond to stress, and our behaviour with other people. Some herbicides and pesticides change the expression of genes. Alterations occur in genes that make detoxification enzymes and stress proteins. They also alter the function of antioxidants and metabolic enzymes in bee cells exposed to high doses or chronic exposure [14]. Such molecular changes suggest that the body is experiencing oxidative and metabolic stress. This can damage neurones and connections, and make the body less able to cope with problems in the outside world.

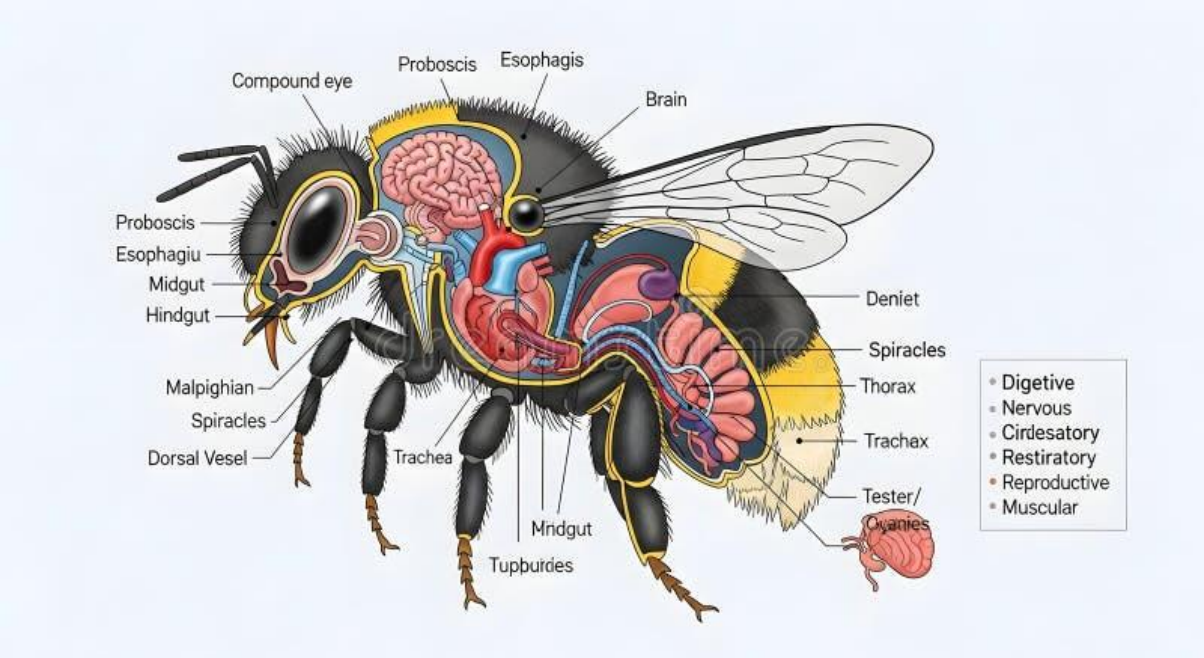

Figure 6: Network‑style diagram of a honeybee silhouette with internal organs and brain, Source: https://www.dreamstime.com/detailed-diagram-bee-s-head-thorax-cross-section-highlighting-internal-detailed-diagram-bee-s-head-thorax-image391596994

Some diseases are more likely to occur in people who are exposed to low levels of pesticides, such as Nosema spp. Bees raised in colonies where the food has low levels of imidacloprid have a lot more parasites, even though they don't have any of the parent drug in their bodies. Infections and pesticides stimulate the immune system and the energy they consume may worsen neurotoxicity, further limiting brain activity and function. Changes in honeybee feeding, regulation of body temperature, social interaction and colony strength after chemical exposure could be due to problems with neuromodulatorysignalling and immune-neural crosstalk.

V. Development impact of the level of the colony

5.1 Hordes, Queens and the Extension of Social Disruption

Eusocial honeybee colonies rely on a long-lived queen to reproduce constantly. Problems at these stages can destabilise the entire colony. Feeding colonies pollen with realistic amounts of fungicides (chlorothalonil, propiconazole) and insecticides (chlorpyrifos, fenpropathrin) causes them to lose a lot more brood, have more larvae that eat each other, and have more queen events (supersedure, loss) than controls, even though the individual pesticide doses are considered "sublethal." In colonies fed pollen containing pesticides, queen rearing is less successful, with a lower probability of queens emerging and reduced viability of their sperm [15]. This means that queens are not able to reproduce as well and their offspring are not as healthy. Further research on beeswax tainted with pesticides reveals that the residues can be harmful to the queen's health and alter the function of pheromones, reducing the likelihood of workers appearing and laying eggs, which in turn affects the colony's ability to stay together and be productive. If workers are stressed a lot they may eat their own brood more often, this is a normal reaction to disease or a lack of protein. This indicates chronic nutritional and toxicological stress in the hive.

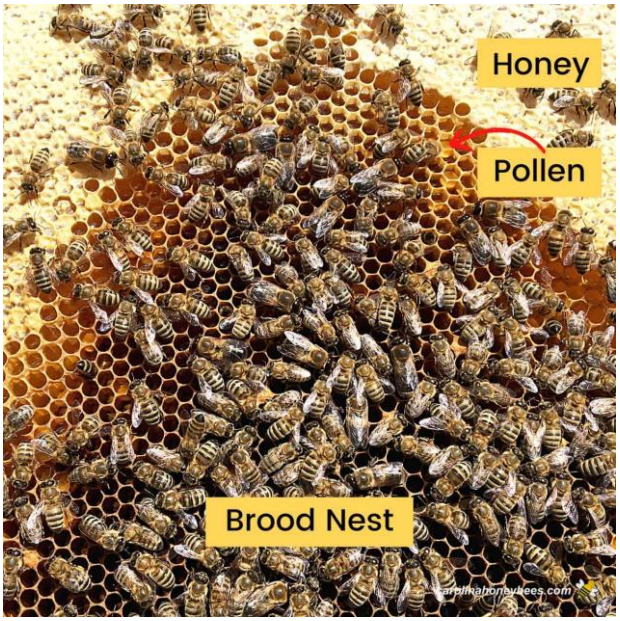

Figure 7: Cutaway diagram of two beehive brood frames, Source: https://carolinahoneybees.com/bee-brood-box/

5.2 Foraging, Survival and Population Trends Performance

Exposure to neonicotinoids over two brood cycles has been shown to reduce the number of adult workers by approximately 28% and the number of brood by 13% at the colony level. Pollen collection and honey production also reduced by 19–29%. Studies on semi-fields and feeder experiments demonstrate that colonies exposed to neonicotinoids have reduced foraging levels, reduced persistence at rewarding food sources and weaker recruitment to profitable patches overall [16]. This indicates that individual-level behavioural problems lead to colony-level reductions in foraging performance. Such short-term drops in workers and food stores slow colony growth and may worsen winter losses if they occur in conjunction with other stresses. Non-lethal pesticides are linked to more queen deaths, fewer swarms and less spring buildup in the long term. This suggests that agrochemicals may not kill all colonies immediately but may rather gradually weaken them and increase the risk of collapse.

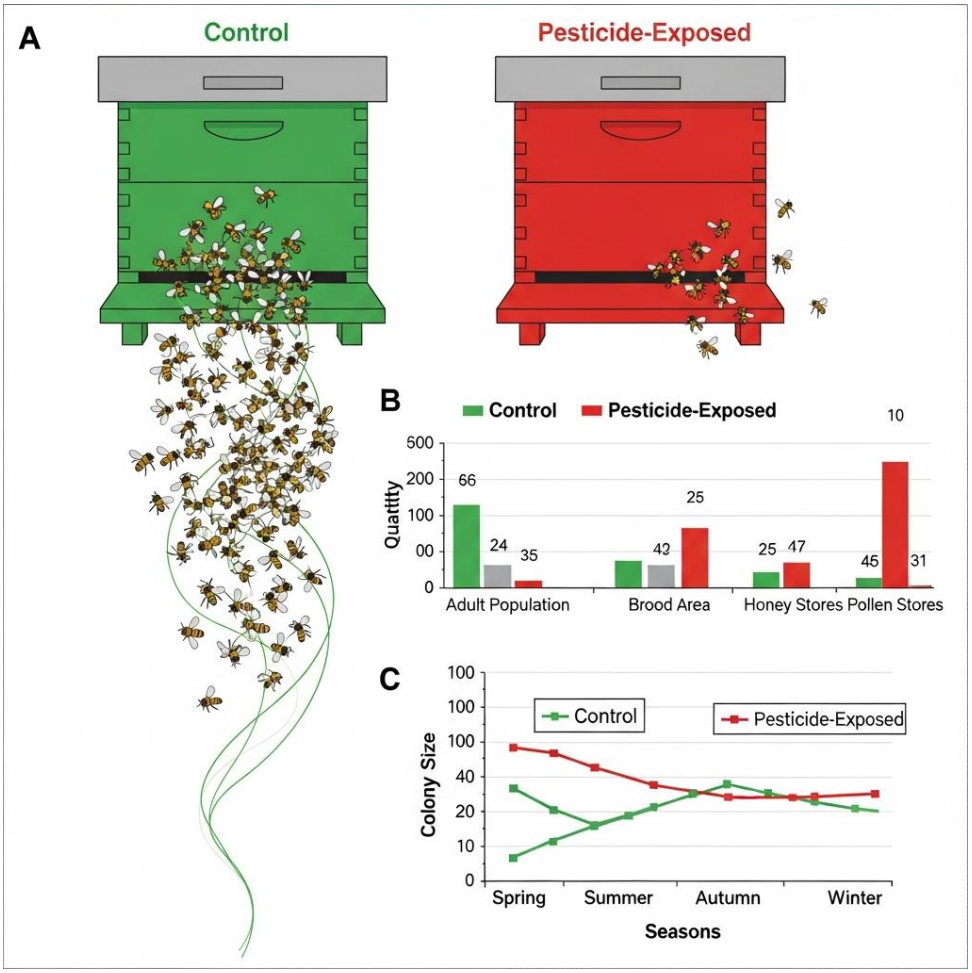

Figure 8: Three -panel infographic for a Hive, Source: Canva Generated

VI. Knowledge gaps and their meaning

While research in this area is rapidly expanding, there remain considerable questions regarding the long term, low dose effects of agrochemical mixtures on honey bee neurobiology, behaviour and colony dynamics in the field. Most of the experimental data come from testing a few insecticides (mostly neonicotinoids) on adult workers in simple lab conditions [23]. But over 70% of approved pesticides do not have strong sublethal data and almost all of them do not have information on how they affect bees when used in combination or together. It is still challenging to determine how to measure the links between certain molecular end-points (e.g. altered nAChR expression or neuropeptidome changes) and well-known conservation goals such as colony strength, overwinter survival, and pollination services. This makes it harder to incorporate them in regulatory risk assessment [24].

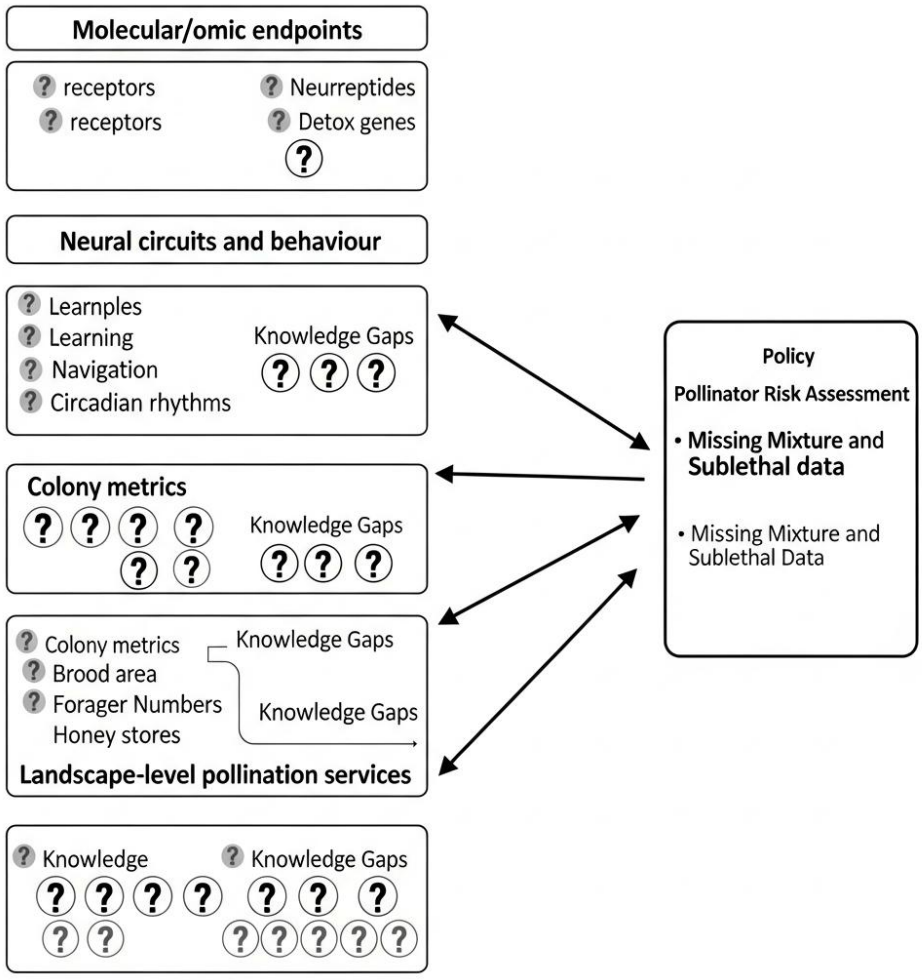

Figure 9: Knowledge Gap Framework, Source: Canva Generated

The current rules for registration of pesticides are still heavily based on acute LD_{90}s for each drug. Tests for sublethal neurobehavioural endpoints, life-stage sensitivity, or binary and higher order mixtures of agrochemicals and biological stressors are limited. Most of the chemical mixtures studied exhibit synergistic or more-than-additive toxicity. These interactions are generally not taken into account when determining how much exposure is "safe" for bees. To fill these gaps, we need to do combined research that looks at mixture toxicity on a range of scales from the molecular to colony level and change regulations so that long-term neurobehavioral outcomes and mixture data are at the center of protecting pollinators.

VII. Conclusion

The many different harmful effects of the agrochemicals used in modern agriculture on the honeybee nervous system often act together to cause greater damage. These effects affect cholinergic receptors, acetylcholinesterase, voltage-gated ion channels and stress response pathways in general. Even if exposures are not technically "lethal," they can still impair learning, memory, navigation, circadian rhythms, brood care, and queen performance. This may result in slowing colony growth, increased overwinter mortality and reduced pollination services. Risk assessment frameworks should not rely solely on acute mortality tests, as there is limited information on long-term and mixed effects. They need to look at neurobehavioral endpoints, development, realistic multi-chemical exposures. Meanwhile, farming needs to move towards integrated pest and pollinator management with fewer neuroactive compounds.

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