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Impacts of Novel Insecticides on *Apis cerana indica*: Ecotoxicological, Behavioural, and Molecular Perspectives

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Abstract

Honey bees play a vital role in pollination, biodiversity maintenance, and agricultural productivity. In Asia, *Apis cerana indica* is a key pollinator with unique ecological and behavioural traits, yet its responses to novel insecticides remain underexplored. This review synthesizes current knowledge on the ecotoxicological, behavioural, biochemical, and molecular impacts of emerging insecticide classes, including neonicotinoids, sulfoximines, butenolides, diamides, and afidopyropen. Evidence highlights both acute and chronic toxicity, with sublethal effects such as impaired foraging, navigation, learning, and communication that compromise colony health and pollination efficiency. Biochemical and molecular studies reveal alterations in detoxification enzymes, oxidative stress biomarkers, and gene expression, suggesting species-specific vulnerabilities compared to *Apis mellifera*. Field-realistic exposures further demonstrate the persistence of risks posed by pesticide residues and synergistic interactions with pathogens, fungicides, and nutritional stressors. However, critical gaps remain in chronic toxicity data, mechanistic insights, and multi-stressor evaluations. Addressing these gaps through standardized protocols, comparative studies, and long-term monitoring will aids to improve risk assessments and to formulate effective Integrated Pest and Pollinator Management strategies. Such approaches are essential to balance agricultural productivity with pollinator conservation and ecosystem resilience.

***Key words*:** *Apis cerana indica*, Novel insecticides, Sublethal effects, Detoxification enzymes, Pollination services, Risk assessment

Honey bees are among the most important pollinators, providing essential ecosystem services and contributing significantly to agricultural productivity and global food security. In Asia, *Apis cerana indica*, the Asiatic honey bee, plays a pivotal role in sustaining biodiversity and crop pollination, often outperforming *Apis mellifera* in local foraging efficiency and resilience to environmental conditions [1]. However, increasing reliance on synthetic insecticides in modern agriculture has intensified concerns about pollinator safety and sustainability. Research on the ecological and mechanistic impacts of novel insecticides on *Apis cerana indica* has emerged as a critical area of inquiry due to the essential role of honey bees in pollination services, agricultural productivity, and ecosystem stability [2-3]. Since the 1990s, the widespread use of systemic insecticides such as neonicotinoids has been closely associated with pollinator declines, as their persistence in nectar and pollen exposes bees to harmful residues [4-5]. More recently, alternative chemistries including sulfoximines, butenolides, afidopyropen, cyantraniliprole, and flupyradifurone have been introduced, yet concerns remain about their effects on non-target species [6-7]. The recognition of pollinators' importance for food security and ecosystem balance has therefore driven research from acute toxicity assessments to more complex evaluations of sublethal and synergistic impacts on bee behaviour, physiology, and colony health [8-9].

Despite extensive toxicological studies, significant knowledge gaps remain regarding the specific impacts of these insecticides on *A. cerana indica*, particularly at colony and population levels [10-11]. Sublethal endpoints such as impaired foraging, reduced brood development, and altered flight ability are less understood and often underrepresented in current risk assessments [2], [12]. Comparative studies indicate differential sensitivity between *A. cerana* and *A. mellifera*, with conflicting evidence as to which species is more vulnerable [13-14]. Biochemical and molecular responses, including detoxification enzyme activities, immune functions, and gene expression changes, have also been insufficiently compared, limiting mechanistic understanding of species-specific vulnerabilities [15-16]. Furthermore, pesticide mixtures and interactions with environmental stressors such as pathogens and nutritional stressors, may produce additive, synergistic, or antagonistic effects, complicating accurate risk assessments [17-18].

The conceptual framework for this review integrates ecotoxicology, bee biology, and mechanistic toxicology to elucidate how insecticide exposure affects colony health,

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pollination services, and population viability in *A. cerana indica*. Key themes include pesticide toxicity profiles, lethal and sublethal behavioural responses, biochemical markers such as detoxification enzymes, molecular endpoints including modulation of gene expression, and physiological impairments mediated by interactions with nicotinic acetylcholine receptors (nAChRs) [6], [19-20]. By synthesizing findings from laboratory, semi-field, and field studies, this review seeks to clarify comparative sensitivities between *A. cerana* and *A. mellifera*, identify existing research gaps, and evaluate the broader ecological consequences. The ultimate goal is to inform pollinator-friendly pest management strategies and strengthen risk assessment frameworks that balance agricultural productivity with pollinator conservation [21-22].

Classification of novel insecticides

Neonicotinoids

Neonicotinoids, including imidacloprid, clothianidin, thiamethoxam, and dinotefuran, consistently induce marked toxicity and behavioural disruptions in honey bees. In *Apis cerana indica*, imidacloprid exposure was shown to reduce foraging activity, climbing ability, sucrose responsiveness, and colony growth, alongside significant impairments in olfactory learning and memory in both larvae and adults [2], [13], [23]. Additionally, sublethal effects include impaired foraging behaviour and cognitive functions, loss of postural control and increased grooming behaviour, which could hinder foraging efficiency, which can lead to decreased colony performance and survival rates [3], [24]. Comparative assessments reported higher LC_{50} values for imidacloprid in *A. cerana* than *A. mellifera* (3.044 vs. 1.76 mg/L), with corresponding behavioural dysfunctions [13]. Residue-based evaluations further confirmed neonicotinoid persistence and acute toxicity, with mortality ranking clothianidin > thiamethoxam > imidacloprid and concomitant reductions in colony development and vigor [3], [10]. Enantioselective analysis revealed greater susceptibility of *A. cerana* to the toxic S-form of dinotefuran, while thiamethoxam exposure was associated with altered flight performance and dysregulation of energy metabolism genes, suggesting prolonged foraging impairment [25-26].

Sulfoximines

Sulfoxaflor, the principal compound among sulfoximines, exhibits pronounced acute and chronic toxicity in honey bees. Comparative bioassays identified it as one of the most toxic insecticides to *Apis mellifera* workers, eliciting significant biochemical, physiological, and behavioural disruptions [21], [27]. Exposure to sulfoxaflor induced marked alterations in enzyme activity, oxidative stress responses, and histopathological damage, including degeneration of brain and midgut tissues [28]. Developmental impairments were also reported in larvae, manifesting as wing deformities and abnormal pupal morphology and behavioural assays demonstrated disrupted optomotor and orientation responses in bees exposed to sulfoxaflor and imidacloprid, indicating interference with neural signaling and sensory integration [29-30]. Transcriptomic and molecular investigations further revealed modulation of detoxification and immune-related genes, along with altered expression of nicotinic acetylcholine receptor (nAChR) subunits, providing mechanistic insight into the observed neurobehavioural deficits [31-32]. Moreover, synergistic interactions between sulfoxaflor exposure and *Nosema ceranae* infection significantly elevated mortality, highlighting its role in immunotoxic stress [33]. Recent studies have also developed novel sulfoximine derivatives with modified binding affinity for bee nAChRs, resulting in reduced toxicity in *A. mellifera* [18].

Butenolides

Flupyradifurone, a systemic butenolide insecticide, exhibits both lethal and sublethal effects across different honey bee species. Sublethal exposure in *Apis cerana* resulted in approximately 20% mortality, accompanied by impaired olfactory learning and memory in both larval and adult stages, though long-term foraging activity remained unaffected [23]. In *A. mellifera*, exposure led to decreased survival and body weight, elevated oxidative stress markers, and apoptosis in neural and midgut tissues, indicating strong physiological stress responses [34-35]. Differential sensitivity was observed in nurse bees and larvae, with neuronal apoptosis and immune gene modulation evident in nurse bees under acute oral exposure [36]. Proteomic and biochemical analyses revealed alterations in larval metabolism and immune pathways, potentially delaying development and compromising resilience [37]. Behavioural assays identified motor impairments, particularly among winter bees, suggesting seasonal modulation of toxicity [38-39]. Interestingly, co-exposure studies demonstrated that bergamot polyphenolic fractions could mitigate flupyradifurone-induced oxidative stress and behavioural abnormalities, improving survival outcomes [40]. At the molecular level, docking simulations revealed binding affinity to bee nicotinic acetylcholine receptors (nAChRs), yet with comparatively low receptor activation, consistent with reports that field-realistic exposures seldom impaired foraging or survival [41-43], [19].

Pyrethroids and fipronil

Pyrethroid insecticides are synthetic derivatives of natural pyrethrins, which are extracted from the flowers of the *Chrysanthemum cinerariaefolium*. These compounds are widely utilized in agriculture and pest control due to their effectiveness against a broad spectrum of insect pests [44]. Comparative assessments indicate that pyrethroids are generally less toxic to honey bees than neonicotinoids, with thiamethoxam causing higher oral mortality under simulated field exposure, while *Apis mellifera* remained particularly sensitive to nitro-substituted neonicotinoids [45]. Earlier studies reported that pyrethroids were less acutely toxic than organophosphates and carbamates in *Apis cerana indica*, though susceptibility varied among compounds [46]. Studies on pesticide exposure highlighted that fipronil and neonicotinoids pose major risks to *A. cerana indica* and other native bees, leading to hive contamination and impairments in physiology and behaviour, with *A. cerana* exhibiting greater sensitivity to several pesticides including fipronil [47-48].

Fipronil exposure induces significant behavioural and physiological disruptions in honey bees, including impaired olfactory learning, agitation, tremors, abnormal grooming, and reduced homing ability that collectively compromise foraging efficiency and colony stability [49-51]. Physiologically, fipronil reduces the motor activity and causes lethargy, while at the molecular level, it downregulates genes related to the circadian clock and juvenile hormone, indicating interference with developmental and metabolic regulation [51-52]. Although its detrimental effects are well documented, some studies suggest that honey bees exhibit partial resilience to moderate exposure, suggesting complex interactions among pesticide stress, detoxification mechanisms, and environmental conditions [52].

Diamides and afidopyropen

The anthranilic diamides cyantraniliprole and tetraniliprole provide examples of systemic insecticides with pronounced developmental and chronic effects in honey bee larvae. These compounds primarily disrupt calcium homeostasis by modulating of ryanodine receptors, affecting muscle and neural excitability, and leading to locomotor deficits, neurotoxicity, and, in severe cases, mortality [53-54]. Cyantraniliprole exposure in *A. mellifera* larvae increased mortality rates and reduced growth indices, reflecting heightened developmental vulnerability under chronic exposure [29].

At the metabolic level, diamide exposure alters carbohydrate catabolism, proteolysis, and amino acid transport, disrupting energy and nutrient metabolism essential for larval growth and development [55-56]. Neurotoxic effects arise from impaired acetylcholinesterase activity and oxidative stress, further compromising neural transmission and sensory integration [53]. Additionally, diamides can perturb developmental regulation by modulating hormone and gene expression pathways involved in molting and metamorphosis, and by inducing structural damage to gut and other tissues, collectively delaying larval maturation [56]. Although the effects of cyantraniliprole and tetraniliprole are less extensively studied than neonicotinoids, their overlapping mechanisms like calcium dysregulation, neurotoxicity, and metabolic disruption underscore the potential for chronic and developmental impacts on honey bee health and highlight the need for further targeted research.

Afidopyropen, a TRPV channel modulator caused significant mortality in *A. cerana* after prolonged exposure, accompanied by altered detoxification enzyme activity, physiological stress, and nutritional deficiencies, indicating colony-level risks despite minimal observed long-term foraging impairment [57].

Baseline toxicity studies

Baseline toxicity studies form the foundation for understanding how different classes of insecticides affect the native honey bee, *A. cerana indica*. These studies establish reference toxicity levels that help evaluate species sensitivity, determine safe exposure limits, and guide integrated pest and pollinator management strategies. As *A. cerana indica* plays a crucial role in pollinating both wild and cultivated flora across Asia, assessing its response to novel insecticides is essential for sustainable agricultural practices. Baseline evaluations typically include acute and chronic toxicity assessments, comparative interspecific sensitivity analyses, and field-realistic exposure trials. Together, these data provide critical insights into how pesticide residues interact with bee physiology and behaviour, forming the basis for risk assessment and pollinator protection frameworks.

Acute oral and contact toxicity

Baseline toxicity data provide essential insights into the sensitivity of *Apis cerana indica* and related species to novel insecticides. Neonicotinoids such as imidacloprid, clothianidin, and thiamethoxam consistently demonstrate high oral and contact toxicity in *Apis cerana indica*, resulting in reduced colony survival and growth [2-3]. *Apis cerana* larvae exhibit greater susceptibility than adults to imidacloprid exposure [23], and comparative studies reveal that *Apis cerana* experiences higher mortality under chlorpyrifos exposure than *Apis mellifera*, underscoring interspecies differences in sensitivity [58]. Neonicotinoids primarily act as nicotinic acetylcholine receptor (nAChR) agonists, with imidacloprid showing high acute oral toxicity but relatively lower contact toxicity, reflecting its potency via ingestion [29], [59]. Similarly, flupyradifurone, though designed to reduced non-target toxicity, shares a comparable nAChR-mediated mechanism and can still impair bee health under chronic exposure [6]. In contrast, diamides such as cyantraniliprole and tetraniliprole target ryanodine receptors, disrupting calcium signaling and affecting muscle and neural function, though they are generally less acutely toxic to non-target organisms. Fipronil, acting through GABA receptor antagonism, exhibits broad-spectrum toxicity, posing particular risks to aquatic organisms and birds, with notable sub-lethal effects in vertebrates [60].

Chronic exposure studies

Chronic exposure to pesticides often induces prolonged sublethal effects that undermine honey bee health and colony resilience. Long-term exposure to neonicotinoids such as thiamethoxam, imidacloprid, and flupyradifurone has been shown to disrupt energy metabolism, impair flight performance, and reduce overall colony strength in both *Apis mellifera* and *Apis cerana indica* [2], [25], [39]. These collectively indicate that chronic neonicotinoid exposure compromises physiological and behavioural functions essential for colony maintenance.

Chronic thiamethoxam exposure reduces flight duration and distance by over 50%, impairing foraging and navigation efficiency [61-62]. Similarly, prolonged imidacloprid exposure decreases metabolic rate, alters nutritional physiology, and depletes energy reserves, ultimately affecting bee health and endurance [55], [63]. Although specific evidence on flupyradifurone is limited, studies indicate comparable neurophysiological effects, consistent with those of other neonicotinoids [39].

Continuous dietary exposure to afidopyropen, acetamiprid, or propiconazole has been linked to elevated mortality and nutritional stress in *A. cerana*, with synergistic combinations accelerating mortality in newly emerged bees [64], [57]. Chronic exposure to these compounds significantly diminishes survival rates and colony strength over time, with combined pesticide residues often producing additive or synergistic toxicity [63], [65]. Sublethal imidacloprid exposure induces histopathological alterations in queen ovaries, potentially reducing fertility and compromising colony development [66]. These reproductive impairments, coupled with reduced brood rearing and worker longevity, result in measurable declines in colony productivity and survival [67-68]. Chronic pesticide exposure collectively disrupts brood production, adult bee populations, and foraging efficiency, ultimately leading to weakened colonies and ecosystem instability. However, not all neonicotinoids exert equal toxicity, highlighting complex interactions between pesticide type, concentration, and bee species sensitivity [57].

Comparative sensitivity between bee species

Multiple studies emphasize the differences in sensitivity among honey bee species. *Apis cerana* generally exhibits higher susceptibility to insecticides than *Apis mellifera*, as evidenced by higher mortality and behavioural impairment, underscoring the need for species-specific risk assessments [70-72], [23]. Comparative evaluations show that *Apis cerana* is less sensitive to imidacloprid and thiamethoxam but more sensitive to acetamiprid compared to *Apis mellifera* [73]. Broader analyses further reveal that *Apis cerana* is approximately an order of magnitude more sensitive to most pesticides, including neonicotinoids, suggesting a lower toxicity threshold [48]. Oral toxicity studies demonstrate consistently lower LD_{50} values in *Apis cerana* than in *Apis mellifera*, suggesting greater

vulnerability to ingestion-based exposure routes [74]. Specifically, the acute oral LD_{50} for chlorpyrifos was 81.8 ng/bee in *Apis cerana* versus 103.4 ng/bee in *Apis mellifera*, confirming its greater sensitivity to organophosphates [70]. These interspecific differences highlight that toxicity assessments relying solely on *Apis mellifera* may underestimate the risks faced by native Asian species like *Apis cerana indica*. Consequently, tailored conservation and pesticide management strategies are essential to protect *Apis cerana* populations in regions with intensive agrochemical use [71-72], [81].

Table 1 Acute and chronic toxicity of novel insecticides on *Apis cerana indica*

Insecticide class	Representative compounds	Exposure type	Key effects	Reference(s)
Neonicotinoids	Imidacloprid, Thiamethoxam, Clothianidin	Oral/Contact	Reduced foraging, impaired memory, colony decline	[2], [13], [23]
Sulfoximines	Sulfoxaflor	Oral	Oxidative stress, brain/midgut damage, immune gene alteration	[28-29], [32]
Butenolides	Flupyradifurone	Oral/Chronic	Impaired olfactory learning, neuronal apoptosis, oxidative stress	[34], [36], [23]
Diamides	Cyantraniliprole, Tetraniliprole	Larval/Chronic	Calcium homeostasis disruption, delayed development	[53], [69]
Afidopyropen	Afidopyropen	Chronic	Altered detox enzymes, physiological stress	[57]

Field-realistic exposure scenarios

Laboratory-derived LD_{50} values often underestimate real-world risks, as field studies reveal continuous low-dose pesticide exposure for *A. cerana indica* colonies in agricultural landscapes [3]. Even at field-realistic concentrations, neonicotinoids and related compounds such as flupyradifurone can impair essential behaviours, including climbing ability and sucrose responsiveness, despite showing limited acute toxicity under laboratory conditions [41], [13].

Sublethal and behavioural effects

Sublethal effects of novel insecticides on *A. cerana indica* encompass behavioural changes, biochemical disruptions, and molecular responses that do not immediately cause death but can impair colony health, reproduction, and pollination efficiency.

Foraging behaviour impairment

Foraging activity is markedly impaired by insecticide exposure across multiple studies. Imidacloprid and other neonicotinoids (clothianidin, thiamethoxam) were shown to significantly reduce foraging efficiency and colony growth in *A. cerana indica*, with concurrent declines in brood development [2-3]. Similar sublethal effects on foraging performance have also been reported in *A. mellifera* under neonicotinoid exposure [76].

Navigation and orientation

Sublethal exposure to neonicotinoids and sulfoximines, such as sulfoxaflor, has been shown to disrupt visual and navigational functions in *A. mellifera*, impairing optomotor responses and visual motion detection [30]. Thiamethoxam and imidacloprid were identified as particularly disruptive to navigation and memory, inducing hyperactive flight behaviour and dysregulation of energy metabolism genes that may lead to long-term deficits in foraging efficiency [25].

Learning and memory

Learning and memory are among the most consistently impaired sublethal endpoints across insecticide exposures. Sublethal doses of imidacloprid, clothianidin, flupyradifurone, and sulfoxaflor significantly disrupted olfactory and visual learning in *A. cerana* and *A. mellifera*, with larvae often more susceptible than adults [31], [10], [71-72]. Moreover, *A. cerana* exhibited greater cognitive impairments than *A. mellifera* under chlorpyrifos exposure, emphasizing species-specific vulnerability [70].

Social behaviour and communication

Sublethal insecticide exposure can impair behaviours critical for colony-level communication. In *Apis cerana*, imidacloprid reduced climbing ability and sucrose responsiveness, affecting trophallaxis and recruitment [13], while in *Apis mellifera*, flupyradifurone altered sucrose responsiveness and induced motor disabilities, particularly in winter bees, potentially disrupting social coordination within colonies [41], [39].

Table 2 Behavioural sublethal effects of novel insecticides

Behaviour affected	Compound/Class	Effect description	Reference(s)
Foraging activity	Imidacloprid, Thiamethoxam	Reduced foraging frequency and colony growth	[2-3]
Navigation	Thiamethoxam, Sulfoxaflor	Disrupted visual orientation and flight ability	[25], [30]
Learning/memory	Imidacloprid, Flupyradifurone	Impaired olfactory learning and memory	[71-72]
Social communication	Imidacloprid, Flupyradifurone	Altered sucrose responsiveness, reduced trophallaxis	[13], [39]

Behavioural sublethal endpoints

Behavioural alterations are often the earliest indicators of insecticide stress in honey bees. Sublethal neonicotinoid exposure consistently reduces foraging activity and colony growth in *Apis cerana indica* and other species, with ecological relevance demonstrated under field conditions [2-3], [78]. Acute oral exposure to thiamethoxam and imidacloprid further impairs homing, flight, and olfactory learning in both adults and larvae, while combined pesticide exposures reduce flight duration and distance [71-72], [74]. Additional behavioural endpoints, including agitation, decreased proboscis extension, and impaired sucrose responsiveness, have also been reported across multiple studies [13], [77].

Insecticide sensitivity thresholds

Thresholds for behavioural and physiological responses are essential for defining safe exposure limits to insecticides. *A. cerana* is generally more sensitive than *A. mellifera* to neonicotinoids, chlorpyrifos, and pyrethroids, as reflected in lower LC_{50} and LD_{50} values [58], [76], [79], with thiamethoxam

and imidacloprid exhibiting particularly narrow safety margins [11]. Behavioural assays, along with contact and oral bioassays, are therefore critical tools for establishing these sensitivity thresholds for regulatory and risk assessment purposes.

Methodological rigor and endpoint diversity

Research on sublethal effects employs diverse methodologies ranging from field exposure studies to controlled laboratory bioassays. Behavioural endpoints are assessed using flight mill assays, olfactory conditioning, and foraging monitoring [12], [75]. Biochemical and molecular endpoints involve enzyme assays, transcriptomics, RNA interference, and metabolomic profiling [13], [18], [15]. Combining these approaches strengthens the understanding of multi-level responses to novel insecticides and provides comprehensive insights into colony health risks.

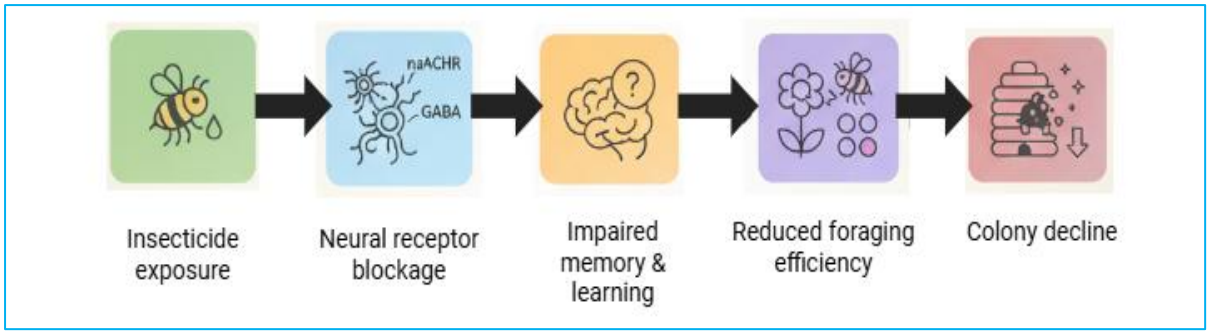

Fig 1 Effect of insecticide exposure on bees

Biochemical and molecular responses

Novel insecticides induce a range of biochemical and molecular alterations in *Apis cerana indica* and related species, which influence detoxification capacity, stress response, immunity, and overall survival. These responses are critical for understanding mechanisms underlying insecticide sensitivity and resilience.

Biochemical response profiles

Changes in biochemical profile provide critical insights into the physiological stress induced by insecticides, with detoxification and oxidative stress enzymes such as cytochrome P450s (CYP450), glutathione S-transferases (GST), carboxylesterases (CarE), catalase (CAT), superoxide dismutase (SOD), and acetylcholinesterase (AChE) commonly used as biomarkers. Sublethal exposure to imidacloprid decreased P450 and CarE activity in *A. cerana*, while GST activity remained unaffected [13], and chronic exposure to acetamiprid or propiconazole modulated P450, GST, and CAT without altering AChE [65]. Oxidative stress biomarkers, including SOD, CAT, and xanthine oxidase, were upregulated under pesticide stress, indicating activation of antioxidant defenses [80]. Pesticide mixtures further influenced enzyme activities, with sublethal dose of imidacloprid reducing AChE and GST in larvae [82] and fungicide mixtures disrupting gut microbiota while upregulating detoxification and immunity-related enzymes [83].

Molecular gene expression changes

Molecular studies have elucidated the gene-level mechanisms underlying biochemical and behavioural responses to insecticides, highlighting detoxification, immune, and neural receptor genes as key targets of sublethal stress. Chronic exposure to acetamiprid or difenoconazole modulated detoxification, immunity, and neural receptor genes in *Apis cerana* [18], while RNA interference of the AccCYP6A13 gene reduced detoxification enzyme activity and increased pesticide sensitivity, confirming its functional role in chemical defense [15]. Sublethal imidacloprid exposure downregulated metabolism and immune genes [13], and novel P450 genes induced by pesticides were shown to enhance survival, with RNAi silencing increasing mortality. Transcriptomic changes under glyphosate exposure revealed enrichment in longevity pathways, indicating herbicide-specific molecular stress responses [84]. Multifactorial stress studies, including sulfoxaflor combined with additional stressors, further demonstrated alterations in survival and gene expression [32], supporting the role of detoxification systems and target-site residues as critical determinants of pesticide susceptibility [82].

Integration of biochemical and molecular responses

Integrating biochemical assays with molecular analyses offers a comprehensive view of insecticide effects, as changes in enzyme activity are often reflected by corresponding gene expression patterns, indicating coordinated detoxification and stress response mechanisms. Transcriptomic, metabolomic, and RNAi studies demonstrate that regulation of detoxification and immunity genes underpins resilience to pesticide stress [79], [15]. Understanding these biochemical and molecular responses is therefore essential for defining sensitivity thresholds, refining risk assessments, and developing strategies to mitigate adverse impacts on honey bee populations.

Table 3 Biochemical and molecular responses in *Apis cerana indica* under pesticide stress

Endpoint	Affected enzyme/gene	Direction of change	Compound(s)	Reference(s)
Detoxification	CYP450, CarE ↓; GST ↔	Reduced detox capacity	Imidacloprid	[13]
Oxidative Stress	SOD, CAT, XO ↑	Increased oxidative response	Multiple insecticides	[80]
Acetylcholinesterase	AChE ↓	Neural disruption	Imidacloprid	[82]
Detox gene expression	AccCYP6A13 ↑	Enhanced resistance response	Acetamiprid, difenoconazole	[15]
Immune pathways	Defensin, PPO genes ↓	Reduced immunity	Imidacloprid	[13]
Longevity pathways	FOXO, mTOR ↓	Reduced lifespan	Glyphosate	[84]

Ecological and environmental implications

Environmental contamination provides multiple routes for honey bee exposure to insecticides, including contaminated nectar, pollen, water, wax, soil, and air. Systemic compounds move through plant tissues into floral resources, while contact occurs via spray drift, dust from seed treatments, and residues on vegetation and hive surfaces. Chronic exposure is further amplified by contaminated water sources and persistent residues within hive matrices, affecting both adult and larval stages. Beyond direct toxicity, sublethal effects on learning, navigation, and foraging behaviour can reduce brood production, colony strength, and pollination efficiency. These impacts cascade to broader ecological consequences, including altered plant reproduction, lower crop yields, and disruption of pollination networks. Such findings underscore the need for integrated risk assessments and management strategies that account for environmental persistence, exposure pathways, and species-specific sensitivity to safeguard pollinators and ecosystem services.

Colony health metrics

Colony-level studies demonstrate that insecticides can reduce brood area, impair reproduction, and increase mortality in *A. cerana indica*. Neonicotinoid residues and chronic exposures to sulfoxaflor and other insecticides have been associated with decreased brood area, higher mortality, reduced colony growth, and impaired foraging performance [86-88]. Combined stressors, including insecticides with nutritional limitations or fungicide mixtures, further disrupt colony development, immune responses, and gut microbiota, compromising overall colony resilience even when acute mortality is low [81-83], [89].

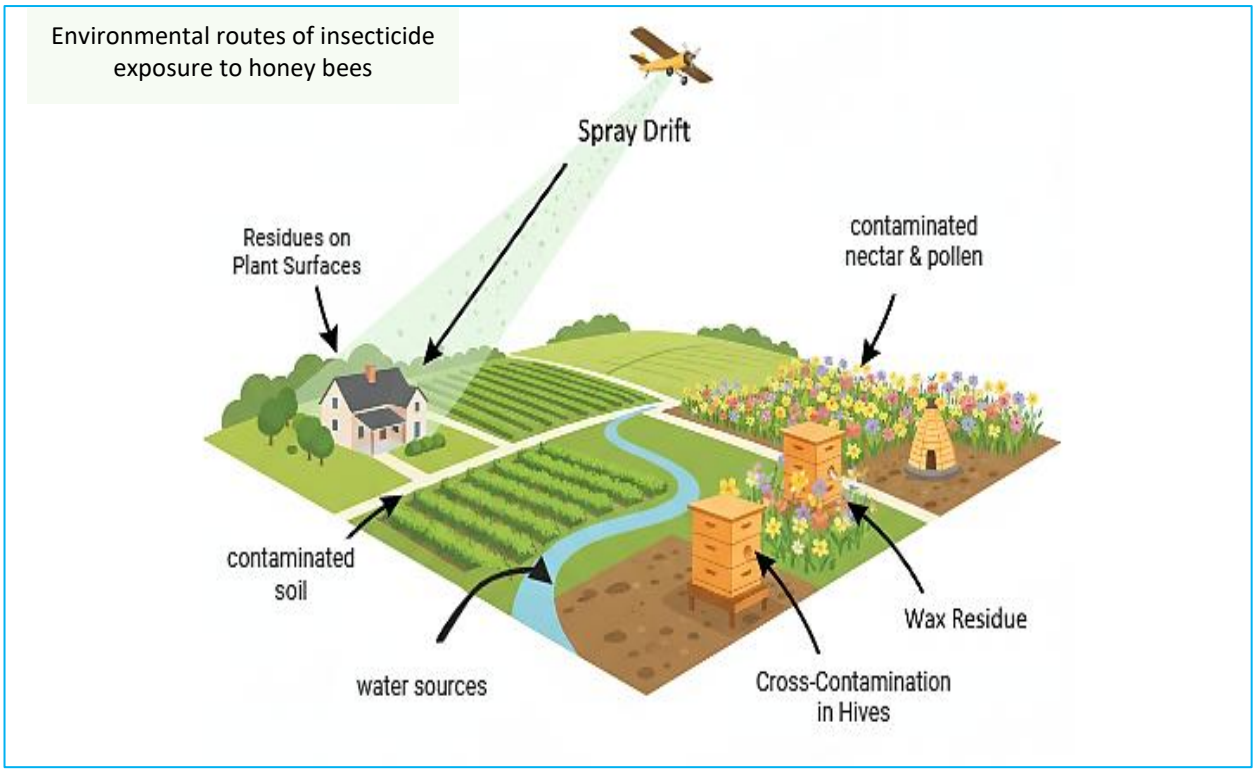

Fig 2 Environmental routes of insecticide exposure to honey bees

Foraging behaviour alterations

Behavioural modifications serve as sensitive indicators of pesticide stress, with studies consistently reporting reduced foraging frequency, altered flight behaviour, and impaired navigation. Neonicotinoid exposure significantly decreased foraging activity in *Apis cerana indica* [2-3], while synergistic pesticide mixtures further reduced flight duration and distance, negatively affecting resource collection [9], [75]. Sublethal exposures also induced accelerated behavioural development and impaired memory or responsiveness, compromising both individual performance and overall colony efficiency [90-93].

Pollination service impact

Alterations in foraging behaviour directly affect pollination efficiency and the provision of ecosystem services. Neonicotinoid exposure reduces flower visitation rates, pollination efficiency, and crop yields in affected colonies [2-3], [82], while flight impairments from pesticide mixtures further limit pollination potential [12]. Indirect effects, including increased parasite loads and reduced pollinator diversity, also compromise ecosystem services [94-96] and sublethal changes in gene expression may affect long-term pollination performance even in the absence immediate mortality [32].

Population risk indicators

Population-level risks from insecticides are reflected in mortality, reproductive impairments, and species-specific sensitivity thresholds. LC_{50} values and hazard quotients indicate greater vulnerability in certain species [97-98], while combined pesticide and resource stress reduces reproductive output, thereby impairing population growth [88]. Sublethal behavioural and physiological effects contribute to long-term declines in bee populations [99-100] and synergistic interactions with fungicides or poor nutrition further elevate these risks [22], [90]. Landscape-level risk assessments incorporating foraging behaviour models provide valuable insights into population-level exposure [101].

Risk management effectiveness

Effective mitigation strategies are essential for protecting native bee populations, with integrated Pest and

Pollinator Management (IPPM) and conservation-oriented practices strongly recommended [96], [102-103]. Risk assessments should incorporate species-specific sensitivity, sublethal effects, synergistic chemical interactions, and multi-stressor contexts [100], [104]. Field-realistic studies indicate that compensatory mechanisms may mask short-term colony-level effects, highlighting the need for long-term monitoring [89], while improved agrochemical management, habitat restoration, and farmer education are key to mitigating ecological impacts of novel insecticides [95], [105-106].

Research gaps and future directions

Despite growing research on the impacts of insecticides on *Apis cerana indica* and other native pollinators, several critical gaps remain. Long-term chronic toxicity studies under field-realistic conditions are needed, particularly for emerging compounds like sulfoximines and butenolides, to capture species-specific vulnerabilities and colony-level effects. Mechanistic insights into detoxification, including transcriptomic, enzymatic, and multi-omics analyses, remain limited, especially under natural environmental conditions. Sublethal effects on learning, memory, foraging, and colony fitness require longitudinal investigation, while the combined impacts of pesticide mixtures, pathogens, and environmental stressors are poorly understood. Standardized toxicity protocols and cross-species comparative studies are essential for reliable risk assessment, and integration of field validation with molecular and behavioural endpoints will ensure ecological relevance. Addressing these gaps will enhance our understanding of pollinator susceptibility, improve predictive toxicology, and guide evidence-based conservation and regulatory strategies.

CONCLUSION

Novel insecticides pose substantial risks to *Apis cerana indica* and related honey bee species, with both lethal and sublethal effects spanning behaviour, physiology, and colony-level dynamics. Evidence consistently shows that neonicotinoids, sulfoximines, butenolides, and other emerging chemistries disrupt essential behaviours such as foraging, navigation, learning, and communication, while also impairing biochemical and molecular defense pathways. Chronic exposures and synergistic interactions with pathogens, fungicides, and nutritional stress further amplify risks, often leading to reduced colony growth, impaired pollination efficiency, and long-term population declines. While most risk assessments continue to rely on *Apis mellifera* as a surrogate species, comparative studies highlight the heightened sensitivity of *Apis cerana indica* and other native pollinators, underscoring the need for species-specific evaluations. Laboratory assays, molecular analyses, and field-based studies together demonstrate that short-term mortality endpoints alone underestimate ecological threats. Instead, integrated approaches incorporating sublethal, behavioural, biochemical, and colony-level endpoints are critical for realistic risk assessment. To safeguard pollinator health and ecosystem services, research and management must prioritize long-term, field-realistic studies, mechanistic insights into detoxification pathways, and multi-stressor interactions. Implementation of Integrated Pest and Pollinator Management (IPPM), habitat restoration, and farmer education will be essential in mitigating risks. Ultimately, bridging toxicological research with conservation and policy frameworks will ensure more sustainable agricultural practices and the protection of pollination services vital to biodiversity and food security.

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