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Network meta-analysis: Acute mortality effects of neonicotinoid insecticides clothianidin, imidacloprid, thiacloprid, thiamethoxam on bumblebee (*Bombus* spp.)

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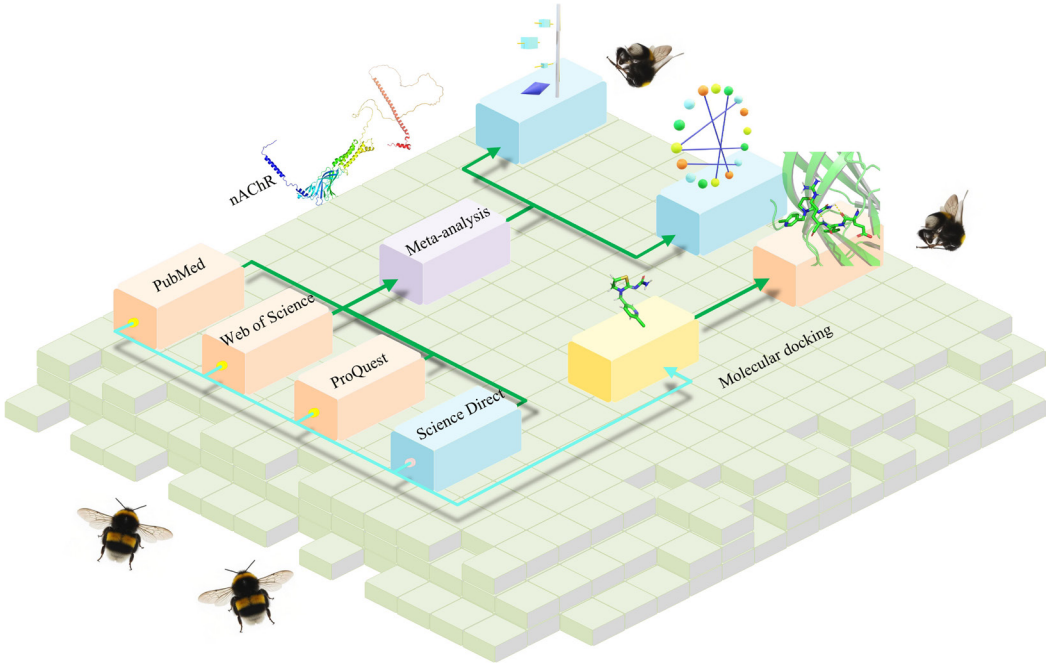
Abstract

Neonicotinoid insecticides are extensively used to manage piercing-sucking pests, but their toxicity profile in bumblebee remains a subject of ongoing debate. This study systematically searched PubMed, ProQuest, ScienceDirect, and Web of Science to perform conventional and network meta-analyses on extracted data. Molecular docking was also conducted on the nicotinic acetylcholine receptors (nAChRs) of bumblebees, aphids, and whiteflies, the binding free energies and key amino acid residues were recorded. Five studies met the inclusion criteria. None of the four neonicotinoids significantly increased acute bumblebee mortality at low exposure concentrations. At medium and high concentrations, clothianidin, imidacloprid, and thiamethoxam were significantly associated with acute mortality. Thiacloprid showed no significant acute lethality at medium concentrations but induced lethal effects at high concentrations. Molecular docking revealed that all four compounds bound to a similar binding pocket in the bumblebee nAChR. This study recommends the cautious application of neonicotinoid insecticides during flowering periods and in areas with bumblebee activity. Large-scale, standardised laboratory and field studies are warranted to evaluate the sublethal effects and long-term ecological impacts.

Graphical abstract



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Key Words

Acute, honeybee, lethal, molecular docking, nAChR

Introduction

Maximising food production from existing croplands has emerged as a critical global challenge due to continuous global population growth and limited arable land (Yang et al. 2024; Simane et al. 2025; Alberto et al. 2026). One strategy to enhance crop yields is to rigorously reduce yield losses caused by insect pests (Ullah et al. 2023; Shaaban et al. 2026; Toth et al. 2026; Yousuf et al. 2026). Worldwide, crops suffer severe damage from pests; among them, piercing-sucking pests (such as aphids, planthoppers, whiteflies, and leafhoppers) cause direct feeding injury and transmit plant viruses, representing the primary threat to agricultural production (Yang et al. 2025; Corrado et al. 2026; Han et al. 2026; Reyes-Proano et al. 2026; Toth et al. 2026). Neonicotinoid insecticides have been widely applied in crop protection since the 1990s. Acting on nicotinic acetylcholine receptors (nAChRs), they specifically disrupt insect neurotransmission and exhibit contact and stomach toxicity, making them key agents for managing piercing-sucking pests (He et al. 2025; Fang et al. 2026).

The most widely used neonicotinoid insecticides include clothianidin, imidacloprid, thiacloprid, and thiamethoxam. However, neonicotinoids also harm non-target insects, such as honeybees and bumblebees (*Bombus* spp. and *Bombus terrestris*). Bumblebees are vital plant pollinators with a global distribution and high foraging efficiency. Their key traits, including cold tolerance, low-light adaptation, and specialised buzz pollination, make them the premier pollinators for solanaceous and berry crops, including tomatoes, eggplants, blueberries, and strawberries (Orr et al. 2025; Yang et al. 2026b; Yang et al. 2026c). Neonicotinoids have been detected in nectar and pollen (Sardar et al. 2025), and bumblebees have even been reported to prefer plants containing neonicotinoids during foraging (Kessler et al. 2015).

Studies have extensively investigated the acute mortality of bumblebees exposed to neonicotinoid insecticides (Cabezas and Farinos 2022). Neonicotinoid concentrations exceeding 500 ng/mL induce mortality in bumblebees within 24 h (Kessler et al. 2015; Kessler et al. 2016; Cabezas and Farinos 2022). However, controversies remain regarding the lethal effects of neonicotinoids on bumblebees. For example, one study reported that 150 ng/mL thiacloprid caused only 13% mortality (Cabezas and Farinos 2022), whereas another reported 100% mortality at 120 ng/mL (Mommaerts et al. 2010). Differences have also been observed among neonicotinoid types, with 100 ng/mL imidacloprid resulting in only 28% mortality (Cabezas and Farinos 2022) and 100 ng/mL clothianidin leading to 80% mortality (Thompson et al. 2015). Therefore, a comprehensive network meta-analysis is essential for reconciling these inconsistencies. To date, only one meta-analysis has examined the effects of neonicotinoids on bumblebees (Dennis and Gibbs 2025). However, its scope was overly broad, covering multiple physiological traits without focused toxicity assessment, and no network meta-analysis was performed to compare insecticides. The present study simultaneously evaluated four neonicotinoids by integrating direct and indirect evidence, providing a comprehensive reference for assessing their acute lethal effects on bumblebees. These findings support evidence-based application strategies and policy decisions for the use of neonicotinoids.

Methods

Information sources and search strategy

The following keywords were searched: (*Bombus* OR Bumblebees OR Bumblebee) AND (Imidacloprid OR Thiamethoxam OR Clothianidin OR Thiacloprid) AND (Mortality OR Death OR dead OR Survival OR Survive). The following databases were searched: PubMed, ProQuest, ScienceDirect, and Web of Science. The search time range was January 1, 2010, to January 1, 2026. Manually screened reference lists of included studies and relevant reviews to identify additional eligible studies. After searching, list the concentrations of neonicotinoid infections in honey and nectar in Table 1.

Study selection and data extraction

To compare the toxicity of neonicotinoid insecticides, only studies examining at least two neonicotinoids simultaneously were included in this analysis. The inclusion and exclusion criteria are provided in Table 2. Two authors independently screened the abstracts for eligibility. Full texts of potentially relevant studies were retrieved and independently assessed by the same two reviewers. Discrepancies were resolved by consultation with a third author. Data, including insecticide concentration, sample size, number of deaths, and mortality rate for meta-analysis, were extracted and recorded as shown in Table 3. Based on molecular weights — clothianidin (249), imidacloprid (255), thiacloprid (252), and thiamethoxam (291) — concentrations in nM were converted to ng/mL.

Table 1. Reported concentrations of neonicotinoid insecticides in honey (nectar).

	Location	Concentration	Range	Sample Number	Reference
Imidacloprid	South Korea	<1 ng/g	0.01–40.7 ng/g	79	(Sardar et al. 2025)
	worldwide	0.35 ng/g	0–6.3 ng/g	198	(Mitchell et al. 2017)
	Kenya	0.3 µg/L	0.1–2.19 µg/L	72	(Mulati et al. 2018)
	worldwide	0.35 ng/mL	0.17–0.5 ng/mL	24	(Rundlof et al. 2015)
Thiamethoxam	South Korea	<1 ng/g	0.01–40.7 ng/g	79	(Sardar et al. 2025)
	worldwide	0.29 ng/g	0–2.7 ng/g	195	(Mitchell et al. 2017)
	Kenya	6.7 µg/L	0.1–47.8 µg/L	72	(Mulati et al. 2018)
	worldwide	0.19 ng/mL	0.17–0.5 ng/mL	16	(Rundlof et al. 2015)
Clothianidin	South Korea	1.13 ng/g	0.12–3.21 ng/g	79	(Sardar et al. 2025)
	worldwide	0.32 ng/g	0–1.8 ng/g	198	(Mitchell et al. 2017)
	worldwide	0.61 ng/mL	0.17–0.7 ng/mL	16	(Rundlof et al. 2015)
Thiacloprid	South Korea	<1 ng/g	0.01–40.7 ng/g	79	(Sardar et al. 2025)
	worldwide	2.4 ng/g	0–46.8 ng/g	198	(Mitchell et al. 2017)
	worldwide	0.35 ng/mL	0.17–0.5 ng/mL	16	(Rundlof et al. 2015)

ng/g ≈ µg/L ≈ ppb ≈ ng/mL ≈ 0.001 ppm. Imidacloprid (Confidor®, Bayer Public Limited Company, Berkshire, England), thiamethoxam (Actara®, Novartis Limited Company, Switzerland), and thiacloprid (Calypso®, Bayer Public Limited Company, Berkshire, England) have recommended application concentrations of 200, 100, and 120 ppm, respectively (Mommaerts et al. 2010).

Table 2. Inclusion and exclusion criteria.

	Inclusion	Exclusion
1	Species evaluated included but were not limited to bumblebees	Bumblebees not used
2	English literature	Non-English
3	Analysis of clothianidin, imidacloprid, thiacloprid and thiamethoxam (at least 2 compounds) in bumblebees	No neonicotinoid treatment for bumblebees or use alone
4	Mortality data in 24 h included	No mortality in 24-h data

Conventional meta-analyses

Based on the clothianidin, imidacloprid, thiacloprid, and thiamethoxam concentrations detected in honey (Table 1) and with reference to the recommended thiacloprid (Calypso®, Bayer Public Limited Company, Berkshire, England) application rates at 200, 100, and 120 ppm (Mommaerts et al. 2010), the insecticide concentrations were categorised as follows: normal (<10 ng/mL) concentration, low risk (10–50 ng/mL) concentration, middle risk (51–500 ng/mL) concentration, and high risk (>500 ng/mL) concentration. For binary mortality data, the odds ratio with 95% confidence interval (CI) was used to quantify the effects of each neonicotinoid compared to the control group. Recorded concentrations, sample sizes, and mortality counts were submitted to Review Manager (Cochrane Collaboration, v5.4; https://cochrane.org/) for analysis.

Network meta-analyses

The data were pooled by group and uniformly compared to the control group to perform network meta-analyses. Network meta-analyses were conducted using the "coda", "rjags", and "gemtc" packages in R software (v4.2, R Foundation for Statistical Computing, Vienna, Austria).

Table 3. Characteristics of included studies included.

	reference	Breed (location)	Temperature and humidity	Neonicotinoid	Record time	Treatment	Colony No.	Colony
1	(Cabezas and Farinos 2022)	Spain	25°C 60%	Imidacloprid 0.05–3 ppm Thiacloprid 150–800 ppm	24 and 48 h	workers	21	queen, 20–40 workers
2	(Kessler et al. 2015; Kessler et al. 2016)	Ireland	25–30°C	Imidacloprid 1–1000 nM Thiamethoxam 1–1000 nM Clothianidin 1–1000 nM	24 h	workers	3–5	NM
3	(Thompson et al. 2015)	Netherlands	21°C	Thiamethoxam 1–100 µg/kg Clothianidin 1–100 µg/kg	1 to 4 days	workers	NM	NM
4	(Raimets et al. 2018)	Belgium	24°C 47%	Imidacloprid 13 µg/L Thiamethoxam 20 µg/L	24 and 48 h	workers	1	NM
5	(Mommaerts et al. 2010)	Belgium	28–30°C 60–65%	Imidacloprid 0.01–200 ppm Thiacloprid 0.01–120 ppm Thiamethoxam 0.01–1 ppm	1, 14, 28, and 49 days	false queen, workers	4	false queen, 5 workers

NM: not mentioned. Notably, all included studies provided 24-h acute mortality data following neonicotinoid exposure. Additionally, Kessler et al. (2015, 2016) correspond to a single study, which was counted only once in the meta-analysis to avoid duplicate data inclusion.

Protein molecular docking

The amino acid sequence of the bumblebee nAChR (XP_043588786.1) was downloaded from the US National Center for Biotechnology Information (NCBI; Bethesda, MD, USA). Tertiary protein structures were generated using SWISS-MODEL (https://swissmodel.expasy.org/). The following ligand structures were obtained from PubChem: clothianidin (CID 86287519), imidacloprid (CID 86287518), thiacloprid (CID 86222983), and thiamethoxam (CID 5821911). Molecular docking was conducted using AutoDock Vina v1.2.0 (https://vina.scripps.edu/) with 100 iterations to ensure reliable results. The best binding free energy (kcal/mol, Δ G) and key hydrogen bond interactions were recorded. Amino acids within 5 Å of the binding pocket were identified. Binding poses were visualised using PyMOL software (v3.1, www.pymol.org). nAChR sequences from aphid (AHW45796.1) and whitefly (AQP31213.1) were downloaded to verify the differential toxicity of thiacloprid among insect species, and the same docking procedure was repeated with all other neonicotinoids.

Results

Literature search and screening

A total of 104 publications were retrieved between January 1, 2010, and January 1, 2026. A total of 5 studies were included in the quantitative analysis. The study selection process is illustrated in Fig. 1A. Detailed characteristics of the 5 included studies are summarised in Table 3. Kessler et al. (2015, 2016) represent the same report with only one additional author.

Effects of neonicotinoid insecticides on acute bumblebee mortality

Results of the conventional meta-analysis are presented in Fig. 1B–E. At concentrations < 50 ng/mL (normal and low-risk levels), none of the four neonicotinoids showed a significant association with mortality. Imidacloprid at 10–50 ng/mL (standard MD = 4.21; 95% CI = 1.00–17.62; $p < 0.001$) showed no significant effect on mortality (Fig. 1D). At concentrations > 51 ng/mL (middle and high-risk levels), thiacloprid (standard MD = 10.67; 95% CI = 0.54–209.64; $p < 0.001$) showed no significant association with mortality (green box, Fig. 1C), whereas the other three insecticides were significantly and positively associated with mortality (Fig. 1B, D, E). The value of the invalid line in the figure is 1, if the 95% CI value range greater than 1 and $p < 0.05$ indicates a significant association. The value range of 95% CI includes 1, indicating no significant association. The 95% CI report indicate a positive correlation within the range of the analysis effect. The p-value report analysis results have statistical significance, and $p < 0.05$ indicates a significant difference.

The results of network meta-analysis comparing each neonicotinoid with the control group is shown in Fig. 2A, B. The findings were consistent with conventional meta-analysis. At < 50 ng/mL (normal and low-risk), none of the four neonicotinoids significantly affected mortality (Fig. 2A). At high concentrations, all four neonicotinoids showed significant positive correlations with mortality with no significant differences among them. At middle-risk concentrations, thiacloprid showed no significant association with mortality (green box, Fig. 2A), whereas the other three neonicotinoids were significantly associated with mortality ($p < 0.005$).

Fig. 2B shows the network plot for the four neonicotinoids and the control group. Network meta-analysis comparing each treatment group with the low-risk imidacloprid group is presented in Fig. 2C. Neither the low-risk concentration nor middle-risk thiacloprid showed a significant association with mortality (green boxes). All other middle- and high-risk groups were significantly and positively associated with mortality.

Molecular docking of neonicotinoids with bumblebee nAChR

Clothianidin, imidacloprid, thiacloprid, and thiamethoxam successfully docked into the bumblebee nAChR, as shown in Fig. 3. The binding free energies (from strongest to weakest binding) were as follows: thiacloprid (–6.23 kcal/mol), imidacloprid (–6.07 kcal/mol), clothianidin (–5.97 kcal/mol), and thiamethoxam (–5.59 kcal/mol). The binding pocket was located in the cavity formed by the region from GLU100 to ASN142. The estimated binding free energy (Δ G) of molecular docking is used to predict the spontaneous binding ability of neonicotinoid molecules to nAChRs. The more negative the binding free energy value, the higher the predicted binding affinity.

Molecular docking of thiacloprid with aphid and whitefly nAChR

Thiacloprid successfully docked into the nAChRs of aphid and whitefly. The binding free energy was −6.77 kcal/mol for aphid (Fig. 4A) and −7.02 kcal/mol for whitefly (Fig. 4B). The binding pocket was located in the extracellular binding domain of the receptor, similar to that in bumblebees.

Discussion

At concentrations below 50 ng/mL, clothianidin, imidacloprid, thiacloprid, and thiamethoxam were not significantly associated with acute mortality. At middle (51–500 ng/ml) and high concentrations (> 500 ng/ml), clothianidin, imidacloprid, and thiamethoxam were significantly associated with acute mortality, whereas thiacloprid showed no signi-

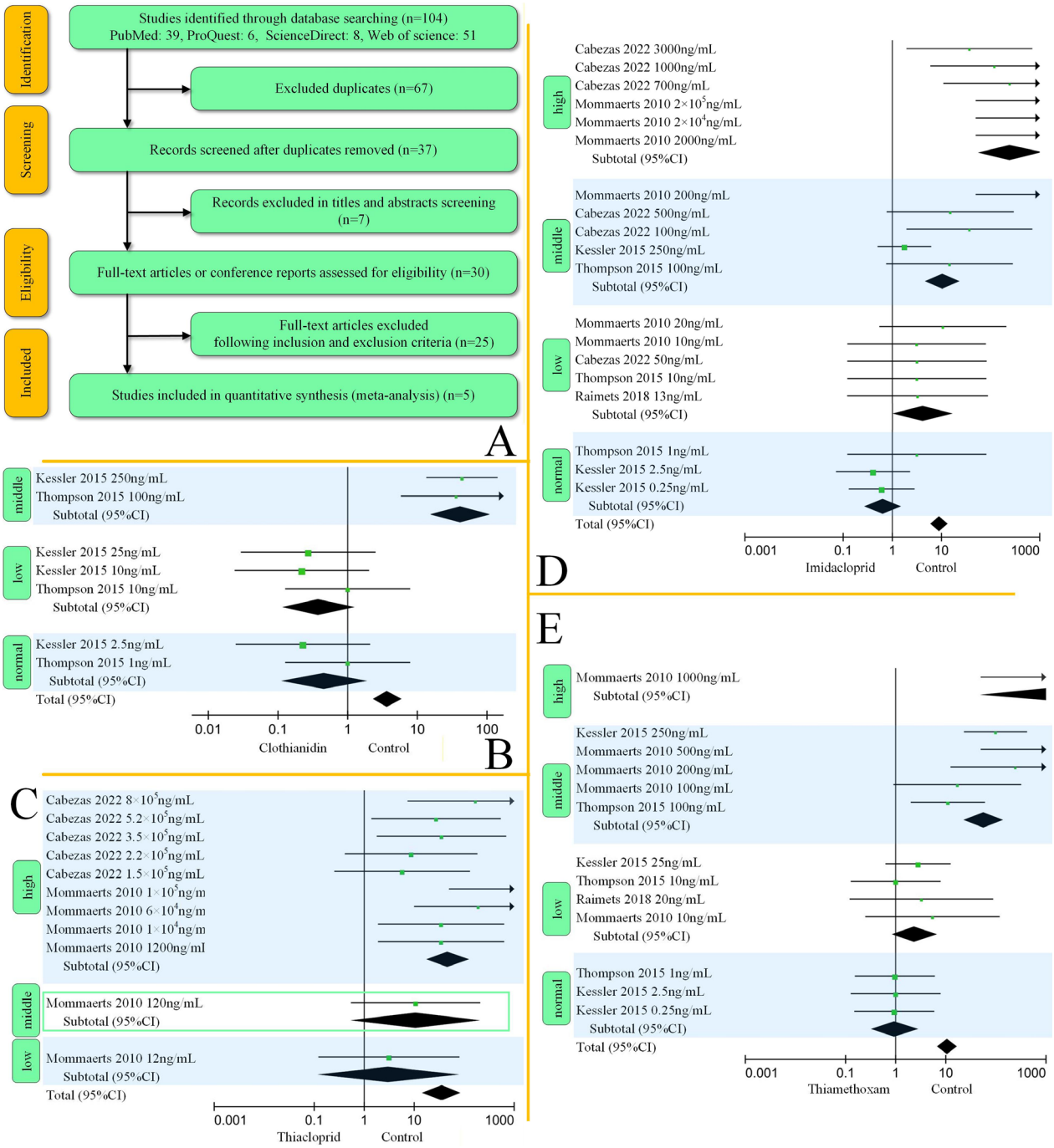

Figure 1. Summary of the study selection process and conventional meta-analysis. **A.** Literature selection process: search identified 104 studies based on the search strategy, 5 of which were included. **B–E.** Conventional meta-analysis forest plot of the effect of neonicotinoids, namely clothianidin (**B**), thiacloprid (**C**), imidacloprid (**D**), and thiamethoxam (**E**), on acute bumblebee mortality. In each forest plot, squares show study-specific odds ratios (OR), horizontal lines show 95% confidence intervals (CI), diamonds show pooled OR, and the vertical line at OR = 1 indicates no effect.

ficant acute lethality at middle concentrations. Conventional meta-analysis can be used to evaluate the lethal effects of each neonicotinoid relative to the blank control group separately, but Table 3 shows that no paper can cover the toxicity studies of the four neonicotinoids. Therefore, further conducting a network meta-analysis, integrating all research data to construct an evidence network, and using a common control group to indirectly compare multiple insecticides, in order to rank the lethal risk of the four neonicotinoids.

Effects of neonicotinoid insecticides on acute mortality of bumblebees

Clothianidin, imidacloprid, and thiamethoxam once accounted for 85% of the neonicotinoid market, and these three compounds have been the most extensively studied (Dennis and Gibbs 2025). The continuous exposure of bumblebees to 13 µg/L clothianidin for 9 days resulted in detectable residues in both workers and queens but

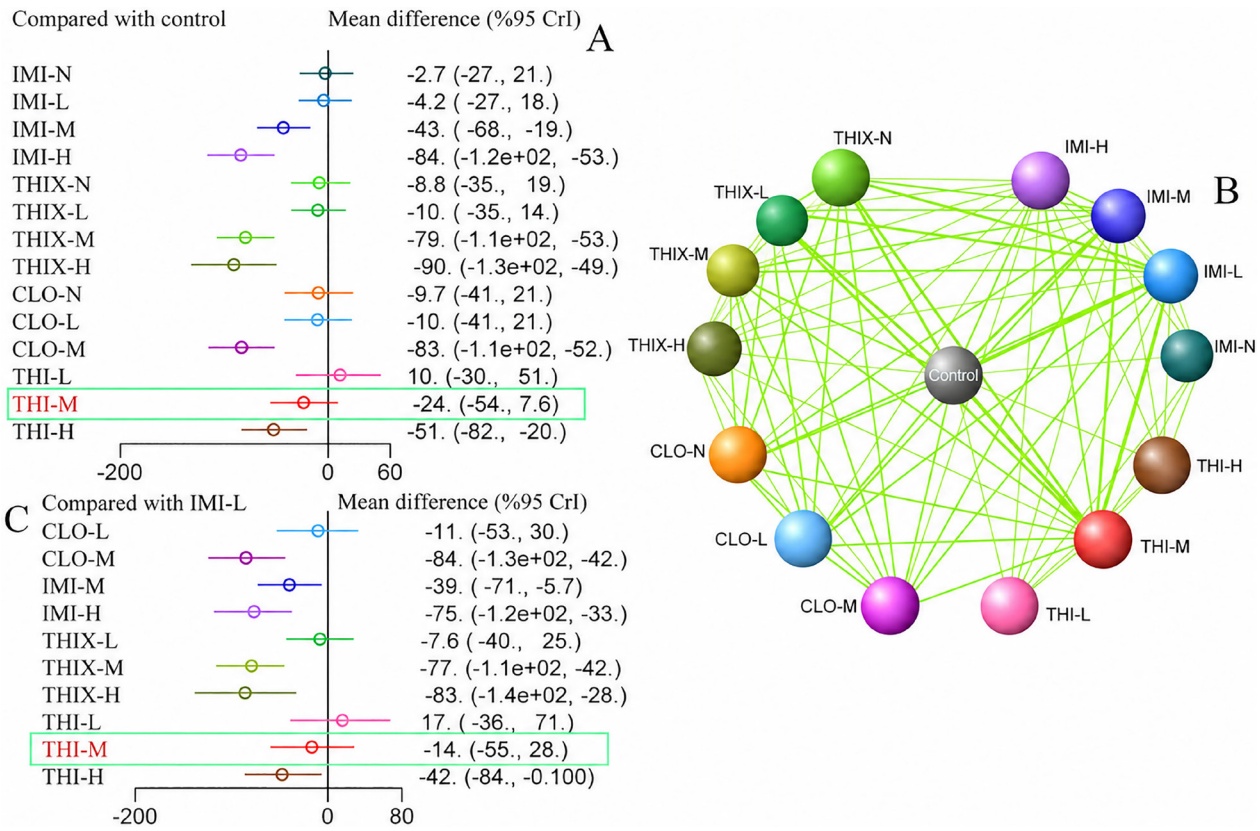

Figure 2. Network meta-analysis of the effects of neonicotinoids on acute bumblebee mortality. **A.** Network forest plot comparing four neonicotinoids with the control group, and horizontal bars show 95% CI, the vertical line at MD = 0 indicates no association, and CI excluding zero indicate evidence of association. **B.** Network diagrams comparing neonicotinoids. **C.** Network forest plot comparing each neonicotinoid group with the low-risk imidacloprid group. Abbreviations: IMI, imidacloprid; THIX, thiamethoxam; CLO, clothianidin; THI, thiacloprid. Suffixes N, L, M, H indicate normal, low, middle, and high risk, respectively (e.g., THI-H = thiacloprid-high). the line thickness represents the number of studies.

without inducing acute mortality (Aarones et al. 2021). This is consistent with results (Figs 1, 2), showing that none of the four neonicotinoids induced acute lethality at low-risk concentrations. Neonicotinoid toxicity varied among bumblebee types; in the same study, 100 ng/mL thiamethoxam killed 80% of workers but only 10% of drones (Minnameyer et al. 2021). Bumblebee populations of different origins also exhibited distinct sensitivity, with alpine bumblebees showing the highest overall survival, followed by shoreline and suburban bumblebees (Tatarko et al. 2025). Together with the data in Table 3 from the present study, these reports explain the inconsistencies observed in the literature. In 2024, the European Union banned clothianidin, imidacloprid, and thiamethoxam, which aligns with findings (Figs 1, 2) that these neonicotinoids caused higher acute mortality at middle-risk concentrations than thiacloprid. However, neonicotinoids are still widely used globally (Dennis and Gibbs 2025). In addition to acute lethality, neonicotinoids have adverse impacts on bumblebee foraging, behaviour, reproductive success, and pollination efficacy (Bai et al. 2025; Dennis and Gibbs 2025). Therefore, this study performed molecular docking to explore the mechanisms underlying such sublethal effects.

Molecular basis of binding mechanisms and toxicity differences between neonicotinoids and insect nAChRs

Molecular simulation can be used to predict the lethal effects of insecticides on target and non-target insects (Lu et al. 2024a; Lu et al. 2024b). However, the binding energy between a compound and its target protein is not positively correlated with its biological efficacy (Yu et al. 2023). This study molecular docking results showed that all four neonicotinoids successfully bound to the nAChR binding pockets of bumblebees, aphids, and whiteflies, which is formed by the folded region spanning amino acids 100–150 (Fig. 3). The present study indicates that a higher binding energy is associated with longer persistence but a slower onset of action. Thiacloprid exhibited the lowest acute toxicity at 24 h but the longest duration of action, posing potential risks. The impacts of neonicotinoids on bumblebees extend beyond acute lethality and include impairments to nesting behaviour, social networks, reproduction, and thermoregulation (Stanley et al. 2015; Crall et al. 2018; Claus et al. 2021). Such sublethal effects may underlie colony collapse disorder.

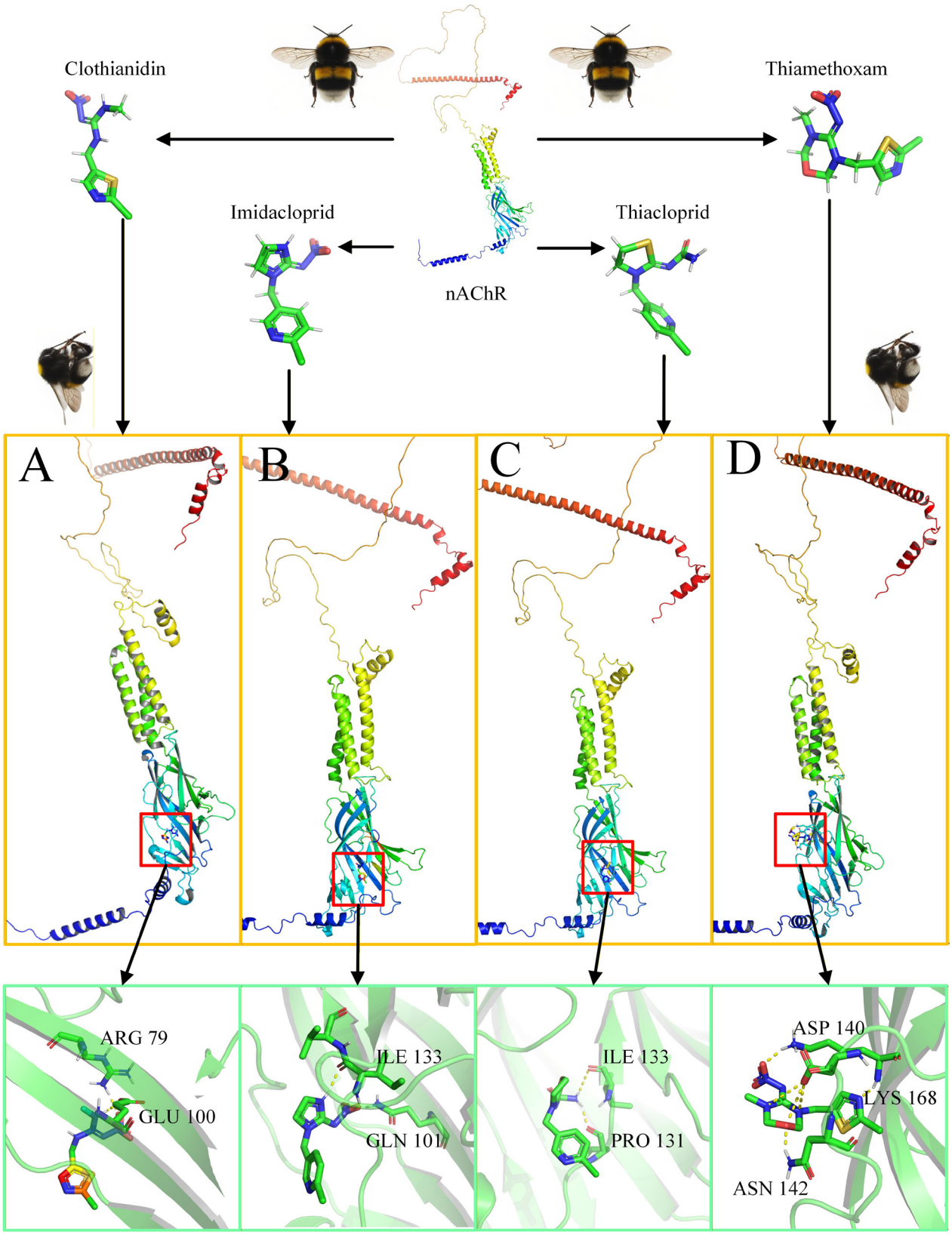

Figure 3. Molecular docking of neonicotinoid with bumblebee nAChR. **A–D.** Show the binding modes of clothianidin, imidacloprid, thiacloprid, and thiamethoxam in the nAChR binding pocket, respectively. Dashed lines represent interactions <5 Å. Binding affinities are labelled at the bottom of each panel.

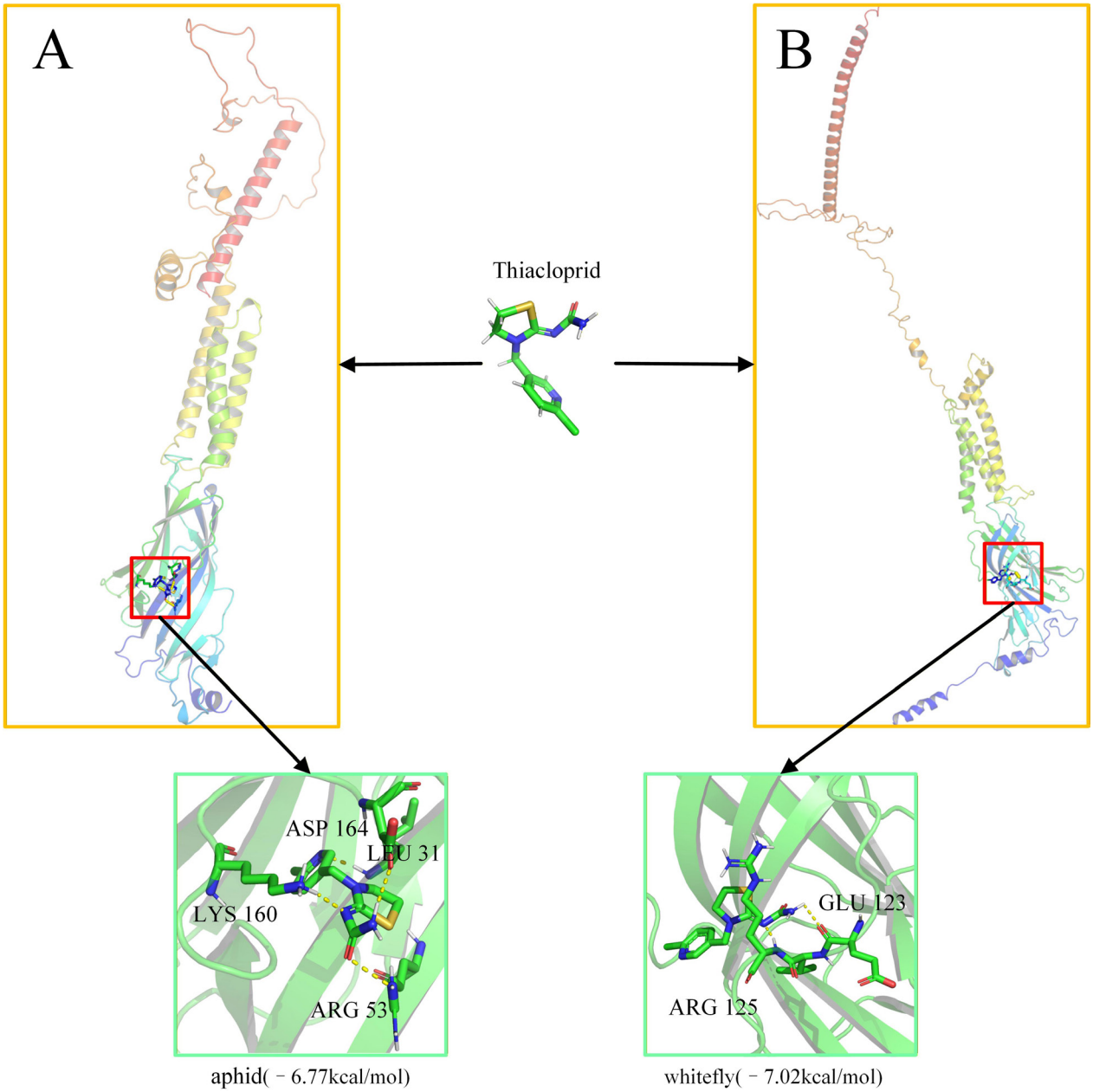

Figure 4. Molecular docking of thiacloprid with target pest nAChRs. **A, B.** Show thiacloprid bound in the binding pocket of aphid and whitefly nAChR, respectively. Dashed lines represent interactions <5 Å. Binding affinities are labelled at the bottom of each panel.

Explanations for academic controversies and the limitations of the present study

This study integrated relevant publications from 2010 to 2026 and reviewed most reports in this field. One major controversy regarding neonicotinoid-induced acute bumblebee mortality is that 100 ng/mL imidacloprid and clothianidin caused 28% (Cabezas and Farinos 2022) and 80% mortality (Thompson et al. 2015), respectively. In comparative toxicity studies, the median lethal dose (LD_{50}) of imidacloprid was nearly fourfold higher than that of clothianidin in honey bees (Li et al. 2017), which could explain this discrepancy.

A second controversy concerning the acute mortality of bumblebees exposed to neonicotinoids is that similar thiacloprid concentrations resulted in 13% (Cabezas and Farinos 2022) and 100% (Mommaerts et al. 2010) mortality. The toxicity of neonicotinoids is highly temperature-dependent. Under identical imidacloprid exposure, a modest 3°C increase precipitated a sudden and significant decline in honeybee flight performance (Kenna et al. 2023). Based on data in Table 3, this study propose that the contrasting mortality rates at similar thiacloprid concentrations are caused by differences in experimental temperature—25°C versus 28°C—between the two studies.

In the present study, the classification of concentrations below 50 ng/mL as low-risk was based on the neonicotinoid concentrations detected in honey (Table 1). Thiamethoxam can be metabolised into clothianidin in plants and exert an insecticidal effect (Tian et al. 2022), which

explains why their toxicity levels are relatively similar. After discussion among the authors, the insecticide concentrations were artificially categorised as follows: normal (< 10 ng/mL), low risk (10–50 ng/mL), middle risk (51–500 ng/mL), and high risk (> 501 ng/mL). However, this classification has certain limitations.

Recommendations for future research

Supplementing forage can effectively reduce the harm of neonicotinoids to bumblebees, increasing the number of live eggs (Ingwell et al. 2021). After application, thiacloprid is redistributed within tomato plants with 23% accumulating in flowers and degradation with a half-life of 3.28 days (Bai et al. 2025). Therefore, future agricultural policy research should provide effective information guidance and coordinate information exchange between tomato-growing farms and bumblebee-breeding farms. In addition, the use of neonicotinoids during the flowering period should be avoided as much as possible to protect wild bumblebees. Molecular docking analyses are an effective approach for the design and development of new insecticides (Yang et al. 2026a); research on minimising harm to non-target insects should also be improved before new insecticides are promoted and applied.

Conclusion

This combined network meta-analysis and molecular docking study suggests that none of the four major neonicotinoids significantly affected 24-h acute mortality in *Bombus terrestris* at environmentally relevant low exposure levels. However, at middle and high concentrations, clothianidin, imidacloprid, and thiamethoxam were significantly associated with acute lethality, whereas thiacloprid showed a relatively lower acute toxicity but a higher binding stability, indicating distinct onset kinetics and persistence. Given the limited available evidence and heterogeneity across experimental paradigms, this study strongly advocate that future pesticide regulatory policies encompass acute toxicity, sublethal behavioural effects, and long-term colony-level impacts. Further high-quality standardised experiments and field validation are needed to comprehensively protect pollinators and ensure agroecosystem sustainability.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statement

Not involving insect and animal experiments.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI.
No AI tools were used in the preparation of this manuscript.

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Xiuyu Lu, Shujun Wang and Xing Wang collected the data and conducted the analysis. Xing Wang and Zhenhua Guo conceived this research. Shujun Wang complete molecular docking experiments.

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Data availability

Please contact the author to request the data.