



Toxicity of neonicotinoid insecticides to honey bees: a network meta-analysis

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Received 31 October 2025 – Revised 7 April 2026 – Accepted 21 April 2026

Abstract – Honey bees (*Apis mellifera*) are essential pollinators vital to ecosystem health and crop production. Neonicotinoid insecticides have raised concerns due to their potential effects on honey bee populations. This study compared the toxicity of six neonicotinoids including imidacloprid, clothianidin, thiamethoxam, acetamiprid, thiacloprid, and dinotefuran using a Bayesian network meta-analysis. Data from 31 studies were analyzed with Markov Chain Monte Carlo simulations. Toxicity outcomes were expressed as odds ratios (ORs) for mortality and standardized mean differences (SMDs) for median lethal dose (LD₅₀) and median lethal concentration (LC₅₀) values, with 95% credible intervals. The surface under the cumulative ranking curve (SUCRA) was used to rank the compounds and determine their relative toxicity to honey bees. For honey bee mortality, dinotefuran had the highest SUCRA value (0.76), indicating the greatest probability of being the most lethal compound (OR = 0.07 compared with control) within the mortality network. On the other hand, clothianidin, scoring 0.38, was found to have the lowest hazard for honey bees among the neonicotinoids assessed. In terms of LD₅₀ values, thiamethoxam had the highest SUCRA value (0.76), indicating the greatest probability of being the most toxic (SMD range – 28.68 to – 34.85 µg/bee compared with other compounds) compound in the LD₅₀ network, while acetamiprid was the least toxic, with a score of 0.05. For LC₅₀ values, imidacloprid, with a score of 0.84, was the most toxic (SMD = – 76.94 ppm compared with acetamiprid), whereas thiacloprid, scoring 0.22, was the least toxic neonicotinoid among those evaluated. Furthermore, a moderate consistency (Spearman's $\rho = 0.72$, $p = 0.136$) was observed between official and literature-based toxicity rank correlations. This network meta-analysis indicates that dinotefuran poses the highest mortality risk to honey bees among neonicotinoids, underscoring the need for cautious use in pollinator-active areas. Conversely, acetamiprid and thiacloprid showed the lowest toxicity among the neonicotinoids evaluated.

neonicotinoid / honey bee / network meta-analysis / toxicity / mortality

1. INTRODUCTION

Pollinators play a crucial role in maintaining ecosystems and are vital for food production and agriculture. It is estimated that around 90% of wild flowering plants and 75% of food crops

rely on animal-mediated pollination (Klein et al. 2007; Tong et al. 2023). More than 200,000 species serve as pollinators, with a significant number being various species of bees (Ollerton 2017; Rader et al. 2020). Among these, the honey bee, particularly the western honey bee (*Apis mellifera*), is the most recognized and extensively managed pollinator species by humans. Similar to numerous insect species, there is a global

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Manuscript editor: James Nieh

decline in pollinator populations (Potts et al. 2010). This reduction poses a significant risk to both natural ecosystems and agricultural production systems (Rhodes 2018).

Synthetic pesticides, including herbicides, fungicides, and insecticides, are widely employed in agricultural practices to protect crops from pests and diseases. Nonetheless, the application of these chemicals presents numerous environmental challenges, with a prominent issue being the effects of insecticides on non-target organisms, such as bees (Pisa et al. 2015).

Neonicotinoids, a class of insecticides known for their nerve-damaging effects, are active substances and have become the fastest-growing and most widely used insecticides globally, targeting a broad range of sucking and some chewing insects. In recent years, concerns have grown regarding the broad environmental risks associated with neonicotinoid insecticides (Goulson and 232 signatories 2018; Giorio et al. 2021). Since their introduction in the 1990s, neonicotinoids have spread rapidly due to their systemic mode of action, high effectiveness at low doses, and perceived low toxicity to vertebrates, including humans (Berheim et al. 2019). Neonicotinoids were historically among the most widely used insecticides globally; however, their use has declined in several regions, particularly within the European Union, following regulatory restrictions implemented between 2013 and 2018 (Kathage et al. 2018; Klingelhöfer et al. 2022). Neonicotinoids are increasingly applied preventatively, such as in seed treatments, to avert pest population growth. However, their extensive and indiscriminate use, along with numerous non-target effects, has raised significant environmental concerns (Krupke et al. 2017; Calvo-Agudo et al. 2019).

The main types of neonicotinoids used in agriculture include imidacloprid, clothianidin, thiamethoxam, acetamiprid, thiacloprid, and dinotefuran. Imidacloprid, one of the earliest developed, remains widely used due to its broad-spectrum effectiveness. Clothianidin and thiamethoxam are systemic insecticides, often used in seed treatments for crops like corn and soybeans, allowing the chemicals to

be absorbed by the plant and offering protection from pests throughout the growing season. Acetamiprid and thiacloprid have slightly different chemical structures, resulting in lower toxicity to bees compared to other neonicotinoids (Iwasa et al. 2004). Dinotefuran has been used in agriculture in several countries, particularly in Asia and North America, and in some regions for structural and urban pest control (Ma et al. 2025). Although effective at controlling insect pests, the widespread use of these chemicals has raised environmental concerns, particularly regarding their impact on non-target species such as pollinators and aquatic organisms (Ensley 2018; Bass and Field 2018). Although cyano-substituted neonicotinoids such as acetamiprid and thiacloprid are generally considered less toxic than nitro-substituted compounds based on individual LD₅₀ reports and the Pesticide Properties Database (PPDB, Lewis et al. 2016), published toxicity estimates vary considerably across studies due to differences in bee species, exposure routes, experimental design, and environmental conditions. To date, no study has quantitatively integrated this heterogeneous evidence using a network-based approach that allows simultaneous probabilistic ranking across compounds and endpoints. In the regulatory and risk-assessment context, toxicity endpoints refer to the specific measured outcomes used to quantify adverse effects in ecotoxicological studies and to support pesticide registration and environmental safety decisions.

Neonicotinoids differ not only in chemical structure but also in their patterns of use and regulatory status. Nitro-substituted compounds (imidacloprid, clothianidin, thiamethoxam, dinotefuran) have historically been widely applied as seed treatments and foliar sprays in arable crops such as maize, oilseed rape, sunflower, and cereals. However, substantial regulatory changes have occurred over the past decade. In the European Union, outdoor uses of imidacloprid, clothianidin, and thiamethoxam have been largely restricted since 2018 due to risks to pollinators, while dinotefuran is not approved for use in the EU. In contrast, cyano-substituted

neonicotinoids such as acetamiprid remain approved for certain uses, reflecting their comparatively lower acute toxicity to bees. These regulatory distinctions highlight the importance of quantitatively synthesizing comparative toxicity data under diverse experimental conditions. An overview of the six neonicotinoid insecticides evaluated in this study, including chemical subgroup, primary uses, application methods, regulatory status in the European Union (EU), and reported acute contact LD₅₀ values for *Apis mellifera* is shown in Table I.

Honey bees can encounter neonicotinoids through nectar or honey, which serve as their energy source, and through pollen, which provides protein. Studies have shown that honey can contain neonicotinoid levels high enough to impact honey bees (Mitchell et al. 2017). Scientific research has established a connection between the decline of bee populations and their exposure to systemic neonicotinoid insecticides, a finding that is increasingly being recognized in the literature (Maini et al. 2010; Farooqui 2013; Lu et al. 2014).

Table I Key characteristics and regulatory status of the six neonicotinoids evaluated in this study

Active substance	Chemical subgroup	Typical application methods	Major target crops/uses	EU regulatory status (2025)*	Reported contact LD ₅₀ (µg/bee)**	Relative acute toxicity to bees
Imidacloprid	Nitroguanidine	Seed treatment, soil drench, foliar spray	Cereals, oilseed rape, maize, horticultural crops	Outdoor uses restricted since 2018; limited greenhouse uses	~0.0037–0.081	Very highly toxic
Clothianidin	Nitroguanidine	Seed treatment, soil application	Maize, oilseed rape, cereals	Outdoor uses restricted since 2018	~0.022–0.044	Very highly toxic
Thiamethoxam	Nitroguanidine	Seed treatment, foliar spray	Maize, oilseed rape, sugar beet	Outdoor uses restricted since 2018	~0.024–0.030	Very highly toxic
Dinotefuran	Nitroguanidine	Foliar spray, soil application, structural/urban pest control	Vegetables, fruit crops (mainly outside EU), urban/structural pests	Not approved in EU	~0.047	Very highly toxic
Acetamiprid	Cyanoamidine	Foliar spray	Fruits, vegetables, ornamental crops	Approved in EU (with restrictions)	~7–14	Moderately toxic
Thiacloprid***	Cyanoamidine	Foliar spray	Fruits, oilseed rape, ornamentals	Approval not renewed in EU (since 2020)	~14–38.8	Moderately toxic

*Regulatory status based on publicly available EU Pesticide Database decisions

**LD₅₀ values represent acute contact toxicity ranges reported in PPDB and regulatory risk assessments; values vary depending on study conditions

***Thiacloprid approval was not renewed in the EU primarily due to concerns related to reproductive toxicity and environmental risks

Network meta-analysis (NMA) is a powerful statistical approach that has been widely applied in various scientific fields (Abdulka-reem 2023; Sharifi et al. 2025; Mahmoudi et al. 2025). It allows for the simultaneous comparison of multiple interventions, even when some have not been directly compared in head-to-head trials. By integrating both direct and indirect evidence within a single analytical framework, NMA enhances the precision of effect estimates and provides a comprehensive ranking of treatments based on their relative efficacy or risk. This method increases the statistical power and scope of traditional meta-analysis, enabling researchers to make more informed conclusions with greater confidence (White 2015).

Regulatory LD₅₀ and LC₅₀ values are typically derived from standardized guideline studies under controlled laboratory conditions. While these values are critical for pesticide registration and risk assessment, they may not fully reflect the variability observed across independent academic studies conducted under diverse experimental conditions. A quantitative synthesis of published toxicity estimates may therefore provide complementary insight into the robustness and consistency of regulatory toxicity classifications.

Consequently, it is essential to rigorously evaluate the acute toxicity of neonicotinoid insecticides to honey bees, given their critical ecological and agricultural role as pollinators. In this study, we employed a Bayesian network meta-analysis to quantitatively synthesize and rank the relative intrinsic toxicity of six major neonicotinoids based on published experimental data, integrating both direct and indirect comparisons across heterogeneous studies while accounting for study-level variability. In addition, we aimed to examine whether the empirical toxicity rankings derived from the literature are consistent with regulatory reference LD₅₀/LC₅₀ values reported in the PPDB (Lewis et al. 2016), thereby assessing the concordance between standardized regulatory benchmarks and the broader body of experimental evidence.

2. METHODS

2.1. Search strategy

The present network meta-analysis (NMA) was executed in accordance with the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Moher et al. 2009). To identify appropriate studies for inclusion in the NMA, a thorough and systematic search of databases was conducted, encompassing PubMed, Springer, Google Scholar, and Elsevier, with no restrictions on language, up to February 2025. The search utilized the following terms: “honey bee,” “*Apis mellifera*,” “neonicotinoid,” “toxicity,” “mortality,” “survival,” “LD₅₀,” “lethal dose,” “LC₅₀,” “lethal concentration,” “imidacloprid,” “clothianidin,” “thiamethoxam,” “acetamiprid,” “thiacloprid,” and “dinotefuran.”

2.2. Selection criteria

The studies deemed eligible for inclusion were selected according to predetermined criteria, which included the following: (1) the reporting of outcomes in terms of mortality/survivability percentages, (2) the availability of data regarding the contact median lethal dose (LD₅₀) or median lethal concentration (LC₅₀) for neonicotinoids, and (3) the comparative analysis of at least one neonicotinoid against another or control treatment. The exclusion criteria consisted of the following: (1) studies presented solely in abstract or review format, (2) studies that did not provide adequate data, (3) duplicate studies, and (4) studies characterized by incomplete methodological designs. Furthermore, any discrepancies that arose during the selection process were addressed and resolved through discussion.

2.3. Data extraction

The titles and abstracts of all acquired publications were individually reviewed to extract

relevant information. The authors collaborated to resolve any inconsistencies that arose during this process. Following this, the full texts of all potentially eligible studies were meticulously examined and assessed to confirm their compliance with the established inclusion criteria. The data collected included the first author's name, publication year, type of neonicotinoid, mortality rate, median contact LD₅₀ and LC₅₀ values for neonicotinoids, honey bee species, the standard error/standard deviation of the mean, the confidence interval and the sample size. The LD₅₀ and LC₅₀ values extracted for the present analysis were obtained directly from the original experimental results reported within the included peer-reviewed studies.

2.4. Statistical analysis

The data obtained was employed to estimate effect sizes, specifically in terms of odds ratios (OR) for mortality and standardized mean difference for LD₅₀ and LC₅₀, standard errors (SE), and 95% credible intervals (CrI) for each individual study. The network meta-analysis was performed utilizing the gemtc package (Van Valkenhoef et al. 2016) within the R programming environment, version 4.4.1 (R Core Team 2024). A Bayesian methodology was adopted, which incorporated three Markov Chain Monte Carlo (MCMC) simulations with differing burn-in iterations (5000, 15,000, and 25,000), followed by actual simulation iterations (10,000, 30,000, and 50,000) with a thinning interval of 1. The heterogeneity among the studies included in the analysis was assessed using the I-squared (I^2) statistic, explained as a measure of how much variability between study results is due to real differences rather than chance. An I^2 value exceeding 50% was indicative of high heterogeneity, whereas a value below 50% suggested low heterogeneity (Vesterinen et al. 2014).

In accordance with the results of the heterogeneity test, either random-effects or fixed-effects consistency models were employed to evaluate the findings. The Gelman-Rubin diagnostic method (Gelman and Rubin 1992) was

utilized to assess the convergence of MCMC iterations, with the optimal MCMC iteration being determined based on the potential scale reduction factor (PSRF). The iteration exhibiting the lowest PSRF value was deemed the most suitable for data analysis. To establish the overall rankings of neonicotinoids based on their toxicity within the framework of network meta-analysis, Bayesian rank probabilities and surface under the cumulative ranking curves (SUCRA) were utilized. SUCRA values range from 0 to 1, where higher values indicate a greater probability that a treatment ranks among the most extreme positions within a given outcome (i.e., highest mortality or lowest LD₅₀/LC₅₀ in the context of toxicity) and was employed for this purpose. The results of the network meta-analysis (NMA) were presented as pooled odds ratios (ORs) for mortality and standardized mean difference (SMD) accompanied by 95% credible intervals (CrI).

A node-splitting analysis was conducted to assess the coherence of network meta-analysis by examining the discrepancies between direct and indirect evidence. To investigate publication bias, Egger's regression test (Egger et al. 1997), described as a statistical method used to assess potential publication bias, was employed. To evaluate the potential influence of study-level characteristics on treatment effect estimates, network meta-regression (NMR) models were constructed by incorporating dose of neonicotinoid, exposure time, honey bee species, and sample size as covariates. The primary NMA model did not include covariates and served as the reference model for comparison. In addition to the fully adjusted NMR model including all covariates simultaneously, intermediate models incorporating individual covariates were explored during preliminary analyses. However, these intermediate models did not provide meaningful improvement in model fit compared to the fully adjusted model and were therefore not retained in the final presentation. Model fit between the primary NMA and the extended NMR model was compared using the deviance information criterion (DIC), a Bayesian model selection metric that balances goodness-of-fit with model

complexity, where lower values indicate a better trade-off between fit and parsimony.

2.5. Comparison with regulatory reference values

To contextualize the toxicity estimates obtained from the network meta-analysis, official acute contact LD₅₀ values for *Apis mellifera* were extracted from the PPDB (Lewis et al. 2016). To formally assess the agreement between LD₅₀ values reported in the literature (included in the NMA) and those listed in the PPDB, a Spearman rank correlation analysis was conducted. This non-parametric test evaluates the strength and direction of the monotonic association between two sets of ranked values. The correlation analysis was used to determine whether the relative ordering of neonicotinoid toxicity derived from published studies was consistent with regulatory reference values.

3. RESULTS

3.1. Study selection process

The study selection process is illustrated in the PRISMA flow diagram presented in Figure 1. Initially, a total of 275 studies were identified through an extensive search of relevant databases and other sources. After dropping 42 duplicate entries, 45 articles were excluded due to their irrelevance to the research topic or because they were formatted as abstracts or reviews. Following this, 157 articles were deemed ineligible for inclusion based on specific criteria, which included a lack of focus on neonicotinoids (89 articles), inadequate data provision (25 articles), or the absence of results in percentage for mortality and in mean for LD₅₀ and LC₅₀ (43 studies). Ultimately, 31 studies were determined to be appropriate for inclusion in the network meta-analysis; of these, 16 studies were focused on honey bee mortality (Laurino et al. 2011; Marzaro et al. 2011; Sgolastra et al. 2012; Farooqui 2013; Matsumoto 2013;

Stanley et al. 2015; Badawy et al. 2015; Williams et al. 2015; Charreton et al. 2015; Grassl et al. 2018; Wood et al. 2019; Shah et al. 2020; Almasri et al. 2020; Tarek et al. 2021; Nasir 2023; Sarmad et al. 2025), 12 studies focused on LD₅₀ (Suchail et al. 2000; Laurino et al. 2011, 2013; Di Prisco et al. 2013; Badawy et al. 2015; Zhu et al. 2015; Yasuda et al. 2017; Calatayud-Vernich et al. 2019; Ulziibayar and Jung 2019; Shah et al. 2020; Tarek et al. 2021; Zhang et al. 2022), and seven studies focused on LC₅₀ (Laurino et al. 2011, 2013; Farooqui 2013; Shaker et al. 2017; Vinothkumar et al. 2020; Ahmed et al. 2023; Sarmad et al. 2025). It should be noted that some studies were investigated two traits.

3.2. Network plots

The comparative network plot of included studies is depicted in Figure 2. As can be seen from the plots, the most direct comparisons were conducted between control and thiamethoxam treatments when mortality was considered. Most comparisons of LD₅₀ and LC₅₀ values of neonicotinoids belonged to clothianidin-imidacloprid (Figure 2b) and acetamiprid-imidacloprid (Figure 2c), respectively.

3.3. Heterogeneity, inconsistency, and publication bias analyses

The majority of *p*-values derived from the node-splitting methodology exceeded the threshold of 0.05 for both direct and indirect comparisons, indicating an absence of local discrepancies. The findings from Egger's test revealed no significant evidence of publication bias (*p* = 0.34). Sensitivity analyses, which entailed the exclusion of smaller studies, produced results that were predominantly consistent. Most direct treatment comparisons were classified as having moderate to high quality, whereas only a limited number of indirect comparisons exhibited a high risk of bias. In conclusion, the network-based synthesis approach demonstrated robust

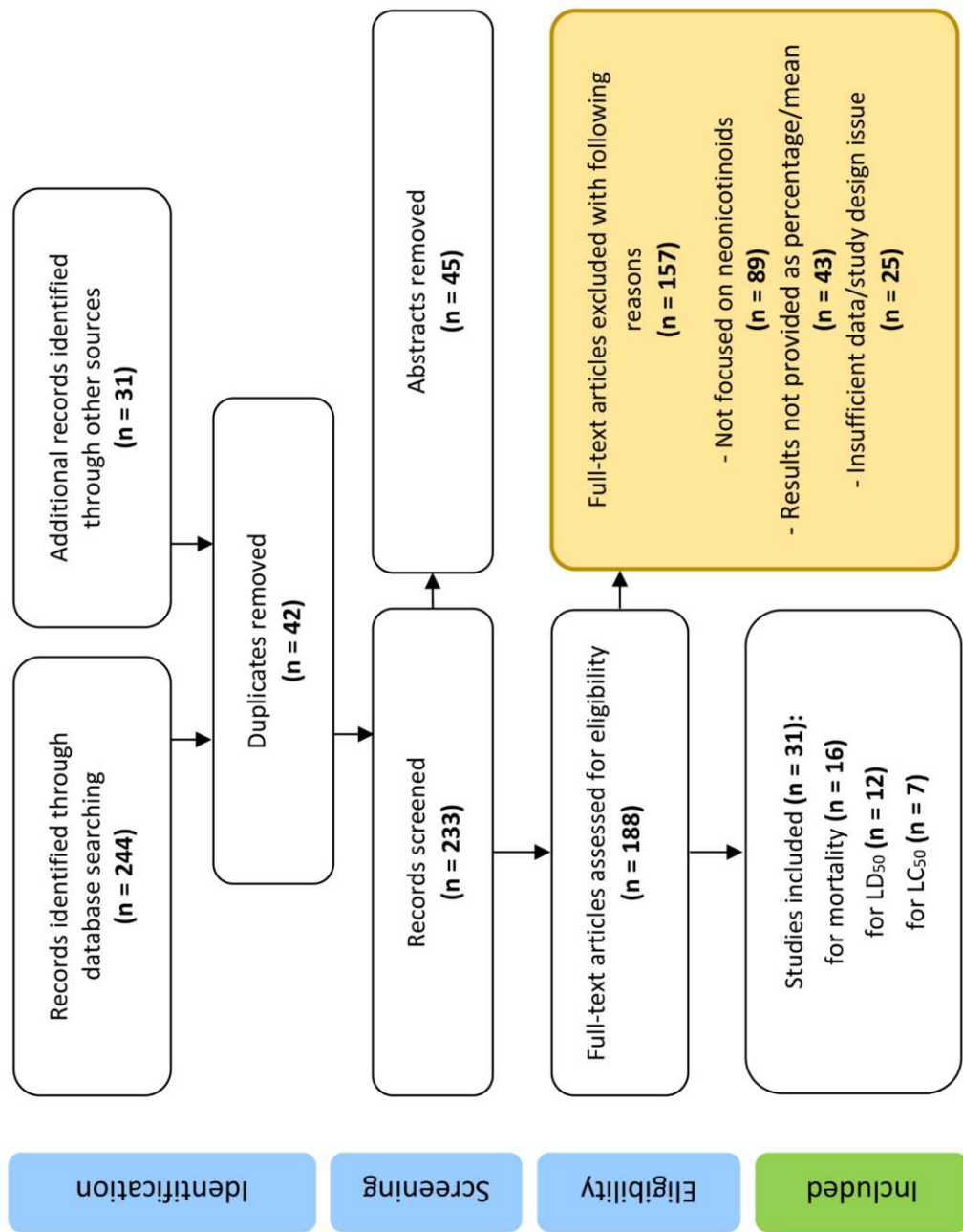


Figure 1. PRISMA flow chart of study selection

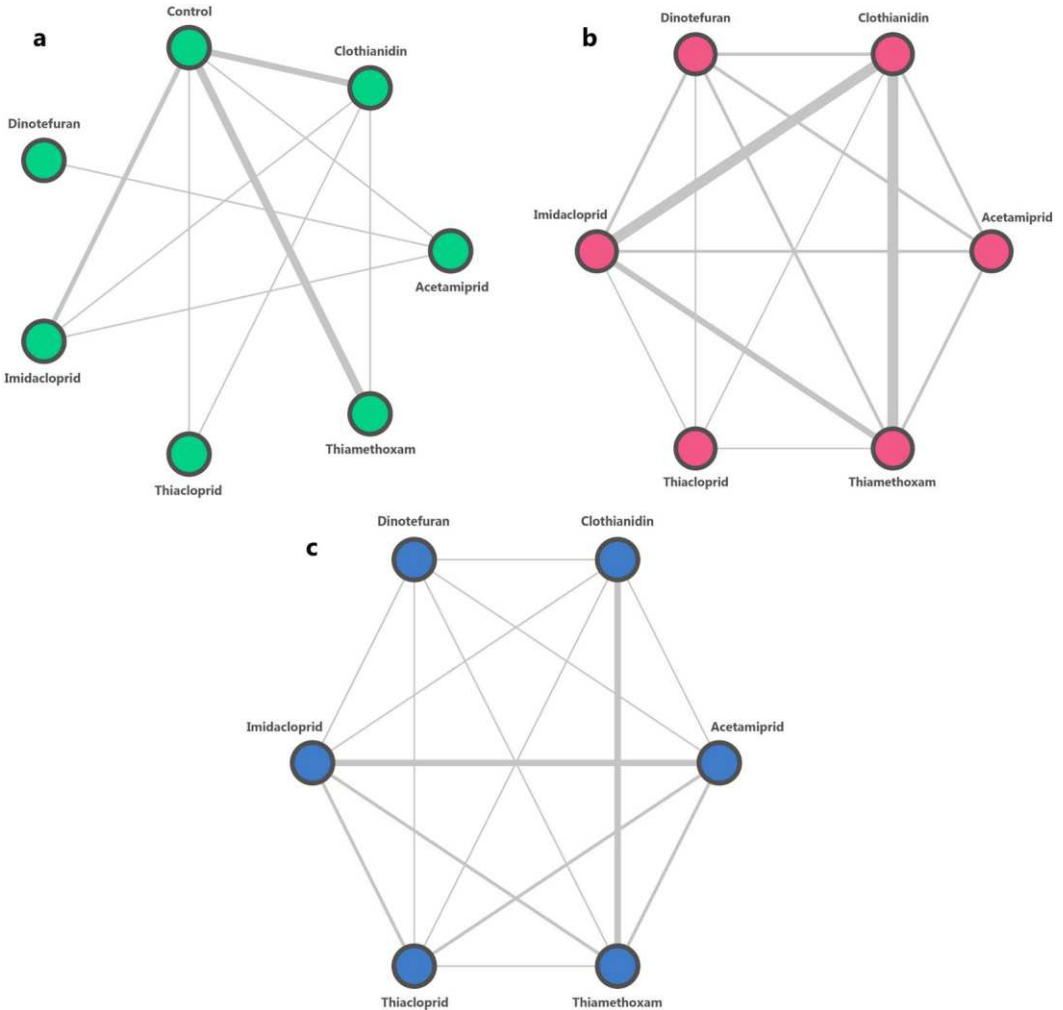


Figure 2. Network plots of the comparison between neonicotinoid insecticides based on their impact on honey bee mortality (a), LD₅₀ value (b), and LC₅₀ value (c). The width of the lines indicates the frequency of studies in which the associated treatments are evaluated against one another.

coherence and validity in evaluating the effects of neonicotinoids on honey bees.

3.4. Network meta-analysis of neonicotinoids toxicity

The pooled estimates derived from the network meta-analyses, which include odds ratios and 95% credible intervals for various neonicotinoid insecticides on honey bees' mortality and

standardized mean difference and 95% credible intervals for neonicotinoids LD₅₀ and LC₅₀ values, are illustrated in Figure 3. A comprehensive comparison was conducted on the toxicity of neonicotinoids including, imidacloprid, clothianidin, thiamethoxam, acetamiprid, thiachloprid, and dinotefuran to honey bees, utilizing both direct and indirect methods. The findings, as illustrated in Figure 3a, indicate that the mortality rate of honey bees in the control group was significantly lower ($p < 0.05$) than that of bees

exposed to dinotefuran (OR = 0.07), imidacloprid (OR = 0.13), and thiamethoxam (OR = 0.12). Additionally, honey bees that came into contact with dinotefuran exhibited higher mortality rates compared to those exposed to other neonicotinoids. As shown in Figure 3b, the LD₅₀ value for acetamiprid was significantly higher by 33.88 µg/bee, 28.68 µg/bee, and 34.85 µg/bee than those of clothianidin, imidacloprid, and thiamethoxam, respectively ($p < 0.05$). However, the LC₅₀ value for acetamiprid was only significantly lower than that of imidacloprid, with a value of 76.94 ppm (Figure 3c).

3.5. Rank probability and SUCRA scores

The rank probability plots illustrating the toxicity of neonicotinoids to honey bees are presented in Figure 4. As shown in Figure 4a, dinotefuran had the highest probability of being ranked as the most lethal compound, followed by thiamethoxam, which peaked as the second most dangerous, and imidacloprid, ranked third. As expected, the control group exhibited the highest rank probability in a single peak, indicating it resulted in the lowest mortality rates among the tested compounds.

According to Figure 4b, acetamiprid stands out with a very high peak, meaning it has a higher rank probability of being less lethal (requiring the highest dose to kill 50% of honey bees' population) in comparison with other neonicotinoid insecticides. Among these, thiamethoxam and clothianidin have comparatively higher peaks in the fifth and sixth bars, suggesting they are more toxic at lower doses compared to other neonicotinoid insecticides.

When considering the LC₅₀ values of neonicotinoid insecticides, imidacloprid displayed a prominent peak in the sixth bar, indicating a high probability of being the most toxic at lower concentrations, followed by thiamethoxam and clothianidin. In contrast, dinotefuran exhibited lower rank probabilities, suggesting that it is likely the least toxic in terms of environmental concentration.

The SUCRA scores for various neonicotinoids evaluated in the network are presented in Figure 5. The SUCRA analysis indicated that dinotefuran, with a score of 0.76, was the most lethal neonicotinoid insecticide concerning honey bee mortality. In contrast, clothianidin, with a score of 0.38, was identified as the neonicotinoid with the lowest hazard for honey bees (Figure 5a). Regarding LD₅₀ values, thiamethoxam and acetamiprid were determined to be the most and least toxic neonicotinoids for honey bees, with scores of 0.76 and 0.05, respectively (Figure 5b). When considering LC₅₀ values, imidacloprid and thiacloprid had scores of 0.84 and 0.22, respectively, indicating that imidacloprid was the most toxic while thiacloprid was the less toxic among the neonicotinoids assessed.

3.6. Network meta-regression

The deviance information criterion (DIC) for the network meta-regression models showed that the DIC value for the primary NMA (1312.8) was higher than that of the NMR model that incorporated dose of neonicotinoid, honey bee species, exposure time, and sample size as covariates (1305.3), indicating improved model fit when these covariates were included. This suggests that accounting for these variables enhanced the explanatory capacity of the model. The I^2 statistic for both the primary NMA and the NMR remained unchanged at 8%.

3.7. Correlation between NMA-derived SUCRA rankings and regulatory PPDB LD₅₀ values

Spearman's rank correlation was calculated between the SUCRA scores from the NMA (reflecting relative ranking of toxicity based on published empirical studies) and the inverse PPDB LD₅₀ values (1/LD₅₀, reflecting regulatory acute toxicity ranking). A moderate positive monotonic association was observed ($\rho = 0.72$, $p = 0.136$; see Figure 6), indicating some agreement between literature-derived and regulatory

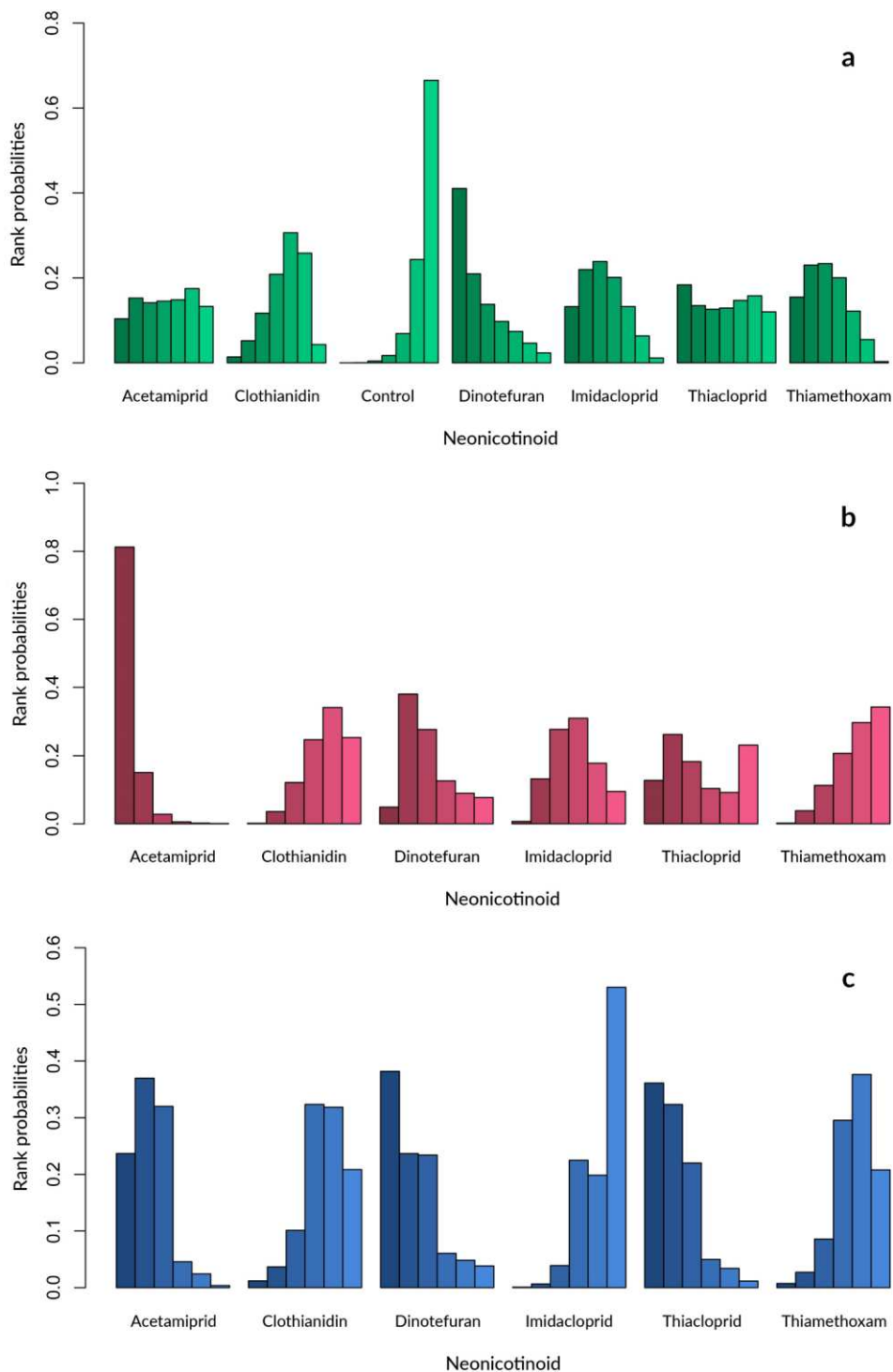


Figure 4. Rank probabilities of neonicotinoid insecticides for mortality (a), LD₅₀ value (b), and LC₅₀ value (c) against honey bees.

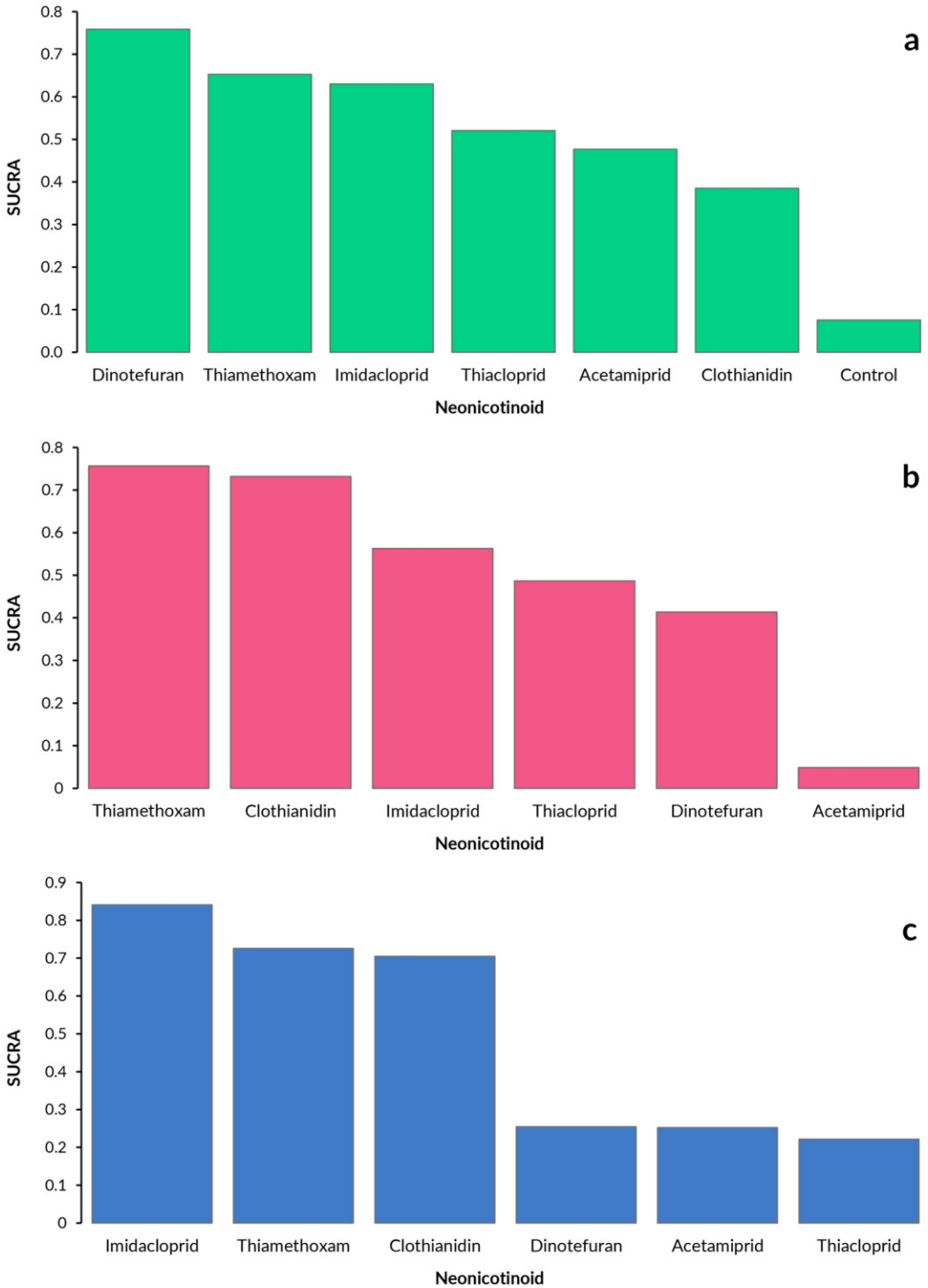


Figure 5. The SUCRA score of neonicotinoid insecticides for mortality (a), LD₅₀ (b), and LC₅₀ (c) against honey bees.

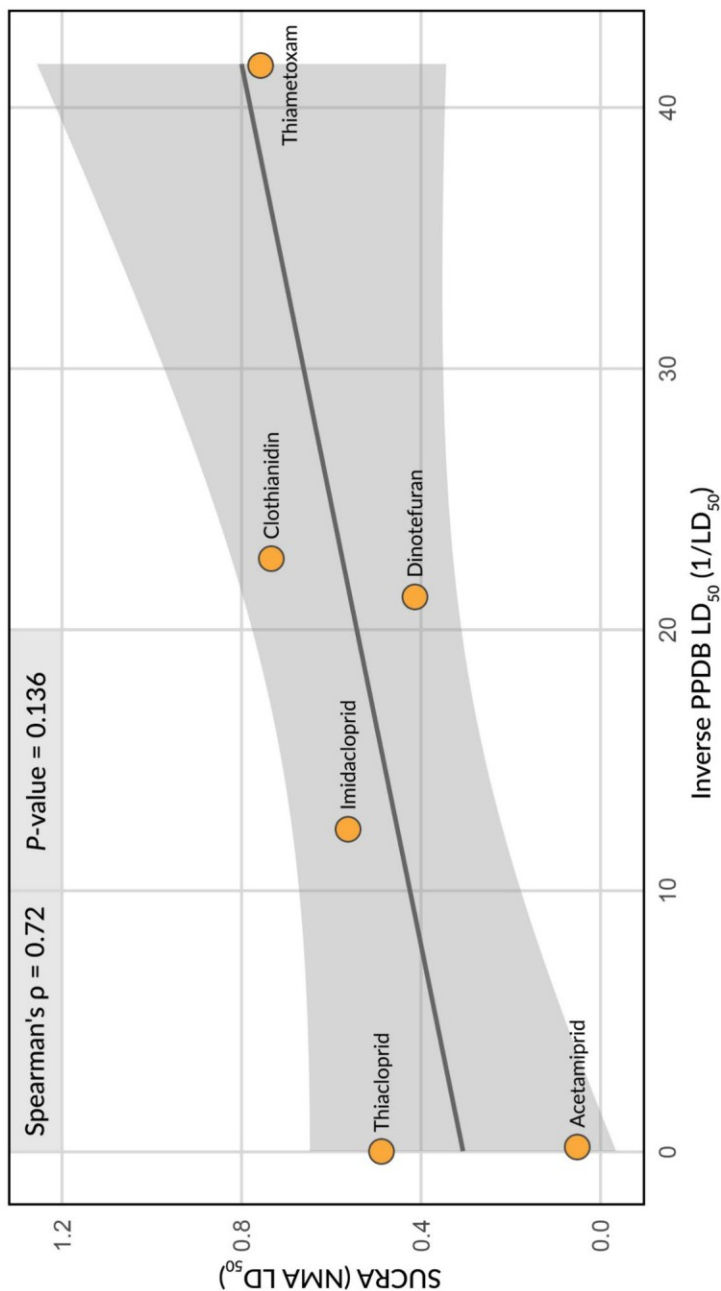


Figure 6. Scatterplot showing the relationship between SUCRA scores from the network meta-analysis for LD₅₀ outcomes (higher SUCRA indicates greater relative acute contact toxicity to honey bees based on empirical literature) and inverse acute contact LD₅₀ values (1/LD₅₀) from the PPDB regulatory database for honey bees (higher values indicate greater toxicity). The gray shaded area represents the 95% confidence band around the fitted line. For the Spearman correlation analysis, LD₅₀ values were inverted (1/LD₅₀) so that higher values consistently correspond to greater toxicity, aligning with SUCRA scores where higher values indicate higher toxicity.

rankings of the six neonicotinoids, although the correlation did not reach statistical significance.

4. DISCUSSION

While regulatory databases provide standardized LD₅₀ values derived from individual studies, they do not account for between-study heterogeneity, indirect comparisons among compounds not tested head-to-head, or uncertainty propagation across multiple endpoints. The present network meta-analysis addresses these limitations by integrating 31 studies within a unified probabilistic framework. In this network meta-analysis, a notable finding was the high mortality rate of honey bees upon contact with dinotefuran. The mortality rate in honey bees exposed to this compound was approximately three, four, two, three, and two times higher than that observed with acetamiprid, clothianidin, imidacloprid, thiacloprid, and thiamethoxam, respectively.

Neonicotinoids exert their insecticidal activity primarily through agonistic action on insect nicotinic acetylcholine receptors (nAChRs), ligand-gated ion channels that mediate fast excitatory neurotransmission in the central nervous system (Tomizawa and Casida 2005; Simon-Delso et al. 2015). Unlike acetylcholine, which is rapidly hydrolyzed by acetylcholinesterase, neonicotinoids bind more persistently to nAChRs, resulting in sustained neuronal depolarization, synaptic dysfunction, paralysis, and ultimately death. While this fundamental mechanism is shared across the class, substantial inter-compound differences in acute and sublethal toxicity arise from variations in receptor subtype selectivity, binding affinity, toxicokinetics, metabolic detoxification, and physicochemical properties influencing bioavailability (Tomizawa and Casida 2005; Matsuda et al. 2009).

Structurally, neonicotinoids are divided into nitro-substituted (nitroguanidine or nitromethylene) compounds, such as imidacloprid, clothianidin, thiamethoxam, and dinotefuran, and cyano-substituted (cyanoamidine) compounds, such as acetamiprid and thiacloprid. This structural distinction has important toxicological

implications. Nitro-substituted neonicotinoids generally exhibit stronger binding affinity to honey bee nAChRs and greater intrinsic potency compared with cyano-substituted analogues (Iwasa et al. 2004; Tomizawa and Casida 2005). Experimental work has shown that honey bee nAChR subtypes display high sensitivity to nitro-substituted compounds, contributing to the very low LD₅₀ values reported for imidacloprid, clothianidin, and thiamethoxam (Iwasa et al. 2004). This mechanistic distinction is consistent with the higher mortality ranking probabilities observed for these compounds in the present network meta-analysis.

Dinotefuran, although sometimes described as a third-generation neonicotinoid, shares the nitroguanidine pharmacophore and acts through the same nAChR-mediated mechanism (Simon-Delso et al. 2015). Its relatively high acute toxicity to honey bees may reflect both receptor affinity and rapid systemic distribution within exposed insects. In addition, some neonicotinoids produce metabolites that retain biological activity at nAChRs, potentially prolonging toxic effects beyond the parent compound's initial binding (Casida 2018). Such toxicodynamic persistence may contribute to the elevated mortality probability associated with dinotefuran in the present synthesis.

Imidacloprid remains one of the most extensively studied neonicotinoids in pollinator toxicology. Beyond its strong affinity for nAChRs, imidacloprid has been shown to produce both acute lethal and sublethal neurobehavioral effects at very low concentrations (Decourtye et al. 2004; Williamson and Wright 2013). Sublethal exposure impairs learning, memory, navigation, and foraging efficiency, indicating that neurotoxicity extends beyond simple lethality metrics (Decourtye et al. 2004; Williamson and Wright 2013; Fischer et al. 2014). These combined toxicodynamic and toxicokinetic factors likely contribute to the consistently low LD₅₀ and LC₅₀ values reported for imidacloprid across regulatory and experimental datasets.

Thiamethoxam presents additional complexity due to its metabolic conversion to clothianidin in plants and insects (Nauen et al. 2003).

This biotransformation may amplify or prolong toxicity depending on exposure route and environmental conditions. From a mechanistic standpoint, both thiamethoxam and clothianidin interact with honey bee nAChRs with high potency (Iwasa et al. 2004). The conversion of thiamethoxam into an active metabolite complicates interpretation of single-compound LD_{50} values and reinforces the value of integrative approaches that synthesize heterogeneous experimental evidence.

In contrast, acetamiprid and thiacloprid consistently demonstrate higher LD_{50} values and lower acute mortality in honey bees. The reduced toxicity of cyano-substituted neonicotinoids is largely attributed to differences in receptor binding and enhanced metabolic detoxification (Iwasa et al. 2004; Manjon et al. 2018). Honey bees possess cytochrome P450 monooxygenases, particularly members of the CYP9Q subfamily, that efficiently metabolize certain neonicotinoids into less toxic derivatives (Manjon et al. 2018). Cyano-substituted compounds appear more susceptible to this detoxification pathway, reducing systemic neurotoxicity relative to nitro-substituted analogues. This mechanistic explanation aligns with regulatory classifications that consider acetamiprid less acutely hazardous to pollinators than imidacloprid, clothianidin, or thiamethoxam.

However, it is critical to recognize that acute LD_{50} values capture only one dimension of toxicity. Sublethal exposure to neonicotinoids has been associated with impaired immune function, oxidative stress, altered gene expression, and increased susceptibility to pathogens such as *Nosema ceranae* (Pettis et al. 2012; Di Prisco et al. 2013). For example, neonicotinoid exposure has been shown to suppress immune-related pathways, potentially increasing vulnerability to viral infections (Di Prisco et al. 2013). Such interactions highlight that colony-level consequences may exceed predictions based solely on acute contact toxicity.

Furthermore, environmental exposure routes influence toxicological outcomes. Systemic translocation into nectar and pollen enables

chronic, low-dose ingestion by foraging bees (Bonmatin et al. 2015; Simon-Delso et al. 2015). Chronic exposure, even at concentrations below acute LD_{50} thresholds, may impair foraging behavior and colony performance (Henry et al. 2012). Therefore, while the present network meta-analysis focuses on mortality and lethal endpoints, its probabilistic ranking should be interpreted within the broader framework of pollinator risk assessment that integrates acute, chronic, and sublethal endpoints.

Although all neonicotinoids share a common nAChR-mediated neurotoxic mechanism, structural differences between nitro- and cyano-substituted compounds, variation in receptor binding affinity, metabolic detoxification capacity, metabolite formation, and exposure dynamics collectively shape their relative toxicity profiles in honey bees. The higher ranking probabilities observed for nitro-substituted compounds in this study are consistent with established mechanistic and regulatory evidence. Conversely, the comparatively lower toxicity ranking of acetamiprid and thiacloprid reflects more efficient detoxification and reduced receptor potency rather than a fundamentally different mode of action. Integrating these mechanistic insights with probabilistic ranking enhances interpretation of comparative toxicity and strengthens the relevance of the findings for evidence-based pollinator protection strategies.

Spearman's rank correlation revealed a moderate positive monotonic association between the SUCRA scores derived from the NMA, reflecting the relative acute contact toxicity of the six neonicotinoids as synthesized from the empirical literature, and the inverse acute contact LD_{50} values from the PPDB database (Spearman's $\rho=0.72$, $p=0.136$). This level of agreement is encouraging, as it indicates that the regulatory rankings of acute contact toxicity to honey bees are broadly consistent with the collective evidence accumulated across independent experimental studies. In other words, the standardized values used in regulatory risk assessments do not appear to diverge markedly from the patterns observed in the published scientific literature.

This concordance is particularly noteworthy because the NMA integrates data from diverse experimental conditions, laboratories, and bee populations, whereas PPDB entries are based on highly standardized test protocols. The observed alignment therefore suggests that regulatory assessments capture the essential relative hazard ordering of these compounds, even when confronted with the natural variability inherent in the wider literature. At the same time, the association did not reach statistical significance at the conventional $\alpha=0.05$ level, indicating that the correspondence is not perfect. Potential sources of discordance may include differences in exposure duration, formulation effects, bee strain sensitivity, or co-exposure factors that are more readily captured in heterogeneous primary studies than in standardized regulatory testing.

A limitation of the present network meta-analysis (NMA) was the restricted sample size in some of the included studies. However, a network meta-regression was conducted to assess the influence of sample size on the overall outcomes. The results indicated that the primary NMA demonstrated a lower deviance information criterion (DIC), which suggests a superior fit of the NMA to the data in comparison to the network meta-regression that accounted for sample size. This finding implies that the effect sizes obtained for neonicotinoid pesticides were not affected by fluctuations in sample size.

A critical concern in NMA is the divergence between direct and indirect comparisons, which poses challenges in the precise estimation and interpretation of treatment effects and comparisons (Van Valkenhoef et al. 2016). This study assessed the inconsistency present in the current NMA through the application of a node-splitting model. The results demonstrated that both direct comparisons and the majority of indirect comparisons were consistent with one another and aligned with the outcomes of the consistency model, with the exception of a few indirect comparisons. Furthermore, the p -values obtained for inconsistency were not statistically significant ($p < 0.05$), thereby supporting the validity and reliability of the NMA findings.

In conclusion, the results of this Bayesian network meta-analysis, derived primarily from laboratory-based acute toxicity data, indicate that dinotefuran exhibits relatively high intrinsic acute toxicity to honey bees among the evaluated neonicotinoids, whereas acetamiprid and thiacloprid (cyano-substituted compounds) consistently show lower intrinsic toxicity profiles under controlled experimental conditions. These findings reflect comparative hazard rather than realized field-level risk. Ecological risk depends on the interaction between toxicity and exposure, which varies substantially according to application method (e.g., seed treatment versus foliar spray), dose, timing relative to flowering, environmental persistence, crop system, and landscape context. Accordingly, regulatory pollinator risk assessments integrate toxicity endpoints with exposure estimates using approaches such as hazard quotients or exposure-to-toxicity ratios. LD_{50} and LC_{50} values alone are therefore insufficient to assess relative field risk or to inform policy decisions without accompanying exposure data.

Beyond ranking intrinsic toxicity, an important objective of this study was to evaluate whether empirical toxicity patterns reported across heterogeneous experimental studies align with regulatory reference values. Overall, the relative rankings derived from the network meta-analysis are broadly consistent with established regulatory classifications, particularly in distinguishing the higher acute toxicity generally associated with nitro-substituted neonicotinoids from the comparatively lower acute toxicity of cyano-substituted compounds. However, the variability observed across independent studies underscores that toxicity estimates are not uniform and may differ depending on experimental design, honey bee population, formulation, and exposure duration. In this respect, quantitative synthesis through network meta-analysis provides complementary insight to standardized regulatory benchmarks by integrating dispersed empirical evidence and accounting for study-level heterogeneity.

Taken together, these findings highlight the importance of cautious, evidence-based

management of neonicotinoids in pollinator-active environments. Agricultural policy and practice should rely on comprehensive risk assessments that integrate toxicity with realistic exposure data, while supporting sustainable pest management strategies that reduce overall pesticide dependency. Future research incorporating field-realistic exposure, chronic and sublethal endpoints, mixture effects, and interactions with additional stressors such as pathogens and nutritional stress will be essential to refine risk evaluation and enhance pollinator protection.

AUTHOR CONTRIBUTION

MR and PM analyzed data and wrote the first draft of the manuscript. SY, FA, and SM collected data. SY, FA, SM, and FH critically revised the manuscript.

FUNDING

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

DECLARATIONS

Ethics approval This study used only publicly available data from previously published articles. No human or animal subjects were involved; therefore, ethical approval was not required.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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