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Review

Lethal, sublethal, and combined effects of pesticides on bees: A meta-analysis and new risk assessment tools

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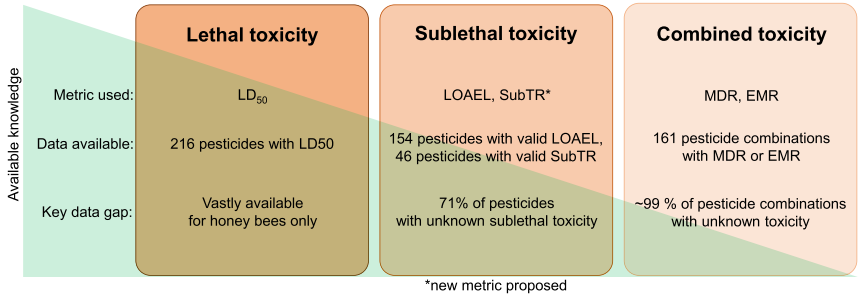
HIGHLIGHTS

- Pesticides cause adverse lethal, sublethal, and combined effects on bees.
- Risk assessments focus on lethal effects, not sublethal or combined ones.
- Vast data gap on sublethal (71 % of pesticides) and combined (~99 %) effects.
- Sublethal Toxicity Ratio (SubTR) proposed to quantify sublethal toxicity magnitude.
- Open access harmonised Lethal, Sublethal, Combined Toxicity Datasets presented.

GRAPHICAL ABSTRACT



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ABSTRACT

Multiple stressors threaten bee health, a major one being pesticides. Bees are simultaneously exposed to multiple pesticides that can cause both lethal and sublethal effects. Risk assessment and most research on bee health, however, focus on lethal individual effects. Here, we performed a systematic literature review and meta-analysis that summarizes and re-interprets the available qualitative and quantitative information on the lethal, sublethal, and combined toxicity of a comprehensive range of pesticides on bees. We provide results (1970–2019) for multiple bee species (*Bombus*, *Osmia*, *Megachile*, *Melipona*, *Partamona*, *Scaptotrigona*), although most works focused on *Apis mellifera* L. (78 %). Our harmonised results document the lethal toxicity of pesticides in bees (n = 377 pesticides) and the types of sublethal testing methods and related effects that cause a sublethal effect (n = 375 sublethal experiments). We identified the most common combinations of pesticides and mode of actions tested, and summarize the experimental methods, magnitude of the interactions, and robustness of available data (n = 361 experiments). We provide open access searchable, comprehensive, and integrated list of pesticides and their levels causing lethal, sublethal, and combined effects. We report major data gaps related to pesticide's sublethal (71 %) and combined (e.g., ~99 %) toxicity. We identified pesticides and mode of actions of greatest concern in terms of sublethal (chlorothalonil, pymetrozine, glyphosate; neonicotinoids) and combined (tau-fluvalinate combinations; acetylcholinesterase inhibitors and neonicotinoids) effects. Although certain pesticides have faced regulatory restrictions in specific countries (chlorothalonil, pymetrozine, neonicotinoids), most are still widely used worldwide (e.g., glyphosate). This work

Abbreviations: ADME, Adsorption, Distribution, Metabolism, and Excretion (ADME); CA, Concentration Addition; EFSA, European Food Safety Authority; EMR, Estimated Mean Ratio; EPA, Environmental Protection Agency; ERA, Environmental Risk Assessment; FRAC, Fungicide Resistance Action Committee; HRAC, Herbicide Resistance Action Committee; IA, Independent Action; IRAC, Insecticide Resistance Action Committee; LD50, median Lethal Dose, the estimated dose causing the death of 50% of the tested population; LOAEL, Lowest Observed Adverse Effect Level; MDR, Model Deviation Ratio; NA, Not Applicable; NOAEL, No Observed Adverse Effect Level; PPDB, Pesticide Property Database; RA, Risk Assessment.

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aims at facilitating the implementation of more comprehensive and harmonised research and risk assessments, considering sublethal and combined effects. To ensure safeguarding pollinators and the environment, we advocate for a more refined and holistic assessment that do not only focus on lethality but uses harmonised methods to test sublethal and relevant combinations.

Contents

1. Introduction

Biodiversity and food production is preserved and enhanced by insect pollinators (Calderone, 2012; Gallai et al., 2009; Garibaldi et al., 2016; Potts et al., 2016). Insect populations, however, are in decline worldwide (Cardinale et al., 2012; Sánchez-Bayo and Wyckhuys, 2019; Wagner et al., 2021). A major insect pollinator is the honey bee (*Apis mellifera* L.), whose importance is increasing given the continuous expansion of land used to cultivate pollinator-dependent crops (Breeze et al., 2011; Klein et al., 2007). Honey bees are used as model species for ecotoxicological trials, environmental monitoring, and as surrogates for other insect pollinators in risk assessments (EFSA, 2013). Their widespread use is because they are relatively easy to manage and monitor, have worldwide distribution, and have a relatively short and well-known biological cycle (Devillers and Pham-Delègue, 2002). Even though they are also crucial to agroecosystems by providing pollination services, other non-*Apis* bee species, such as bumblebees and solitary bees, are more difficult to rear and not as well studied (Garibaldi et al., 2013). Risk assessments addressing this data gap have focused on two model genus, *Bombus* and *Osmia* (EFSA, 2013).

Bee health is threatened by multiple stressors, a major one being pesticides (Goulson et al., 2015). Pesticides, individually or in combination, can cause both lethal and sublethal effects to bees (Tosi and Nieh, 2019). A lethal effect is defined as the one that causes the death of an individual bee. The standard endpoint for lethal toxicity is the medial Lethal Dose (LD_{50}), the estimated dose causing the death of 50 % of the tested population in a given time, which is used globally in research and risk assessment activities (EFSA, 2013; OECD/OCDE, 1998). However, even when standard protocols are used, the LD_{50} values of individual pesticides can vary as they are dependent on specific laboratory (e.g., temperature, relative humidity) and honey bee conditions (subspecies, physiology, season of the experiment, disease prevalence) (Decourtye and Devillers, 2010; Tosi and Nieh, 2019). Thus, a comprehensive harmonised dataset of LD_{50}'s would enable more accurate representation of lethal toxicity estimations.

A sublethal effect is one that does not cause the death of the individual, rather it causes a non-lethal effect. The survival and health of social species, such as the honey bee, rely on the efforts of multiple interacting individuals. Thus, sublethal effects can have broad and subtle effects at the colony level (Belzunces et al., 2012; Desneux et al., 2007). Pesticides can cause multiple adverse sublethal effect on bees, including alteration of bee learning and memory (Decourtye et al., 2003), social networks (Crall et al., 2018), motor functions and phototaxis (Tosi and Nieh, 2017), respiratory rhythm (Hatjina et al., 2013), thermoregulation (Tosi et al., 2016), orientation and navigation (Fischer et al., 2014), flight (Tosi et al., 2017), and homing (Henry et al., 2012). While various methods to detect sublethal effect are developed, they are marginally assessed in risk assessments, if at all, also given an absence of standardization and harmonisation (EFSA, 2013). Other reviews on sublethal effects of pesticides on bees (Barascou et al., 2019; Havard et al., 2020; Noi et al., 2021) have focused on the main behavioural and reproductive endpoints at individual level and extract qualitative values outside systematic review methods. For a quantitative assessment of sublethal toxicity, data should be reported as the Lowest Observed Adverse Effect Level (LOAEL) or the No Observed Adverse Effect Level (NOAEL) (EFSA, 2013). Here, we present a comprehensive systematic literature review that addresses and helps interpret both qualitative and quantitative information derived from sublethal toxicity studies in bees.

When pesticides are found in the environment, they are seldom found alone, rather they often occur in combination (Tosi et al., 2018; Traynor et al., 2021). Pesticide mixtures can be intentional, when created by farmers to increase a treatment's efficiency (i.e., tank mixes), or unintentional; for instance, when bees forage on different crops with different spray regimes or pesticides spray drift onto unintended sources (Heys et al., 2016). Single and multiple pesticide exposure can occur through multiple routes such as nectar (Mitchell et al., 2017), pollen (Tosi et al., 2018), and water (Samson-Robert et al., 2014) before they are stored in the colony (Krupke et al., 2012; Traynor et al., 2021). The effects of pesticides in mixtures can have additive or non-additive (*i.e.*, synergism, antagonism) effects. Additive effects imply that the effect of each pesticide is cumulative

in an additive way: a chemical does not interact with other chemicals in the same mixture, meaning they do not enhance or decrease each other's toxicity during the adsorption, distribution, metabolism, and excretion (ADME) (More et al., 2019). Additive effects indicate that the magnitude of the combined effect equals the sum of the magnitude of the individual effects. Risk assessments typically assume additive effects, as it simplifies the calculation of risk (More et al., 2019). Interactions (non-additive effects) are more complex than additive ones. Two types of interactions are possible: antagonism – combined toxicity is below the sum of each chemical's toxicity – or synergism – combined toxicity is greater than the sum of each chemical's toxicity. These effect types are difficult to include in risk assessments because a different, and more complex, set of calculations and tests are needed (Heys et al., 2016; More et al., 2019). Pesticide combined effects are not measured in the current risk assessment schemes (EFSA, 2013; More et al., 2019; Topping et al., 2020). In part, this is because there is limited information on the combined effects of pesticides on bees (Carnesecchi et al., 2019; Cedergreen, 2014). A comprehensive overview on the qualitative and quantitative combined toxicity in bees is needed. This will allow the development of new tools that more accurately summarize the toxicity and risk of mixed exposures to bees.

For additive effects, Concentration Addition (CA) or Independent Action (IA) is applied as reference models (More et al., 2019). CA models assumes that chemicals share the same mode of action (similar mechanism of toxicity and target site), whereas IA models consider differences in the modes of action of different chemicals (Heys et al., 2016). Interaction effects occur when the combined toxicity deviates from the reference additive model (either CA or IA). The Model Deviation Ratio (MDR) is used to quantify the magnitude of the deviation between the predicted and the observed mixture toxicity (Belden et al., 2007). Like the MDR, the Estimated Mean Ratio (EMR) can estimate the interaction type and its magnitude, although it does so less accurately than the MDR. The EMR is especially reliable for potentiation experiments, *i.e.*, where one of the chemicals in the mixture is non-toxic individually (see Section 2.3 and SI for more details) (Carnesecchi et al., 2019). Conclusions based on combined effects are more robust when supported by MDR, EMR, and a test investigating of the potential deviation from dose addition. The MDR and EMR quantitative results define synergistic, antagonistic, or additive effects based on set thresholds (Table S6; Carnesecchi et al., 2019; Cedergreen, 2014).

Here, we provide an overview of the known toxicological effects of pesticides on bees. We seek to document the state of existing knowledge of pesticide effects and provide future perspectives for a more accurate assessment of pesticide toxicity and risk. We use a systematic literature review approach (Clarke, 2011) to provide both qualitative and quantitative information on the lethal, sublethal, and combined toxicity of a wide range of pesticides in bees. To do this we 1) integrated multiple international toxicity databases to provide harmonised results on the lethal toxicity of pesticide in bees; 2) documented the types of sublethal testing methods and related effects as available in the literature, documenting the amount levels of pesticides that are known to cause a sublethal effect; and 3) identified the most common combinations of pesticides and mode of actions tested, extracting information on the experimental methods (*i.e.*, exposure mode) and assessing the magnitude of the interactions and the robustness of available data.

Our aim is to provide a comprehensive list of pesticides and their levels causing lethal, sublethal, and combined effects. We explore data gaps and the resulting implications for pesticide risk assessment. We highlight the major concerns related to sublethal and combined pesticide risks, identifying pesticides and modes of action of greater sublethal and combined effects concerns, highlighting those with potential health risk to bees.

2. Material and methods

We performed a systematic literature review and meta-analysis on the lethal, sublethal, and combined toxicity of pesticides on bees; the data collected are reported in the Lethal, Sublethal, and Combined Toxicity Datasets, respectively (10.6084/m9.figshare.20208659).

We used specific databases to extract information on the inherent properties of pesticides and their lethal toxicity (see below). We used peer-reviewed scientific articles when punctual specific information was missing.

For sublethal and combined effects, we reviewed published data using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) procedure (SI methods, Figs. S1–S2, Tables S1–S3) (EFSA, 2010; Schaefer and Myers, 2017). Within PRISMA, we followed the PECO (Population, Exposure, Comparison, Outcome) method used for toxicology research without the Comparison element (EFSA, 2010; Schaefer and Myers, 2017). Because a single reference may have studied more pesticide exposures and more endpoints, the number of pesticides screened and the number of references do not necessarily correspond to the number of experiments performed. In this work, each experiment is defined as a trial that reported the results of a unique endpoint and pesticide exposure. Our literature review was concluded in May 2019. We extracted both qualitative and quantitative data for each experiment performed, when possible.

We will use a global approach that is not limited by pesticide authorisation changes across time and space (*i.e.*, a pesticide use authorisation may be different depending on countries and years), and thus focus on chemical toxicity independently on the authorisation status of pesticides. Governmental websites provide up-to-date information on pesticide authorization (*i.e.*, https://ec.europa.eu/food/plants/pesticides/eu-pesticides-database_en). We used Insecticide Resistance Action Committee (IRAC), Fungicide Resistance Action Committee (FRAC), and Herbicide Resistance Action Committee (HRAC) classifications to define pesticide functions and mode of actions. When multiple pesticides of the same chemical group display similar effects, they may be grouped by chemical group name (*i.e.*, neonicotinoids) in the text for simplicity. We classified the insecticides used by beekeepers to control varroa as varroacides (*i.e.*, thymol), as they tend to be more common in hive matrixes than other pesticides, because they are directly applied inside honey bee colonies. We used NA when the results were “Not Applicable”, for example when the pesticide's type or Mode of Action was unknown or not found.

2.1. Lethal toxicity

We used major databases to extract lethal pesticide information on honey bees to consider for toxicity variability: the EFSA OpenFoodTox, the Pesticide Property DataBase (PPDB), the Environmental Protection Agency (EPA) (Lewis et al., 2016). When data from the databases was missing, we used scientific peer-reviewed literature to extract qualitative information on pesticides and harmonise the key reference point for lethal toxicity (LD_{50}, Lethal Toxicity Dataset, Carnesecchi et al., 2020). We additionally calculated the minimum, the maximum, the range, and the second and third quartile for each pesticide's LD_{50}. We thus did not perform a systematic literature review for lethal toxicity, as preliminary searches confirmed that the information was mostly available through the databases.

2.2. Sublethal toxicity

From each scientific article, we extracted the studied bee species, bee type (larvae *vs* adults), exposure mode, feed quality and quantity, the sublethal testing method used, the pesticide tested, and the LOAEL. We included experiments that reported a significant effect of the pesticide as compared to control.

2.2.1. Types of sublethal experiments

Pesticides can cause numerous types of sublethal effects, which can be measured as multiple endpoints through different experimental methods. We categorized the sublethal effects observed to comprehensively accommodate multiple measures of sublethal testing methods and effects. We used three main sublethal effect categories (physiology, behaviour, cognition) and multiple subcategories (Table S4; Belzunces et al., 2012; Desneux et al., 2007; Pisa et al., 2017; Tosi and Nieh, 2019).

For each experiment, we further extracted the information related to the pesticide exposure mode (acute *vs.* chronic, oral *vs.* contact).

2.2.2. Sublethal toxicity quantification and magnitude

For each pesticide, we determined the lowest dose or concentration that was shown to significantly alter bee health *via* sublethal effects as compared to control (LOAEL). LOAEL values for each pesticide were separately extracted and summarized by type of sublethal experiment, thus taking into consideration the sublethal testing method and endpoint used, the exposure mode, the studied bee species, and the subject age (larvae *vs* adults).

Using the sublethal (LOAEL) and lethal (LD_{50}) toxicities of each pesticide, we calculated the Sublethal Toxicity Ratio (SubTR). The SubTR is the ratio between a pesticide's LOAEL and LD_{50}, thus corresponding to a sublethal to lethal toxicity ratio. It measures the intrinsic potency of a chemical's sublethal effects, in other words the impact of a pesticide's sublethal effect as compared to the standard lethal one. The SubTR can be used to quantify the magnitude of the sublethal toxicity of a pesticide. Its formula is reported in Eq. (1):

$$\mathrm{SubTR}_i = \frac{\text{sublethal toxicological endpoint}_i}{\text{lethal toxicological endpoint}_i} = \frac{\mathrm{LOAEL}_i}{\mathrm{LD}_{50\ i}} \tag{1}$$

The SubTR outcome corresponds to the amount of lethal dose causing a sublethal effect: the lower the SubTR, the lower the dose causing a sublethal effect as compared to the lethal effect. Simplifying, the lower the SubTR, the worse for the organisms. The SubTR can be used to highlight pesticides that cause relevant sublethal effects. Because the LD_{50} values were typically available for adult honey bees only, we calculated the SubTR for experiments using adult honey bees.

The numerator and denominator of the SubTR should be calculated using the same exposure mode. In this work we computed the toxicity data from oral and contact exposure modes separately, to improve accuracy. In cases where the reviewed literature did not present standardized exposure data (*i.e.*, if the exposure was expressed as a concentration, but not as a dose of pesticide per bee), we estimated the daily doses ingested per organism following standard methods (OECD/OCDE, 2017; EFSA, 2013, 2012). To limit variability inherent in extrapolating data from incomplete datasets, we estimated daily doses only from studies that used standard feed (50 % sucrose solution; EFSA, 2013, 2012). We used the average consumption of sugar per bee per day (50 mg) and the density of 50 % sucrose solution (1.22965 kg m^{-3}; EFSA, 2013, 2012). When the only value available to estimate the LOAEL was a concentration, its unit measure may indicate a value per day (Sublethal Toxicity Dataset).

2.2.3. Pesticide exposure monitoring and sublethal toxicity testing: data availability

We compiled a list of all pesticides and metabolites screened by major pesticide monitoring surveys that used honey bees in multiple places in Europe and the U.S.A. to collect information on each pesticide exposure monitoring activity (Monitored Pesticides Dataset). We specifically collected and merged lists of pesticides screened in exposure monitoring surveys performed both internationally by the European Union Reference Laboratory (eurl-bee.anses.fr) and the European Horizon 2020 project Poshbee (poshbee.eu), and at national level in Spain (Calatayud-Vernich et al., 2018), Italy (Porrini et al., 2016; Tosi et al., 2018), and the U.S.A. (APHIS, Traynor et al., 2021; Pacific North West project, unpublished). The monitoring surveys were selected based on the availability of pesticide screening data. This list was developed to represent a real-world benchmark of the most screened pesticides in environmental exposure monitoring surveys. The number of times a pesticide was included in the list of screened pesticides of a monitoring survey allowed to quantify the frequency different pesticides are screened for in real-world monitoring activities. This information, together with the sublethal toxicity data we collected, allows us to identify if a pesticide may be over or under investigated as compared to their toxicity. The data availability on sublethal toxicity of the pesticides screened in monitoring surveys highlights data gaps that would impede estimations of sublethal risks.

2.3. Combined toxicity

We provide qualitative and quantitative information on additive and non-additive toxicity, including experiments that tested combinations in single-dose as well as full dose-response designs. We further propose a set of methods to estimate the magnitude of the interaction and the robustness of available data.

We used three parameters to estimate the magnitude of the combined toxicity and the robustness of the available data:

- the Model Deviation Ratio (MDR) (Belden et al., 2007; Carnesecchi et al., 2019; Cedergreen, 2014), as defined in Eq. (2):

$$\mathrm{MDR} = \frac{\text{predicted TU}_m}{\text{observed TU}_m} \tag{2}$$

where the MDR is used as quantitative measure for the compliance between observed mixture toxicity and the toxicity predicted by Concentration Addition. The Toxic Unit (TU) quantifies the interactions of pesticides in binary combinations and corresponds to the ratio of the expected dose of the mixture and its LD_{50} (Jonker et al., 2005). The MDR thus represents the magnitude of the deviation between the predicted model (predicted Toxic Unit of the mixture, TU_m) and the experimental data (observed TU_m, Belden et al., 2007).

- The Estimated Mean Ratio (EMR) (Carnesecchi et al., 2019; More et al., 2019), as defined in Eq. (3):

$$\mathrm{EMR} = \frac{\mathrm{EM}_i}{\mathrm{EM}_{ij}} \tag{3}$$

where EM_i represents the experimental dose (e.g., LD_{50}, LC_{50}, EC_{50}) of given single chemical (chemical *i*) applied in the study and EM_{ij} indicates the estimated toxicity of the binary mixture chemical i + chemical j.

- Evidence of non-additive effects (Table S6).

The MDR is calculated using the LD_{50} of both pesticides and of the mixture (i.e., sum of single TUs, i.e., TU_m). When the LD_{50} for one of the two tested products was not measured in the experiment, the single dose administered is used for MDR calculations (Jonker et al., 2005; More et al., 2019). The EMR computes the LD_{50} of the most toxic chemical in the mixture (i.e., chemical *i*) and the LD_{50} of the mixture (chemical i + j). Because the MDR calculation requires the same and more data than those needed for the EMR calculation, the EMR can be calculated when the MDR is available, but not *vice versa*. Here, we propose to use an integrated approach that uses MDR and EMR to estimate the type of interaction between two chemicals, and to measure the magnitude of their combined toxicity. The availability of MDR and EMR is also a good proxy measure for data robustness, because their calculation requires relevant quantitative data on combined toxicity. Reliable experimental designs should result in an ability to calculate both measures of interactive effects.

We compared the number of possible pesticide combinations bees could be exposed to given real-world data on pesticide exposure with the number of pesticide combinations tested in ecotoxicity experiments. We estimated the number of possible unique combinations resulting from the number of pesticides bees are exposed to using the combination formula:

$$C\,(n,k) = \frac{\mathrm{n!}}{(\mathrm{n-k})!\mathrm{k!}} \tag{4}$$

where n is the total number of pesticides bees can be exposed to (i.e., the number of pesticides found in bee food) and k is the subset of chosen

pesticides taken at a time without repetition (i.e., k = 2 to investigate binary combinations).

3. Results

The results are reported in three datasets that summarize the known qualitative and quantitative lethal (Lethal Toxicity Dataset), sublethal (Sublethal Toxicity Dataset), and combined (Combined Toxicity Dataset) toxicity data. These open access and searchable datasets are intended to help researchers and risk assessors identify research gaps and to encourage more standardized approaches. All datasets are freely available at 10.6084/m9.figshare.20208659. Details of our literature searches, including search parameters, are available in the Supplementary Information.

3.1. Lethal toxicity

We searched for the oral and contact LD_{50s} of 377 pesticides (Lethal Toxicity Dataset), including all pesticides screened in pesticide exposure monitoring surveys (Monitored Pesticides Dataset). We collected oral LD_{50} data on honey bees for 159 pesticides and contact LD_{50} data for 199. Both oral and contact LD_{50} are available for 142 pesticides, while 216 pesticides have either an oral or contact LD_{50}. The systemic insecticides neonicotinoids and fipronil have the greatest oral toxicity ($LD_{50\ imidacloprid}$ = 0.0037 μg bee^{-1}; $LD_{50\ clothianidin}$ = 0.0039 μg bee^{-1}; $LD_{50\ fipronil}$ = 0.0042 μg bee^{-1}; $LD_{50\ thiamethoxam}$ = 0.0056 μg bee^{-1}). Cyfluthrin is the pesticide with greatest contact toxicity (LD_{50} = 0.001 μg bee^{-1}; pyrethroid insecticide). Flonicamid has the lowest oral (LD_{50} = 53,300 μg bee^{-1}) and contact (LD_{50} = 51,100 μg bee^{-1}; pyridine insecticide) toxicities.

Insecticides were the most toxic pesticides. Insecticides with IRAC 5 mode of action (nicotinic acetylcholine receptor (nAChR) allosteric modulators) were the most toxic (lowest mean oral and contact LD_{50}), followed by (in order of decreasing toxicity) IRAC 2, 22, 3, 4, 1, 21 when considering oral exposure, and by IRAC 6, 3, 22, 2, 21, 1 when considering contact exposure.

All original data and references are available in the Lethal Toxicity Dataset.

3.2. Sublethal toxicity

We identified 241 articles (Fig. S2), spanning five decades (Fig. 1), that examined sublethal effects. Seventy five percent of articles meeting our inclusion criteria were published in the last decade.

The preponderance of past experiments used *Apis* (84 % of studies, n = 377 of experiments, Fig. 2A), and mainly Western honey bees (*A. mellifera*, 78 %). Most non-*Apis* studies investigated *Bombus* (12 %; *Bombus terrestris*: 11 %), and only rarely *Megachile rotundata*, *Melipona quadrifasciata*, *Osmia lignaria*, *Partamona helleri*, *Scaptotrigona xanthotrica*, and *Osmia rufa* (<1 % for each species).

Sublethal and combined effect studies on bees are a relatively new field. The earliest *Apis* studies that met the validity criteria were performed in the 1970's. The first studies on different bee genera that met the validity criteria occurred later, *i.e.*, 1988 (*Megachile*), 1994 (*Bombus*), 2003 (*Osmia*), and 2015 (*Melipona*, *Partamona*, and *Scaptotrigona*). Nonetheless, previous *Apis* and non-*Apis* sublethal (Tasei, 1977; Tasei et al., 1977) studies were available, but outside our validity criteria (e.g., not in English).

3.2.1. Types of sublethal experiments

The different types of sublethal experiments (n = 375) are described in Table S4. Most of the sublethal experiments tracked "physiological" measures (main category, 53 %), mainly within the "biochemical" subcategory (31 % of all experiments; n = 375, experiments reporting a valid sublethal category). The second most common experiments investigated bee behaviour (27 %, with the "activity" subcategory being the major portion, 15 % of all studies), followed by cognition (19 %, with the "learning and memory" subcategory corresponding to 15 % of all studies) endpoints (Fig. 2B).

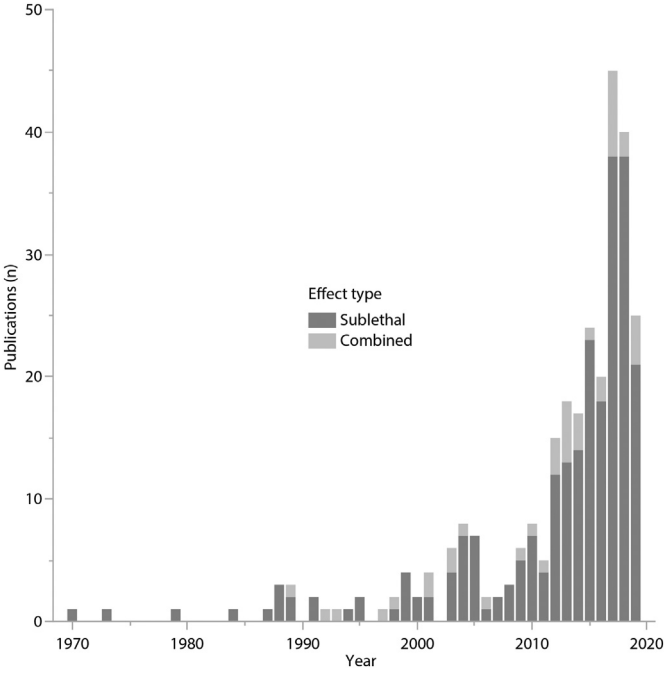

Fig. 1. Annual trend of published peer-reviewed scientific articles investigating pesticide sublethal toxicity (dark grey) and combined lethal toxicity including interactions (light grey) in bees. We report articles (n = 282 overall) that met the systematic literature review inclusion criteria. The number of publications investigating sublethal or combined effects of pesticides by journal are provided in Fig. S3.

A variety of exposure modes were used in these experiments (Fig. 2C). Oral chronic experiments were the most frequent (56 %, n = 329 of experiments with valid exposure mode).

3.2.2. Sublethal toxicity quantification and magnitude

A total of 386 unique sublethal experiments were identified with at least one known scientific article. Only 43 % (168) of the experiments included usable LOAEL data, allowing the quantification of the pesticide level causing significant sublethal effect(s) (Figs. 3–4). Seventy one percent of all pesticides screened (Fig. 4B, n = 358) had no known sublethal toxicity (*i.e.*, LOAEL availability). Data is missing on the LOAEL of 59 %, 84 %, and 89 % of insecticides, fungicides, and herbicides, respectively (Fig. 4B). When comparable LOAEL and lethal toxicity data were available, we were able to quantify the magnitude of the sublethal effect as compared to the lethal one by calculating the SubTRs (Figs. 3–4, S4–S5, Table 1; $n_{pesticides}$ = 46; $n_{experiments}$ = 127). The lower a SubTR value, the worse for bees: a smaller ratio of the lethal dose is needed to elicit a sublethal effect. SubTR values were calculated and categorized by the exposure mode, sublethal endpoint measured (e.g., locomotion, homing), and by pesticide mode of action.

Oral chronic experiments most frequently resulted in low SubTR values (18 % with SubTR <0.0001), indicating that this exposure leads to greater sublethal toxicity (Fig. 3A).

Experiments that measured physiological endpoints for sublethal effects, specifically biochemical ones (Figs. 3B, S4) were the most sensitive, capturing significant effects at low pesticide exposures, when compared to other sublethal endpoint measured ($\chi^2_{(DF=4,\ n=10)}$ = 6.5786, p = 0.03728). In fact, 17 % of experiments that measured physiological endpoints (n = 48), and 20 % of experiments that measured its biochemical subcategory (n = 35) have SubTR's lower than 0.0001, meaning that the sublethal effect occurs at a pesticide level that is 1/10000th of the pesticide's LD_{50}. While less frequent (n = 5), experiments that measured the feeding behaviour were also sensitive, with 20 % resulting in a SubTR lower than 0.0001.

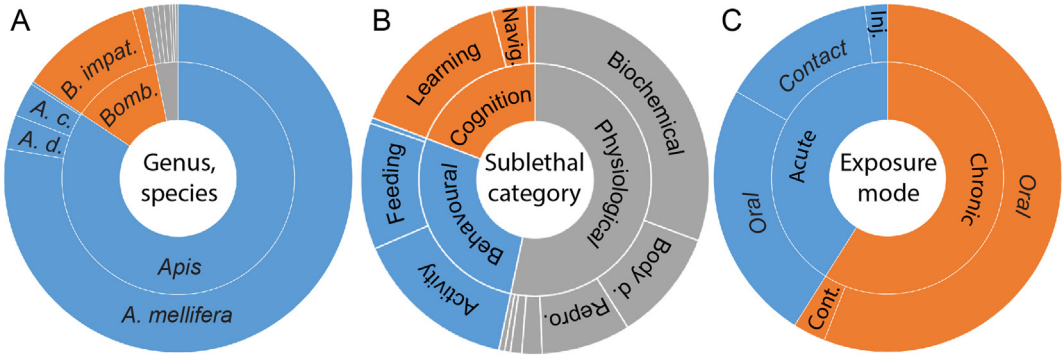

Fig. 2. Proportions of experiments demonstrating a significant sublethal effect of pesticides by the studied (A) bee genus and species, (B) sublethal effect category, and (C) exposure mode. We report in (A) the bee genus (internal ring) and species (external ring) (n = 377), in (B) the main category (internal) and sub-category (external) of sublethal effect type tested (*i.e.*, endpoint measured) (n = 375), and in (C) the exposure type in relation to its duration (internal) and feeding method (external) (n = 329). We describe the full lists of sublethal test categories in Table S4. We use abbreviations in (A) "A. c." for *Apis cerana*, "A. d." for *Apis dorsata*, "B. impat." for *Bombus impatiens*, "Bomb." for *Bombus*; (B) "Navig." for Navigation, "Body d." for Body development, "Repro." for Reproduction; and (C) "Cont." for Contact, "Inj." for Injection. The full data is available in the Sublethal Toxicity Dataset.

Most experiments investigating sublethal effects of pesticides focused on insecticides (72 % of all experiments with known pesticide function; n = 611), and specifically on the nAChR agonist mode of action group, IRAC 4 (22 % of all experiments with known pesticide mode of action, n = 552, Figs. 3C, 5). The most tested pesticides were three neonicotinoids (IRAC 4A, $n_{imidacloprid}$ = 58 experiments, $n_{thiamethoxam}$ = 25, $n_{clothianidin}$ = 17) and a phenylpyrazole ($n_{fipronil}$ = 22 experiments; IRAC 2B) (Fig. 4A). At least three sublethal experiments were performed on 28 unique insecticides, one herbicide (glyphosate) and one fungicide (chlorothalonil) (Fig. 4A).

Nine pesticides had a SubTR lower than 0.0001, meaning that they can cause sublethal effects at levels 10,000-fold lower than their LD_{50} (Table 1, Sublethal Toxicity Dataset). The fungicide chlorothalonil is the pesticide with the lowest SubTR: a level 100,000-fold lower than its lethal level (LD_{50}) caused a significant sublethal effect. The neonicotinoids (IRAC 4A), especially acetamiprid, caused significant sublethal effects at low levels. One thiamethoxam experiment on honey bee larvae and one chlorantraniliprole experiment on the stingless bees *Partamona helleri* F. and *Scaptotrigona xanthotrica* M. also have low SubTRs (respectively 0.000023 and 0.000053). Because the LD_{50s} on larvae or non-*Apis* species were not available, these SubTRs were calculated using LD_{50} values calculated on adult honey bees. This suggests the SubTR approach can be applied on honey bee larvae or non-*Apis* species even with incomplete toxicological data. To improve the accuracy of this assessment, lethal toxicological data on larvae or non-*Apis* species should be collected.

Glyphosate (HRAC G) is the herbicide that most frequently caused sublethal effects at low levels (75 % of Glyphosate experiments with SubTR lower than 0.0001, Fig. 4A, Table 1). Similarly, 100 % of the fungicide

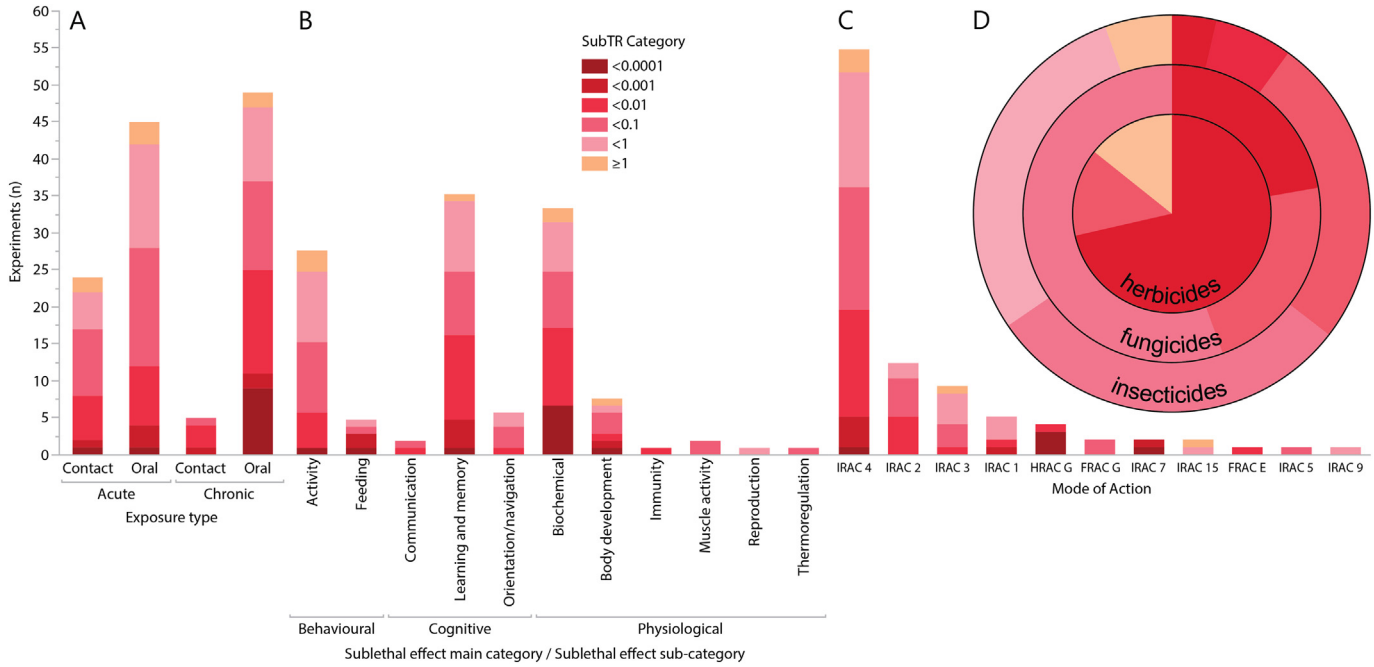

Fig. 3. Number of experiments categorized by magnitude of the sublethal effect by (A) exposure mode, (B) sublethal endpoint measured, (C) pesticide mode of action, and (D) pesticide function. We report the 127 experiments that demonstrated a significant sublethal effect and provided sufficient data for Sublethal Toxicity Ratio (SubTR) calculation. The proportion of each SubTR category per bar is reported in different colours; darker bar colours reflect lower SubTR, and thus greater sublethal toxicity as compared to lethal. Further details on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) procedure are reported in the methods and in Figs. S1–S2, Tables S1–S3. All data is available in the Sublethal Toxicity Dataset.

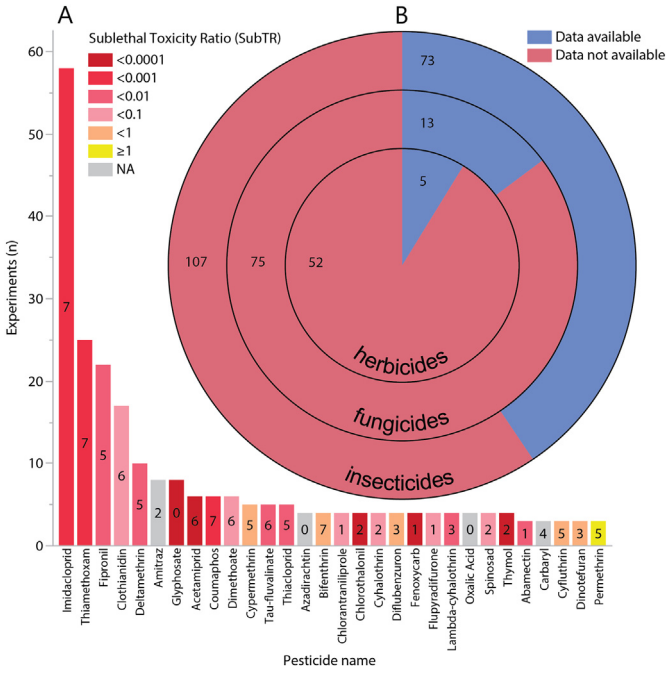

Fig. 4. (A) Number of sublethal toxicity experiments conducted per pesticide, and (B) the proportion of pesticides that are missing the sublethal toxicity level by pesticide function. In (A), for each pesticide, we report the number of experiments demonstrating their significant sublethal effect (Y axis), the magnitude of sublethal toxicity (Sublethal Toxicity Ratio, SubTR; colour scale), and their inclusion in pesticide monitoring surveys (the number of surveys screening for each pesticide exposure is reported within each bar). In (A), for ease of display, we display only pesticides with at least three separate experiments showing a significant sublethal effects (Y $axis_{min}$ = 3). In (B), we show the proportion of pesticides (n = 325, excluding 11 pesticides with unknown pesticide function) for which the LOAEL is known (data available) or unknown (data not available) by pesticide function. In (B), the total data gap (across pesticide functions) on pesticide sublethal toxicity is 71 %. All data is available in the Sublethal Toxicity Dataset. Up to date information on pesticide authorisation in the EU can be retrieved at https://ec.europa.eu/food/plants/pesticides/eu-pesticides-database_en.

chlorothalonil (FRAC M) experiments caused significant sublethal effects at 10000-fold lower level as compared to its lethal effects (SubTR lower than 0.0001, Fig. 3C, D).

3.2.3. Pesticide exposure monitoring and sublethal toxicity testing: data availability

A total of 331 pesticides were identified in our seven exposure monitoring surveys (Monitored Pesticides Dataset). The most frequently studied pesticides were also frequently screened for their environmental contamination through exposure monitoring surveys (Fig. 4A, number within each bar). Among all pesticides that were most frequently tested for sublethal effects (*i.e.*, with at least three separate experiments showing a significant sublethal effects, Fig. 4A), only one herbicide (glyphosate), one insecticide (azadirachtin) and oxalic acid were not monitored for its residues in the environment (Fig. 4A).

LOAELs are unknown for 73 % of the 331 pesticides commonly screened by exposure monitoring surveys (Monitored Pesticides Dataset). LOAELs are mostly unknown for the majority of insecticides (60 %), fungicides (85 %), and herbicides (91 %) that are more frequently screened by monitoring surveys.

3.3. Combined toxicity

The scientific literature on the effects of binary chemical combinations in bees spans four decades, with 42 articles (Fig. 1). Most of the publications on combined effects were published in the last decade (68 % of the articles meeting the inclusion criteria were published in 2011 or after). Most studies tested honey bees only (94 %, of 255 studies with known bee species).

We found results for 361 combined pesticide experiments and 299 unique pesticide combinations. A recent long-term monitoring study found that bees were exposed to 120 pesticides and/or metabolites overall (Traynor et al., 2021), resulting in 8,214,570 possible unique binary pesticide combinations. We decided to estimate binary combinations (k = 2, formula #2) rather than more than two items given that this is the easiest and most frequent method to test combinations. Data on the toxicity levels of binary combinations are only available for less than half of a one thousand of a percent of possible binary combinations (<0.0005 %).

Among the combined effect results (n = 249), 83 % showed interactions (72 % synergistic and 11 % antagonistic) with the remaining 17 % showing no interaction, thus additive effects (Figs. 5). The most frequently tested combinations were between two insecticides or an insecticide and a fungicide (Fig. 5, Combined Toxicity Dataset). Grouped by mode of action, the most frequently tested pesticides were sodium channel modulators (IRAC 3) in combination with acetylcholinesterase inhibitors (IRAC 1), SBI fungicides (FRAC G) and insecticide synergists (IRAC 27, Fig. 5). The varroacide tau-fluvalinate (IRAC 3) was the most investigated pesticide (Figs. 5B, 6C), tested in combination with the varroacide coumaphos (IRAC 1), the synergist insecticide piperonyl butoxide (IRAC 27, Whalon et al., 2009), or the fungicide prochloraz (FRAC G).

NAChR competitive modulators (IRAC 4), such as clothianidin, were frequently studied, often in combination with the sterol biosynthesis inhibitor propiconazole, a fungicide (FRAC G, Fig. 5).

Tested combinations mostly caused synergism (Fig. 5). Only a few of the most frequently tested combinations showed a univocal combined toxicity result between mode of actions (44 %, Fig. 5A) and individual pesticides (55 %, Fig. 5B). Most of the combinations showed a blend of synergistic, additive, and antagonistic results. We thus further analysed the results in terms of robustness of the experiment design related to combined toxicity (Fig. 6).

Table 1
Pesticides with the greatest impact in terms of sublethal effect as compared to lethal ones. We listed the pesticides with the lowest (<0.0001) Sublethal Toxicity Ratio (SubTR) values because the lower the SubTR, the lower the dose causing a sublethal effect (as compared to the lethal effect). The pesticide's mode of action, LD_{50}, LOAEL, SubTR, the endpoints measures (see Table S4 for further details), and the corresponding reference are reported. The pesticides are ordered in ascending SubTR order, since the lowest the SubTR, the worst for the organisms. All data is available in the Sublethal Toxicity Dataset.

Pesticide name	Mode of action (target site)	LD_{50} (μg bee^{-1})	LOAEL (μg bee^{-1}) (10^−6)	SubTR (10^−6)	Sublethal effect category	Reference
Chlorothalonil	FRAC M05	40	200	5	Physiological (Biochemical)	Christen et al., 2019
Pymetrozine	IRAC 9B	117	2033	17	Physiological (Biochemical)	Badawy et al., 2015
Glyphosate	HRAC G	100	2033	20	Behav. (Feeding), Cogn. (Learn., mem.)	Gonalons et al., 2018; Herbert et al., 2014
Fenoxycarb	IRAC 7B	204	6000	29	Physiological (Body development)	Aupinel, 2007
Acetamiprid	IRAC 4A	14.53	488	34	Physiological (Biochemical)	Badawy et al., 2015
Metolachlor	HRAC K3	110	5000	45	Physiological (Biochemical)	Helmer et al., 2015
Atrazine	HRAC C1	100	5000	50	Physiological (Biochemical)	Helmer et al., 2015
Thymol	NA (varroacide)	200	10,000	50	Behavioural (Activity)	Bergougnoux et al., 2013
Folpet	FRAC M04	236	12,100	51	Physiological (Biochemical)	Christen et al., 2019

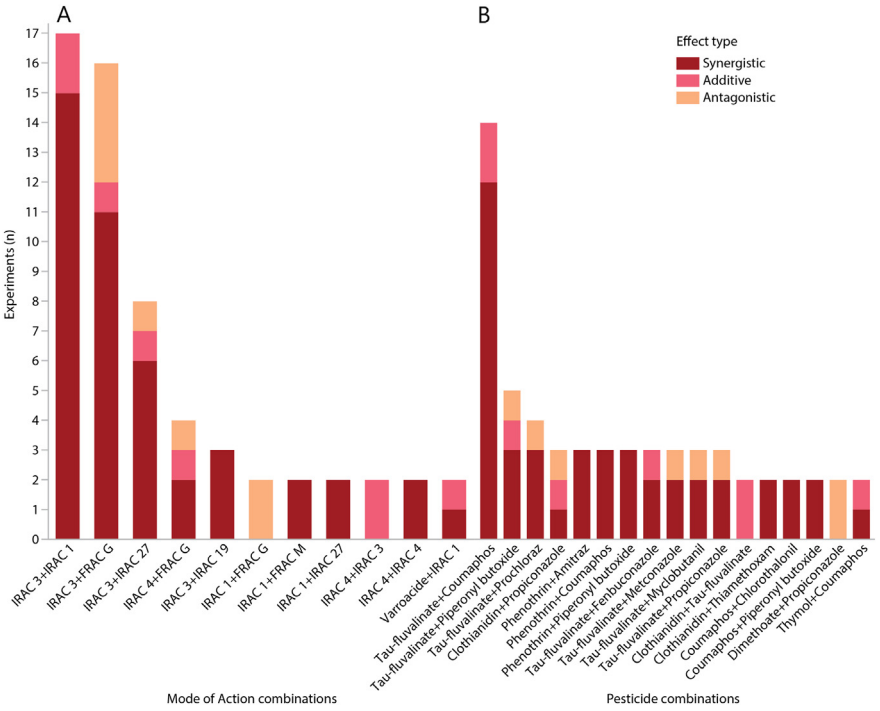

Fig. 5. Number of experiments reporting a combined effect on bees by (A) mode of action or (B) pesticide combinations. In (A), we use the Insecticide Resistance Action Committee (IRAC) and the Fungicide Resistance Action Committee (FRAC) to define pesticide's mode of actions. When the mode of action was not available, we report the pesticide function. Only results derived from at least two experiments are reported (Y $axis_{min}$ = 2). All data is available in the Combined Toxicity Dataset.

A proportion of identified experiments (62 %) provided sufficient quantitative data to allow the calculation of the MDR and the EMR, leading to a more robust assessment of combined effects (Fig. 6, n = 258). Only 36 % of the experiments had a greater robustness with both MDR and EMR available. Most of the experiments with greater data robustness demonstrated synergistic effects (26 %), while only 6 % and 4 % lead to additive or antagonistic effects, respectively (Fig. 6A).

When we include only the most robust combined toxicity results (that are thus based on MDR, EMR, and significance), the variability of combined effects is widely reduced (Fig. S6, n = 28). Following this approach, 80 %

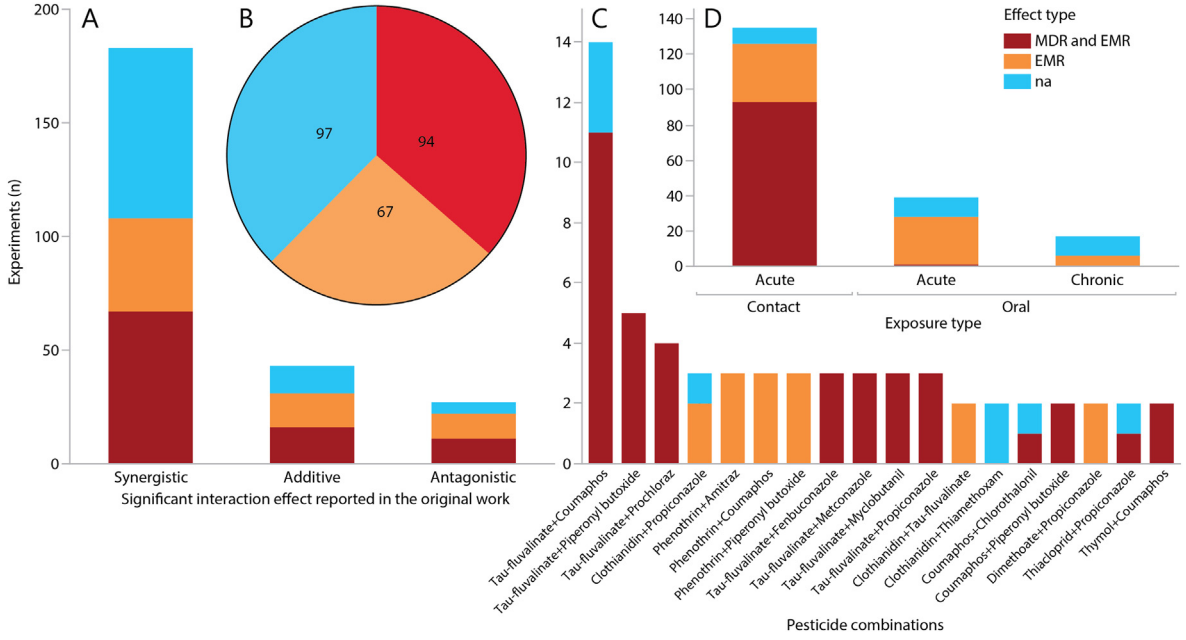

Fig. 6. Number of experiments investigating the combined effects of pesticides in bees in relation to the robustness of the data available (A) by combined effect type, (B) overall, (C) by pesticide combination, and (D) by exposure mode. The availability of the Model Deviation Ratio (MDR) and the Estimated Mean Ratio (EMR) represent an estimate of data robustness. The experimental design is more robust when MDR and EMR are available. We use "na" when the data of scientific articles reporting a combined effect do not provide sufficient data to estimate the MDR or the EMR, e.g., when the results showed a significant interaction effect without a dose-response. See the text for MDR and EMR calculations. For ease of display, in (C), we only display pesticide combinations that were tested by at least two experiments (Y $axis_{min}$ = 2). All data is available in the Combined Toxicity Dataset.

of the combinations showed a univocal synergistic effect for each single pesticide, and only 20 % showed both synergistic and antagonistic results (Fig. S6, Combined Toxicity Dataset).

The most frequent exposure mode was acute contact (49 %, Fig. 6D). None of the studies included in this work used a contact chronic exposure.

4. Discussion

Our literature review shows a large and troubling lack of information on the sublethal and combined toxicity of pesticides to bees. This means that the sublethal and combined risk of most pesticides cannot be accurately assessed. There are no valid sublethal toxicity data on 71 % of pesticides (Fig. 4B). A large knowledge gap also occurs in understanding impacts of combined effects: the vast majority of the binary combinations effects that can theoretically occur in the field are unknown (e.g., ~99 %) (Barascou et al., 2019; Carnesecchi et al., 2019; Cedergreen, 2014; Havard et al., 2020; Noi et al., 2021; Siviter et al., 2021). Accurate risk assessment is further complicated by past sublethal and combined effects studies that did not use standardized methods (Fig. 6). The task of filling these data gaps is daunting. Prioritising the testing of binary combinations that occur most frequently in the field could fill critical data gaps quickly. The urgency felt by the academic community to address these gaps is also encouraging, as the last decade saw 75 % and 68 % of publications on sublethal and combined effects published, respectively (Figs. 1, S7).

The western honey bee is the bee that is used the most in risk assessment studies. This extensive use is attributable to their near global distribution and ease of management. It is easy to test large number of related individuals of western honey bees and perform comparable experiments worldwide. Honey bees, however, are not the only insect pollinators that contribute to biodiversity by providing critical pollination services (Brittain et al., 2013). Pesticide toxicity varies across species (Arena and Sgolastra, 2014), and so pesticide assessments should also consider a wider range of test organisms. While research on non-*Apis* bees is growing (Fig. S7), with 89 % of all experiments conducted on non-*Apis* species in or after 2010 (Fig. S7), more effort to include sublethal and combined toxicity of non-*Apis* bees in risk assessment is necessary.

Our literature review, combined with our application of established and new methods to assess sublethal and combined pesticide risk, highlight the expected risk of insecticides and the less expected risk posed by fungicides and herbicides. Our results raise concern about the impact of herbicides and fungicides on bee health either at single sublethal doses or in combination with other active ingredients. When compared to other pesticides, neonicotinoids (IRAC 4A) cause sublethal effects at smaller fractions of an LD_{50}; however, small fractions of multi-site activity fungicides (FRAC M) and the herbicide glyphosate (HRAC G) can also result in important adverse sublethal outcomes. Current risk assessments do not require thorough investigations on the impacts of fungicides and herbicides on pollinators, and pesticide survey efforts often do not screen for them (Fig. 4A). In part this is because both groups of pesticides are usually considered safe for bees, a concept that is challenged if sublethal or combined effects are considered. Risk assessments should accurately evaluate the individual and combined, lethal and sublethal impact of all products in their evaluation process.

While the overall lack of knowledge regarding sublethal and combined pesticide effect is troubling, it is of particular concern when one considers the quantity of pesticide classes found in real world samples (Tosi et al., 2018; Traynor et al., 2021). Furthermore, while major fungicides were typically screened in pesticide monitoring surveys, herbicides – especially glyphosate, is not (Fig. 4A, but see El Agrebi et al., 2020). Our work focused on the toxicity of active ingredients, although there is evidence of adverse effects caused by inactive ingredients (e.g., inert ingredients such as adjuvants, solvents, carriers), highlighting the need to assess the risk of both inactive ingredients and pesticide formulations to bees (Rinkevich et al., 2015). Even with the increased efforts to collect exposure and toxicity data, large gaps remain limiting the quality of real-world risk assessment of pesticides on bees.

This work aims to facilitate using sublethal and combined effects in pesticide risk assessment as well as interpreting residue data collected in pesticide surveys and poisoning incidents. The data structure proposed (Lethal, Sublethal, and Combined Datasets), based on risk assessment approaches (EFSA, 2013; More et al., 2021, 2019), can serve as model for designing experiments which results can be more useful for implementation by risk assessors and policy makers as in the case of current EFSA and ECHA guidance documents on honey bee (EFSA et al., 2022; ECHA, 2020). This work can also provide the basis for interpreting the risk related to bee poisoning incidents in the field (Chauzat et al., 2010; Kadlikova et al., 2021). We propose and demonstrate the use of the Sublethal Toxicity Ratio (SubTR) value to quantify the magnitude of the sublethal toxicity of a pesticide. SubTR values, calculated from existing literature data, highlighted pesticides with important sublethal toxicities. Tests that measured biochemical outcomes as sublethal effect were the most sensitive, capturing effects at low pesticide levels (SubTR <0.0001). Nonetheless, the real impact of pesticides should be assessed through a range of sublethal testing methods covering also cognitive and behavioural traits. Oral chronic experiments were more frequent and more sensitive exposure modes as compared to contact exposure ones (SubTR <0.0001). We used the LOAEL as sublethal toxicological reference because it is relatively easy to derive from scientific literature and has been a standard reference for decades (Davis et al., 2011, SI Methods, Section 2). Risk assessment may use other values as thresholds, such as the NOAEL or the Bench Mark Dose (BMD). The BMD may be more reliable than the LOAEL approach, given that it requires dose-responses and is thus less dependent on sample size and pesticide dose selection (Hardy et al., 2017). Determining these other values for sublethal effects, however, is more complicated and so fewer data are available. Ongoing efforts to develop *in vivo* and *in silico* models to predict these effects (Carnesecchi et al., 2020) should advance the science; so will more standardized experimental protocols. As these data do become available, risk assessment should consider reporting and using SubTR values. These should be derived from the most accurate sublethal threshold available.

To provide a more robust demonstration of pesticide interactions and to quantify the magnitude of those interactions, we used an integrated approach that combined MDR (Model Deviation Ratio) and EMR (Estimated Mean Ratio) values, as well as statistical testing of the null hypothesis that combined effects are additive. Our approach described the combined toxicity of pesticides by identifying and quantifying their synergistic, additive, or antagonistic relationship (Figs. 5–6, S6). The observed high rate of synergistic effects may be an artifact from the high number of experiments investigating synergism reported in the available scientific literature. The variability in measured combined pesticide effects (only 55 % have an univocal combined effect) is reduced when experiments providing MDR, EMR, and significance results are considered (Fig. S6). The 25 % of studies that calculated these values for a combination of pesticides, most commonly documented a univocal combined effect (80 %, Fig. S6, Combined Toxicity Dataset).

There are no sublethal or combined effect assessment tests required for current environmental risk assessments for bees. While refined methods for the implementation of sublethal and combined effects in risk assessment have been recently developed (Tosi and Nieh, 2019), there are still numerous knowledge and procedural gaps that remain in need of address. Most authorized pesticides do not have sublethal (LOAEL, NOAEL) or combined (MDR, EMR) toxicity information. Even when LOAEL data is available, a wide range of experiments report unit measures that are inadequate for sublethal risk assessments. For example, when testing chronic exposures, the LOAEL is often reported as a concentration, and not as a (daily) dose. Although many LOAEL values can be converted into appropriate toxicological units (*i.e.*, from concentration in food to dose per bees), an accurate conversion requires knowledge of the type of exposure (acute or chronic), the type of food provided in the oral exposure (*i.e.*, pollen or nectar, and their nutritional content, corresponding to carbohydrate or protein content), and the type and age of bees (*i.e.*, in-hive or forager). In fact, food intake varies depending on the type of food and age of bees (EFSA, 2013; Rortais et al.,

2005). Because many factors influence pesticide effects in bees, including age, season, pest and pathogens, and nutritional stress (Alaux et al., 2010; More et al., 2021; Tong et al., 2019), most of the included literature involved laboratory studies (a highly controlled environment). Risk assessments should provide NOAEL or LOAEL sublethal information for individual pesticides, and test binary pesticide combinations that are more likely to both co-occur in the environment and interact synergistically. Experiments should include essential information, often missing, such as pesticide levels, food consumption, exposure mode and duration, and sample size. When possible, we recommend reporting daily dose intake of food and pesticides, and using larger sample sizes which increases the strength of the statistical tests leading to more accurate results. The accuracy of sublethal measurements should be improved, and their connection to Specific Protection Goals (*i.e.*, avoiding unacceptable decreases in colony population or increases in forager mortality, Rortais et al., 2017) explored and defined through common efforts of multiple stakeholders, including researchers, risk assessors, and policy makers.

The European commission recommends that pesticides be authorized when they have "no unacceptable acute or chronic effect on colony survival and development, taking into account effects on honey bee larvae and honey bee behaviour" (European Commission, 2009), but risk assessments to date have typically used lethal toxicity endpoints for adult bees. The absence of standardized protocols for sublethal and combined testing leads to an inability to fulfil EU mandates. Following the methodological recommendations presented in this work, as well as more comprehensive ecotoxicological testing, would go a long way to facilitating properly informed pesticide policy. The development and implementation of standardized sublethal testing protocols is also needed. These protocols should be used to fill large knowledge gaps in sublethal and combined pesticide research and risk assessment. Sublethal and combined assessments should also become a standard part of risk assessments in bees.

5. Conclusions

This meta-analysis demonstrates how much we do not know about the sublethal and combined effects that pesticides have on bees. We propose new methods and approaches for analysing and interpreting the lethal, sublethal, and combined effects of pesticides in bees. This research allows for new insights on pesticide ecotoxicity and identifies concerns for bee health. Our results highlight the importance of considering the underestimated sublethal and combined impact of fungicides and herbicides on bees. We hope our integrative overview of the available ecotoxicological data in bees (the Lethal, Sublethal, and Combined Toxicity Datasets and the Monitored Pesticides Dataset) will facilitate the implementation of our proposed approach to future research and risk assessment, one that better accounts for real-world complexities. Our data can act as the building stone for standardized and harmonised lethal, sublethal, and combined toxicity datasets, aiming at benefitting researchers and risk assessors. Risk assessors aim to keep people and the environment safe from the unacceptable consequences of pesticide use. The use of harmonised and standardized approaches from experimental designs to data collection and interpretation, such as we describe here, can help risk assessors more effectively meet their laudable mandate. We conclude emphasising the need for a more refined and holistic assessment of pesticide risks that do not only focus on lethality, towards a healthier environment for bees.

CRediT authorship contribution statement

Conceptualization: ST.
Methodology: ST, CS, MPC.
Data collection, curation: CS, ST, EC.
Data analysis, visualization: ST, CS.
Writing – original draft: ST, CS.
Writing – review & editing: ST, CS, EC, MPC, DVE.
Supervision: ST, MPC, DVE.
Funding acquisition: MPC, DVE, ST.
Project administration: MPC, ST.
Resources: MPC, ST, DVE.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

The Supplementary Information file includes additional figures and tables. The four datasets are freely available as Figshare repository at doi:10.6084/m9.figshare.20208659. The "Lethal Toxicity Dataset" reports lethal toxicity data of pesticides in bees. The "Sublethal Toxicity Dataset" reports sublethal toxicity data of pesticides in bees. The "Combined Toxicity Dataset" reports the combined toxicity data of pesticides in bees. The "Monitored Pesticides Dataset" reports the pesticides screened by exposure monitoring surveys. Supplementary figures and tables to this article can be found online at doi:https://doi.org/10.1016/j.scitotenv.2022.156857.

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