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Impacts of neonicotinoids on biodiversity: a critical review

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Abstract :

Neonicotinoids are the most widely used class of insecticides in the world, but they have raised numerous concerns regarding their effects on biodiversity. Thus, the objective of this work was to do a critical review of the contamination of the environment (soil, water, air, biota) by neonicotinoids (acetamiprid,

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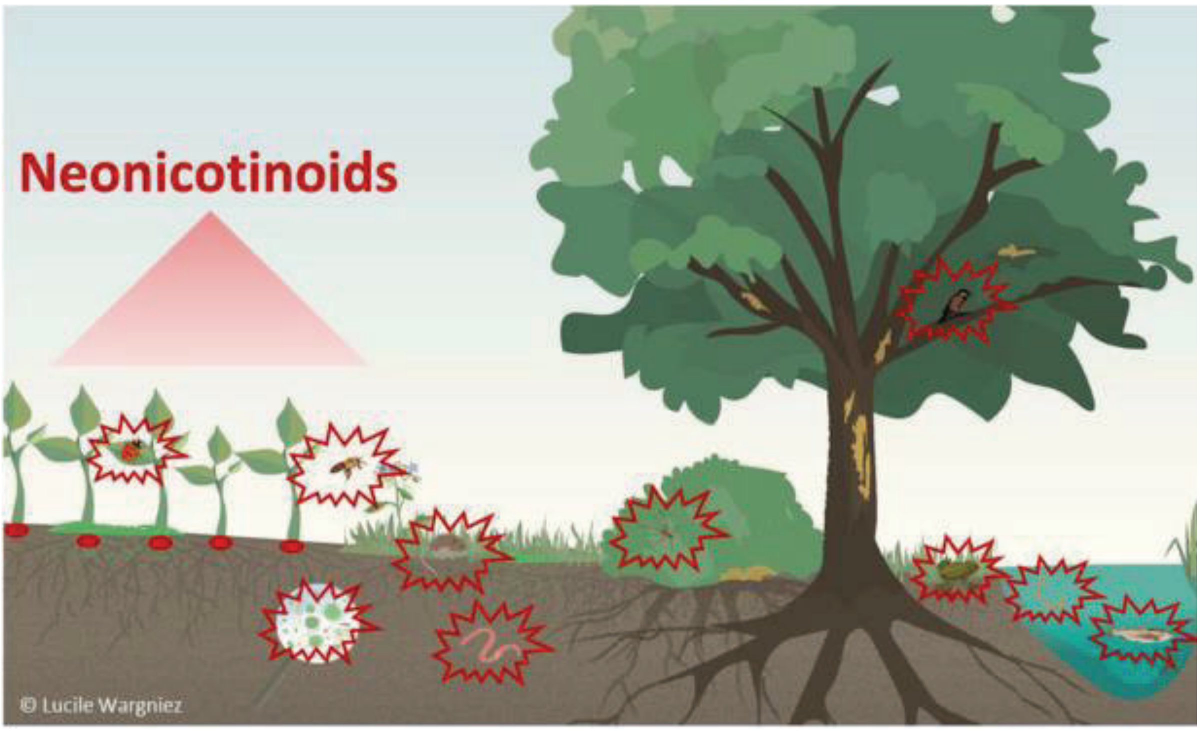
clothianidin, imidacloprid, thiacloprid, thiamethoxam) and of their impacts on terrestrial and aquatic biodiversity. Neonicotinoids are very frequently detected in soils and in freshwater, and they are also found in the air. They have only been recently monitored in coastal and marine environments, but some studies already reported the presence of imidacloprid and thiamethoxam in transitional or semi-enclosed ecosystems (lagoons, bays, and estuaries). The contamination of the environment leads to the exposure and to the contamination of non-target organisms and to negative effects on biodiversity. Direct impacts of neonicotinoids are mainly reported on terrestrial invertebrates (e.g., pollinators, natural enemies, earthworms) and vertebrates (e.g., birds) and on aquatic invertebrates (e.g., arthropods). Impacts on aquatic vertebrate populations and communities, as well as on microorganisms, are less documented. In addition to their toxicity to directly exposed organisms, neonicotinoid induce indirect effects via trophic cascades as demonstrated in several species (terrestrial and aquatic invertebrates). However, more data are needed to reach firmer conclusions and to get a clearer picture of such indirect effects. Finally, we identified specific knowledge gaps that need to be filled to better understand the effects of neonicotinoids on terrestrial, freshwater, and marine organisms, as well as on ecosystem services associated with these biotas.

Graphical abstract



Keywords : Pesticides, Plant protection products, Ecotoxicity, Ecotoxicology, Agrosystems, Collective scientific assessment

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Introduction

Neonicotinoids are systemic insecticides (i.e., they diffuse throughout the treated plants to protect them from pests) that act on the central nervous system of insects by targeting nicotinic acetylcholine receptors (nAChRs) in the brain (Simon-Delso et al. 2015; Thompson et al. 2020). They are the world's fastest-growing and currently the most widely used class of insecticides against a broad spectrum of sucking and chewing insects (plant hoppers, thrips, micro-lepidopteras), and they are also involved in veterinary medicine (e.g., against fleas in pets) and in biocidal products such as those used for the treatment of livestock buildings or in pest baits for domestic use (Klingelhöfer et al. 2022; Thompson et al. 2020). In agriculture, neonicotinoids are mainly applied through seed treatments, but they are also employed as granular application, spraying or soil treatment (Simon-Delso et al. 2015; Thompson et al. 2020). The five most used active substances are acetamiprid, clothianidin, imidacloprid, thiacloprid and thiamethoxam (clothianidin is also the main transformation product of thiamethoxam). Among these substances, only acetamiprid is still approved in the European Union (EU Pesticides database 2023). Clothianidin and thiamethoxam were withdrawn in 2019, while imidacloprid and thiacloprid were withdrawn in 2020 (European Commission 2023). However, for example in France, derogations have been granted in 2021 and 2022 for the use of coated seeds treated with imidacloprid or thiamethoxam in the context of the infestation of beet crops by aphids (JORF 2021; JORF 2022). Consequently, because of their wide use all over the world, and because of the high persistence of clothianidin, imidacloprid and thiamethoxam (average half-life in soils is 121 days for thiamethoxam (PPDB 2023), 187 days for imidacloprid (PPDB 2023) and 545 days for clothianidin (PPDB 2023) which could reach 20 years (Thompson et al. 2020)), neonicotinoids are likely to be ubiquitous in the environment, and present a potential environmental health concern (Bonmatin et al. 2015; Goulson 2013; Humann-Guilleminot et al. 2019a; Morrissey et al. 2015).

Neonicotinoids were first presented as having key attributes such as systemic nature, versatility in application (especially as seed treatments), selective toxicity to arthropods, lower binding efficiencies to vertebrate compared to invertebrate receptors, and assumed lower impacts on non-target aquatic and terrestrial organisms (Simon-Delso et al. 2015; Thompson et al. 2020). Neonicotinoids should also theoretically not target organisms lacking nAChRs and thus nervous systems, such as protists, fungi, prokaryotes and plants (Simon-Delso et al. 2015).

However, neonicotinoids appeared to have lethal and sublethal effects on non-target organisms, including pollinators, insect predators and vertebrates (especially birds) (Alsafran et al. 2022; Mineau and Kern 2023; Mineau and Palmer 2013; Simon-Deslo et al. 2015). Thus, for many years, the use of neonicotinoid-based products in agriculture has raised concerns in several countries, particularly because of their effects on pollinators (Demortain 2021; Suryanarayanan 2013), and EFSA (2018) concluded that most uses of neonicotinoid substances do represent a risk to wild bees and honeybees. In addition, as more than 80% of neonicotinoid seed treatments can remain in the soil (Alford and Krupke 2017; Sur and Stork 2003), soil invertebrates may be exposed to high doses of neonicotinoids, with recognized lethal and sublethal effects (Gunstone et al. 2021). Neonicotinoids also contaminate freshwater ecosystems worldwide and could impact aquatic invertebrates, over broad spatial scales (Cavallaro et al. 2019; Hallmann et al. 2014; Morrissey et al. 2015). Moreover, they were demonstrated to exert negative effects on terrestrial and aquatic vertebrates (Gibbons et al. 2015; Thompson et al. 2020; Wood and Goulson 2017).

In this context, the objective of this work was to do a critical review of (1) the contamination of the environment (soil, water, air, biota) by neonicotinoids and (2) their impacts on terrestrial and aquatic biodiversity. Although the literature focused on the ecotoxicological effects of neonicotinoids is abundant, to the best of our knowledge, no review has been published on the overall impacts of these substances on the whole biodiversity.

Bibliographic corpus

The review of the literature on the impacts of neonicotinoids on biodiversity was performed under the framework of a French collective scientific assessment focused on the impacts of plant protection products (PPPs) on biodiversity and ecosystem services (Pesce et al. 2023). Collective scientific assessment seeks to inform public policy and to foster public debate by analyzing the literature, but it is neither a meta-analysis nor a systematic review (Pesce et al. 2021). Though not quantitative, this review gives a detailed and complete overview of the impacts of neonicotinoids on the whole biodiversity.

In this framework, the bibliographic corpus was adapted and constructed as follows: six queries (Q) focused on neonicotinoids (Q1), ecotoxicology (Q2), biodiversity (Q3), terrestrial ecosystems (Q4), freshwater ecosystems (Q5) and marine ecosystems (Q6) were defined with related keywords (Table SI1). The literature search was conducted on the Web of Science^{TM}, from 2000 to 2020.

The corpus of publications was then built by combining Q1 with Q2, Q3, Q4, Q5 or Q6. The combination of Q1*Q2 yielded 7349 references; that of Q1*Q3, 457 references; Q1*Q4, 3309 references; Q1*Q5, 841 references; and Q1*Q6, 252 references. After removing duplicates, the total number of references was 7697.

The time course of the 7697 references showed a strong increase in the number of publications related to the impacts of neonicotinoids from 2000 to 2020 (Fig. 1). Among the five neonicotinoids retained in this review, imidacloprid was the most studied one (4218 occurrences in titles and abstracts), well above thiamethoxam (1672), acetamiprid (1176), clothianidin (887) and thiacloprid (674) (Fig. 2). The bibliometric measurements also demonstrated that terrestrial invertebrates were the most studied organisms and especially honeybees (Fig. 3). Apart from terrestrial invertebrates, fish come at the thirty second place (Fig. 3). In the first 35 occurrences, there are no other taxonomic group.

The categorization of references was based on titles and abstracts. The selected corpus was then divided according to the expertise of the different authors who proceeded to in-depth analysis of each reference. The literature search was focused on the most integrative and ecologically realistic studies as possible. The results of single-species tests were not systematically reviewed, and were only used if they provided explanatory elements for processes observed under realistic environmental conditions.

The corpus was finally manually completed by various documents, papers and books known to the authors and which were not present in the 7697 references, and over time until April 2023. At the end, a total of 308 publications were retained and cited in this work.

Terrestrial ecosystems

Contamination of soils, plants and air

Neonicotinoids are found in all environments: soil, water (see section "Contamination of freshwater and marine environments" below), plants and air.

Contamination of soils

Soil contamination by neonicotinoids has been studied under various climates, soil types, and agricultural practices (Table 1). A large study conducted on 74 French cultivated soils showed that imidacloprid (limit of quantification LOQ = 1 µg/kg) was present in 91% of the soil samples (excluding seven organically grown soils, with no detectable traces) although only 15% of the sites had been planted with treated seeds the year of the monitoring (Bonmatin et al. 2005a). In addition, imidacloprid was detected in 100% of the soils which received treated seeds (corn, wheat or barley) during the sampling year, and in 97% of the soils which received the same treatment one or two years before the study. Concentrations were higher in the soils which had been treated consecutively during two years before the monitoring than in those that received treated seeds only one year before, indicating that imidacloprid accumulates in soils over time. Silva et al. (2019) found that imidacloprid was present in 7% of the examined European topsoil samples (LOQ = 10 µg/kg, one order of magnitude higher than the above study) with a maximum content of 60 µg/kg, while Pelosi et al. (2021) found imidacloprid in 90 % of French sampled soils (n=180, 26 % when considering concentrations >10 µg/kg, LOQ = 0.4 µg/kg) and concentrations reaching 160 µg/kg (Table 1). Thiamethoxam was present in 20% of the French soils at low concentrations (maximum of 2 µg/kg, LOQ = 0.4 µg/kg) (Pelosi et al. 2021). In Switzerland, imidacloprid (LOQ = 0.9 10^{-3} µg/kg) was quantified in 94% of cultivated field soils (n=82) and in 71% of ecological focus area soils (annual, biennial and perennial herbaceous plant species; n=68) (Humann-Guilleminot et al. 2019a). Clothianidin (LOQ = 1.6 10^{-3} µg/kg) was also frequently observed in the sampled soils (77% of cultivated fields and 46% of ecological focus areas); followed by thiacloprid (LOQ = 1.6 10^{-3} µg/kg; 28% and 13%), thiamethoxam (LOQ = 1.9 10^{-3} µg/kg; 27% and 6%) and acetamiprid (LOQ = 2.0 10^{-3} µg/kg; 13% and 3%) (Humann-Guilleminot et al. 2019a). Similarly, Riedo et al. (2021) repeatedly observed imidacloprid (59% of soils, maximum concentration of 24 µg/kg, LOQ = 0.14 µg/kg), clothianidin (55%, 57 µg/kg, LOQ = 0.15 µg/kg), thiamethoxam (21%, 24 µg/kg, LOQ =0.15 µg/kg) and thiacloprid (10%, 14 µg/kg, LOQ = 0.073 µg/kg) in various Swiss agricultural soils (Table 1). The highest concentration of imidacloprid in Switzerland was measured by Chiaia-Hernandez et al. (2017) and was found to be 138 µg/kg (LOQ = 3 µg/kg) (Table 1). Recently, Froger et al. (2023) monitored 111 PPP residues (48 fungicides, 36 herbicides, 25 insecticides and/or acaricides, and two safeners) in 47 soils sampled across France under various land uses (arable lands, vineyards, orchards, forests, grasslands, brownfields). The most frequently quantified neonicotinoid was clothianidin (17% of the soil samples, maximum concentration of 2.7 µg/kg, LOQ = 0.5 µg/kg) followed by imidacloprid (9%, 13.8 µg/kg, LOQ = 2 µg/kg), thiacloprid (6%, 0.26 µg/kg, LOQ = 0.05 µg/kg) and acetamiprid (2%, 0.48 µg/kg, LOQ = 0.01 µg/kg) (Table 1). Thiamethoxam was not quantified (LOQ = 0.5 µg/kg). In English arable soils, where neonicotinoids have been used as seed treatments, the concentrations of clothianidin ranged from < 0.02 to 13.6 µg/kg (LOQ = 0.02 µg/kg), that of imidacloprid from <0.09 to 10.7 µg/kg (LOQ = 0.09 µg/kg) and that of thiamethoxam from < 0.02 to 1.5 µg/kg (LOQ = 0.02 µg/kg) (Jones et al. 2014). Overall, most of the reviewed works focusing on the presence of neonicotinoids in soils is centered on imidacloprid, while the other substances are much less targeted. The environmental conditions, crops, agricultural practices, analytical methods and sampling time and strategies may explain the differences observed between the reviewed studies but, in general, they show the ubiquitous contamination of soils by neonicotinoids (Bonmatin et al. 2015; Froger et al. 2023).

Contamination of plants

Neonicotinoids enter plants through the roots and/or leaves, and are transported into various organs, including foliage, flowers, pollen and nectar (Bonmatin et al. 2015). They are frequently detected in cultivated plants, as well as in wild plants. Bonmatin et al. (2005b) measured imidacloprid concentrations in corn whose seeds have been treated with this insecticide and observed that 76% of stem and leaf samples at flowering contained more than 1 µg/kg of the substance (LOQ = 0.1 µg/kg). They also quantified from 1 to 10 µg/kg of imidacloprid in sunflower flower heads, with notable variations depending on crop stage and seed variety. In the 29 analyzed samples of sunflower pollens, only two contained traces of imidacloprid. In parallel, imidacloprid was detected in untreated sunflower heads grown on soil treated in previous years (from 0.1 to 2 µg/kg). In sugar beet crop treated with 90 g/ha of imidacloprid as seed coating, the concentration of imidacloprid in leaves initially reached 12.4 mg/kg (fresh weight), then decreased but remained above 1 mg/kg 80 days after sowing, and was below the limit of detection (LOD = 10 µg/kg) at harvest (Rouchaud et al. 1994). Humann-Guilleminot et al. (2019a) analyzed imidacloprid, clothianidin, thiamethoxam, thiacloprid and acetamiprid in plant samples taken from 79 cultivated fields (mainly from cereals and beetroots, but also from potatoes, rapeseed, maize, peas and flax) and 69 ecological focus areas over Switzerland. The neonicotinoids were detected in 97% of plant samples taken in cultivated fields, and in 93% of plant samples from ecological focus areas. The most frequently detected substance was imidacloprid (87% in cultivated fields and 84% in ecological focus areas), followed by thiacloprid (43% and 59%), clothianidin (39% and 12%), acetamiprid (34% and 45%) and thiamethoxam (19% and 7%).

Neonicotinoid residues were also detected in various wildflowers present in non-treated area surrounding crops grown from treated seeds, with residues in foliage ranging from 0.06 to 106 µg/kg (LOQ ranged from 0.06 to 0.60 µg/kg) (Botias et al. 2015; Botias et al. 2016). The authors pointed that these residues may overlap with lethal toxicity levels for some insect species (e.g., *Aphis glycines*). In addition, the widespread contamination of wild plants in agricultural landscape likely increases the exposure duration of pollinators though it is often supposed to be restricted to the crop flowering time (Botias et al. 2015).

Finally, in guttation droplets, potentially consumed by non-target species, works conducted in various European countries showed neonicotinoid concentrations of hundreds of mg/L at the emergence of plant, but only of a few µg/L one month after its emergence (Bonmatin et al. 2015; Tapparo et al. 2011).

Contamination of air

Neonicotinoids may also reach the atmosphere. The measurement of their concentrations relies on active air sampling systems and by trapping compounds on a sorbent from which the compounds are extracted and analyzed. Most of the time, the measured concentrations represent the sum of the compounds present in the atmosphere in both particulate and gaseous forms. Désert et al. (2018) monitored PPP concentrations in ambient air samples collected from February 2012 to December 2017 at one rural and six urban sites in the French Provence-Alpes-Côte d'Azur region. Imidacloprid was quantified in four locations, with concentrations higher than 1 ng/m^3 (LOD = 0.081 ng/m^3), but with a low frequency of quantification (1 to 2% depending on the site). As it was detected both in the rural and urban sampling sites, the authors suggested an atmospheric transport from agricultural areas to cities given the air mass retro-trajectories. In the French Phytatmo database (2023), which synthetizes the data obtained by the French Approved Air Quality Monitoring Associations (AASQAs) from 2002 up to now, the average imidacloprid concentration, calculated from 18 quantifications, was equal to 0.39 ng/m^3, with a maximum of 2.3 ng/m^3 (Table 1), which was higher than the range of concentrations reported by Coscollà and Yusà (2016) (from 0.012 to 0.014 ng/m^3) or by Raina-Fulton (2015) (from 0.01 to 0.36 ng/m^3 in the particulate phase, LOD = 0.0039 ng/m^3) in Canada. The analysis of the Phytatmo database (2023) also showed that acetamiprid and thiamethoxam were only detected once, while thiacloprid was found at an average concentration of 0.17 ng/m^3 out of 17 quantifications, and at a maximum concentration of 0.47 ng/m^3. In Canada, for the particulate phase, Raina-Fulton (2015) and Coscollà and Yusà (2016) reported acetamiprid concentrations of 0.006 ng/m^3 and 0.018 ng/m^3, respectively, and Raina-Fulton (2015) observed clothianidin concentrations ranging from 0.01 to 0.09 ng/m^3.

Impacts on terrestrial biodiversity

Terrestrial heterotrophic microorganisms

Most studies devoted to the effects of neonicotinoids on functional activities and biodiversity of terrestrial heterotrophic microorganisms concerned imidacloprid. Acetamiprid, clothianidin and thiamethoxam were scarcely addressed, while there was no data for thiacloprid.

In laboratory experiments, Cycoń and Piotrowska-Seget (2015a) evaluated the impact of imidacloprid on soil microbial activities in soils spiked at the agricultural dose and at ten times this dose (1 and 10 mg/kg, respectively). At the agricultural dose, imidacloprid decreased microbial respiration, total bacterial count, and dehydrogenase, phosphatase and urease activities after 14 days. However, these effects were transient and the measured microbial functions recovered after 56 days of exposure. At ten times the agricultural dose, imidacloprid decreased the microbial parameters but no recovery was observed after 56 days suggesting irremediable impacts on communities. Consistently, nitrate concentration decreased while ammonium concentration increased, in agreement with the high sensitivity of nitrifying and nitrogen-fixing bacteria to imidacloprid. Under the same experimental conditions, the effect of imidacloprid on the structure of ammonia-oxidizing archea (AOA) and bacteria (AOB) communities was analyzed using Denaturing Gradient Gel Electrophoresis (DGGE) (Cycoń and Piotrowska-Seget, 2015b). At the agricultural dose, imidacloprid did not affect the α diversity of the bacterial communities. However, at ten times the dose, imidacloprid decreased the α diversity of the AOA community in a durable way, and temporarily that of the AOB community. In addition, at the highest dose, imidacloprid decreased nitrification and increased ammonification. To determine the role of the microbial community diversity in the fate and impact of imidacloprid and acetamiprid, Zhang et al. (2017) used soil microcosms cropped with *Brassica* *chinensis* L. They showed that the diversity of the microbial community did not affect the amount of imidacloprid or acetamiprid remaining in the soil but, when microbial diversity decreased, the amount of insecticide exported from the soil to the plant increased. Finally, a study conducted on microbial strains isolated from soil and exposed to imidacloprid or thiamethoxam in Petri dishes showed that both neonicotinoids altered the functions of *Klebsellia* sp. strain 19, a phosphate-solubilizing rhizobacterium exhibiting Plant Growth Promoting Rhizobacteria (PGPR) properties (Ahemad and Khan 2011). Thus, these two insecticides could compromise the PGPR activity of microbial inoculant used to decrease crop dependence on chemically derived fertilizers.

In field conditions, soybean imidacloprid treated seeds decreased the number of *Rhizobia* by a factor of three, while the number of *Rhizobia* was not affected after foliar application (Sarnaik et al. 2006). In contrast, regardless of the mode of application, the insecticide had no effect on phosphate solubilizing bacteria (Sarnaik et al. 2006). Li et al. (2018) studied the impact of imidacloprid or clothianidin treated seeds on the wheat rhizosphere microbial communities over nine months. The analysis of 16S rRNA and ITS amplicons generated from soil-extracted DNA revealed changes in the α and β diversities of bacterial and fungal communities during plant development, but did not reveal any change due to seed treatment with each of the two insecticides. Furthermore, under these conditions, no effect of imidacloprid or clothianidin on some biocontrol agents (*Bacillus*, *Pseudomonas*, *Streptomyces*…) was observed in the wheat rhizosphere.

Two studies examined the impact of thiamethoxam on the taxonomic and metabolic diversity of soil bacterial communities using a laboratory setting. In forest land soils spiked with different amounts of thiamethoxam, an altered composition of the community was observed (Yu et al. 2020): the relative abundance of *Gemmatimonadetes* and OD1 decreased when compared to the control while the relative abundance of *Chloroflexi* and *Nitrospirae* increased. On the other hand, the catabolic diversity of the microbial community in soils treated with the lowest dose (0.02 mg/kg) of thiamethoxam was higher than that of the control while it was lower at the highest doses (0.2 mg/kg and 2 mg/kg). Analyzing soil samples from experimental plots where thiamethoxam was applied in field conditions, Filimon et al. (2015) showed that the insecticide only slightly reduced the phosphatase activity but reduced the number of nitrifying bacteria by about 60%.

In general, studies concerning the effects of neonicotinoids on terrestrial heterotrophic microorganisms revealed contradictory results depending on whether they were conducted in the laboratory (often under unrealistic agricultural conditions), showing impacts on the structure and on different microbial activities, or in the field (in more realistic conditions), showing no or very little effect of these substances.

Terrestrial invertebrates

Neonicotinoids have negative impacts on terrestrial invertebrates (pollinators, natural enemies, earthworms...) in agricultural environments despite variable responses depending on the traits and groups considered, as summarized below.

Pollinators

Neonicotinoids are likely to have greater effects on insect pollinators than other insecticides because they are systemic insecticides regularly found in pollen, nectar, and other vegetative parts of plants throughout their flowering period (Krupke et al. 2012; Krupke and Long 2015), leading to risks of pollinators exposure via the oral route as well as through contact for a longer period of time. In addition, during their application, neonicotinoids can also contaminate the surrounding environments (Krupke et al. 2012; Krupke and Long 2015). Comparative toxicity studies among the different categories of neonicotinoids are scarce, but Arena and Sgolastra (2014) provided some insights. They showed that nitro-substituted neonicotinoids ("N-nitroguanidines"; including imidacloprid, thiamethoxam or clothianidin) were generally more toxic to pollinators than cyano-substituted neonicotinoids ("N-cyanoamidines"; including acetamiprid or thiacloprid).

Honeybees. Exposure of honeybees (*Apis mellifera*) to neonicotinoids has been repeatedly demonstrated (e.g., Bonmatin et al. 2015; Hladik et al. 2016; Mitchell et al. 2017; Zhang et al. 2023). In pollens sampled in 2002-2003 before spring, summer, autumn and winter, in apiaries located in five French departments, imidacloprid and/or its 6-chloronicotinic acid transformation product were detected in 69% of the 81 samples, and quantified in 13.5% and 34.6% of the samples, respectively (Chauzat et al., 2006). The frequency of detection did not vary much according to the sampling period. This study was then continued until the end of 2005 (Chauzat et al. 2011): imidacloprid was detected in 11.2% of the bees (average concentration of 1.2 μg/kg) and in 40.5% of the pollen samples (0.9 μk/kg), and 6-chloronicotinic acid was detected in 18.7% of the bees (1.0 μg/kg) and in 33% of the pollen (1.2 μg/kg). In different sites cultivated with a corn/rapeseed rotation whose seeds were treated with thiamethoxam (or not), residues of thiamethoxam and clothianidin in pollens were close to the LOQ (1 μg/kg) in both corn and oilseed rape (from 1 to 2 μg/kg), and the amounts in oilseed rape nectar were lower than 1 μg/kg (LOQ = 0.5 μg/kg) (no corn nectar was analyzed) (Pilling et al. 2013). Wiest et al. (2011) detected imidacloprid in 1% of pollen and 2% of honey but nothing in bees sampled from hives located in the French Pays de la Loire region. Thiamethoxam and clothianidin were not detected in any of these samples. The multiple potential exposure pathways and the size of the pollinator activity zone make it challenging to fully identify and quantify the exposure of pollinators to neonicotinoids (van der Sluijs et al. 2013).

In parallel of the awareness raised by exposure data on the possible role of neonicotinoids in the massive decline of insects, honeybees have been the subject of extensive research focused on the toxicological effects of neonicotinoids. Particular concern resulted from studies focused on honeybee behavior which revealed neonicotinoid-induced impairment of memory and learning abilities (Tison et al. 2019; Willemsen and Hailey 2001) because such impairment is likely to affect navigation parameters and the ability to return to the hive (Henry et al. 2012; Henry et al. 2014). With regard to interaction with other factors or stressors, neonicotinoids were found to increase the susceptibility of honeybees to pathogens (*Nosema*) (Grassl et al. 2018; Müller 2018; Pettis et al. 2013; Uhl and Brühl 2019). Furthermore, the effects of neonicotinoids were demonstrated to increase with decrease in temperature: the ability of bees to return to the hive following exposure to thiamethoxam decreased at lower temperatures (< 28°C) (Henry et al. 2014; Monchanin et al. 2019). Finally, neonicotinoids can interact with other PPPs as observed for clothianidin and propiconazole (fungicide) which impact honeybee survival via synergistic effects (Sgolastra et al. 2017).

However, the issue of the effects of neonicotinoids on honeybees has been the subject of much controversy. In their large-scale monitoring study, Rolke et al. (2016) showed that honeybee colonies placed in clothianidin-treated oilseed rape crops exhibited developmental and reproduction performances similar to those of non-exposed colonies. Under the same crop treatment, clothianidin was not found to pose a risk to colonies in terms of health, development, and overwintering success of honeybee colonies (Belsky and Joshi 2020). This result was also found by Rundlöf et al. (2015) for clothianidin-rapeseed treated seed in combination with non-systemic pyrethroid (beta-cyfluthrin) treatments. Conversely, Samson-Robert et al. (2017) observed an increased mortality of honeybee colonies located in environments dominated by clothianidin-treated grain corn. More recently, Schott et al. (2021) demonstrated lethal effects of clothianidin on honeybee larvae, but found short-term resilience of colonies to treatments, which may result from compensation mechanisms (increased brood size). As to adults, seed treatments with clothianidin, thiamethoxam or imidacloprid resulted in increased worker bees mortality, but effects on colony growth were not observed thereafter (Lin et al. 2021). Actually, the effects of neonicotinoids on colony size vary across study areas (Woodcock et al. 2017). Spatial features, such as landscape characteristics and especially landmarks density (landscape elements that are used as visual cues for the orientation of bees), as well as the bee experience in the studied area (e.g., homing experiments carried out with foragers familiar or not with the release point), influence the performance of individuals and therefore of colonies, which in turn can either limit or exacerbate the neonicotinoid-induced effects (Henry et al. 2014).

To go further into toxicity mechanisms and their consequences for bee colony survival, LaLone et al. (2017) built a network of six Adverse Outcome Pathways (AOPs) and used weight of evidence (WoE) evaluation to describe plausible causal relationships between neonicotinoid mechanisms of action (activation of nicotinic acetylcholine receptor as molecular initiating event and downstream molecular, cellular, or organism-level key events) and colony death, as adverse outcome of regulatory concern. However, WoE assessment identified uncertainty, and thereby need for further research, in some upstream-to-downstream key-event relationships (e.g., between mitochrondrial dysfunction and learning/memory, or between role change in the colony and further larval development).

Wild bees. Beside works on the emblematic species *Apis mellifera*, some studies have focused on wild bees. In ground nesting species (*Eucera pruinosa*), soil treatment with imidacloprid was found to affect reproduction (decreased number of nests and larvae) and pollen consumption whereas no effect was observed with thiamethoxam used as seed treatment (*Cucurbita pepo*) (Chan and Raine 2021). However, seed treatments may lead to soil contamination, even in fields adjacent to crops and in non-cropped borders, and affect native bee nesting and richness (Main et al. 2020; Rundlöf et al. 2015). In the field, exposure to various neonicotinoids and/or other PPPs have lethal and sublethal effects, as shown for the solitary bee *Osmia bicornis*: clothianidin or thiamethoxam, used in combination with other insecticides (beta-cyfluthrin) or fungicides (fludioxonil and metalaxyl-M) impaired the reproduction (Woodcock et al. 2017), as did the mixture of thiacloprid and prochloraz (fungicide) (Alkassab et al. 2020), while clothianidin and propiconazole (fungicide) induced mortality (Sgolastra et al. 2017). In a multistress context, the effects of neonicotinoids on wild bees can be exacerbated by food resource limitation (Stuligross and Williams, 2020). Indeed, the diversification of non-crop floral resources can provide complementary resources, counteracting the negative effects of neonicotinoids as shown on *O. bicornis* reproduction and larval development (Klaus et al. 2021). With regard to other physiological mechanisms underlying population-level responses under field conditions, the negative effects of neonicotinoids observed on *Osmia cornuta* reproduction (Stuligross and Williams 2020) or at population level (fitness, density; Sandrock et al. 2014) may have a male component (thiamethoxam-altered male fertility; Strobl et al. 2021a) or not (clothianidin unaffected male survival, emergence and reproductive physiology; Strobl et al. 2021b). Using simple generalized and linear mixed models (GLMM), Stuligross and Willams (2021) demonstrated how past and current exposure to neonicotinoids profoundly impact both individual reproduction and population growth rate of orchard blue bees (*Osmia lignaria*).

The impact of neonicotinoids on wild social bees of the *Melipona* group is very little studied. However, the meta-analysis of Botina et al. (2020) highlighted lethal effects on both larvae and adults, especially marked for imidacloprid.

In bumblebees, the effects of neonicotinoids were found to be expressed at the organism level (molecular, cellular, and physiological responses; lethal and sublethal effects) as well as at the population level (mortality, altered colony structure and turnover) (Camp and Lehmann 2021). Colonies of *Bombus terrestris* and *Bombus impatiens* exposed to acetamiprid, clothianidin or imidacloprid exhibited lower growth rates and decreased production of new queens (Camp et al. 2020; Rundlöf et al. 2015; Whitehorn et al. 2012). In addition, a suite of effects was observed, including increased mortality of new queens, delayed nest foundation (Wu-Smart and Spivak 2018), acute and chronic effects on worker foraging activity (Gill and Raine 2014), reduced fecundity and brood production (imidacloprid; Laycock et al. 2012), disruption of their flight activity and endurance (imidacloprid; Kenna et al. 2019), and altered queen condition upon overwintering (thiamethoxam and clothianidin; Fauser et al. 2017). Some works also showed that seed treatments affect *Bombus* spp. densities in adjacent fields and in non-cropped borders (Main et al. 2020; Rundlöf et al. 2015). With respect to interactions with other stressors, no synergistic nor additive effects could be detected between neonicotinoids (mixture of thiamethoxam and clothianidin) and the trypanosome parasite *Crithidia bombi* on post hibernation performances (queen survival and body mass) of *B. terrestris* (Fauser et al. 2017).

With a multi-species dynamic Bayesian occupancy model, Woodcock et al. (2016) highlighted the high impact of neonicotinoid seed treatments as use in oilseed rape on the extinction of 62 species of wild bee populations. Their model was spatially and temporally explicit and related population persistence to exposure over a wide time period of 18 years. This paper identifies the need of developing national scale management strategies to support wild bee populations persistence over the long-term.

Butterflies. The impacts of neonicotinoids on lepidopterans are very little investigated, but the few studies addressing this issue underline a critical role of the timing and mode of exposure. In the monarch butterfly (*Danaus plexippus*), exposure of young adults to realistic doses of imidacloprid did not affect oocyte production, but significantly decreased insect longevity, with likely consequences for population development, migration, and overwintering (James 2019). On the contrary, under exposure to clothianidin-treated plants in the larval stage, there was no significant effect on parameters characterizing monarch migration (flight orientation, movement speed; Wilcox et al. 2021). Using a linear mixed effect random slope model, Gilburn et al. (2015) demonstrated that the populations of 15 butterfly species commonly occurring at farmland sites in England declined due to the use of neonicotinoids.

Overview of the effects of neonicotinoids on pollinators. In 2018, EFSA (2018) confirmed that the use of neonicotinoids causes a risk to wild bees and honeybees. Although results appeared sometimes contradictory, many studies highlighted negative effects of neonicotinoids on pollinators. The contradictions occasionally observed can be explained by several methodological biases (Walters 2016): (1) laboratory experiments consider exposure conditions (in particular doses and durations) to neonicotinoids that are not really representative of those observed in natura in relation to agricultural practices; (2) most of the studies focus on honeybees or bumblebees, whereas susceptibility to insecticides varies greatly among the different groups of pollinators (Lundin et al. 2015; Rundlöf et al. 2015); (3) studies are most often focused on one type of neonicotinoid which makes generalization difficult. Furthermore, there is a need to combine laboratory and field approaches, and to address the effects of neonicotinoids at the sub-individual and individual levels, as well as the consequences for colonies and populations (see LaLone et al. 2017). For example, Henry et al. (2015) showed that the mortality in honeybee colonies near neonicotinoid (thiamethoxam and imidacloprid)-treated oilseed rape fields was higher than in colonies surrounded by less treated fields. However, this effect was not observable at the colony level during and after the flowering period of oilseed rape, because the impact of this loss was buffered by the colonies' demographic regulation response. While very few models exist that are devoted to the effects of neonicotinoids at the bee colony/population levels, this research area appears promising given the difficulty of actually detecting unintended effects of neonicotinoids in the field using conventional risk assessment methods (Lundin et al. 2015). In particular, Henry et al. (2017) advocated the potentialities of mechanistic models in a multiple stressor context. Since then, the honeybee colony model (BEEHAVE, Becher et al. 2014) has been extended to the colony development of bumblebees in a realistic landscape (Becher et al. 2018), and to translate results from standard laboratory studies to relevant parameters and processes for simulating bee colony dynamics (Preuss et al. 2022). On a regulatory point of view, significant efforts have been undertaken at the EU level to improve risk assessment of the effects of neonicotinoid on bees with, among others, the development of the ApisRAM population model (Adriaanse et al. 2023; EFSA PPR Panel 2015; EFSA Scientific Committee et al. 2021).

Natural enemies

Overall, neonicotinoids have negative impacts on natural enemies such as predators (mites, ladybugs) and parasitoids, especially in field crops (Douglas and Tooker 2016). By disrupting prey-predatory and host-parasitoid interactions, neonicotinoid-treated seeds also alter arthropod communities as a whole (Chen et al. 2016; Disque et al. 2019; Dubey et al., 2020).

Ants. In *Tetramorium caespitum*, increased mortality and disruption of locomotion without loss of hunting behavior was observed after exposure to imidacloprid (Penn and Dale 2017). In other ant species (*Pogonomyrmex occidentalis*, *Lasius niger*, *Lasius flavus*), imidacloprid was also found to alter socio-behavioral traits (e.g., foraging, nest building, competition behavior) at environmentally relevant concentrations under experimental exposure (Sappington 2018; Thiel and Kohler 2016).

Bugs. Prey consumption was reduced in predatory bugs (*Pentatomidae*) feeding on herbivorous preys previously exposed to imidacloprid-treated plants, even when prey density increased (lack of a type II functional response) (Resende-Silva et al. 2019). Studies with *Orius insidiosus* concluded that imidacloprid was moderately to highly toxic when applied as seed treatment, while foliar toxicity showed conflicting results (Naranjo 2001). In *Podisus nigrispinus* predatory bugs, sublethal effects of thiamethoxam treatments resulted in longer larval development, decreased adult body weight and delayed oviposition (Torres et al. 2003). Imidacloprid may also alter the predatory behavior of spined soldier bugs (*Podisus maculiventris*), with negative consequences in terms of weight gain (Resende-Silva et al. 2019). However, some of these effects were only seen at certain treatment doses (> 0.5 mg/plant) (Torres et al. 2003), and were sometimes transient (Pekar and Kocourek 2004).

Carabids. When fed with slugs contaminated with thiamethoxam, *Chlaenius tricolor* carabid beetles displayed altered mobility twitching and mild motor difficulties, up to partial to extensive paralysis (Douglas et al. 2015).

Forficulidae. As dominant earwig species in temperate orchards, *Forficula auricularia* is the most studied forficulidae species in the laboratory. Shaw and Wallis (2010) demonstrated impaired mobility and movement coordination in 70 % of earwigs exposed to thiacloprid, and that more than 80 % of them died after 10 days exposure. Thiacloprid was also shown to reduce larval growth and to decrease adult foraging behavior (Fountain and Harris 2015). Acetamiprid significantly decreased the predation behavior of adult males by 28 % but not of females nor nymphs when applied in apple orchards at the agricultural rate (Malagnoux et al. 2015).

Lacewings. Survival of the green lacewings *Chrysoperla carnea* reduced when adults feed on imidacloprid-treated plants (Rogers et al. 2007). In addition, imidacloprid was found to disrupt the mobility of individuals (appearance of tremors; Rogers et al. 2007). It has to be underlined that, upon multigeneration exposure, this species was able to develop strong resistance to acetamiprid (Mansoor and Shad 2020).

Ladybugs. Ladybugs are impacted by neonicotinoids via prey ingestion, especially at early larval stage in *Coleomegilla maculata* feeding on cereal aphids exposed to thiamethoxam (Bredeson et al. 2015). Thiamethoxam reduces the mobility of ladybugs (the time to turn around when placed on their backs increases with the concentration of ingested insecticide) but not the number of eggs, while a negative correlation between the increase in the concentration of the insecticide and the number of developing eggs has been shown (Bredeson and Lundgren 2018). Wang et al. (2018a) evaluated the toxicity of thiamethoxam to *Harmonia axyridis*, a predator of the *Myzus persicae* aphid, and its effect in term of functional response, by three exposure routes: direct contact of *H. axyridis* with thiamethoxam residues; cabbage leaves infested with *M. persicae* treated systematically with thiamethoxam which exposed *H. axyridis* to the insecticide indirectly (referred as systemic application, mimicking direct soil drench or seed treatments); and cabbage leaves infested with *M. persicae* treated with thiamethoxam by leaf-dip which exposed *H. axyridis* to thiamethoxam residues on both cabbage leaves and thiamethoxam-treated *M. persicae* (referred as leaf dip treatment, mimicking foliar spray application). Predation was negatively affected under the three conditions, but particularly when ladybugs were exposed following leaf dipping. For all exposure routes, *H. axyridis* rapidly recovered predatory ability, however, sublethal effects of thiamethoxam may reduce the population growth of *H. axyridis* and, therefore, impair the biological control of *M. persicae*, especially after leaf or contact exposure.

Parasitoid hymenoptera. Acetamiprid was demonstrated to cause significant reductions in the abundances of various groups of parasitoids (Aphelinidae, Braconidae, Encytidae, Eulophidae, Eupelmidae, Ichneumonidae, Mymaridae, Platygastridae, Proctotrupidae, Pteromalidae, Scelionidae, Trichogrammatidae) (Khans and Alhewairini 2019), and these losses were generally accompanied by an increase in pest infestation levels (Saito et al. 2008). In various parasitoid species, systemic applications of imidacloprid were often minimally detrimental, whereas foliar applications could be highly toxic (Naranjo 2001).

Predatory mites. In the presence of neonicotinoids (acetamiprid, clothianidin, imidacloprid, thiacloprid or thiamethoxam), disruption of mite behavior (*Panonychus ulmi*, *Tetranychus urticae*), without loss of abundance, resulted in loss of biological control activity (Beers et al. 2005). Predatory mites (Phytoseiidae) are affected by acetamiprid, but studies have shown that they can develop resistance (Fountain and Medd 2015) which led to a growing interest in their use in sustainable agriculture (Duso et al. 2014; Fountain and Medd 2015).

Spiders. For several spider families (Araneidae, Lycosidae), contact exposure to neonicotinoids (acetamiprid, imidacloprid) appeared to be the most toxic pathway (compared to consumption of treated prey) inducing lethal and sublethal effects such as disruption of web construction (Pekar 2012). Furthermore, neonicotinoids (acetamiprid, thiacloprid) were demonstrated to affect the richness of spider communities (Rosas-Ramos et al. 2020).

Detritivorous arthropods

In a three-year field experiment, Pearsons and Tooker (2021) showed that seed treatments (corn, soybean) with neonicotinoids (clothianidin, imidacloprid) reduced saprophagous arthropod (millipede, springtails, oribatid mites) density and activity (litter decomposition) by more than 10%.

Earthworms

Earthworms are likely to be exposed to neonicotinoids in soils. For example, in a French arable landscape, Pelosi et al. (2021) observed residues of imidacloprid in 79% of the sampled earthworms (*Allolobophora chlorotica*, n=155; maximum concentration of 777 µg/kg; 43 % of the earthworms contained imidacloprid concentrations >100 µg/kg, LOQ = 0.4 µg/kg), while thiacloprid was found in 34% of the earthworms (maximum concentration of 42.1 µg/kg, LOQ = 0.1 µg/kg).

Neonicotinoids (e.g., acetamiprid, clothianidin, imidacloprid, thiamethoxam) have negative effects on several endpoints of various earthworm species (e.g., *Eisenia fetida*, *Lumbricus terrestris*, *Aporrectodea caliginosa*), from sub-individual to community levels: tissue integrity, physiological activity, behavior, growth, reproduction, and survival (Dittbrenner et al. 2010; Dittbrenner et al. 2011a; Dittbrenner et al. 2011b; Qi et al. 2018; Tu et al. 2011; Wang et al. 2015). They are also known to be toxic to compost worms (*E. fetida*) in laboratory conditions: they affect reproduction, cellulase activity and tissues, among others (Wang et al. 2015).

Nematodes

Compared to arthropods, nematodes tend to be less sensitive to neonicotinoids (Kudelska et al. 2017; Neury-Ormanni et al. 2019; Bradford et al. 2020). In entomopathogenic species (*Steinernema glaseri*, *Steinernema carpocapsae*, *Steinernema feltiae*, *Heterorhabditis bacteriophora*, *Heterorhabditis megidis*), a positive effect of imidacloprid was observed at low dose on reproduction (Koppenhöfer et al. 2003).

Terrestrial vertebrates

Birds (excluding raptors)

Numerous studies demonstrated that bird decline in agroecosystems is related to the use of neonicotinoids (Ertl et al. 2018; Lennon et al. 2019; Li et al. 2020; Mineau and Palmer 2013; Mineau and Kern 2023).

In agricultural areas and other environments across Europe and North America, the analyses of neonicotinoid residues in various biological components (eggs, feathers, livers, plasmas) of several avian trophic groups such as nectarivores, granivores, insectivores and carnivores showed ubiquitous exposure of birds (gamebirds, house sparrows, hummingbirds, songbirds…) (Bishop et al. 2020; Bro et al. 2016; Fuentes et al. 2023; Humann-Guilleminot et al. 2019b; Humann-Guilleminot et al. 2021; Lennon et al. 2020a; Lennon et al. 2020b; Poisson et al. 2021; Prouteau 2021; Roy et al. 2020). The prevalence of exposure greatly varies from one study to another and among species, but, even if some studies detected neonicotinoids only in a few individuals (e.g., Graves et al. 2022), the vast majority of works underlined pervasive exposure of numerous species and pointed out high frequencies of detection.

Granivorous birds are directly exposed to neonicotinoids following the consumption of neonicotinoid treated seeds (Lopez-Antia et al. 2016; Prosser and Hart 2005; Roy et al. 2019). For example, Lennon et al. (2020b) demonstrated that the detection of clothianidin in the plasma of several farmland bird species increased from 11% before sowing to 51% after sowing. In French cereal dominated landscape, where neonicotinoid treated seeds were widely used, the eggs or livers of grey partridge (*Perdix perdix*) and of some *Columba* species were found to be contaminated by neonicotinoids (Bro et al. 2016; Millot et al. 2017). In Ontario fields (Canada), the analysis of carcasses of wild turkey (*Meleagris gallopavo silvestris*), which consumes neonicotinoid-coated seeds, showed detectable levels of clothianidin and/or thiamethoxam in 22.5% of individuals (detection of both substances in 5%) (MacDonald et al. 2018). These studies underlined that the crop sowing periods are the most at risk (especially in autumn compared to early spring, Millot et al. 2017) for bird exposure through neonicotinoid treated seeds, because it also corresponds to a period of low food availability and of migration stopover for some species. Along agricultural gradients in Minnesota (USA), at least one neonicotinoid among the seven compounds screened (acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, thiacloprid, thiamethoxam) was detected in 93 % and 80 % of fecal pellets of sharp-tailed grouse (*Tympanuchus phasianellus*) and greater prairie-chickens (*T. cupido*), respectively, and in 90 % and 76 % of their livers, respectively (Roy and Chen 2023). Imidacloprid and clothianidin were the most detected substances. To document the exposure of wild bird communities, Anderson et al. (2023) analyzed seven neonicotinoids (acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, thiacloprid, thiamethoxam) in plasma samples from 55 species across 17 avian families, in four counties in Texas (USA). Imidacloprid was detected in 36 % of samples (n=294), and two birds contained imidacloprid, acetamiprid and thiacloprid. Clothianidin, and thiamethoxam were not detected but their LOD (0.3 µg/L, 0.05 µg/L, respectively) were higher than that of imidacloprid (0.005 µg/L). Temporal variations have been evidenced, with lower frequencies of detection in summer and winter than in spring and fall which correspond to the usual planting days for the most common crops across the state. Some species showed higher prevalence of exposure such as the American robin (*Turdus migratorius*) and the red-winged blackbird (*Agelaius phoeniceus*). Importantly, the study evidenced a chronic or repeated exposure of wildlife since six birds out of seven re-sampled over time exhibited at least one detection of neonicotinoid, and three exhibited multiple exposure at different time points (Anderson et al. 2023). In Europe, several measurements of neonicotinoid residues in bird carcasses (livers or gizzards) revealed very large numbers of accidental direct bird poisonings (passerine, *Columba* and game species) following the ingestion of neonicotinoid-treated seeds, especially with imidacloprid (Berny et al. 1999; Bro et al. 2010; Buchweitz et al. 2019; Millot et al. 2017; Mineau and Kern 2023; Mineau and Palmer 2013). Despite biases in the detection of carcasses in the field survey (de Snoo et al. 1999; Vyas 1999), a significant number of birds have been categorically identified as victims of acute and lethal poisoning induced by neonicotinoids used in seed treatments. Nevertheless, these lightning mortality events would likely not be the primary cause of the significant decline of some bird species (gray partridge) in agricultural environments, but they are undeniably an aggravating factor (Millot et al. 2017). This is all the more since many other direct sublethal (physiological and behavioral) and indirect effects of neonicotinoids have been demonstrated, for many more species than just granivores (Gibbons et al. 2015; Wood and Goulson 2017). Improved seeding techniques can limit the risk of direct poisoning by ensuring that treated seeds are effectively buried so that the proportion of seeds on the surface after planting is low (McGee et al. 2018). However, the effectiveness of these methods depends on planting techniques and on seed type and are not generalizable to all coated seed situations (McGee et al. 2018). Coatings have been suggested to induce an aversion which limits ingestion to a few coated seeds, representing only a small fraction of the neonicotinoid LD50 (Lethal Dose causing the death of 50% of exposed organisms) (Avery et al. 1994), but these results have been shown to depend on the experimental context, including the availability of alternative food resources or the state of food stress (Millot et al. 2017; Mineau and Kern 2023; Mineau and Palmer 2013). Furthermore, the repellent effect results from the induction of a physiological disorder following initial ingestions of treated seeds, involving that significant sublethal effects can occur well before ingestion of a lethal dose (Lopez-Antia et al. 2014; Lopez-Antia et al. 2015; Mineau 2017). It has to be underlined that some passerine species, especially *Fringillidae*, can de-husk seeds which lowers their direct exposure by ingestion (Prosser and Hart 2005). Other contexts of neonicotinoid poisoning of passerines (American goldfinches *Spinus tristis*) have also been identified in public spaces in California (Rogers et al. 2019): the mortality of birds was due to the ingestion of natural elm seeds remaining on the ground which were contaminated with imidacloprid during the drench application.

While neonicotinoids were initially thought to be less harmful to birds than insects due to their lower affinity for vertebrate nicotinic receptors, mounting evidence now challenges this view and birds appear to be more sensitive to neonicotinoids than other vertebrates (Mineau and Kern 2023; Mineau and Palmer 2013). The acute toxicity of neonicotinoids was reported to be underestimated by a factor of ten for some wild bird species compared to the one determined on model species of mallard or bobwhite quail (*Colinus virginianus*) (Mineau and Kern 2023; Mineau and Palmer 2013). Chronic toxicity is poorly taken into account, as well as sublethal effects which are scarcely investigated.

Several reviews of the individual and sub-individual effects of neonicotinoids on birds have been published (Gibbons et al. 2015; Moreau et al. 2022; Pisa et al. 2015; Wood and Goulson 2017). The literature shows that imidacloprid induces weight loss or reduces energy reserves (fat mass) in the white-crowned sparrow (*Zonotrichia leucophrys*) (Eng et al. 2017; 2019). In hummingbirds (*Selasphorus rufus*), the consumption of imidacloprid in flower nectar induces underactivity and decreased energy expenditure (-25%), with no other effect detected on feeding activity or immune response (Bishop et al. 2018; English et al. 2021). On the contrary, some studies showed an impact of imidacloprid on the immune status of adult (Lopez-Antia et al. 2013) and juvenile (Lopez-Antia et al. 2015) red-legged partridges (*Alectoris rufa*). These contrasting results could be explained by interspecific variability and various exposure conditions (dose x species x biomarkers x duration) (English et al. 2021; Gibbons et al. 2015; Lopez-Antia et al. 2015). Behavioral alterations were also observed (Eng et al. 2019), and disruption of flight and/or navigation efficiency emerged as a sensitive and relevant endpoint of imidacloprid exposure and sublethal effect on the white-crowned sparrow (Eng et al. 2017). These effects have been associated with loss of energy reserves. Thus, even if transient under the tested conditions, these sublethal effects can likely lead to impaired migration success of white-crowned sparrows using agricultural environments as staging areas (Eng et al. 2017; 2019). Furthermore, reductions in feeding and activity most often resulting in weight loss and risk to survival have been demonstrated in migratory birds exposed to sublethal doses of imidacloprid (Eng et al. 2017; 2019). Finally, exposure to sublethal dose of acetamiprid has been associated to reduced sperm density in the house sparrow (*Passer domesticus*) (Humann-Guilleminot et al. 2019c).

In controlled experiments on red-legged partridges (*Alectoris rufa*) fed with control seeds or seeds treated with imidacloprid at 20%, 100% or 200% of the recommended dose, analyses in livers showed an increase in the accumulation of imidacloprid with exposure time, and mortality of 50% of the females within five days even at agricultural or lower doses (Lopez-Antia et al. 2013; Lopez-Antia et al. 2015). Moreover, breeding investment was lowered with reduced clutch size, eggs size and fertilization rate, and chick survival was diminished when birds were exposed to imidacloprid.

Sabin and Mora (2022) performed an ecological risk assessment to evaluate the potential effects of neonicotinoids (acetamiprid, clothianidin, imidacloprid, thiamethoxam) on populations of the northern bobwhite (*C. virginianus*) in the South Texas Plains Ecoregion (USA). The assessment of the exposure of both juveniles and adults showed levels which can induce adverse effects on growth, reproduction success, and long-term survival.

The analysis of the literature thus demonstrated that neonicotinoids are one of the factors responsible of the decline in the abundance and diversity of birds. Depending on the bird species and their diet, this impact results mainly either from a direct effect (e.g., ingestion of treated seeds), or from an indirect effect (e.g., reduction in food resources following the decline of prey). Such indirect effects are addressed hereafter in the "Food webs" section.

Raptors

Several works showed the presence of neonicotinoids in raptors. Imidacloprid was detected in the blood of Eurasian eagle owl (*Bubo bubo*) in Spain (Taliansky-Chamudis et al. 2017), imidacloprid and thiacloprid in the blood of honey buzzards (*Pernis apivorus*) in Finland (Byholm et al. 2018), and acetamiprid, clothianidin, thiacloprid, and thiamethoxam in the feathers of barn owls (*Tyto alba*) in Switzerland (Humann-Guilleminot et al. 2021). The detection frequencies were contrasted: 3% of the analyzed samples were positive in the Eurasian eagle owl, whereas in the insectivorous honey buzzard, imidacloprid and thiacloprid were detected in 40 and 70% of the samples, respectively. In the barn owl, more than 80% of the individuals were positive, notably for thiacloprid, the frequent detection in chicks suggesting a trophic exposure. The feeding specialization of the barn owl on insects would not be sufficient to explain the high detection frequency of neonicotinoids. In northern Germany, Badry et al. (2021) investigated the impregnation of the livers of three raptor species (red kite *Milvus milvus*, common buzzard *Buteo buteo*, Montagu's harrier *Circus pygargus*; n=186). Among the neonicotinoids, only thiacloprid was detected in two red kites. Recently, no neonicotinoid was detected in the blood of chicks of the same three raptor species in Germany (Badry et al. 2022). No study examining the toxicity of neonicotinoids on raptors has been identified.

Mammals (excluding chiropterans)

One of the largest mammalian studies conducted to date resulted in the simultaneous analysis of 480 substances in muscle of 42 wild boars (*Sus scrofa*), 79 roe deer (*Capreolus capreolus*) and 15 deer (*Cervus elaphus*) in Poland (Kaczynski et al. 2021). The five neonicotinoids were among the most frequently detected compounds (imidacloprid and thiacloprid showing mean concentrations in the top five values). They were detected in 100% of the wild boar samples, while acetamiprid was detected in three deer, and thiacloprid and clothianidin were detected in two deer. Acetamiprid, clothianidin and thiacloprid were detected in 13 roe deer (16.5%). The mean residue concentrations ranged from 0.6 μg/kg (thiamethoxam) to 4.3 μg/kg (imidacloprid) in the liver. In France, multi-residues analyses targeting 140 PPPs (67 withdrawn and 73 currently used PPPs) and transformation products were performed in hair samples of small omnivorous rodents (wood mouse *Apodemus sylvaticus*) and insectivorous shrews (greater white-toothed shrew *Crocidura russula*) sampled in arable landscapes (Fritsch et al. 2022). Again, acetamiprid, imidacloprid and thiacloprid were among the most frequently detected substances (more than 80% of individuals) and/or quantified at high concentrations (up to 70.7 μg/kg) (Fritsch et al. 2022). The ubiquity of exposure to neonicotinoids was demonstrated as residues were detected in all animals regardless of the type of habitat (hedgerows, cereal crops, grasslands) or of the agricultural practices (conventional or organic farming) (Fritsch et al. 2022). Assessing the exposure of wild raccoons (*Procyon lotor*) captured in Hokkaido (Japan) to neonicotinoids (acetamiprid, imidacloprid, clothianidin, dinotefuran, thiacloprid, thiamethoxam, and desmethyl-acetamiprid), Shinya et al. (2022) showed that either one of the six screened neonicotinoids or one transformation product was detected in the urine of 90% of the raccoons. Neonicotinoids were also found in the hair of red fox (*Vulpes vulpes*) in Italia; acetamiprid, clothianidin, and imidacloprid being detected in 100% of the analyzed individuals (n=11), and thiacloprid in 91% of them (Picone et al. 2023).

The toxicity of neonicotinoids to mammals have been reviewed by Tomizawa (2004) and Gibbons et al. (2015), showing the potential for various deleterious effects on growth, development and reproduction as well as other sub-lethal effects such as genotoxic and cytotoxic effects, immunotoxicity, neuro-behavioral disorders and changes in behaviors related to anxiety and fear, impairments of the thyroid and retina, and reduced movement. The study of the effects of imidacloprid (112 and 225 mg/kg, daily gavage for 60 days, which is above realistic environmental exposure concentrations) on rat reproduction, a mammal model organism, showed a decrease in sperm vitality and number, a reduction in sex organ mass, and a decrease in the production of sex hormones FSH and LH in males (Nafaji et al. 2010; Tetsatsi et al. 2019). A significant impact of imidacloprid on the rat body weight was also reported but no published evidence of reproductive disorders in relation to neonicotinoid exposure in wild mammals was found. However, most of the research on mammals have been performed on rats or mice, and under laboratory conditions, hampering the assessment of direct toxicity to wild mammals which may exhibit different sensitivity and may be exposed to other chemical or biological stressors. As for birds, Gibbons et al. (2015) emphasized that neonicotinoids can also impact terrestrial mammals via indirect effects which are reviewed in the "Food webs" section.

Chiropterans

The exposure of wild bats to clothianidin, imidacloprid and thiamethoxam was demonstrated through the detection of the three substances in the hair of big brown bats (*Eptesicus fuscus*) sampled in Missouri (USA) (Hooper et al. 2022). Imidacloprid showed the highest frequency of detection and was found in all samples (Hooper et al. 2022). In Turkey, in a large screening targeting 322 PPPs and organic contaminants in adult bat carcasses of *Pipistrellus pipistrellus* and *Myotis myotis*, 87 compounds were detected but they didn't include neonicotinoids (Kuzukiran et al. 2021). Habitat preferences of these bats (urban and forest species) may limit their exposure to neonicotinoids. Several studies mention a risk of exposure of chiropterans to neonicotinoids by the trophic route, based on the monitoring of chiropteran activities and dosages in their prey present in the foraging sites (Stahlschmidt and Brühl 2012; Stahlschmidt et al. 2017).

In rare experimental studies, Hsiao et al. (2016) and Wu et al. (2020) reported the neurotoxic effects of imidacloprid (at 20 mg/kg/day) on the echolocation ability of insectivorous bats (*Hipposideros terasensis*). Memory loss in bats has been associated with apoptosis lesions in certain areas of the hippocampus (Hsiao et al. 2016). Another study supports these behavioral data and suggests that altered echolocation movements likely affects bat movement and hunting activities (Wu-Smart and Spivak 2018). In addition, neonicotinoid use appears to be associated with an increased frequency of white-nose syndrome, caused in chiropterans by a fungal infection, in both the USA and Europe (Bayat et al. 2014; Oliveira et al. 2021). Upon awakening, bats experience a massive inflammatory response phase with destruction of part of the immune tissue before reconstruction making them particularly vulnerable to infection (Mineau and Callaghan 2018). Neonicotinoids can thus come as an aggravating factor during this critical period. In their review, Mineau and Callaghan (2018) concluded that there is sufficient evidence to support the assert that bats are being negatively affected by neonicotinoids, directly through functional impairment, and indirectly through reduction in insect abundance (trophic cascades are detailed in the "Food webs" section): the levels of neonicotinoid residues in the environment are high enough to put bats at risk of motor impairment and death. Knowledge remains currently too incomplete to be able to thoroughly characterize the impacts of neonicotinoids on chiropterans.

Reptiles

Neonicotinoids (imidacloprid and thiamethoxam) have been detected in several Mongolian racerunner (*Eremias argus*) organs and tissues (blood, brain, heart, lungs, stomach, intestine, liver, kidney, skin, fat, and gonads), showing different internal distributions and post-exposure temporal variations depending on the substance considered. However, the limited number of individuals which were analyzed prevents any attempt at generalization (Wang et al. 2018b; Wang et al. 2019).

The exposure of *E. argus* to thiamethoxam and imidacloprid under controlled conditions led to variations in thyroid, stress or sex hormone levels, endocrine gland damage, or changes in expression of genes involved in endocrine functions (Wang et al. 2019; Wang et al. 2020). Yang et al. (2020) also reported the endocrine disrupting effect of imidacloprid to *E. argus* with decreased levels of testosterone and estradiol in plasma. Further research is required to better characterize the impacts of neonicotinoids on reptiles.

Amphibians

Amphibians are one of the biological groups most affected by the collapse of biodiversity on a planetary scale, in particular because of the use of PPPs (Hayes et al. 2010). However, the number of studies of the effects of neonicotinoids on the terrestrial stages of amphibians is low. Comparing dermal exposure of *Hyla gratiosa* and *Hyla cinerea* to imidacloprid via direct exposure of the frog present on the soil at the time of insecticide spraying, and via indirect exposure following soil contact after application, van Meter et al. (2015) showed that cumulative concentrations and bioconcentration factors were significantly higher for the direct exposure. In the Pampa region of Argentina, imidacloprid was detected in the terrestrial *Leptodactylus latinasus* frog living in close association with row crops (soybean, corn, wheat) (Brodeur et al. 2022).

Thompson et al. (2022) used both aquatic mesocosms, and terrestrial locomotor and behavior trials to study the effects of sublethal exposure of the wood frog (*Rana sylvatica* or *Lithobates sylvaticus*) to imidacloprid. The results showed a decrease in larval survival to metamorphosis under imidacloprid exposure in interaction with shorter hydroperiod. However, the effect of imidacloprid depends on the frog stage: terrestrial locomotor performances were improved following aquatic exposure of the larvae, while an important loss in these performances was observed after terrestrial exposure to imidacloprid. In addition, high effects on population sex structure and sexual development were observed: a skewed juvenile sex ratio was evidenced in imidacloprid treatments with about 10% fewer males than in controls, and 15.7% of individuals exposed to imidacloprid could not be assigned to either sex (ambiguous reproductive organ morphology) (Thompson et al. 2022). A great deal of research remains to be done.

Aquatic ecosystems

Contamination of freshwater and marine environments

Freshwater environment

Neonicotinoids used in agricultural fields can enter surface waters (from rivers to lakes) through spray drift, dust from coated seeds, runoff, subsurface flow (for example, subsurface tile drainage), input of treated leaves, and/or plant decomposition in water (Alford and Krupke 2019; Stehle et al. 2018; Wang et al. 2023). The primary routes of transfer are direct contamination due to spray drift or to dust abrasion of coated seeds, and re-distribution from surface runoff or subsurface drainage (Schaafsma et al. 2019; Wettstein et al. 2016). Neonicotinoids are stable in water, and because of their high mobility, they are mainly transported in the dissolved phase (Bonmatin et al. 2015; Morrissey et al. 2015; PPDB 2023).

After neonicotinoid applications, the delivery ratio to surface water was estimated to be less than 2% for thiamethoxam and clothianidin together, and 0.48% for imidacloprid (Frame et al. 2021; Wettstein et al. 2016). The detection rates in surface water are higher after seed treatment than after spraying (Wettstein et al. 2016). In North America, clothianidin was found before, during and after planting (i.e., in 98% of the samples), while the detection of thiamethoxam mainly occurred in the post-plant season (54% of the samples), and that of imidacloprid during the planting season (48% of the samples) (Evelsizer and Skopec 2018). Clothianidin is both a PPP and a transformation product of thiamethoxam which could explain its higher frequency of detection (Wang et al. 2023).

Neonicotinoids have been quantified in various types of surface waters including wetlands, ditches, ponds and rivers (Table 1). Acetamiprid, imidacloprid, and thiamethoxam are the most frequently detected substances (Pietrzak et al. 2019). Overall, maximum concentrations of neonicotinoids in surface waters were found to be 9.14 µg/L for imidacloprid, 6.90 µg/L for thiamethoxam, 4.00 µg/L for acetamiprid, 3.50 µg/L for clothianidin, and 1.37 µg/L for thiacloprid (Alford and Krupke 2019; de Araújo et al. 2022; Criquet et al. 2017; Evelsizer and Skopec

2018; Kuechle et al. 2019; Nélieu et al. 2021; Pietrzak et al. 2019; Schaafma et al. 2019; Wang et al. 2023) (Table 1). Most of these reported maximum concentrations exceed the ecological thresholds for neonicotinoid water concentrations (0.2 µg/L for short-term acute exposure and 0.035 µg/L for long-term chronic exposure) which were defined to avoid lasting effects on aquatic invertebrate communities (Morrissey et al. 2015). A recent review provided a meta-analysis of neonicotinoid concentrations in water, based on more than 40 papers published in ten countries (Wang et al. 2023). It reported mean concentrations of 0.222 µg/L (n=1056) for clothianidin, 0.120 µg/L (n=879) for imidacloprid, 0.059 µg/L (n=863) for thiamethoxam, 0.023 µg/L (n=428) for acetamiprid, and 0.011 µg/L (n=295) for thiacloprid.

Some mitigation measures could consist in improving the application material to prevent dust during planting of treated seeds, and to improve water interception of surface and subsurface flow thanks to buffer zones such as wetlands. For example, in constructed wetlands, removal of neonicotinoids due to direct accumulation in macrophytes and to enhanced biodegradation was estimated to range from 10 to 100% in 28 days (Liu et al. 2021; Main et al. 2017).

Marine environment

Neonicotinoids have only been recently monitored in coastal and marine environments. Consequently, data are just available for imidacloprid and thiamethoxam, which are generally searched for using passive integrative POCIS samplers or directly in water. In mainland France, these substances were not found in the Channel/North Sea coast (Menet-Nedelec et al. 2018). On the contrary, on the other two maritime facades (Bay of Biscay and Mediterranean), imidacloprid and thiamethoxam were quantified quite frequently (with maximum frequencies of detection of 20%) in the coastal waters of the Arcachon Basin (maximum of 0.14 µg/L and 0.0039 µg/L for imidacloprid and thiamethoxam, respectively, in spot samples) (Auby et al. 2011; Tapie and Budzinski 2018) (Table 1), in transitional waters of the Gironde estuary (maximum imidacloprid concentration of 0.0053 µg/L with integrative sampling) (Levesque et al. 2018), in Marennes-Oléron bay (maximum of 0.0238 µg/L and 0.0004 µg/L for imidacloprid and thiamethoxam, respectively, with integrative sampling) (Pepin et al. 2017), and in Mediterranean lagoons (maximum of 0.028 µg/L and 0.0025 µg/L, for imidacloprid and thiamethoxam, respectively with integrative sampling) (Munaron et al. 2020; Munaron et al. 2023). Imidacloprid has also been detected in the Charente estuary and in the Loire estuary since 2006 (GIP Loire Bretagne 2013). According to ecotoxicological data collected in the OBSLAG (Observatory of the Mediterranean Lagoons) study, only imidacloprid would cause a chronic risk for the biota of lagoon ecosystems (exceeding its chronic marine predicted no effect concentration PNEC in several lagoons since the beginning of the monitoring in 2017) (Munaron et al. 2022). This risk can be extended to the Arcachon basin and Marennes-Oléron bay given the reported data. No neonicotinoid was found in French marine sediments and no reference from the French overseas territories mentions their research in the water of the marine environment.

Only scarce information is available evidencing the contamination of marine waters worldwide. In the Queensland region of Australia, streams flowing into the marine waters of the Great Barrier Reef were found to be contaminated with imidacloprid at levels ranging from 0.0005 to 1.3 µg/L (Warne et al. 2022). The contamination concerned observation sites located in downstream sectors near the mouths of large rivers (Warne et al. 2022). This pattern appeared similar in the Bohai Sea (China), where Naumann et al. (2022) observed the seasonal variation in neonicotinoid concentrations in rivers and marine water. In their study, the detection frequency of acetamiprid was 100% in both river (n=72) and marine (n=81) waters in summer and fall. Despite dilution in the coastal environment, the risk quotient associated with the contamination levels were reported as high risk for marine organisms regarding imidacloprid, thiamethoxam and acetamiprid (Naumann et al. 2022). Due to their slow degradation rates in the environment and binding properties to particulate organic matter (PPDB 2023), neonicotinoids are likely to accumulate in sediments: Chen et al. (2022) reported contamination of marine sediments in East China Sea, due to the Yangtze River inputs, several tenths of kilometer from the river mouth. The mean concentration of total neonicotinoids was 11.9 µg/kg (dry weight). The authors concluded that marine sediments were a major sink for neonicotinoids, highly used in continental China as PPPs (Chen et al. 2022).

Impacts on aquatic biodiversity

Aquatic microorganisms

Few studies have been published on the effects of neonicotinoids on aquatic microorganisms. They suggest that imidacloprid does not affect the activity and respiration of aquatic microbial decomposers (Kreutzweiser et al. 2007; Kreutzweiser et al. 2008). With the exception of the study of Neury-Ormanni et al. (2020a), who observed that an exposure of the freshwater diatoms *Planothidium lanceolatum* and *Gomphonema gracile* to 5 µg/L imidacloprid resulted in indirect effects via competition and predation, effects of neonicotinoids on different microalgae (e.g., *Desmodesmus subspicatus*; Malev et al., 2012) and cyanobacteria (e.g., *Synechocystis* sp.; Li et al., 2010) were only observed at very high concentrations (i.e., several mg/L), irrelevant to environmental contamination levels. Using a quantitative structure activity-toxicity modeling approach, Gökçe and Saçan (2019) also predicted an absence of effects of acetamiprid on microalgae exposed to up to 100 mg/L. Neonicotinoids are therefore unlikely to be toxic to aquatic microbes, including primary producers, except under extreme events of contamination.

Aquatic invertebrates

Works focused on the effects of neonicotinoids on aquatic invertebrates are increasingly investigated (as compared to other insecticide classes, such as carbamates and organophosphates) due to the relative recentness of their use (first homologations date back from the 1990s), and to the risk specifically posed to aquatic invertebrates because of the levels of water contamination reported (see above). Morrissey et al. (2015) highlighted strong evidence that water-borne neonicotinoid exposure is frequent, long-term and at concentrations which commonly exceed several existing water quality guidelines. In addition, several monitoring studies of watercourses in either agricultural or urban landscapes demonstrated a significant contamination of freshwater amphipods (*Gammarus pulex*) by neonicotinoids (e.g., Shahid et al. 2018a; Švara et al. 2021).

Despite awareness of these contamination levels, works devoted to the effects of neonicotinoids on aquatic invertebrate biodiversity are still limited. A first review published in 2015 noted the weak level of knowledge available on the effect of neonicotinoids on the invertebrate fauna of freshwater and marine environments (Pisa et al. 2015). Since then, various field case studies have provided data and documented/predicted effects of neonicotinoids on aquatic invertebrate communities. For example, in Canadian wetlands near treated rapeseed crops, a correlation was established between neonicotinoids (acetamiprid, clothianidin, imidacloprid, thiamethoxam) transfer during rainfall events and changes in emergent insect (Diptera) diversity (Cavallaro et al. 2019). Through an experimental rice mesocosm study, imidacloprid was found to significantly reduce populations of various insects (dragonfly, bug, beetle) (Kobashi et al. 2017). A drastic decline in zooplankton biomass in Japanese brackish lakes also coincided with the introduction of neonicotinoids (clothianidin, imidacloprid, thiamethoxam) in rice agriculture since the 1990s, followed by collapse of predator fish populations (Yamamuro et al. 2019). In the Netherlands, where imidacloprid residues in water are particularly high, correlations between these residues and decline in arthropod taxa such as mayflies, odonates, diptera, and some crustaceans were revealed on a national scale (van Dijk et al. 2013). This was also observed in a study adopting a PAF (Potentially Affected Fraction) approach, but with much lower proportions of species potentially affected by neonicotinoids taking into account the co-occurrence of other PPPs in the studied environments (Vijver and van den Brink 2014).

Comparing recorded or predicted concentrations of neonicotinoids in the aquatic environment to ecotoxicity thresholds has raised some concerns for the potential effects of these insecticides in freshwater environments. The review by Sánchez-Bayo et al. (2016) reported widespread effects of neonicotinoids on aquatic species in the USA, and the major risk for aquatic invertebrates was reaffirmed in 2017 (Wood and Goulson 2017). More recently, a study based on an agricultural region located in an ecologically important wetland (Nebraska's Rainwater Basin, USA), showed negative correlations between neonicotinoid concentrations and macroinvertebrate biomass (which represents potential resources for various migratory birds) despite concentrations below the acute toxicity risk thresholds proposed by the USEPA (Schepker et al. 2020).

Long-term ecological impact of neonicotinoids is a particularly salient issue for aquatic invertebrates. The chronic risk mainly results from the ability of neonicotinoids to reach aquatic environments (high solubility in water) and to persist there when they are adsorbed on particles (Armbrust and Peeler 2002). However, this risk is poorly assessed because most often based on toxicity tests on *Daphnia*, an organism more tolerant than insects and other arthropods to neonicotinoids (Beketov and Liess 2008; Wood and Goulson 2017). Neonicotinoids can have chronic effects on abundance and community structure of freshwater arthropods and other macroinvertebrates at doses in the µg/L range and below (Beketov and Liess 2008; Kattwinkel et al. 2016). After cessation of treatments, the onset of delayed effects was also demonstrated in situ (limnocorrals) for much lower concentrations of imidacloprid and clothianidin (< 0.05 µg/L) resulting in a significant advancement of the emergence date of chironomids and zygopteran odonates (Cavallaro et al. 2018; Williams and Sweetman 2019). From a functional point of view, the desynchronization of phenology of these organisms could have important consequences on ecosystems, especially in terms of biomass input to the terrestrial environment (trophic resource for terrestrial predators such as birds). Lethal and sublethal effects of thiacloprid have been demonstrated in various aquatic invertebrates, several days after exposure, for moderate acute toxicity concentrations (Beketov and Liess 2008). Neury-Ormanni et al. (2020b) documented altered feeding behavior in chironomids exposed to environmental doses of imidacloprid. The insecticide induced changes in motility, feeding selectivity, and browsing ability. The reduced abundance and altered emergent aquatic insect assemblages in wetlands exposed to neonicotinoids could explain the reduction in densities of insectivorous birds in such environments (Cavallaro et al. 2019).

Investigating the idea of long-term impact of neonicotinoids beyond the lifespan of exposed individuals, recent works with the model amphipod crustacean, *G. pulex*, suggested the development of tolerance towards clothianidin within populations from watercourses in agricultural landscapes (Becker and Liess 2017; Becker et al. 2020; Shahid et al. 2018b). According to the authors, in these populations, the evolution of resistance by natural selection could be facilitated by factors acting at the population and/or community levels: distance from non-tolerant populations, which would favor selection locally by limiting gene flow and the influx of non-adapted genes into populations (Hoffmann and Willi 2008), and low community diversity which would intensify intra-specific competition in gammarids. Nevertheless, the shift in sensitivity of this non-target species to the neonicotinoid appeared very moderate (less than three-fold change in LC50 for example) in comparison to the genetic resistance reported for other neurotoxic insecticides (pyrethroids and organophosphates) in the amphipod *Hyalella azteca* (Gamble et al. 2023; Weston et al. 2013). In addition, an inverse pattern with increased sensitivities of long-term exposed *G. pulex* populations towards imidacloprid was found in non-agricultural context presenting complex mixture of organic contaminants (Švara et al. 2021). Overall, these results demonstrate the unsuspected importance of evolutionary adaptative processes underway in natural populations unintentionally exposed to neonicotinoids, and the urgency to develop assessment tools specifically focused on long-term effects (Oziolor et al. 2016). Such processes should be anticipated, at least in insects and probably in other arthropods, from the current knowledge on the selective evolution of resistance to neonicotinoids in pests, based either on target-site mutation or on metabolic resistance (Bass et al. 2015).

Although environmentally less realistic than field approaches, experimental studies performed in mesocosms and in the laboratory (e.g., common garden), offer the statistical power required to test patterns observed in natura (Barmentlo et al. 2021), as well as interactions with other environmental factors susceptible to alleviate or aggravate the effects of neonicotinoids, such as PPP mixtures (Sanchez-Bayo and Goka 2012; Rico et al. 2018; Sol Dourdin et al. 2023), temperature/climate (Mohr et al. 2012; Sumon et al. 2018; Rico et al. 2018), nutrients/fertilizers (Barmentlo et al. 2019; Chara-Serna et al. 2019), vegetation disturbance (Cavallaro et al. 2019), and indirect effects between species representative of different functional groups in the community (e.g., such as predator-prey relationships; Miles et al. 2017). In this regard, Alexander et al. (2013) used artificial streams to examine the impact of mixing three insecticides expected to act additively, i.e., imidacloprid (which acts on the acetylcholine receptor) and two organophosphates which act on the acetylcholine esterase enzyme, chlorpyrifos and dimethoate, and under oligotrophic vs mesotrophic (nitrate input), along a Toxic Unit (TU) gradient established for concentrations consistent with environmental data. The study showed a significant interaction between insecticides and nutrients on macroinvertebrate communities, with notably, under mesotrophic condition and low insecticides pressure, an increase in the total abundance and species richness of ephemeropteran, plecopteran and trichopteran insects. At higher insecticides pressure, the overall density of these groups and the entire community was the most reduced in mesotrophic streams. In contrast, for other species groups such as chironomids, detritus feeders, and the odonate predator *Gomphus* spp., no significant interaction between insecticides and nitrate was detected. In oligotrophic environments, increasing PPP doses decreased predation intensity, which in turn affected abundance patterns while, in mesotrophic environments, a bottom-up effect of nutrients on the periphyton explained the variation in macroinvertebrates abundance and richness. Such cause-and-effect relationships were also analyzed with Structural Equation Modeling (SEM) approaches which describe effect pathways among different variables of interest (Miller et al. 2020; Schmidt et al. 2022). At low doses, the toxicity of PPPs appeared hidden by nutrients because of increased compensatory consumption, expression of adaptive plasticity at the intraspecific level, or differential responsiveness across taxa, processes which are not captured by traditional community study methods (taxonomic determination and records of relative abundances). Interactions between nutrients and PPP can thus result in a redirection of energy within food webs towards non-productive pathways (Davis et al. 2010) or in a shift in communities towards more tolerant groups (Vinebrooke et al. 2004). This type of interactions was also studied in terms of convergence/divergence of invertebrate community structure in open artificial ditches (naturally assembled communities), by combining NPK elements with thiacloprid (Barmentlo et al. 2019). Following thiacloprid treatments designed to maintain concentrations for one month (two spikes separated by two weeks), no effect of treatments, other than an increase in total abundance after four months due to nutrient input, was found in terms of taxon richness, overall abundance, or within-treatment community divergence/convergence through time (β dispersion). However, significant changes were observed in community composition under the effect of thiacloprid, nutrients and combination thereof. This effect persisted several months after the disappearance of thiacloprid from the medium. The main compositional changes were a reduction in the abundance of insects and large predators, and an increase in multivoltine species. Some results, such as the particularly strong increase in *Helophorus* beetles under nutrients and thiacloprid, may reflect a PPP-induced rippling effect on the community amplified by nutrient supply. This study shows that thiacloprid, in addition to its short-term toxicity, induces indirect longer-term ecological effects.

Overall, the corpus analyzed pointed to a marked impact of neonicotinoids on aquatic arthropods at low doses, as demonstrated once again in a recent study which reports the decline in emerging aquatic insects during a three-month semi-field experiment considering environmentally realistic contamination scenarios of thiacloprid (Barmentlo et al. 2021). However, more studies remain to be performed to determine the relationship between the impacts of neonicotinoids and fitness of organisms, in relation to the ecological functions to which they contribute, as well as on the relationship between the impacts of neonicotinoids on the nervous system and the behavior of aquatic invertebrates.

Aquatic vertebrates

Amphibian larvae and tadpoles

The sensitivity of amphibian species to neonicotinoids through water contamination has been rarely studied. Green frog (*Rana clamitans*) tadpoles were found to be relatively insensitive to imidacloprid with mortality observed after 96h of exposure to high concentrations only (150 mg/L) (Puglis and Boone 2011). This lack of sensitivity is likely due to differences in the vertebrate nicotinic acetylcholine receptor relative to their invertebrate homologs (Li et al. 2016). On the contrary, spotted marsh frog tadpoles (*Limnodynastes tasmaniensis*) suffered high mortality rates (up to 17%) when they were exposed to imidacloprid concentrations as low as 0.50 µg/L (Sievers et al. 2018). This exposure level reduced swimming speed and distance, and escape responses which then made the tadpoles more susceptible to predation, while increasing erratic swimming (Sievers et al. 2018). The toxicity of imidacloprid has also been demonstrated in the tadpoles of *Leptodactylus luctator* and *Physalaemus cuvieri* (Samojeden et al. 2022). The consequences of exposure to environmental concentrations (3-300 µg/L) led to a decrease in size, to morphological malformations (for the two species), and to changes in tadpole swimming activity (only for *L. luctator*).

In the current literature, there is limited evidence of the effects of neonicotinoids on amphibians under chronic exposure to aquatic environmental concentrations. However, neurotoxic responses can be observed. Campbell et al. (2022; 2023) demonstrated the ability of imidacloprid to cross the blood-brain barrier and to concentrate over 300-fold in the brain of juvenile northern leopard frogs (*Rana pipiens*) with some consequences on foraging behavior (e.g., a decrease in reaction times to a food stimulus by 1.5 to 3.2 times for organisms exposed to concentrations up to 10 µg/L). At concentrations ranging from 0.1 to 10 µg/L and over a 21 day exposure period, bioaccumulation of imidacloprid in frog brains is accompanied by a decreased reactivity in individuals subjected to feeding stimuli. Beyond the active substance, the transformation product imidacloprid-olefin was detected in the brains of amphibians at much lower concentrations, which does not mean that this compound cannot be responsible for any toxic action. Surprisingly, exposure of leopard frogs to imidacloprid led to increased growth primarily affecting body length (Campbell et al. 2022). Recent research has further demonstrated that wood frogs (*R. sylvatica* or *L. sylvaticus*) exposed to imidacloprid (10 or 100 µg/L) at the tadpole stage were less likely to escape simulated predator attacks in the laboratory, suggesting that exposure to this insecticide may negatively impact tadpole perception and cognitive function (Lee-Jenkins and Robinson 2018; Sweeney et al. 2021). However, at a lower concentration of 0.1 µg/L, imidacloprid did not induce any modulation of acetylcholinesterase activity in bullfrog (*Lithobates catesbeiana*) tadpoles after three weeks of exposure (Rios et al. 2017). For other less studied neonicotinoids as chlothianidin, frog tadpoles are among the least sensitive species in case of laboratory exposure at sublethal concentrations (Miles et al. 2017). The tadpoles are tolerant to clothianidin, confirming the low toxicity of neonicotinoids in vertebrates (Miles et al. 2017). As stated in the section focused on the impacts of neonicotinoids on amphibians during their terrestrial life, numerous research remain to be done to characterize their impacts on amphibians in aquatic media.

Fish

In general, neonicotinoids exhibit low acute toxicity to fish. The 96h LC50 of clothianidin ranges from 93.6 mg/L for sheepshead minnow (*Cyprinodon variegatus*) to 117 mg/L for bluegill sunfish (*Lepomis macrochirus*) (Anderson et al. 2015). A similar trend is observed for imidacloprid, with 96h LC50 ranging from 211 mg/L for rainbow trout (*Oncorhynchus mykiss*) to 280 mg/L for common carp (*Cyprinus carpio*) (Anderson et al. 2015). Two formulations of thiamethoxam have 96h LC50 above 100 mg/L (Anderson et al. 2015). These results indicate that fish are insensitive to neonicotinoids, probably because of the properties of the vertebrate nicotinic acetylcholine receptor (Li et al. 2016).

Nevertheless, the available data indicate that exposure of aquatic vertebrates to sublethal concentrations of neonicotinoids results in pro-oxidative responses from which genotoxic perturbations arise. A short 48h exposure of the freshwater cichlid fish (*Australoheros facetus*) to imidacloprid concentrations of 100 and 1000 µg/L affected the integrity of fish erythrocyte DNA (COMET assay and micro-nuclei test) (Iturburu et al. 2018). Under short-term exposure to a much lower concentration of thiamethoxam (3.75 µg/L), the siluriform catfish (*Rhamdia quelen*) showed activity inhibition of two liver enzymes, adenylate kinase and pyruvate kinase, as early as 24h of exposure (Baldissera et al. 2018). These inhibitions were associated with a decrease in ATP levels in the liver. The energetic deregulation appeared to persist after the fish were no longer contaminated (Baldissera et al. 2018). Beyond these non-specific effects, neonicotinoids can act on the nervous function of non-target organisms, given their mode of action (binding to nicotinic acetylcholine receptors at neuromuscular junctions leading to insect paralysis) (Kimura-Kuroda et al. 2012). Imidacloprid was found to be neurotoxic to adult rainbow trout (*O. mykiss*) exposed for 21 days to high concentrations (10 and 20 mg/L) (Topal et al. 2017). This neurotoxicity resulted in inhibition of acetylcholinesterase activity, oxidative stress, and a concomitant increase in DNA damage in the fish brains (Topal et al. 2017).

Neurotoxicity of neonicotinoids may also impact the behavior of fish. A laboratory test developed to investigate two key responses of fish anti-predator behaviors revealed that zebrafish (*Danio rerio*) larvae exposed for 24 hours to acetamiprid exhibited increased fear reflex and faster habituation compared to unexposed larvae (Faria et al. 2020). The concentrations tested in this study were considered to be realistic (0.04 and 0.40 µg/L) in relation to measured concentrations of acetamiprid in surface water (0.008 to 44 µg/L) (Faria et al. 2020). The modulations of fish larvae anti-predator behavior observed in the laboratory raise questions about the environmental reality of such effects and about their hypothetical consequences in terms of survival capacity in the environment. Könemann et al. (2021) observed that zebrafish larvae were able to avoid imidacloprid contamination, but did not react to other neonicotinoids such as thiacloprid. In addition, the experimental ablation of olfaction abolished aversive responses of individuals, indicating that fish may sense insecticides. In this species, the assessment of neural activity in 289 different brain regions revealed a particular modulation of hypothalamic areas involved in the fish stress response, indicating that the observed behavioral patterns are close to those observed for other stress responses (Könemann et al. 2021). Juvenile medaka (*Oryzias latipes*), exposed to imidacloprid under rice cultivation field conditions, were consecutively infected by a *Trichodina* parasite (Sánchez-Bayo and Goka, 2005). Such pathology was linked to the chemical stress induced by imidacloprid. If toxicity of imidacloprid to vertebrates was extensively studied, the toxicity related to imidacloprid transformation products (5-hydroxy-imidacloprid, imidacloprid-urea and 6-chloronicotinic acid) was not taken into account until now, despite their presence in various tissues as observed, for example, in muscle, gonads, brain and gills in Goldfish (*Carassius auratus*) (Xu et al. 2023).

A few studies deal with the combined effects of neonicotinoids with other PPPs but sometimes with experimental approaches that are more or less relevant in the context of ecological risk assessment. Thus, adult zebrafish exposed by immersion during 24 hours to high concentrations of imidacloprid (13.75 mg/L) associated with the organophosphate insecticide dichlorvos (7.5 mg/L) and the herbicide atrazine (1.5 mg/L) showed high levels of lipid peroxidation, particularly in the liver, compared to fish exposed to the same active substances tested in isolation (Shukla et al. 2017). Although this type of study is useful to test the hypothesis of expected synergistic effects, it does not allow estimation of the actual environmental risk, particularly in view of the contamination of surface waters reported by the authors (in the Ebro River in Spain: minimum concentration of imidacloprid of 0.0016 µg/L and maximum concentration of 0.015 µg/L) (Shukla et al. 2017). It is therefore important to consider such data with caution when assessing the ecotoxicity of neonicotinoids. Similarly, mixture of the order of mg/L imidacloprid and organophosphate insecticide triazophos used to assess embryotoxicity to zebrafish early larvae (blastula stage: 2h post-fertilization) exposed during 96h revealed a strong synergistic effect in terms of acute toxicity (Wu et al. 2018). Although relevant in terms of mixture toxicity assessment, such high concentrations still lack environmental relevance. It is worth noting that, though concentrations were still high, synergistic effects were also demonstrated on zebrafish larvae (72h post-hatching) for various combinations of imidacloprid with atrazine, butachlor, chlorpyrifos or lambda-cyhalothrin (mixtures containing from two to five substances) (Wang et al. 2017).

No study has been devoted to the effects of neonicotinoid mixtures on aquatic vertebrates (Anderson et al., 2015). In addition, there is a lack of ecosystem-scale studies (mesocosm approaches and/or field studies) to investigate the effects of these insecticides. Work is also needed on sub-lethal or chronic effects to reflect environmental concentration levels. Finally, most of the studies focus on imidacloprid, with very little attention paid to the effects of other neonicotinoids.

Aquatic birds

Aquatic birds include waterbirds, which live in freshwater environments, and seabirds, which feed on the resources of seas and oceans.

The exposure of seabirds to neonicotinoids (acetamiprid, clothianidin, imidacloprid, thiacloprid, thiamethoxam) was characterized by analyzing residues in feathers sampled from the piscivorous Sandwich tern (*Thalasseus sandvicensis*) and the mixotrophic Mediterranean gull (*Ichthyaetus melanocephalus*) in fledglings from the Lagoon of Venice (Distefano et al. 2022). Neonicotinoids were detected in both species, and imidacloprid and clothianidin were the most often quantified ones (100% in Mediterranean gulls and 58% in Sandwich terns, and 100% in Mediterranean gulls and 61% in Sandwich terns, respectively). The detection of thiacloprid was lower (<20% of samples in both species) (Distefano et al. 2022). On the contrary, no residue of neonicotinoids was found in the liver or blood of white-tailed sea eagles (*Haliaeetus albicilla*) and ospreys (*Pandion haliaetus*) (Badry et al. 2021; Badry et al. 2022).

For waterbirds, data are even more scarce. In some rice-growing regions, aquaponic practices involve ducks for the control of weed and pest in rice fields (Mburia, 2016). In this very particular context, ducks may be contaminated with neonicotinoid residues (Khidkhan et al., 2022).

To date, no result on the direct effects of neonicotinoids on seabirds and waterbirds were available in the literature. Thus, even if the toxicity of neonicotinoids to aquatic vertebrates is presumed to be limited, there are still many areas of knowledge that need to be clarified and completed such as toxicity of transformation products, and levels of impregnation of agricultural wetland-living organisms by native substances and their transformation products (Frank and Tooker, 2020).

Food webs

Neonicotinoids can affect terrestrial and aquatic biodiversity by spreading through food webs, by the propagation of adverse biological effects in food webs and disturbance of trophic interactions (e.g., reduced predation rate, increased mortality of predators), and/or by reducing food resources (Alsafran et al. 2022). However, the number of results which have been published in the literature remains limited.

Terrestrial ecosystems

Focusing on insects, Tooker and Pearsons (2021) reviewed the mechanisms underlying the effects of insecticides on food webs. They highlighted how neonicotinoids influence trophic interactions and food webs, and contribute to insect declines. Neonicotinoids spread across trophic levels, primary and secondary consumers being exposed through several routes (including dietary and trophic routes), and they may also bioaccumulate in some organisms (Tooker and Pearsons 2021). Neonicotinoids distort food webs by significantly decreasing insect abundance and diversity of both preys and consumers, as evidenced in various ecosystems (e.g., croplands, woodlands, watercourses). Depopulated and less diversified insect communities lead to food scarcity for their predators, thereby adversely impacting their local population dynamics. Importantly, food web disruption can occur even when neonicotinoids do not bioaccumulate or biomagnify in food webs, depending on the sensitivity of the taxa constituting the lower trophic levels (i.e., toxic effects on prey inducing adverse effects on higher levels via trophic cascades) and/or the sensitivity of higher trophic levels (i.e., relatively low concentrations but high enough to induce toxic effects on sensitive predators) (Tooker and Pearsons 2021).

In terrestrial invertebrates, thiamethoxam has been reported to have no effect on the predation rates of two predators, *Orius insidious* insidious flower bug and *Hippodamia convergens* ladybug, after consuming aphids reared on thiamethoxam-treated plants (Esquivel et al. 2020). On the contrary, insidious flower bug survival, unlike that of ladybugs, was reduced following aphid consumption. However, the reduction in bug survival was only observed in the first few weeks after thiamethoxam application, and no reduction was noted one month after treatment or beyond. In an urban context (Central Park, New York City, USA) where trees were treated with imidacloprid against an alien beetle (*Anoplophora glabripennis*), unexpected outbreaks of a formerly innocuous herbivore, *Tetranychus schoenei* (Tetranychidae), followed insecticide applications to elms (Szczepaniec et al. 2011). Changes in the structure of arthropod communities sampled in elm canopies after imidacloprid treatments were evidenced, mainly related to an increase in the abundance of *T. schoenei*. Laboratory tests showed that exposure to imidacloprid through consumption of imidacloprid-treated elm foliage enhanced the fecundity of *T. schoenei* by 40%: adult *T. schoenei* fed leaves from treated elms laid more eggs than when fed with leaves from untreated elms (Szczepaniec et al. 2011). However, no effect of imidacloprid on *T. schoenei* fecundity was detected when mites were directly sprayed with the insecticide. The longevity of mites was also not affected by exposure to imidacloprid via food. Two model predators of spider mites, the Coccinellidae *Stethorus punctillum* (adult) and the Chrysopidae *Chrysoperla rufilabris* (larva), showed significant decrease in feeding rates when offered mites from imidacloprid-treated elms as preys. Moreover, the predators exhibited signs of intoxication (partial or complete lack of response to touch, tremors, regurgitation, excessive grooming, and inability to right themselves when placed on their back) and deleterious effects when exposed to imidacloprid by consuming prey from leaves of treated trees such as impaired mobility and reduced longevity (about one-two days when mites fed from treated trees versus 9-13 days when *T. schoenei* fed from untreated trees) (Szczepaniec et al. 2011). By stimulating reproduction of mites while poisoning insect predators of spider mites which may reduce top-down regulation, imidacloprid tree treatments finally led a non-target innocuous herbivore to reach a pest status (Szczepaniec et al. 2011). This study underlined how neonicotinoids may disrupt ecosystem functioning and impair ecological balance that ultimately can favor pest outbreaks. Studying the effect of thiamethoxam on the spider mite (*Tetranychus urticae*, considered as a pest in various agricultural systems) and its predator *Phytoseiulus persimilis*, Pozzebon et al. (2011) showed that the neonicotinoid was toxic to both *T. urticae* and *P. persimilis*, but that the impact of thiamethoxam varied according to the routes of exposure. The authors demonstrated that topical exposure led to sublethal effects in predators and preys while residual and contaminated food exposures led to both lethal and sublethal effects. In addition, toxicity increased when several exposure routes were involved. By limiting exposure to thiamethoxam to ingestion of contaminated food only, the impact of the insecticide was more favorable to *P. persimilis* than to its prey (Pozzebon et al. 2011).

The propagation of sublethal effects of neonicotinoids via trophic interactions was evidenced in a three-level food chain gathering wild strawberry (*Fragaria vesca*), wood cricket (*Nemobius sylvestris*) and nursery web spider (*Pisaura mirabili*): strawberries were treated with imidacloprid at different doses and crickets were allowed to feed on them (Uhl et al. 2015). In this tritrophic system, feeding, mass gain, thorax growth and mobility of wood crickets was reduced, and herbivory and predation diminished at sublethal imidacloprid doses in the non-target organisms (Uhl et al. 2015). The effects of thiamethoxam, applied as a soybean seed treatment, on interactions between soybeans, non-target herbivorous mollusks (pests), and predatory insects was studied in the laboratory and in the field (Douglas et al. 2015). In the laboratory, the slug *Deroceras reticulatum* was not affected by thiamethoxam, but predatory ground beetles (*Chlaenius tricolor*) which ate these slugs were affected or died in over 60% of cases. In the field, thiamethoxam seed treatments decreased the activity and density of predatory arthropods, thereby releasing slug predation and reducing soybean densities by 19% and yield by 5%. The analyses of thiamethoxam residues revealed a transfer in food webs: they showed that insecticide concentrations decreased throughout the food chain, but that levels in slugs collected in the field were still high enough to adversely affect predatory insects. According to Douglas et al. (2015), this work on the trophic transfer of thiamethoxam challenges the idea that seed treatments with neonicotinoids specifically target herbivore pests, and underscores the need to consider predatory arthropods and soil organism communities in neonicotinoid risk assessment and management.

If neonicotinoids can affect vertebrates through direct effects, as reviewed above, they can also affect wildlife through a reduction in food resources (Gibbons et al. 2015). Further, the trophic transfer of neonicotinoids has been recently evidenced, especially in birds. The presence of 54 residues of PPPs or transformation products was investigated in the food bolus (insects) provided by the parents of the tree swallow (*Tachycineta bicolor*) to their chicks, in 40 Canadian farms (Poisson et al. 2021). This multi-residue analysis included seven neonicotinoids (acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, thiacloprid, thiamethoxam). The results attested to the ubiquitous trophic exposure, with nearly half of the food boluses showing contamination by at least one substance, clothianidin being among the most frequently detected PPPs (9%). Mixtures of 2 to 16 PPPs, among which five (clothianidin, dinotefuran, imidacloprid, thiacloprid, thiamethoxam) of the seven neonicotinoids, were also detected in 21% of the food boluses (and 45% of the contaminated boluses). A study conducted in Switzerland reported that at least one neonicotinoid was detected in 100% of food boluses collected from Alpine swift (*Tachymarptis melba*) provisioning their nestlings, 75% of the food boluses exhibiting measurable concentrations (Humann-Guilleminot et al. 2021). Both acetamiprid and thiacloprid were found, and thiacloprid showed the highest occurrence (up to 66.7%) and the highest concentrations (up to 0.6 µg/kg). Surveys on birds in the USA and Europe revealed exposure/accumulation of neonicotinoids in all trophic groups such as nectarivores and granivores, insectivores and predators including top-predators (raptors), and piscivores, strongly suggesting the occurrence of trophic transfer in food webs (Badry et al. 2021; Bishop et al. 2020; Bro et al. 2016; Byholm et al. 2018; Distefano et al. 2022; Humann-Guilleminot et al. 2021; Taliansky-Chamudis et al. 2017). In 60 sites over a wide cereal plain in France, the bioaccumulation of several neonicotinoids has been evidenced in both granivorous/omnivorous rodents, and insectivorous shrews as well as in earthworms and carabid beetles, which were their potential preys (Pelosi et al. 2021; Fritsch et al. 2022). Finally, residues in tissues have also been detected in terrestrial invertebrates and vertebrates, including wildlife species other than granivores (which can be exposed directly via ingestion of treated seeds) as detailed in previous sections (e.g., chiropterans).

Some studies highlighted the potential for neonicotinoids to negatively impact terrestrial insectivorous vertebrate abundance and diversity through indirect effects related to the reduction in quantity and quality of food resources. Such indirect effects have rarely been studied on vertebrates but Gibbons et al. (2015) showed that systemic insecticides can induce effects on wildlife via trophic cascades: the reduction in food supply related to the use of imidacloprid led to impairments in fish species.

Long before major publications based on large-scale correlative analyses between PPP use and population, Tennekes and Zillweger (2010) argued that neonicotinoid contamination of surface waters in Europe was one of the factors responsible for the continental-scale decline in insect biomass, which in turn led to many of the widespread declines in birds (golden oriole *Oriolus oriolus*, northern wheatear *Oenanthe oenanthe*, starling *Stumus vulgaris*…). This was studied by Hallmann et al. (2014) who observed that insectivorous bird populations in the Netherlans declined in areas with surface water concentrations of imidacloprid higher than 0.02 µg/L. Spatial differences in land-use changes related to agricultural intensification (urban area, natural area, cropped area, fertilizers) have been considered but they did not alter the significance of the observed effects. In the USA, Li et al. (2020) found that the increase in neonicotinoid use was related to reductions of 4% and 3% in grassland and insectivorous bird biodiversity, respectively, over 2008-2014. Such a trend was also found for non-grassland and non-insectivorous birds, with an average annual rate of reduction of 2%. Recently, Kraus et al. (2021) conducted surveys in wetlands of cropland and grassland landscapes which allowed to characterize cross-ecosystem fluxes of PPPs mediated by aquatic insect emergence, and discussed their implications for terrestrial insectivores. Aquatic insects were estimated to transfer fluxes ranging from 2 to180 µg of total insecticides per wetland per day to the terrestrial ecosystem. Seven PPPs were detected in newly emerged insects, among which clothianidin and imidacloprid, and biomass of emerging aquatic insects was reduced up to 73% in cropland wetlands. The authors suggested that the availability of emerging adult aquatic insect prey for insectivores was reduced by insecticides, and that accumulated insecticide could be responsible for insectivore exposure to insect-borne PPPs. Along the observed gradient in PPP levels among the different wetlands, a decrease of 43% in insect emergence but an increase of 50% in insect-mediated PPP flux with increasing insecticide concentrations were reported (from 3 to 577 ng of insecticide per gram of insect) (Kraus et al. 2021). In addition, the presence of these neonicotinoids also led to a reduction in insect resources for consumer invertebrates (Kraus et al. 2021). Although bioaccumulation in organisms and transfer in food webs have been demonstrated together with sublethal and lethal effeccts propagated along food chains, the major process involved in shaping the impact of neonicotinoids in food webs is considered as being food web simplification (Tooker and Pearsons 2021). Such indirect effect of neonicotinoids affects both prey and predator populations through trophic cascade mechanisms and feedbacks. The initial decrease in resources when lower trophic levels are directly impacted by the use of the insecticides affect the dynamics of consumer populations at higher trophic levels through food scarcity (bottom-up control). When consumers are adversely impacted either directly (toxicity) or indirectly (lack of food supply), a subsequent decrease in predation occurs, affecting the dynamics of prey populations (top-down control). Compensatory mechanisms for consumers to overcome the decrease of one or a few food resources, such as switching to other food items, hardly occur when the predator of concern are specialist species, and seemed currently hampered in the case of neonicotinoids because of their widespread use (huge spatial extent worldwide, perennial and frequent use), the ubiquity of their environmental contamination, their broad toxicity to non-target fauna, and time-cumulative toxicity (Tooker and Pearsons 2021).

Aquatic ecosystems

Adverse effects of neonicotinoids can propagate through aquatic food webs via contaminated primary producers (Lima-Fernandes et al. 2019). Lima-Fernandes et al. (2019) used imidacloprid-contaminated and uncontaminated black alder tree (*Alnus glutinosa*) leaves to feed the stonefly shredder *Protonemura* sp., which were later given as prey to *Isoperla* sp. They showed that survival, body length and biomass of the shredders as well as leaf decomposition were 20% to 50% greater in the uncontaminated treatment in comparison to imidacloprid exposure. The biomass and length of predators were 11% and 4.3% higher, respectively, when fed with uncontaminated prey than when fed with imidacloprid exposed prey (Lima-Fernandes et al. 2019).Bioaccumulation of imidacloprid has been evidenced in both *Desmognathus* salamanders (*D. monticola* and *D. fuscus*) and benthic macroinvertebrates sampled from water streams adjacent to treated hemlock stands in the USA (Crayton et al. 2020), which represents a potential source of exposure for consumers at higher trophic levels. If exposure via the trophic route was likely for salamanders, several non-exclusive routes of exposure might be involved in the subsequent bioaccumulation, including dermal and dietary uptake (Crayton et al. 2020).

Hayasaka et al. (2012) showed that successive applications of imidacloprid and the phenylpyrazole insecticide fipronil (also a systemic insecticide) in experimental rice fields resulted in reduced growth of medaka fish, *Oryzias latipes*, adults and fry, most likely through reduced medaka prey abundance. Indeed, the concentrations (approximately 1 to 50 μg/L) were too low to have a direct effect on fish. As indicated above, the decline of emerging insects from aquatic ecosystems towards riparian and surrounded terrestrial landscapes strongly decrease the prey availability for numerous consumers, and overall minor energy transfer across ecosystems (Kraus et al. 2021).

In a Japanese lacustrine ecosystem, Yamamuro et al. (2019) demonstrated the existing relationship between decline in fishery yields and neonicotinoids. The use of neonicotinoids on watersheds since 1993 coincided with an 83% decrease in average zooplankton biomass in spring, causing the smelt (*H. nipponensis*) harvest to collapse from 240 to 22 tons. Young smelts consume zooplankton crustaceans, and their decreased abundance was linked to the reduction of zooplankton biomass caused by the introduction of neonicotinoids. This study demonstrates the indirect effects of neonicotinoids along an aquatic food web through cascading effects.

Waterbirds living and feeding in lakes and ponds (ducks, waders, cormorants...) may depend on aquatic invertebrates as their food source. Consequently, the depletion of this food source must necessarily affect them (Sánchez-Bayo et al. 2016). Duckling abundance is thus related to aquatic macroinvertebrate abundance, which is consistent with other studies, and collectively suggests that neonicotinoids contamination could influence duckling abundance indirectly by impacting aquatic macroinvertebrate communities (Tyler 2022). The available data indicate that the effects of neonicotinoids on aquatic bird life are indirect, as for other bird families, and are associated with the direct toxic impacts of these contaminants on invertebrates (Sánchez-Bayo et al. 2016).

Conclusion

Neonicotinoids, in particular imidacloprid, and to a lesser extent thiamethoxam and clothianidin, are very frequently detected in soils and freshwaters, even several years after their use. In addition, the presence of acetamiprid, imidacloprid, thiacloprid and thiamethoxam was observed in the air. Neonicotinoids have only been recently monitored in coastal and marine environments (since 2010s), but many studies report the presence of imidacloprid and thiamethoxam in different transitional ecosystems such as Mediterranean lagoons.

This contamination of the environment leads to the exposure of non-target organisms and impacts biodiversity. The ecotoxicological effects of neonicotinoids depend on the studied organisms, but this review showed that these substances have particularly high direct and indirect impacts on terrestrial invertebrates and vertebrates, and on aquatic invertebrates. The impacts on aquatic vertebrates are less documented.

The effects of neonicotinoids on terrestrial heterotrophic microorganisms vary according to the conditions: in field studies, these substances have little or no effect, while in the laboratory, impacts on the structure and on different microbial activities were observed (however, the tested concentrations are sometimes unrealistic).

Laboratory studies are not always environmentally relevant, but they are complementary to field approaches as they can help to understand the effects at lower levels of biological organization (sub-individual, individual) that have consequences on higher levels (populations, community) observed in the field. Although contradictory results have been noted in the literature, neonicotinoids have negative effects (mortality, mobility disturbance) at the individual level on pollinators (honeybees in particular). In addition, exposure to neonicotinoids increases the susceptibility of honeybees to diseases and pests. Despite the importance of wild pollinators and their crucial role in pollination, the number of studies focused on the impacts of neonicotinoids on this highly diverse group of organisms is very limited. Furthermore, neonicotinoids have been shown to have effects on other terrestrial invertebrates such as natural enemies, earthworms or nematodes. Neonicotinoids are also largely involved in the decline of birds. Consumption of treated seeds is mainly responsible for neonicotinoid direct poisoning, but birds could be exposed to these insecticides especially by trophic route after consumption of contaminated insects. Neonicotinoids have negative effects on bats, amphibians, and on reptiles (though available data are still scarce for this group). For aquatic invertebrates and vertebrates, the data on the effects of neonicotinoids remain limited. The available results indicate correlations between neonicotinoid concentrations and declines in arthropod taxa. Neonicotinoids seem to be not very toxic to aquatic vertebrates such as fish, but recent studies provide worrying results for amphibians. However, the number of studies remains low and few studies focused on marine organisms. In addition to their toxicity to directly exposed organisms, neonicotinoid-induced indirect effects via trophic cascades have been demonstrated to affect some species (terrestrial and aquatic invertebrates) but data are still too few to get a clear picture.

This critical review highlighted numerous knowledge gaps. First, there was a lack of data regarding the effects of neonicotinoids on primary producers (although the mode of action of neonicotinoids is unlikely to result in effects; Anderson et al. 2015), aquatic heterotrophic microorganisms, wild pollinators, raptors, mammals, reptiles, amphibians, aquatic vertebrates, and on organisms in the marine environment in general. In addition: (1) the majority of studies focused on only one neonicotinoid making generalization difficult; (2) while imidacloprid is the most commonly studied neonicotinoid, data are limited for the other substances; (3) most laboratory studies do not reflect realistic and representative uses under in field application conditions; (4) very few studies consider transformation products and mixtures with other PPPs; (5) the number of studies considering the impact of neonicotinoids on high levels of biological organization (i.e., beyond individual and population) is low; (6) the effects of neonicotinoids on maintenance of pest regulation and soil functions are hardly reported; (7) there is a lack of time series to survey mid- or long-term effects as well as post-exposure effects; (8) there is a lack of data regarding the effects of neonicotinoids on ecosystem functioning and services, yet the few existing studies suggest that they might significantly alter important provision and regulation ecosystem services (Pesce et al. 2023). More research remains to be done to better characterize the impacts of neonicotinoids to protect biodiversity.

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Figures

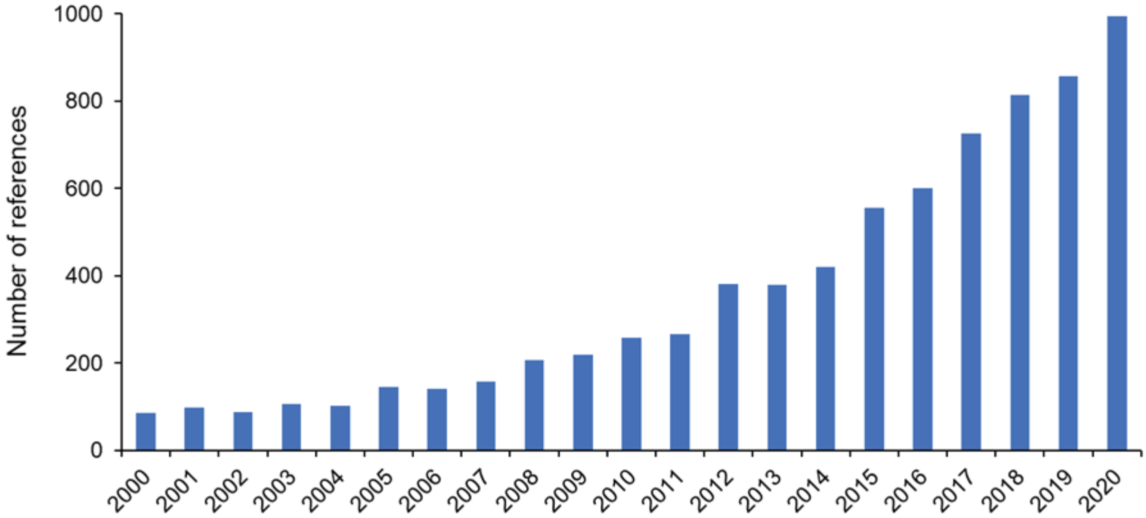

Fig. 1 Time course of references focused on the impacts of neonicotinoids on biodiversity.

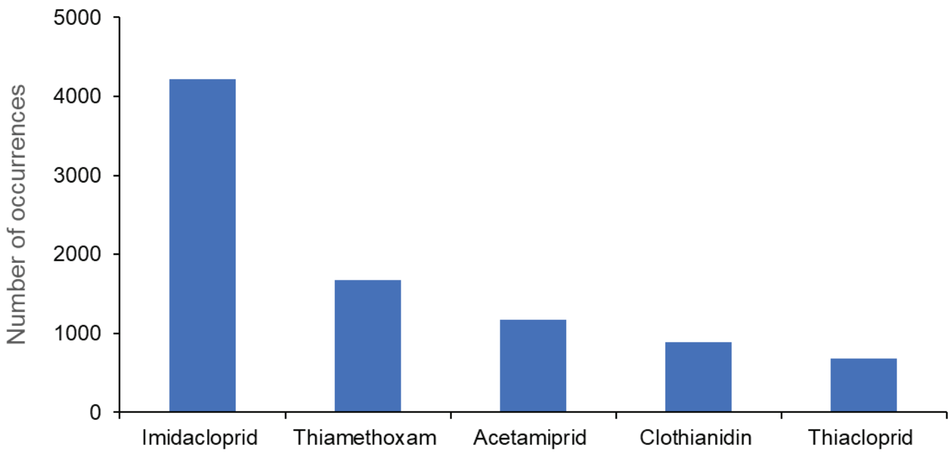

Fig. 2 Occurrences of imidacloprid, thiamethoxam, acetamiprid, clothianidin and thiacloprid in title and abstract of the references constituting the bibliographic corpus on the impacts of neonicotinoids on biodiversity, from 2000 to 2020.

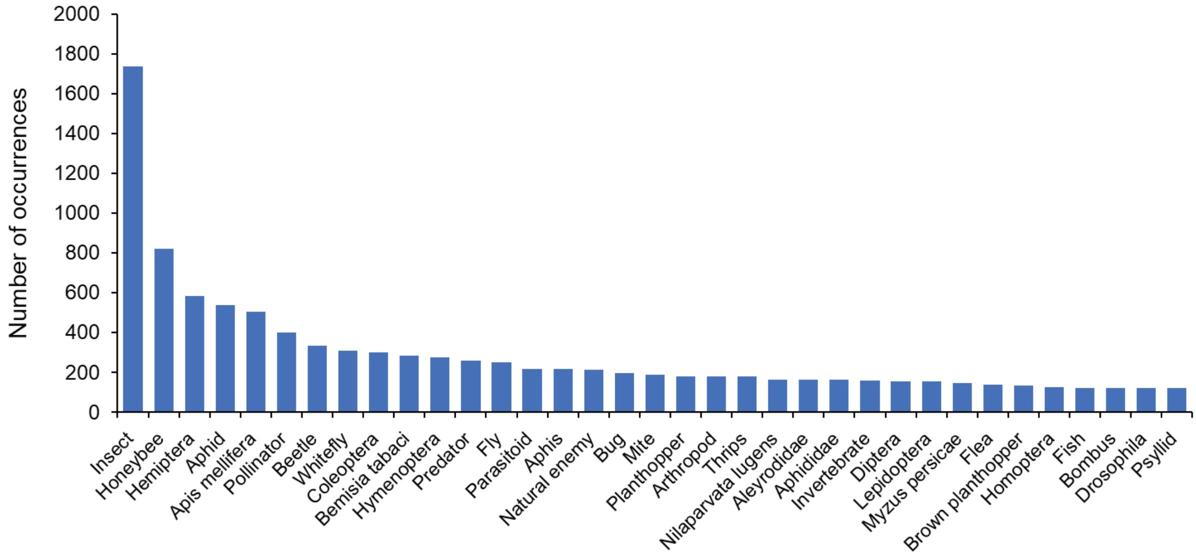

Fig. 3 Occurrences of the first 35 organisms studied in the bibliographic corpus on the impacts of neonicotinoids on biodiversity, from 2000 to 2020. Occurrences are counted from titles and abstracts. When occurring, alternative spellings were gathered into one category, for example “honeybee”, “honey bee”, “honeybees” and “honey bees”.

Table

Table 1 Maximum concentration levels of acetamiprid, clothianidin, imidacloprid, thiacloprid and thiamethoxam in soil, air and water observed in France, Europe and in the world. nd: not determined, *particulate phase.

Neonicotinoid	Geographic zone	Soil		Air		Water	
		Concentration (µg/kg)	Reference	Concentration (ng/m^3)	Reference	Concentration (µg/L)	Reference
Acetamiprid	France	0.48	Froger et al. (2023)	0.26	Phytatmo database (2023)	nd	nd
	Europe	nd	nd	0.031 (Spain)	Coscollà and Yusà (2016)	4.00 (Spain, freshwater)	de Araújo et al. (2022)
	World	nd	nd	0.036* (Canada)	Raina-Fulton (2015)	2.86 (Turkey, freshwater)	de Araújo et al. (2022)
Clothianidin	France	2.7	Froger et al. (2023)	nd	nd	nd	nd
	Europe	57 (Switzerland)	Riedo et al. (2021)	nd	nd	nd	nd
	World	nd	nd	0.09* (Canada)	Raina-Fulton (2015)	3.50 (USA, drained wetlands)	Evelsizer and Skopec (2018)
						0.132 (USA, freshwater)	de Araújo et al. (2022)
Imidacloprid	France	160	Pelosi et al. (2021)	2.3	Phytatmo database (2023)	2.22 (peri-urban ponds)	Nélieu et al. (2021)
						0.905 (agricultural/urban rivers)	Criquet et al. (2017)
						0.14 (marine waters)	Auby et al. (2011)
	Europe	138 (Switzerland)	Chiaia-Hernandez et al. (2017)	0.014 (Spain)	Coscollà and Yusà (2016)	0.342 (Spain, freshwater)	de Araújo et al. 2022
	World	nd	nd	0.36* (Canada)	Raina-Fulton (2015)	9.14 (USA, freshwater)	Wang et al. (2023)
Thiacloprid	France	1.4	Pelosi et al. (2021)	0.47	Phytatmo database (2023)	nd	nd
	Europe	14 (Switzerland)	Riedo et al. (2021)	nd	nd	0.159 (Portugal, freshwater)	de Araújo et al. (2022)
	World	nd	nd	nd	nd	1.37 (Australia, lagoon)	Wang et al. (2023)
Thiamethoxam	France	2.0	Pelosi et al. (2021)	0.06	Phytatmo database (2023)	0.0039 (bay)	Tapie and Budzinski (2018)
	Europe	24 (Switzerland)	Riedo et al. (2021)	nd	nd	0.215 (Portugal, freshwater)	de Araújo et al. (2022)
	World	nd	nd	nd	nd	6.90 (USA, drained wetlands)	Evelsizer and Skopec (2018)
						3.82 (Canada, freshwater)	Wang et al. (2023)

Supplementary Information

Table SI1 List of bibliographic queries and keywords

Query	**Keywords**
Neonicotinoids (Q1)	TS=(neonicotinoid* OR acetamiprid OR clothianidin OR imidacloprid OR thiacloprid OR thiamethoxam) AND PY=(2000-2020)
Ecotoxicology (Q2)	TS=(biomarker* OR "mode of action" OR "pesticide adaptation" OR bioaccumulat* OR biodisponibility OR biomonitoring OR ecotoxic* OR effect* OR epigenetics OR epigenome OR exposome OR exposure* OR genotoxicity OR immunotoxicity OR impact* OR resistance OR neurotoxicity OR recovery OR reprotoxicity OR resilience OR respons* OR toxicit* OR toxicology OR transgenerational OR risk* OR endpoint)
Biodiversity (Q3)	TS=("bio diversity" OR biodiversity OR "biological diversity" OR "plant diversity" OR "vegetation* diversity" OR "weed diversity" OR "animal diversity" OR "faunal diversity" OR "invertebrate diversity" OR "arthropod diversity" OR "insect diversity" OR "microbial diversity" OR "bacterial diversity" OR "species diversity" OR "species richness" OR "species abundance" OR "functional diversity" OR "genetic diversity" OR biomarker* OR bioindicator* OR "bio indicator*" OR "population dynamic*" OR "food web" OR "structural response")
Terrestrial ecosystems (Q4)	TS=("soil fauna*" OR "soil biota*" OR "soil organism*" OR "soil animal*" OR microorganism* OR "micro organism*" OR bacteria* OR bee* OR pollinator* OR pollinating insect* OR wasp OR earthworm* OR nematod* OR protozoa* OR collembol* OR mesofauna* OR macrofauna* OR microfauna* OR "meso fauna*" OR "macro fauna*" OR micro fauna* OR "soil decomposer*" OR microbiota* OR "micro biota*" OR mite$ OR enchytraeid* OR microarthropod* OR "micro arthropod*" OR lumbricid* OR acarina* OR animal* OR mammal* OR isopod* OR diplopod* OR invertebrate* OR arthropod* OR insect* OR arachnid* OR crustacean* OR odonata* OR dictyoptera* OR orthoptera* OR

	hemiptera* OR hymenoptera* OR coleoptera* OR diptera* OR butterfl* OR beetle* OR grasshopper* OR earwig* OR grasshopper* OR carabid* OR andrenidae OR ant$ OR “aphid enem*” OR apidea OR apis OR apoidea OR bombus OR bombyliidae OR bumbleblee OR coccinellid* OR colletidae OR eristalinae OR “generalist predator*” OR “ground beetle$” OR halictidae OR honey bee OR honeybee OR hoverfl* OR lacewing$ OR “lady beetle$” OR “lady bird$” OR ladybeetle$ OR ladybird$ OR lepidoptera OR megachilidae OR melittidae OR “natural enem*” OR papilionidae OR parasitoid* OR “rove beetle$” OR sarcophagidae OR “solitary bee$” OR spider* OR staphylin* OR “stink bug$” OR syrphid* OR syrphinae OR tachinidae OR “wild bee$” OR vertebrate* OR rodent* OR bat$ OR chiropteran$ OR amphibian* OR herpetofauna* OR reptile* OR lizard$ OR bird$ OR partridge$ OR songbird$ OR raptor$ OR eagle$ OR owl$ OR “food web” OR “trophic web” OR “food cycle” OR carabid* OR “microbial communit*” OR phytotoxicit* OR “non-target plant” OR “non target plant”) AND TS=(landscape* OR field* OR grassland* OR “terrestrial ecosystem*” OR soil* OR meadow* OR agroecosystem* OR “agro ecosystem*” OR orchard* OR vineyard*OR “field margin*” OR “field boundar*” OR hedgerow* OR pasture* OR fallow* OR “arable crop*” OR “buffer strip*” OR “buffer zone*” OR Ditch OR “grass$ cover” OR “grass$ strip*” OR hedge* OR “vegetated filter strip*” OR “vegetative buffer$” OR air OR atmosphere)
Freshwater ecosystems (Q5)	TS=((continental NEAR aquatic NEAR ecosystem*) OR fish OR fishes OR insect* OR invertebrate* OR macroinvertebrate* OR “macro invertebrate*” OR crustacean* OR mayfly* OR ephemeroptera* OR stonefly* OR plecoptera* OR caddisfl* OR trichoptera* OR coleoptera* OR diptera* OR chironomid* OR mollusca* OR snail* OR mussel* OR annelid*OR protozoa* OR microorganism* OR “micro organism*” OR bacteria* OR plankton* OR zooplankton* OR phytoplankton* OR benthos* OR benthic* OR amphibian* OR alga* OR microalga* OR “micro alga*” OR macrophyt* OR rotifera* OR cladocera* OR copepod* OR mammal* OR bird$ OR “food web” OR “trophic web” OR “food cycle” OR periphyt* OR biofilm OR fung* not (fish fluor* in situ hybrid*)) AND TS=(floodplain* OR “flood plain*” OR fluvial* OR impoundment* OR “inland water” OR lagoon* OR lake* OR lentic* OR lotic* OR marsh* OR pond* OR reservoir* OR riparian* OR river* OR springs OR stream$ OR swamp* OR “water body” OR wetland* OR watershed OR mesocosm* OR sediment OR microcosm OR channel OR freshwater)
Marine ecosystems (Q6)	TS=((marine NEAR aquatic NEAR ecosystem*) OR fish OR fishes OR insect* OR invertebrate* OR macroinvertebrate* OR “macro invertebrate*” OR crustacean* OR mayfly* OR ephemeroptera* OR stonefly* OR plecoptera* OR caddisfl* OR trichoptera* OR coleoptera* OR diptera* OR chironomid* OR mollusca* OR snail* OR mussel* OR annelid*OR protozoa* OR microorganism* OR “micro organism*” OR bacteria* OR plankton* OR zooplankton* OR phytoplankton* OR benthos* OR benthic* OR amphibian* OR alga* OR microalga* OR “micro alga*” OR macrophyt* OR rotifera* OR cladocera*

	OR copepod* OR mammal* OR bird* OR “food web” OR “trophic web” OR “food cycle” OR biofilm not (fish fluor* in situ hybrid*)) AND TS=(coastal* OR estuar* OR wetland* OR brackish* OR shore* OR swamp* OR lagoon* OR “coral reef*” OR saltmarsh* OR “salt marsh*” OR bay OR delta OR ocean OR sediment OR microcosm)