



Pesticide impacts on avian species with special reference to farmland birds: a review

Jérôme Moreau · Juliette Rabdeau · Isabelle Badenhauter ·
Mathieu Giraudeau · Tuul Sepp · Malaury Crépin · Agathe Gaffard ·
Vincent Bretagnolle · Karine Monceau 

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Abstract For decades, we have observed a major biodiversity crisis impacting all taxa. Avian species have been particularly well monitored over the long term, documenting their declines. In particular, farmland birds are decreasing worldwide, but the contribution of pesticides to their decline remains controversial. Most studies addressing the effects of agrochemicals are limited to their assessment under controlled laboratory conditions, the determination of lethal dose 50 (LD₅₀) values and testing in a few species, most belonging to Galliformes. They often ignore the high interspecies variability in sensitivity,

delayed sublethal effects on the physiology, behaviour and life-history traits of individuals and their consequences at the population and community levels. Most importantly, they have entirely neglected to test for the multiple exposure pathways to which individuals are subjected in the field (cocktail effects). The present review aims to provide a comprehensive overview for ecologists, evolutionary ecologists and conservationists. We aimed to compile the literature on the effects of pesticides on bird physiology, behaviour and life-history traits, collecting evidence from model and wild species and from field and lab experiments to highlight the gaps that remain to be filled. We show how subtle nonlethal exposure might be pernicious, with major consequences for bird populations

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J. Moreau
Équipe Écologie Évolutive, UMR CNRS 6282
Biogéosciences, Université Bourgogne Franche-Comté,
Dijon, France

J. Moreau · J. Rabdeau · M. Crépin · A. Gaffard ·
V. Bretagnolle · K. Monceau (✉)
UMR CNRS 7372 Centre d'Études Biologiques de Chizé,
La Rochelle Université, 79360 Villiers-en-Bois, France
e-mail: karine.monceau@univ-lr.fr

I. Badenhauter
Unité de Recherche Pluridisciplinaire Prairies Plantes
Fourragères, INRAE, 86600 Lusignan, France

M. Giraudeau
UMR IRD, CREEC, Université de Montpellier,
224-CNRS 5290 Montpellier, France

M. Giraudeau
Centre de Recherche en Écologie Et Évolution de La Sante
(CREES), Montpellier, France

M. Giraudeau
Littoral Environnement Et Sociétés (LIENSs), UMR 7266,
CNRS- La Rochelle Université, La Rochelle, France

T. Sepp
Department of Zoology, University of Tartu, Tartu, Estonia

V. Bretagnolle
LTSER "Zone Atelier Plaine & Val de Sèvre", CNRS,
79360 Villiers-en-Bois, France

and communities. We finally propose several prospective guidelines for future studies that may be considered to meet urgent needs.

Keywords Agricultural intensification · Biodiversity crisis · Bird decline · Cocktail effect · Ecotoxicology · Life-history traits · Population dynamics · Sublethal effects

Introduction

Over the last century, worldwide land-use changes, primarily including the extension of agricultural and urban areas at the expense of natural land, have increased the human footprint and resulted in major ecosystem shifts (Ellis et al., 2010). These profound environmental modifications have directly altered ecosystem functioning, a process exacerbated by its temporal association with climate change, provoking the current biodiversity crisis (Chapin et al., 2000; Maxwell et al., 2016; Vitousek et al., 1997). One major driver of this crisis is the intensification of agriculture, which results from the need to feed a rapidly growing human population. Indeed, agricultural intensification is the second most prevalent threat to biodiversity, just after resource overexploitation (Maxwell et al., 2016), and its effects may even worsen within the coming decades (Kehoe et al., 2017). Since agricultural intensification is intimately linked with the use of pesticides, these chemicals have long been suspected to contribute to the loss of biodiversity observed worldwide, but direct evidence of their effects is surprisingly scant (see Wood & Goulson, 2017; Stanton et al., 2018 for recent reviews).

Although pesticides have been used for millennia (ancient Greeks used sulphur as an insecticide), synthetic pesticide use has only recently increased, especially with the expansion of organic chemistry since the 1930s (review in Casida & Quistad, 1998). Despite repeated alerts from scientists regarding their suspected impact on wildlife (Carson, 1962; Krebs et al., 1999; the ‘first’ and ‘second’ *Silent Spring*, respectively), their use has never stopped increasing (Casida & Bryant, 2017; Casida & Quistad, 1998). In 2015, pesticides valued at over 17 billion US \$ were sold worldwide (Casida & Bryant, 2017), with China, the United States of America (US) and Argentina

being the three primary users (Sharma et al., 2019). The number of publications analysing the effects of pesticides on living organisms has also increased over the last 30 years, particularly in relation to human health (Köhler & Triebkorn, 2013). Recently, pesticides have even received growing attention from the public health sector, politicians and ecology movements.

Due to their general lack of specificity and toxicity, pesticides may induce deleterious side effects in nontarget species, such as bees (e.g., Sánchez-Bayo & Goka, 2014). In addition to bees, pesticides may further impact food security by affecting the ecosystem service of crop pollination (Goulson et al., 2015; Hladik et al., 2018). Furthermore, although only 2% of available pesticides target vertebrates (rodenticides targeting coypu and voles, for example, Sánchez-Bayo, 2011), many nontarget vertebrates are affected by these toxic molecules (Berny et al., 2010; Boatman et al., 2004; Donald et al., 2001; Gibbons et al., 2015; Guitart et al., 2010a, 2010b; Martínez-López et al., 2007; Mineau & Whiteside, 2013; Vyas, 2017). Birds and mammals may be exposed through direct contact with pesticides or by consumption of contaminated food. Ingesting a large quantity of pesticides can be lethal (i.e. short-term effects), but chronic exposure to smaller amounts can elicit sublethal effects (i.e. long-term effects). Pesticides can affect vertebrates at the intracellular level, altering their physiology, which in turn affects life-history traits, such as survival and reproduction. The impacts of pesticides on demographic traits may cascade into generational effects with consequences for population dynamics or may even disrupt community structure (Walker et al., 2012). Although the toxicity of pesticide molecules is controlled under standardised experimental trials before approval (EFSA, 2009; OECD, 2016), sublethal delayed effects are likely underestimated by regulatory agencies due to the limitations of extrapolation of the indices to natural conditions and other species (EFSA, 2009; Mineau & Palmer, 2013; Walker, 2006). Even though the mode of action of a pesticide molecule in the target species may be known, the full spectrum of its adverse effects on all wildlife fauna is indeed never investigated and is therefore unknown (Köhler & Triebkorn, 2013).

In agricultural landscapes, including both farmlands and grasslands (considering the agricultural landscape a mosaic of both farming areas and less managed

grasslands), declining biodiversity has been particularly well monitored and documented for avian species because many long-term ringing and monitoring schemes involving birds exist in many countries on different continents (e.g. France, Sweden, UK, US, Europe, North America; Comolet-Tirman et al., 2015; DEFRA, 2021; Li et al., 2020; Rosenberg et al., 2019; Stanton et al., 2018; Wretenberg et al., 2006). We chose to focus on farmland bird species (i.e. species exploiting resources in agricultural areas), including grassland species and migratory species. Farmland birds exploit resources from a narrow ecological range, making them less flexible to shift to alternative resources than generalist species. Subsequently, the term ‘farmland birds’ refers to birds using farmlands in a broader sense. The impact of pesticides on farmland birds is primarily assessed using measurements of biodiversity loss (i.e. correlational studies) without investigating the processes leading to the observed patterns (Chiron et al., 2014; Geiger et al., 2010; Mineau & Whiteside, 2013; Mitra et al., 2011; Robinson & Sutherland, 2002; Stanton et al., 2018). Since the 1990s, this topic has received growing interest (Fig. 1). Various reviews have been published (e.g. Blus, 2011; Elliott &

Bishop, 2011; Gibbons et al., 2015; Mitra et al., 2011 for a few examples), but they often focus on certain classes of pesticides, while birds are exposed to hundreds of molecules of different chemical natures. Moreover, while these syntheses usually analyse the links between direct and indirect effects of pesticides at the individual level (including physiology and behaviour), the fitness consequences that drive population and community trends are often lacking, limiting the possibility of identifying caveats to be filled and proposing future directions. Our main goal here is to highlight the importance of considering the sublethal effects of pesticides in population declines, not just lethal effects or toxicological data, on a list of species as a catalogue of lethal concentration or dose 50 (LC₅₀ or LD₅₀) or parameters such as no-observed-effect concentration/level (NOEC/NOEL) and others obtained under controlled laboratory conditions. Although many good reviews already exist in different fields, none of these syntheses embraces the problem from a systemic (interdisciplinary) viewpoint. With the present review, we propose a global overview of the pesticide-related decline of bird species based on the available literature, which covers many disciplinary fields that

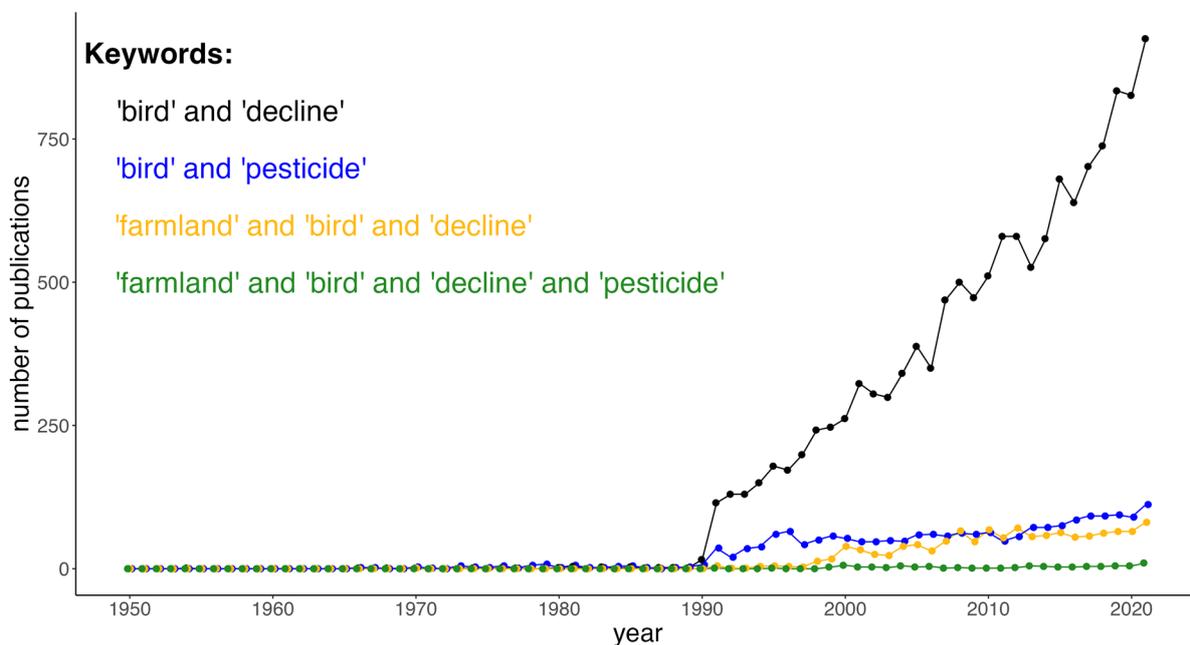


Fig. 1 Number of scientific articles published from 1950 to 2021, obtained using different combinations of keywords in all fields. Data were extracted from the Web of Science (July 2022). ‘bird’ AND ‘decline’: 13 432 articles, ‘bird’ AND ‘pes-

ticide’: 1 969 articles, ‘bird’ AND ‘decline’ AND ‘farmland’: 1 202 articles and ‘bird’ AND ‘decline’ AND ‘farmland’ AND ‘pesticide’: 82 articles

have never been unified to date in any review. Although this review is mostly written for ecologists, evolutionary ecologists and conservationists, providing basic information from toxicology and more in-depth close-up for ecological processes, any scientist from another field will also find useful information beyond the scope of their own research. We believe that this problem is quite complex, especially due to the involvement of different resolution scales, from the molecular to the community level, among research, applied science, regulation, public policies and societal concerns. This topic deserves an interdisciplinary approach rather than compartmentalization, which leads to a misunderstanding of the problem as a whole. In this philosophy, our manuscript covers a wide range of topics that aim to (I) provide a summary of knowledge on the decline of farmland bird species in relation to pesticide use due to intensive farming; (II) present basic information on pesticides, including a brief history, including the evolution of their modes of action, formulation, use and regulation; (III) describe the gaps between tests under laboratory and field conditions; (IV) synthesize current knowledge about how pesticides may affect birds at the individual level (i.e. physiology, behaviour and life-history traits) and the fitness consequences at the population and community levels; (V) present public policies for pesticide use and how they modulate bird population trends and finally; and (VI) propose future promising directions regarding the contribution of research and public policies to curtailing current dramatic trends. For this ambitious purpose, we reviewed a large body of literature based on both field and experimental studies, including studies from different taxa and ecosystems when information from farmland birds was missing. Although a review is never exhaustive, we did our utmost to compile a representative large sample of published articles (more than 300 papers, some of them shown in Table S1) to obtain an overview of the avian taxonomic group, pesticide molecules and type of studies that have mostly been performed to date. We also believe that providing all these references in Table S1 could help motivate future meta-analyses, which is not the goal of the present manuscript.

The decline of farmland birds in relation to intensive farming

The decline of bird populations has been documented since the early 1950s, primarily by addressing trends

in the range and abundance of species from several taxonomic groups. Figure 1 presents the number of peer-reviewed articles published up to 2021 obtained from the Web of Knowledge (as of July 2022) using different combinations of four keywords: 'bird', 'decline', 'farmland' and 'pesticide'. Until the 1990s, however, relatively few studies on this topic have been published (Fig. 1, first publication addressing population dynamic modelling in 1954, Capildeo & Haldane, 1954). Since the 1990s, evidence has accumulated that bird populations are declining, and although this affects some nonfarmland species (Rosenberg et al., 2019), farmland birds exhibit the steepest declines in both Europe (Burns et al., 2021; Gregory et al., 2019; Inger et al., 2015) and North America (Rosenberg et al., 2019; Stanton et al., 2018). In North America, 74% of the 77 farmland species declined from 1966 to 2013, with trends varying from -16.5 to -39.5% (Stanton et al., 2018). In the United Kingdom (UK), the Farmland Bird Indicator (19 species) displayed an overall decline of -45% from 1970 to 2019 (DEFRA, 2021). Similar trends were observed in Denmark (Heldbjerg et al., 2018) and Sweden (Wretenberg et al., 2006). This decline is more pronounced in specialist than in generalist species (Julliard et al., 2003; DEFRA, 2021; Heldbjerg et al., 2018). Some flagship species, such as the grey partridge (*Perdix perdix*) in Europe, have been carefully monitored over the years as game birds. In the UK, hunting bags have been monitored since 1793, which revealed the collapse of the population in the nineteenth century as well as more recently, since 1952 (Kuijper et al., 2009; Potts & Aebischer, 1995). Correlational studies have linked the loss of avian diversity and/or its abundance to an increase in cereal yields as a proxy of intensification (Geiger et al., 2010; Jerrentrup et al., 2017). However, although the role of agricultural intensification is largely acknowledged to explain bird declines (Krebs et al., 1999; Chamberlain et al., 2000; Donald et al., 2001, 2006; Robinson & Sutherland, 2002; Newton, 2004; Wretenberg et al., 2006; Geiger et al., 2010; Chiron et al., 2014; Teillard et al., 2015; Jerrentrup et al., 2017; Stanton et al., 2018; Reif & Hanzelka, 2020 but see Kusack et al., 2020), the relative contributions of the different components associated with this intensification remain mostly unknown. For instance, the loss of resources (food and/or nesting sites) (Brickle et al., 2000; Campbell et al., 1997; Stanton et al., 2018), fragmentation/destruction of habitats (Chamberlain & Crick, 1999; Ludwig et al., 2009; Traba & Morales,

2019; Wilson et al., 1997), mechanization of agriculture (Crick et al., 1994; Green, 1995) and pesticide use (Chiron et al., 2014; Filippi-Codaccioni et al., 2010; Geiger et al., 2010; Julliard et al., 2006; Li et al., 2020; Mineau & Whiteside, 2013; Mitra et al., 2011; Stanton et al., 2018; Tassin de Montaigu & Goulson, 2020) have been alternatively proposed as the primary drivers of bird declines (Fig. 1 in Stanton et al., 2018).

To date, the contribution of pesticides to the decline of avian species has mostly been indirectly assessed. For example, several studies have found higher bird density or species richness on organic farms than on conventional farms (Fluetsch & Sparling, 1994; McKenzie & Whittingham, 2009; Mondelaers et al., 2009; Batáry et al., 2010; Chamberlain et al., 2010; Smith et al., 2010) or between untreated and pesticide-sprayed areas (Douthwaite, 1992; Henderson et al., 2009; McKenzie et al., 2011). A recent historical analysis conducted from 1978 to 2012 revealed a negative relationship between the abundance of northern bobwhites (*Colinus virginianus*) and their exposure to neonicotinoid insecticides (neonics) (Ertl et al., 2018a). Similarly, a wide panel dataset from US neonic use and bird populations revealed a significant negative impact of this family of pesticides on avian biodiversity (Li et al., 2020). However, the processes linking individual exposure to pesticides to population decline remain poorly investigated, especially *in natura*.

Pesticide basics: history, mode of action, formulation and regulation

Pesticides represent a highly diverse chemical group; for instance, 1472 different active molecules are listed in the European Commission Pesticide database, although only 452 are currently authorised (July 2022, EU Pesticides database: https://food.ec.europa.eu/plants/pesticides_en). These compounds are categorised into four major classes depending on their pest target, insecticides, herbicides, fungicides and rodenticides, but they can also target other groups, such as Acarina, Mollusca or Nematoda, as well as birds (the case of avicides is not developed here). They belong to different chemical families that have diversified with the progress of the chemical industry (see Table 1 for the most common chemical families and molecules).

A brief historical overview of the evolution of the modes of pesticide action

Before the origination of modern chemistry, pests were mostly treated with nonspecific inorganic products, including sulphur, copper and arsenic (Casida & Quistad, 1998). Botanical extracts such as nicotine were also used in the 1600 s (Tomizawa & Casida, 2005). The first modern synthetic pesticides were organochlorine compounds (OCs), which were used between the 1940s and 1970s, particularly with the development of dichlorodiphenyltrichloroethane (DDT), targeting the vectors (mosquitoes, fleas) of malaria and typhus, followed by its chlorinated derivatives (Casida & Quistad, 1998; Jayaraj et al., 2016). These pesticides had serious ecological and sanitary consequences due to their wide spectrum, persistence in biological tissues and bioaccumulation (i.e. storage within organisms in different tissues, Sánchez-Bayo, 2012) and were banned by the Stockholm Convention on Persistent Organic Pollutants in 2001 (most OCs were included in the ‘Dirty Dozen’). Some OCs, such as lindane, are still in use, although with restrictions related to public health in North America. The use of DDT, which is the most emblematic remnant molecule, is still allowed in developing countries (mostly in India), as it is cost-effective and has broad-spectrum effects for malaria and leishmaniasis control, following the recommendations of the World Health Organization (WHO, van den Berg et al., 2017).

The modes of action of modern pesticides are diverse and depend on the molecules involved and the targeted physiological pathways (see Table 1 for an overview). However, in some cases (e.g. for Dicofol, an analogue of DDT that is prohibited in Europe), the mode of action is either nonspecific or unknown. The mode of action of the active molecules should show specificity for the targeted species, limit the emergence of resistance and guarantee the safety of non-target species (Casida & Durkin, 2017). However, this is not always the case. For example, organophosphate (OP) and carbamate (CB) insecticides are acetylcholinesterase (AChE) inhibitors, and their mode of action involves the phosphorylation or carbamoylation of serine in the esteratic site of this enzyme, resulting in the accumulation of acetylcholine, which is normally hydrolysed by AChE (see Table 1; Maroni et al., 2000; Casida & Durkin, 2013). Due to the common nature of AChE throughout the animal kingdom, the toxicity

Table 1 Examples of molecules per chemical family and their mode of action. Data were collected from the Insecticide Resistance Action Committee (IRAC, <https://irac-online.org>), the Herbicide Resistance Action Committee (HRAC, <https://www.hracglobal.com>), the Fungicide Resistance Action Committee (FRAC, <https://www.frac.info>), the Rodenticide Resist-

ance Action Committee (RRAC, <https://rrac.info>), Maroni et al. (2000) and Casida (2009). *F* fungicide, *H* herbicide, *I* insecticide and *R* rodenticide. By July 2022, 452 active substances are approved by EU Commission (bold font), 1020 are not approved (normal font) and ^{NA} stands for the molecules not (yet) considered for approval

Chemical family/sub-family	Examples of molecules	Class	Physiological function	Physiological target
Amino-acids	Glyphosate	H	Cellular metabolism	5-enolpyruvylshikimate-3-phosphate (EPSP) synthase inhibition
Benzopyrones				
<i>Coumarins</i>	<i>1st generation:</i> Warfarin, Coumatetralyl <i>2nd generation:</i> Bromadiolone, Difenacoum, Brodifacoum,	R	Blood clotting—Anti-vitamine K	Vitamin K Epoxide reductase inhibition
<i>Indandiones</i>	Chlorophacinone, Diphacinone	R	Blood clotting—Anti-vitamine K	Vitamin K Epoxide reductase inhibition
Carbamates (CBs)				
<i>Dithiocarbamates</i>	Febram ^{NA} , Mancozeb, Maneb, Metiram , Thiram, Zineb, Ziram	F	Multi-site activity	–
<i>Thiocarbamates</i>	Butylate, Cycloate, Molinate, Pebulate, Tiocarbazil, Vernolate	H	Cellular metabolism	Lipid synthesis inhibition
<i>Methylcarbamates</i>	Aldicarb, Carbaryl, Carbofuran, Methiocarb	I	Nervous system / muscular activity	Acetylcholinesterase inhibitor
<i>Ethylcarbamates</i>	Fenoxycarb	I	Growth regulator	Juvenile hormone mimic
Diamides	Chlorantraniliprole , Cyantraniliprole , Cyclaniliprole, Flubendiamide , Tetraniiprole ^{NA}	I	Nervous system / muscular activity	Ryanodine receptor modulators
Diphenylamines	Bromethalin	R	Nervous system	Uncoupling of oxidative phosphorylation
Imidazoles	Pefurazoate, Prochloraz	F	Sterol biosynthesis in membranes	Cell membrane ergosterol synthesis inhibitors
Metadiazoles and Isoxazolines	Broflanilide ^{NA} , Fluxametamide ^{NA}	I	Nervous system / muscular activity	GABA-gated chloride channel allosteric modulators

Table 1 (continued)

Chemical family/sub-family	Examples of molecules	Class	Physiological function	Physiological target
Neonicotinoids (neonics)	Acetamiprid , Clothianidin, Dinotefuran, Imidacloprid, Nitenpyram, Thiacloprid, Thiamethoxam	I	Nervous system / muscular activity	Nicotinic acetylcholine receptor modulator (competition)
Nicotinoids	Nicotine	I	Nervous system / muscular activity	Nicotinic acetylcholine receptor modulators (competition)
N-Phenylphthalimides	Flumioxazin	H	Light processes	Protoporphyrinogen oxidase inhibitors
Organochlorines (OCs)	<i>Dichlorodiphenyl-based molecules and analogous</i>			
	Dichlorodiphenyltrichloroethane (DDT), Methoxychlor	I	Nervous system / muscular activity	Sodium channel modulators
	<i>Cyclodienes</i>			
	Aldrin, Chlordane, Dieldrin, Endosulfan, Endrin, Heptachlor	I	Nervous system / muscular activity	GABA-gated chloride channel antagonists
	<i>Benzene hexachloride isomers</i>			
	Lindane	I	Nervous system / muscular activity	GABA-gated chloride channel antagonists
Organophosphates (OPs)	Acephate, Chlorpyrifos, Dimethoate, Fenitrothion, Malathion , Methamidophos, Parathion, Profenofos, Triazophos	I	Nervous system / muscular activity	Acetylcholinesterase inhibitors
Phenoxies	Dichlorprop, 2,4-D , MCPA	H	Growth regulator	Synthetic auxins
Phenylamides	Benalaxyl, Benalaxyl-M , Metalaxyl , Metalaxyl-M	F	Nucleic Acids metabolism	RNA polymerase I inhibitors
Phenylpyrazoles	Ethiprole, Fipronil	I	Nervous system / muscular activity	GABA-gated chloride channel antagonist
Phenylpyrroles	Fenpiclonil, Fludioxonil	F	Osmotic signal transduction	MAP/histidine-kinase (os-2, HOG1) inhibitor
Phthalimides	Captafol, Captan , Folpet	F	Multi-site activity	–
Pyrethrins/Pyrethroids	Allethrin, Cypermethrin , Deltamethrin , Flumethrin ^{NA} , Permethrin, Tetramethrin	I	Nervous system / muscular activity	Sodium channel modulator
Pyridines	Clopyralid , Picloram	H	Growth regulator	Synthetic auxins
Secosteroids	Cholecalciferol	R	Calcium metabolism	Hypercalcemia
Spinosyns	Spinetoram	I	Nervous system / muscular activity	Nicotinic acetylcholine receptor modulator (allosteric)
Sulfonylureas	Flupyrsulfuron-methyl, Metsulfuron-methyl , Tritosulfuron	H	Cell metabolism	Inhibition of amino acid synthesis
Sulfoximines	Sulfoxaflor	I	Nervous system / muscular activity	Nicotinic acetylcholine receptor modulator (competition)
Terpenes	Methoprene	I	Juvenile hormone mimic	Juvenile hormone analogous

Table 1 (continued)

Chemical family/sub-family	Examples of molecules	Class	Physiological function	Physiological target
Triazines	Anilazine	F	Multi-site activity	Unspecified mechanism
	Atrazine, Cyanazine, Desmetryn, Terbutryn	H	Light processes	Photosynthesis inhibitor
Triazoles	Cyproconazole, Fenbuconazole, Metconazole , Tebuconazole , Triadimefon	F	Sterol biosynthesis in membranes	Cell membrane ergosterol synthesis inhibition

of these agents is problematic, including for humans (Ghasemi et al., 2015; Mostafalou & Abdollahi, 2017). Since the 1990s, they have been progressively replaced by neonics, which still target neural function but are competitive agonists of nicotinic acetylcholine receptors (nAChE), a strategy aimed at increasing target specificity to insects and not vertebrates (Table 1, Tomizawa & Casida, 2003). Neonics have become the most widely used insecticide class in the world (Casida, 2018; Casida & Durkin, 2013; Tomizawa & Casida, 2005). They now represent one-third of insecticides used worldwide (Gibbons et al., 2015), despite being shown to impact nontarget species (Henry et al., 2015; Simon-Delso et al., 2015; Wood & Goulson, 2017).

Compared to the golden age of the pesticide industry in its early time, the development of new molecules is more and more traded-off by the cost of development and the increasing pressure for safety (though the efficiency of the regulatory processes is questionable, see below) (Casida & Quistad, 1998; Qu et al., 2021; Sparks, 2013). This results in an economic choice to produce wide-spectrum chemical pesticides for large markets instead of pest-specific products for specific problems, although the technology to produce more specific environmentally friendly products such as biopesticides (i.e. substances or organisms controlling pests naturally including viruses, fungi, bacteria, RNA interference) is available (Marrone, 2019; Fletcher et al., 2020; Liu et al., 2021; Qu et al., 2022).

Pesticides with complex formulations for different uses

Pesticide products are not only composed of active molecules but also include adjuvants (or co-formulants) that facilitate their application (see below) and increase their stability within the environment or their efficiency

against pests or are added for storage reasons (Castro et al., 2014). Although adjuvants are usually considered inert, some either increase the direct toxicity of the active molecule or are toxic on their own (Mullin et al., 2015). For example, some commercial formulations of glyphosate-based herbicides are more toxic than the glyphosate molecule itself due to added adjuvants (Castro et al., 2014; Mesnage et al., 2014, 2015; Vincent & Davidson, 2015 but see Bridi et al., 2017 for similar results in both glyphosate and Roundup® in zebrafish). This is also the case for polyethylene glycol (PEG) added to the neonic imidacloprid, which enhances the neurotoxicological effects of the pesticide molecule (Rawi et al., 2019). Other examples include silicone-based copolymers, such as organosilicon surfactants used to facilitate spraying, that are toxic to nontarget species such as bees (review in Chen et al., 2018).

Pesticides are applied in field crops using either liquid (e.g. direct spraying, soil application) or solid formulations (e.g. seed coating, granules). Herbicides are only applied by direct spraying, while fungicides are applied by spraying or seed coating. Over the last two decades, seed coating with insecticides has become the most widely used method against insects (Hladik et al., 2018) due to the marked increase in the use of neonics (often with fungicides). More generally, seed coating allows the application of the active substance directly at the site of action and is considered to reduce the quantity used relative to sprays and granules (Jeschke et al., 2011). However, this approach also means that crops are pre-emptively treated without any consideration of pest pressure (Douglas & Tooker, 2015). Moreover, even though seed coating reduced the amount of pesticides used to treat the crops, the heterogeneity in seed distribution may increase the quantity of active molecules in some parts of the plots (see Lopez-Antia et al., 2016). It increases seed conspicuity to granivorous organisms,

leading to a major risk of exposure to lethal doses for wildlife since these substances affect nontargeted animals (Lennon et al., 2020; Roy & Coy, 2020; Roy et al., 2019). Contact (i.e. pesticide molecules that act only on the part of the plant exposed to the molecule) or systemic (i.e. pesticides that are transported in the whole plant) pesticides may be used independently of the application method, but seed coating primarily involves systemic fungicides and insecticides. As systemic pesticides, these agents are absorbed by plant roots and transported throughout plant leaves, flowers, nectar and pollen, meaning that plant-feeding organisms may consume pesticide compounds (Jeschke et al., 2011).

Pesticide regulation with an emphasis on bird toxicity tests

Overview of pesticide regulation worldwide

In the approval process, manufacturers must test the innocuity of the molecule to ensure security throughout the global chain, including the environment and nontarget species, food products and users (farmers) and consumers, especially humans. Environmental fate and risk assessments should include toxicity data relative to the molecule to be approved in its typical formulation and toxicity data on potential impurities, degradation products and metabolites before and after application in standard use (FAO & WHO, 2013). The responsibility for approval belongs to competent national authorities leading to a lack of homogeneity worldwide, enhanced by the differences between developed and developing countries (Handford et al., 2015; FAO & WHO, 2019; Zikankuba et al., 2019). In 1985, the Food and Agriculture Organisation (FAO) in association and the WHO edited the International Code of Conduct on the Distribution and Use of Pesticides, which was updated in 2014 (FAO & WHO, 2014). Several guidelines and resources have been successively released to help governments improve their legislation for pesticide management in agriculture and to provide a more homogeneous framework (FAO & WHO, 2021). Nonetheless, heterogeneity still exists. The European Union (EU), Brazil, China and the US are the world's largest consumers (and producers) of pesticides (Donley, 2019). Among these nations, the EU has proposed one of the most stringent regulatory processes (Regulation (EC) No 1107/2009) for the

approval of new pesticide molecules (Handford et al., 2015; Kudsk & Mathiassen, 2020). For instance, 72 pesticides approved by the US (mostly regulated by the Environmental Protection Agency, EPA) for outdoor agricultural use are banned in the EU (Donley, 2019). As the purpose of our synthesis is not to provide a critical review of the existing legislation worldwide, we chose to focus hereafter on what is presented as the strictest one, i.e. the EU regulatory process. Within the EU, applications are submitted by manufacturers to a Rapporteur Member State who produces a report. This report is then reviewed by the European Food Safety Authority (EFSA) and all Member States (EFSA, 2018). The European Commission (EC), based on EFSA's conclusion, decides whether to approve the new active substance. Following EC authorization, each Member State may (or not) implement their own approval process for commercial products, including the newly authorised pesticide molecule. Molecules are initially approved for up to 15 years depending on the risk they may involve (the renewal of the authorization follows a similar process). Regarding the fate and behaviour of the active substance within the environment, Regulation (EC) 1107/2009 clearly states that it cannot be approved if considered a persistent organic pollutant (POP), which requires all of the following three points to be verified: (i) the half-life of dissipation (DT_{50} , i.e. the time required for the degradation of 50% of the applied active compound in the soil or the water-sediment system, measured under either laboratory or field conditions) is greater than 2 months in water or 6 months in soil and sediments, (ii) the propagation of the active molecule is potentially high (i.e. detected over long distances) and (iii) the bioaccumulation factor is high and/or toxicity to nontarget species (including birds) is detected.

Standard toxicity tests for risk assessment in birds in the EU

The application requires the manufacturers to provide a review of the relevant literature in the last 10 years and mandatory safety studies that cover basic information regarding the physical and chemical characteristics of the molecule, its toxicology, its behaviour within the environment and effects on nontarget species (listed in Annex II and III of the Directive 91/414/EEC still applicable for Regulation (EC) 1107/2009). These studies must comply with the

EFSA guidelines in agreement with standard protocols produced by the Organisation for Economic Co-operation and Development (OECD).

EFSA's risk assessment for birds (Question No EFSA-Q-2009-00,223, Annex II Sect. 8.1 and Annex III Sect. 10.1 of the Directive 91/414/EEC) is based on a three-tiered approach (EFSA, 2009). The first step aims to screen molecules on an indicator species in the most extreme conditions of exposure to identify low-risk molecules, i.e. those producing no detectable effects in these conditions, and will not be further considered in the process. The other molecules that failed the previous screening step are then tested under more realistic conditions of exposure in the first-tier risk assessment, which includes acute and reproductive risk assessments. If the first-tier risk assessment results are not compliant with the threshold limits, a refined higher-tier risk assessment is required. This last step follows a case-by-case approach to eliminate 'unacceptable impact', e.g. long-term effects on the abundance of nontarget species and visible mortality (see Appendix C in EFSA, 2009). The combination of the results from each step allows characterising overall risk.

EFSA bases its guidelines on the standard avian toxicity tests from OECD, which include acute oral, short-term dietary and reproductive toxicity tests. A summary of the major characteristics of these tests is provided in Table 2. Classically, they are performed on quail species (Japanese or bobwhite quails, *Coturnix japonica* or *C. c. japonica* and *Colinus virginianus* respectively) or mallard ducks (*Anas platyrhynchos*). While mallard ducks could be used for acute toxicity tests (they are considered a preferred species in US EPA guidelines OCSPP 850.2100, for example), they are not recommended due to a higher risk of regurgitation (EFSA, 2007). Overall OECD guidance does not aim to limit the number of species that can be used but to provide robust, captive/laboratory-breed species from different orders that can be available any time of the year (OECD, 2016).

Depending on the tests, different endpoints are reported based on the observations during all the trials (Table 2). Classically, LD₅₀ (i.e. the dose that kills half of the population tested) is provided for acute toxicity. Although short-term dietary toxicity tests are not mandatory for the submission process, they allow determination of the LC₅₀ (i.e. the concentration that kills half of the population tested) on

which reproductive toxicity tests are further based (using half of the LC₁₀ as the highest concentration and lower from this one). For this latter category, the NOEC is used as the endpoint (see section 'Improving ecological risk assessment' for a discussion on this estimator). The relevance of reproductive toxicity tests *per se* has been discussed elsewhere (see Mineau et al., 1994, 1996a, 1996b; Mineau, 2005a). Indeed, these tests show different flaws regarding their design, and especially concerning their capacity to predict consequences in field conditions (Mineau et al., 1996a; Mineau, 2005a). Despite several alerts from experts (Mineau et al., 1994, 1996a, 1996b; Mineau, 2005a), the basic design of these tests has never been updated so far.

Gaps between tests under laboratory and field conditions

Cocktail effects

Pesticides are complex formulations that are often used in a mixture, and different molecules are used simultaneously or sequentially for the same or different crops in the same area, resulting in a cocktail effect with potential interactions between/among molecules and consequences for target and nontarget organisms (Bro et al., 2016; Lopez-Antia et al., 2016, review in Hernández et al., 2017). Three primary scenarios concerning these effects have been defined (see Fig. 1 in Hernández et al., 2017): (i) the molecules do not interact and thus exhibit additive effects or independent effects if they act on the same target; (ii) the molecules interact and function synergistically (i.e. the effects will be greater than the additive effects of the molecules considered separately); and (iii) the molecules interact and function antagonistically (i.e. the effects will be reduced compared to the additive effects of the molecules considered separately). Basically, risk assessments only consider the additive effects of molecules as a conservative measure, and no interaction is considered (Belden et al., 2007; EFSA, 2009; Heys et al., 2016), which means that molecules are tested independently and very rarely in a mixture that would reflect the real conditions of exposure in the field. Studies designed to test the effects of these pesticide mixtures include concentration addition models (review in Belden et al.,

Table 2 Summary of OECD standard toxicity tests. LD_{50} Lethal Dose 50, LC_{50} Lethal Concentration 50, *NOEC* No-Observed Effect concentration. Data were extracted from OECD (1984, 1993, 2016)

	Acute oral toxicity test OECD 223 (adopted in 2016) (OECD, 2016)	Dietary toxicity test OECD 205 (adopted in 1984) (OECD, 1984)	Reproduction toxicity test OECD 206 (adopted in 1984) (OECD, 1993)
General study design characteristics			
Design options	Limit dose test (low toxicity), LD_{50} -slope test (dose-response curve required), LD_{50} -only test (only median lethal dose required)	-	-
Exposure duration	A single exposure	5 days	More than 20 weeks (at least 10 weeks before egg-laying) <i>Via</i> the diet (adult only)
Administration pathway	Capsule or gavage	<i>Via</i> the diet	-
Volume of the dose	Less than 10 ml/kg body weight	-	At least 24 (12 pairs) or 32 mallards (8 groups of 1 male and 3 females) or 36 quails (12 groups of 1 male and 2 females)
Number of birds per concentration levels	At least one per dose and up to 5 per dose (depending on the stage)	10	Minimum of 3 dietary levels Based on LC_{50} (see OECD 205)
Concentration levels	1 to 10 levels	1 treatment + 2 controls Minimum 5 dietary levels	Maximum 1000 ppm
Maximal concentration	2000 mg/kg body weight	-	At least the 20 weeks of exposure + 14 days for hatchlings
Duration of observations	14 days	Minimum 8 days up to 21 days	-
Validity of the test	Invalid if more than 10% mortality is observed in the control group	Invalid if: -more than 10% mortality is observed in the control group -less than 80% of the concentration of the molecule not maintained in the diet -lowest level doses should not provoke mortality/toxic effects	Invalid if: -more than 10% mortality is observed in the control group -a limited number of 14-day-old chicks per hen (depending on the species) -eggshell thickness below an average value (depending on the species) -less than 80% of the concentration of the molecule is maintained in the diet
Model species			
Preferred test species from the same source (population/breeder)	Bobwhite and Japanese quails	Mallard ducks Bobwhite and Japanese quails Pigeons Ring-necked pheasants Red-legged partridges	Mallard ducks Bobwhite and Japanese quails

Table 2 (continued)

	Acute oral toxicity test OECD 223 (adopted in 2016) (OECD, 2016)	Dietary toxicity test OECD 205 (adopted in 1984) (OECD, 1984)	Reproduction toxicity test OECD 206 (adopted in 1984) (OECD, 1993)
Age of individuals	Mature (but not in breeding condition) with breeding history	Chicks 10–17 days old for all species except for pigeons (56–70-day-old)	Mallards: 9 weeks–2 months Bobwhite quails: 20–24 weeks Japanese quails: proven breeders
Sex	Not necessarily separated except if sex differences are suspected	–	Both sexes
Experimental conditions (housing)			
Housing modality	Housed individually (preferred)	5 to 10 birds/pen (except for pigeons housed individually)	Adults: by pair or association of 1 male and 2–3 females (depending on the species) Hatchlings: in group
Housing size	1000 cm ²	Depending on the species 300 to 2500 cm ² /bird	Depending on the species 0.15 to 1 m ²
Temperature	15–27 °C	Depending on the species and the age of the individuals during the test	22 ± 5 °C for adults 14 to 38 °C for eggs and hatchlings
Photoperiod (L: light/D: dark)	8L/16D	8L/16D	Adults: 7–8L/16D to 16–18L/6–8D Hatchlings: 14L/10D
Food and water	<i>Ad libitum</i>	<i>Ad libitum</i>	Water <i>ad libitum</i>
Observations and results			
Measure effects	Mortality Clinical symptoms Body weight Food consumption	Mortality Clinical symptoms Body weight Food consumption	For adults and hatchlings: Clinical symptoms Body weight Food consumption Egg characteristics Eggshell thickness Hatchability (including normal hatchlings) Young survival NOEC
Endpoints	LD ₅₀ , LD ₅₀ slope and confidence interval	LC ₅₀	

2007). Interestingly, some pesticide families, such as OPs, CBs and pyrethroid insecticides, azole fungicides and triazine herbicides, are often involved in synergistic effects (Cedergreen, 2014; Rizzati et al., 2016). Such synergistic effects have been observed, for example, in bees exposed to a mixture of deltamethrin (pyrethroid insecticide) and prochloraz (imidazole fungicide) (Chalvet-Monfray et al., 1996; Colin & Belzunces, 1992; Meled et al., 1998).

Although the lethal effect of a single pesticide might be efficiently tested under laboratory conditions (Mineau, 2002), an extrapolation of the sublethal effects fitting the complexity of realistic environmental exposure is difficult to produce. This may explain why the predictions made from experimental studies and the effects measured in wild conditions are often poorly correlated (Shore & Douben, 1994; Story & Cox, 2001). This discrepancy is even more important that the models used to set threshold levels in tier-risk assessments are mainly based on a single route of contamination, the oral route (considered to be the main route of exposure in birds, see section ‘Modes of exposure’), while some molecules may be mainly incorporated *via* other routes of exposure (Mineau & Whiteside, 2005).

The fate of pesticides within the environment

Environmental contamination occurs *via* different pathways and may involve high levels of pesticides (Galon et al., 2021; Giorio et al., 2021). It is estimated that only 2–20% of the neonics used to coat seeds are absorbed by crops; thus, up to 95% of the active molecules remain available in the soil and water on average (Hladik et al., 2018). In addition, pesticides may contaminate the air through their dispersion during spraying, their volatilization after application or their distribution *via* the dust generated during the sowing of coated seeds (Giorio et al., 2021; Socorro et al., 2016). When pesticides are sprayed, the fraction of the applied pesticides that is dispersed in the air is estimated to be ca. 15–40% (Socorro et al., 2016). Pesticide transport may occur over short or long distances up to thousand kilometres in the atmosphere (Shen et al., 2005), which explains why they can be found in remote locations such as in the Arctic (Balmer et al., 2019). Air contamination results in diffuse pollution through pesticide deposition in soils, surface waters and all types of organisms. In treated fields, pesticides

accumulate in soils and then enter waterways *via* runoff. Similarly, systemic pesticides may contaminate both soils and water after plant death and decomposition (Bonmatin et al., 2015; Giorio et al., 2021). The lateral movement of pesticides (i.e. the horizontal transfer of pesticides from the application site to the surrounding areas) in soils may occur and explain why wild plants and hedgerows are contaminated with substances such as neonics near seed-treated crops (Botías et al., 2016; Wood & Goulson, 2017).

Detoxification occurs through the degradation of pesticides, which is the only process that clears pesticides from the environment (Fenner et al., 2013). Pesticide persistence in the environment depends on sorption (i.e. the process by which one substance becomes attached to another) onto soil or water–sediment particles, which slows their dissipation and degradation (Fenner et al., 2013). The degradation of pesticides involves biotic processes (mediated by the action of microorganisms or plants) and abiotic processes (photochemical and chemical transformation) (Fenner et al., 2013). How a pesticide may be degraded is determined by its chemical properties/formulation and the environmental conditions to which it is exposed. In principle, a pesticide is registered for use if its persistence in the environment does not considerably exceed its intended period of use (i.e. ranging from a few days to several weeks or years, depending on the plant). In the soil, the DT_{50} of 67 pesticides was shown to range from 20 to 100 days for 45% of the pesticides, while the DT_{50} exceeded a year for 15% of the pesticides, meaning that one year after their application, 50% of the applied amount of these pesticides was still present in the soil and would continue to accumulate with each year of application (calculated from Supplementary Material provided by Silva et al., 2019). The pesticide’s DT_{50} and DT_{90} (obtained from the Pesticide Properties Database - PPDB, Lewis et al., 2016 at <https://sitem.herts.ac.uk/aeru/ppdb/en/atoz.htm>) exhibit marked differences among pesticide formulations but also for a given pesticide among soil or sediment types and across studies (Fenner et al., 2013; Goulson, 2013). Glyphosate and its primary metabolite aminomethylphosphonic acid (AMPA) are the most common pesticide residues found in soils in Europe (Silva et al., 2019). Depending on field conditions, AMPA may persist up to 21 times longer than glyphosate in soils (Bento et al., 2016). Imidacloprid, one of the top-selling insecticides, exhibits DT_{50} values ranging from 77 to 425 days

under laboratory conditions, but under realistic conditions, strong evidence suggests that the DT_{50} can reach 1250 days (Goulson, 2013; Wood & Goulson, 2017). Overall, our knowledge regarding the factors that affect the persistence of pesticides and their metabolites identified (for neonics, see Simon-Delso et al., 2015) *in natura* as well as their persistence once taken up by plants (Giorio et al., 2021) or their consumers is extremely limited (Goulson, 2013).

Considering the restrictive framework of the tests performed for approval regarding the large number of variables that are likely to impact the fate of a pesticide (e.g. environmental conditions, the chemical nature of the formulation) and, consequently, the exposure of nontarget species, our understanding of the true effect of pesticides appears to be greatly limited and relies on indirect evidence and hypothetical deduction (Köhler & Triebskorn, 2013). Farmland birds may potentially be exposed to pesticides throughout their entire lives, and there is evidence that these species can be impacted by pesticides. This is even more important for migrating species, for instance, due to heterogeneous regulation policies worldwide (see above). OPs have also been found on the feet of dead migratory songbirds in Canada, overwintering in Central America (Alharbi et al., 2016). Banned molecules such as DDT have been observed in birds in several studies (e.g. Luzardo et al., 2014; Botha et al., 2015; Abbasi et al., 2016; see a recent review from India, which is the current major user of DDT, Malik et al., 2018), as well as molecules such as neonics that are partially banned (or on the way to being banned) (e.g. Byholm et al., 2018; Humann-Guillemot et al., 2019a, 2021; Millot et al., 2017). In Brazil, OCs were mostly banned in 1985, with some exceptions until 2007; nonetheless, some molecules, such as heptachlor, were still found in raptor feathers in 2015 (Aver et al., 2020). Hereafter, we synthesize this knowledge regarding farmland birds.

Effects of pesticides on farmland birds

Compared to the overall available pesticide literature on birds, the links between farmland bird trends and pesticide use have been poorly investigated (Fig. 1), mostly due to the difficulties in considering environmental complexity and long-term monitoring. Two primary pathways can be distinguished: (i) indirect

effects, wherein pesticides affect the resources used by birds (Campbell et al., 1997), and (ii) direct effects, wherein pesticides affect the birds themselves, with effects on the organism's physiology (Mitra et al., 2011, see also Fig. 2 in Bennett & Ettoreson, 2006 for an overview of a complex problem).

Indirect effects: the impact on resources

Indirect effects occur through the depletion of resources (Potts, 1986; Blackburn & Wallace, 2001; Boatman et al., 2004; Hart et al., 2006; Henderson et al., 2009; Geiger et al., 2010; McKenzie et al., 2011; Smith et al., 2010; Girard et al., 2014 see also Campbell et al., 1997 for a review). At each level of the food chain (i.e. primary producers: weeds/seeds and first- and higher-order consumers: invertebrates/vertebrates), resource abundance and/or diversity are greater in organic farms than in conventional farms (Brickle et al., 2000; Blackburn & Wallace, 2001; Morris et al., 2005; Hart et al., 2006; Bradbury et al., 2008; Henderson et al., 2009; McKenzie & Whittingham, 2009; McKenzie et al., 2011; Girard et al., 2014; Tuck et al., 2014), although factors other than pesticides may account in part for these differences, such as grassland and hedge abundance within the landscape, smaller field sizes and higher crop diversity (Batáry et al., 2010; Butet et al., 2010; Fischer et al., 2011; Martin et al., 2020; Santangeli et al., 2019). The role of land-use intensity at the regional scale has also recently been shown to modulate the extent of organic farming benefits for avian biodiversity (Kirk et al., 2020).

Bird declines might result from the depletion of resources for nesting (i.e. the protection of suitable sites for nests) and/or food resources. Pesticides, specifically herbicides, may alter the structure of vegetation within crops and field margins. This alteration in ground cover can also lead to reductions in shelter and nesting sites for ground-nesting/feeding species, thus reducing protection against predators and nesting site availability (Robinson & Sutherland, 2002). Food depletion related to pesticide use is commonly considered to occur through three main mechanisms: (i) the depletion of arthropods used as feeding resources, especially during chick-rearing (due to insecticides); (ii) the depletion of weeds that are exploited by the arthropod prey of insectivorous bird species (due to herbicides); and (iii) the depletion of weeds that produce seed and plant biomass for granivorous/herbivorous bird species (due to herbicides) (Boatman et al.,

2004). One may also consider a fourth supplementary level associated with the control/eradication of small mammals (rodents) that are hunted by predatory bird species (see the outcomes of Baudrot et al., 2020 for mammal predator-rodent dynamics related to the use of rodenticides). Food resource availability during the breeding season may represent a constraint on bird reproduction (Ruffino et al., 2014), and the rarefaction of food items due to pesticide use is often associated with deteriorated chick body condition and fledgling success in species such as corn buntings (*Miliaria calandra*), grey partridges (*Perdix perdix*), skylarks (*Alauda arvensis*) and yellowhammers (*Emberiza citronella*) (Morris et al., 2005; Hart et al., 2006, see Boatman et al., 2004 for a synthesis). In tree swallows (*Tachycineta bicolor*), food availability measured along a gradient of agricultural intensification in southern Quebec (Canada) seems to be the major driver of breeding success (Ghilain & Bélisle, 2008; Garrett et al., 2022) rather than the direct effect of pesticides found in food boluses (Poisson et al., 2021). The depletion of food resources could be particularly important in birds since the body condition of nestlings/fledglings strongly determines their subsequent survival (for a recent review, see Ronget et al., 2018). Food depletion may also compromise adult birds through the trade-off between survival and future reproduction (Stearns, 1992). Basically, resource allocation for reproduction reduces adult survival in the case of poor feeding resources due to a required increase in foraging effort, which implies a higher cost for survival and future reproductive events (Martin, 1995; Roper et al., 2018). Clutch size may also be impacted due to its link with food availability (Martin, 1987; Millon et al., 2008; Rands, 1985; Ruffino et al., 2014).

Therefore, the indirect effects of pesticides affect the availability of both nesting and feeding resources. These effects may be even more deleterious for specialist species than for generalists (which can shift to another habitat and access more resources) due to their higher sensitivity to habitat quality (Chiron et al., 2014; Filippi-Codaccioni et al., 2010; Teillard et al., 2015; Wretenberg et al., 2006), although detailed quantification of such effects requires long-term population monitoring, and such data are currently scant. Few studies have yet shown a negative relationship between pesticide use (neonics) and avian population decline, considering other factors related to agricultural intensification (Hallmann et al., 2014; Li et al., 2020).

Direct effects: different modes of exposure and different implications

Although pesticides are deliberately used to kill birds in some cases (avicides or illegal poisoning; see, for example, Plaza et al., 2019), the direct effects of pesticides on birds mostly result from unintentional exposure. Contamination through ingestion, respiration or percutaneous absorption through acute (punctual) or chronic (repeated over time) exposure may result in either short- (lethal, Poliserpi et al., 2021) or long-term (sublethal) toxic effects, which are less conspicuous but, in the long run, may affect the population (Lopez-Antia et al., 2015a, 2018).

Modes of exposure

Contamination may occur *via* the respiratory pathway and/or during preening if individuals have been exposed to spraying or to contact with plants, soil or water following spraying (Mineau, 2011; Sánchez-Bayo, 2011). The absorption of chemical components may also occur through the skin on the legs; dermal absorption is likely a substantial factor in the intoxication of birds, with some molecules being more toxic *via* this pathway than through ingestion (see Hudson et al., 1979 for example, see Driver et al., 1991). However, this pathway is often ignored in toxicity tests, and existing data are mostly derived from mammalian model species (Maul et al., 2018; Mineau, 2002, 2011, 2012).

Ingestion of contaminated food/water (whatever the origin of such contamination) is considered the primary mode of avian exposure to pesticides (Lopez-Antia et al., 2016 but see Driver et al., 1991 and Mineau, 2011), although the relative importance of the various potential pathways of exposure may differ among species depending on their habitat use and behaviour (Best & Fischer, 1992; Boutin et al., 1999). Birds can be exposed to both primary and secondary poisoning (Albert et al., 2010; Krone et al., 2017; Story & Cox, 2001). The former relates to the ingestion of toxic baits targeting pest species, coated seeds or water contaminated by remnant pesticides, while the latter consists of the ingestion of contaminated organisms, such as treated plants or poisoned rodents or insects (Aktar et al., 2009; Berny & Gaillet, 2008; Millot et al., 2017). Although the consumption of lethal quantities of coated seeds (mostly neonics)

appears to be infrequent (McGee et al., 2018; Turaga et al., 2016), treated seeds do not seem to be avoided, especially during the sowing period of winter cereals (Lennon et al., 2020; Lopez-Antia et al., 2016; Roy & Coy, 2020; Roy et al., 2019). Although the number of seeds consumed by birds represents an overall concentration of active molecules below LD₅₀, individuals may ingest doses that are known to produce acute and/or chronic exposure (lowest observed adverse effect level, LOAEL; see Table 4 in Roy & Coy, 2020). Studies finding no ‘imminent danger’ to wildlife (see Turaga et al., 2016 for an example) should, however, refer to LOAEL rather than to LD₅₀, which is not representative of the risk to granivorous birds endangered by treated seed consumption (see section ‘Improving ecological risk assessment’ for a discussion on these endpoints).

Depending on their chemical properties, bioavailability within the environment and affinities with biological tissues, pesticide molecules may be bioaccumulated (i.e. stored within the organism in different tissues) and/or biomagnified (i.e. accumulated along the trophic chain). The level of biomagnification also depends on the diet, with top predators that prey upon birds tending to accumulate higher levels of contaminants than those preying on mammals (see above, Walker, 1983; Mañosa et al., 2003; van Drooge et al., 2008). For instance, due to their high level of lipophilicity and persistence within the environment, OCs are known to accumulate within organisms, including eggs, and through the trophic chain (see van Drooge et al., 2008; Luzardo et al., 2014), while CBs and OPs are rapidly metabolised or excreted, although they are potentially more acutely toxic (Walker, 1983; Sánchez-Bayo, 2011, 2012). Fungicides (metalaxyl, tebuconazole and fludioxonil, see Table 1), which are also quite common for seed treatments, are widely distributed within organisms after exposure but do not seem to bioaccumulate due to rapid metabolism and excretion (Gross et al., 2020). This is also the case for neonics, which are supposed to have a low toxicological impact on birds (Casida, 2018). Although neonics might be rapidly metabolised and excreted in ruby-throated hummingbird (*Archilochus colubris*) (measured in the lab, English et al., 2021) or in wild rufous (*Selasphorus rufus*) and Anna’s (*Calypte anna*) hummingbirds (Bishop et al., 2018, 2020), some evidence may call into question their fate along the trophic chain. First, neonics were detected in nongranivorous

birds such as honey buzzards (*Pernis apivorus*), barn owls (*Tyto alba*) and Alpine swifts (*Tachymarptis melba*), suggesting that they have been exposed to pesticides through their food (most likely insects in all cases, Byholm et al., 2018; Humann-Guillemot et al., 2021). Second, recent experimental studies have demonstrated neonic accumulation within organisms, although over a relatively short time, for at least 22 days (in *Alectoris rufa*: Lopez-Antia et al., 2015a, see also in *Colinus virginianus*: Ertl et al., 2018b and in *Meleagris gallopavo silvestris*: MacDonald et al., 2018). The biological processes of degradation are not sufficiently well known to predict the fate of these molecules, and thus, their transfer through the trophic chain and accumulation are questionable. Moreover, even if neonics and fungicides, for instance, are rapidly excreted from organisms, this may not prevent sublethal and synergistic effects, but data on vertebrate species are still lacking (Gross et al., 2020; Zubrod et al., 2019).

Finally, although eggshells are known to protect embryos from the external environment during their development, they do not provide complete protection against pesticide exposure. First, embryos can be contaminated through the maternal transfer of lipophilic pesticides in the yolk. This phenomenon is well documented in poultry due to its potential effects on human health (Donoghue, 2001; Guo et al., 2018; MacLachlan, 2008). Second, embryos can be contaminated through the eggshell and chorionic membranes if exposed to spraying, contaminated air, water or vegetation or contaminated feathers of the parents (Bro et al., 2015, 2016; Hussein et al., 2014; Ortiz-Santaliestra et al., 2020). Studies quantifying pesticides in eggs have mostly focused on nonfarmland birds (see, for example, Martínez-López et al., 2007; Vorkamp et al., 2014; Corcellas et al., 2017, see Table S1 for all the species concerned), although few of them investigated farmland bird specialists such as partridges (grey partridges, *Perdix perdix*: Bro et al., 2016 and red-legged partridges, *Alectoris rufa*: Ortiz-Santaliestra et al., 2020) or non-specialists such as *Athene cunicularia hypugaea* (Stuber et al., 2018).

The impact on individuals then depends on the complex combination of the mode of exposure, the mode of action of the molecules involved, their toxicity (conferred by their chemical properties), their concentration, the stage of exposure (embryo, chick or adult) and the repetition of exposure (acute versus

chronic exposure). It is also highly dependent on individual and species sensitivities and ecology (Grue & Shipley, 1984; Patnode & White, 1991; Peraica et al., 1993). Small bodied-size species that need to feed continuously to maintain their high metabolic rate, such as hummingbirds, will not be able to avoid exposure when pesticides are applied and may be more prone to overcome the effect of (chronic) pesticide exposure (English et al., 2021; Mineau et al., 1996b). On the other hand, a species that feeds only part of the day may be less contaminated, especially when the peak of feeding activity is not at the same time as the application period. However, the toxicity of pesticide molecules is usually only tested in a few individuals from a few model species under laboratory conditions before approval (classically, Japanese or bobwhite quail or mallard duck; see section ‘Standard toxicity tests for risk assessment in birds in the EU’ and Table 2 and Bean et al., 2019 for an example of neonics), which do not reflect the variability in the field. Exposure may lead to internal damage that affects individual physiology, metabolism or life-history strategies, leading either to death (i.e. lethal effects) or to (delayed) sublethal effects.

Lethal effects (short-term effects)

Lethal effects are characterised by the death of the individual soon after exposure and reflect acute toxicity. The ingestion of seeds coated with neonics or exposure to other insecticides that impair nervous function, such as CBs and OPs (AChE inhibitors, Casida & Durkin, 2013; Maroni et al., 2000), can have lethal effects on birds (Elliott et al., 1996, Addy-Orduna et al., 2019; Poliserpi et al., 2021). This has been reported, for example, among granivorous grey partridges (*P. perdix*) following the ingestion of treated seeds (Milot et al., 2017) and is highly suspected in greyish baywings (*Agelaioides badius*) (Poliserpi et al., 2021). Many studies have reported massive bird deaths worldwide caused by pesticide poisoning (Africa: Ogada, 2014; Europe: Berny, 2007; van Drooge et al., 2008; Guitart et al., 2010b; Gómez-Ramírez et al., 2014; Milot et al., 2017; Asia: Muralidharan, 1993; North America: Frank & Braun, 1990; Mineau et al., 1999; Fleischli et al., 2004; Mineau, 2013; Murray, 2017; and South Africa: Goldstein et al., 1999, see Table S1 for all the species concerned when documented). Depending on the

trophic position, this poisoning may result from secondary poisoning, especially in bird apex predators. Indeed, they can be impacted by anticoagulant rodenticides (ARs) by preying or scavenging upon rodents previously exposed to these toxic agents (Cooke et al., 2022; Herring & Eagles-Smith, 2017; Lin et al., 2022; Murray, 2017; Rattner et al., 2014). The potential impact of rodenticides is even more pronounced since the development of the second generation of this kind of pesticide (SGAR for Second Generation Anticoagulant Rodenticide) with increased storage in their liver; therefore, raptors are potentially exposed to higher doses of these toxins (Herring & Eagles-Smith, 2017). For example, in France, most red kites (*Milvus milvus*) and most Réunion harriers (*Circus maillardi*) found dead in the field were contaminated with rodenticides used to control rodent outbreaks (Berny & Gaillet, 2008; Coeurdassier et al., 2019; Fourel et al., 2017). The ubiquity of ARs in living nestling raptors has been recently evidenced (see Badry et al., 2022) as well as their sub-lethal effects (Vyas et al., 2022).

Except on certain occasions when bird carcasses are found in the vicinity of evident contaminated food resources, it is often difficult to decipher whether death occurs due to direct lethal effects or (long-term) sublethal effects.

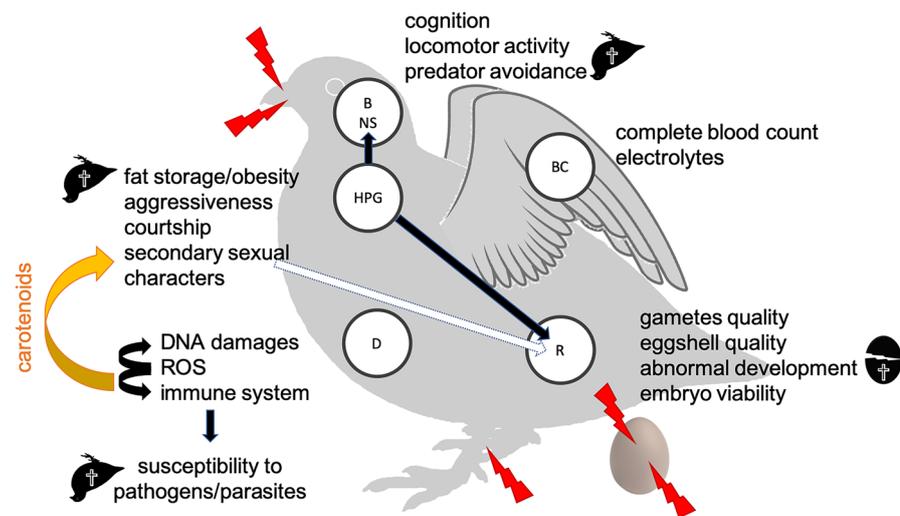
Sublethal effects (long-term effects)

Delayed sublethal effects are more pernicious and cannot be reliably estimated or predicted from classical laboratory tests based on the estimation of the LD₅₀ or surrogate parameters in the slightly longer-term (NOEC, for example, see Table 2), although sub-lethal clinical signs could be considered instead of LD₅₀ (Callahan & Mineau, 2008). Here, we propose an integrative pathway for these effects at different levels within the organism, from intracellular perturbations to life-history traits (i.e. survival and reproduction, Fig. 2) mostly resulting from experimental studies (Table S1).

Blood chemistry

Few studies have investigated the effects of pesticides on blood chemistry, including electrolytes, fat, proteins, glucose and enzymes, likely because these elements are linked to major functions (see

Fig. 2 Schematic representation of sublethal pesticide effects on birds. White circles represent major physiological functions/systems. *B* brain, *NS* nervous system, *HPG* hypothalamic–pituitary–gonadal axis, *BC* homeostasis, *D* detoxification, *R* reproduction. Black arrows indicate the direct effects of one function on another. White dotted arrows indicate an indirect link (through behavioural pathway). Red lightning bolts indicate the mode of exposure (see text for details)



below) and are thus not directly analysed. Except in the case of exposure to rodenticides which led to an analysis of coagulation time (see Vyas et al., 2022), most of the time, the origin of the modifications is not clear. For example, thiram (CBs), lindane (OCs), fipronil (phenylpyrazoles) and imidacloprid (neonics) decrease haematocrit (i.e. the ratio of the volume of red blood cells to the total volume of blood) (Lopez-Antia et al., 2013, 2015b, 2015c; Mandal et al., 1986). However various processes can lead to such a decline, including (i) those directly linked to red blood cells (i.e. haemolysis, haemorrhage or reduced erythropoiesis) (Mandal et al., 1986), (ii) lipid peroxidation (Lopez-Antia et al., 2015b) or (iii) indirect effects due to starvation (see Grue et al., 1997), when associated with decreases in other plasmatic compounds, such as magnesium, albumin, total protein and triglycerides (Lopez-Antia et al., 2015c). Triazole fungicides, for instance, decrease the levels of cholesterol and triglycerides, likely through endocrine disruption (Fernández-Vizcaíno et al., 2020; Lopez-Antia et al., 2018). These alterations are linked to other disorders developed thereafter.

Oxidative stress and detoxification

Pesticides have been shown to increase oxidative stress by increasing reactive oxygen species (ROS) production, lipid peroxidation and DNA damage (see Bagchi et al., 1995 experiments on rats). Oxidative stress is known to be a mediator in the

(complex) cascade leading to both cell apoptosis (often linked to neurodegenerative pathologies in humans, for instance, see Ghasemi et al., 2015) and cell immortalization (i.e. cancers, Franco et al., 2009). Oxidative stress has been mostly studied in the context of bird exposure to neonics (Hoshi et al., 2014; Lopez-Antia et al., 2013, 2015a; Lv et al., 2020; Ortiz-Santaliestra et al., 2015). The accumulation of cytotoxic ROS is limited by the detoxifying activity of the integrated antioxidant system, including endogenous enzymes and non-enzymatic exogenous compounds. This detoxification function can also be impaired by pesticides, with altered liver and hepatic vitellogenin gene expression, leading to significant oxidative damage (Hoshi et al., 2014; Khalil et al., 2017). After exposure to pesticides, the levels of antioxidants, such as glutathione peroxidase 4 (GPx4) and manganese superoxide dismutase (Mn-SOD), can also be reduced (Hoshi et al., 2014). In quails exposed to neonics, superoxide dismutase (SOD) activity decreased while alanine and aspartate aminotransferase activities increased, and these enzymes are common markers of liver damage (Lv et al., 2020). However, some studies observed an increase in antioxidant defences, such as SOD activity and vitamin and carotenoid levels, in plasma after exposure to thiram or imidacloprid (Lopez-Antia et al., 2013, 2015a, 2015b). Carotenoids are keystone molecules since along with their biological proprieties, they are involved in several functions, acting as essential molecules used in cellular pro-

cesses, such as immunocompetence and vitamin A synthesis, as well as potential antioxidants that enhance immune defence and play roles in communication displays in birds (Burton, 1989; Møller et al., 2000; McGraw & Ardia, 2003; Weaver et al., 2018 see below), although a recent study failed to highlight such trade-offs (Koch et al., 2018). If carotenoids are simultaneously required for several functions (Fitze et al., 2007), because they represent a limited resource, there should be a trade-off in their allocation between self-maintenance and secondary sexual ornamentation functions (Baeta et al., 2008). Consequently, when self-maintenance is threatened by pesticides, carotenoids should be allocated to cellular functions at the expense of the expression of secondary sexual characteristics, with consequences for sexual selection and mate choice (see below).

Immune system and resistance to pathogens

The immune system is an organism's most important and sophisticated line of defence against pathogens. Therefore, any alterations in this system induced by pesticides may compromise the resistance of individuals to potential pathogenic attacks and thus impair survival. Recent data on the use of neonics associated with pathogen outbreaks have suggested that these chemicals might be responsible for immunosuppression in birds, as observed in mammals (Mason et al., 2013). Pesticides may alter the immune system through several pathways (Banerjee, 1999). First, these molecules may directly modulate immune defence by either suppressing or enhancing the effectors involved. For instance, phenylpyrazoles, CBs, OCs and neonics reduce the avian cellular immune response, resulting in a reduced inflammatory response (Grasman et al., 1996; Lopez-Antia et al., 2013, 2015a, 2015b, 2015c, but see Bustnes et al., 2007; see Mitra et al., 2011 and Gibbons et al., 2015 for review). More specifically, studies have demonstrated a decrease in leukocyte levels (a reduction in monocytes, lymphocytes and basophils) but also heterophilia or even eosinophilia (Garg et al., 2004; Grasman et al., 1996; Gromysz-Kałkowska et al., 1985; Mandal et al., 1986). Second, modulation of the immune system may occur through alterations in the principal organs responsible for the production of the effectors. For example,

lymphoid tissues located in the thymus, producing T cells, and spleen (monocyte storage) are altered (Day et al., 1995; Galloway & Handy, 2003; Garg et al., 2004). Pesticides may therefore also impair the acquired immune response *via* the alteration of T cells (Lopez-Antia et al., 2013). Finally, the immune system may be altered through two additional indirect pathways: pesticide-induced hormonal disorders (see below) and increased oxidative stress levels. These negative consequences of pesticide exposure on the immune system might strongly affect host-pathogen dynamics through increased susceptibility to parasites (see Moreau et al., 2021) and ultimately host population dynamics.

Alteration of the nervous system

Several families of pesticides, specifically insecticides, not only attack the nervous system of target pests but also the nervous system of nontarget species (Table 1, review in Maroni et al., 2000; Tomizawa & Casida, 2003, 2005; Walker, 2003; Casida & Quistad, 2004; Casida, 2009, 2011, 2018; Casida & Durkin, 2013; Casida & Bryant, 2017). For example, CBs and OPs inhibit AChE, a major enzyme in the nervous system, thus altering the behaviour of nontarget species (review in Grue et al., 1997; Story & Cox, 2001; Walker, 2003; Mitra et al., 2011). AChE degrades acetylcholine, a neurotransmitter involved in the sympathetic and parasympathetic nervous systems through cholinergic synapses. CBs and OPs phosphorylate AChE, thereby inactivating it. Thus, acetylcholine accumulates at its receptors, resulting in the hyperstimulation of cholinergic receptors. Similarly, OCs basically inhibit the gamma-aminobutyric acid (GABA) receptor in the brain, except for DDT and its analogues, which act similarly to pyrethroids as sodium channel modulators (review in Casida, 2009; Jayaraj et al., 2016). Neonics also target neural function as competitive agonists of nAChE, although their effects are assumed to be lessened in vertebrates due to the reduced prevalence of this receptor (Casida, 2018; Tomizawa & Casida, 2003, 2005). However, there are contrasting reports of neonic impacts (e.g. imidacloprid) on AChE activity: some authors have reported no changes, e.g. in red-legged partridges (*Alectoris rufa*, Lopez-Antia et al., 2015a) or ruby-throated

hummingbirds (*Archilochus colubris*, English et al., 2021), while others observed increase impacts in rock pigeons (*Columba livia domestica*, Abu Zeid et al., 2019) and decreased impacts in Japanese quails (*Coturnix coturnix*, Rawi et al., 2019). Although neonics do not directly act on AChE, they induce neuronal degeneration, which in turn may affect AChE activity (Abu Zeid et al., 2019; Rawi et al., 2019). For example, decreased activity might be associated with an altered neural function (Rawi et al., 2019), while increased activity could be suggestive of enhanced axonal repair (Abu Zeid et al., 2019). The symptoms associated with an alteration in the nervous system often result in overall decreases in activity and coordination behaviours (Elliott et al., 1996); reductions in foraging activity, leading to starvation and body weight loss (Grue & Shipley, 1984; Hart, 1993; Eng et al., 2017, 2019, but see Rudolph et al., 1984); enhanced vulnerability to predators (Hunt et al., 1992); decreases or increases in territorial/nest defence (Fox & Donald, 1980; McEwen & Brown, 1966) or aggressiveness (Farage-Elawar & Francis, 1988); reductions in parental care and changes in incubation behaviour (Bennett et al., 1991; Grue et al., 1982); delayed migration (Eng et al., 2019); and/or ataxia (lack of voluntary coordination of muscle movements) (Avery et al., 1993; Fisher & Metcalf, 1983; Foudoulakis et al., 2013; Grue & Shipley, 1984). Most of these effects lead to the death of the individuals. CBs and OPs may also induce hypothermia through the excitation of cholinergic synapses in the preoptic anterior hypothalamus (POAH) (review in Grue et al., 1997). Additionally, neurotoxic pesticides may compromise more complex functions involved in learning and memory. For example, white-crowned sparrows' (*Zonotrichia leucophrys*) ability to correctly orient themselves for migration was altered after exposure to imidacloprid (neonics) or chlorpyrifos (OPs) (Eng et al., 2017).

Alteration of the nervous system may also impair other functions, with a cascading effect. Indeed, some neurotransmitters play a crucial role in neuroendocrine regulation. For example, the GABA signalling pathway is involved in the regulation of the hypothalamic-pituitary-gonadal (HPG) axis (for details on physiological mechanisms in mammals; see the review by Maffucci & Gore, 2009).

Therefore, pesticides that perturb GABA-gated channels may be involved in impairing the endocrine system and can thus also be considered endocrine disruptor chemicals (no known studies in birds; for fishes, see two contrasting studies involving fipronil: Bencic et al., 2013 and Sun et al., 2014).

Endocrine disruption

Some pesticides are considered endocrine disruptors and may act through different pathways associated with the HPG axis (see Fig. 3 in Grue et al., 1997). First, pesticides may mimic hormones. For example, DDT or fipronil are oestrogenic: they mimic the action of oestrogens (steroid hormones), resulting in an increase in the oestradiol concentration (associated with a decrease in testosterone) and leading to either a feminization phenomenon in male bird embryos and/or a decrease in adult fertility (Fry & Toone, 1981; Khalil et al., 2017; Lopez-Antia et al., 2015c). This may explain why a female-biased sex ratio could be observed under conventional farming (e.g. in *Tachycineta bicolor*: Baeta et al., 2012; in *Parus major*: Bouverier et al., 2016). In some cases, it can be associated with a change in oestrogen receptor (ER α) gene expression with a potential effect on male fertility (Khalil et al., 2017). Second, pesticides can alter the synthesis and metabolism of natural hormones, interfering with higher physiological levels. For example, pesticides such as triazole fungicides may modulate the cytochrome P450 aromatase (CYP19) responsible for the conversion of androgens to oestrogens (Saxena et al., 2015, see also Ronis et al., 1994, 1998 for the effects on other cytochrome P450 enzyme families in quails), which may affect male sexual behaviour (through neuro-oestrogen regulation see Fig. 1 in Ubuka & Tsutsui, 2014; Balthazart, 2017), sex determination (Major & Smith, 2016) and cognition (Bailey & Saldanha, 2015). For example, a reduction in plasma oestradiol was demonstrated in red-legged partridges (*Alectoris rufa*) exposed to tebuconazole (Fernández-Vizcaíno et al., 2020). Third, pesticides may alter endocrine glands and, thus, hormonal secretions. For instance, corticosterone (stress hormone) levels are linked to DDT exposure in red kites (Monclús et al., 2018). Thyroid

gland secretions (measured as triiodothyronine/T3 and/or thyroxin/T4) are perturbed (increased or decreased, depending on the species), as are the thyroid itself and androgen hormones following exposure to DDT, imidacloprid and/or mancozeb. This may in turn influence individual homeostasis, behaviour and gonad development (Kamel & Cherif, 2017; Mayne et al., 2005; McArthur et al., 1983; Pandey & Mohanty, 2017). The effects of imidacloprid and mancozeb on the endocrine system were recently studied in male red munias (Mohanty et al., 2017; Pandey & Mohanty, 2015, 2017; Pandey et al., 2017). These studies demonstrated overall decreases in T3 and T4 (hypothyroidism) and changes in pituitary hormone secretion (thyrotropin, or thyroid-stimulating hormone, TSH), suggesting an effect of these molecules on the adenohypophysis gland (Pandey & Mohanty, 2015, 2017). Additionally, decreased expression of gonadotropin-releasing hormone (GnRH) and androgen receptors and increased expression of gonadotropin inhibitory hormone (GnIH), associated with decreases in the secretion of luteinizing hormone (LH), follicle-stimulating hormone (FSH) (pituitary hormones) and testosterone (steroid hormone), were observed, resulting in inhibition of the development of the testes, which exhibited reduced volume (Mohanty et al., 2017; Pandey et al., 2017). Prolactin (PRL, pituitary hormone) and oestradiol (E2) are also impacted and increased to different extents, depending on the pesticide molecules involved (Mohanty et al., 2017; Pandey et al., 2017). A reduction in steroid hormones was detected following exposure to glyphosate in mallard ducks (*Anas platyrhynchos*, Oliveira et al., 2007). Modulation of sex steroids (i.e. a decrease in testosterone associated with an increase in oestradiol and PRL) may thus reduce sexual motivation in males as well as their attractiveness to females, consequently exerting a negative impact on population dynamics (see below). The effects of imidacloprid and mancozeb are more complex, as they lead to opposite effects depending on whether they are used alone or in a cocktail (alone: increase in TSH and mixed: decrease in TSH), demonstrating the difficulty of predicting pesticide cocktail effects when molecules have different targets (imidacloprid: nAChE,

mancozeb: multiple sites, see Table 1) (Pandey & Mohanty, 2017).

As the HPG axis is the regulator of reproductive function and overall homeostasis and behaviour, major reproductive perturbations are expected following exposure to pesticides (Grue et al., 1997).

Reproduction

Pesticide exposure might impair several aspects of reproduction, such as the production of sexual ornaments, mating success or offspring quality and number, compromising the production and survival of the next generation.

These effects can be mediated through their action as endocrine disruptors, influencing several endocrine processes, notably the secretion of steroid hormones, potentially affecting the production of sexual ornaments and/or the motivation to reproduce (see above). For example, pesticides have been shown to alter carotenoid-based secondary sexual traits involved in sexual selection (Lopez-Antia et al., 2013, 2014, 2015a, b, c; Pandey et al., 2017; Moreau et al., 2021). As carotenoid-based colouration has been proposed to represent an honest signal of individual quality due to the involvement of these pigments in both antioxidant and immune processes (Møller et al., 2000), the decreased conspicuousness of male ornaments may reduce their attractiveness to females. However, grey partridge males exposed to pesticides exhibited increased activity during the courtship season, possibly to compensate for their reduced attractiveness to females or the decreased motivation of females (Moreau et al., 2021; see also McArthur et al., 1983 on DDT's effects on dove courtship behaviour). Nonetheless, less conspicuous ornaments may decrease female investment in reproduction, as observed in mallards (*Anas platyrhynchos*) and red-legged partridges (*Alectoris rufa*) (Alonso-Alvarez et al., 2012; Giraudeau et al., 2011). In individuals exposed to neurotoxic pesticides (see above), courtship behaviour may also be affected.

During mating, fecundation requires functional gametes. Males exposed to pesticides, such as neonicotinoids, OPs, CBs or glyphosate, exhibited decreased fertility due to alterations in testicular tissues and/or

the apoptosis of germ cells, suggesting that spermatozoid production might be compromised (Hoshi et al., 2014; Khalil et al., 2017; Maitra & Mitra, 2008; Maitra & Sarkar, 1996; Mohanty et al., 2017; Oliveira et al., 2007; Rasul & Howell, 1974; Tokumoto et al., 2013). However, while spermatozoid density decreased by half, sperm mobility and sperm oxidative status do not seem to be altered by exposure to neonics (Humann-Guillemot et al., 2019b). Similarly, exposure to triazole reduced the number of spermatids in the testes of exposed Japanese quails (*Coturnix c. japonica*) but without any consequences on their fertility (Grote et al., 2008). In females, the ovaries decrease in size, become atrophic or exhibit abnormal granulosa cells following CB and neonic exposure (Hoshi et al., 2014; Weppelman et al., 1980). Few studies have focused on the abnormal development of reproductive organs. Although these studies strongly suggest impaired reproductive function, no direct evidence has linked these modifications to reproductive traits or whether a threshold exists between damage and consequences on reproductive success. This is likely the result of partitioning between descriptive physiological studies and eco-evolutionary studies. Moreover, these studies have primarily involved model species such as chickens (*Gallus g. domesticus*: Rasul & Howell, 1974; Weppelman et al., 1980) and quails (*Coturnix sp.*: Tokumoto et al., 2013; Hoshi et al., 2014; Khalil et al., 2017), while only one examined a wild species, the red munia (*Amandava amandava*: Mohanty et al., 2017). Furthermore, these studies have primarily focused on males; these effects in females are generally geared towards egg production.

In contrast, the effects of pesticides on egg and offspring quality and quantity have been more intensively studied. First, the effect of OCs, particularly DDEs (DDT derivatives), on eggshell thickness has been reported for many species, even after the ban of these molecules (Wiemeyer & Porter, 1970; Blus et al., 1972; Newton, 1973; Newton et al., 1986, 1989, 1990; Fox & Donald, 1980; Hartley et al., 1995; King et al., 2003; Martínez-López et al., 2007; Jagannath et al., 2008; Steyn et al., 2018, reviewed in Cooke, 1973 and Peakall, 1993), as these pesticides inhibit calcium integration in the egg gland (for reviews, see Lundholm, 1987, 1997). For example, eggshell thickness varied from +0.4% to -35% in brown pelicans

(*Pelecanus occidentalis*) in the US before the ban on DDT (Blus et al., 1972). In some cases, however, DDT/DDE exposure is unrelated to eggshell thickness (Hernández et al., 2018; Stuber et al., 2018), potentially due to low-dose exposure. Surprisingly, in red-legged partridges (*Alectoris rufa*), the effect of thiram (a CB) on eggshell thickness was reduced in fertilised eggs, while it was increased in unfertilised eggs (Lopez-Antia et al., 2015b). Eggshell robustness is especially important since it conditions the survival of the embryo and prevents the failure of embryonic development (Odsjöa & Sondell, 2014). Although eggshell thinning is often linked to pesticide exposure, one should be cautious in discarding other potential intrinsic effects, such as embryonic shell erosion (see Orłowski & Halupka, 2015 for a recent review). Second, egg shape (e.g. Lopez-Antia et al., 2015b) and volume (e.g. Hernández et al., 2008; Moreau et al., 2021) might also be impacted by the mother's pesticide exposure, with consequences for the quantity of nutritive resources available to the embryo during its development (Lopez-Antia et al., 2015b). Alternatively, females can deposit more resources in their eggs to prepare their offspring for the toxic environment in which they will live. Hence, in red-legged partridges (*Alectoris rufa*) exposed to neonics or CBs (imidacloprid and thiram, respectively), the egg yolks were richer in α -tocopherol, lutein and zeaxanthin, which are nonenzymatic antioxidants (Lopez-Antia et al., 2015a, 2015b). Third, the transgenerational transfer of toxic molecules from the female to the embryo is also possible due to the lipophilic nature of some contaminants, as egg yolk lipoproteins are produced by the liver of female birds (Bro et al., 2016; Donoghue, 2001). Several studies have detected pesticide molecules within eggs (Blus et al., 1972; King et al., 2003; Martínez-López et al., 2007; Jagannath et al., 2008; Corcellas et al., 2017; Hernández et al., 2018; Steyn et al., 2018; Stuber et al., 2018, see Table S1 for details), but the origin of the contamination is not always known, since pesticide exposure may occur during egg formation (yolk formation) and/or egg-laying in the wild (through eggshell and chorionic membranes) (Bro et al., 2015, 2016). Regardless of the source, early exposure of embryos to pesticides (CBs, OPs, OCs) may favour abnormal development and hatching failure, but studies investigating these potential effects usually involve the injection of pesticide molecules directly into the eggs, which does

not necessarily mimic transgenerational transfer due to the absence of metabolic processes (Dunachie & Fletcher, 1966; Korhonen et al., 1982; Vila & San Martín de Viale, 1982; Deli & Kiss, 1988; Hussein et al., 2014; Seifert, 2014; Gobeli et al., 2017). With respect to DDT (and DDEs), these molecules are highly lipophilic and are stored in the fat tissues of the females for a long period and then transmitted to the eggs (Wiemeyer & Porter, 1970 for example). However, this is not always the case. For example, Gobeli et al., (2017) injected bobwhite quail (*Colinus virginianus*) eggs with imidacloprid and observed several developmental disorders in the embryos. Although this experiment strongly argued in favour of the potential teratogenic effect of neonics, it did not reflect field conditions, since imidacloprid has thus far never been detected in eggs from females subjected to realistic exposure to this molecule (Lopez-Antia et al., 2015a). Overall, teratogenic effects are poorly investigated in birds compared to other vertebrates (see Garcês et al., 2020). Therefore, an assessment of the vertical transfer of the molecule of interest is required before testing its potential effects on embryo development.

Results regarding alterations in male and/or female reproduction, including egg alterations, are numerous and include reductions in clutch size (Bennett et al., 1991; Grue et al., 1997; Hernández et al., 2008; Lopez-Antia et al., 2015a, 2018; McArthur et al., 1983; Weppelman et al., 1980), delayed laying of the first egg or cessation of laying (Bennett et al., 1991; Lopez-Antia et al., 2015a, 2015b), egg infertility (Hernández et al., 2008; Lopez-Antia et al., 2015b, 2018) and, more generally, increases in hatching failure (Fox & Donald, 1980; McArthur et al., 1983; Hernández et al., 2008 but see Batt et al., 1980; Lopez-Antia et al., 2015b). However, the hatching failure rate is typically measured as the percentage of eggs hatched to the total number of eggs laid and thus represents an integrative measure of reproductive failure. Considering the percentage of unhatched fertile eggs provides information specifically on embryo viability, potentially explaining some discrepancies among studies that have used these two variables (Batt et al., 1980 and Lopez-Antia et al., 2015b were both based on fertile egg hatching failure). In any case, the consequences of reproductive failure are a reduced number of fledglings produced (Bennett et al., 1991; Hernández et al.,

2008; Lopez-Antia et al., 2018; Ortiz-Santaliestra et al., 2020), which in turn may affect recruitment within the population and thus population dynamics in a cascading manner.

Consequences for population dynamics and communities

In the previous sections, we showed that pesticides affect bird physiology, behaviour and life-history traits (Fig. 2), resulting in reproduction and survival alterations which are the main components of population dynamics. However, studies linking these effects at the individual level to the consequences at either the population or community levels remain scarce. Indeed, at the population level, studies are usually correlational, linking the intensification of agricultural practices and/or pesticide use to bird population trends or sizes (Chamberlain et al., 2000; Chiron et al., 2014; Donald et al., 2001, 2006; Jerrentrup et al., 2017; Li et al., 2020; Newton, 2004; Robinson & Sutherland, 2002; Stanton et al., 2018; Teillard et al., 2015; Wretenberg et al., 2006). Basically, it requires long-term monitoring census, reproductive outputs and survival rates to be estimated, and to date, only the grey partridge monitoring in the UK provides reliable data on such aspects (see Potts, 1986, 2012; Potts & Aebischer, 1995). Population dynamic modelling has also been used, but these studies usually rely on laboratory individual-based toxicity data (Bennett & Etterson, 2006, 2007; Bennett et al., 2005; Crocker & Lawrence, 2018; Etterson & Bennett, 2013; Etterson et al., 2017; Roelofs et al., 2005). As previously stated, toxicological data are of limited interest in this context because (i) they are usually obtained from a limited number of individuals from a very limited number of model species; (ii) model species do not necessarily reflect the diversity of ecological and life-history traits within a single taxon (e.g. birds); (iii) such studies do not reflect the complexity of biotic and abiotic interactions, including unpredictable cocktail effects; and (iv) they do not consider transgenerational effects (see Mineau, 2005b; Dalkvist et al., 2009; Hilbers et al., 2018). Another method that can be adopted is a probabilistic approach to estimate mortality risk (and thus relevant for explaining population decline) based on toxicity data confronted with the results from necropsy (see Mineau & Whiteside, 2006; Thomas et al., 2011).

At the community level, relevant studies are even scarcer if we exclude those comparing conventional *versus* organic farmlands. Pesticides, particularly herbicides, are negatively correlated with the community specialisation index (Chiron et al., 2014). Indeed, specialist bird species are highly dependent on farmlands for nesting and foraging, and agricultural intensification, including pesticide use, disrupt these behaviours (Devictor et al., 2008; Filippi-Codaccioni et al., 2010; Pocock, 2011). The decline in specialist farmland bird species may result in the replacement of these species by generalist species, leading to biotic homogenisation (Clavel et al., 2011). However, no study has yet formally addressed the impact of pesticide use on the structure of bird communities.

Public policies targeting pesticide reduction and their effects on bird populations

As previously stated in section ‘Pesticide regulation with an emphasis on bird toxicity tests’ regarding the regulation of pesticides worldwide, we mostly based our analysis on European regulatory processes, considered the most stringent worldwide, also perfectible.

Pesticides have primarily been developed to increase crop productivity since the Second World War to feed the rapidly growing human population, which is still a matter of concern. In Europe, the Common Agricultural Policy (CAP, launched in 1962) has stimulated the expansion of intensive agriculture with consequences on biodiversity loss. However, since the 1990s, CAP has included environmental targets to encourage farmers to be more respectful of their environment through agri-environment schemes (AESs) that remunerate farmers who embrace environmentally friendly farming practices. AESs include policies such as input reduction and conversion to organic farming, among others. These incentives seem to have had limited effects in minimising the decline of bird populations at national levels (Princé et al., 2012; Gamero et al., 2017; Pe’er et al., 2014, 2019; but see Santangeli et al., 2019), although at the local level, at least in some targeted bird species, positive effects have been observed (Wrbka et al., 2008; Bretagnolle et al., 2011; Báldi & Batáry, 2011; Batáry et al., 2015; Schlaich et al., 2015;

Colhoun et al., 2017; McHugh et al., 2017; Walker et al., 2018; Bretagnolle et al., 2019). In some of these cases, however, negative trends are still being observed (Colhoun et al., 2017; Bellebaum & Koffijberg, 2018; Calvi et al., 2018; Bretagnolle et al., 2018a; Daskalova et al., 2019). In addition, some AES policies have had positive effects for some species but negative effects for others, depending on their ecology (Baker et al., 2012; Ewald et al., 2010), making compromise difficult. The recent erosion of farmland bird biodiversity in Czechia (previously the Czech Republic), which entered the European Union in 2004 with nine other countries from eastern Europe, led to questions regarding the CAP and, more precisely, the limit of the AESs and their extent in terms of both benefits for the biodiversity and generalisation within territories (Reif & Vermouzek, 2019). In addition, pesticide-based AES policies only concern the use of currently authorised pesticides. Many molecules have been banned over the last several decades following the discovery of their harmful environmental or health effects, but many of these molecules remain as residues in soils and/or water for extended periods. An emblematic example is the case of DDT, which was banned for agricultural purposes in 1972 in the US (1979 in Europe) before being definitively banned worldwide for agricultural use under the Stockholm Convention due to its effects on the environment and human health (see Toft et al., 2004 for a review concerning the impact of DDT on human health). In France, a national health survey performed in 2006–2007 revealed that DDT residues were still detectable in human serum despite being banned in 1971, even in sampled individuals who were born after the complete ban was enacted (see Table 25 in Fréry et al., 2017). This suggests that the effects of DDT might still be present, although largely ignored. Another example is provided by atrazine, a herbicide molecule banned in Europe in 2004, which is still detectable in the soil after 22 years (Jablonowski et al., 2009). The most recent generation of pesticides, such as neonics, were supposed to be less persistent than the first generation, such as OCs. In Europe, despite an EU moratorium in 2014, neonics were still detectable in bee-attractive crop nectar between 2015 and 2018 (Wintermantel et al., 2020). Therefore,

banning harmful molecules does not necessarily eradicate the problem, although it does limit the ubiquity of some molecules. European governments are now under pressure to ban glyphosate, which is currently allowed until 2022, although a few countries, such as Austria, have already banned this molecule. Interestingly, the impact of glyphosate on wildlife has received limited scientific attention, despite it being the most commonly used herbicide (with many commercial formulations), and its use was allowed as early as 1974 (Kissane & Shepard, 2017, reviewed in Gill et al., 2018, Table S1). Glyphosate and its metabolites may be implicated in the decline of bird populations through indirect effects on nesting and foraging sites (modified vegetation structure, Gill et al., 2018) and food resources. Although low doses of glyphosate do not seem to affect the immediate survival of birds, high doses lead to starvation and death (Eason & Scanlon, 2002; Evans & Batty, 1986). Moreover, contaminated food does not seem to be avoided, at least by Japanese quails (Ruuskanen et al., 2020), inducing changes in the avian microbiota (Shehata et al., 2013), endocrine

disruption and alterations in male reproductive organs (Oliveira et al., 2007) as well as haematological, biochemical and genotoxic alterations in cockerels (Hussain et al., 2019). Researchers identified glyphosate in different organs (liver, spleen, intestine, heart and even muscles) in broiler chickens and determined how to neutralise it to ensure the safe consumption of chicken meat for consumers (Shehata et al., 2014). Due to their ubiquity in all environments and the few known studies on glyphosate, birds may represent valuable biosentinels, and researchers should be encouraged to investigate this topic more thoroughly (Kissane & Shepard, 2017). Scientific evidence collected in the field and experiments with captive birds under controlled conditions is required to provide robust arguments for reconsidering the use of such pesticides. However, despite the few existing studies, banning glyphosate is expected to be a long and difficult process since it is the most widely used herbicide worldwide, affecting many economic interests (Kudsk & Mathiassen, 2020). Nonscientific actors (citizens, farmers) and authorities at the local, national and international scales will

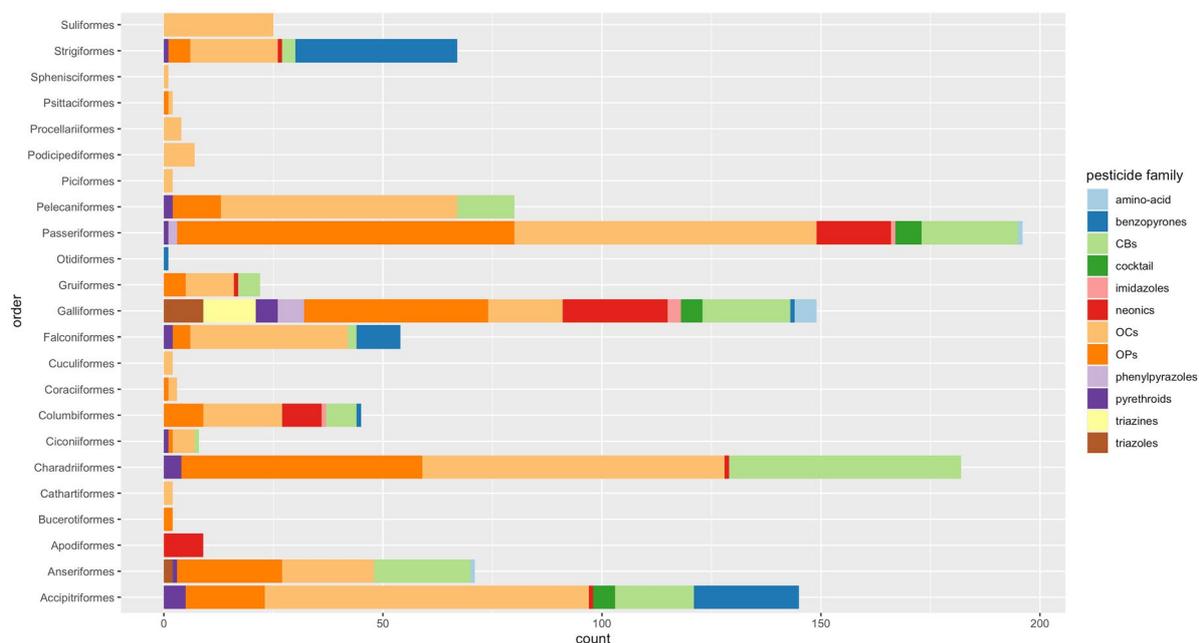


Fig. 3 Distribution of pesticide molecules tested by bird order. For each study listed in Table S1, data were duplicated depending on the number of species, pesticide molecules, modality of the tests (field vs. lab) and location. From the global data-

base given in Table S1, 13 studies on more than 20 species were excluded as well as two studies involving molecules that are rarely investigated (phenylpyrroles and phenylamines, one study in each case) resulting in 1081 occurrences

also play an important role in the future in driving politics to change relevant legislation (see Möhring et al., 2020).

So, what next?

For this review, we screened a large body of peer-reviewed literature using Web of Science, based on keyword searches associating ‘bird’ and ‘pesticide’ (used in agriculture) or the type of molecules (i.e. insecticide, herbicide, fungicide, rodenticide), their chemical family (e.g. carbamate, neonicotinoid) or the name of the molecules from the main chemical families (e.g. for neonics: acetamiprid, clothianidin, etc.) (instead of ‘pesticide’). We voluntarily excluded papers on polar locations to include only species potentially directly exposed to pesticides for agricultural purposes. This resulted in a total of 330 studies, 371 species, 72 families and 23 orders (provided in Table S1). Although we did not perform a meta-analysis of the results obtained in these studies, we tried to provide a synthesis of the studies cited in the text (and more in Table S1). OCs were

overrepresented (ca. 40% of cases, mostly DDT, Table S1, Figs. 3 and 4), likely because they are the oldest and the most persistent pesticides, as well as OPs and CBs. However, this does not explain why other old molecules, such as glyphosate (homologated for ca. 45 years) have been poorly investigated thus far in birds (less than 1% of cases, Table S1). Depending on the country and continent, studies investigating pesticide effects are different and reflect local/national pesticide legislation; OCs are problematic and highly present in Asia, especially in India, which is the major producer/consumer of DDT (Fig. 4). Most cases are represented by raptors (Accipitriformes, Falconiformes, Strigiformes), accounting for ca. 24%, while Passeriformes and Galliformes account for ca. 18% and 14% respectively (Fig. 3). From a wider perspective, ca. 80% of cases involved the field monitoring of birds with the primary aim of quantifying their degree of exposure to one or several molecules (Fig. 5). Field studies were predominant in all orders except Galliformes (Fig. 5). Indeed, most of the model species used for lab experimentation belong to Galliformes (domestic species such as chickens and quails that are

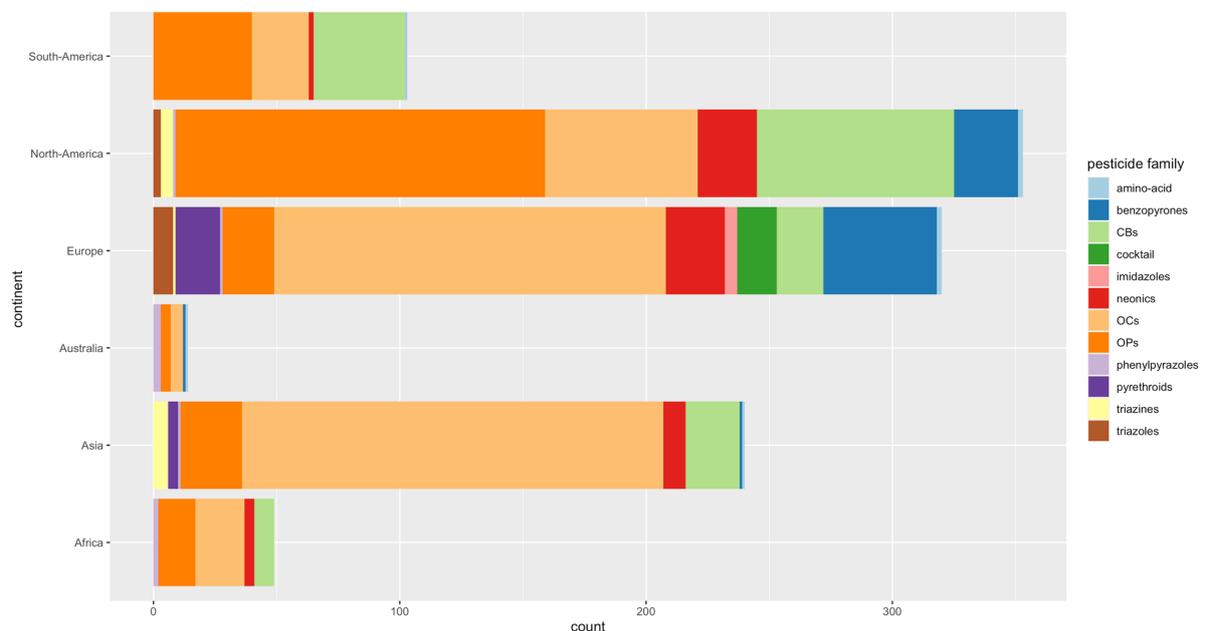


Fig. 4 Distribution of pesticide molecules tested by continent. For each study listed in Table S1, data were duplicated depending on the number of species, pesticide molecules, modality of the tests (field vs. lab) and location. From the global data-

base given in Table S1, 13 studies on more than 20 species were excluded as well as two studies involving molecules that are rarely investigated (phenylpyrroles and phenylamines, one study in each case) resulting in 1081 occurrences

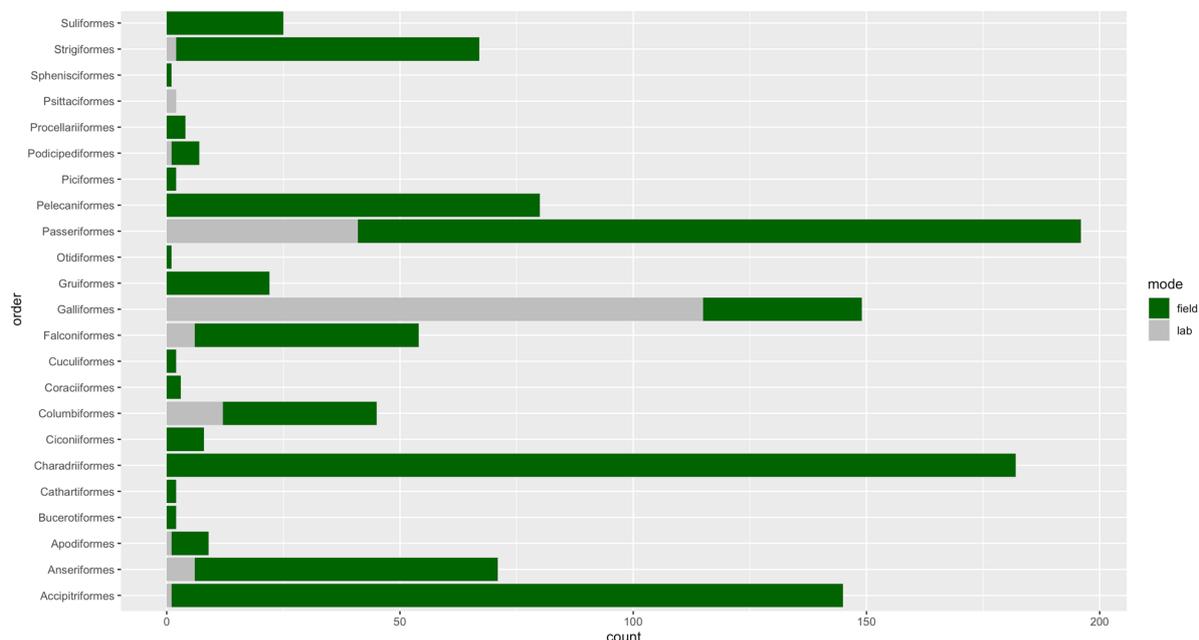


Fig. 5 Distribution of study modalities (field vs. lab) by bird order. For each study listed in Table S1, data were duplicated depending on the number of species, pesticide molecules, modality of the tests (field vs. lab) and location. From the

global database given in Table S1, 13 studies on more than 20 species were excluded as well as two studies involving molecules that are rarely investigated (phenylpyrroles and phenylamines, one study in each case) resulting in 1081 occurrences

available at any time of the year, OECD, 2016). This is also why all pesticide molecules were represented in this group (Fig. 3).

Finally, few studies are available for understanding how pesticides are linked to bird population declines. In this review, we have summarized the evidence published on pesticide effects on birds and their relationships with their declines in farmland landscapes. Most evidence seems to indicate a causal relationship between these two phenomena, but the mechanisms involved are only superficially understood. Pesticides may harm birds through a multitude of non-exclusive pathways making a general trend to determine neither easy nor useful due to the heterogeneity of pesticide use worldwide (Fig. 4) and the heterogeneity of national legislations. As we showed through the text, the pesticide question is complex, at different levels involving local to international legislations, methodological issues, and biological processes. As we initially stated, although the audience of this review is large, it is mostly directed towards ecologists, evolutionary ecologists and conservationists. One challenge for biologists is to provide biological-relevant

facts that will serve decision-makers, rather than proposing revisions to the current system including registration processes (which are out of our own skills). Therefore, the key research areas we identify thereafter focus on ecological and evolutionary processes that should be addressed to provide reliable support to improve and change the way pesticides are regulated, i.e. from the biological processes and up to the limit of our disciplinary fields, i.e. risk assessment (Fig. 6). Priorities are provided below in order of appearance.

Updating experimental designs to document causalities in natura

Published studies investigating the relationships between the decline of farmland birds and their exposure to pesticides rely either on correlational studies in the field or experimental laboratory manipulations using pesticide doses that rarely mimic field conditions. While the latter type of study might provide warnings about the potential deleterious effects of pesticides, they do not provide an efficient

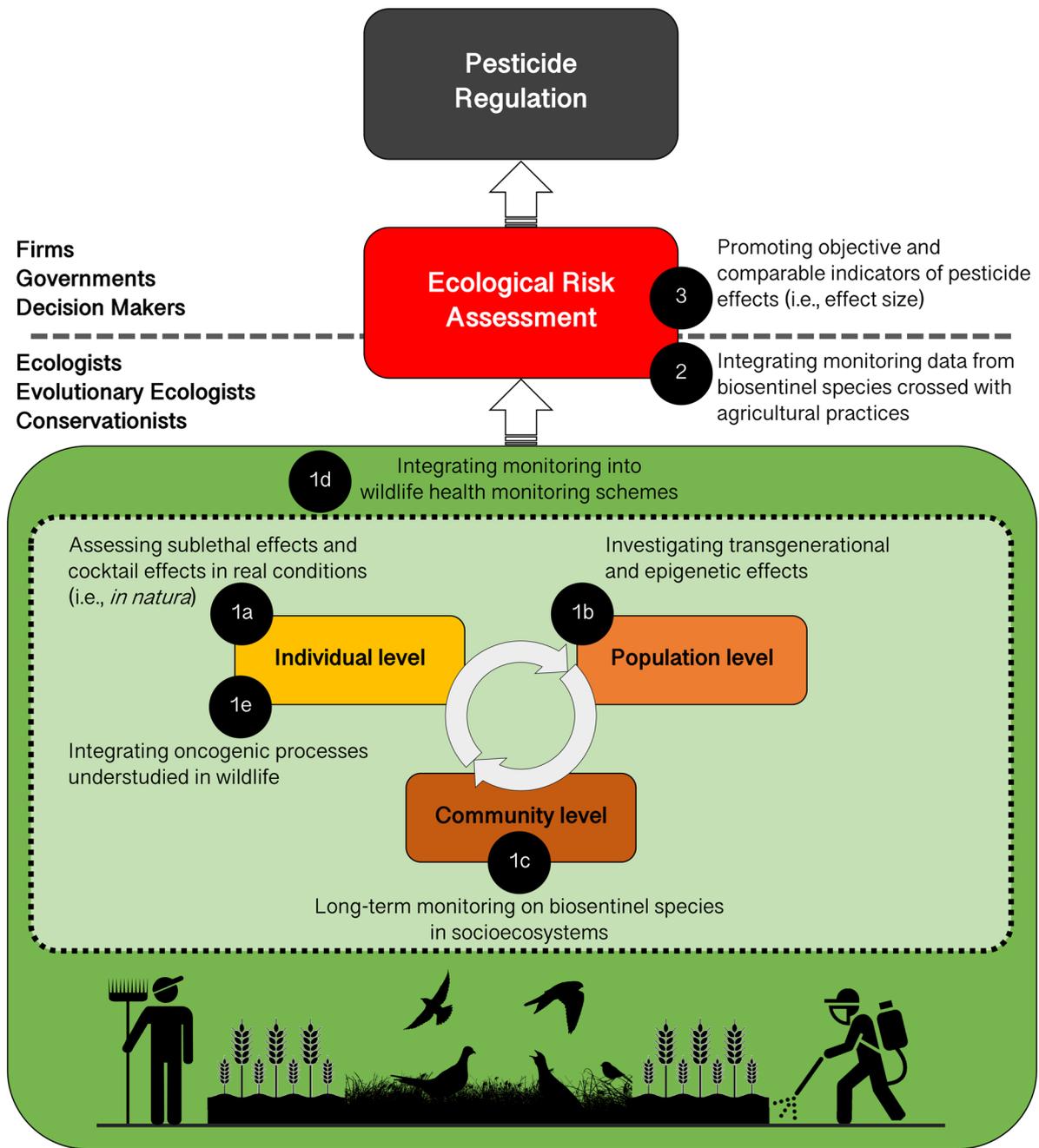


Fig. 6 Schematic view of the key research topics to be developed by ecologists, evolutionary ecologists and conservationists up to the limit of their skills. The numbers in black dots

follow the order in section ‘So, what next?’ and reflect the order of priorities we defined, associated with key points to be developed. See text for details

understanding of the processes leading to population declines. The EFSA’s guidelines as well as the evidence presented above argue in favour of increasing our knowledge regarding the sublethal effects

of pesticides, especially their interconnection with physiological processes and life-history traits that ultimately drive population dynamics (EFSA, 2009). However, the detection of sublethal effects can only

be achieved by matching field conditions for a significant portion of the individual's lifespan and examining these life-history traits at the population level. Therefore, we urge scientists to adapt their experimental procedures to setups and designs that match realistic field conditions to the greatest extent possible. In addition to the many pesticide molecules that are potentially used, our attention should be focused in particular on those that are both the most commonly used and most harmful (Tassin de Montaigu & Goulson, 2020) but without excluding those that are not supposed to be at risk (*sensus* lethal risk). A global approach of the exposure in the field (i.e. considering cocktail effects) should be thus preferred.

Refining experimental protocols to fit natural exposure

Under controlled conditions, we first propose to adapt experimental designs to fit, as closely as possible, natural conditions, e.g. not only limiting the design to the active molecule at the dose used for coating, for instance. Indeed, granivorous birds may feed on seeds from the treated crop that have felt on the ground during harvesting. Contrary to coated seeds, these seeds are not treated themselves but contain residual levels of pesticides from the different treatments on the crop plants (Moreau et al., 2021). Therefore, an interesting experimental design consists of comparing food sources of equivalent nutritional values obtained from conventional *versus* organic agriculture (see Moreau et al., 2021). Such a comparison may thus allow a more reliable estimation of the consequences of natural exposure to understand casualties rather than just testing doses found in coated seeds. Moreover, seeds from the treated plants may store different molecules resulting from different treatments, as several molecules are used either simultaneously or sequentially during the season, and many additional molecules are produced by the degradation of the original molecules. It is therefore important to test for potential synergistic or antagonistic effects (Heys et al., 2016). This example of experimental design is feasible but requires additional analyses, including energetic and pesticide titration for each variety of seeds from each kind of agricultural practice, but may raise important concerns both for wildlife and for humans because the seeds that are

produced are often destined for the human food industry (see Moreau et al., 2021 for an example).

Assessing transgenerational and epigenetic effects

Another important aspect that urgently needs to be clarified includes the transgenerational and/or epigenetic effects of pesticides. While some molecules are known to be transmitted to eggs, the effects of this transfer on chicks (dispersion, survival, etc.) are poorly understood. Endocrine-disrupting chemicals, such as metoxychlor (an OC), may affect parents and their offspring by altering hormone secretion and sexual behaviour, which may be reinforced by continual exposure, exacerbating population declines (Ottinger et al., 2005). Such demonstration of transgenerational and/or epigenetic effects of pesticides does not exist in birds, while these effects have already been demonstrated in other biological models. In invertebrates, transgenerational pesticide exposure may increase the cost of the inducible immune system in offspring, potentially impacting their survival (Heine-Fuster et al., 2017). In zebrafish, the maternal transfer of fipronil results in elevated exposure to its sulfone metabolite, altering thyroid hormone secretions in offspring and inducing malformations (Xu et al., 2019). Epigenetic transgenerational effects (i.e. inherited modifications of gene regulation without DNA changes; for review, see Vandegheuchte & Janssen, 2011) may also contribute to maintaining low fertility in avian populations exposed to endocrine disruptors; however, these effects have mostly been investigated in animal models such as rats (Manikkam et al., 2012, 2014; Song et al., 2014; Ben Maamar et al., 2018; Kubsad et al., 2019 see Warner et al., 2020 for a recent review) but are lacking in birds.

Promoting long-term monitoring of biosentinel species in socioecosystems

Long-term monitoring data on a broad spectrum of biological traits (physiological, behavioural and life-history traits and transgenerational effects) of populations and communities within farmland landscapes should be conducted along different gradients of agricultural practices from full conventional to full organic agriculture. These types of monitoring require close collaboration between scientists

and stakeholders over several years at large landscape scales, such as in long-term socioeconomic research (LTSER) platforms, allowing transdisciplinary approaches (Mirtl et al., 2018; Angelstam et al., 2019; for example, for agricultural landscapes, see Bretagnolle et al., 2018b). Such large monitoring programmes will provide (i) direct quantification *in natura* of the impact of pesticides on bird populations and communities and (ii) more reliable data for estimating parameters to implement population and community dynamic models, which should result in the development of more accurate predictive models. It may allow, for instance, the monitoring of biosentinel species such as the community of passerine birds in different contexts of agricultural practices to provide relevant data to be incorporated into predictive models. It also allows long-term monitoring references to wildlife health monitoring schemes (see below). Detailed knowledge of the landscape, the soil occupancy and the agricultural practices over decades is also an essential asset to perform spatially explicit sampling designs and minimize some bias which is almost impossible in basic field studies (see Bretagnolle et al., 2018c). For example, confounding variables, e.g. hedges and proportion of organic farming surroundings which are often correlated (hedges being usually more preserved in organic farming areas for the ecosystemic services they provide) can be decorrelated with this design and thus considered statistically. This has allowed, for instance, to show differences in vigour behaviour between passerines caught in hedges surrounded by either a large proportion of organic or conventional treated crops (Moreau et al., 2022).

More generally, this type of research infrastructures allows experimentation to be performed with stakeholder engagement and is promising for identifying solutions that consider biodiversity, food production, economics and human health. These observatories must go beyond the simple question of how pesticides impact biodiversity and consider ecosystems under a more unifying concept, such as the *One Health* concept (Ruegg et al., 2019).

Including early warning signals in wildlife health monitoring schemes

To date, wildlife monitoring schemes mostly rely on the necropsies of animals found dead in the field

(see Berny, 2007). The creation of large networks to investigate the sublethal effects of pesticides on wildlife and especially on live animals is challenging because of methodological issues (Stephen et al., 2018; Valverde et al., 2022). One major challenge is to develop early warning monitoring protocols to prevent fatalities. Blood sampling can be valuable to assess the exposure of live birds to different toxics (see Espín et al., 2016). A recent study, for instance, highlighted the prevalence of rodenticide exposure in raptor nestlings in Germany without any visible effects (i.e. direct mortality, Badry et al., 2022). However, despite blood sampling representing the most promising way to reveal potential sub-lethal exposure, they require specific permits (depending on the country legislation), and other biomarkers should thus be developed. For example, integrating standardised behavioural measures into classical long-term ringing and monitoring programmes, which already exist in many countries for many species, may be an efficient way to collect a lot of data. Although selecting relevant biosentinel species is a challenge *per se* (Badry et al., 2020 for example), this could be applied to a large panel of monitored species present at a large continental scale such as the Eurasian black cap (*Sylvia atricapilla*), the common whitethroat (*S. communis*), the great tit (*Parus major*) or the common nightingale (*Luscinia megarhynchos*) for West-Palaearctic examples (see Moreau et al., 2022). The house sparrow (*Passer domesticus*) would be also an interesting alternative because of its worldwide presence. Compared to apex bird predators that are mostly exposed to pesticides through bioaccumulation/biomagnification processes (Badry et al., 2020), passerine birds are potentially more directly exposed to pesticides through their feeding habits (granivorous, insectivorous species). To the potential raptor biosentinels proposed by Badry et al. (2020), other raptors might also be added, as being easily monitored. This is the case of species nesting on the ground such as harrier species *Circus* sp. Among them, *Circus pygargus* or *Circus cyaneus* are widely distributed in the Old World, nest on the ground in cereal crops in Europe for the breeding period and migrate to Africa and central Asia during winter. Their populations are actively protected in Europe and could thus be valuable as biosentinel species for raptors. In addition, the nestlings' behaviour could easily be monitored (see Rabdeau et al., 2019 for an example on *C. pygargus*).

Towards unexplored directions: oncogenic processes

While it is known that pesticides affect the viability of farmland birds at the population level and that pesticides exert negative effects at the cellular and molecular levels (reviewed above), a missing link that remains is the specific pathologies resulting from pesticide exposure in birds. One of the possible explanations for the increased mortality resulting from pesticide exposure might be oncogenic processes. In humans, a growing body of evidence, including cohort studies and meta-analyses, has linked occupational pesticide exposure to different types of cancers (Andreotti et al., 2009; Multigner et al., 2010; van Maele-Fabry et al., 2008). In addition, a reduction in pesticide exposure in the general population through organic food consumption has been recently associated with a marked reduction in cancer prevalence (Baudry et al., 2018). In line with these results, the WHO's International Agency for Research on Cancer (IARC) has classified several molecules, including the herbicide glyphosate and the insecticides malathion and diazinon, as probably or possibly carcinogenic to humans. As recently proposed in several articles (Giraudeau et al., 2018; McAloose & Newton, 2009; Pesavento et al., 2018; Sepp et al., 2019), pollutants known to impact oncogenic processes in humans, pets or laboratory model species might also favour the development of neoplasia in wild organisms. Similar to oncogenic processes resulting from pesticide exposure in humans (Sabarwal et al., 2018) or livestock (Šutiaková et al., 2011) and pets (Hayes et al., 1991), we propose here that wildlife neoplasia occurrence might be affected by pesticides. Poultry studies have shown that diet and inflammatory status affect cancer prevalence in birds (reviewed in Hawkrige, 2014). Studies in poultry are therefore likely a good starting point for predicting the health effects of specific pesticides on farmland birds and for designing studies to investigate these effects. For example, in a study on broilers, chlorpyrifos (an OP), one of the most widely used insecticides in agriculture, was shown to cause lesions and cell proliferation in several organs, including the liver, pancreas and kidneys (Kammon et al., 2011). In addition to the histopathological approach, changes at the molecular level could be targeted, since, at the mechanistic level, genetic and/or epigenetic alterations are proposed to be the primary pathways linking cancer and pesticide exposure (Maqbool

et al., 2016; Mostafalou & Abdollahi, 2012; Shadnia et al., 2005).

Given that this topic has never been studied, we urgently call for new studies designed to investigate whether pesticide exposure may be associated with an increase in the prevalence of oncogenic processes in wild animals inhabiting farmland areas, especially farmland birds. Since farmland birds are likely in close contact with pesticides not only through their diet but also *via* skin contact, egg contact and inhalation, their exposure levels are likely more similar to those of people working with pesticides than people consuming nonorganic food. Thus, we need to develop non-invasive markers of cancers to broadly investigate the prevalence of oncogenic processes in wild populations exposed to different levels of pesticides. Liquid biopsy to quantify circulating tumour cells and measurements of the copper stable isotope ratio $^{65}\text{Cu}/^{63}\text{Cu}$ constitute promising tools for achieving this necessary step (Alix-Panabieres, 2020; Gourlan et al., 2019). Useful information can also be gained through the general wildlife health surveillance programmes that are currently underway in many countries (Pewsner et al., 2017); this may allow the coupling of thousands of necropsies routinely performed every year with pesticide measurements, which are currently lacking. These programmes might also help to estimate whether farmland birds and, more generally, wild vertebrates could be used as sentinels for detecting carcinogenic geographical areas and pesticide molecules that can also impact human cancer prevalence. Then, once robust data on cancer prevalence become accessible for individuals exposed or not to pesticides, comparative studies should be a useful tool for assessing whether certain life-history strategies might make some species more vulnerable to pesticide-associated cancers than others to predict which parts of the ecosystem might be the most vulnerable.

Improving ecological risk assessment

Although the EU has perhaps the most stringent review process worldwide for allowing pesticides into the market (i.e. Regulation 1107/2009, see section '[Pesticide regulation with an emphasis on bird toxicity tests](#)' in this review), there is ample and growing evidence that pesticides, even when authorised, can have deleterious effects on either

humans or the environment, or both (Robinson et al., 2020). The current approach to ecological risk assessment (ERA) is therefore not entirely efficient and is still criticised because it primarily results from laboratory tests in a few model species involving a limited set of toxic agents (Brühl & Zaller, 2019; Schäfer et al., 2019). Scientific misconduct, lack of transparency, conflicts of interest (reviewed in Robinson et al., 2020) and lack of ecological realism (Dalkvist et al., 2009; Forbes & Calow, 2013; Larsen et al., 2020; Schäfer et al., 2019) also raise much concern about the adopted risk assessments. Beyond the issue of scientific integrity, including both ethics and independence, which should be the rule in any discipline, ERAs should incorporate different kinds of predictive models (e.g. energy budget, demographic, individual/agent-based models) based on field data to make them more effective in capturing environmental complexity (Dalkvist et al., 2009; Forbes & Calow, 2013; Forbes et al., 2011; Hilbers et al., 2018). This complexity includes the biotic compartment (i.e. the focal species population, the trophic web), the landscape context and the way it is managed (Etterson et al., 2021; Schäfer et al., 2019), which thus required working not only on birds themselves but in a larger framework, i.e. the socioecosystem (see above). Thus, we need generic models for several species (Forbes et al., 2011) as well as specific models for highly representative species (Andrade et al., 2012) and interspecies correlation models (Raimondo et al., 2007). Despite the global acceptance of the usefulness of such approaches, regulatory agencies are still reluctant to consider them, likely due to their conceptual accessibility and the balance between time and cost of acquiring a large amount of data versus added value (Forbes et al., 2011; Raimondo et al., 2018). An effort should therefore be made to facilitate the insertion of these models into ERAs.

Moving towards the assessment of effect sizes in ecotoxicological studies

Classically, toxicology studies rely on determining different concentrations, levels or doses identified according to different terms: NOEC/NOEL, No Observed Adverse Effect Level (NOAEL),

Lowest Observed Concentration or Level (LOEC/LOEC) and Lowest Observed Adverse Effect Level (LOAEL). As stated in the 'Introduction' section, we chose not to present these estimators, although they are considered meaningful in the field of toxicology. The use of such classical indicators has been widely criticised in the past, mostly because they are directly derived from the experimental design (Laskowski, 1995; Jager, 2012) and based on null hypothesis significance testing (NHST), which is also widely criticised (see Erickson & Rattner, 2020 for a recent review of ecotoxicology). Indeed, these values are misleading in the sense that they are often interpreted as the limit at which an active substance will change from safe to toxic, completely neglecting biological variability (Laskowski, 1995). In practice, these limits are purely subjective since they are highly dependent on the experimental setup based on the a priori concentration or levels, with few replicates (see Table 2). Instead, statisticians have argued in favour of more objective estimations of the effects provided by effect sizes and associated confidence intervals (see the review by Nakagawa & Cuthill, 2007). Several authors from the field of ecotoxicology have already argued in favour of this practice (see, for example, Newman, 2008 or Mair et al., 2020). From a regulatory perspective, it requires the definition of the level of negligible/acceptable effects, but this may be challenging (see Volume 34 of *Environmental Toxicology and Chemistry*, which addresses 'Statistical Challenges in Ecotoxicology', Green, 2015). One non-negligible advantage of the use of effect sizes would be the possibility of direct comparisons among studies, including those from different fields, even if they are not performed under the same conditions (Nakagawa & Cuthill, 2007).

Conclusions

The contribution of pesticides to the decline of farmland bird species currently remains controversial. Most studies examining the effects of agrochemicals are limited to the assessment (not always accurately) of lethal and reproductive effects on a restricted number of model species (mostly Galliformes) with exposure designs that do not reflect field conditions. Field studies are primarily restricted to monitoring programmes that estimate the level of contamination

of the most persistent molecules, such as DDT. Only a few studies truly consider the delayed sublethal effects of pesticides on the physiology, behaviour and life-history traits of individuals and their consequences at the population level. Even fewer studies have been conducted in realistic field conditions. In the present review, we showed that pesticides are diverse in their chemical properties, formulations and modes of action. Adjuvants are usually supposed to be neutral, and only the active molecule is considered for its effects. Trials for formulation approval only integrate additive effects of different molecules, while synergism or antagonism may exist, making cocktail effects unpredictable in these conditions. Regulatory approaches are still heterogeneous worldwide, leaving bird populations and especially migratory species highly exposed to pesticides. Compared to field conditions, cocktail effects, which are the rule (several pesticides being classically used sequentially or simultaneously), are therefore largely neglected. We compiled evidence on the complex effects of pesticides on bird physiology, behaviour and life-history traits, showing that they might be responsible for the decline in avian populations, especially for farmland specialist species. We also highlight the need for innovative experimental designs that integrate cocktail effects and realistic doses for exposure to better capture hidden processes that underlie bird population declines. Additionally, we suggest that transgenerational and oncogenic processes should be considered, as they may represent, similar to mammals, a source of additional sensitivity and mortality currently remain largely ignored thus far in birds. We also argue in favour of improved statistical practices (effect sizes) to increase the accuracy of the reporting of pesticide effects and facilitate comparisons among different experiments from different fields. The current decline in global biodiversity, including that of birds, extends beyond the limits of ecology, as it is also a societal and economic problem that exceeds the limits of disciplinary fields according to the *One-Health* concept. One major societal goal of modern agriculture is to produce enough food to feed the growing human population while being more respectful of the ecosystem by capitalizing on ecosystem services instead of chemicals. Integrated pest management (IPM, not developed here as it is beyond the scope of our review) which does not completely discard the use of chemicals but in a rational way (and

not a prophylactic use) should be at least promoted (see Hillocks, 2020). Biopesticides could also be promoted and associated with IPM to provide more sustainable solutions (Liu et al., 2021; Marrone, 2019). However, similarly to synthetic pesticides, their effects on non-target species must also be correctly assessed (see Cappa et al., 2022). Changing mindsets is probably the most difficult step in this context, and incentives should, therefore, be revised to support farmers in their conversion towards organic or agro-ecological practices (de Snoo et al., 2013). Stakeholders, including farmers as a priority, but also citizens and local authorities, should be involved in such research schemes to encourage transdisciplinary projects that involve the different layers of society (see, for example, Bretagnolle et al., 2018b for an illustration of the LTSER platform that allows this type of research).

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Declarations

Conflict of interest The authors declare no conflict of interest.

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