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A brief review on models for birds exposed to chemicals

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Abstract

"A Who's Who of pesticides is therefore of concern to us all. If we are going to live so intimately with these chemicals eating and drinking them, taking them into the very marrow of our bones - we had better know something about their nature and their power." — Rachel Carson, Silent Spring.

In her day, Rachel Carson was right: plant protection products (PPP) like all the other chemical substances that humans increasingly release into the environment without further precaution, are among our worst enemies today (Bruhl and Zaller, 2019; Naidu et al, 2021; Tang et al, 2021; Topping et al, 2020). All compartments of the biosphere, air, soil and water, are potential reservoirs within which all species that live there are impaired. Birds are particularly concerned: PPP are recognized as a factor in the decline of their abundance and diversity predominantly in agricultural landscapes. Due to the restrictions on vertebrates testing, *in silico* based approaches are an ideal choice alternative given input data are available. This is where the problem lies as we will illustrate in this paper. We performed an extensive literature search covering a long period of time, a wide diversity of bird species, a large range of chemical substances and as many model types as possible to encompass all our future need to improve environmental risk assessment of chemicals for birds. In the end, we show that poultry species exposed to pesticides are the most studied at the individual level with physiologically based toxicokinetic models. To go beyond, with more species, more chemical types, over several levels of biological organization, we show that observed data are crucially missing (Gilbert, 2011). As a consequence, improving existing models or developing new ones could be like climbing Everest if no additional data can be gathered, especially on chemical effects and toxicodynamic aspects.

Keywords: ecotoxicology, avian species, toxicokinetic-toxicodynamic models, drug, diet.

1 Introduction

As early as 1962, Rachel Carson warned about the devastating effects of plant protection products (PPP) on terrestrial vertebrates in her pioneering book *Silent Spring* (Carson, 1962). Later in 1967, Ratcliffe reported that birds ingesting the synthetic pesticide DDT (dichloro-diphenyl-trichloroethane) had a tendency to lay eggs with thin shells that broke prematurely in the nest. This was confirmed by Cade et al (1971) as resulting in marked population

declines, a problem that has driven bald eagles, the national symbol of the United States, along with peregrine falcons and other bird species, to the brink of extinction, with populations collapsing by up to 80%. Since then, all around the world, extensive studies have been carried out to understand the mechanisms underlying this phenomenon. The results of these studies are summarized in a recent collective expertise (ESCO, Pesce et al (2021)), especially chapter 9 (Mamy et al (2022), p623-720) focusing on terrestrial vertebrates to report on the state-of-the-art about: (i) active substances, types or families of PPP for which effects on wildlife are proven, probable, possible or null; (ii) the relationship between the exposure features in different groups of terrestrial vertebrates and the induced effects; (iii) the main mechanisms (in particular direct and indirect ones) inducing the main effects; (iv) the identification of the most influential environmental factors (agronomic, ecological...); (iv) the impact of PPP on functions and ecosystem services provided by terrestrial vertebrates.

Basically, Mamy et al (2022) identified as highly probable the causal link between the use of PPP and the decline in invertebrate and bird populations observed over several decades, particularly in agricultural areas, in interaction with landscape simplification. Depending on the bird species and their diet, PPP impacts are mainly the result of either a direct effect (*e.g.*, ingestion of PPP-treated seeds by granivorous birds) or an indirect effect (*e.g.*, reduction of food resources due to the decline of prey); see Chapter 9 in Mamy

et al (2022) for more details. Environmental monitoring networks in various European countries, including France, have revealed a large number of cases of PPP poisoning of birds in the vicinity of agro-ecosystems. For granivorous birds, the recorded cases since the beginning of the 2000s are mostly caused by the ingestion of seeds treated with neonicotinoids (Bishop et al, 2018), more specifically imidacloprid (Rogers et al, 2019). For insectivorous birds, the impact of PPP is mainly expressed indirectly, through the decline in food resources. Several studies in Europe have demonstrated the existence of significant correlations between the use of PPP and the concomitant decline in insect communities and bird populations (Hallmann et al, 2014; Bowler et al, 2019; Møller, 2019). In addition to these correlations, effects through the consumption of contaminated prey have recently been demonstrated by a multi-residue analysis of the diet of nestlings (Poisson et al, 2021); these effects, which lead to the decline of certain populations, are mainly due to the presence of neonicotinoids in the environment (Humann-Guillemainot et al, 2021). Apart from the lethal effects of PPP, flight efficiency and orientation of birds may also be impaired in response to exposure. Such sublethal effects have been observed, for example, in migratory birds stopping over in agricultural areas, thus compromising the smooth running of the critical migration period (Eng et al, 2017, 2019).

The field of modeling has been particularly prolific in recent years, for example in the prediction of contaminant transfer based on the physico-chemical characteristics of the substances involved, combined with scenarios incorporating different types of crops, climate and soil (Servien et al, 2022). But numerous models have also been developed to better describe how organisms accumulate the chemicals and how the internal damages translate into effects on their life history traits (Larras et al, 2022b). Modeling is also repeatedly mentioned as a potential solution for integrating the processes involved at different spatial and temporal scales. For example, it is not uncommon in the literature to find work that combines ecotoxicological models, to describe the impacts of PPP, with ecological models, which describe the links between organisms and the functions they ensure within ecosystems. In particular, there are spatially explicit models that take into account not only the exposure of organisms, but also the toxic potential of PPP and the adverse effects they have on demography, while taking into account variability in both the landscape and exposure (Topping et al, 2005, 2016; Topping and Weyman, 2018; Topping et al, 2020). Nevertheless, as modeling strongly relies on the collection of experimental data and the metadata to which they are associated, data availability is the major constraint to which model building and the testing of their performances faces, especially at large spatial and temporal scales. All of this finally prevents a wider use of models in environmental risk assessment.

An interesting perspective of the use of population modeling is the possibility
 to extrapolate bio-monitoring data related to PPP bioaccumulation or specific
 effects in terms of population risk of extinction. Based on a matrix population
 model, [Goutte et al \(2018\)](#) provided a nice illustration with the South polar
 skua, a large seabird, for which long term demographic monitoring disclosed
 a possible effect of an organochlorine insecticide on the breeding success, thus
 compromising the population viability. One of the key points of population
 models is their ability to support extrapolation from one species to another,
 as illustrated for birds by [Etterson et al 2017](#). Such a rapid cross-species
 transposition of population models (especially stage-structured ones) benefits
 from the recent construction of large ecological databases gathering together
 demographic traits particularly helpful in conservation science. For instance,
 De Zwaan *et al.* have recently compiled a huge data set of alpine breeding
 records for 1,310 bird species, representing 12.0% of extant species and cover-
 ing all major mountain regions across the five continents, except Antarctica
 ([de Zwaan et al, 2022](#)). **Benefiting of such data collections is the condition to**
support parameter inference for population models, especially when a large
number of species is involved. Such data bases are also particularly helpful
when ranking species vulnerabilities is required in relationship with the dif-
ferent uses of PPP ([Forbes et al, 2015](#); [Etterson et al, 2017](#)).

The EU Regulation 1107/2009 defines all requirements before placing PPP on
 the market, in association with data requirements from regulations 283/2013

and 284/2011. In particular, an assessment is required regarding the risks for bird reproduction when they are exposed to PPP. In this perspective, the OECD guideline 206 provides the way data must be collected through standard toxicity test protocols whereby birds are exposed to the active substance of interest for a period of 20 weeks. However, the expected exposure period of active substances and their numerous degradation products in field (as determined by EFSA guidelines), can be much shorter thus creating disparities between both methodologies. For non-vertebrate species, such an issue can be overcome by additional testing. However, owing to the need to avoid vertebrate testing, this option is not valid for birds. Therefore, the use of *in silico* approaches predicting toxicity endpoints for birds can be helpful (European Food Safety Authority et al, 2023). In particular, toxicokinetic (TK) models, relating the exposure concentration to the fate of chemicals within an organism, coupled with toxicodynamic (TD) models, that make the link between cellular, biochemical and physiological damages and individual effects on life history traits, are potentially useful tools to refine risk assessment of PPP for birds, especially under a regulatory framework where such models remain still underused.

EFSA recently formulated recommendations to develop open source generic physiologically based TK (PBTK) models for a range of relevant species among which birds play an important role (European Food Safety Authority et al, 2023). Larras et al (2022a) also established how huge is the gap between

the set of models used in PPP regulatory reports and those existing in the literature, thus highlighting the need for the implementation of more sophisticated models into PPP regulation. With the idea of describing the whole cascade of impairments, from the exposure conditions to the apical effects, PBTKTD models clearly appear as the most appropriate tool to focus with effects at the individual level in the perspective of moving towards the next generation risk assessment practice. Nevertheless, accounting for molecular initiating events (usually based on omic-type data) and the subsequent series of intermediate steps and key events leading to an adverse outcome is also of great interest to provide a clear-cut mechanistic representation of critical toxicological effects; this is what are allowing Adverse Outcome Pathways (AOP) approaches ([Vinken, 2013](#)). Hence, combining AOP with PBTKTD models could help in finely refining risk assessment. Similarly, linking individual effect models such as PBTKTD models with population and community ones could complement protection schemes including both direct and indirect effects ([Forbes et al, 2017](#)). One inside the other, PBTKTD models are the key pillars of a comprehensive approach along the gradient of effects at all levels of biological organization ([European Food Safety Authority et al, 2023](#)).

However, as already stated above, moving towards more complex models necessarily means benefiting of more data. In particular, no generic PBTKTD models are available for refined environmental risk assessment of birds and mammals, since data requirements are very high ([Astuto et al, 2022](#)). Here

lies the dilemma facing PPP risk assessors for birds, *i.e.* discourage the use of additional vertebrate testing, while acquiring sufficient and appropriate data to improve assessment models. Clearly, the way forward seems to be an intensive search of the literature for information already collected. In this context, this paper presents a state-of-the-art of the different kinds of models that have been developed in the last decades to sustain the deciphering of chemical effects on birds. Notice that we do not detail the different types of model (done by [Larras et al \(2022b\)](#); [Astuto et al \(2022\)](#)) to focus on where reusable data feeding these models can be caught up.

After giving full details on the bibliographical methodology we adopted, we present the general trends that emerge from our corpus of articles. We give a breakdown of models by type (e.g., TD, food web) and by level of organization (e.g., individual, community), before specifically examining bird models crossing model type with their inputs (e.g., exposure routes) and outputs (e.g., measured internal concentration). Then, we conclude in identifying the main gaps, as well as some ideas for overcoming them, and to go beyond.

2 Methods

Scientific articles were screened within several bibliographic databases including Clarivate Web of Science ©, PubMed ([McEntyre and Ostell, 2002](#)), Google Scholar ([López-Cózar et al, 2019](#)), Scopus ([Baas et al, 2020](#)), and the co-authors' personal databases (those provided by [Kuo et al \(2022\)](#), > 500

entries, and [Mamy et al \(2022\)](#), > 2500 entries). The final paper collection was achieved in February 2023, covering a period from the end of the seventies until today.

The bibliographic queries were performed following several steps summarized in Figure 1. Google Scholar was first requested with an initial Scopus keyword equation (data not shown) providing a preliminary collection of few papers that were scrutinized through titles and abstracts to refine the final query equation. Then, the above-mentioned bibliographic databases were all required with the final Scopus keyword equation (Figure 1). From there, we excluded references of books, book chapters, editorials and notes, to only keep peer-reviewed journal articles. Finally, we excluded all papers not referring to modeling issues. In particular, we excluded papers without any model, or containing pure descriptive models, such as those with only basic hypothesis testing methods. Purely general papers without case studies were also removed from our collection.

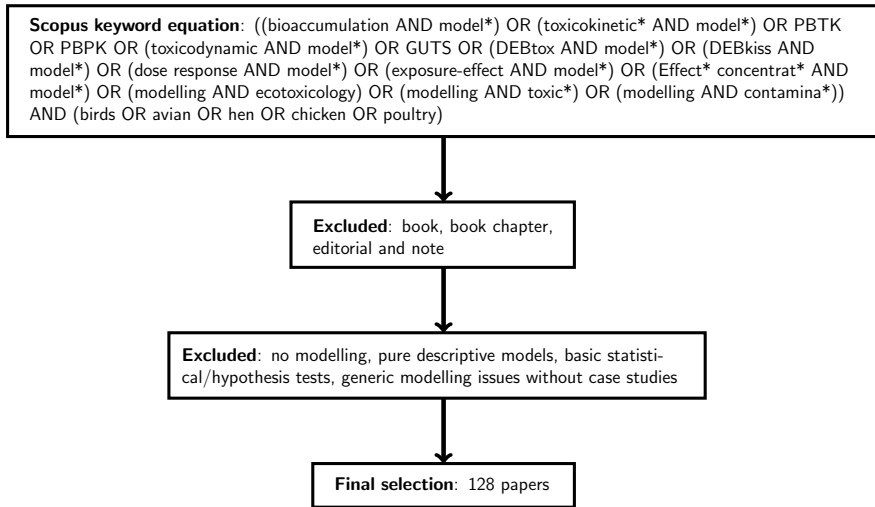


Fig. 1 Diagram of the bibliographic method we used to build the final corpus of scientific papers analyzed in this review.

Additionally to the terms we used in our query, our paper collection was only limited to research and review papers published in peer-reviewed journals and written in English. At the end of the process, we had a total of 130 papers (97 from the bibliographic databases and 33 from the co-authors' personal databases). All these papers have been gathered together within a metadata file (in comma separator value format) available at <https://doi.org/10.5281/zenodo.7685817>. In addition to the classical fields defining a bibliographic reference, this metadata file records information about the biological species (wild/domestic, feeding regime, common and Latin names), the chemical substances (group, name, CAS number) and/or the models (model type, level of biological organization that is concerned) that have been used by the authors. The metadata file also inventories the

exposure routes and the measured endpoints provided in the papers. In the end, the metadata file has 130 rows and 59 columns. A critical step in the assembly of this metadata was the identification of the model type used by the authors. To proceed, we first separated models processing at the individual level, that is the most employed. Among them, dose-response models were easy to classify. For the rest of the papers, a careful check within the different sections of the papers finally allowed us to clearly identified the type of model.

The paper collection, no reference being duplicated, was imported into the R software (R Core Team, 2022) and analyzed to quantify the scientific production per year, feeding groups (distinguishing between carnivores, frugivores, granivores, herbivores, insectivores, omnivores, and piscivores), chemical groups (according to their usage), level of biological organization (individual, population community)) and model types (see Table 1 hereafter). In the end, our paper collection led us to identify the main research tendencies related to the employment of models in support of a better deciphering of the impacts of chemical substances on birds. This also allowed us to highlight advantages and drawbacks of these models.

Additionally to the metadata file, the supplementary material provided at <https://doi.org/10.5281/zenodo.7685817> contains all resources to identically reproduce the figures we are presenting below.

3 Results

Without claiming exhaustivity, our collection of papers (fully listed at the end of the manuscript) shows that studies involving models in bird ecotoxicology started to be published during the late seventies, with a slight increase from 2000, then only few papers each year (Figure 2). Half of the 130 papers focused on granivores (namely, seed-eating birds (Anadón et al, 2011; Fournier et al, 2015; Pollet et al, 1985)). Among wild species, groups of carnivores (*i.e.*, predatory birds, such as raptors (Azmanis et al, 2021; Engelman et al, 2012; Rattner et al, 2020)) and piscivores (*i.e.*, birds foraging for and eating fish or other sea life (An et al, 2006; Goutte et al, 2018; Sánchez et al, 2019)) are similarly represented (between 9 and 14 %) (Figure 3, upper panel). A bit less than one third of the papers investigated drugs, while around 20% of them focused on PPP (Figure 3, lower panel). Regarding trace metallic elements, mercury and derivatives have been the most studied (Smith et al, 2009; Nichols et al, 2010; Jackson et al, 2011). Exposure routes, all chemical substances combined, covered the full range of bird feeding regimes via their food sources. Exposure via injection or oral administration were the most widely studied regarding toxicokinetic-toxicodynamic aspects. Last but not least, exposure models describing the contamination routes, dealt with environment (*i.e.*, exposure via air, or not specified), food, or more rarely water *via* drinking (Nelson et al, 1998; Conder et al, 2009; Moore et al, 2018).

The salient point, which is not directly visible from Figure 3 but which follows directly from it, is the total absence of studies that address the effects of PPP on bird species of interest for the regulatory environmental risk assessment. For example, European regulations 283/20134 and 284/20135 recommend determining the acute oral toxicity of an active substance to a quail species (Japanese quail, *Coturnix coturnix japonica* or bobwhite quail, *Colinus virginianus*), while data on additional species, such as *Serinus canaria*, may be requested by other legislative frameworks (European Food Safety Authority et al, 2023). These quail and canary species were totally absent from our set of studies. On the contrary, poultry species are studied a lot, and the most, with a majority of the related papers employing toxico-/phamarco-kinetic (TPK) models. Laying hens and broiler chicken species were both studied, the latter being much more used (47 out of 130 papers). Regarding chicken, exposures to drugs and PPP were the most investigated contaminants, while modeling speaking, TPK models are almost exclusively used among the 47 papers.

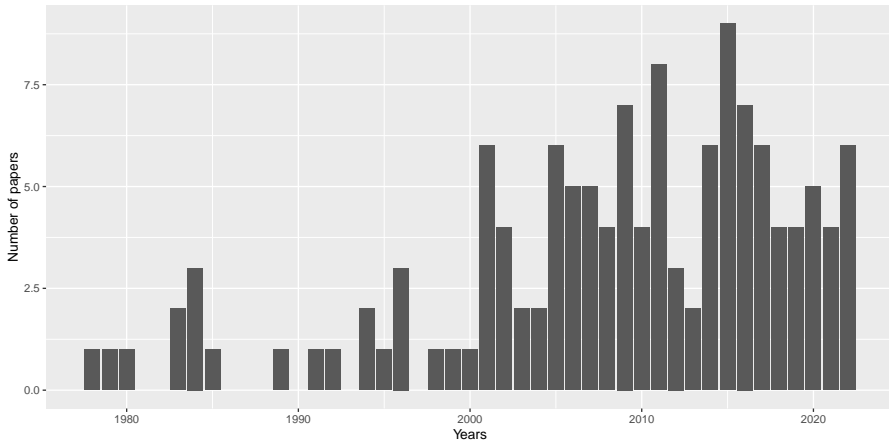


Fig. 2 Number of papers published per year among our collection of 130 scientific articles.

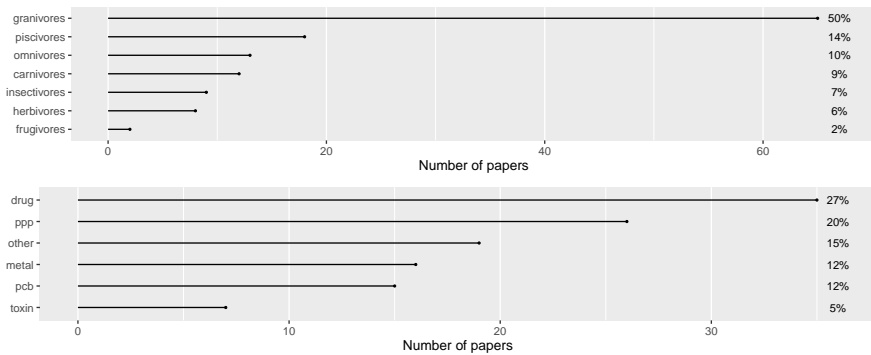


Fig. 3 Number of papers per feeding groups (upper panel) and chemical groups (lower panel) among our collection of 130 scientific articles.

306 About 80% of the studies were conducted at the individual level (Table 1, left
 307 panel). Those papers mainly addressed toxicokinetics or bioaccumulation of
 308 one or several substances in the organisms, leading to model concentration
 309 changes over time either in the whole body ([Abou-Donia, 1979](#); [Tarazona et al,](#)

2015), or in different organs (Bean et al, 2019; Suknikom et al, 2016), including eggs (MacLachlan, 2010; Hekman and Schefferlie, 2011). Toxicokinetic aspects of drugs in chicken or laying hens were the most frequent combination (Furusawa et al, 1996; Henri et al, 2017), investigating residues of chemical in muscles or eggs, which suggested food consumption purpose. Toxicodynamic and dose-response studies have also been conducted, describing the effect of a chemical at the individual level, over time or not (Eagles-Smith et al, 2009; Zhao et al, 2014). However, Toxicodynamic and dose-response studies were rarer, probably because they would imply experiments with vertebrates that are subject to restrictions. Another plausible explanation could be a lack of interest in toxic effects on laboratory species themselves, contrary to the indirect effects that its diet may have on human health (Rani et al, 2021). In this perspective, TPK models are the appropriate tools.

At the population level, several model frameworks have been employed such as individual-based models (Hallam et al, 1996), matrix demographic models (Goutte et al, 2018), or Monte Carlo Markov Chain models (Bennett and Etterson, 2007). Such models describe the effect of a chemical at the population level, either by incorporating critical effect concentrations on the chosen endpoints (*e.g.*, survival, reproduction, behavior) together with an exposure scenario (Etterson and Bennett, 2013), or by directly negatively impacting

one or several vital rates, such as survival rate or reproductive success, compared to a scenario without contamination ([An et al, 2006](#)).

At higher levels of biological organization and/or with spatially explicit models, studies are much rarer (less than 5%) (Table 1, right panel). Community level papers from our collection used food chain models to investigate bioaccumulation via two case studies (organochlorine accumulated in Arctic birds ([Borgå et al, 2004](#)) and polychlorinated biphenyls accumulated in eggs of San Francisco bay birds ([Gobas and Arnot, 2010](#))). In our database spatially explicit models were population models including a compartment describing environmental changes and/or where birds were located in space, allowing to investigate for example habitat modification impact ([Nacci et al, 2005](#)), feeding habits ([Matsinos and Wolff, 2003](#)), or crop rotation ([Topping et al, 2005](#)).

Table 1 Number (#) of papers per model type (left) and per level of organization (right), among our collection of 130 scientific articles.

Model type	Meaning or Based on	#	Biological level	#
TPK	Toxico-/Pharmaco-Kinetic	89	Individual	104
TD	Toxico-Dynamic	12	Population	22
DR	Dose response	4	Community	2
Energy-based	Dynamic Energy Budget theory	5	Landscape	3
ODE based	Ordinary Differential Equations	11		
IBM	Individuals or Agents	3		
Food web	Multiple trophic interactions	2		
Spatial	Spatially explicit	3		
Exposure	Exposure profile feature	13		
Other	Any other type	6		

By crossing views on our paper collection, classified by both model types (columns) and either model outputs (measured internal concentration, pink lines / measured endpoints, blue lines) or model inputs (exposure routes, orange lines), we finely deciphered what were the main objectives of most of the studies on birds exposed to chemicals. As shown in Figure 4, most of the studies employed TPK models to investigate drug effects on birds after injection or oral administration (Kuo et al, 2022), by measuring the time course of internal concentrations at the whole organism level (Gögebakan and Eraslan, 2015), or distinguishing target organs (Yang et al, 2014).

Figure 4 (second column and blue lines) also clearly demonstrates that toxico/pharmaco-dynamics and dose-response analyses are under-represented (see also Table 1, left panel), which points to a crucial gap in observed data of chemical effects on bird life history traits. While the lack of toxico/pharmaco-dynamic models can be understood easily enough (due to their difficult handling and implementation), it is much more surprising to find so few studies involving dose-response models, while they are today the basis of the regulatory environmental risk assessment. Moreover, there are today no general accepted methods that are currently available for how to calibrate and validate toxicokinetic-toxicodynamics (TKTD) models without animal testing (European Food Safety Authority et al, 2023). As a consequence, due to the 3R requirements (European Parliament and European Council, 2010), such a lack in effect quantifier models prevents to attempt interconnecting individual and population levels in the perspective of gaining in ecological relevance, while still including information for which it is easier to obtain experimental observations. Contamination via food represented the main exposure route ($\sim 45\%$) within studies covered by our 130 papers (Figure 4, fourth orange line). For example, Meda *et al.* developed a physiologically based pharmacokinetic model to investigate the main factors involved in the transfer of α -hexabromocyclododecane to broiler meat (Méda et al, 2020); Fournier et al (2015) assessed the impact of physiological characteristics of laying hen on the transfer of ingested PCBs to their eggs. Regarding exposure models, they have been developed to address levels of chemical contamination in the field,

mainly for PPP. For example, Moore *et al.* developed probabilistic models to estimate, during the breeding season and the spring and fall migrations, how many chlorpyrifos and malathion granules Kirtland's warblers ingest and, from that, the quantity of pesticide ingested (Moore et al, 2018).

Among the 130 papers, some studies were generic in scope, but for different reasons. A total of 41 papers (31.5%) concerned several biological species that were simultaneously studied as exposed to a same chemical (Newsted et al, 2006; Samuels and Ladino, 1984). A total of 45 papers (34.6%) reported effects of several chemicals on one bird species (Topping et al, 2005; Wayland et al, 2008). And only 8 papers out the 130 were general reviews covering a wide spectrum of species-compound combinations (see for example Kuo et al (2022)). It is worth to note that only two papers dealt with the impacts of multiple stressors: the first on white-tailed eagle populations (Korsman et al, 2012); the second on the common loon (Nacci et al, 2005). One of the most striking points of our review is that only 9 papers (~7%) gave access to raw data, potentially reusable for further studies.

emphasizes how frequent TPK studies applied to chickens were, as well as that toxico/pharmaco-kinetic models were equally frequently employed, while no chemical substances appeared more studied than another one.

4 Conclusion

Our bibliographic corpus showed a certain diversity in model types, chemicals, exposure routes and feeding groups. Nevertheless, we identified a huge gap in models dealing with chemical effects on birds at the individual level, even if we found a large collection of papers on toxico/pharmaco-kinetic aspects. This is far from being a negligible source of information. However, originally interested in toxicokinetic-toxicodynamic models on birds exposed to PPP, it was clear that we would have very few previous studies at our disposal on which to capitalize. Focusing on bird species targeted by the regulatory environmental risk assessment and their exposure to PPP in addition, we ended up with no dedicated resources to draw on. Both bad and good news in the end. Indeed, we had found a new niche in which to innovate and develop new modeling tools to support next generation risk assessment for birds. In such a perspective, the key point will undoubtedly be the availability of raw data to build clever and comprehensible mechanistic effects models, generic enough to be employed for a wide battery of bird species and chemical compound combinations. Under the umbrella of Open Science, achieving such dreamed tools, should mandatorily imply full compliance to the FAIR data principles. To do so, we could recommend adding non invasive endpoint measurements on birds together with

the current practice of TPK studies, or *in vitro* studies that are considered as a good alternative to *in vivo* testing to better decipher TPK properties. Such data could advantageously support further development of the TPK part of TPK-TPD models, tools that now make sense to our community, which more broadly advocates the need to modernize wildlife risk assessment through improved collaboration, data sharing, application of standardized exposure scenarios, better communication of assumptions and uncertainties of models, and post-regulatory monitoring (Morrissey et al, 2023).

5 Supplementary Information

All supplementary information mentioned in this manuscript is available at <https://doi.org/10.5281/zenodo.7685817>.

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Authors contributions Dominique Lamonica and Lison Charvy: Paper collection, Metadata collection and curation. Dominique Lamonica: Metadata investigation, Methodology, Visualization, Analysis. Dominique Lamonica and Sandrine Charles: Writing - Original draft preparation. Sandrine Charles: Investigation, Supervision, Validation, Writing - Reviewing and Editing. Dave Kuo, Clementine Fritsch, Michaël Coeurdassier and Philippe Berny: Investigation, Reviewing and Editing.

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Competing interests The authors declare no competing interests.

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