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1 A brief review on models for birds exposed to  
2 chemicals

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22 **Abstract**

23 *“A Who’s Who of pesticides is therefore of concern to us all. If we are going to*  
24 *live so intimately with these chemicals eating and drinking them, taking them*  
25 *into the very marrow of our bones - we had better know something about their*  
26 *nature and their power.”* — Rachel Carson, Silent Spring.  
27

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

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

## 55 1 Introduction

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

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

77

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

85 [et al \(2022\)](#) for more details. Environmental monitoring networks in various  
86 European countries, including France, have revealed a large number of cases  
87 of PPP poisoning of birds in the vicinity of agro-ecosystems. For granivorous  
88 birds, the recorded cases since the beginning of the 2000s are mostly caused  
89 by the ingestion of seeds treated with neonicotinoids ([Bishop et al, 2018](#)),  
90 more specifically imidacloprid ([Rogers et al, 2019](#)). For insectivorous birds,  
91 the impact of PPP is mainly expressed indirectly, through the decline in  
92 food resources. Several studies in Europe have **demonstrated the existence of**  
93 **significant correlations** between the use of PPP and the concomitant decline  
94 in insect communities and bird populations ([Hallmann et al, 2014](#); [Bowler](#)  
95 [et al, 2019](#); [Møller, 2019](#)). **In addition to these correlations, effects through**  
96 **the consumption of contaminated prey have recently been demonstrated by**  
97 **a multi-residue analysis of the diet of nestlings** ([Poisson et al, 2021](#)); these  
98 **effects, which lead to the decline of certain populations, are mainly due to the**  
99 **presence of neonicotinoids in the environment** ([Humann-Guilleminot et al,](#)  
100 [2021](#)). Apart from the lethal effects of PPP, flight efficiency and orientation  
101 of birds may also be impaired in response to exposure. Such sublethal effects  
102 have been observed, for example, in migratory birds stopping over in agricul-  
103 tural areas, thus compromising the smooth running of the critical migration  
104 period ([Eng et al, 2017, 2019](#)).

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

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

148

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

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

169

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



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

192

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

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

206

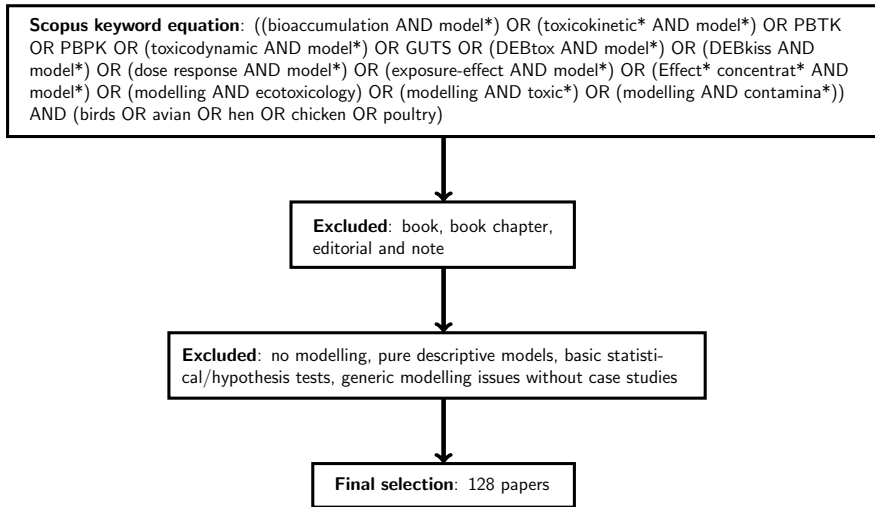
207 After giving full details on the bibliographical methodology we adopted, we  
208 present the general trends that emerge from our corpus of articles. We give a  
209 breakdown of models by type (e.g., TD, food web) and by level of organiza-  
210 tion (e.g., individual, community), before specifically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

## 214 2 Methods

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

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

222  
223 The bibliographic queries were performed following several steps summarized  
224 in [Figure 1](#). Google Scholar was first requested with an initial Scopus keyword  
225 equation (data not shown) providing a preliminary collection of few papers that  
226 were scrutinized through titles and abstracts to refine the final query equation.  
227 Then, the above-mentioned bibliographic databases were all required with the  
228 final Scopus keyword equation ([Figure 1](#)). From there, we excluded references  
229 of books, book chapters, editorials and notes, to only keep peer-reviewed jour-  
230 nal articles. Finally, we excluded all papers not referring to modeling issues. In  
231 particular, we excluded papers without any model, or containing pure descrip-  
232 tive models, such as those with only basic hypothesis testing methods. Purely  
233 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.

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

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

253

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

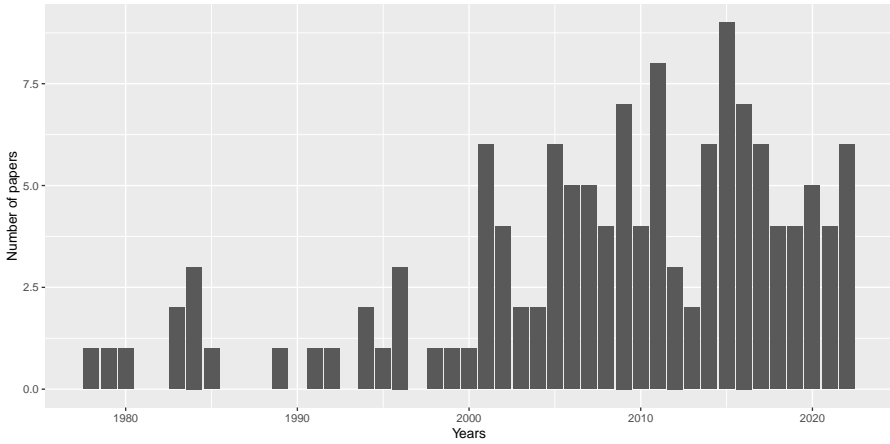
264

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

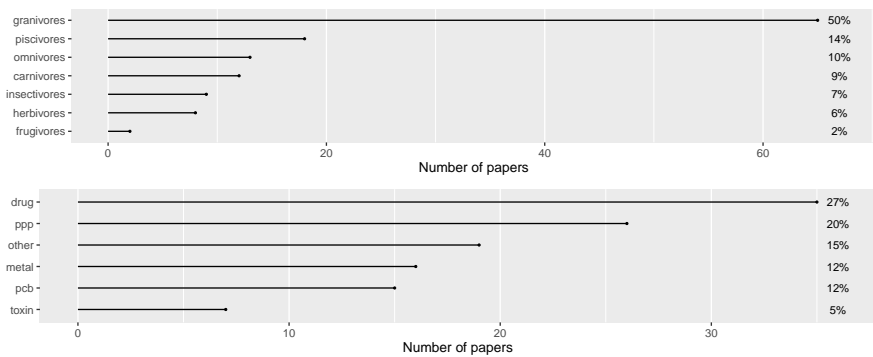
### 3 Results

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).

290 The salient point, which is not directly visible from Figure 3 but which follows  
291 directly from it, is the total absence of studies that address the effects of PPP  
292 on bird species of interest for the regulatory environmental risk assessment.  
293 For example, European regulations 283/20134 and 284/20135 recommend  
294 determining the acute oral toxicity of an active substance to a quail species  
295 (Japanese quail, *Coturnix coturnix japonica* or bobwhite quail, *Colinus vir-*  
296 *ginianus*), while data on additional species, such as *Serinus canaria*, may be  
297 requested by other legislative frameworks ([European Food Safety Authority](#)  
298 [et al, 2023](#)). These quail and canary species were totally absent from our set of  
299 studies. On the contrary, poultry species are studied a lot, and the most, with  
300 a majority of the related papers employing toxico-/pharmacokinetic (TPK)  
301 models. Laying hens and broiler chicken species were both studied, the latter  
302 being much more used (47 out of 130 papers). Regarding chicken, exposures  
303 to drugs and PPP were the most investigated contaminants, while modeling  
304 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.

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



309 2015), or in different organs (Bean et al, 2019; Suknikom et al, 2016), includ-  
310 ing eggs (MacLachlan, 2010; Hekman and Schefferlie, 2011). Toxicokinetic  
311 aspects of drugs in chicken or laying hens were the most frequent combination  
312 (Furusawa et al, 1996; Henri et al, 2017), investigating residues of chemical in  
313 muscles or eggs, which suggested food consumption purpose. Toxicodynamic  
314 and dose-response studies have also been conducted, describing the effect of  
315 a chemical at the individual level, over time or not (Eagles-Smith et al, 2009;  
316 Zhao et al, 2014). However, Toxicodynamic and dose-response studies were  
317 rarer, probably because they would imply experiments with vertebrates that  
318 are subject to restrictions. Another plausible explanation could be a lack  
319 of interest in toxic effects on laboratory species themselves, contrary to the  
320 indirect effects that its diet may have on human health (Rani et al, 2021). In  
321 this perspective, TPK models are the appropriate tools.

322

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

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

332

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

343

**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		

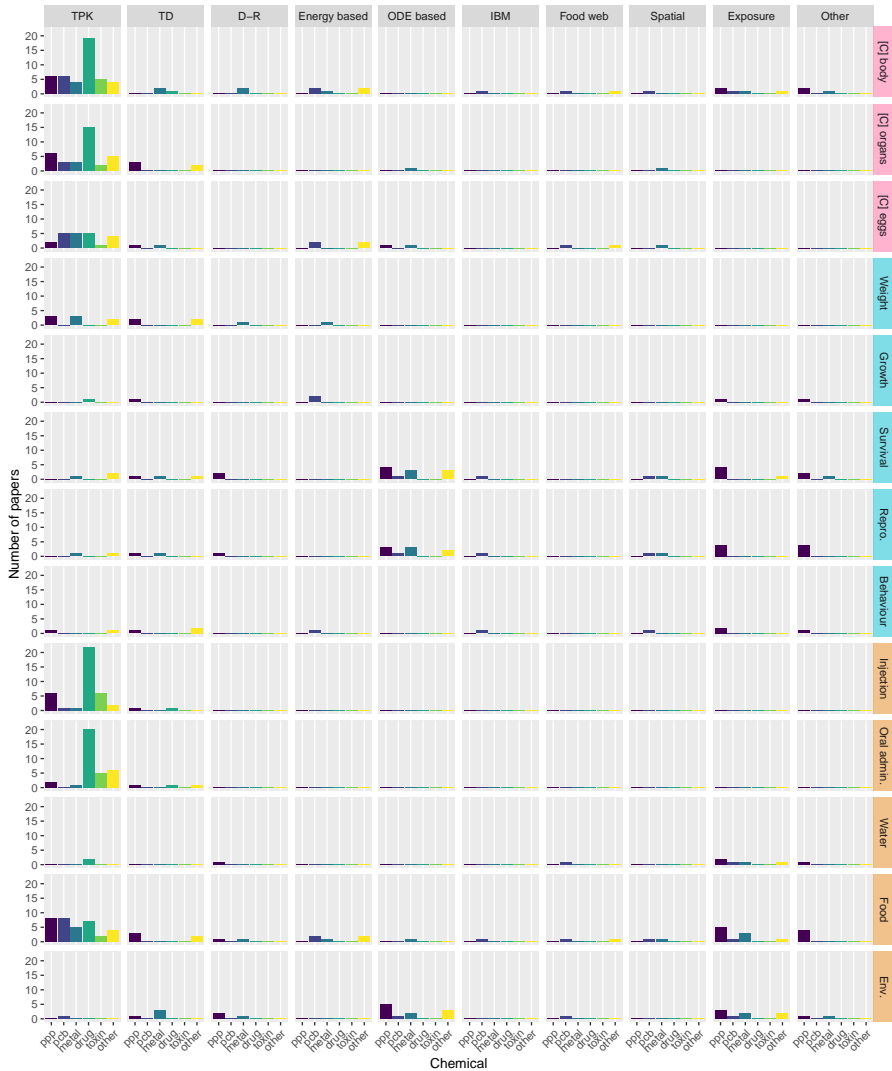
344 By crossing views on our paper collection, classified by both model types  
345 (columns) and either model outputs (measured internal concentration, pink  
346 lines / measured endpoints, blue lines) or model inputs (exposure routes,  
347 orange lines), we finely deciphered what were the main objectives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

354 Figure 4 (second column and blue lines) also clearly demonstrates that  
355 toxico/pharmaco-dynamics and dose-response analyses are under-represented  
356 (see also Table 1, left panel), which points to a crucial gap in observed data of  
357 chemical effects on bird life history traits. While the lack of toxico/pharmaco-  
358 dynamic models can be understood easily enough (due to their difficult  
359 handling and implementation), it is much more surprising to find so few  
360 studies involving dose-response models, while they are today the basis of the  
361 regulatory environmental risk assessment. Moreover, there are today no gen-  
362 eral accepted methods that are currently available for how to calibrate and  
363 validate toxicokinetic-toxicodynamics (TKTD) models without animal testing  
364 ([European Food Safety Authority et al, 2023](#)). As a consequence, due to the  
365 3R requirements ([European Parliament and European Council, 2010](#)), such a  
366 lack in effect quantifier models prevents to attempt interconnecting individual  
367 and population levels in the perspective of gaining in ecological relevance,  
368 while still including information for which it is easier to obtain experimental  
369 observations. Contamination via food represented the main exposure route  
370 ( $\sim 45\%$ ) within studies covered by our 130 papers (Figure 4, fourth orange  
371 line). For example, Meda *et al.* developed a physiologically based pharma-  
372 cokinetic model to investigate the main factors involved in the transfer of  
373  $\alpha$ -hexabromocyclododecane to broiler meat ([Méda et al, 2020](#)); [Fournier et al](#)  
374 ([2015](#)) assessed the impact of physiological characteristics of laying hen on  
375 the transfer of ingested PCBs to their eggs. Regarding exposure models, they  
376 have been developed to address levels of chemical contamination in the field,

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

381

382 Among the 130 papers, some studies were generic in scope, but for differ-  
383 ent reasons. A total of 41 papers (31.5%) concerned several biological species  
384 that were simultaneously studied as exposed to a same chemical (Newsted  
385 *et al.*, 2006; Samuels and Ladino, 1984). A total of 45 papers (34.6%) reported  
386 effects of several chemicals on one bird species (Topping *et al.*, 2005; Wayland  
387 *et al.*, 2008). And only 8 papers out the 130 were general reviews covering a  
388 wide spectrum of species-compound combinations (see for example Kuo *et al.*  
389 (2022)). It is worth to note that only two papers dealt with the impacts of  
390 multiple stressors: the first on white-tailed eagle populations (Korsman *et al.*,  
391 2012); the second on the common loon (Nacci *et al.*, 2005). One of the most  
392 striking points of our review is that only 9 papers (~7%) gave access to raw  
393 data, potentially reusable for further studies.



**Fig. 4** Cross-view of the 130 papers analyzed in this review, categorized by model type (columns) and model outputs (measured internal concentration, pink lines, measured endpoints, blue lines) or model inputs (exposure routes, orange lines). At column-line intercepts, histograms show the number of papers as a function of the studied chemical(s).

394 Results displayed in Figure 4 also appeared in a limpud manner within the title-  
 395 based word cloud provided as graphical abstract. This word cloud specifically

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

## 399 4 Conclusion

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

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

## 426 5 Supplementary Information

427 All supplementary information mentioned in this manuscript is available at  
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