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

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23 **Abstract**

24 *“A Who’s Who of pesticides is therefore of concern to us all. If we are going to*  
25 *live so intimately with these chemicals eating and drinking them, taking them*  
26 *into the very marrow of our bones - we had better know something about their*  
27 *nature and their power.” — Rachel Carson, Silent Spring.*  
28

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

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

## 56 1 Introduction

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

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

78

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

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

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

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

149

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

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

170

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



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

193

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

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

207

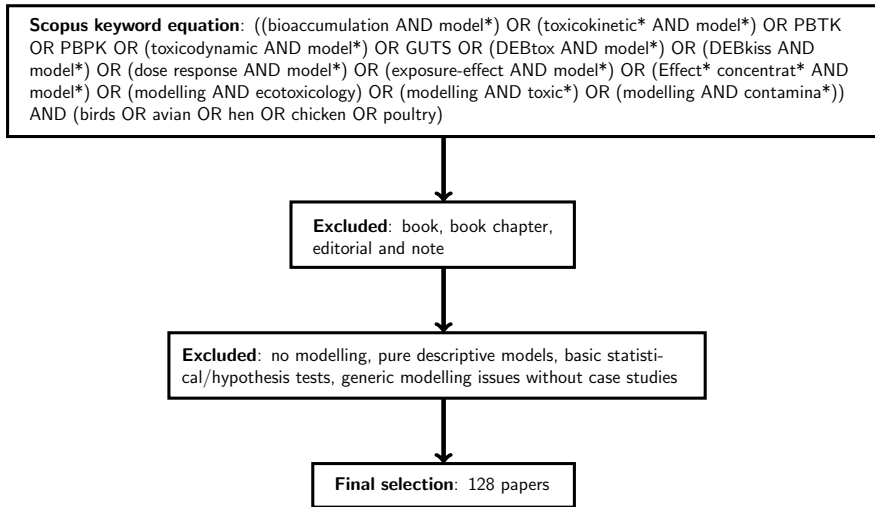
208 After giving full details on the bibliographical methodology we adopted, we  
209 present the general trends that emerge from our corpus of articles. We give a  
210 breakdown of models by type (e.g., TD, food web) and by level of organiza-  
211 tion (e.g., individual, community), before specifically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

## 215 2 Methods

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

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

223  
224 The bibliographic queries were performed following several steps summarized  
225 in [Figure 1](#). Google Scholar was first requested with an initial Scopus keyword  
226 equation (data not shown) providing a preliminary collection of few papers that  
227 were scrutinized through titles and abstracts to refine the final query equation.  
228 Then, the above-mentioned bibliographic databases were all required with the  
229 final Scopus keyword equation ([Figure 1](#)). From there, we excluded references  
230 of books, book chapters, editorials and notes, to only keep peer-reviewed jour-  
231 nal articles. Finally, we excluded all papers not referring to modeling issues. In  
232 particular, we excluded papers without any model, or containing pure descrip-  
233 tive models, such as those with only basic hypothesis testing methods. Purely  
234 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.

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

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

254

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

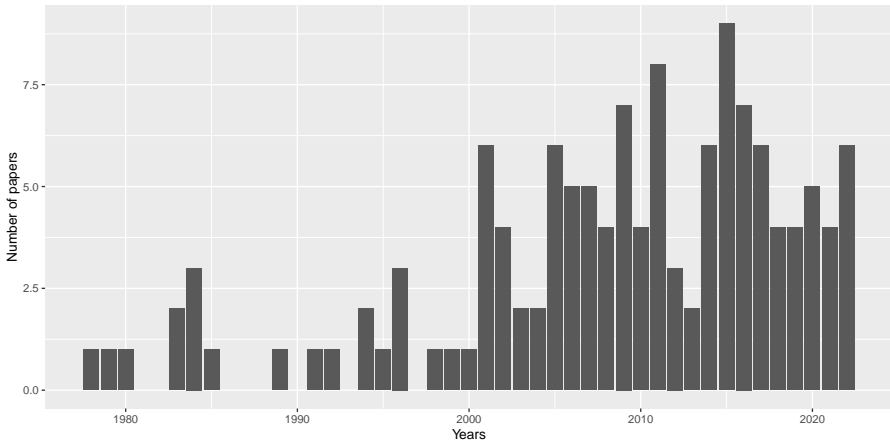
265

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

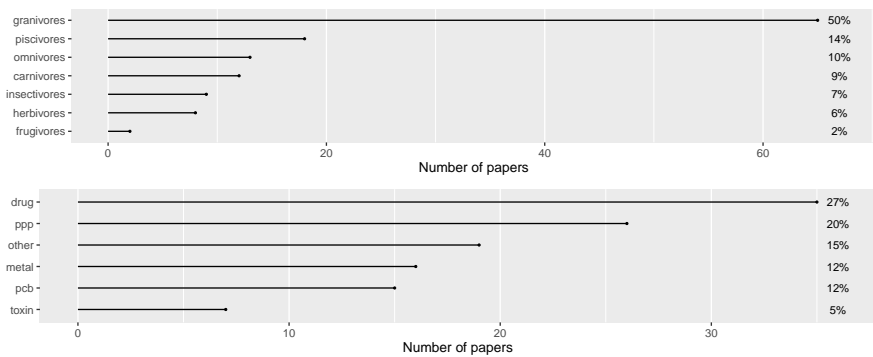
### 3 Results

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).

291 The salient point, which is not directly visible from Figure 3 but which follows  
292 directly from it, is the total absence of studies that address the effects of PPP  
293 on bird species of interest for the regulatory environmental risk assessment.  
294 For example, European regulations 283/20134 and 284/20135 recommend  
295 determining the acute oral toxicity of an active substance to a quail species  
296 (Japanese quail, *Coturnix coturnix japonica* or bobwhite quail, *Colinus vir-*  
297 *ginianus*), while data on additional species, such as *Serinus canaria*, may be  
298 requested by other legislative frameworks ([European Food Safety Authority](#)  
299 [et al, 2023](#)). These quail and canary species were totally absent from our set of  
300 studies. On the contrary, poultry species are studied a lot, and the most, with  
301 a majority of the related papers employing toxico-/pharmaco-kinetic (TPK)  
302 models. Laying hens and broiler chicken species were both studied, the latter  
303 being much more used (47 out of 130 papers). Regarding chicken, exposures  
304 to drugs and PPP were the most investigated contaminants, while modeling  
305 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,](#)



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

323

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

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

333

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

344

**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		

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

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

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

382

383 Among the 130 papers, some studies were generic in scope, but for differ-  
384 ent reasons. A total of 41 papers (31.5%) concerned several biological species  
385 that were simultaneously studied as exposed to a same chemical (Newsted  
386 *et al.*, 2006; Samuels and Ladino, 1984). A total of 45 papers (34.6%) reported  
387 effects of several chemicals on one bird species (Topping *et al.*, 2005; Wayland  
388 *et al.*, 2008). And only 8 papers out the 130 were general reviews covering a  
389 wide spectrum of species-compound combinations (see for example Kuo *et al.*  
390 (2022)). It is worth to note that only two papers dealt with the impacts of  
391 multiple stressors: the first on white-tailed eagle populations (Korsman *et al.*,  
392 2012); the second on the common loon (Nacci *et al.*, 2005). One of the most  
393 striking points of our review is that only 9 papers (~7%) gave access to raw  
394 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).

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

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

## 400 **4 Conclusion**

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

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

## 427 5 Supplementary Information

428 All supplementary information mentioned in this manuscript is available at  
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