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REVIEW

A Critical Review of Bioaccumulation and Biotransformation of Organic Chemicals in Birds

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Abstract

A literature review of bioaccumulation and biotransformation of organic chemicals in birds was undertaken, aiming to support scoping and prioritization of future research. The objectives were to characterize available bioaccumulation/biotransformation data, identify knowledge gaps, determine how extant data can be used, and explore the strategy and steps forward. An intermediate approach balanced between expediency and rigor was taken given the vastness of the literature. Following a critical review of > 500 peer-reviewed studies, > 25,000 data entries and 2 million information bytes were compiled on > 700 organic compounds for ~ 320 wild species and 60 domestic breeds of birds. These data were organized into themed databases on *bioaccumulation and biotransformation*, *field survey*, *microsomal enzyme activity*, *metabolic pathway*, and *bird taxonomy and diet*. Significant data gaps were identified in all databases at multiple levels. Biotransformation characterization was largely fragmented over metabolite/pathway identification and characterization of enzyme activity or biotransformation kinetics. Limited biotransformation kinetic data constrained development of an avian biotransformation model. A substantial shortage of in vivo biotransformation kinetics has been observed as most reported rate constants were derived in vitro. No metric comprehensively captured all key contaminant classes or chemical groups to support broad-scope modeling of bioaccumulation or biotransformation. However, metrics such as biota-feed accumulation factor, maximum transfer factor, and total elimination rate constant were more readily usable for modeling or benchmarking than other reviewed parameters. Analysis demonstrated the lack of bioaccumulation/biotransformation characterization of shorebirds, seabirds, and raptors. In the study of bioaccumulation and biotransformation of organic chemicals in birds, this review revealed the need for greater chemical and avian species diversity, chemical measurements in environmental media, basic biometrics and exposure conditions, multiple tissues/matrices sampling, and further exploration on biotransformation. Limitations of classical bioaccumulation metrics and current research strategies used in bird studies were also discussed. Forward-looking research strategies were proposed: adopting a chemical roadmap for future investigations, integrating existing biomonitoring data, gap-filling with non-testing approaches, improving data reporting practices, expanding field sampling scopes, bridging existing models and theories, exploring biotransformation via avian genomics, and establishing an online data repository.

Keywords Bioaccumulation · Biotransformation · Biomagnification · Avian · Toxicokinetics · Biomonitoring · Risk assessment

Abbreviations

AUC	Area under the curve
B	Bioaccumulation
BAF	Bioaccumulation factor
BFAF	Biota-feed accumulation factor
BMF	Biomagnification factor
BSAF	Biota-sediment/soil accumulation factor
BT	Biotransformation
BWF	Biota-water factor
C&M byproducts	Combustion and manufacturing byproducts
CL	Clearance
DDT	Dichloro-diphenyl-trichloroethane
EROD	7-Ethoxyresorufin-*O*-deethylase
F	Pharmacokinetic bioavailability
$f_{MB/\Sigma MB}$	Fraction or yield of metabolite
GST	Glutathione *S*-transferase
HOC	Hydrophobic organic compound

Extended author information available on the last page of the article

IEx	Interspecies extrapolations
k_{abs}	Absorption rate constant
k_{elim}	Elimination rate constant
k_m	First order biotransformation rate constant
k_{MB}	Metabolite formation rate
K_{OW}	Octanol–water partition coefficient
k_{PC}	Metabolism rate
k_T	Total elimination rate constant
k_{up}	Uptake rate constant
maxTF	Maximum transfer factor
MTBF	Maternal transfer burden fraction
NP	Non-prediction
OCSPP	Office of Chemical Safety and Pollution Prevention
ODF	Ovo-diet concentration factor
ODP	Out-of-domain prediction
OECD	Organization for Economic Cooperation and Development
OMF	Ovo-maternal concentration factor
P450	Cytochrome P450
PAH	Polycyclic aromatic hydrocarbon
PBDE	Polybrominated diphenyl ether
PBPK	Physiologically based pharmacokinetic
PCB	Polychlorinated biphenyl
PCDD	Polychlorinated dibenzo-*p*-dioxin
PCDF	Polychlorinated dibenzofuran
PFAS	Per-/poly-fluoroalkyl substance
PK	Pharmacokinetic
POP	Persistent organic pollutant
PROD	7-Pentoxyresorufin-*O*-deethylase
QSAR	Quantitative structure–activity relationship
RAx	Read-across
TF	Transfer factor
TG	Test guideline
TK	Toxicokinetic
TPR_{field}	Field tissue-plasma ratio
TPRss	Steady-state tissue-plasma ratio
USDoD	United States Department of Defense
USEPA	United States Environmental Protection Agency
USGS	United States Geological Survey
V_d	Volume of distribution
$V_{d,central}$	Volume of distribution in the central compartment
$V_{d,peripheral}$	Volume of distribution in the peripheral compartment
$V_{d,SS}$	Volume of distribution at steady state

Contents

1 Introduction 2
1.1 Birds 3
1.2 Chronic and Lethal Effects of Chemical Pollution on Birds 4
1.3 Bioaccumulation in Birds: Why is it Difficult to Interpret? 5
1.3.1 Compound Chemistry and Source Distribution 5
1.3.2 Dynamic Avian Trophic Interactions 6
1.3.3 Gut Physiology, Feeding Strategy, and Dietary Preference 6
1.3.4 Free Ranging vs Domesticated 6
1.3.5 Physiological Differences and Energetic Needs 7
1.3.6 Home Range and Micro-habitat Utilization .. 7
1.4 Modeling Avian Bioaccumulation 7
1.5 Biotransformation in Birds 8
1.6 Previous Reviews on Avian Bioaccumulation and Data Gaps 8
1.7 Objectives of Current Review 9
2 Methodology 10
2.1 Literature Search Strategy 10
2.1.1 Search Keywords 10
2.2 Data Organization and Structure 10
2.2.1 Main Bioaccumulation/Biotransformation Database 11
2.2.2 Field Survey Database 11
2.2.3 Enzyme/Microsomal Activity Database 11
2.2.4 Metabolic Pathway Database 11
2.2.5 Bird Taxonomy and Diet Database 11
2.3 Data Gap Identification and Parameter Screening 12
2.3.1 Identifying Candidate Parameters 12
2.3.2 Parameter Quality Dimensions 12
2.3.3 Data Coding 13
2.3.4 Data gaps and Parameter Screening 14
3 Results and Discussion 15
3.1 Main Bioaccumulation/Biotransformation Database 15
3.2 Field Survey Database 16
3.3 Enzyme/Microsomal Activity Database 18
3.4 Metabolic Pathway Database 19
3.5 Bird Taxonomy and Diet Database 21
4 Primary B/BT/TK/PK Metrics for Modeling or Benchmarking 21
4.1 Screening for key B/BT/TK/PK parameters 23
4.2 Multipronged characterizations of biotransformation ... 24
4.3 Metabolites in the Main and Field Databases 25
4.4 Enzymatic Activity and its Dependence 26
4.4.1 Dose-Dependent Responses in Avian Enzymatic Activity 27
4.4.2 Non-chemical Factors on Microsomal Enzymatic Responses 28
4.5 Taxonomic Distribution 28
5 Data and Knowledge Gaps and Future Needs 28
5.1 Research Limitations and Technical Constraints 29
5.2 Chemical Diversity 29
5.3 Biotransformation at Exploratory Phase 29
5.3.1 Challenges in Characterizing Biotransformation 29
5.3.2 Microsomal Assays and Metabolic Profiles .. 30
5.3.3 New Enzyme Pathways: AO and FMO 30
5.4 Higher Bird Diversity of Shorebirds, Seabirds, and Raptors 31
5.5 Wild Bird Species for B/BT Characterization 31
5.6 Basic Biometrics, Exposure Conditions, and Physiological Parameters 32
5.7 Multiple Tissue/Matrix Sampling 32

5.8 Non-invasive Sampling 33
5.8.1 Egg Sampling 33
5.8.2 Feather Sampling 34
5.8.3 Excrement Sampling 34
5.9 Chemical Activity in Environmental Media as Reference 34
6 Strategies Going Forward 35
6.1 Construct a Chemical Roadmap 35
6.2 Match and Merge for B Data 35
6.3 Clarify Existing B/TK/PK Theories and Develop a Unified Theoretical Framework 36
6.3.1 Clarifying B Models and Metrics 36
6.3.2 Develop a Theoretical Framework for Interconversion of B/TK/PK Data 36
6.3.3 Expedient Derivation of In Vivo Biotransformation Rate Constant 37
6.3.4 Clarifying BT Models and Parameters 37
6.3.5 Linking BT Kinetics with Enzymatic Activities 38
6.4 Improving Data Reporting Practices 38
6.5 Expanding the Scope of Field Sampling 38
6.6 Non-testing Approaches for B/BT Gap-Filling 39
6.6.1 Read-Across and Interspecies Extrapolations 39
6.6.2 Quantitative RAx and IEx 39
6.6.3 Limitations of Non-testing Approaches 39
6.7 Linking B and BT to Avian Genomics 39
6.8 Online Data Repository 40
6.9 Open-Ended Questions and Explorations 40
6.9.1 Which B Metric(s) for Birds? 40
6.9.2 Foraging Strategy, Dietary Preference, Life-Stage Events, and Avian Ecology? 40
6.9.3 How Important is Air Exposure to Bioaccumulation in Birds? 40
6.9.4 Avian Biotransformation of Chemical Mixtures? 41
6.9.5 Incorporating BT into Avian Ecological Risk Assessment? 41
6.9.6 Tissue-Specific B/BT in Birds? 41
7 Summary 41
8 Supplementary Information 42
9 References 43

1 Introduction

1.1 Birds

Birds are a diverse and large group of species that occupy many critical ecological roles and provide numerous ecosystem services (Sekercioglu 2006; Whelan et al. 2008). They are active players in the trophic transfer of nutrients and contaminants, functioning as mid-level consumers to apex predators. Birds serve critical ecological functions as pollinators and seed dispersers (Corlett 2017; Egerer et al. 2018; Garcia et al. 2010) and support plant diversity and growth by suppressing herbivory via predation (Bock et al. 1992; Mäntylä et al. 2011; Powell et al. 1991). Several birds are keystone species (e.g., vultures *Accipitridae*, African hornbills *Bucerotidae*) (Buechley et al. 2018; Capoccia et al. 2018; Trail 2007) or can act as ecosystem engineers in selected ecosystems (e.g., Little Auk *Alle alle*, Black-backed Woodpecker, *Picoides arctius*) (González-Bergonzoni et al. 2017; Tremblay et al. 2015). Birds support a variety of ecosystem services, including global cycling of nutrients (Otero et al. 2018) and soil formation (Simas et al. 2007; Souza et al. 2014), and serve as indicators of environmental health (Furness and Greenwood 1993; Gregory and Strien 2010). Eggs and flesh of domestic and wild birds are important food sources, and their feathers are used decoratively, functionally, and even spiritually by humans. Birds are of cultural importance and have served as symbols of nations and organizations. Of aesthetic value, birds have been the subject of many world-famous artists, writers, poets, and composers, and their observation has been a perpetual source of fascination. Regrettably, avian population declines and extinctions attributable to habitat loss, unregulated harvest and other anthropogenic causes of mortality have been reported in North America and elsewhere (Rosenberg et al. 2019; Burns et al. 2021).

Birds constitute an important class of vertebrates to consider in environmental benchmarking, chemical modeling, risk assessment, and management of chemical contaminants. Historically, birds have been one of the reported species to suffer the consequences of pollution (Carson 1962; Oaks et al. 2004; Ratcliffe 1967; Hoffman et al. 2003). Reports of anthropogenic environmental contaminants affecting birds and other wildlife began to accumulate during the industrial revolution of the 1850s (Hoffman et al. 2003). These reports included cases of arsenic and lead poisoning, industrial smokestack emission toxicity, and hydrogen sulfide fumes in the vicinity of oil fields (Hoffman et al. 2003). The high chemical sensitivity of birds makes them good bioindicators of environmental contamination, and have long been used as sentinel species (Espín et al. 2016; Golden and Rattner 2003; Grove et al. 2009; Smits and Fernie 2013; Verreault et al. 2010). With many apex predators in different ecosystems, birds are ideal for understanding and evaluating the ultimate fate and ecotoxicological effects of organic chemicals in various environments and can contribute to similar advances in other vertebrates (Arnold et al. 2014; Price et al. 2015). Birds of prey are frequently used as sentinels for environmental pollution due to their high trophic position, long lifespan, and large foraging habitats that allow for spatiotemporal exposure and ecotoxicological fate assessments of relevant chemicals (Busch et al. 2020; Donald et al. 2001; Emmerson et al. 2016; Gómez-Ramírez et al. 2014; Movalli et al. 2017; Sun et al. 2019).

The history of bird exposure to pollutants is long. One of the most prominent examples is the massive decline of the raptor population globally due to eggshell thinning after bioaccumulation caused by exposure to dichloro-diphenyl-trichloroethane (DDT) (Newton and Bogan 1974). While acute intoxication from pollutants generally appears as a less poignant and immediate threat, severe indirect effects of pollutants, primarily agrochemicals, on farmland birds are well-described drivers of population declines (Stanton et al. 2018). Other threats at the population level associated with chemical exposure have been reported for various avian taxa, such as global lead poisonings of raptor and waterbird species (Sonne et al. 2019). However, there is currently no systematic long-term survey of birds at the individual or population level assessing acute or chronic effects of the myriad chemicals or chemical mixtures (Badry et al. 2020).

Various anthropogenic factors and activities have led to the decline and endangerment of wild birds (Furness 1993). Leading causes of direct bird mortality include predation by domestic cats (Loss et al. 2013b), collision with buildings, wind or tidal turbines, and electrocution by powerlines (Bernardino et al. 2018; Johnson et al. 2018; Loss et al. 2013a, 2014; Marques et al. 2014). Lead poisoning or catastrophic oil spills can lead to massive death of birds (Bernanke and Köhler 2009; Haney et al. 2014a, b; Harwell and Gentile 2006; Henkel et al. 2012) as well as ingestion of marine debris (Roman et al. 2019). Habitat loss and fragmentations due to urbanization and other human land uses have also contributed to population declines and a loss of avian diversity (Andrén 1994; Beninde et al. 2015; Kociolek et al. 2011; Rosenberg et al. 2019; Burns et al. 2021). Particularly, intensification of agricultural practices resulted in a substantial decline of Europe's farmland bird populations during the past 50 years (Busch et al. 2020; Donald et al. 2001; Emmerson et al. 2016).

1.2 Chronic and Lethal Effects of Chemical Pollution on Birds

Specific cases of avian population decline and chronic sublethal effects have been linked to contaminants. Oil spills have contributed to long-term effects including reduced reproductive success (Barros et al. 2014; Golet et al. 2002; Vidal and Domínguez 2015) and altered demographics in the presence of other environmental stressors (e.g., reduced food availability) (Golet et al. 2002; Votier et al. 2005). Other high-profile effects and impacts of pollution on birds include lead poisoning of White-tailed Eagle (*Haliaeetus albicilla*) (Fisher et al. 2006; Helander et al. 2009; Kenntner et al. 2001) and California Condor (*Gymnogyps californianus*) (Finkelstein et al. 2012), diclofenac-induced collapse of *Gyps* vulture populations

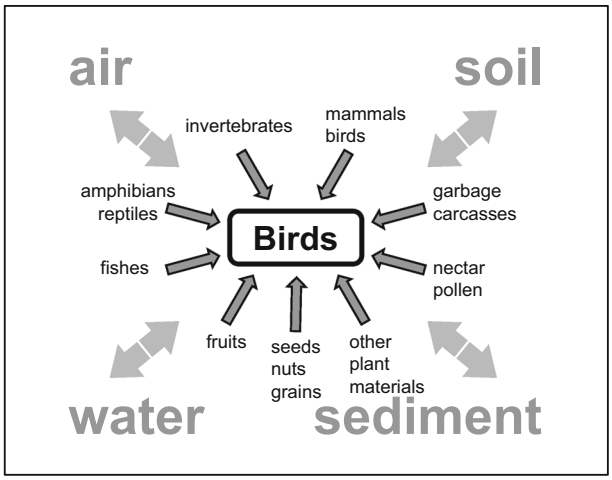


Fig. 1 A general schematic of the diversity in diet and environmental media interactions of birds (diet categories followed those defined in Wilman et al. 2014)

(Movalli et al. 2018; Oaks et al. 2004), and the poisoning of Red Kite (*Milvus milvus*) by pesticides and rodenticides (Berny and Gaillet 2008; Coeurdassier et al. 2012). Recent reviews considered chemically-contaminated diets as a critical anthropogenic threat to avian scavenger species (Buechley and Şekercioğlu 2016; Cuthbert et al. 2014). These cases echo the well-documented historical decline in Peregrine Falcon (*Falco peregrinus*), Sparrowhawk (*Accipiter nisus*), and Bald Eagle (*Haliaeetus leucocephalus*) populations following large-scale and widespread application of DDT > 60 years ago (Carson 1962; Hickey and Anderson 1968; Ratcliffe 1967).

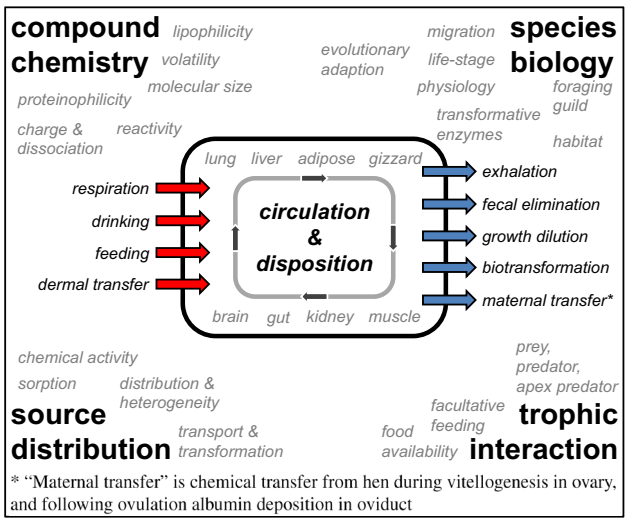


Fig. 2 Uptake (red arrows) and elimination (blue arrows) in bioaccumulation/biomagnification of chemicals in birds and their dependence on compound chemistry, source distribution, trophic interaction, and species biology (Color figure online)

In various countries and regions, regulatory guidelines exist to ensure that commercial substances will not adversely affect bird populations. Currently, pesticide registrants are required to submit toxicity data to regulatory agencies to determine potential risk to birds as part of registration submission packages. Examples of common test guidelines (TGs) include those developed by the European Food Safety Authority (EFSA), the Organization for Economic Cooperation and Development (OECD), and the US Environmental Protection Agency (EPA) to evaluate avian subacute dietary toxicity [Guidance of EFSA Risk Assessment for Birds and Mammals (EFSA 2009), OECD TG 205 (OECD 1984a), USEPA Office of Chemical Safety and Pollution Prevention (OCSPP) 850–2200 (USEPA 2012b)], acute oral toxicity of chemicals [Guidance of EFSA (EFSA 2009), OECD TG 223 (OECD 2016), OCSPP 850–2100 (USEPA 2012a)], and risks to avian reproduction [Guidance of EFSA (EFSA 2009), OECD TG 206 (OECD 1984b), or OCSPP 850–2300 (USEPA 2012c)]. Avian toxicity data generated according to these guidelines are generally used to evaluate risk to birds following exposure to chemicals via the food chain (e.g., ingestion of fish and/or invertebrates). These tests often need to be complemented by additional lines of evidence provided by other studies (e.g., field studies) that are not subjected to any specific guidelines. However, field study heterogeneity in terms of species, protocols, and data reporting can make the results challenging to interpret. Furthermore, the evaluation of contaminants' bioaccumulation and biotransformation is important to determine the internal exposure to potentially harmful chemicals and to ultimately better inform food web models. However, there are currently no TGs specifically designed to evaluate bioaccumulation and biotransformation in birds.

Food web accumulation of various pollutants in birds has been revealed by the elevated contaminant levels in high trophic-level predatory birds resulting from transfer and concentration of pollutants from diet/prey (i.e., biomagnification), which may be further compounded by their reduced ability to eliminate contaminants by metabolism. The population collapse of top avian predators in the 1950s following widespread DDT exposure (Carson 1962; Hickey and Anderson 1968; Peakall 1974) remains the most vivid illustration of how trophic transfer of bioaccumulative pollutants can lead to large-scale adverse toxicological effects (e.g., mortality events, population crash). Through long-range migrations, birds can act as vectors of accumulative pollutants, bringing and introducing them into distant pristine ecosystems via trophic interactions and elimination of fecal and uric acid waste, which may eventually lead to the transfer and magnification of pollutants in local top predators (Beck et al. 2015). With the persistence of legacy contaminants and the widespread application of new chemicals, exposure and bioaccumulation studies continue to expand and gather research and monitoring momentum (Cipro et al. 2010; Maul et al. 2006; Xu et al. 2014; Movalli et al. 2019).

1.3 Bioaccumulation in Birds: Why is it Difficult to Interpret?

Birds pose many unique and unprecedented challenges to the investigation of bioaccumulation and biomagnification. Unlike fish and aquatic invertebrates, which are confined to specific and highly localized habitats, birds exhibit considerable mobility and interact broadly with all major environmental compartments (e.g., air, water, soil, and sediment) (Fig. 1). Chemical exposure conditions are often unknown for free ranging birds. Together with diverse diets, the evaluation on the field accumulation of a contaminant in birds is more difficult due to various confounding ecological and environmental factors such as seasonal niche changes and climate change–induced shifts in the food web (Dietz et al. 2019). Bird species vary in their suitability for chemical monitoring based on ecological traits such as migratory behavior and feeding ecology (Badry et al. 2020).

Bioaccumulation and biomagnification are influenced by the close coupling of compound chemistry, source distribution, trophic interaction, and species biology (Fig. 2). In addition, interspecies differences in gut physiology, diet preference, foraging strategies, environmental interactions, mobility and migration, physiological differences, and other species-specific life traits have important consequences for chemical uptake and metabolism of organic chemicals in birds (Fig. 2). These aspects are briefly reviewed in the following paragraphs.

1.3.1 Compound Chemistry and Source Distribution

Greater bioaccumulation potential can be expected when the compound exhibits stronger associations with lipids (i.e., lipophilic) or with proteins (i.e., proteinophilic) (Arnot and Gobas 2006), and when chemical transport across the tissue/cell membrane is governed by a resistance or barrier model (Erickson and McKim 1990a, b; Hayton and Barron 1990). Source distribution refers to the presence and chemical activity of the target organic compound among different environmental compartments (e.g., surface water, soil, sediment, air) and prey species. Characterization of chemical source distribution is a major challenge for measuring and assessing bioaccumulation potential in birds in their native habitats, particularly for species that have access to multiple food sources among different environmental compartments (e.g., shorebirds, waterfowl) or species with long-range predatory capacity (e.g., raptors).

1.3.2 Dynamic Avian Trophic Interactions

Avian trophic interactions are highly dynamic, which renders the study of bioaccumulation complex in this group. Although greater bioaccumulation is generally observed in predatory and scavenging birds than in lower trophic species due to longer life spans and feeding at higher trophic levels, exceptions have been reported where similar levels of bioaccumulation were observed (Barghi et al. 2018; Peng et al. 2015). This complexity is best illustrated by the work of Custer et al. (2010), in which the biomagnification patterns among three species, insectivorous Tree Swallow (*Tachycineta bicolor*), omnivorous Spotted Sandpiper (*Actitis macularius*), and piscivorous Belted Kingfisher (*Ceryle alcyon*), shifted and varied among different organic contaminants. Indeed, many birds can select and switch among different diets or prey, depending on food availability, life-stage need (e.g., parental phase), seasonality, migratory modes (e.g., obligatory, facultative, or nomadic migrant), and whether they are in migration or resting (Jenni-Eiermann and Jenni 1996; Ramenofsky and Wingfield 2006; Robart et al. 2019). Chemical exposure and uptake may be further complicated by the ingestion of soil and sediment during foraging, which can account for 7 – 30% of the diets in various sandpipers, Canada Goose (*Branta canadensis*), American Woodcock (*Scolopax minor*), and Wild Turkey (*Meleagris gallopavo*) (Beyer et al. 1994). Geophagy can have bioaccumulation and other toxicological implications for birds foraging in habitats with heavily contaminated soils or sediments (Beyer and Fries 2003). Field biomagnification or bioaccumulation in wild birds may be estimated using the instantaneous dietary contaminant levels determined from properly performed stomach content analysis (Ketyam et al. 2016; Woodley et al. 2004); however, similar assessment would be difficult, especially for long-range migrants for which there is uncertainly in diet and contaminant exposure during migration (Kunisue et al. 2003; Minh et al. 2002).

1.3.3 Gut Physiology, Feeding Strategy, and Dietary Preference

Intake of contaminated food items is a major chemical uptake pathway in birds. Uptake is influenced by life history, gut physiology, and diet preference, all known to vary among species. Aerial species have evolved with smaller intestines to improve flight energetics by reducing digesta burden (Price et al. 2015). Similar adaptive change in digestive physiology has led to a considerably shorter digestive tract in migratory species (e.g., geese, various species) than in nonmigratory birds (e.g., grouse, various species) (Sedinger 1997).

Bioaccumulation of chemicals in birds is facilitated with higher digestive efficiency, which generally improves with longer retention time (Barton and Houston 1993; Hilton et al. 2000). Retention time is, in turn, influenced by gut physiology (e.g., length and plasticity) (Karasov 1996), diet composition and quality (Castro et al. 1989; Hilton et al. 2000), and foraging mode (e.g., pursuit versus search) (Barton and Houston 1993; Hilton et al. 1999). Diet composition and quality can modulate digestive efficiency through changes in both gut morphology and digestive enzyme activities (Kohl et al. 2017; Rott et al. 2017). Varying dietary preference and specialization can therefore lead to different exposure risk and bioaccumulation potentials in different birds (Geduhn et al. 2016).

Feeding strategy and dietary preference of birds change with seasonality and life stage. For instance, with migrant birds, invertebrates can be preferred in spring for breeding and nurturing while a carbohydrate-rich diet may be sought in the pre-migratory phase. Hyperphagia (i.e., increased feeding) has been observed in birds preparing for migratory flights (Agatsuma and Ramenofsky 2006; Jenni-Eiermann and Jenni 1996) and in those offering post-hatch parental care (Koch et al. 2002; Smiley 2019) and would lead to fattening (i.e., increased lipid mass). However, lipid storage varies with migration as the birds switch to a lipid-based energy pathway during flight (Jenni-Eiermann et al. 2002; Karasov and Pinshow 1998). All of these examples suggest that diet (hence contaminant) sources, feeding rate, and physiology (body and tissue lipid content) are likely variable with the seasons. Opportunistic predators (e.g., Bald Eagle), facultative migration (Robart et al. 2019), and food availability (Richards 2003; Robart et al. 2019) also can contribute to more variability in both diet and feeding strategy.

1.3.4 Free Ranging vs Domesticated

Metabolic responses to xenobiotics between free ranging wild birds and domestic breeds maintained in captivity (Matz et al. 1998; McKernan et al. 2009; Nakayama et al. 2020; Newton et al. 1990; Vyas et al. 2006) suggest that the bioaccumulation or biomagnification potentials of chemicals in wild species likely deviate from those in common domesticated test species (e.g., ducks, quail). Domesticated birds are likely to retain their body mass on a constant basis, whereas wild birds may rapidly gain and lose a large proportion (e.g., > 33%) of their body weight during critical life stages, such as egg-laying and migration (Scanes 2015). Female American Kestrels (*Falco sparverius*), for example, rapidly gain (then lose) 25–30% of their body mass during clutch formation and egg laying (Smallwood and Bird 2020). Some data on contaminant uptake and elimination are available from controlled experiments

using domesticated species, but more limited for captive wild species (e.g., Bardo and Bird 2009) and are likely not extendable to most wild free-ranging birds (e.g., Vyas et al. 2006). The large number of standardized laboratory experiments providing data that support the development of bioaccumulation models in fish or aquatic invertebrates overshadows that available for wild birds.

1.3.5 Physiological Differences and Energetic Needs

Differences in physiological and energetic needs during critical life stages influence bioaccumulation and biotransformation of organic chemicals in birds. Energy and protein requirements for clutch formation are much greater in large species such as Adelie Penguins (*Pygoscelis adeliae*) and Common Eiders (*Somateria mollissima*)(30%, 70%, respectively), than in small species, such as Blue Tits (*Cyanistes caeruleus*) and other passerines (4%, 40%, respectively)(Meijer and Drent, 1999). Furthermore, some large species deposit sufficient body reserves to permit complete fasting during egg formation and/or incubation, whereas smaller species must forage for energy and nutrients required during egg formation (Meijer and Drent, 1999).

Migratory species exhibit hyperphagia (Bairlein and Gwinner 1994), which leads to substantial weight gain in a relatively short time period, building up subcutaneous fat that will be metabolized in the process of extensive migratory flights (remobilization). During migration, many species of birds (e.g., passerines, shorebirds, raptors) deplete their body reserves (e.g., fat, muscle) while flying, then must regain those reserves at migratory stopovers to continue (e.g., Biebach et al. 1986; Dunn 2002; Fusani et al. 2009; Yong and Moore 1997). These changes in body reserves during egg formation and laying, and during migration, may have important implications for the uptake, metabolism, biotransformation, and accumulation of environmental chemicals (Marteinson et al. 2016 and references therein) by wild birds.

1.3.6 Home Range and Micro-habitat Utilization

Home range and habitat utilization of birds affect their uptake of chemicals. Avian home range size is influenced by the complex interplay of sex differences, breeding stage and seasonality (Rolando 2002; Bengtsson et al. 2014; Rühmann et al. 2019; Zurell et al. 2018) as well as food availability (Rolando 2002; Rühmann et al. 2019), body weight (Peery 2000), and landscape connectivity (Harris and Reed 2002). Home range size is widely distributed among individual birds and can vary by $\sim$ 1 to 4 orders of magnitude within a population (Peery 2000; García-Ripollés et al. 2011; Fischer et al. 2013). In addition to home range variability, accurate description of chemical exposure is further complicated by significant intra-population variation in local fine-scale habitat utilization and resource selection that are not readily predictable and transferrable (Bengtsson et al 2014; Zurell et al. 2018). Field avian bioaccumulation of organic chemicals and its variability need to be understood, assessed, and modeled in the context of the home range dynamics and microscale resource selection.

1.4 Modeling Avian Bioaccumulation

Bioaccumulation can be understood as a dynamic state established through the kinetic interactions of various chemical uptake and elimination processes. Over the past 40 years, various models have been developed for bioaccumulation in fish and invertebrates (e.g., bioconcentration factor or bioaccumulation factor (BAF) models) (Arnot and Gobas 2004; Chen and Kuo 2018; Jager 1998; Kuo and Chen 2021; Kuo and Di Toro 2013b; Meylan et al. 1999) or specific uptake/elimination processes (e.g., uptake rate constant) (Barber 2003; Brooke et al. 2012). These models are generally successful despite differences in their underlying chemical basis (e.g., logK_{OW}, molecular fragments, molecular descriptors, or solvation parameters) and approach (e.g., empirical versus mechanistic) adopted in these models (Arnot et al. 2009; Krause and Goss 2020; Kuo and Di Toro 2013a, b; Zhao et al. 2008).

Predictive bioaccumulation and biotransformation models with *broad chemical domain* remain elusive for birds. Avian models have been developed for the biotransfer and bioaccumulation of xenobiotics into eggs and specific tissues (Donoghue, 2001; Drouillard et al., 2001, 2007; Drouillard and Norstrom, 2003; Norstrom et al. 2007; MacLachlan, 2008, 2009, 2011). These models conceptualize toxicokinetic processes with varied mechanistic assumptions, physiological bases, and mathematical approaches that may not be readily reconciled with each other as they are contextualized to specific exposure scenarios and endpoints. A notable development is an avian bioaccumulation model for persistent organic pollutants (POPs) in Herring Gulls (*Larus argentatus*) (Norstrom et al. 2007). This toxicokinetic-based model requires comprehensive calibration and has been only applied to four POPs (logK_{OW} = 5.40–6.89). Biotransformation is omitted in the model because of its focus on POPs and model sensitivity to calibration has not been examined. The model may be extended to a broader spectrum of chemicals and avian species. Energetics is considered explicitly but not coupled to the toxicokinetic depiction of bioaccumulation (Norstrom et al. 2007). Except for the model developed by Norstrom and coworkers, most of the avian models have not addressed the biological and ecological

factors highlighted in Sect. 1.3. These deficiencies reflect the need for a unified theoretical framework and a broad-scope model for bioaccumulation and biotransformation of organic chemicals in birds.

1.5 Biotransformation in Birds

Among the various uptake and elimination processes (Fig. 2), biotransformation is one of the most critical for understanding bioaccumulation, fate, and ecotoxicity of organic chemicals in exposed organisms, including birds. The importance of biotransformation in ecotoxicology is long recognized, as exemplified in early studies on fish (Clements et al. 1994; Luthe et al. 2002), worms (Driscoll and McElroy 1996), and other invertebrates (Rust et al. 2004). Biotransformation and chemical partitioning have been shown to be critical in providing accurate predictions on the bioconcentration factor of organic chemicals in fish, with greater influence than growth dilution, fecal elimination, or even bioavailability correction for dissolved/particulate organic matter (Kuo and Di Toro 2013b). Similarly, biotransformation toxicokinetics can provide the mechanistic link and interpretation needed to understand the toxicity of pollutants observed in birds (Drouillard et al. 2007; Naidoo et al. 2010, 2018; Rattner et al. 2014, 2020) and eventually support the development of chemical toxicodynamics in birds.

Determining biotransformation kinetics can be challenging. Early work by van der Linde et al. (2001) suggested that biotransformation rate constants may be obtained *indirectly* by taking the arithmetic difference in toxicokinetic parameters. Such an indirect approach has led to the establishment of the first biotransformation kinetics database for organic chemicals in fish (Arnot et al. 2008b) and the subsequent development of predictive models (Arnot et al. 2009; Kuo and Di Toro 2013a). Various mathematical theories have been developed for extracting biotransformation kinetics *directly* from experimental data (Ashauer et al. 2012; Kuo and Chen 2016; Schuler et al. 2003). However, direct quantification of biotransformation remains difficult, primarily due to the analytical challenges of identifying and quantifying metabolites from raw instrumental signals (Malmquist et al. 2013; Rösch et al. 2016).

Interspecific differences in metabolism are currently omitted in predictive biotransformation models (Arnot et al. 2008a; Kuo and Di Toro 2013a). However, evidence suggests that such an omission is likely inappropriate for birds. A notable example of an interspecies metabolic difference is that New World Turkey Vultures (*Cathartes aura*) are about 100 times more tolerant to diclofenac than Old World *Gyps* vultures (Rattner et al. 2008). Similar interspecific differences are observed in bird mortality rates following carprofen or flunixin exposure (Cuthbert et al. 2007) and the accumulation of polychlorinated dibenzofurans among Tree Swallow (*Tachycineta bicolor*), Spotted Sandpiper (*Actitus macularia*), and Belted Kingfisher (*Ceryle alcyon*) (Custer et al. 2010). Differences in biotransformation between domestic poultry and wild birds are also demonstrated in the molecular and transcriptional responses to anticoagulant rodenticides (Nakayama et al. 2020; Watanabe et al. 2010, 2015). In addition, diversity in the avian gut microbiota and microbiome can contribute to differing intestinal biotransformation capacities for xenobiotics. Gut microbiota differ considerably among avian species and it is shaped by food preference and life traits of the particular bird species (e.g., Grond et al. 2018; Kohl 2012). A strong association between diet specialization and biotransformation capacity has been noted, with a lower level of monooxygenase activity observed in more specialized (piscivorous) avian predators (Walker 1998). Consequently, biotransformation kinetics are critical for understanding and interpreting field bioaccumulation and biomagnification in birds. Furthermore, differential sensitivity in biotransformation capacity and pathways among avian species should be examined within the current toxicokinetic framework.

1.6 Previous Reviews on Avian Bioaccumulation and Data Gaps

A number of reviews of the accumulation of organic contaminants in birds have been published over the past few decades. These include meta-analyses on polybrominated diphenyl ethers (PBDEs) (Chen and Hale 2010) and organohalogens (Abbasi et al. 2016), exposure pathway of pharmaceuticals (Shore et al. 2014), and transfer of dioxins and polychlorinated biphenyls (PCBs) from feed/soil to eggs (Schoeters and Hoogenboom 2006) and liver (Ghimpeţeanu et al. 2014). Other reviews have focused exclusively on the disposition of veterinary drugs and toxicants in poultry. Patel et al. (2018) examined common antibacterials and anthelmintics in poultry meat, focusing on dose and exposure routes. Goetting et al. (2011) reviewed the pharmacokinetic studies of a large suite of veterinary drug families (e.g., β-lactams, macrolides, fluoroquinolones, sulfonamides, tetracyclines, etc.) in laying hens and their eggs. In-depth reviews on mycotoxins (Girgis and Smith 2010), fusariotoxins (Guerre 2015), and lincomycin (Hornish et al. 1987) in poultry have been noted. However, critical pharmacokinetic parameters (e.g., clearance rate, bioavailability) have often been omitted in these works.

Focused reviews of the accumulation of legacy contaminants from feed/soil to poultry tissues, milk, and eggs and their elimination half-lives in various tissues/matrices

have been published (Kan 1978; MacLachlan 2011; Schoeters and Hoogenboom 2006). Although chemically more comprehensive and relevant to toxicokinetic modeling in general, these reviews are principally for domestic poultry species and products. It is unclear to what extent similar toxicokinetic characterization of organic chemicals is available in wild birds.

Walker and co-workers have extensively investigated activities of various monooxygenases in birds, and provided thorough discussions on avian forms of cytochrome P450 (P450) and associated monooxygenases and their roles in the biotransformation of xenobiotics (Ronis and Walker 1989; Walker 1980; Walker and Ronis 1989). While directly relevant to metabolism, these works focused on the interspecies difference in enzymatic activities and have not addressed how the measurement of these activities may be translated and incorporated in the contexts of toxicokinetics or bioaccumulation dynamics.

Despite their ecological importance, the current understanding of bioaccumulation and biotransformation of organic contaminants in birds is fragmented. While many reviews have been published, none have addressed the broad environmental interactions and diverse foraging strategy of birds (Fig. 1), and the coupling of bioaccumulation and biotransformation with compound chemistry, source distribution, species biology and tropic interaction (Fig. 2). Investigation of these complex topics could help reduce the fragmented understanding of these topics.

Simple biota-water/biota-sediment partitioning can provide acceptable initial estimates of the bioconcentration of hydrophobic organic chemicals in fish (Mackay 1982), worms (Jager 1998), and benthic organisms (Tracey and Hansen 1996). Various toxicokinetic models and quantitative structure–activity relationship (QSAR) models have been developed for the bioconcentration factors in fish (Arnot and Gobas 2004; Barber 2003; Kuo and Di Toro 2013b; Meylan et al. 1999; Zhao et al. 2008), invertebrates (Chen and Kuo 2018; Kuo and Chen 2021), and various terrestrial animals (Gobas et al. 2016; Hoke et al. 2016; van den Brink et al. 2016). These modeling successes largely depend on the collection of bioaccumulation data obtained through standardized tests under closely controlled environments. However, similar standardized protocols have not been fully developed for birds. In this context, tallying and compiling existing data is the logical first step toward the development of bioaccumulation and biotransformation models or assessment tools for organic chemicals. A comprehensive review on extant literature supports the need to quantitatively clarify the influences of source distribution and exposure, trophic interaction dynamics, and species biology and behavior (Fig. 2) on bioaccumulation and biotransformation in birds.

1.7 Objectives of Current Review

Herein, we review the current knowledge base and identify critical data gaps in bioaccumulation (B) and biotransformation (BT) of organic chemicals in birds. This review had the following objectives:

(i) Characterize and categorize published bird B/BT information and data. Classify quantitative endpoints and qualitative knowledge about avian B/BT based on type of investigations, experimental and exposure conditions, biological matrices examined, avian biological and ecological traits, and chemical classes.

(ii) Present an organizational framework for B/BT and related toxicokinetic (TK) and pharmacokinetic (PK) measurements with the potential to facilitate meta-analysis, benchmarking, and model development.

(iii) Identify metrics and parameters that can facilitate benchmarking, characterization, and modeling of B/BT of organic chemicals in birds by screening and examining B/BT/TK/PK parameters along different chemical, ecological, sampling, and data dimensions.

(iv) Identify key data gaps, research needs and priorities, and technical challenges and constraints in characterizing B/BT of organic chemicals in birds based on the review of compiled data and information.

(v) Outline strategies for advancing bioaccumulation and biotransformation science in birds. Develop strategies by covering chemical prioritization and expeditious characterization of B/BT, experimental and field sampling practices, interdisciplinary data integration and theory development, and data communication and sharing.

(vi) Pose open-ended questions that underline the core assumptions and limitations in extending established B/BT theory and characterization practice to birds and offer new perspectives and possibilities on how these challenges may be met.

These objectives were achieved through a detailed review of published literature, meta-analyses on the types and quantities of measurements and information reported, and a cross-disciplinary reflection on what may be needed for effective progress on this subject. Because of the vastness of the literature and the goal of clarifying the data landscape expeditiously, an intermediate approach that balanced expediency and rigor over a more exhaustive search strategy was adopted.

This work provides a critical first step in supporting the development of avian bioaccumulation, biotransformation, and physiologically-based pharmacokinetic (PBPK) models across diverse classes of organic chemicals and micropollutants. By organizing modeling-relevant experimental data within a comprehensive data framework that includes physiology, taxonomy, foraging strategy, experimental design, exposure conditions, and compound chemistry, this review provides the basis to explore the many facets of bioaccumulation and biotransformation in birds and to support the development of quantitative models and assessment tools. This review is the first of its kind to provide a bird's-eye view of both avian field and laboratory literature across various experimental and theoretical landscapes, pointing out the plausible paths and challenges to be resolved.

2 Methodology

A multipronged search strategy was adopted to locate relevant bioaccumulation and biotransformation studies and data. This included direct literature search (primary experiments and review articles), investigator-oriented search, chemical-oriented search, avian taxa-oriented search and discipline-oriented search. All studies deemed relevant to bioaccumulation or biotransformation of organic compounds in birds were compiled. Relevant literature that lacked the data or information required for a given database were stored for reference but designated as *not used*.

2.1 Literature Search Strategy

Primary experimental studies and review articles on bird bioaccumulation or biotransformation were identified using keywords via standard scientific search engines (i.e., Web of Science, Science Direct, and Google Scholar). Data or subject reviews on bioaccumulation or biotransformation of organic chemicals in birds were identified and explored. Avian source documents (i.e., listed in Sect. 1.6) focused on chemical classes, toxicological or pharmacokinetic themes, or microsomal responses following chemical exposure. These documents served as mini-depositories of experimental studies for in-depth data compilation. References cited within these source documents or information from more recent studies were screened for B/BT data. This screening was effective for identifying works with similar scientific objectives and comparable experimental design and measurement protocols. In addition, studies published by the same investigator(s) (investigator-oriented search) were retrieved for review. This approach took advantage of the fact that the same researcher or research team tended to remain engaged in the same scientific topic over an extended period of time, and allowed all bird-related work from the same group to be identified and compiled. Relevant B/BT references were actively searched using chemical names, families, or other identifiers. This approach ensured the review was conducted with sufficient chemical diversity.

2.1.1 Search Keywords

Various keywords were used in combinations to ensure the broadest coverage of uptake process/characterization, avian species and habitats, and chemical classes. Bioaccumulation, biomagnification, biotransformation, toxicokinetics, and pharmacokinetics of organic chemicals constituted the main focus of this review as the principal keywords. Terminologies related to these core keywords were adopted to improve search returns (e.g., disposition and clearance are common terms used/reported in pharmacokinetic studies). Since diverse characterizations have been developed for biotransformation, additional search terms were included to cover various assays and experiments (e.g., metabolism, metabolite, microsome, cytochrome, etc.). Bird and taxa keywords include common descriptors for species of regulatory or conservation concern (e.g., vulture, osprey, eagle, etc.), species in specific habitats (e.g., wader, shorebird), and standard test species (Mallard, *Anas platyrhynchos*, quail) and more commonly domesticated poultry (chicken) species.

The keywords used in literature searches included the following: (i) *subject keywords*: bird, avian, bioaccumulation, biomagnification, toxicokinetics, pharmacokinetics, kinetics, disposition, elimination, clearance, depuration, metabolism, metabolic, metabolite, biotransformation, transformation, tissue distribution, hepatic, liver, microsome, microsomal, or cytochrome for discipline-oriented search; (ii) *bird- or taxa-related keywords*: poultry, chicken, hen, quail, turkey, duck, gull, tern, raptor, bird of prey, scavenger, shorebird, wader, kestrel, osprey, eagle, hawk, owl, vulture, or passerine; and (iii) *chemical keywords*: legacy, emerging, organochlorines, flame retardants, chlorinated, brominated, pharmaceuticals, drugs, antibiotics, personal care products, agrochemicals, pesticides, insecticides, herbicides, neonicotinoids, or pyrethroids for chemical-oriented search. Ultimately, > 500 articles were deemed relevant and subsequently processed for data curation and classification.

2.2 Data Organization and Structure

Retrieved B/BT data were organized into five different databases based on the nature of observations reported: (i) *main bioaccumulation/biotransformation*, (ii) *field*

survey, (iii) *enzyme/microsomal activity*, (iv) *metabolic pathway*, and (v) *bird taxonomy and diet*. This organization was adopted to minimize redundant documentation and to better align with the overarching goal of identifying data/information gaps. The five databases are described briefly below (additional details provided in Supplementary Information S1 and S2).

2.2.1 Main Bioaccumulation/Biotransformation Database

This was the principal database for standard bioaccumulation factors and biotransformation parameters. Reported/computed toxicokinetics, pharmacokinetics, and various accumulation and transfer factors were documented, as these measurements also reflect the biological fate of organic chemicals in birds.

2.2.2 Field Survey Database

This database contained qualitative information on avian field studies that focused on organic chemicals. Chemical identities and properties, common name and taxonomy of birds, sampled tissues or biological matrices, site description, measurement basis, and availability of fundamental avian physiological properties were noted. These studies carried tissue or matrix concentration measurements that may be used to estimate field bioaccumulation factors if the background chemical levels at study sites were available and could be retrieved.

2.2.3 Enzyme/Microsomal Activity Database

Reports of in vivo or in vitro activities associated with enzymes, microsomal fractions, or cytochrome fractions of domestic or wild birds were archived in this database. The documentation focused on the types of activity measured and the exposure conditions studied; actual measurements were omitted. Basic chemical and biological identities, type of activities reported, and microsomal protein concentrations were noted.

2.2.4 Metabolic Pathway Database

Reports of metabolites following in vivo or in vitro exposure as well as proposed biotransformation pathways were documented in this database. The number of metabolites identified, proposed biotransformation pathway, and tested tissues or matrices were described.

2.2.5 Bird Taxonomy and Diet Database

Taxonomy and breed identifiers, common names, common avian group, habitat group, average dietary fraction, and foraging strategy of birds included in all databases were documented.

The main B/BT database had the following data sections: (i) chemical identification, properties, and classifications; (ii) reference and site description; (iii) bird identity, taxonomy, and biometrics; (iv) tissue or matrix chemical concentration; (v) exposure medium and properties; (vi) laboratory versus field measurement, ambient temperature, and chemical analysis; (vii) exposure duration and dosage; (viii) pharmacokinetic parameters; (ix) main bioaccumulation metrics; (x) biomagnification (biomagnification factor)-related parameters; (xi) toxicokinetic parameters; (xii) general biotransformation, in vitro biotransformation assay condition and parameters; (xiii) data referencing and dates; and (xiv) chemical formulation and study type. In addition, availability of $\delta^{15}N$ and $\delta^{13}C$ was noted, as they can reflect the trophic position and foraging strategy of birds and the origin of their diet, including the influence of anthropogenic food sources that may be $\delta^{13}C$ enriched if they are corn based (e.g., Caron-Beaudoin et al. 2013). Uncertainties (i.e., one standard deviation) and qualitative descriptions of key B/BT data, biometrics, and medium properties were archived. The documented uncertainties and the characterization of experimental protocol can support future review of data quality. These data sections were distributed over 174 columns.

The following key bioaccumulation metrics were compiled in the present review: (i) bioaccumulation factor (*BAF*), defined as the ratio of field biota (or tissue) concentration to aqueous chemical concentration; (ii) biota-sediment/soil accumulation factor (*BSAF*), defined as biota (or tissue) concentration over sediment (or soil) chemical concentration; and (iii) biomagnification factor (*BMF*), defined as biota (or tissue) concentration over prey chemical concentration. In response to the variety of experiments documented in the literature and the lack of standard *BAF*, *BSAF*, or *BMF* measurements, a number of bioaccumulation-related metrics were adapted in this review. These included the following: (i) biota-feed accumulation factor (*BFAF*), defined as biota (or tissue) concentration over feed concentration; (ii) biota-water factor (*BWF*), defined as biota (or tissue) concentration divided by drinking water concentration; (iii) transfer factor (*TF*), defined as biota concentration divided by daily dose applied; (iv) maximum transfer factor (*maxTF*), defined as the *maximum* biota concentration observed during the chemical uptake/elimination divided by daily dose applied; (v) steady-state tissue-plasma ratio (*TPRss*), defined as tissue-specific concentration internally referenced to plasma level; (vi) ovo-diet concentration factor (*ODF*), defined as the egg concentration divided by diet concentration applied to the adults; (vii) ovo-maternal concentration factor (*OMF*), defined as the concentration in egg

divided by the concentration in maternal tissues; and (viii) maternal transfer burden fraction (*MTBF*), defined as the mass fraction of chemical intake that is passed into the egg/hatchlings. These new metrics enabled a greater number of bioaccumulation relevant values to be archived.

The bird taxonomy and diet database had the following data sections: (i) species, breed for domesticated poultry, and other groupings; (ii) taxonomy and conservation status; (iii) dietary fraction; and (iv) foraging strategy. Taxonomy and related information were obtained by matching the reported scientific name to entries in two extant avian taxonomy databases (BirdLife International 2018; Wilman et al. 2014). Diet fraction and foraging strategy were obtained from the database compiled by Wilman et al. (2014) without further verification. These should be considered as general reference values for a given species. Bird taxonomy and diet information were distributed over 34 columns.

In addition to taxonomic classification, birds were categorized by their habitats (i.e., *habitat group*) and by common names (i.e., *common group*). Habitat grouping allowed different birds to be classified under broad ecological systems (e.g., terrestrial, aquatic, shore, etc.) and dietary interactions. A total of eight different habitat groups were adopted (see Table S2.1). The common grouping was created to merge related species into simpler nontaxonomic labels to facilitate communication to non-biologist professionals and the general public. For instance, Common Greenshank (*Tringa nebularia*), Terek Sandpiper (*Xenus cinereus*), and Ruff (*Philomachus pugnax*) were all considered to belong to the sandpiper common group, whereas Razorbill (*Alca torda*), Little Auk or Dovekie (*Alle alle*), Common Murre (*Uria aalge*), and Thick-billed Murre (*Uria lomvia*) were all classified under the group auk. A total of 87 common bird groups were adopted (Table S4.4).

A detailed explanation on the data structure and the specific parameter/information in the main and bird databases are provided in Supplementary Information S1 and S2, respectively. Data structure of the other databases are not elaborated any further as these databases were considerably smaller in size and quantitative data.

2.3 Data Gap Identification and Parameter Screening

Identifying data gaps in existing B/BT/TK/PK metrics and screening these parameters for candidates with immediate potential for modeling and benchmarking applications were two major objectives of this review. The main database was the primary focus since it carried the most quantitative B/BT data, and the process of identifying parameters now follows.

2.3.1 Identifying Candidate Parameters

All B/BT/TK/PK parameters curated were first subjected to preliminary screening. Since the objective was to find parameters with immediate potential for modeling or benchmarking avian B/BT against a wide spectrum of organic chemicals, only parameters with *abundant observations*, *large ranges of value*, and *diverse data sources* were selected based on the criteria described in the next paragraph.

2.3.2 Parameter Quality Dimensions

The candidate parameters were further described along the following characteristics: *meta data and reference basis*, *chemical diversity*, *bird ecology*, and *sampling tissue or matrix*. An ideal parameter for B/BT modeling or benchmarking should have the following characteristics, with quantitative coding provided in the next paragraph: (i) it should have a large and diversified observational basis (i.e., measurements from multiple data sources) to help reduce uncertainty and bias in the metric; (ii) the parameter needs to reflect the wide spectrum of chemical structures and physicochemical properties in chemicals of environmental and ecotoxicological interest; (iii) the parameter should encompass major avian species and habitats to ensure the relevant predictions for major ecosystems or field

Table 1 Overview of databases related to B/BT of organic chemicals in birds

Database	References (*n*)	Data entries (*n*)	Birds (*n*)[a]	Chemicals (*n*)[a]
Main B/BT	264	5729	139	365
Field survey	226	17,485	291	560
Enzyme/microsomal	84	1712	79	65
Metabolic pathway	59	216	50	57
Bird taxonomy/diet	–	486	390	–

B bioaccumulation, *BT* biotransformation

[a]Number of unique avian species, breed, and generic groups. Number of chemicals and chemical groups

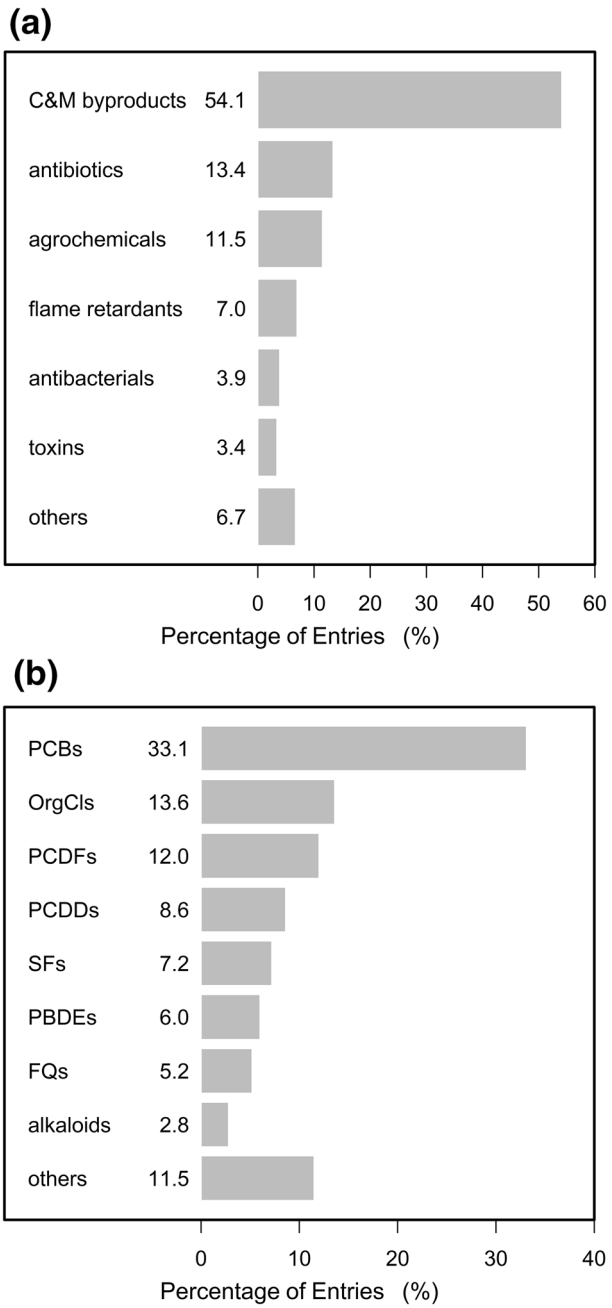


Fig. 3 Distribution of chemicals in the main database (n = 5729) by **a** applications and **b** chemical or contaminant groups. *C&M byproducts* combustion and manufacturing byproducts, *PBDE* polybrominated diphenyl ether, *PCB* polychlorinated biphenyl, *PCDD* polychlorinated dibenzodioxin, *PCDF* polychlorinated dibenzofuran

environments; and (iv) the parameter should have measurements made on commonly sampled tissues or matrices to help maintain continuity in both experimental methods and theoretical interpretations. These criteria were used with the assumption that the examined B/BT/TK/PK parameters will serve as a critical metric in regulatory,

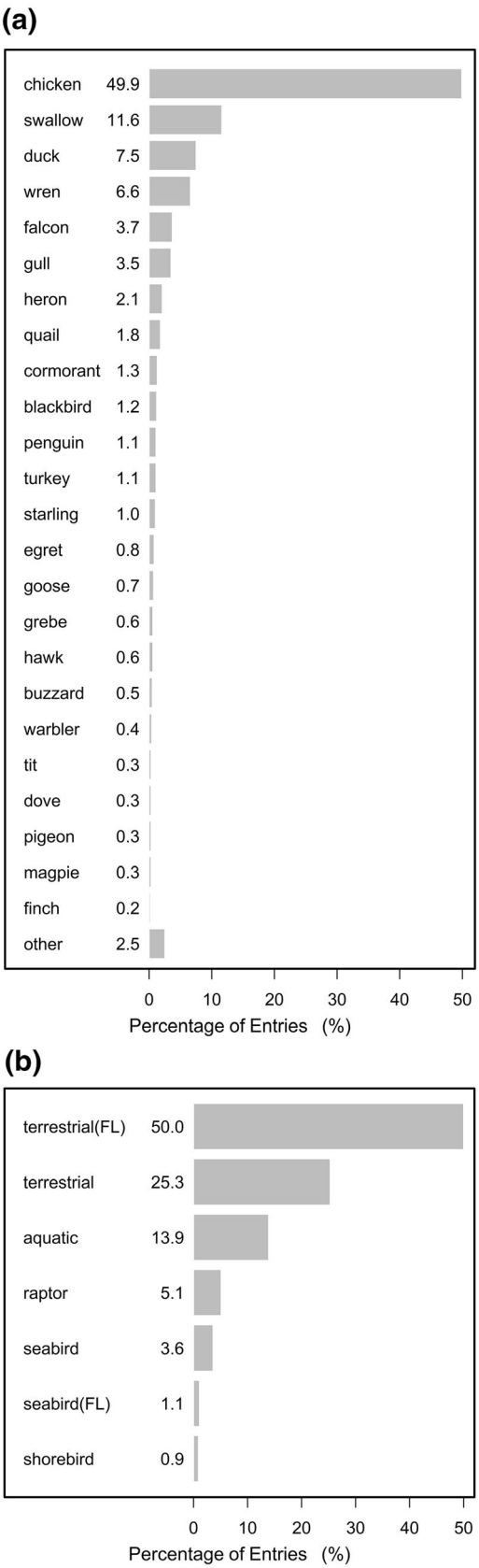


Fig. 4 Distribution of avian species in the main database (n = 5729) by **a** common bird categories and **b** habitat groups. *FL* flightless

Table 2 Types of studies in the main bioaccumulation database (additional details in Supplementary Information S1.3)

Study type	Data entries (*n*)
Field studies (n = 1684)	
Bioaccumulation	1656
Depletion	28
Farm studies (n = 503)	
Bioaccumulation	503
Laboratory bioaccumulation studies (n = 2455)	
Brief exposure ($t < 7$ days)	
Uptake	65
Depletion	357
Weekly exposure (7 days $\leq t \leq$ 14 days)	
Uptake	245
Depletion	384
Sustained exposure ($t >$ 14 days)	
Uptake	1048
Depletion	150
Uptake + Depletion	206
Laboratory pharmacokinetic studies (n = 475)	
Uptake	99
Depletion	104
Uptake + Depletion	256
Sustained implantation	16
Other laboratory studies (n = 499)	
Maternal transfer	180
Depletion after hatch	8
Air-cell study	
Uptake	144
Albumen uptake	6
Biotransformation	4
In vitro biotransformation	157

benchmarking, prioritization, remediation, risk assessment, or scientific modeling settings.

2.3.3 Data Coding

Quantitative coding was used to evaluate each quality dimensions. Each dimension consisted of a set of attributes that were characterized on the basis of abundance of data records. The attribute quantities were then translated into a five-tiered coding system to facilitate downstream inspection: *trace* (○, $n < 10$), *low* (■ , $10 \leq n < 100$), *moderate* (■■ , $100 \leq n < 200$), *high* (■■■ , $200 \leq n < 1000$), and *abundant* (■■■■ , $n > 1000$). For instance, there were 1314 BMF data entries obtained from 11 references, and BMF would be coded as having an *abundant* number of data entries but a *low* number of references. A total of 52 attributes were evaluated.

2.3.4 Data gaps and Parameter Screening

Data gaps were identified along the different parameter dimensions for the selected B/BT/TK/PK metrics. Attributes with no data or with *trace* (○, $n < 10$) levels of measurements were considered as having insufficient useable data. The data gaps were visually presented by the aforementioned data codes in various tables. The selected candidate parameters were evaluated along the previously described quality dimensions. Candidates with relatively few gaps in the different dimensions were deemed as having greater potential for modeling or benchmarking avian bioaccumulation or biotransformation.

3 Results and Discussion

An overview of the resulting five databases (see HESI Bird Databases attachment to be served by journal: RECT) is provided in Table 1. The main B/BT and the field databases were the principal information sources of interest in this review and discussion of findings are provided in the following sections.

3.1 Main Bioaccumulation/Biotransformation Database

The literature search resulted in a main database that contains > 5700 entries of B, BT, PK, and TK data from > 260 primary references. The database covers 365 organic chemicals, dominated by those classified as combustion and manufacturing byproducts (i.e., PAHs, PCBs, PCDDs, PCDFs), emerging pharmaceuticals, agrochemicals, and industrial chemicals (Fig. 3a). These include mostly PCBs, organochlorines, furans, and dioxins (Fig. 3b). Approximately 90 different avian species were documented in the database. Data entries are dominated by domesticated chickens, followed by swallows, ducks, wrens, falcons, and gulls (Fig. 4a). Three-quarters of the entries are associated with waterfowl, raptors, and seabirds, and the remaining records to a smaller portion with terrestrial birds (Fig. 4b).

A summary of different types of bioaccumulation and biotransformation studies is provided in Table 2. Overall, field/farm bioaccumulation, laboratory uptake/depletion, and pharmacokinetic studies appear to be dominant, with 2187, 2455, and 475 data entries, respectively. Field bioaccumulation observations (n = 1656 entries), short-exposure (n = 1051), and sustained exposure (n = 1404) constitute the majority of the data. Considerable data on

drugs and polar organic chemicals are documented in the pharmacokinetic and veterinary literature. Transfer and transformation data on organic chemicals in bird eggs are abundant (i.e., ~ 340 entries).

Biotransformation studies constitute a minor fraction of the main database. There are only about 160 entries with explicit characterization of BT kinetics (mostly in vitro) (Table 2). Metabolites are reported in 14% of entries within which 55% merely report metabolite detection but without further quantification; the remaining 45% have documented concentrations, ratios, and percent conversions of metabolites. A description of the metabolites is provided in Sect. 4.3.

3.2 Field Survey Database

The field database contains nearly 17,500 entries of chemical monitoring records in various avian tissues or matrices derived from field samples. It contains approximately 560 chemicals or chemical groups, dominated by combustion and manufacturing byproducts, agrochemicals, and emerging industrial chemicals (Fig. 5a). This dominance in legacy compounds largely reflects the evolution of interest in contaminant classes. Major chemical classes include PCBs, organochlorines, PBDEs, perfluorinated chemicals, furans, and dioxins (Fig. 5b). Approximately 290 different avian species are found in the database, with gull, falcon, cormorant, and hawk samples comprising 35% of all entries (Fig. 6a). Field data are mostly associated with seabirds, raptors, waterfowl, and to a smaller extent with terrestrial birds (Fig. 6b).

Field monitoring of organic chemicals in birds has been performed on different tissues and biological matrices as well as on a whole-body basis. The most analyzed matrices are egg (45% of all data entries), liver (29%), muscle (15%), fat (13%), and blood/plasma (8%). The remaining tissues/matrices, including kidney, brain, and gizzard, are examined in < 5% of the records. Contaminant concentration in feathers, a promising non-invasive matrix for routine field monitoring of chemical accumulation, is reported in < 1% of the entries. Only 8% of the records have whole-body measurements. Few studies have reported chemical concentration in multiple biological matrices, with less than 10% of the records measuring three or more biological matrices. While egg, liver, muscle, fat, and blood/plasma are the most commonly measured matrices, < 4% of the records cover three or more of these, and only 0.4% cover four of them.

The database reveals diverse experimental and data reporting practices in field studies. Pooled chemical measurements (e.g., summed PCBs or polycyclic aromatic hydrocarbons (PAHs)) are still commonly reported (9% of entries). Concentration is reported on a tissue weight (i.e., both dry and/or wet weight; 58%) and lipid weight basis (42%); merely 0.1% of the records contain both. Stable isotope analyses on $\delta^{15}N$ and $\delta^{13}C$ are available on 19% and 16% of the records, respectively. Only 11% of the records report metabolite detection.

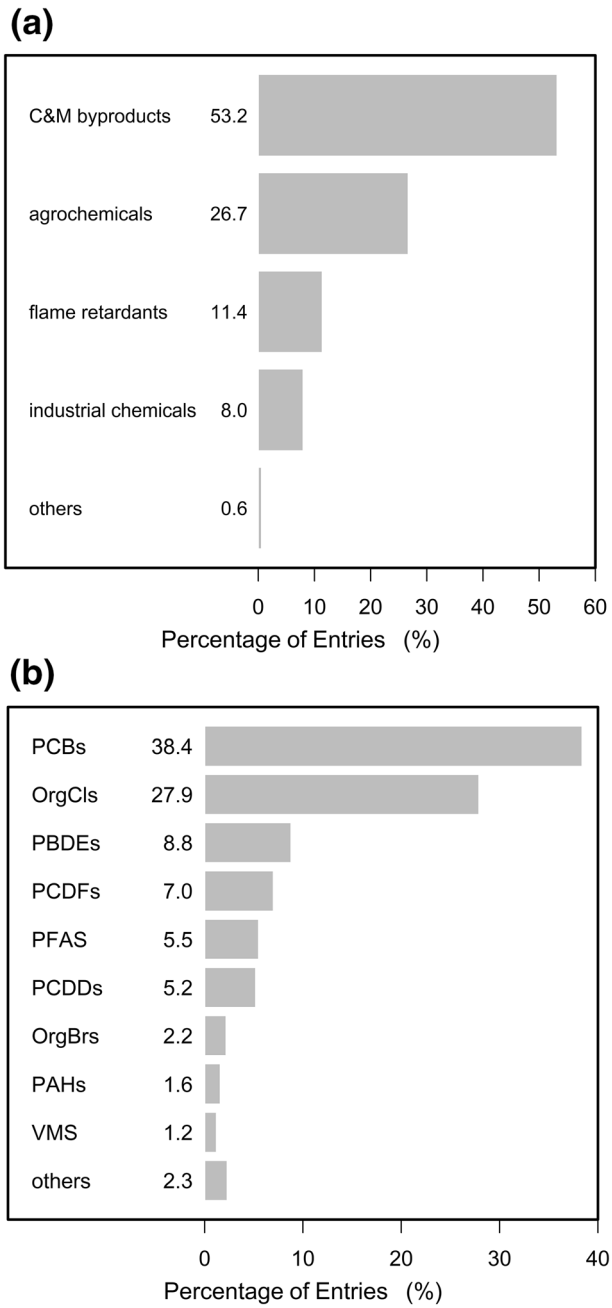


Fig. 5 Distribution of chemicals in the field database (n = 17,485) by **a** applications and **b** chemical or contaminant groups. *C&M byproducts* combustion and manufacturing byproducts, *OrgBr* organobromine, *OrgCl* organochlorine, *PAHs* polynuclear aromatic hydrocarbon, *PBDE* polybrominated diphenyl ether, *PCB* polychlorinated biphenyl, *PCDD* polychlorinated dibenzodioxin, *PCDF* polychlorinated dibenzofuran, *PFC* perfluorinated chemical, *VMS* volatile methyl siloxane

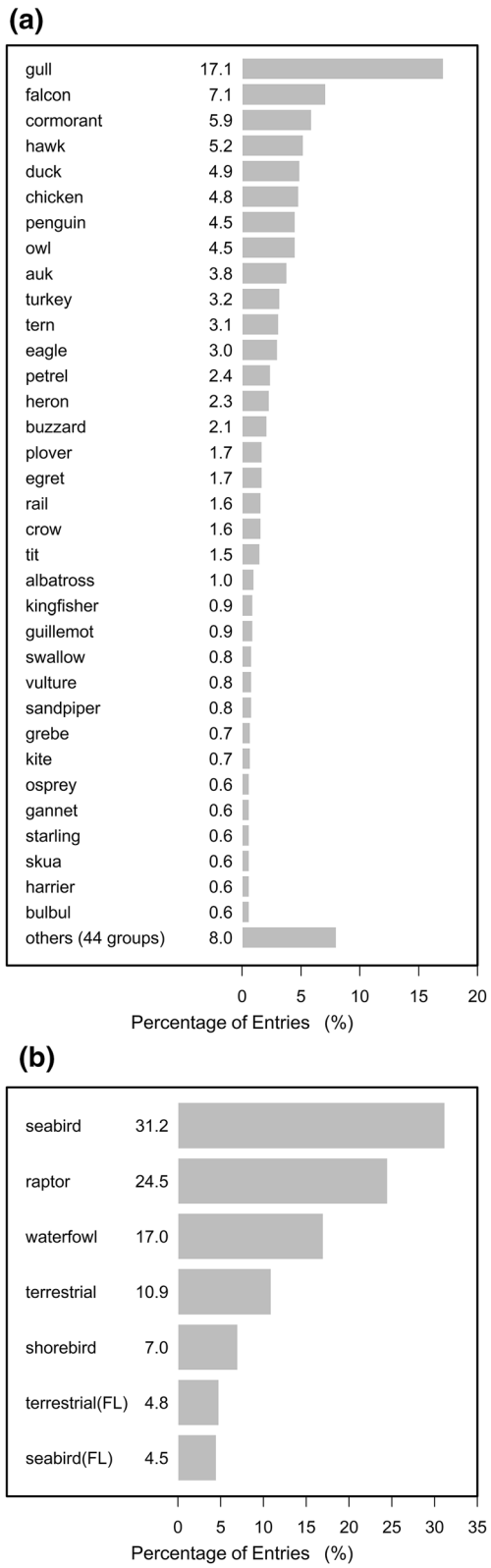


Fig. 6 Distribution of avian species in the field database (n = 17,485) by **a** common bird categories and **b** habitat groups. *FL* flightless

3.3 Enzyme/Microsomal Activity Database

The microsomal database contains > 1700 entries gathered from > 80 references. It covers 78 bird species and 66 chemicals or exposure conditions (e.g., chemical mixture, crude oil, baseline reference response, etc.). Sampled birds are split evenly between domestic and wild species, with quail, duck, gull, and chicken as the major test species (Fig. 7a). Overall, microsomal enzyme activities are mostly associated with terrestrial birds, seabirds, and waterfowl (Fig. 7b). Records encompassing shorebirds are rare.

A wide variety of enzymatic assays are used on cellular fractions isolated from liver. Microsomal enzyme activities (i.e., of P450 isozymes) are measured mostly as biomarker endpoints (e.g., 7-ethoxyresorufin-O-deethylase (EROD)) and a measure of cytochrome P450 1A (CYP1A) activity. Assays on hepatic fractions account for 86% of the entries, followed by renal and intestinal fractions. Over 40 different enzymatic responses are noted, with EROD, hydroxylase, and *N*-demethylase constituting nearly half of the records (Fig. 8a). A detailed breakdown of enzymatic assays by metabolism phase, assay substrates, and test frequency is presented in Table 3. Chemicals tested using generic fractions (e.g., microsomal, S9) are summarized in Supplementary Information S3. Commonly used substrates include: (i) aminopyrine and various alkylresorufins for dealkylases; (ii) aldrin for epoxidase; (iii) aniline, benzo(a)pyrene, and coumarin for hydroxylases; (iv) various nitroaromatics for GST; and (v) *p*-nitrophenol and *o*-aminophenol for uridine diphosphate glucuronyl transferase (Table 3).

Enzymatic activities are often reported without adequate exposure or body burden quantification of avian field samples. Half (50%) of the records are without well-defined chemical exposure or dosage data, and the remaining entries are principally associated with PCBs, heterocyclics, organochlorines, and PAHs (Fig. 8b). Even for domestic birds exposed under controlled settings, 30% of the records have no chemical dose or body/tissue burden information. Approximately, 25% of the data entries are associated with wild birds without contaminant exposure characterization, and nearly 7% of the entries are obtained from known contaminated sites. Characterizing background levels of myriad of contaminants in birds from heavily polluted sites is analytically challenging with the limited tissue/matrix samples available, and relatively few studies attempt quantify a broad suite of contaminants of interest.

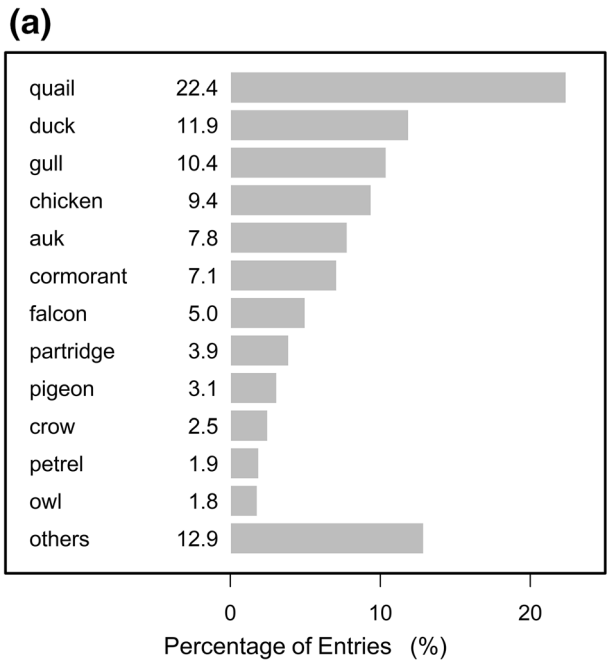


Fig. 7 Distribution of avian species in the microsomal database (n = 1712) by **a** common bird categories and **b** habitat groups. *FL* flightless

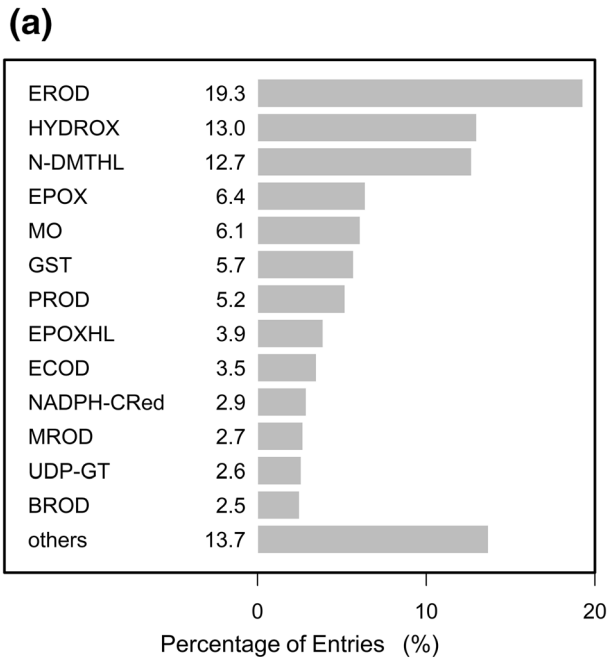


Fig. 8 Distribution of measurement in the microsomal database (n = 1712) by **a** enzymatic test and **b** exposure conditions (full descriptions for the abbreviated tests are available in Table 3)

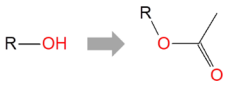
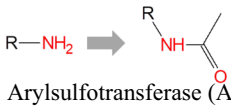
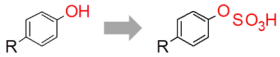
The current data entries include exposure to various inducers or inhibitors of enzymes. These include 3-methylcholanthrene, phenobarbital, β-naphthoflavone, isosafrole, and α-naphthoflavone (i.e., under "*others*" in Fig. 8b). These reagents do not have direct environmental relevance.

Most records in the database lack adequate documentation of exposure condition and P450 enzyme/microsomal characterization. Exposure dosage and duration are only reported in 45% and 30% of the entries, respectively. Partial or full biometric information has been provided in 74% of the records. Despite the interest of most studies on enzymatic activities of the cytochrome fraction, only 44% and 9% of the entries have reported P450 and cytochrome b_5 concentration or activity, respectively. Approximately,

Table 3 P450s with chloroplast or mitochondiral targeting signals

Phase	Category	Specific enzyme	Substrate used	Frequency
I	Dealkylases	N-demethylase (N-DMTHL)	Aminopyrine	171
			o-Ethylmorphine	14
			Benzphetamine	12
			Erythromycin (ERND)	6
			Aniline	5
			Ethylmorphine	5
			Methylaniline	4
			N,N-dimethylaniline	4
			p-Nitroanisole	3
		O-demethylase	*p*-Nitroanisole	15
		O-deethylase/O-dealkylases	Ethoxyresorufin (EROD)	306/24
			Methoxyresorufin (MROD)	28/18
			Pentoxyresorufin (PROD)	65/24
			Ethoxycoumarin (ECOD)	36/24
			Benzyloxyresorufin (BROD)	18/24
			Methoxycoumarin (MCOD)	—/20
			Propoxycoumarin (PCOD)	—/20
			Butoxycoumarin (BCOD)	—/2
	Epoxidase	Epoxidase (EPOX)	Aldrin	110
	Epoxide hydrolase	Epoxide hydrolase (EPOXHL)	HEOM[a]	32
			Styrene oxide	7
	Esterase	Esterase (ESTR)	Procaine	3
	Hydroxylases	Aryl hydrocarbon hydroxylase (AHH)	Benzo(a)pyrene	9
	R—H ➡ R—OH	Hydroxylase (HYDROX)	Aniline	129
			Benzo(a)pyrene	35
			Coumarin (COH)	34
			4-Chlorobiphenyl	24
			Hexachloroethane	12
			Biphenyl	10
			HCE[a]	7
			HEOM	2
			p-Nitrophenol	2
			Testosterone	2
	Oxidase	N-oxidase (N-OXID)	*N,N-dimethylaniline*	4
	$R—NH_2 \rightarrow R—NH_2^+O^-$			
	Oxidoreductases	NADPH/NADH cytochrome *c* reductase (NADPH-CRed/NADH-CRed)		49/21
	$NADPH \rightarrow NADP^+ + H^+ + 2e^-$	NADH ferricyanide reductase (NADH-FeCNRed)		7
		NADPH oxidase (NADPH-OXID)		2

Table 3 continued

Phase	Category	Specific enzyme	Substrate used	Frequency
II	Transferases	Acetyltransferase (ATT)	Sulfamethazine	3
				
		N-acetyltransferase (N-ATT)	2- Aminofluorene	1
			p-Aminobenzoic acid	1
			β-naphthylamine	1
			Isoniazid	1
			Sulfamethazine	1
		Arylsulfotransferase (ARYLST)	2-Naphthol	3
				
		Sulfotransferase (SFT)	Estrone	1
			2-Naphthol	1
			Dehydroepiandrosterone	1
			Taurolithocholate	1
		Glutathione S-transferase (GST)	*p*-Nitrophenol	18
			1-Chloro-2,4-dinitrobenzene	15
			1,2-Dichloro-4-nitrobenzene	7
		(GS-H = glutathione)	Dinitrobenzene	4
			Sulfobromophthalein	1
			Ethacrynic acid	1
			Trans-4-phenyl-3-buten-2-one	1
			1,2-Epoxy-3-(p-nitrophenoxy) propane	1
		Uridine diphosphate glucuronyl transferase (UDP-GT)	*o*-Aminophenol	18
			p-Nitrophenol	6
			Bilirubin	1
			Chloramphenicol	1
			Diethylstilbestrol	1
			Digitoxigenin-monodigitoxoside	1
		(X = target chemical/xenobiotic; glucuron = glucuronyl)	Estrone	1
			Morphine	1
			1-Naphthol	1
			Phenolphthalein	1
			Testosterone	1
			Valproic acid	1

[a]HCE = 1,2,3,4,9,9-hexachloro-1,4,4,a,5,6,7,8,8a-octahydro-exo-7,8-epoxy-1,4-methanonaphthalene, HEOM = 1,2,3,4,9,9-hexachloro-1,4,4,a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4-methanonaphthalene

43% of entries have reported tissue mass-based microsomal protein.

3.4 Metabolic Pathway Database

The pathway database covers 49 avian species and 56 parent organic chemicals or chemical groups. Nearly, 70% of the entries are associated with tissues from domesticated bird while the rest are related to the wild species (9% in captivity, 91% raised wild). Identification of metabolites or the metabolic pathway has been primarily conducted on liver, egg, plasma, and muscle (Fig. 9a). Approximately, 85% of the metabolite entries are from in vivo exposure. Metabolic pathway is available for mostly veterinary chemicals or common xenobiotics except PBDE 47 and PBDE 99. A breakdown of data entries by chemical group is shown in Fig. 9b.

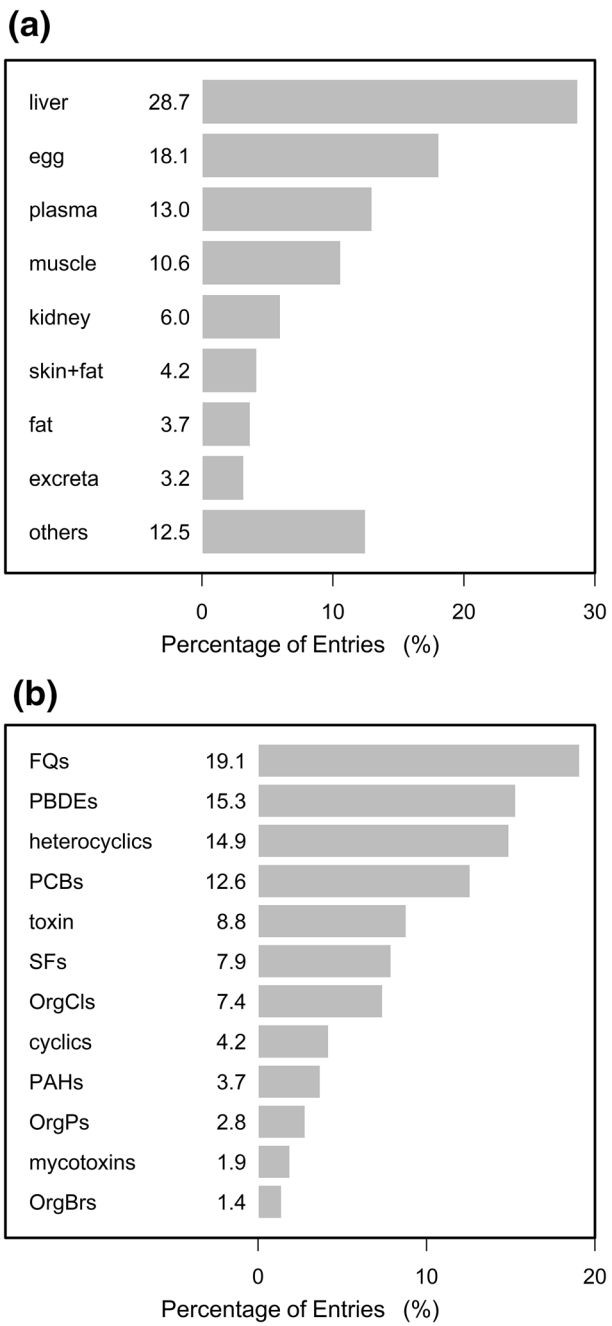


Fig. 9 Distribution of data in the pathway database ($n = 216$) by **a** tissue/matrix and **b** chemical groups. *FQ* fluoroquinolone, *HOC* hydrophobic organic compound, *OrgBr* organobromine, *OrgCl* organochlorine, *OrgP* organophosphorus, *PAH* polynuclear aromatic hydrocarbon, *PBDE* polybrominated diphenyl ether, *PCB* polychlorinated biphenyl, *SF* sulfonamide

3.5 Bird Taxonomy and Diet Database

A total of 320 avian species, 62 poultry breeds, and 8 generic groups are documented in this review. These species and breeds are taxonomically grouped under 21 orders and 56 families. The 62 poultry breeds are mostly associated with chicken ($n = 37$), turkey ($n = 10$), duck ($n = 5$), and goose ($n = 2$). Eight generic groups are used to designate birds without clear taxonomic description.

The distribution of species and breed among the different orders, families, common groups, and habitat groups are documented in Supplementary Information S4. Wild birds are distributed across > 80 common groups, predominated by gulls, owls, terns, falcons, sandpipers, and cormorants (Supplementary Information Table S4.4 and Figure S4.3). Chicken, turkey, duck, and pigeon are the dominant domestic species. The documented birds have an average body mass that ranges from 8.1 g (White-bellied Sunbird, *Cinnyri talatala*) to 111,000 g (Common Ostrich, *Struthio camelus*).

The documented birds are well distributed across habitat group descriptors and diet guilds. The major habitat groups are terrestrial, seabirds, aquatic, raptors, shorebirds, and terrestrial (flightless). Diet classification (Wilman et al. 2014) shows that birds fall under one of four classes: carnivore (vertebrates-fish-carrion; 37%), omnivore (25%), invertebrate feeders (including insectivore; 20%), and granivore (14%). Birds with diets dominated by fruit or nectar are largely not represented in the current review. Quantitative descriptions of diet intake and foraging strategy are available (Supplementary Information Figure S4.5).

4 Primary B/BT/TK/PK Metrics for Modeling or Benchmarking

A total of 27 B/BT/TK/PK parameters are identified from the main B/BT database. They consist of 12 bioaccumulation metrics and factors, 3 biotransformation parameters, 3 toxicokinetic rate constants, and 9 pharmacokinetic variables (Table 4). These parameters are very diverse in both definition and derivation, and collectively provide a comprehensive picture of the biological fate of organic chemicals in birds. The full list of parameters includes more information than is required for practical modeling, risk assessment, chemical management, or public communication purposes. An ideal bioaccumulation parameter should be readily determined, widely used, and capable of reflecting the wide spectrum of organic chemicals.

Ten plausible parameters for further use in modeling or benchmarking are identified and proposed in the present review: *BFAF*, *BMF*, *BSAF*, *BWF*, *maxTF*, *TF*, k_T, clearance (*CL*), area under the curve (*AUC*), and elimination constant (k_{elim}). These parameters have a large number of observations (i.e., $n > 200$) and a large value range ($\sim$ 5–10 log units). An exception is clearance *CL* ($n = 167$), which was selected because it is useful for estimating the elimination of chemicals. Both k_{MB}

Table 4 Range of bioaccumulation, biotransformation, toxicokinetic, and pharmacokinetic parameters identified from the main B/BT database

Metric	Entries (*n*)	Range[a]	Range difference (log unit)[a]
Bioaccumulation (B)[b]			
BAF	40	–	–
BFAF	1673	2.6×10^{-6} to 13,000	− 5.6 to 4.1 [9.7]
BMF	1314	0.9×10^{-3} to 2400	− 3.0 to 3.4 [6.4]
BSAF	506	7.6×10^{-3} to 19,000	− 2.1 to 4.3 [6.4]
BWF	167	38×10^{-6} to 2.7	− 4.4 to 0.4 [4.8]
maxTF	747	62×10^{-6} to 3200	− 4.2 to 3.5 [7.7]
TF	263	40×10^{-6} to 290	− 4.4 to 2.5 [6.9]
ODF	95	8.0×10^{-3} to 360	− 2.1 to 2.6 [4.7]
OMF	113	0.10 to 1.9	− 1.0 to 0.29 [1.3]
MTBF	6	–	–
TPR_{ss}	113	0.11 to 15	− 0.95 to 1.2 [2.2]
TPR_{field}	17	–	–
Biotransformation (BT)[c]			
k_{PC}	39	–	–
k_{MB}	110	80×10^{-3} to 1300	− 1.1 to 3.1 [4.2]
$f_{MB/\Sigma MB}$	92	24×10^{-3} to 1.0	–
Toxicokinetic (TK)[d]			
k_{up}	15	7.2×10^{-3} to 0.60	− 2.1 to − 0.22 [1.9]
k_T	806	0.15×10^{-3} to 160	− 3.8 to 2.2 [6.0]
k_m	1	–	–
Pharmacokinetic (PK)[e]			
V_d	96	49×10^{-3} to 61	− 1.3 to 1.8 [3.1]
$V_{d,central}$	22	–	–
$V_{d,peripheral}$	7	–	–
$V_{d,SS}$	53	42×10^{-3} to 10	− 1.4 to 1.0 [2.4]
F	150	0 to 1.0	–
CL	167	0.28×10^{-3} to 23,000	− 3.6 to 4.4 [8.0]
AUC	199	2 to 4,700,000	0.21 to 6.7 [6.9]
k_{abs}	99	1.1×10^{-3} to 310	− 2.9 to 2.5 [5.4]
k_{elim}	204	92×10^{-6} to 1200	− 4.0 to 3.1 [7.1]

[a]Range and range difference are not computed for metrics with a small number of entries (i.e., $n < 50$). Values in square brackets represent range difference in log space

[b]Bioaccumulation metric values are presented in mixed units due to different concentration or normalization bases (i.e., volume plasma versus tissue weight; wet weight versus lipid weight). *BAF* = bioaccumulation factor, *BFAF* = biota-feed accumulation factor, *BMF* = biomagnification factor, *BSAF* = biota-soil/sediment accumulation factor, *BWF* = biota-water factor, *maxTF* = maximum transfer factor, *MTBF* = maternal transfer burden factor, *ODF* = ovo-diet concentration factor, *OMF* = ovo-maternal concentration factor, *TF* = transfer factor, *TPRss* = steady-state tissue-plasma ratio, *TPRfield* = field tissue-plasma ratio

[c]k_{MB} = metabolite formation rate ($pmol_{MB}/mg_{protein} \cdot min$), k_{PC} = metabolism rate ($pmol_{PC}/mg_{protein} \cdot min$)

[d]k_m = biotransformation rate constant (d^{-1}), k_T = total elimination rate constant (d^{-1}), k_{up} = uptake rate constant (d^{-1})

[e]*AUC* = area under curve (ng h ml^{-1}), *CL* = clearance rate (ml kg^{-1} min^{-1}), *F* = pharmacokinetic bioavailability, k_{abs} = absorption rate constant (min^{-1}), k_{elim} = blood/plasma elimination rate constant (min^{-1}), V_d = volume of distribution (L kg^{-1}), $V_{d,central}$ = volume of distribution in the central compartment (L kg^{-1}), $V_{d,peripheral}$ = volume of distribution in the peripheral compartment (L kg^{-1}), $V_{d,SS}$ = volume of distribution at steady state (L kg^{-1})

(metabolite formation rate) and $f_{MB/\Sigma MB}$ (fraction or yield of metabolite) are direct descriptors of biotransformation kinetics and pathways; with nearly 100 data entries, they are promising BT parameters. However, current k_{MB} and $f_{MB/\Sigma MB}$ values have been obtained from only a few references (n = 3 and 4, respectively), suggesting a lack of diversity in data sources. Consequently, no BT parameters have been identified as definitive metrics by the present review.

4.1 Screening for key B/BT/TK/PK parameters

The screening of the 10 candidate parameters along different parameter quality dimensions important for modeling or benchmarking is summarized in Table 5. *BFAF*, *BMF*, *maxTF*, and k_T all have a large number of data points. However, *BMF* along with *BSAF*, *BWF*, and *TF* may be less suitable because they have relatively few references. Abundant primary references can safeguard against potential laboratory/study-specific biases. A suitable parameter should also have broad coverage among avian species, both domesticated and wild. *BSAF*, *BWF*, and k_T can satisfy this criterion but not the remaining parameters (Table 5), as B/PK/TK data are reported more frequently for domestic species than for wild species (i.e., ~ 10 domestic breeds versus 1 wild species). No domestic bird has been covered in the *BMF* data subset, although particular poultry breeds (e.g., chicken, duck) have been extensively studied to yield *BFAF*, *BWF*, *BSAF*, and *maxTF*.

Different parameters seem to focus on different classes of chemicals and only limited parameters are able to capture all major contaminant groups. Overall, PK parameters (i.e., *CL*, *AUC*, k_{elim}) tend to cover polar and even hydrophilic chemicals but not legacy hydrophobic organic compounds (HOCs), whereas B metrics (i.e., *BMF*, *BSAF*) appear to have the opposite chemical coverage (Table 5). *BFAF*, *maxTF*, and k_T are the exceptional parameters that balance well across a wide log K_{OW} and chemical size range as well as different chemical classes and broader contaminant groups.

With respect to different habitat groups, terrestrial birds and waterfowl are generally well covered by all major metrics. *BMF* and k_T appear to have the broadest habitat group coverage, followed by *BFAF*, *maxTF*, and *CL* (Table 5). The mapping shows that observations of shorebirds, seabirds, and raptors are generally lacking.

The majority of the B metrics have abundant measurements for most of the major tissues/matrices except plasma (Table 5). *BFAF* stands out among the four *B* parameters with a large number of liver, fat, muscle, and egg measurements. *BMF* has good data coverage of whole body, egg, and muscle samples. *BSAF* data are predominantly related to egg and whole body so may be less preferable to *BFAF* or *BMF* in terms of tissue coverage. *BWF* is the only B parameter with plasma measurement because drinking water exposure experiments are frequently conducted in pharmacokinetic studies. *MaxTF* and k_T are the only parameters that capture all eight major biological matrices. With the PK parameters (*CL*, *AUC*, and k_{elim}) lacking measurements with nonplasma matrices (e.g., liver, muscle, or fat), it would be challenging to interpret these PK data in the toxicokinetic or PBPK modeling frameworks.

All 10 candidate parameters exhibited significant data gaps in particular parameter quality dimensions (Table 5). With limited observation ranges and complementary toxicokinetic measurements, the current avian data may be used to develop correlative bioaccumulation models with little mechanistic elements for specific chemical-biological space (e.g., *BMF* model for bioaccumulation of HOCs in waterfowl and terrestrial birds). However, the data cannot support the development of a full, life stage resolved avian bioaccumulation model with broad chemical and biological scope (e.g., foraging behavior and range, migration, trophic interactions).

While comprehensive modeling of avian bioaccumulation potential is currently unattainable, Table 5, nonetheless, indicate that *BFAF*, *maxTF*, and k_T may be more readily used in characterizing the avian bioaccumulation potential of organic chemicals. With strong data basis, broad chemical functionalities, and coverage of diverse avian species and habitats, these metrics may surpass other B/BT/TK/PK parameters for provisional use in bioaccumulation monitoring or benchmarking and can readily provide a preliminary understanding of avian bioaccumulation without extensive additional measurements. It may be possible to adopt *BFAF*, *maxTF*, and k_T for more critical roles in model development, method standardization, or even long-term ecological risk assessment of avian B/BT of organic chemicals. This adoption will require the mechanistic meanings of these metrics to be explored and elaborated, and their applications and limitations understood and illustrated using B data from different combinations of birds, chemicals, and biological matrices.

However, *BFAF*, *maxTF*, and k_T provide limited mechanistic insights into bioaccumulation under different exposure scenarios and should be complemented by other toxicokinetic measurements. *BFAF* and *maxTF* reflect the bioaccumulation potential of a chemical via controlled uptake but not that of exposure in field settings; k_T represents the total elimination potential of a chemical but does not provide the breakdown of different elimination mechanisms. Moreover, the three parameters are not direct indicators for the biotransformation potential of organic chemicals. Much theoretical groundwork remains to be completed for *BFAF* and *maxTF* regarding the

Table 5 Screening of 10 candidate avian bioaccumulation and biotransformation parameters along different dimensions[a]

Parameter	BFAF	BMF	BSAF	BWF	maxTF	TF	k_T	CL	AUC	k_{elim}
Meta data										
Data (*n*)	1673	1314	506	167	747	263	806	167	199	204
References (*n*)	55	11	7	14	82	11	88	52	57	60
Species	■	■	○	○	■	■	■■	■	■	■
Wild	○	■	○		○	○	■	○		
Domestic	■		○	○	■	○	■	■	■	■
Field		■■■■	■■	○			○			
Farm/laboratory	■■■■		■■■	■■	■■■	■■■	■■■	■■	■■■	■■■
LogK_{OW} and molecular weight										
LogK_{OW}										
< − 4					○		○		○	○
− 4 to 0	■■■			■	■■		■■	■	■	■
0 to 4	■■■			■	■■■	○	■■■	■	■■	■■
4 to 8	■■■	■■■■	■■■	■	■■	■■	■■■	■	■	○
> 8	■■■	■	■■		■	■	■	■		
Molecular weight (g/mol)										
< 100	■						○			
100 to 500	■■■	■■■■	■■■	■■	■■■	■■■	■■■	■■	■■	■■
> 500	■	■	■	○	■	■■	■■	■	■	■
Chemical groups										
PAHs						○				
PBDEs		■			■	■■	○			
PCDDs	■■■	■	■■			■	■			
PCDFs	■■■	■	■■			■	■			
PCBs	■■■	■■■■	■			■	■	■		
Organochlorines	■■■	■	■■	■	■	■	■	■		
Organobromines	○	○					■			
Organophosphorus					○		○			
Fluoroquinolones	○			■	■■■		■■	■	■	■
Cyclics					■	■	■	○	■	■
Heterocyclics	■			○	■		■	○	■	■
Tetracyclines	■			■			■	○	■	■
Sulfonamides	■■			■	■■	○	■■	○	■	■
Macrolides	■			○	○		■	○	○	○
PFCs[b]	■	■		○			■			
Toxins	■■				■			■	■	■
Contaminant groups										
Legacy HOCs[b]	■■■■	■■■■	■■■	■	■	■■	■■■	■		
Industrials	■	■		○	■	■■	■			
Pharmaceuticals	■■■			■■	■■■	■	■■■	■■■	■■	■■
Agrochemicals	■				■		■	○	○	○
PCPs[b]						■				
Habitat groups										
Waterfowl	■■	■■■	■	■	■	■■	■■	○	■	■
Shorebird		■					○			
Seabird		■			■		■	■		
Seabird (flightless)							○			

Table 5 (continued)

Parameter	BFAF	BMF	BSAF	BWF	maxTF	TF	k_T	CL	AUC	k_{elim}
Raptor	■	■				■	■	■		
Terrestrial	■	■■■	■■	■	■	■	■■	■	■	■
Terrestrial (flightless)	■		■■■	■■	■■■	■	■■■	■■	■■	■■
Tissues										
Whole body	■	■■■	■		○		■			
Muscle	■■■	■■	○	■	■■	■	■■	○	○	○
Plasma				■	■■■	○	■	■■	■■■	■■■
Fat	■■■		○	○	■	■	■			
Liver	■■■	■	○	■	■	■	■■		○	○
Kidney	■			■	■	○	■		○	○
Egg	■■■	■■■	■■■	■	■	■■	■	○	○	○
Feather					○		○			

[a]Blank cell = no entries, ○ = $n < 10$, ■ = $10 \leq n < 100$, ■■ = $100 \leq n < 200$, ■■■ = $200 \leq n < 1000$, ■■■■ = $n > 1000$ entries. *AUC* area under curve, *BFAF* biota-feed accumulation factor, *BMF* biomagnification factor, *BSAF* biota-soil/sediment accumulation factor, *BWF* biota-water factor, *CL* clearance rate, *HOC* hydrophobic organic compound, *maxTF* maximum transfer factor, *PCP* personal care product, *PFC* perfluorinated chemical, *TF* transfer factor, k_T total elimination rate constant, k_{elim} blood/plasma elimination rate constant

[b]*C&M byproducts* = combustion and manufacturing byproducts, *PCP* = personal care product, *PFC* = perfluorinated chemical

toxicokinetics of different uptake scenarios. Although the toxicokinetic role of k_T is well established in whole-body B/TK models for fish and invertebrates (see Sect. 1.4), its dependence on specific tissue, biological species, life stage events, and exposure media and modes is less understood. Exploring these aspects with the compiled avian data is a logical step toward building a broad-spectrum avian B/BT model.

4.2 Multipronged characterizations of biotransformation

Biotransformation of organic chemicals in birds has been investigated from a number of directions through different methodologies. These approaches generate characterizations that may be classified into six categories: (i) identifying of metabolites, (ii) deciphering metabolic pathways, (iii) monitoring of metabolic enzyme activities, (iv) quantifying parent compound depletion and metabolite formation, (v) characterizing transformation kinetics at the enzyme–substrate level (i.e., rate per mass protein basis), and (vi) characterizing metabolic kinetics at the whole-organ or whole-body level (i.e., rate per mass tissue/body weight basis). A graphical summary of these categories is provided in Fig. 10. All six aspects of biotransformation are interrelated and interdependent. Collectively, they are important for a thorough assessment of the ecotoxicological and environmental risks of an organic chemical (or a contaminant family). Identification of metabolites, for instance, can help uncover metabolic derivatives with high toxicity potential (e.g., paraoxon). This is the first critical step prior to any pathway analysis or kinetic investigations. The metabolic pathway needs to be established if understanding metabolite formation kinetics is the goal. Similarly, enzymatic activities provide insight into the biochemical regulation and response under chemical exposure.

A total of 149 in vitro biotransformation related rate constants have been compiled in the main database. These include 39 parent chemical transformation rate constants and 110 metabolite formation rate constants for 6 and 4 parent compounds, respectively (Table 4). This review demonstrates a significant lack of avian in vivo biotransformation rate constants ($n = 5$ for 2 chemicals). Most in vivo characterizations have been limited to identification/measurement of metabolites or their fractions.

Microsomal enzymatic studies appear to dominate the characterization of avian biotransformation research. The microsomal database ($n = 1712$) is considerably larger than the pathway database ($n = 216$), the in vitro rate constants ($n = 149$), or the metabolite fractions ($n = 92$; main database) (Table 8). Metabolic pathway is only proposed in 20% of the entries in the pathway database. These proposed pathways are mostly associated with poultry and domesticated species (e.g., Japanese Quail, *Coturnix japonica*) and only three wild species are examined (one goose and two passerines). This demonstrates a lack of focus on top predators (e.g., raptors) as well as shorebirds, seabirds, and terrestrial birds. Furthermore, these proposed pathways correspond to 13 chemicals, mostly poultry-related veterinary drugs and aflatoxins with PBDE 47 and PBDE 99 as the only recognized hydrophobic contaminants. Additional

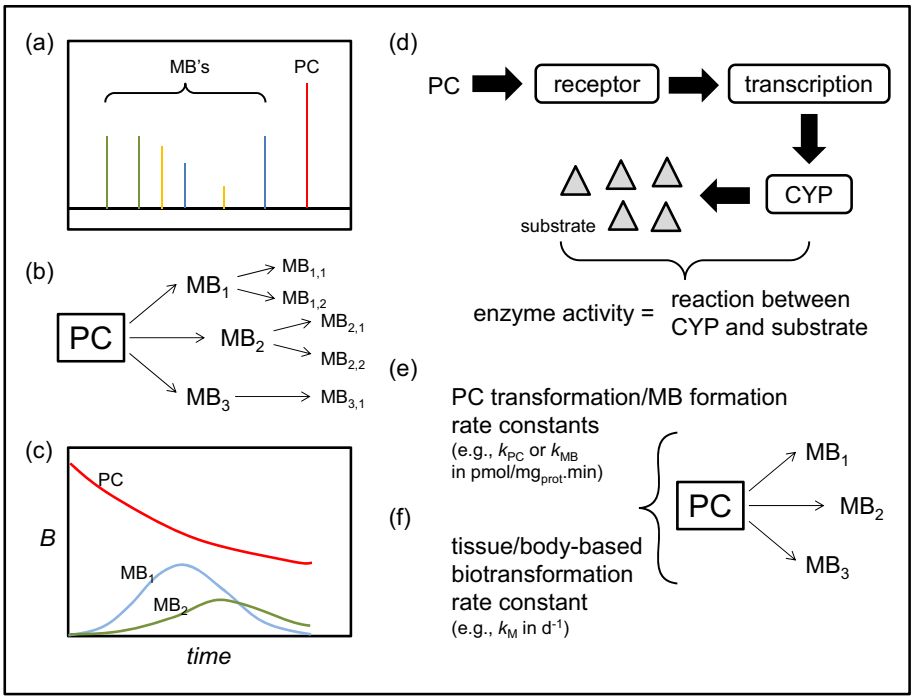


Fig. 10 Characterization of chemical biotransformation in birds: **a** metabolite identification, **b** pathway determination, **c** biotransformation tracking, **d** metabolic enzyme activity monitoring, **e** characterization of biotransformation kinetics at the microsomal level, and **f** characterization of biotransformation kinetics at the whole-organ or whole-body level. *B* bioaccumulation, *CYP* cytochrome P450, *MB* metabolite, *PC* parent compound

metabolites are reported from various B/BT/TK/PK studies as well as field studies. Further discussions of the metabolite structure and microsomal activity data are presented in Sects. 4.3 and 4.4 respectively.

Overall, biotransformation characterization studies are shifting from microsomal activity responses toward biotransformation kinetics across different chemical classes. Based on references compiled in the present review, microsomal enzymatic tests were adopted as the primary study focus between the 1970s and 2000s, but later receded into an ancillary role in more recent biotransformation studies. Such a shift likely reflects growing interest in toxicokinetics and the development of process-based bioaccumulation/biomagnification models. BT kinetic investigations are becoming commonplace, however only a few species are being examined. Existing BT kinetic data (i.e., parent compound transformation rate constant, metabolite formation rate constant, metabolite fraction) are distributed between wild and domesticated species at 3:2 ratio. However, only four wild species have been studied for BT kinetics: Mallard, Snow Goose (*Chen caerulescens*), Herring Gull, and Common Merganser (*Mergus merganser americanus*). Top predatory birds under represented in the BT kinetic data. Most BT kinetic data are obtained in vitro or in ovo; metabolite fractions can be determined in pharmacokinetic studies if the evolution of metabolites is monitored.

4.3 Metabolites in the Main and Field Databases

More than 100 metabolites have been identified in various laboratory and field studies. These metabolites are categorized into 12 groups according to their transformation pathways (i.e., "*MetaboliteType*" in the main and field databases). A summary of the abundance of metabolites by their parent compound structure/class is provided in Table 6.

Of the field studies, > 99% of the identified metabolites entries (n = 1882) are associated with legacy organochlorines (e.g., dichlorodiphenyldichloroethylene, chlordanes, heptachlor), PCBs, and PBDEs (Table 6). These metabolites are mostly dechlorinated (44%), oxygenated (22%), hydroxylated (18%), and sulfonated (13%) intermediates.

A greater variety of metabolites is observed in the B/BT/TK/PK studies (i.e., the main database) where metabolites associated with organochlorines (49%), sulfonamides (24%), and fluoroquinolones dominate (9%) (Table 6). Interest in sulfonamide and fluoroquinolone metabolism mostly originated from their veterinary pharmaceutical applications. A substantial number of metabolites (14%) are identified for parent compounds in other families (i.e., cyclics, heterocyclics, tetracyclines, etc.), and other veterinary pharmaceuticals. Dechlorination (29%), hydroxylation (20%), and oxygenation (13%) dominate the metabolic processes in the main database.

4.4 Enzymatic Activity and its Dependence

With the lack of chemical exposure/dosage characterization and compound variety, a macroscopic assessment of dose-dependent activity across different chemical functionalities and metabolic enzymes may be difficult. Enzymatic activity generally reflects exposure condition (e.g., chemical concentration and uptake rate, or dosing level and dietary intake frequency), duration of exposure, and compound chemistry. Chemical acclimatization (development of tolerance), tissue specificity, and interspecific difference can influence enzymatic response. The interplay of these factors on dose-dependent activity relationships in the metabolism of xenobiotics is complex and difficult to delineate based on existing data and studies (Abiola et al. 1989; Brausch et al. 2010; De Roode et al. 2002; Elliott et al. 1997; Lavrijsen et al. 1990; McKernan et al. 2009; Miranda et al. 1987; Powell et al. 1998). The task is sometimes exacerbated by low sensitivity of enzymatic response to chemical exposure level, with activity varying by no more than 30% for a factor of 10 difference in dose or concentration (Lavrijsen et al. 1990; Elliott et al. 1997; Powell et al. 1998).

4.4.1 Dose-Dependent Responses in Avian Enzymatic Activity

Four broad types of dose-dependent enzyme activity behavior (i.e., plateau, peaking, increasing, and declining) may be identified from the reported data (Supplementary Information S5). In the first type, enzyme activity increases with the logarithm of applied chemical dose. This is observed in various hepatic and renal hydroxylase, O-deethylase (e.g., EROD, PROD), and N-demethylase activities. In the second type, a plateau response in activity is observed at varying dose levels. This has been seen in

Table 6 Frequency and types of metabolites by parent compound chemical group reported in the main database and the field database[a]

Metabolite type	Cyc	FQs	HetCyc	OrgCls	PAHs	PBDEs	PCBs	SFs	TetCyc	Others
Main database (n = 510 entries)										
Addition										
Acetylated								39		2
Aminated	5		6							
Glucuronidated								17		
Hydroxylated		6	6			26		63		
Methylated			4							
Oxygenated		11		66						
Sulfonated				32						
Removal/cleavage										
Dechlorinated				147						
Dehydroxylated	4									
Demethylated		16								
Deoxygenated			2							
Others[b]	12	11	8	4				1	3	19
Field database (n = 1882 entries)										
Addition										
Hydroxylated				15	6	41	285			
Methylated						23	3			
Oxygenated				407						
Sulfonated				30		18	196			
Removal/Cleavage										
Dechlorinated				835						
Others[b]	4			19						

[a]*Cyc* cyclic, *FQ* fluoroquinolone, *HetCyc* heterocyclic, *OrgCl* organochlorine, *PAH* polycyclic aromatic hydrocarbon, *PBDE* polybrominated diphenyl ether, *PCB* polychlorinated biphenyl, *SF* sulfonamide, *TetCyc* tetracycline. Note blank cell = no entries

[b]Other transformation pathways. See "*MetaboliteType*" in the main and field databases

several alkylresorufin O-deethylases, alkylcoumarin O-deethylase, and N-demethylase activities. The third response type is a decline of enzymatic activity with increasing dose, indicative of inhibition. While less frequently observed, it has been reported for coumarin 7-hydroxylase in Grey Partridge (*Perdix perdix*), alkylcoumarin O-deethylases in Japanese Quail, and NADPH cytochrome *c* reductase in Northern Bobwhite (*Colinus virginianus*). Finally, peaking and/or saturation of metabolic activity has been reported in selected bird-enzyme combinations. Varying enzymatic responses likely reflect the differences in enzyme–substrate interaction kinetics and the biochemical regulation of the detoxification processes in various species of birds.

4.4.2 Non-chemical Factors on Microsomal Enzymatic Responses

Further quantitative interpretation of dose-dependent activity responses in enzymatic or microsomal studies may be challenging due to several nonchemical factors that could influence kinetics. Significant intraspecific variation in enzymatic response by as much as two orders of magnitude has been observed in puffins (*Alcidae*) and razorbills (*Alcidae*) exposed to persistent organochlorines (Walker 1990). However, such variation could not be solely explained by differences in body size within the population (Ronis and Walker 1989). Enzyme responses may vary among tissues and organs. For instance, increased exposure to PCBs led to higher ECOD and EROD activities in the intestinal fraction but lower activities in the hepatic fraction of Japanese Quail (Miranda et al. 1987). Similarly, opposing dose-dependent activity responses were reported across different hepatic enzymes (Supplementary Information S5) from Grey Partridges after a 2-week PCB exposure (Abiola et al. 1989). Species difference can also be important. For instance, increasing the exposure to PBDE-71 has induced higher EROD activity in domestic chicken but no change activity was apparent in Mallard and American Kestrel (McKernan et al. 2009). Such variation in response may be related to diet speciation in different avian species (Walker 1990).

Activity varies with exposure duration, suggesting the importance of kinetics and sampling timing. For example, EROD activity reached steady state within 1–3 days at low doses of benzo(a)anthracene but took as long as 30 days to plateau at a higher dose (Brausch et al. 2010). The role of exposure duration was apparent in findings reported by Elliott et al. (1997) and Lavrijsen et al. (1990). The dependence of enzymatic activities on exposure duration implies that enzymatic characterizations after short-term exposure may not be extrapolated for interpreting enzymatic responses in wild birds that may be continuously exposed.

Finally, acclimatization can influence enzyme activity response significantly as well. De Roode et al. (2002) showed that a more pronounced and dramatic EROD response was elicited in Common Murre (*Uria aalge*) inhabiting the heavily polluted Baltic Sea but not in guillemots from the Atlantic Ocean. The influence of these nonchemical factors on metabolic enzymes activities suggests that sufficient observations will be needed before the responses can be quantitatively linked to different avian species and different chemicals. It is also critical to consider exposure to chemical mixtures that may have synergistic or antagonistic effects on the direction or level of responses.

4.5 Taxonomic Distribution

Overall, all four databases seem to have a good distribution with respect to taxonomic orders and families. A total of 12–19 avian orders and 17–49 families are compiled in the four databases. A summary of the taxonomic presence of different orders and families among the four databases is presented in Table 7. As expected, the field database has the highest taxonomic diversity (19 orders and 49 families), with 17 of the families having > 200 data entries. This is followed by the main database (6 families with ≥ 200 entries) and the microsomal database (2 families with ≥ 200 entries). Because the pathway database is relatively small, none of the families have ≥ 200 entries, with Phasianidae (chickens, quail, partridges) having the most ($n = 127$).

5 Data and Knowledge Gaps and Future Needs

This work reveals a general lack of critical data for constructing a broad-scope avian bioaccumulation model under either laboratory or field exposure conditions. The classical bioaccumulation metrics relevant to birds—*BAF*, *BMF*, and *BSAF*—are lacking in quantity (i.e., *BAF*) and in data sources (i.e., *BMF*, *BSAF*), and are mostly limited to HOCs (i.e., log $K_{OW} \geq 4$). For toxicokinetics, although the total elimination rate constant (k_T) is widely available ($n > 800$) and has broad coverage among chemicals, habitat groups, and biological matrices (Table 5), the uptake rate constant (k_{up}) is rarely reported (i.e., 15 entries from 2 studies only, $< 1\%$ in both total data entries and studies in the main database). Consequently, toxicokinetic- or physicochemical-based modeling of the classical bioaccumulation metrics cannot be completed due to the

Table 7 Avian orders and families documented in the four databases in this review

Order and family	Main	Field	Microsomal	Pathway
Accipitriformes				
Accipitridae	■	■■■■	■	○
Anseriformes				
Anatidae	■■■	■■■	■■■	■
Cathartiformes				
Cathartidae		■		
Charadriiformes				
Alcidae	○	■■■	■■	○
Charadriidae	○	■■■		
Chionidae		■		
Haematopodidae	○	■		
Laridae	■■■	■■■■	■■	■
Recurvirostridae	○	○		
Rostratulidae		○		
Scolopacidae	○	■■■	○	
Stercorariidae		■■		○
Ciconiiformes				
Ciconiidae		■		
Columbiformes				
Columbidae	■	■■	■	○
Coraciiformes				
Alcedinidae	○	■■		
Falconiformes				
Falconidae	■■■	■■■■	■	■
Galliformes				
Odontophoridae	■	○	■■	
Phasianidae	■■■■	■■■■	■■■	■■
Gaviiformes				
Gaviidae		■		
Gruiformes				
Rallidae		■■■	○	
Otidiformes				
Otididae			■	
Passeriformes				
Acrocephalidae	■			
Corvidae	■	■■■	■	
Dicruridae		○		
Estrildidae	■	○		
Hirundinidae	■■■	■■		
Icteridae	■	■	○	
Laniidae		○		
Mimidae		○		
Muscicapidae		■		
Nectariniidae				○
Paridae	■	■■■		
Passerellidae	○	○		
Passeridae		○	■	
Pycnonotidae		■■	○	
Sturnidae	■	■■	○	○
Sylviidae		○		
Troglodytidae	■■■	○		
Turdidae	○	■	○	
Zosteropidae				○
Pelecaniformes				
Ardeidae	■■	■■■	■	○
Pelecanidae		■		
Scopidae		○		
Threskiornithidae		■		
Phoenicopteriformes				
Phoenicopteridae		■		
Podicipediformes				
Podicipedidae	■	■■	○	
Procellariiformes				
Diomedeidae		■■■	○	
Hydrobatidae			○	
Procellariidae	○	■■■	■	○
Sphenisciformes				
Spheniscidae	■	■■■		○
Strigiformes				
Strigidae		■■■		○
Tytonidae	○	■■	■	○
Struthioniformes				
Struthionidae	○		○	
Suliformes				
Anhingidae		■		
Phalacrocoracidae	■	■■■■	■■	○
Sulidae		■■		

[a]○ = $n < 10$, ■ = $10 \leq n < 100$, ■■ = $100 \leq n < 200$, ■■■ = $200 \leq n < 1000$, ■■■■ = $n > 1000$ entries

paucity of relevant data. Specific challenges, data gaps, and associated research needs are discussed below.

5.1 Research Limitations and Technical Constraints

The shortage of B/BT data is partly the consequence of various research limitations and technical constraints. In field samples obtained at highly contaminated sites, limited sample mass for various biological matrices from individual birds can limit the number of chemicals to be analyzed, due to their body size, or can even make measurement impossible. Accurate characterization of *BMF* requires chemical concentrations of the diet, necessitating accurate

chemical analysis of "stomach" (proventriculus and gizzard) content, the quantity of which is generally low in birds. It is unclear to what extent the digestive tract content and dietary chemical concentration vary with time and space for birds with different foraging strategies and habitats. In addition, a portion of sample may be needed for lipid/protein characterization. The use of species-average body and tissue weights or tissue-specific average lipid/protein content may not always be feasible without incurring substantial uncertainties. For instance, lipid content can change dramatically in migratory seasonal breeders (Karasov and Pinshow 1998) due to a switch from a carbohydrate-based to lipid-based energy pathway (Jenni-Eiermann et al. 2002). Furthermore, intra-tissue distribution of lipid to organ mass may not be uniform and tissue homogenization is needed prior to lipid/protein analysis.

The second constraint in the study of avian bioaccumulation is the absence of species diversity in mechanistic studies. B/PK/TK data are reported more frequently for domestic species than for wild species (i.e., ~ 10 domestic breeds to 1 wild species). Only 15 wild species were used in various B/BT/TK/PK experiments (i.e., excluding field biomagnification studies) and this is barely 6% of the number of wild species documented in the field database (i.e., 281 species). Few wild species are not used in controlled studies because of their protected status and the challenge of maintaining them in a healthy state in captivity. A way to circumvent the issue may be to adopt new wild birds for regular laboratory studies with diet mimicking that in the wild; however, this will require the establishment of long-term avian research colonies with a well-supported facility, committed research staff, and continuous funding.

5.2 Chemical Diversity

Greater diversity in target chemicals is needed for different contaminant groups to provide a more robust understanding of B/BT in avian species. Legacy HOCs and emerging industrial chemicals dominate 99% of the field database entries. In the context of birds, expansion toward pharmaceuticals, agrochemicals, personal care products, emerging chemicals of concern, and mixtures in combination with legacy chemicals (e.g., PCBs) that continue to be accumulated is needed to better reflect actual environmental exposure. The limited PAH data in field surveys should be addressed; their ubiquity in various terrestrial and aquatic ecosystems makes them and their metabolites excellent benchmarking compounds for birds (Fernie et al. 2018a, b).

5.3 Biotransformation at Exploratory Phase

5.3.1 Challenges in Characterizing Biotransformation

Generally, biotransformation characterization in birds is at the exploratory stage. Less than 10% of the reviewed chemicals have been characterized in some quantitative way for biotransformation; similarly, metabolite entries make up ~ 10% of those in both the main and field databases. These characterizations are scattered among transformation kinetics, enzyme activities, metabolite identification, and pathway analysis. Furthermore, benchmark chemicals are currently lacking, as only a limited number of compounds have been thoroughly characterized in all aspects of their metabolism (i.e., kinetics, pathway, enzymatic induction/inhibition, etc.). The challenge of quantifying metabolites without suitable analytical standards and the difficult task of deciphering plausible transformation pathways from a myriad of raw spectral signals have driven experimental studies toward more qualitative ends.

The ongoing exploration of mathematical frameworks for biotransformation kinetics and the diverse scientific endpoints of existing metabolic studies have contributed to the current state of knowledge. Plausible biotransformation parameters for future studies include *metabolite formation rate* (Briels et al. 2018; Honey et al. 2000; Krieger et al. 2017) and *metabolite fraction* ($f_{MB/\Sigma MB}$) (both having approximately 100 data entries) as well as *metabolism rate* ($n = 40$) (Briels et al. 2018; Greaves et al. 2016; Honey et al. 2000). The *metabolite formation rate* may have the most potential for modeling, as it can be converted to both *metabolite fraction* and *metabolism rate*; however, all existing rate data have been obtained from only three references, suggesting a lack of diversity in data source and the need for further research for better characterization and understanding. All three BT parameters are predominantly associated with in vitro studies, with the work of Briels et al. (2018) as the only exception. Most of the in vivo BT data entries ($n = 534$) have reported concentrations of a parent compound (36%) and/or metabolites or merely qualitative identification of specific metabolites (52%). The general lack of quality BT data/parameters implies that large-scale meta-analysis and mechanistic modeling of biotransformation of organic chemicals in birds is still not possible.

Additional data and theory gaps deserve further attention and research effort. There is a strong need for in vivo biotransformation data, as current BT kinetic data are

associated only with in vitro and *in ovo* studies. Even if the long-term direction is toward in vitro characterizations, following the development of in vitro protocols with fish (OECD 2018a, 2018b), a set of reference in vivo measurements will help fill data gaps.

5.3.2 Microsomal Assays and Metabolic Profiles

More high-quality data are needed on biotransformation using microsomal-based assays and the pathway database (Phase I and II metabolism). The current pathway database is relatively small in size ($n = 216$). Less than 10% of the > 700 chemicals/chemical groups reviewed here have any documentation on metabolites/metabolic pathways, suggesting biotransformation is underinvestigated. Furthermore, test substrates for various enzyme tests (e.g., dealkylases, hydrolases) need to be standardized for methodological consistency. Some of the commonly employed substrates (i.e., Sect. 3.3 and Table 3) can serve as candidates.

Expansion of the pathway database and metabolite profiles can help identify potentially toxic metabolites and support interspecies comparisons of metabolic pathways. Currently, in vitro entries account for only 15% of the pathway database. Future research activities should align with the long-term goal toward in vitro ecotoxicological characterization while ensuring that such in vitro characterizations accurately reflect what occurs in vivo (i.e., in vitro in vivo extrapolation). Field measurements can be very useful if the dominant metabolites can be identified and reported along with the tissue/matrix concentration of the target chemical. Such information enables qualitative interspecies comparison of biotransformation pathways and serves as a starting point for further toxicokinetic-oriented investigations. Additional in vitro data can support the development of bridging protocols between in vitro and in vivo BT results.

5.3.3 New Enzyme Pathways: AO and FMO

Investigation should be expanded from cytochrome P450 to aldehyde oxidase (AO) and flavin containing monooxygenase (FMO)—two superfamily enzymes with potential to biotransform xenobiotics. AOs and FMOs are broad-spectrum enzymes active in phase I metabolism of xenobiotics (Kitamura et al. 2006; Cashman 2008; Garattini and Terao 2012; Huijbers et al. 2014; Fan et al. 2016). AOs are molybdo-flavoenzymes that can oxygenate a wide range of aza- and oxo-heterocycles (Kitamura et al. 2006; Garattini and Terao 2012; Fan et al. 2016; Lepri et al. 2017) and the hydrolysis of amides (Lepri et al. 2017). FMOs metabolize nucleophilic heteroatom-containing chemicals (Cashman 2008; Rossner et al. 2017) and include various monooxygenases, hydroxylases, epoxidases, and reductases (Huijbers et al. 2014; Rossner et al. 2017). AO and FMO are potentially important pathways for the metabolism of xenobiotics. For instance, in vivo biotransformation of imidacloprid by AO was demonstrated in mice (Swenson and Casida 2013), and FMO can breakdown organic contaminants such as alkylphenols and bisphenol A (Huijbers et al. 2014). Currently, AO and FMO pathways have been investigated mostly in humans and mice in drug development and metabolism studies (Cashman 2008; Garattini and Terao 2012; Fan et al. 2016). Because of their broad substrate specificities towards heteroatoms of N, O, and S, AOs and FMOs are likely active in the biotransformation of drugs, agrochemicals, and many emerging contaminants where these moieties/functionalities are present. AO is present in several birds including chicken, turkey, Mallard as well as Zebra Finch (*Taeniopygia guttata*) and Budgerigar (*Melopsittacus undulatus*) (Kurosaki et al. 2013). FMOs are prevalent in all domains of life (i.e., Archaea, Bacteria and Eukarya; Mascotti et al. 2015; Nicoll et al. 2020) though the genomic presence of avian FMO remains to be demonstrated. Because of their phylogenetic prevalence and their importance in biotransformation, the roles of AO and FMO should be explored and better characterized in birds.

5.4 Higher Bird Diversity of Shorebirds, Seabirds, and Raptors

However, a greater diversity of avian species may be needed in characterizing all types of measurements in relation to the uptake, biotransformation, and accumulation of chemicals that wild birds are exposed to in their different habitats. Many coastal areas, deltas, and estuaries are heavily affected by organic pollution (Cuevas et al. 2018; Gaw et al. 2014; Sousa et al. 2018). Shorebirds are important avian indicators of pollution at these sites because they interact with a wide suite of organisms in the intertidal, littoral, and benthic zones. Currently, however, shorebirds are under-reported, as they account for < 1% of entries in the main, microsomal, and pathway databases. However, shorebirds are mostly absent in all major B/TK/PK parameters, including *BFAF*, *maxTF*, and k_T (Table 8); *BMF* is the exceptional parameter, with Grey Heron (*Ardea cinerea*) as the only shorebird documented. Similarly, only one species has been reported in the microsomal database (Sanderling, *Calidris alba*) and the pathway database (Grey Heron, *Ardea cinerea*).

Birds of prey are usually apex predators of aquatic or terrestrial food webs and thus can bioaccumulate environmental chemicals throughout their respective food webs. There are likely important differences in biotransformation kinetics and metabolic pathways among birds of prey

Table 8 Number of avian species (breeds) by habitat groups in different bioaccumulation and biotransformation information and databases

Database	Data entries (n)[a]	Waterfowl	Shorebird	Seabird	Seabird (FL)	Raptor	Terrestrial	Terrestrial (FL)
Main								
BFAF	1673	3				1	4	1 (14)
BMF	1314	6	1	3		3	3	
k_T	806	6		1		1	12	1 (19)
maxTF	747	4		1			9	2 (17)
BSAF	506	1					3	1
TF	263	3				1	4	1 (3)
Field	17,485	53	44	73	8	63	45	1 (4)
Microsomal	1712	9 (7)	1	20		7	28 (3)	2 (6)
Pathway	211	7 (2)	1	9	1	7	6 (2)	1 (13)

[a]Number of data entries with different parameters and databases. *BFAF* biota-feed accumulation factor, *BMF* biomagnification factor, *BSAF* biota-sediment/soil accumulation factor, *FL* flightless, k_T total elimination rate constant, *maxTF* maximum transfer factor, *TF* transfer factor. Note blank cell = no entries

compared to other groups of birds (e.g., passerines). For example, interspecific variation in toxicity of the nonsteroidal anti-inflammatory drug diclofenac (Rattner et al. 2008) suggest possible (likely vast) differences in the metabolism of this compound among raptors. Similar interspecies differential sensitivity to other organic chemicals has been reported in other avian species (Custer et al. 2010; Cuthbert et al. 2007).

Additional seabird and raptor data are needed for the major B/TK/PK parameters (Table 8). Raptors may serve as valuable sentinel groups, since greater bioaccumulation in avian species compared to mammalian predators has been observed in field studies (Hallanger et al. 2011; Hop et al. 2002), suggesting that avian carnivores may be an important guild to include in terrestrial bioaccumulation studies. Currently, Common Kingfisher (*Alcedo atthis*), Audouin's Gull (*Larus audouinii*), Herring Gull, and Yellow-legged Gull (*Larus michahellis*) are the only seabirds characterized for the major B/TK/PK parameters; similarly, Eurasian Sparrowhawk (*Accipiter nisus*), Common Buzzard (*Buteo buteo*), Peregrine Falcon (*Falco peregrinus*), and American Kestrel are the only raptors with partial B/TK/PK measurements. It is possible to expand field *BMF*, *BAF*, or *BSAF* measurements for more shorebirds, seabirds, and raptors though it may be difficult to perform toxicokinetic or pharmacokinetic experiments on wild species. Similar expansions of metabolites and pathway detection or baseline microsomal activities would facilitate our understanding of the diverse biotransformation mechanisms equipped in different avian species.

While more diverse species data can add to our knowledge of the major B/TK/PK parameters (e.g., shorebirds, seabirds, and raptors), logistics must be considered, and the selected species must be those for which invasive or terminal sampling is ethical and/or possible. Species with large population densities may be excellent candidates since they may be present in human modified environments and not classified as protected due to their abundance. These species can include those that exploit anthropogenic food sources or invasive species. Non-invasive sampling of feathers, addled eggs, and excrement are plausible alternatives for monitoring organic chemicals in protected avian species (see Sect. 5.8).

5.5 Wild Bird Species for B/BT Characterization

There are numerous physiological differences between domestic and wild birds that likely influence both bioaccumulation and biotransformation of organic chemicals. Much research to date has focused on the biotransformation of chemicals using chickens and other domesticated avian species (e.g., Mallard, Japanese Quail, see Fig. 7a or Sect. 3.4). Physiological differences, migration, and other factors have the potential to affect bioaccumulation and biotransformation of contaminants (see Sect. 1.3).

Currently, wild avian species are substantially undercharacterized. Although close to 320 wild species are included in our main database compared to ~ 60 domestic breeds, B/BT/TK/PK characterization for wild birds has been low (only 1 entry for wild birds reported for every 10 domestic bird entries in the main database). Wild birds constitute no more than 30%–50% of the records in the microsomal and pathway databases. More investigations focusing on wild birds can help to build an understanding of B/BT that is relevant to wild species.

5.6 Basic Biometrics, Exposure Conditions, and Physiological Parameters

Thorough characterization of biometrics and exposure conditions that include body/tissue weights, lipid content, and protein content is critical for B/BT modeling. Body size has been shown to influence the biotransformation of organic chemicals. It has been demonstrated that avian hepatic monooxygenase activity correlates with body size logarithmically (Walker 1990). Body size is critical in modeling the in vivo biotransformation rate constant of organic compounds in other species (Arnot et al. 2009). Lipid and protein content are needed to normalize tissue/matrix chemical burden to a common basis (e.g., lipid/organic carbon normalized, equivalent aqueous concentration, or fugacity) for comparison with the chemical activity in various environmental compartments/media. However, body/tissue weights and lipid content are substantially under-reported in both the main database (20% and 50% for weight and lipid, respectively) and the field database (21% and 48%, respectively).

None of the reviewed field studies report protein measurements on the whole animal or the analyzed tissues/matrices. The omission of protein content can hamper proper interpretation of the field bioaccumulation and biomagnification of specific emerging contaminants, which tend to be more protein associated rather than lipid associated or somewhere in between (e.g., numerous chemicals classified as per-/poly-fluoroalkyl substances (PFASs)). Various standard assays have been developed for protein quantification (Lowry et al. 1951; Bradford 1976; Smith et al. 1985) and may be adopted for avian B/BT tests.

Clear documentation for chemical exposure conditions (e.g., concentration in exposure medium, dose in feed, exposure duration, etc.) can facilitate further quantitative analysis of enzymatic responses and can connect these responses to the intake and elimination of the chemical. Nearly 50% of the records in the microsomal database lack background chemical exposure information (i.e., baseline exposure), whereas 18% are related to chemical mixture (e.g., PCBs, crude oil) (Fig. 8b). Further quantitative interpretation of these mixture-induced enzymatic measurements can be very challenging without proper exposure information.

Additional physiological parameters and properties can help in pursuing large-scale PBPK-based B/BT assessments/models. Core properties include body composition, organ weight, tissue protein and lipid content, tissue permeability, and blood flow (Cortright et al. 2009; MacLachlan 2010; Méda et al. 2020). Some of the physiological properties may be estimated from individual body weight via allometric relationships (Espié et al. 2009). Most of these properties are readily available for poultry (e.g., chicken, turkey) but they may need to be retrieved from avian literature or estimated for wild species.

5.7 Multiple Tissue/Matrix Sampling

Sampling multiple tissues from the same individual can provide insights on the disposition of a chemical within a bird and reflect its true B/BT potential. The subtle differences among tissues in the internal chemical flux and transformation are lost as chemical signals when only whole-body analysis is considered (e.g., 14% and 8% in the main and field databases, respectively). Fortunately, both experimental and field studies have reported many observations and characterizations of specific tissues. There are close to 60 different tissues or biological matrices reported for various measurements and characterizations in the four databases. A qualitative summary of the most frequently reported tissues in the four databases is shown in Table 9. All eight selected biological matrices and whole-body measurements are frequently reported in field measurements (Table 9). However, within the main B/BT/TK/PK database, muscle, fat, liver, egg, and plasma appear to dominate the records. Overall, the most commonly analyzed matrices are egg (45% of all data entries), liver (29%), muscle (15%), fat (13%), and blood/plasma (8%).

The dominance of selected tissues in the various databases may support the adoption of liver, muscle, fat, and blood/plasma as *core tissues* or *matrices* for all studies and assessments. These tissues represent organs/components with distinctive related functions: circulation and disposition (blood/plasma), storage and partitioning (fat), metabolism and detoxification (liver), and potential for biomagnification (muscle/flesh). Furthermore, plasma concentration may indicate recent uptake, while adipose and liver levels reflect accumulation or storage of lipophilic contaminants. These aspects overlap with the key modeling elements in existing bioaccumulation models (i.e., toxicokinetics and partitioning) and provide essential organ-specific data needed for PBPK models (Cortright et al. 2009; Lautz et al. 2020; Yang et al. 2015). Within the constraints of limited resources and matrix sample mass, focusing on the *core* tissues can help researchers optimize their effort. For consistency, sampling of *core matrices* may be extended to various B/BT/TK/PK experiments as well as in vitro assays and pathway characterization.

Different metabolites have been found in various tissues/matrices within the same avian species (Nagata and Fukuda 1994; Shan et al. 2012), indicating that different transformation pathways may be active. Liver, gut, and kidney are tissues known for their biotransformation capacities (Anadón et al. 2008; Nagata and Fukuda 1994; Shan et al. 2012). In the pathway database, liver, egg,

Table 9 Abundance of tissue-specific measurements and characterizations in the four databases

Database	Muscle	Fat	Liver	Egg	Plasma	Kidney	Brain	Gut	Whole
Main[a]									
BFAF	■■■	■■■	■■■	■■■	■	■	■	■	■
BMF	■■		■	■■■	○		■	■	■■■
BSAF	○	○	○	■■■					■
maxTF	■	■	■	■	■■	■	■	■	○
TF	■	■	■	○	○	○	○		
k_T	■■	■■	■■	■■	■■	■	■	○	■
Field	■■■■	■■■■	■■■■	■■■■	■■■■	■■■	■■■	■■■	■■■■
Microsomal			■■■■			■■	■	■	
Pathway	■	■	■	■	■	■	○	○	○

[a]○ = $n < 10$, ■ = $10 \leq n < 100$, ■■ = $100 \leq n < 200$, ■■■ = $200 \leq n < 1000$, ■■■■ = $n > 1000$ entries. *BFAF* biota-feed accumulation factor, *BMF* biomagnification factor, *BSAF* biota-sediment/soil accumulation factor, k_T total elimination rate constant, *maxTF* maximum transfer factor, *TF* transfer factor. Note blank cell = no entries

plasma, and muscle constitute 29%, 18%, 13%, and 11% of the entries, respectively; however, the kidney and gut merely account for 6% and 1%. This low representation in the database suggests that the metabolic roles of the gut and kidney need to be better understood and clarified in future biotransformation-oriented experiments. Tissue-specific measurements avoid whole-body averaging of chemical signals, and they are likely to provide more accurate biotransformation kinetics as well as a clearer view of the roles of different organs in the detoxification of absorbed organic chemicals.

5.8 Non-invasive Sampling

Eggs and feathers are useful sampling matrices for monitoring chemical exposure because they are noninvasive. They are widely sampled matrices in regional avian and other vertebrate monitoring programs (e.g., Espín et al. 2016; Rattner et al. 2005). In the field database, eggs constitute 45% of reported measurements and are the most sampled biological matrix. Chemical burden in egg can reflect the extent of both bioaccumulation and maternal transfer of contaminant in a wild population. Addled eggs, when available, can also be used for the study of threatened species; however, caution must be used in the interpretation of residues because they may not be representative of the general population (e.g., high contaminant load may have contributed to infertility or embryo mortality) (Espín et al. 2016).

5.8.1 Egg Sampling

Currently, substantial data are available on the transfer, uptake, or biotransformation of organic chemicals in eggs (i.e., ~ 340 entries; Table 2). These measurements reflect growing interest in the tissue distribution and *in ovo* transfer (Gebbink and Letcher 2012; Greaves and Letcher 2014; Smythe et al. 2020) and transformation of organics in bird eggs via various innovative experimental techniques (e.g., injection in air cell or in albumen) (Dean et al. 2017; McKernan et al. 2009, 2010). The biological fate (e.g., metabolism) of the majority of organic chemicals in bird egg injection studies is not incorporated in bioaccumulation assessment or chemical management frameworks as such toxicity screening studies are not directly indicative of contaminant trophic transfer. Nonetheless, these works provide critical links to understand and evaluate chemical residue effects on embryonic development—a grey area in current bioaccumulation and toxicity assessment schemes but of pivotal importance to the conservation of vulnerable and endangered avian populations.

Egg chemical burden is useful not only for assessing the chemical-induced developmental stress experienced by wild bird populations but also for understanding any transgenerational effect that the contaminant may exert (MacLellan et al. 1996; Marteinson et al. 2010; Winter et al. 2012). Various theories and models of transfer/accumulation of chemicals into eggs have been developed through different mechanistic and mathematical perspectives (Donoghue 2001; Donoghue et al. 1997; MacLachlan 2011; Van Eijkeren et al. 2006); however, large-scale application or validation over different chemicals or avian species is yet to be attempted.

5.8.2 Feather Sampling

Feather sampling is one of the least intrusive and destructive sampling methods. Thus, when collected properly, feathers have potential application for use in all wild bird species regardless of their conservation status.

Feathers are an effective pollution indicator, acting as an active/passive sampler of spatially and temporally integrated contaminant activity in the environment with which the target bird interacts. Studies have reported significant correlations among concentrations of legacy organic pollutants in plasma, feathers, and preen oil (Eulaers et al. 2011; Løseth et al. 2019; Yamashita et al. 2007). Further evidence and investigations could help to demonstrate feathers as a reliable biomonitoring matrix for agrochemicals and other emerging contaminant classes (Jaspers et al. 2019).

It is unclear to what extent a chemical may be transferred to the feather via internal disposition after intake. For instance, chemical transfer into the feathers may occur when the feather is growing, thus the concentration of the chemical in the feather may not reflect exposure during the sampling period unless recently grown. Furthermore, contaminants may adsorb to the feathers or be introduced via preen oil, and these will confound the interpretation of internal chemical transfer to feathers and necessitates adequate chemical cleaning of feathers prior to chemical analysis (Jaspers et al. 2007, 2008a). Thus, potential external contamination of feathers can be a confounding factor. Feathers have sampling limitations similar to other matrices; they have been suggested as more suitable for monitoring metals, and legacy and/or persistent organic contaminants but are less indicative of perfluorinated chemicals (Løseth et al. 2019). It is unlikely that feather samples can provide useful measurements for characterizing the avian biotransformation potential of chemicals. These limitations aside, it would be helpful to expand feather-based observations of organic chemicals in wild birds due to the relative ease of collection of the feathers and nondestructive nature of the sampling.

5.8.3 Excrement Sampling

Urates and fecal material, and in combination guano or droppings, may serve as non-invasive samples particularly for endangered species. Various studies have shown that birds are biological vectors of organic and inorganic pollutants to distant, pristine environments via flight and excretion (Casini et al. 2001; Blais et al. 2005; Roosens et al. 2007; Desjardins et al. 2019). Excrement sampling is much less common in field or laboratory studies and has been limited to POPs (Blais et al. 2005; Evenset et al. 2007) and heavy metals (Berglund et al. 2015; Eeva et al. 2020). Population level B/BT characterization as well as temporal or spatial variation of contaminant body burden may be better reflected through excrement sampling and mapping as it is non-invasive and non-disruptive to the bird population. The feasibility of using avian droppings for continuous monitoring of a wide spectrum of organic compounds and their metabolites in birds could be explored for both chemical exposure and species conservation purposes.

5.9 Chemical Activity in Environmental Media as Reference

In addition to sampling multiple biological matrices, contaminant levels in standard environmental compartments or media (e.g., air, water column, sediment, or soil) in avian habitat should be concurrently measured for reference purposes. Although it is challenging to determine the exact habitat or home range of wild birds, these measurements allow an alternative evaluation on the extent of contaminant concentrations and potential bioavailability that might affect bioaccumulation or biomagnification, regardless of the trophic level and dietary habits of the bird. With sufficient measurements of environmental media and residue concentrations in birds, data can be readily converted to the respective B metrics (i.e., *BAF* or *BSAF*) to support validation or construction of field B/BT models. Knowledge of environmental concentrations of target pollutants is critical for understanding exposure to contaminants that are rapidly metabolized and demonstrate little or no bioaccumulation.

In addition, field measurements are useful for constructing and examining spatiotemporal changes in a target contaminant (e.g., de Solla et al. 2016; Fernie et al. 2017; Gewurtz et al. 2013, 2016; Hebert et al. 1999; Henny et al. 2010; Letcher et al. 2015; Vorkamp et al. 2019; Sun et al. 2019, 2020). With reference environmental chemical concentrations available, one can track and compare the changes in target compounds in birds versus those in various environmental media. Such analysis provides valuable evidence to the effectiveness of existing chemical management policy by indicating if pollution is increasing or decreasing over time, and if remediation efforts and regulatory decisions are effective.

Since chemical concentration likely varies throughout the habitat, environmental sampling at multiple locations within a large site (or habitat) is recommended. Such spatial data allow the heterogeneity of chemical distribution at a site to be quantified and help evaluate variability in B/BT metrics. Standard protocols and techniques for sampling organic compounds in various environmental media are readily available (e.g., USGS 2006; USDoD 2013; Stuart and Batley 2016).

6 Strategies Going Forward

6.1 Construct a Chemical Roadmap

A chemical roadmap could be constructed, based on a combination of quantitative evidence and expert opinion, to prioritize and coordinate B/BT research, address specific knowledge gaps, and streamline use of resources. This roadmap could list and rank chemicals of concern according to compound chemistry and toxicity (i.e., physicochemical properties, compound structure, ecotoxicological characteristics), environmental release (i.e., production-related, accidental, final deposition, or through purposeful use), and its geographical distribution. Additional target compounds could include chemical families and contaminant groups identified in regional reconnaissance programs, sorption and biodegradation studies, or existing fish and invertebrate ecotoxicological databases. With the roadmap as a point of departure, types of experiments/measurements, species/biological matrices of interest, and field sampling regions may be determined.

The roadmap may be constructed using a scoring system in which each known or proposed organic compound is evaluated against various criteria. The following principles are proposed for the evaluation process. Compounds (including metabolites) with high toxicities, bioaccumulation potential, and potential for environmental release (reflected in high production or application volume), and novel chemical functionalities/structures, could be given greatest priority. The potential to bioaccumulate may be initially assessed by evaluating the compound's affinity for lipid and protein or by inference from B/BT measurements in fish and invertebrates (e.g., read-across species). Chemical classes whose metabolites or pathways remain largely unknown could be given high priority. For compounds of similar priority, those with robust datasets in birds and other organisms have been employed in various B/BT/TK/PK experiments would be preferred, because they will likely support interspecies comparison and interconversion of B/BT/TK/PK parameters. A few representative compounds for large chemical families (e.g., PAHs, PCBs, PBDEs, etc.) could be selected to maximize structural variety. Lastly, novel chemical functionalities/classes of interest to the development of new industrial chemicals/products could receive priority for B/BT characterization and evaluation to avoid producing, applying, and widely releasing chemicals with characteristics similar to those of classic POPs, PBDEs, or PFAS on a global scale.

Prioritization of legacy and contemporary pollutants and the effect of exposure to chemical mixtures (including co-exposure to heavy metals) on B/BT can be considered. Although numerous field studies have demonstrated that wild birds may be exposed to multiple organic contaminants (Jones et al. 1996; Mo et al. 2013; Ross et al. 2008; Van den Steen et al. 2009; Verreault et al. 2005a, b; Yohannes et al. 2017) or both organic chemicals and heavy metals (Berny et al. 2015; Helander et al. 2002, 2009) in their habitats, the effects of chemical mixture on B/BT has not been extensively explored. Combined exposure to multiple chemicals and complex mixtures is a well-recognized challenge for fish, wildlife and human health risk assessment and management (Holmes et al. 2018; Hayes et al. 2019; Kumar et al. 2020; Drakvik et al. 2020). Various multi-tiered assessment protocols that combine in silico models, in vitro characterizations, read-across, and systems toxicology have been suggested and illustrated for specific chemical categories (e.g., pesticides, phthalates, etc.) (Bopp et al. 2016; Holmes et al. 2018; Kumari and Kumar 2020). Most of these efforts, however, have focused on toxicity rather than B/BT/TK. The latter is critical for interpreting and assessing B/BT at field conditions where birds are exposed to multiple chemicals or complex mixtures.

A proper balance between legacy and contemporary pollutants is essential for developing predictive QSARs and other correlative models that can guide the development of new nonbioaccumulative chemicals. Several plausible referencing or scaling strategies could be explored. One approach would be to adopt chemicals characterized for fish and other standardized test species where mature B/BT models with a sufficiently diverse chemical training set have been developed. This approach helps establish a common chemical basis for evaluating interspecies sensitivity of B/BT behaviors. A more economic strategy would be to adopt the mean ratios of legacy versus contemporary/emerging pollutants from different extant test species as a benchmark for birds. Referencing to the legacy-contemporary chemical balance in rodent or even human toxicological studies might be possible though very demanding from a resource standpoint.

6.2 Match and Merge for B Data

Two strategies may be used to expeditiously increase the number of field B/BT observations. First, additional field B data may be obtained by merging measurements from different environmental monitoring programs of birds, invertebrates, fish, water, sediment, and soil data that match at the same sampling sites or geographical area. *BAF*, *BMF*, and *BSAF* can be estimated with chemical burdens in birds at locations where the environmental media have also been sampled. This match-and-merge approach may facilitate compilation of large quantities of field data from existing data archive (e.g., Contaminant Data Display & Download by San Francisco Estuary

Institute (San Francisco Estuary Institute 2019)). Second, minor mechanistic focus can be incorporated into existing regional bird monitoring programs. These can be an additional biological matrix analysis on major known metabolites, TK measurements, or an in vitro microsomal assay of tissue from injured wild specimens being euthanized for humane reasons. Gathering one minor additional characterization on a regular basis can amass to a formidable quantity of valuable data over time.

A fair number of field avian monitoring programs or schemes have been implemented in Europe and North America. These included decade-long programs such as the Predatory Bird Monitoring Scheme in the United Kingdom (Pereira et al. 2009; Walker et al. 2008), the Great Lakes Herring Gull Monitoring Program in Canada (Gewurtz et al. 2013; Hebert et al. 1999), the SAGIR network in France (Berny and Gaillet 2008; Millot et al. 2017), and the Pan-European Raptor monitoring program in Europe (Badry et al. 2020; Derlink et al. 2018; Espín et al. 2016). For instance, Espín et al. (2016) reported and examined the scope and focus of some 182 raptor sampling schemes implemented in Europe. Of the 346 published works associated with these schemes, field work on heavy metals (i.e., lead, mercury, and cadmium) accounts for 50% the published studies, while the remaining studies are on POPs (40%), anticoagulant rodenticides (6%), and PFASs (3%). There is effort to draw samples from multiple raptor collections in Europe to better support contaminant monitoring and research (e.g., Movalli et al. 2019). These programs and schemes could potentially provide a large quantity of field B/BT observations with matching chemical characterization in environmental media.

Chemical contaminant levels in different bird species are archived in various environmental specimen banks (Schulze et al. 2007; Tanabe 2006). These data potentially cover large spatiotemporal scales and different ecotypes, and could be utilized for chemical risk and bioaccumulation assessment. However, in many cases no guidance is available on how to make use of such monitoring data for evaluating B/BT/TK/PK. Thus, large-scale research projects have been initiated (e.g., Life Apex, https://lifeapex.eu/) using wild birds and mammals to assess the degree of contaminant exposure across European countries and to evaluate the usefulness of biomonitoring data in chemical risk and bioaccumulation assessment. These projects aim to elaborate guidance documents for industry, risk assessors, and regulators on crucial data, their reliability, and factors to be considered in using monitoring data efficiently in B assessment in a weight-of-evidence approach.

Additional bioaccumulation and biotransformation data associated with poultry meat may be available in government programs on food safety or ecotoxicological characterization of new chemicals. These programs may not cover wild birds effectively, but they may have archived valuable B/BT/TK/PK data obtained under controlled settings.

6.3 Clarify Existing B/TK/PK Theories and Develop a Unified Theoretical Framework

6.3.1 Clarifying B Models and Metrics

Clarification of existing B/TK/PK metrics and their theoretical origins could be elaborated upon and examined in depth. In addition to the bioaccumulation metrics proposed in Table 2, nearly 10 additional bioaccumulation metrics have been reported (Drouillard et al. 2001, 2007; Drouillard and Norstrom 2003; MacLachlan 2009, 2011; Stephens et al. 1995). A review of these models and metrics could provide clarity and clues on the best way(s) to investigate bioaccumulation and maternal transfer of organic chemicals in birds.

6.3.2 Develop a Theoretical Framework for Interconversion of B/TK/PK Data

When limited empirical data are available, an effective strategy is to develop a theoretical framework that enables parameters obtained from different types of experiments to be converted or translated into B/BT parameters of interest. This framework may allow, for instance, the interconversion between PK-based k_{elim} and TK-based k_T, or the translation of a *per os* tissue concentration–time profile into a dietary uptake rate constant. Although not all parameters may be interchanged, such possibilities deserve consideration. Even when B/BT/TK/PK parameters are only partially interchangeable, we can benefit by utilizing the large amount of experimental veterinary and human pharmacokinetic literature developed over decades as an alternative data source for B/BT/TK data.

Interconversion between PK and B/TK data will require mathematical and theoretical consistency across the models underlying existing B/BT/TK/PK parameters. However, such consistency is currently absent. For example, while k_T (TK) and k_{elim} (PK) are both elimination rate constants, they are determined from different mathematical models; they may equate with each other under specific conditions, but this remains to be examined. k_{elim} is mostly determined using the classical two-compartment model (Baggot 1978), which divides an organism into two compartments (i.e., central and peripheral) without clear physiological delineation. Consequently, PK-derived parameters may not be directly applicable to specific organs (e.g., liver) or useful for PBPK modeling.

Similar theoretical review could be developed for connecting BT parameters from in vivo whole-body and

tissue/matrix-specific experiments to those from in vitro assays (e.g., k_{MB}, $f_{MB/\Sigma MB}$), and possibly with microsomal enzymatic responses (e.g., EROD, GST) as well. Maternal transfer and egg biotransformation—two aspects critical for assessing cross-generational effects of organic contaminants in birds— could be integrated as well. A common framework could streamline the myriad terminologies, definitions, and variable systems dispersed through the current literature under different disciplines.

6.3.3 Expedient Derivation of In Vivo Biotransformation Rate Constant

A method to derive the biotransformation rate constant based on time-course concentration data could be made more expedient. Few BT studies have reported transformation kinetics that can be readily incorporated into TK/PK-based bioaccumulation models. Several studies have reported time data of parent compound and metabolite concentrations (Intorre et al. 1997; Lynch et al. 1994) but without any BT kinetics, possibly due to the lack of a proper BT model and metabolic pathway. A means is needed to quantify biotransformation kinetics more directly from raw concentration data without a complete pathway analysis as a prerequisite. Kuo and Di Toro (2022) recently demonstrated the possibility of deriving an in vivo biotransformation rate constant accurately using early-time biota concentration data without rigorous data-fitting routines.

6.3.4 Clarifying BT Models and Parameters

Greater clarity could be developed in various BT models and parameters. Different BT experiments have been conducted on birds for different scientific goals. These include metabolite identification (Shan et al. 2012; Wang et al. 2014), pathway deduction (Krieger et al. 2017; Liu et al. 2011; Zheng et al. 2015), enzymatic activities (Bailey et al. 1998; Knight and Walker 1982; Rivière et al. 1985), inhibition/induction responses (Carpenter et al. 1985; Helgason et al. 2010; Verbrugge et al. 2001), disposition of metabolites (Bonassa et al. 2017; Nagata and Fukuda 1994), and transformation kinetics (Greaves et al. 2016; Honey et al. 2000). These efforts generated a variety of useful parameters and characterizations, including compound-specific rates (Greaves et al. 2016; Honey et al. 2000), metabolite fractions (Fournier et al. 2010; Geertsma et al. 1987; Honey et al. 2000; Short et al. 1988), percentage conversion (Cecil et al. 1973), or merely metabolite concentrations (Intorre et al. 1997; Lynch et al. 1994). It is currently unclear how these parameters may be integrated into B/TK modeling. Mathematical relationships could be established to facilitate data conversion and rate extrapolations from in vitro assays to in vivo responses or enhance the connectivity between toxicokinetics and pharmacokinetic disposition data.

6.3.5 Linking BT Kinetics with Enzymatic Activities

Linking enzymatic activities and biotransformation kinetics can be appealing given the abundance of P450 activity measurements already available for many species of wild birds. It is not clear whether microsomal enzyme activity can be used to extrapolate to biotransformation kinetics due to the paucity of such data for birds. There have been human studies connecting in vitro biotransformation to compound structure (Bu 2006) and linking enzyme induction kinetics to structural functionality (Fried et al. 2007). A fish biotransformation study reported both microsomal enzyme activity and in vitro biotransformation kinetics without linking them quantitatively (Hou et al. 2018). Given the dominant role of the P450 enzymes in xenobiotic biotransformation (Walker 1998; Brown et al. 2008) and the abundance of P450 activity measurement already available in many wild birds, developing an enzymatic activity-based biotransformation kinetics model may be a plausible alternative to generating in vitro and in vivo BT kinetics.

6.4 Improving Data Reporting Practices

Improving data reporting practices can enhance B/BT data availability and quality derived from laboratory and field studies. Previous work identified various biological and chemical factors that could be measured and reported in B/BT and food web assessment in birds and mammals (Borgå et al. 2004; van den Brink et al. 2016). The basic practice of reporting biometric properties and avoiding pooled measurements (across chemical group, individuals, or sampling sites) could be employed whenever possible. Given the prominence of avian field studies and chemical biomonitoring programs, developing a *core data reporting checklist* could serve as a reminder of basic variables critical for immediate needs and long-term monitoring, spatiotemporal meta-analysis, or modeling purposes. A preliminary checklist is presented in Table 10. Additional initiatives and projects improving communication on the use and reporting of field monitoring data among stakeholder groups (e.g., researchers, field biologists, risk assessors, regulators, and industry) could be established to enhance data collection and streamline calculation of B/BT/TK/PK metrics.

6.5 Expanding the Scope of Field Sampling

Ideally, field sampling would include more sites, avian species and chemical measurements. Our analysis revealed the paucity of field B/BT data on agrochemicals and pharmaceuticals. Although exposure and adverse effects of drugs (e.g., Bean et al. 2018; Oaks et al. 2004; Whitlock et al. 2018) and agrochemicals (e.g., Pandey and Mohanty 2015) on wild bird have been described, broad field bioaccumulation surveys of these chemicals in wild birds are generally lacking.

Existing field literature has focused overwhelmingly on selected regions (i.e., highly affected by pollution or agrichemical use), potentially introducing geographical and ecological biases. This bias is evident in the field database with overwhelming representation of waterbirds (i.e., waterbird/terrestrial bird data entry ratio $\sim$ 5:1) with very few records of fructivorous and nectarivorous birds (three and zero species, respectively; Supplementary Information S6). New sites may be selected by focusing on locations proposed for remediation or species designated under special conservation status. This focus could enable field B/BT measurements to be interpreted in a meaningful ecotoxicological context while reinforcing conservation efforts. An overview of field sampling locations/regions examined in this review is available in Supplementary Information S7. New sampling sites—with new species—could help construct a spatially comprehensive mapping of organic contamination in birds.

A few exemplary studies are portrayed here for their expanded scopes. Transcontinental studies can provide a macroscopic view on the prevalence of contaminants. Examples include the survey of legacy organochlorines and metabolites in tissues and eggs across the United States (Jarman et al. 1993; reviewed in Rattner et al. 2005), the tracking of volatile methylsiloxanes and organophosphate esters in European starlings (*Sturnus vulgaris*) and congeneric gull (*Laridae*) eggs across Canada (Lu et al. 2017), and the mapping of PCBs and other legacy organochlorines in some 60 avian species in the Asia Pacific regions (Kunisue et al. 2003). Field studies with broad chemical scope can support and refine management policy toward particular chemical classes. Notable works include the studies of Grey Partridge with field exposure to $>$ 100 agrochemicals that were tracked by a combination of surveys and residue measurements in bird carcasses in France (Bro et al. 2015; Millot et al. 2015) and the spatiotemporal examination of $>$ 70 flame retardants in Peregrine Falcon in Canada (Fernie et al. 2017). Field surveys of multiple avian species afford valuable snapshots of contaminant presence as a function of their habitats, foraging guilds, and migratory behavior (Barghi et al. 2018; Jaspers et al. 2006; Jin et al. 2016) as well as supporting interspecies comparison on biotransformation (Jaspers et al. 2008b).

6.6 Non-testing Approaches for B/BT Gap-Filling

6.6.1 Read-Across and Interspecies Extrapolations

The paucity of B/BT data for birds may be partly overcome using assessment approaches such as read-across (RAx) and interspecies extrapolations (IEx) in combination with other quantitative in silico methods to provide initial estimates. Ecotoxicological properties estimated from these methods can provide a preliminary but insightful portrait of those critical measurements needed for the large chemical and taxonomic landscapes in bird B/BT data; however, these estimates do not substitute for empirical experimental characterizations or field observations.

These non-testing approaches make statistical inferences on an ecotoxicological property (e.g., toxicological endpoint) of a query chemical or species/taxon using the data of reference chemicals or surrogate species based upon their structural or taxonomic similarity. Proper grouping or categorization to apply these methods may include chemical analogues (i.e., analogue approach) and endpoint-specific categories (i.e., category approach) (ECETOC 2012; Rovida et al. 2021). Proper grouping is critical for the success of these inferencing methods (Ball et al. 2016; ECETOC 2012; Lamon et al. 2019) as they perform best when the query chemical (or biological species) and the reference chemicals (or surrogate species) are structurally (or taxonomically) similar, with prediction accuracy declining as chemical dissimilarity (or taxonomic distance) increases (Raimondo et al. 2007; Dyer et al. 2008; Schüürmann et al. 2011). As tools for risk assessment or chemical registration, these non-testing approaches have harnessed various degrees of regulatory acceptance as an effective means to fill in critical ecotoxicological data gaps without in vivo testing (ECETOC 2012; Ball et al. 2016). Their regulatory acceptance largely depends upon the nature of the ecotoxicological endpoints/information, the availability of relevant data or measurements, and possibly the assessment outlook upheld by the regional authorities (ECETOC 2012; Chesnut et al. 2018).

6.6.2 Quantitative RAx and IEx

RAx and IEx have been applied extensively to toxicity evaluation or prediction. Notable examples of quantitative RAx include the acute fish toxicity of organic compounds (Schüürmann et al. 2011), human cell and bacterial toxicity of nanoparticles (Gajewicz 2017), and acute and chronic rat toxicity (Helma et al. 2018; Helman et al. 2019). IEx has been applied, with some success, to toxicity

Table 10 Core data reporting checklist for field and laboratory avian B/BT studies

I	Biometrics
	Body weight, tissue weight
	Lipid content, protein content, water content (tissue-specific)
	Life-stage characterization
	Sex
	Age class
II	Target chemical concentrations in biota
	Whole-body
	Liver, muscle, fat, plasma/blood
	Eggs
	Other tissues/matrices
III	Target chemical concentrations in environmental/exposure media
	Soil, sediment, water, air, prey/feed
	Organic carbon content (soil, sediment), dissolved and particulate organic carbon (water), lipid content and protein content (prey, feed)
	Medium or ambient temperature
IV	Exposure condition and duration
V	Stable isotope measurements (for monitoring biomagnification or trophic transfer)
	$\delta^{15}N$ and $\delta^{13}C$ (tissues and diet)
VI	Reporting of raw measurements for each chemical/analyte at each site (i.e., do not pool or aggregate raw data)
VII	Detection frequency of target chemical at each site or bird samples
VIII	Sampling site description and sampling time
	Known source(s) of target chemical nearby the site
	Distance to the nearest urban center and population size of the urban center

characterization across different species such as fish, laboratory rodents, and humans (Gold et al. 1989; Escher et al. 2013; Margiotta-Casaluci et al. 2014). A notable development is the interspecies correlation estimation (ICE) model that allows quantitative inference of acute toxicity from surrogate species/taxa (Raimondo et al. 2007; Dyer et al. 2008). Japanese Quail and Mallard were found to be good surrogates for avian wildlife (Raimondo et al. 2007).

6.6.3 Limitations of Non-testing Approaches

Limitations inherent in RAx and IEx can restrict their usefulness for providing meaningful estimates of critical avian B/BT/TK parameters. Since similarity is the core element of RAx or IEx, the utility of these models is mostly limited to chemicals or species/taxa akin to those in the existing B/BT/TK data. Prediction accuracy of RAx methods have been found to decline with increasing chemical dissimilarity (Schüürmann et al. 2011) or greater applicability domain distance (Helma et al. 2018). Findings of Dyer et al. (2008) illustrated that species sensitivity distribution in fish and invertebrates was best predicted using surrogate fish and the aquatic invertebrate *Daphnia magna*, respectively. Inferencing bird B/BT/TK data from existing avian literature may be feasible only for structurally similar chemicals, and accurate extrapolation from existing fish or invertebrate data to avian species may be challenging.

RAx models may be less versatile for novel chemical functionalities as they seem to produce more no-predictions (NPs) or out-of-domain predictions (ODPs) than standard QSARs when applied to out-of-domain chemicals (Helma et al. 2018; Zhou et al. 2021; see Supplementary Information S8). Additionally, expert judgement may be needed when interpreting RAx outputs as suggested by various technical guidance documents and opinions (ECETOC 2012; OECD 2017; Benfenati et al. 2019; Rovida et al. 2021). Expert inspection and pruning may be necessary for reducing prediction errors (Helma et al. 2018) or improving chemical grouping/clustering (Date et al. 2020). This dependence of outcomes on personal experience or expertise is undesirable and fully automated RAx have been advocated (Hartung 2016; Gajewicz et al. 2017).

6.7 Linking B and BT to Avian Genomics

Genomics offers new dimensions to examine bioaccumulation and biotransformation of organic chemicals in birds. A worldwide genomic database for 363 bird species representing 92% of all avian families is now available as part of the Bird 10,000 Genomes (B10K) Project (Feng et al. 2020). Genomic data provide an alternative approach to define and measure the relatedness of different birds (Braun et al. 2019) and may help explain the interspecies difference in B/BT responses to organic chemicals. The full potential of genomic analysis in ecological risk assessment and toxicological modeling has not been adequately explored.

6.8 Online Data Repository

An open-access online data repository of various types of avian B/BT/TK/PK data would substantially benefit the scientific community. While many of the recently published works are freely accessible, the data within are often not in a readily usable form or may even remain *hidden* (e.g., chemical pooling such as ΣPCDDs or ΣPAHs or site pooling). The databases presented in this review may serve as initial data templates for various types of experimental and field data. An online repository would allow standard data query and access as well as submission of digitalized avian B/BT/TK/PK data. Such a repository would be an invaluable resource for environmental data analytics (i.e., historical trend and spatial evolution of contaminants in birds), contaminant benchmarking (i.e., concentrations in environmental media and various bird tissues/matrices), and construction of QSARs or B/BT/PBPK models.

6.9 Open-Ended Questions and Explorations

Several critical questions become apparent through the present review. These questions highlight the core assumptions and limitations of conventional bioaccumulation theory to birds as well as demonstrate the major obstacles inherent in the current practice of characterizing avian B/BT. These major issues await serious inspection, exploration, and resolution.

6.9.1 Which B Metric(s) for Birds?

How relevant are the classical B metrics (i.e., *BSAF*, *BAF*, and *BMF*) to accumulation of organic chemical in birds? The *BMF* requires diet composition and diet contaminant level, which, in principle, should be determined from proper analysis of food content of the "stomach" (proventriculus and gizzard) of the individuals. However, as these analyses are rarely performed in field work, average composition and chemical activity may have to be assumed. Furthermore, stomach content analysis only provides a snapshot of the diet/chemical uptake at the time of sampling and does not fully reflect all chemical exposure routes. How reliable are these semi-estimated *BMF*s? Philosophically, are such *BMF*s still considered "observations" and should they be used to construct field biomagnification models? Furthermore, as many birds have diverse diets, could there be multiple *BMF*s for any given bird species if individual birds forage opportunistically and differently? While *BAF* and *BSAF* can be determined, they may be mechanistically less meaningful since many avian species interact extensively with water, soil, and sediment. And finally, if these limitations may have made the classical *BSAF*, *BAF*, and *BMF* less relevant and more difficult to interpret in birds, should a new metric(s) and theory be developed for monitoring and modeling purposes?

6.9.2 Foraging Strategy, Dietary Preference, Life-Stage Events, and Avian Ecology?

How do other biological and ecological factors (i.e., Sect. 1.3) influence variability in avian B/BT? If dietary intake is a dominant bioaccumulation mechanism for birds, should their foraging strategy be considered in the development of B/BT theory? Foraging strategy reflects the extent to which a given bird may interact with its environment, and this may be a useful modeling parameter for bioaccumulation or biomagnification of organic chemicals. How should bioaccumulation be characterized in migratory species, especially those with long migratory ranges? Given the diverse diets and habitats of birds, should particular species be designated for standard B/BT tests? If so, what birds should be used, given that only limited species can be maintained in a laboratory or captive environment?

Further complication arises as the feeding strategy and dietary preference of birds change with seasonality and life stage. Can the neglect of the influences of seasonality and life-stage events be justified in existing TK/PK models where rate constants are typically assumed to be time independent? If such an assumption has to be made, what is the error or uncertainty incurred from the simplification?

6.9.3 How Important is Air Exposure to Bioaccumulation in Birds?

How important is air exposure (including airborne particulates) as a chemical accumulation mechanism for birds?

No explicit study on respiratory exposure has been found in this review, and for studies with birds, documentation of chemical concentration in the gaseous phase has been very rare (Sorais et al. 2020; Węgiel et al. 2018). Air is to birds as water is to fish, so can one expect respiratory intake or release to be important at least for selected organic chemicals? If respiratory uptake can be significant in birds, how important is it compared with dietary uptake? Do birds have a similar physicochemical dependence on respiratory uptake rate as those in fish, worms, and other invertebrates?

6.9.4 Avian Biotransformation of Chemical Mixtures?

Exposure to contaminant mixtures presents a different challenge in interpreting biotransformation products and dynamics. Several studies have documented a large suite of metabolites following exposure to contaminant mixtures (e.g., PCBs, PBDEs) in various wild birds (Fernie and Letcher 2010; Huber et al. 2015; Jaspers et al. 2008b; Jörundsdóttir et al. 2010; Verreault et al. 2005a, 2006). Decoupling metabolites produced from multiple transformation pathways is difficult. Is it possible to depict biotransformation dynamics (without knowledge of the transformation pathways) in contaminant mixtures? Can biotransformation be activated or suppressed by exposure to complex mixtures? These are very realistic exposure scenarios, particularly after catastrophic events (e.g., oil spill).

6.9.5 Incorporating BT into Avian Ecological Risk Assessment?

Which BT parameters may be adopted for B evaluation in ecological risk assessments? How accurately can in vivo BT kinetics and metabolite profiles be constructed from in vitro assays? Which tissue(s), assay(s), and/or cellular fraction(s) should be used? Can in vitro BT characterization be incorporated into ecological risk assessments of organic chemicals? How should the details of biotransformation (e.g., selectivity, transformation pathway, conversion ratio, etc.) and TK parameters (e.g., k_M) be balanced? These questions reveal the core B/BT information needed and facilitate the streamlining of their characterization.

6.9.6 Tissue-Specific B/BT in Birds?

The tissue/matrix dependence of metabolite profiles presents a difficult reality for large-scale measurement or modeling of biotransformation, given that the metabolite profiles remain unknown for most organic chemicals. Studies have demonstrated that both the number and structure of metabolites can vary among biological matrices (Nagata and Fukuda 1994; Shan et al. 2012). Should B/BT characterization be pursued and evaluated on a tissue-specific basis? If this is the case, would it not be logical to replace the classical bioaccumulation model with the PBPK model?

7 Summary

This effort reviewed the literature on the bioaccumulation and biotransformation of organic chemicals in birds and compiled relevant data and references to support future research tasks. The compiled data were organized into five themed databases on bioaccumulation and biotransformation, field survey, microsomal enzyme activity, metabolic pathway, and avian taxonomy and diet. Significant data gaps were identified in all databases at multiple levels. Overall, legacy hydrophobic organic compounds dominate the data entries.

The field database covered a large number of avian species and habitats although it lacked entries of pharmaceuticals and agrochemicals. Basic but critical biometrics, environmental medium concentrations of target chemicals, and cross-tissue sampling were not often available from field studies. Analysis disclosed the lack of bioaccumulation, toxicokinetic, or pharmacokinetic measurements as well as metabolic pathway characterization of shorebirds, seabirds, and raptors.

Diverse characterizations of biotransformation were observed. These varied from pathway construction and metabolite identification to measurement of enzymatic activity. Biotransformation kinetics were reported in a limited number of studies and mostly associated in in vitro experiments. There were few estimated of avian in vivo biotransformation rate constants. Limited biotransformation kinetic data constrained the development of an avian biotransformation model. Although > 130 metabolites were identified, they were associated with a limited number of parent chemicals. Chemical exposure or tissue concentration data were often missing in enzyme activity studies, making it challenging for quantitative interpretation of biotransformation. Existing work on biotransformation is thus complementary at best and can benefit from the standardization of reporting metrics.

Twenty-seven B/BT/TK/PK parameters were selected and evaluated for their potential use as benchmarking or modeling metrics based on a list of screening and parameter quality criteria. Since no metric comprehensively captured all key contaminant classes, chemical groups, or habitat groups, the current data were considered inadequate for developing broad-scope avian B/BT models. Biota-feed accumulation factor, maximum transfer factor, and first-order elimination rate constant were deemed more readily

usable than the other parameters for provisional avian bioaccumulation evaluation and assessment.

Technical constraints of avian research were been identified along with data gaps. These included the need for greater chemical and avian species diversity, chemical measurements in environmental media, basic biometrics and exposure conditions, multiple tissue/matrix sampling, and greater exploration of biotransformation. Limitations of classical bioaccumulation metrics and current research strategies were discussed.

Finally, several forward-looking strategies on bioaccumulation/biotransformation of organic chemicals in birds were proposed:

1. A roadmap that prioritizes environmental contaminants for avian B/BT characterization based on compound chemistry and toxicity, environmental release potential, and geographical prevalence could be constructed to better coordinate research efforts and resources. The candidate compounds may be identified using a scoring system that maximizes physicochemical and structural variety and balances legacy and contemporary pollutants. Recognized as a critical challenge for human and wildlife health risk management, the effects of chemical mixtures on B/BT could be better understood.
2. Integration of environmental and biomonitoring data from existing programs and archives could provide additional field B/BT data. Quantitative read-across and interspecies extrapolation may fill in some of the data gaps by providing tentative estimates of B/BT/TK/PK parameters for compounds with strong structural resemblance to those in the reference or training set, or for birds where data are available in surrogate avian species.
3. Substantial groundwork could clarify existing B/TK/PK theories and models and be used to develop a unified theoretical framework for the biological fate of organic chemicals in birds. Five specific areas were highlighted. (i) Understand and compare the theoretical origins, connections, and limitations of different B/BT/TK/PK parameters to clarify their suitability for B/BT characterization and assessment in birds. Nearly 40 B/BT metrics and related parameters have been reported in the literature. These metrics and the underlying models conceptualize and characterize B/BT and maternal transfer of organic chemicals differently as they are formulated for specific experimental designs and exposure scenarios. (ii) Construct a unified theoretical framework to help resolve formulation inconsistency and bridge mechanistic gaps between the different B/BT/TK/PK models. This framework could facilitate the interconversion of B/TK/PK data obtained from different types of experiments and support avian in vitro-in vivo extrapolations. This framework will require the identification of common elements in different formulations as the theoretical basis of the modeling framework. (iii) Generate in vivo whole-body and tissue-specific biotransformation rate constants, which is currently lacking substantially, is critical for the development of avian B/BT models. A feasible solution may be derivation of biotransformation kinetic parameters based on the more frequently reported time-course concentration or fraction data of parent compound and metabolites. (iv) Examine how various quantitative in vivo and in vitro BT parameters (e.g., biotransformation rate constant, metabolite formation rate constant, metabolite fractions, percentage conversion, etc.) may be integrated into B/TK/PK models and clarify the theoretical relationships among them to facilitate interconversion of data. (v) Explore the possibility of inferring biotransformation kinetics from enzymatic activities. This would require an understanding of how enzymatic responses and biotransformation kinetics are correlated at different exposure conditions and durations.
4. Field sampling scope could be expanded to encompass less-investigated compounds and bird species at new sites to provide a fuller, unbiased picture of the degree and extent of chemical exposure and bioaccumulation in wild birds. Using avian genomics to characterize, explore, and interpret interspecies differences in BT could reveal new insights. Genomics could allow species relatedness and makeup of BT-relevant genes to be measured and compared more objectively.
5. To improve the usability of future avian B/BT data, a reporting checklist was proposed for both laboratory and field avian B/BT studies. Biometrics, exposure concentration and condition, life-stage characterization, and raw concentrations are critical properties for monitoring or model development. Building an open-access online avian data repository with data query, access, and submission functions could support environmental data analytics, contaminant benchmarking, and development of quantitative B/BT/TK/PK models.

The present review concluded with a series of explorative, open-ended questions that probe various core assumptions and limitations inherent in extending the conventional approaches to understand avian bioaccumulation and biotransformation of organic chemicals. These questions addressed the suitability of conventional B metrics, the role of ecology and life stage in B/BT, the importance of air exposure on chemical uptake, the role of BT in ecological risk assessment, the dependence of BT on

chemical mixture, and the potential need for tissue-specific B/BT characterization.

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Availability of Data and Material The data described here are open to the public (see included Excel spreadsheet). Updated versions of the databases will be announced and available at https://github.com/tfdkuo/BBBT and https://osf.io/davtr/?view_only=95ac699e2bd0492fbc7977cd63fb5e77 (Bird Bioaccumulation and Biotransformation).

Code Availability Not applicable.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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