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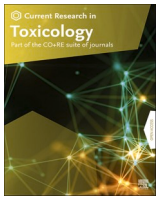

# Sublethal effects of early-life exposure to common and emerging contaminants in birds

Jacquelyn Grace [a,b,*], Elena Duran [b], Mary Ann Ottinger [c], Terri Maness [d]

[a] Department of Ecology and Conservation Biology, Texas A&M University, College Station, TX 77840-2258, USA
[b] Ecology and Evolutionary Biology Interdisciplinary Doctoral Program, Texas A&M University, College Station, TX 77840-2258, USA
[c] Department of Biology and Biochemistry, University of Houston, Houston, TX 77204, USA
[d] School of Biological Sciences, Louisiana Tech University, Ruston, LA 71272, USA

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ABSTRACT

The plight of wild birds is becoming critical due to exposure to environmental contaminants. Although laboratory studies have provided insights into the developmental effects of chemical exposures, less is known about the adverse effects of environmental chemicals in developing wild birds. Early life stages are critical windows during which long-term organization of physiological, behavioral, and neurological systems can occur. Thus, contaminant exposure at early life stages can directly influence survival and reproductive success, with consequences for population stability and resilience in wild species. This review synthesizes existing knowledge regarding both short- and long-term effects of early-life exposure to widespread contaminants in birds. We focus especially on wild birds and on contaminants of concern within the Gulf of Mexico as an example of a habitat under anthropogenic stress from exposure to a complex mixture of chemicals and changing land uses that exacerbate existing vulnerabilities of wildlife in this region. Chemical contaminants for discussion in this review are based on avian mortality records from the Wildlife Health Information Sharing Partnership (WHISPers) database and on additional review of the literature regarding avian contaminants of concern for the northern Gulf of Mexico, and include oil and associated polycyclic aromatic hydrocarbons, dioxin and dioxin-like compounds, flame retardants, pesticides, heavy metals, and plastics. We provide an overview of effects in bird species at both the pre-hatching and post-hatching early life stages, discuss differences in sensitivities by route of exposure, life stage, and life history, and provide recommendations for future research. We find that additional research is needed on altricial species, post-hatching early-life exposure, long-term effects, and on ecologically relevant contaminant concentrations and routes of exposure. Given the increasing frequency and intensity of anthropogenic stressors encountered by wild animals, understanding both lethal and sublethal impacts of contaminants on the health of individuals and populations will be critical to inform restoration, management, and mitigation efforts.

## Introduction

Bird numbers are dramatically declining worldwide (Hallmann et al., 2014; Inger et al., 2015; Rosenberg et al., 2019), a loss that is associated with a myriad of factors, including environmental contaminants (Hallmann et al., 2014; Haney et al., 2014; Hao et al., 2021). The impact of contaminants is most obvious during major die-off events, for example, thousands of oiled seabirds washing up on beaches following the Deepwater Horizon Spill in the Gulf of Mexico (Haney et al., 2014). However, sublethal effects can also have major, long-lasting impacts on individuals, especially when those effects are experienced early in life (*e.g.*, Brunson et al., 2005; Spencer and Verhulst, 2007; Zimmer and Spencer, 2014; Bolton et al., 2017; Grace et al., 2017b; Grace and Anderson, 2018; Dupont et al., 2019b). Early-life sublethal experiences and exposures can alter physiological, neurological, and behavioral organization to an extent that is often not possible at later time points, once central nervous system development is complete (Seckl, 2001, 2004; Cottrell and Seckl, 2009; Ottinger and Dean, 2022). These early-life effects can have short- and long-term consequences for future survival (*e.g.*, Lindström, 1999; Monaghan et al., 2012; Grace et al., 2017a) and reproductive success (*e.g.*, Lindström, 1999; Zimmer et al., 2013; Dupont et al., 2019a; Grace et al., 2019), and thus, impact population

* Corresponding author at: Department of Ecology and Conservation Biology, Texas A&M University, College Station, TX 77840-2258, USA.
*E-mail address:* jacquelyn.grace@ag.tamu.edu (J. Grace).

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dynamics.

The responses of birds to environmental stressors are of special interest to ecologists, because avian diversity can be a functional indicator for the resilience and overall health of an ecosystem (Smits and Fernie, 2013; McCloy et al., 2022, 2024) and birds are valuable providers of ecosystem services (Sekercioglu, 2007). In the wild, birds are conspicuous, relatively easy to approach and observe, and display behavioral complexity similar to that of mammals (Konishi et al., 1989; Henriksen et al., 2011). Regarding mechanisms and pathways of response, the avian endocrine and neuroendocrine systems are similar in many ways to those of mammals (*e.g.*, the hypothalamic–pituitary–adrenal and hypothalamic-pituitary–gonadal axes; Wingfield, 2005). Developmentally, the extra embryonic membranes of eggs function similarly to the placenta and umbilical cord in mammals (Henriksen et al., 2011). From a practical perspective, bird embryos develop almost entirely outside of the mother's body, within an egg that was formed in a short time window (approximately 4–14 days) (Henriksen et al., 2011). Thus, oviparous birds are frequently used as models for studying early-life stressors because their developing embryos are accessible outside the mother's body. Additionally, since birds do not have a direct physiological link with their offspring after hatching (such as maternal lactation), it is easier to isolate the effects on the offspring from maternal influences, unlike in mammalian models (Spencer et al., 2009).

Sensitivities of avian species to contaminants vary depending on developmental mode, in addition to trophic level, and diet (Ottinger et al., 2008). There is a spectrum of developmental strategies in birds that span from altricial chicks requiring extensive parental care post-hatching to precocial chicks being fully mobile upon hatching with less post-hatch parental care. Precocial birds, such as the Japanese quail (*Coturnix japonica)*, have often been the subject of toxicological studies and regulatory testing. These and other precocial birds are well developed at hatch, with sexual differentiation of the reproductive endocrine systems and functional competency of other physiological systems already relatively complete (Ottinger et al., 2008; Adkins-Regan, 2009; Ottinger and Dean, 2022). Thus, precocial species are most vulnerable at the embryonic stage, whereas species with altricial young remain sensitive for a much longer period post-hatching, although they may conversely retain a degree of neuroplasticity thereby contributing to resilience (Ottinger et al., 2008). However, the underlying mechanisms of biological action for contaminants are expected to remain consistent across avian developmental modes, even if the severity of impacts varies with timing of exposure.

In this review, we synthesize existing knowledge regarding both short- and long-term effects of early-life exposure to contaminants in birds. We focus especially on wild birds and on common contaminants of concern within the Gulf of Mexico as an example of a habitat under anthropogenic stress from exposure to a complex mixture of chemicals and changing land uses that exacerbate existing vulnerabilities of wildlife in this region. We further focus on direct effects of contaminants on avian early life stages, while recognizing that indirect effects on embryos and young birds through altered parental health and behavior are probably common, as well. For example, exposure to organophosphate pesticides can impair foraging in adult birds, which could have deleterious effects on young birds being fed or incubated/brooded by parents (Grue et al., 1997). The effects of our selected contaminants on adults are reviewed in other sources and we refer the reader to these for more information on indirect effects on young birds (*e.g.*, Fry, 1995; Walker, 2003; Ottinger et al., 2009; Harris and Elliott, 2011; Hao et al., 2021).

### *Selection of contaminants for this review*

The Gulf of Mexico has areas of high human population density, as well as agricultural, military, and industrial activities, all of which contribute to water and shoreline contamination. Contaminants included in this review were selected in two ways. First, we examined reported avian mortality records for the five United States Gulf states in the Wildlife Health Information Sharing Partnership (WHISPers) database for the last ten years (January 1, 2014 – December 31, 2023). For a summary of avian morbidity and mortality events submitted to the database for the continental United States in 2023 see Dusek et al. (2024) and for aquatic birds from 1971 to 2005 see Newman et al. (2007). Most records in the database are of adult birds, and we assume that the factors that strongly impact adults may also impact young birds and embryos. Mortality events attributed to toxic compounds are included here if current research suggests they also pose a sublethal hazard to birds. Mortality events attributed to pollutants in the WHISPers database included (from most to least number of birds affected): heavy metals (copper, lead, or mercury), avicide (4-aminopyridine), organophosphates, entanglement, petroleum, and anticoagulant rodenticides. We do not discuss the avicide and anticoagulant agents listed here because these chemicals mainly kill adult birds. We also omit entanglement because this is primarily a physical threat, and not toxicological. We additionally reviewed literature regarding avian contaminants of concern in the Gulf of Mexico, and these were also included in this review. The most widespread contaminants of concern in the Gulf of Mexico include polycyclic aromatic hydrocarbons (PAHs), dioxin and dioxin-like compounds, flame retardants, metals (lead, mercury, arsenic, cadmium, silver, nickel, tin, chromium, zinc, and copper), and pesticides (Ward, 2017). Microplastics (Grace et al., 2022) and per- and polyfluoroalkyl substances (PFAS) are also emerging contaminants of concern for the Gulf of Mexico (Pulster et al., 2022) but in this review we only discuss plastics because little is known about PFAS effects on avian early-life stages. Within this framework, we came to our final list of contaminants for this review: oil and associated polycyclic aromatic hydrocarbons, dioxin and dioxin-like compounds, flame retardants, pesticides, heavy metals, and plastics.

Exposure to these contaminants can occur prior to hatching via maternal deposition in eggs and/or contamination of the egg surface. For example, there is significant maternal deposition of endocrine disrupting chemicals into the eggs of wild, free-living birds (*e.g.*, Custer et al., 2010), and laboratory studies have demonstrated that endocrine disrupting chemicals readily transfer from the hen into the egg and partition in the egg compartment according to lipid solubility (Lin et al., 2004; Ottinger et al., 2005). Post-hatching, young birds can be exposed to these contaminants through direct contact, secondary contact from residues on the feathers of parents that return to brood nestlings, or through ingestion. Thus, for each contaminant of interest we separately discuss both pre-hatching and post-hatching effects and summarize existing studies in Tables 1 and 2, respectively.

## Oil and associated polycyclic aromatic hydrocarbons (PAHs)

The Gulf of Mexico is one of the most important regions for oil and gas production, refinement, and processing in the United States. Forty-seven percent of the total United States (U.S.) petroleum refining capacity, and 49 % of the total U.S. natural gas processing plant capacity are located along the Gulf Coast. Additionally, offshore production in the Gulf accounts for 15 % of total U.S. crude oil production and 3 % of dry natural gas production (U.S. Energy Information Administration, 2023).

Oil and associated chemicals from leaks and spills such as the Deepwater Horizon Oil Spill present a significant risk for marine and coastal species. Routes of exposure for adults, young birds, and eggs include direct oiling (*i.e.*, fouling), ingestion, inhalation, aspiration, and absorption. Adult birds are at highest risk of fouling because of their greater mobility; however, young birds and eggs can also be fouled through overwash of nesting areas with contaminated water, or through contact with the contaminated feathers of parents during incubation/brooding. Both adults and young can ingest and aspirate oil and PAHs through consumption of contaminated food, accidental ingestion during foraging activities, or by preening oiled feathers (Goodchild et al.,

**Table 1**
Summary of studies investigating the effects of pre-hatching (*i.e., in ovo*) contaminant exposure on birds; see text for details and reference citations.

| Chemical category | Method of exposure | General effects | Lab studies[1] | Field studies | Altricial[2] | Precocial[3] |
|---|---|---|---|---|---|---|
| Oil and PAHs | Surface application, injection | Embryotoxicity, teratogenic effects, changes to regulation of the AhR pathway, reduced heart rate, metabolic rate, embryonic growth, and embryo viability | ✓ | – | ✓ | ✓ |
| Dioxin and dioxin-like compounds (TCDD and PCBs) | Injection, dietary exposure of parents, correlation | Increased metabolic costs, immunosuppression, changes to cardiac development and gene expression, gross abnormalities (*e.g.,* edema, skeletal and beak malformations), endocrine disruption, brain assymetries, distended yolk | ✓ | ✓ (Obs[4]) | ✓ | ✓ |
| Flame retardants (FRs) | | | | | | |
| PBDEs | Injection, dietary exposure of parents | Delayed hatch, oxidative stress, reduced thyroid weight, DNA damage, changes to organ morphology | ✓ | ✓ (Obs) | ✓ | ✓ |
| Organophosphate FRs | Injection | At high doses: delayed pipping, differential gene expression, increased liver somatic index, reduced thyroid hormone, impaired growth, gallbladder development, and circulation | ✓ | – | – | ✓ |
| Pesticides | | | | | | |
| Organophosphate pesticides | Injection, immersion, surface application | Increased mortality, reduced growth, morphological malformations, anuria, gastroschisis, immunosuppression | ✓ | – | – | ✓ |
| Neonicotinoids | Injection, immersion and surface application to embryos | At high doses: teratogenic effects, suppression of neural crest, negative impacts on neural tube survival and heart tube formation | ✓ | – | – | ✓ |
| Heavy metals | | | | | | |
| Lead | Injection, immersion | Developmental abnormalities, reduced hatching success, impaired chick viability | ✓ | ✓ (Obs, Exp[5]) | ✓ | ✓ |
| Mercury | Injection, correlation | Neuro-inflammation, decreased hatchability, embryonic malpositioning, erythrocyte abnormalities, decreased pre-fledging body condition | ✓ | ✓ (Obs) | ✓ | ✓ |
| Copper | Injection, immersion | Mixed metabolic effects, reduced organ growth, reduced vital organ growth, increased oxidative damage, hepatocyte damage and necrosis, increased malondialdehyde, reduced glutathione, structural malformation (when combined with other pollutants) | ✓ | – | – | ✓ |
| Plastics | Injection | Heart defects, death of neural crest cells, organ and tissue malformations | ✓ | – | – | ✓ |

[1] Includes studies of wild birds held in captivity.
[2] Studies included species with altricial or semi-altricial young.
[3] Studies included species with precocial or semi-precocial young.
[4] Observational studies.
[5] Experimental (*i.e.,* manipulative) studies.

2020). Additionally, PAHs can be inhaled following natural or anthropogenic combustion (Abdel-Shafy and Mansour, 2016). The molecular response pathway following PAH ingestion is well characterized and highly conserved across vertebrates and invertebrates. PAHs and other contaminants (*e.g.*, dioxin-like compounds) activate the aryl hydrocarbon receptor (AhR), a transcription factor that then translocates to the nucleus and induces expression of target genes with AhR-responsive DNA elements, including cytochrome P450 1A (CYP1A). CYP1A enzymes oxidize PAHs and other foreign chemicals that bind to the AhR, which facilitates their excretion by increasing their water solubility. In addition, the CYP1A enzymes can also bioactivate and result in increased toxicity of the metabolized or secondary compounds produced (Franci et al., 2018; Rothhammer and Quintana, 2019; Zhu et al., 2019). Activation of AhR-dependent detoxification typically increases the production of reactive oxygen species and oxidative stress, although the AhR pathway is also a mediator of the antioxidant system that protects against oxidative stress (Grishanova and Perepechaeva, 2022).

*Pre-hatching exposure to oil and PAHs*

Oiling of eggs can block egg pores, thus reducing embryonic oxygen availability (Hoffman, 1978), and this in combination with direct transfer of PAHs (Goodchild et al., 2020), can induce embryotoxic effects (Hoffman, 1978). The principal route of embryonic exposure, however, appears to be through maternal deposition of PAHs into lipophilic components of the egg (Franci et al., 2018). Embryonic exposure to PAHs results in reduced heart rate, metabolic rate (Goodchild et al., 2020), embryonic growth rate (Hoffman, 1978), and embryo viability (Hoffman, 1978; Franci et al., 2018; Goodchild et al., 2020) in addition to teratogenic effects including incomplete or abnormal skull ossification (Hoffman, 1978). Reduced embryonic growth rate may prolong the incubation period, resulting in increased energetic costs for parents (Goodchild et al., 2020), which may lead to increased nest abandonment or reduced subsequent reproductive success. *In ovo* exposure to PAHs also results in small changes to methylation of the CYP1A promoter region which persist until shortly after hatching (Brandenburg and Head, 2018) and may impact the regulation of the AhR pathway.

*Post-hatching exposure to oil and PAHs*

Post-hatching, young birds can ingest or inhale oil and PAHs, however little is known regarding the effects of mode of exposure on developmental outcomes. Sub-lethal ingestion of certain crude oils by semi-precocial (*i.e.*, herring gull, *Larus argentatus*; Atlantic puffin, *Fractercula arctica*) and precocial chicks (*i.e.*, mallard, *Anas platyrhynchos*) generally results in depressed growth, hypertrophy of hepatic, adrenal, and nasal tissue, and osmoregulatory impairment (Miller et al., 1978; Peakall et al., 1982, 1983), although these effects depend on the type of crude oil ingested (Peakall et al., 1983). Osmoregulatory impairment has been further investigated in mallard ducklings, for which a single oral dose of crude oil halted development of an adaptive response to

**Table 2**
Summary of studies investigating the effects of post-hatching (*i.e.,* hatching through fledging) contaminant exposure on birds; see text for details and reference citations.

| Chemical category | Method of exposure | General effects | Lab studies[1] | Field studies | Altricial[2] | Precocial[3] |
|---|---|---|---|---|---|---|
| Oil and associated PAHs | Ingestion | Hypertrophy of hepatic, adrenal, and nasal tissue, osmoregulatory impairment, hemolytic anemia and histological lesions (at high doses), altered red cell morphology, Heinz body formation, endocrine disruption, reduced growth, subcutaneous fat, thymus, and bursa | ✓ | ✓ (Exp[5]) | – | ✓ |
| Dioxin and dioxin-like compounds | Ingestion, correlation | Immunosuppression, altered cardiac development, liver enlargement, decreased bursa weight, endocrine disruption, asymmetrical brain regions, vitamin A deficiency | ✓ | ✓ (Obs[4]) | ✓ | ✓ |
| Flame retardants (FRs) | | | | | | |
| PBDEs | Injection, dietary exposure of parents | Impaired reproduction, altered immune response, reduced viability | ✓ | ✓ (Obs) | ✓ | ✓ |
| Organophosphate FRs | Ingestion | Behavioral changes, decreased metabolism and growth, changes to thyroid structure | ✓ | – | – | ✓ |
| Pesticides | | | | | | |
| Organophosphate pesticides | Ingestion | Reduced brain cholinesterase activity, immunosuppression, reduced white blood cell counts, reduced body weight, impaired thermoregulation | ✓ | ✓ (Obs, Exp) | ✓ | ✓ |
| Neonicotinoids | None | Indirect food web effects (hypothesized) | – | – | – | – |
| Heavy metals | | | | | | |
| Lead | Ingestion, injection, correlation | Variable, can include lower survival, decreased health, increased oxidative stress | ✓ | ✓ (Obs, Exp) | ✓ | ✓ |
| Mercury | Ingestion, correlation | Endocrine disruption, reduced later reproductive success, accelerated telomere attrition | ✓ | ✓ (Obs) | ✓ | ✓ |
| Copper | Ingestion | Reduced bursa of Fabricius growth, reduced lymphocyte production, reduced cell-mediated response, anemia, liver and GI tract damage | ✓ | ✓ (Obs) | ✓ | ✓ |
| Plastics | Ingestion | Reduced body mass and growth, altered serum chemistry, damage and inflammation of GI tract and spleen, kidney damage | – | ✓ (Obs) | ✓ | ✓ |

saltwater ingestion (*i.e.*, increased water and $Na^+$ transport across the intestinal mucosa) and abolished this response when it previously existed (Crocker et al., 1974). High doses (10 ml/kg) of crude oil appear toxic to avian red blood cells due to destructive oxidative damage, inducing severe hemolytic anemia. It can also alter red blood cell morphology, degenerate their mitochondria, and induce Heinz body formation (Leighton et al., 1983; Leighton, 1985). High doses of crude oil in semi-precocial chicks (*i.e.*, herring gull and Atlantic puffin) also leads to maladaptive morphological changes, including reduced subcutaneous fat, reduced thymus and bursa, and histological lesions in liver, spleen, bone marrows, kidney, thymus and adrenals (Leighton, 1986).

Crude oil ingestion also affects avian endocrine development, specifically the hypothalamic–pituitary–adrenal (HPA) and hypothalamic-pituitary-thyroid (HPT) axes (Peakall et al., 1981; Rattner and Eastin, 1981). Corticosterone, the primary avian glucocorticoid increases for up to two weeks following a single oral dose of crude oil in black guillemot (*Cepphus grylle*) and herring gull nestlings (Peakall et al., 1981), and is depressed after chronic dosage in mallard ducklings (Rattner and Eastin, 1981), in a classic response of the HPA axis to chronic stress. Thyroxine (a thyroid hormone) also exhibits a short-term increase in circulating concentration following a single oral dose of crude oil (Peakall et al., 1981), but no long-term changes in concentration were observed following chronic dosage (Rattner and Eastin, 1981).

Very few studies have investigated fitness effects of early-life sublethal doses of crude oil or PAHs in birds, a necessary next step in understanding the population-level consequences of such exposure. Dose-dependent studies are particularly useful given the range of exposure levels in wild birds. In wild Cassin auklets (*Ptychoramphus aleuticus*) crude oil dosing of adults decreased laying at all doses (high, medium, low), and decreased hatching success of eggs at high doses. However, for those chicks that did hatch, growth rate and fledging success were unchanged compared to controls (Ainley et al., 1981). These results support a strong effect of maternal deposition of PAHs on embryo viability; however, this mechanism of exposure may not have long-term consequences for surviving chicks. Instead, direct post-hatching exposure of chicks is probably more important. Further research is needed on the importance of mode of exposure and avian developmental mode (*i.e.*, precocial vs. altricial) for exposure outcomes.

## Dioxin and dioxin-like compounds: Polychlorinated biphenyls (PCBs) and 2,3,7,8-tetrachlor-odibenzo-p-dioxin (TCDD)

Dioxins are naturally released through volcanoes and forest fires, while anthropogenic sources include incineration of waste, manufacture of pesticides, chlorine bleaching of paper/pulp (Antos et al., 2015), and agriculture (Amaral-Sliva et al., 2020). Dioxins and dioxin-like compounds produce toxic effects in a wide variety of organisms through the aryl hydrocarbon receptor signaling pathway, which is highly conserved across vertebrates and invertebrates (see "Oil and associated polycyclic aromatic hydrocarbons"). In birds, variation in sensitivity to dioxins and dioxin-like compounds is associated with amino acid identities within the AHR1 ligand binding domain (sites 324 and 380 specifically) (Karchner et al., 2006; Head et al., 2008). This allows classification of birds genotypically into high, low, and moderate sensitivity groups (Farmahin et al., 2013). There are several classes of dioxins and dioxin-like compounds, including polychlorinated dibenzo-*p*-dioxins (PCDDs, 75 congeners), polychlorinated dibenzofurans (PCDFs, 10 of which are dioxin-like), and polychlorinated biphenyls (PCBs, 12 of which are dioxin-like) (White and Birnbaum, 2009). In this review, we focus on two dioxin and dioxin-like compounds, 2,3,7,8-tetrachlor-odibenzo-p-dioxin (TCDD), and selected PCBs.

TCDD is generally considered the most toxic PCDD (Amaral-Sliva et al., 2020), while PCBs encompass a very large group of compounds that vary according to their toxic equivalency (TEQ) as well as their effects on endocrine systems (see Ottinger & Dean, 2011, 2022). PCBs have a very long half-life in the environment and remain chemically

stable in the sediment and become available when the sediment is disturbed (*e.g.*, rain events and dredging). TCDD and PCBs are lipophilic and can cross cellular membranes to bind cytoplasmic AhR receptors (Head and Kennedy, 2007; Yu et al., 2017; Hale et al., 2019; Amaral-Sliva et al., 2020). Wild birds exposed through their diet store these lipophilic compounds in their fatty tissue, which females then pass onto their offspring by maternal deposition into their eggs (Bohannon and Ottinger, 2017). There are many studies on the effects of dioxins and dioxin-like compounds in birds, and further information on the mechanisms that affect differential sensitivities between species (Bianchini and Morrissey, 2020). Most notably, recent approaches using Adverse Outcomes Pathways (AOP) bring together mechanisms of action with outcomes for the individual and consequently the population (Doering et al., 2018; Villeneuve et al., 2014). This AOP is useful for dioxins and dioxin-like compounds and includes understanding the actions of pesticides and other environmental chemicals (see below).

*Pre-hatching exposure to TCDD and PCBs*

Sublethal exposure to TCDD *in ovo* in domestic chickens has long-term effects on metabolism and immune function in chicks, including increased metabolic costs and diminished immune responses (Amaral-Sliva et al., 2020), and the development of brain asymmetries, especially in the forebrain and tectum (Henshel, 1998). Similarly, exposure to PCBs during embryonic development resulted in deformities and impacted immune function in chickens (Lavoie and Grasman, 2007). In the laboratory, there are numerous effects that span effects on cardiac development, gene expression, gross abnormalities, and endocrine disruption (Carro et al., 2018; Dean et al., 2018, 2019; Ottinger et al., 2018). In the field, observational and experimental studies document both short- and long-term effects of exposure to PCBs and/or PCDDs in a variety of precocial/semi-precocial (*e.g.*, gulls, terns), and altricial/semi-altricial species (*e.g.*, herons, swallows, wrens, bluebirds, chickadees, starlings, osprey, kestrel, eagles). These effects include edema and beak defects, brain asymmetry, altered vitamin A status, shortened limbs, immunosuppression, heart deformities, bone abnormalities, and reduced thyroxine, hatchling mass, and hatching success (Harris and Elliott, 2011). In the Great Lakes region of the United States, PCB exposure *in ovo* is associated with increased mortality and abnormalities (*i.e.*, Great Lakes embryo mortality, edema, and deformity syndrome) in embryos and chicks of bald eagles (*Haliaeetus leucocephalus*), cormorants, gulls, and terns (Fry, 1995). Indeed, the presence of deformities was once considered a diagnostic of Great Lakes contamination and the negative effects on wildlife. Laboratory studies, however, have failed to replicate the syndrome, and the cause-and-effect relationship between PCBs and the deformity syndrome has since been questioned through reanalysis of historical data and alternative explanations (Harris and Elliott, 2011). Interestingly, dosing female zebra finches with PCBs had effects on the song brain system of the offspring (Hoogesteijn et al., 2008). This supports the importance of considering maternal deposition of hormones, other chemicals, and environmental chemicals on the developing embryo. Changing global temperatures may exacerbate the effects of toxins such as PCBs. For example, incubation temperature can interact with PCB-126 exposure *in ovo* to affect embryo and chick mortality, and the probability of hatching with a distended yolk, which is often fatal, in killdeer (*Charadrius vociferus*; Lunny et al., 2020).

*Post-hatching exposure to TCDD and PCBs*

The effects of dioxins and dioxin-like compounds have been extensively examined over a range of chemicals. As reviewed by White and Birnbaum (2009), there are numerous adverse health effects of these compounds across vertebrate species, including wild birds (reviewed in Harris and Elliott, 2011). Liver enlargement may be a generalized response, although in black guillemots this effect was sex-specific, and no effect on organ size was observed in tree swallows (*Tachycineta bicolor*; reviewed in Harris and Elliott, 2011). Decreased bursa of fabricius weight has also been observed in common tern and American kestrel chicks exposed to PCBs post-hatch, with possible negative impacts on immune function (reviewed in Harris and Elliott, 2011). For the many correlative wild studies, separation of *in ovo* and post-hatch exposure is not possible, because concentrations of PCBs and TCDD in tissues may reflect either exposure route. These studies, in both semi-precocial and altricial birds suggest effects on heart weight and shape, decreases in some thyroid hormones, immunosuppression, and decreases in vitamin A stores. Studies in tree swallows showed increased heart abnormalities that were observed at hatch (Carro et al., 2018). Laboratory studies of captive birds also support decreases in vitamin A in association with PCBs and changes to immune and endocrine function (Harris and Elliott, 2011). Very few studies examine long-term effects on fitness and productivity of early-life exposure to dioxins and dioxin-like compounds, and this is a much-needed area of research.

## Flame retardants (brominated and chlorinated compounds, and organophosphates)

Flame retardants (FRs) are chemical additives that prevent or delay fire propagation in combustible materials. They are incorporated into a wide variety of materials, including textiles, electronics, vehicles, and polyurethane foams, and are critical for preventing injuries, mortalities, and loss of property, worldwide (Pantelaki and Voutsa, 2019). FRs are classified into three categories based on chemical composition: (1) inorganic FRs, (2) halogenated FRs, including brominated and chlorinated FRs, and (3) organophosphorus-containing FRs (Pantelaki and Voutsa, 2019). Between avian species there appears to be a high degree of variation in sensitivity to each chemical (Guigueno and Fernie, 2017).

*Brominated and Chlorinated FRs*

Brominated and chlorinated FRs are the cheapest available FRs, and thus extensively used in manufacturing. This group of halogens encompasses the high-profile compounds dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyl (PCB), and hexachlorobenzene (HCB), and polybrominated diphenyl ethers (PBDEs). Many of these compounds have been added to the Stockholm Convention, which entered into force in 2004, because of the high bioaccumulation levels in top predators, adverse health effects, and environmental persistence (Guigueno and Fernie, 2017). Brominated and chlorinated compounds have since decreased substantially in the environment (Guigueno and Fernie, 2017), although their residues continue to be detected across a diverse range of environments (Choo et al., 2019). Here, we focus on PBDEs which were banned from use and production in the European Union and voluntarily phased out in the United States because of their status as a persistent organic pollutant (POP) (Pantelaki and Voutsa, 2019). However, PBDEs are resistant to degradation by heat, light, acids, bases, and reducing or oxidizing compounds (Rahman et al., 2001), and thus are persistent in the environment (Choo et al., 2019), making them a continuing pollutant of concern.

*Pre-hatching exposure to polybrominated diphenyl ethers (PBDEs)*

Avian embryos can be exposed to PBDEs through maternal transfer into eggs, although the relationship between maternal and egg contaminant concentrations can be variable (Eng et al., 2013). Embryonic effects of PBDEs appear to depend on species, with some species displaying higher sensitivity than others. For example, egg cell injection of PBDE in American kestrels (*Falco sparverius*) resulted in delayed hatch, shorter humerus length, reduced total thyroid weight, and elevated levels of oxidized and reduced glutathione, thiobarbituric acid reactive substances, and 8-OH-dG, which are markers of oxidative stress and DNA damage in embryos (Rattner et al., 2013). However, common tern (*Sterna hirundo*) eggs exposed to the same concentrations of PBDE displayed only delayed hatch times and some evidence of oxidative DNA

damage, but no effects on humerus length, organ weight, or glutathione and thiobarbituric acid levels (Rattner et al., 2013). No effect of embryonic PBDE or PBDE-congener exposure has been found on hatching success in American kestrels, common terns (Rattner et al., 2013), or zebra finches (*Taeniopygia guttata*) (Winter et al., 2013), and no long-term effect was found on growth of chicks, hematocrit, hemoglobin, or thyroid hormone levels at sexual maturity in zebra finches (Winter et al., 2013). However, long-term effects on reproductive success were found in zebra finches, with birds exposed pre-hatching to the PBDE-congener BDE-99 having smaller clutch sizes and longer time intervals between laying and producing offspring with significantly smaller pre-fledging body mass (Winter et al., 2013). In the American kestrel, PBDEs can reduce eggshell thickness, leading to increased vulnerability to predation and reduced viability as well as adversely affecting immune responses (Fernie et al., 2005, 2009; Buck et al., 2020). Exposure to PBDEs can also impair pipping behavior (McKernan et al., 2009) and is correlated with reduced reproductive success at high concentrations (*i.e.,* above 1,000 ng/g ww) in wild, free-living osprey (*Pandion haliaetus*; Henny et al., 2009).

*Post-hatching exposure to PBDEs*

Post-hatching exposure to PBDEs in wild avian species can disrupt endocrine function (Fernie et al., 2005; Guigueno and Fernie, 2017). PBDEs have been implicated in neurobehavioral abnormalities in birds, but few effects were found in exposed chicks, suggesting that avian neural tissue is more vulnerable *in ovo* (reviewed in Guigueno & Fernie, 2017). Growth of zebra finch and European starling (*Sturnus vulgaris*) chicks dosed with PBDEs post-hatching was not affected by the exposure (Eng et al., 2014; Currier et al., 2015). Conversely, post-hatch exposure to BDE-99 did exert long-term effects on mating behavior in zebra finches (Eng et al., 2012); pre-hatch exposure resulted in effects on the song control system (Eng et al., 2018). Assessing the sublethal effects of these compounds on nestling birds using growth as a physiological endpoint may be too simplistic and more nuanced physiological indicators may be needed to understand the impacts of these compounds on nestling wild birds.

*Organophosphate Flame Retardants (FRs)*

In response to the decrease in brominated and chlorinated compounds, organophosphates were introduced as an alternative flame retardant, and are some of the most used flame retardants, today. Organophosphate FRs are not chemically bound to the materials they are added to and are thus easily released into the environment through volatilization, abrasion, and dissolution (Pantelaki and Voutsa, 2019). Like brominated and chlorinated compounds, they can increase rapidly in the environment and high concentrations are observed in avian predators (Guigueno and Fernie, 2017), although less research has been conducted on their toxic effects and bioaccumulation (Pantelaki and Voutsa, 2019). Organophosphates are lipophilic, and thus rapidly distribute into tissues and fate. In this review, we focus on three widely used organophosphate FRs which are contaminants of emerging concern: triphenyl phosphate (TPHP), tris(1-chloro-2-propyl) phosphate (TCPP), and tris(1,3-dichloro-2-propyl) phosphate (TCDPP). TPHP is widely used as a flame retardant, plasticizer, lubricant, and in paints, glues, and hydraulic fuel (Guigueno et al., 2019). It rapidly degrades in the environment but can be passed *in ovo* from avian mothers to offspring, suggesting continuous environmental exposure (Guigueno et al., 2019). TCPP and TCDPP are high production organophosphate FRs that are used predominantly in polyurethane foam (Farhat et al., 2013). They are rapidly metabolized in fish, rats, and chicken embryos and so have little potential to bioaccumulate. Unlike TPHP, however, TCPP and TCDPP do not degrade easily in soil or water and so are environmentally persistent (Farhat et al., 2013).

*Pre-hatching exposure to organophosphate FRs*

At environmentally relevant concentrations, *in ovo* exposure to TCPP and TDCPP appear to have little effect on embryonic development or morphology for precocial domestic chickens (*Gallus gallus domesticus*) (Farhat et al., 2013). However, *in ovo* exposure to TCPP and TDCPP at concentrations above currently documented environmental levels had much stronger effects on embryonic development. In domestic chickens, high levels of TCPP are associated with delayed pipping time, reduced structural size, increased liver somatic index (a potentially adaptive response to increased detoxification demands), and upregulation of the xenobiotic metabolizing enzyme CYP3A37, deiodinase I (typically a marker of hypothyroidism), and liver fatty acid-binding protein (involved in fatty acid transport and metabolism; Farhat et al., 2013). High concentrations of TDCPP exposure *in ovo* were associated with impaired embryonic growth, and a reduction in free plasma thyroid hormone (T4) (Farhat et al., 2013), elevated plasma bile acids (Farhat et al., 2014), and markedly impaired gallbladder development in domestic chickens (Farhat et al., 2013), and with hepatic sinusoidal dilation, a sign that circulation is impaired in Japanese quail (Jacobsen et al., 2017). High TDCPP exposure was also associated with upregulation of CYP2H1 and CYP3A37 (Farhat et al., 2013) and differential expression of genes involved in immune function, lipid homeostasis, growth and development, and oncogenesis in domestic chickens (Farhat et al., 2014). Microarray analysis has determined that this differential expression was due to dysregulation of 47 genes at high doses of TDCPP, five of which remained dysregulated at low doses (Farhat et al., 2014). Thus, current levels of TCPP and TDCPP contamination do not appear to pose extreme hazards to avian embryonic development, but increased levels may have dramatic effects.

*Post-hatching exposure to organophosphate FRsguig*

Post-hatching exposure to environmental levels of TPHP is associated with some behavioral and physiological changes, including increased aggression (but not fear behavior or general activity) and suppressed thyroid gland structure in female Japanese quail (*Coturnix japonica*; Guigueno and Fernie, 2017; Guigueno et al., 2019; Hanas et al., 2020). Dosing of TPHP above the documented environmental exposure has additional effects in Japanese quail, including decreased neophobia (Hanas et al., 2020), decreased metabolism and growth in domestic chicks, and enhanced thyroid structure in males, but suppression of thyroid structure in females (Guigueno and Fernie, 2017; Guigueno et al., 2019). Further research into the effects of environmentally relevant levels of organophosphate FRs at early life stages is needed, especially for wild and altricial or semi-altricial birds.

## Pesticides

Here we provide a brief overview of two widely used pesticides of concern for avian wildlife: organophosphate and neonicotinoid insecticides.

*Organophosphate pesticides*

Organophosphate pesticides (OPs) are widely recognized as having lethal and sublethal effects on vertebrate animals, including birds (Mitra et al., 2021). They can include a variety of compounds, such as malathion, parathion, diazinon, chlorpyrifos, and others (Roberts and Reigart, 2013) and range in their fat-solubility (Freed et al., 1976). OPs are toxic to both invertebrates and vertebrates because they irreversibly inhibit the enzyme acetylcholinesterase (AChE), leading to an accumulation of the neurotransmitter acetylcholine and hyperstimulation of cholinergic receptors. This causes symptoms including seizures, respiratory failure, and, eventually, death (reviewed in Mitra et al., 2021). OPs were previously considered safe for non-target vertebrates because they are metabolized and excreted easily. However, OPs and some other AChE inhibitors are metabolically activated such that intermediate

compounds can have high toxicity (Singh et al., 2023). Birds are especially sensitive to OPs, at least in part because birds have higher activity of acetylcholinesterase in their brains than mammals, leading to more rapid binding of organophosphates and other cholinesterase inhibitors to acetylcholinesterase (reviewed in Mitra et al., 2021).

In a review of a spectrum of pesticides, ethoprop was notable due to being highly toxic to birds and wide use (De Montaigu and Goulson, 2020). A separate review by Katagi and Fujisawa (2021) considered the pesticides that are applied to seeds as additional sources of risk for birds, with bioaccumulation of a suite of compounds that could be maternally deposited. In addition, toxicity studies with northern bobwhite quail revealed that the exposure route affected the level of toxicity and inhibition of AChE. Both the parent compound and metabolized secondary products can be toxic (see Katagi and Fujisawa, 2021 for detailed listings). There are documented cases of raptor poisoning with organophosphate pesticides as early as 1985–1995 across the United States, United Kingdom, and Canada (for review, see Mineau et al., 1999). These documented cases of lethality from pesticides resulted from both on and off label use of the compounds, seed treatments, granular pesticides, and contaminated food items. Finally, OPs were one of the major causes of adult avian mortality attributed to toxicosis in the Gulf states according to our search of the WHISPers database.

*Pre-hatching exposure to organophosphate pesticides*

Laboratory studies have demonstrated the embryotoxic effects of OPs on Japanese quail, mallards, chickens, and pheasants (*Phasianus colchicus*). These effects include embryo mortality, malformations of the axial skeleton, anuria, gastroschisis, stunted growth, altered sexual differentiation, edema, immunosuppression, genotoxicity, and decreased hatchability, although effects varied based on the avian species, specific organophosphate insecticide tested, and of course by concentration of insecticide applied (Hoffman, 1990; Uggini et al., 2010; Uggini and Suresh, 2013). These studies typically involve immersion of eggs in pesticides, topical application of pesticides on eggs, or injection of pesticides into the egg cell. Immersion of eggs is unlikely in the field; thus, this route of exposure is probably not ecologically relevant. Topical application in natural settings is possible if pesticides are deposited onto eggs from parent plumage (Fry, 1995), although ecologically relevant concentrations via this route are unknown.

Regarding the ecological validity of injections into the egg cell, it is currently unclear whether OPs are maternally deposited in eggs and/or pose a risk to the developing embryo. Some OPs are lipophilic and may accumulate in fatty deposits (Freed et al., 1976), thus it is possible that they may maternally transfer to egg yolks as documented with other lipophilic compounds such as methoxychlor, an organochlorine pesticide (Ottinger et al., 2005), and soy phytoestrogens (Lin et al., 2004; Ottinger et al., 2009). However, organophosphates are typically much more rapidly metabolized than organochlorines (Mitra et al., 2021 but see Freed et al., 1976 for some exceptions), and thus may not persist in eggs or be transferred at all. Thus, the ecological relevance of studies that use injection of organophosphate insecticides into eggs (*e.g.*, Lehel et al., 2014) is unknown. At least two studies have documented cross-generational effects of pesticide mixtures including organophosphates in birds (*i.e.*, domestic chicken and gray partridge, *Perdix perdix*; Gaffard et al., 2022; Khan et al., 2015). In both the mechanism of parental effects on offspring was unknown and the pesticide mixture included another class of pesticide that is known to be maternally deposited in eggs (Khan et al., 2015; Liu et al., 2017; Gaffard et al., 2022). Future research on ecologically relevant exposure pathways for avian embryos is needed to establish relevant experimental paradigms for pre-hatching effects of OPs in birds.

*Post-hatching exposure to organophosphate pesticides*

Young birds are probably exposed to OPs in the same ways that adults are, through the food supply and for more precocial chicks, the environment. Nestling birds may be more sensitive to sublethal doses of organophosphate pesticides than adults (Grue and Shipley, 1984), although effects vary somewhat by species, dosage, pesticide, timing and duration of exposure, and measured trait. Sublethal effects of organophosphate pesticide exposure in young birds include reduced body weight in nestling European starlings (*Sturnus vulgaris*) and white-throated sparrows (*Zonotrichia albicollis*), sometimes resulting in reduced body weight at fledge (see Grue et al., 1997). Free-living nestling European starlings orally dosed with dicrotophos at 5- and 15-days old had reduced brain cholinesterase activity (Grue and Shipley, 1984). Exposures to methidathion and chlorpyrifos in domestic chicks were associated with reduced white blood cell counts, neutrophils, and lymphocytes, while effects on packed cell volume, hemoglobin, and red blood cell counts were pesticide specific (Ojezele and Abatan, 2009). Similarly, oral exposure to organophosphate pesticides resulted in dose-dependent immunotoxicity (decreases in humoral immunity, cell-mediated immunity, and phagocytic activity, pathological changes to the bursa of Fabricius, spleen, and thymus) in chicks (Shahzad et al., 2015). Organophosphates can also impair thermoregulation (Grue et al., 1997; Mitra et al., 2011), an effect that has been noted in mallard ducklings, resulting in increased mortality at low ambient temperatures, but within thermoneutral range for mallard ducklings (Martin and Solomon, 1991). Apparent hypothermia may be an adaptive response to toxins, lowering body temperature to reduce effects of toxins (reviewed in Grue et al., 1997), but this effect can clearly be lethal when weather conditions are not favorable. Taken together, organophosphate pesticides of various types appear to have highly toxic effects at all life stages, with adverse effects on neural and associated behaviors posing risks for productivity. Although some of the most potent compounds are no longer used in high quantities, many have become legacy chemicals, with residues still available in the environment to affect wildlife.

*Neonicotinoids*

Neonicotinoid insecticides have been used since the 1990′s to protect crops and lawns, and to kill fleas and ticks on domestic animals and are still of global importance (Matsuda et al., 2020). This class of insecticides are agonists that bind to nicotinic acetylcholine receptors (nAChRs) of postsynaptic neurons, leading to nervous stimulation at low concentrations, paralysis, and death at high concentrations (Kundoo et al., 2018). Neonicotinoids have high selective toxicity to insects, because of their stronger binding to insect nAChRs than those of vertebrates (Kundoo et al., 2018), making them highly preferred over organophosphates that have high toxicity for humans and wildlife (Gobeli et al., 2017). However, there is growing concern that neonicotinoids may have adverse effects on non-target organisms, including birds (Li et al., 2020). Neonicotinoids are systemic in action, and are widely applied to seeds, after which they spread throughout the growing plant (Kundoo et al., 2018). They are also water soluble and therefore pose a threat to both aquatic and terrestrial animals (Wood and Goulson, 2017). For a thorough review of neonicotinoid toxicity and exposure routes for wildlife we refer the reader to Gibbons et al. (2015) and Wood et al. (2017).

*Pre-hatching exposure to neonicotinoids*

Birds are believed to be exposed to neonicotinoids *in ovo* through maternal transfer and/or through contact of the egg with neonicotinoids and diffusion through the egg membranes. Several studies have demonstrated negative effects of neonicotinoid (specifically imidacloprid) exposure to avian embryonic development at a range of exposures, including teratogenic effects, suppression of neural crest generation, and depressed neural tube cell survival, and negative impacts on heart tube formation (Hussein et al., 2014; Gao et al., 2016; Hussein and Singh, 2016; Liu et al., 2016; Salvaggio et al., 2018). However, environmentally relevant exposure levels were frequently not considered in these studies, where the interest lay in modeling effects on human health outcomes. In contrast, a study in Japanese quail found that injection of

imidacloprid into the egg cell resulted in no morphological changes to the heart, liver, lungs, or kidneys (Gobeli et al., 2017).

Neonicotinoid exposure can also have indirect effects on young bird development, through effects on parents. For example, a reduced cellular immune response was detected in partridge chicks whose parents were fed imidacloprid-treated seeds as 20 % of their diet. Imidacloprid was not detected in the egg yolk, thus this effect does not appear to be due to maternal transfer, but rather an indirect mechanism (Lopez-Antia et al., 2015). Although the mechanism resulting in immune changes in offspring is unclear, imidacloprid-treated parents displayed reduced clutch sizes, delayed laying, and higher levels of carotenoids and vitamins in yolks produced (probably due to smaller clutch sizes; Lopez-Antia et al., 2015). Future studies are needed of both wild avian species exposed to ecologically relevant concentrations of neonicotinoids, and of the impact of timing of exposure on developmental outcomes.

*Post-hatching exposure to neonicotinoids*

Very few studies have investigated the impacts of early-life post-hatching exposure to neonicotinoids on birds. However, for insectivorous birds, indirect effects probably include reduced food supply related to the collapse of insect populations following neonicotinoid treatment (reviewed in Gibbons et al., 2015). Recent evidence suggests negative effects of neonicotinoids on non-target insect species (reviewed in Wood and Goulson, 2017), and this disruption to the food web is suspected to contribute to large scale declines of birds in correlation with neonicotinoid use (Li et al., 2020). However, nearly all studies on the toxicity of neonicotinoids for non-target insect species have been conducted in honeybees (*Apis mellifera*), and increased research is needed in other invertebrates (Wood and Goulson, 2017). Indirect food web effects are difficult to identify experimentally, and further studies are necessary to establish a causal link between neonicotinoid use, food supply, and bird population sizes and reproductive success. Direct effects of neonicotinoid exposure on young birds are essentially unknown and warrant further investigation given the apparent toxicity of neonicotinoids on adult birds at ecologically relevant doses (Addy-Orduna et al., 2019), and the documented and predicted exposure of many bird species across foraging guilds (*e.g.*, insectivorous, nectivorous, granivorous, frugivorous, omnivorous; Anderson et al., 2023; Bishop et al., 2020; Gibbons et al., 2015; Wood and Goulson, 2017).

## Heavy metals

In the WHISPers database, heavy metals were the main toxicological cause of avian mortality in the northern Gulf of Mexico over the past ten years. Here, we focus on the three most significant and well-researched metals from the standpoint of toxicology and environmental contamination: lead, mercury, and cadmium (Scheuhammer, 1987) as well as copper, which was identified as a major cause of avian mortality in our WHISpers database search. Young birds are particularly sensitive to toxic effects of metal exposure, and altricial species tend to be more vulnerable than precocial species (Scheuhammer, 1987).

### *Lead (Pb)*

A large body of research has demonstrated the significant health risks of lead to humans and wildlife (Scheuhammer, 1987; Roux and Marra, 2007; Pain et al., 2019). In response, the United States phased out several major sources of environmental lead following the establishment of the Clean Air Act including lead-based paint and leaded gasoline in 1978 and 1986, respectively. The U.S. also banned lead shot for waterfowl hunting in 1991, and a growing number of states have banned the use of small lead fishing weights (Roux and Marra, 2007; Pain et al., 2019). However, a variety of sources of lead contamination continue to exist in the U.S., including mining and smelting operations (Besser et al., 2007), and most notably for birds, lead-based ammunition, which is unregulated except for in waterfowl hunting and poses a significant health threat to scavenging birds (Bellinger et al., 2013). Because lead is non-biodegradable and continues to be used world-wide, concentrations accumulate in the environment and pose a risk to wildlife including birds (Roux and Marra, 2007; Rainio et al., 2015).

Birds are exposed to lead primarily through water and food and secondarily through inadvertent or purposeful soil consumption, or dermal absorption while swimming (Beyer et al., 1994; Burger, 1995). Lead has a long residence time in the environment and bioaccumulates in plants and animals (Burger and Gochfeld, 1994; Roux and Marra, 2007; Rainio et al., 2015; Usman et al., 2020). Plants absorb lead through the soil and store it primarily in leaves and seeds (Olivares, 2003). Birds are then exposed to accumulated lead directly through consuming fruits, or indirectly by consuming phytophagous insects and soil invertebrates (Roux and Marra, 2007). Birds can also be exposed by consuming meat contaminated with lead ammunition (Plaza and Lambertucci, 2019), ingesting spent lead ammunition or fishing lures in the environment (Pain et al., 2019), or ingesting soil directly (Beyer et al., 1994). Dietary lead accumulates predominantly in the bones, livers, and kidneys of birds (Scheuhammer, 1987; Pain et al., 2019), and in adult birds, females accumulate lead faster than males, especially during egg formation and laying (Scheuhammer, 1987). Ingested lead can also be excreted by birds through normal excretion, deposition in the uropygial gland, salt gland, or feathers, or through excretion into egg contents or eggshells (Burger and Gochfeld, 1991, 1994). Young birds can thus be exposed to lead through maternal deposition in eggs, or through post-hatching diet. See Franson & Pain (2011) Pain et al. (2019) for reviews of the effects of lead in different avian taxa.

*Pre-hatching exposure to lead*

Studies on the pre-hatching effects of lead exposure in wild bird populations have elucidated significant effects on embryonic development. Exposure to lead during critical stages of embryogenesis can induce a myriad of adverse outcomes, including developmental abnormalities, reduced hatching success, and impaired chick viability (reviewed in Burger, 1995; Burger and Gochfeld, 2000; Kertész and Fáncsi, 2003). Furthermore, the transgenerational transmission of lead toxicity via egg deposition underscores the long-term ecological implications of anthropogenic lead contamination in avian habitats (Burger, 1994).

*Post-hatching exposure to lead*

The effects of early post-hatching lead exposure on developing birds appear to depend on dosage, species, and exposure route. Herring gull chicks experimentally exposed to post-hatching lead had significantly lower survival rates, were less healthy (measured by begging and walking scores and by the number of times they stumbled when walking) and had a lower degree of accuracy when pecking at parents' bills to stimulate feeding (Burger and Gochfeld, 1994). These deficits were homologous to those observed in the field among chicks with high lead exposure (Burger and Gochfeld, 1994). In contrast, experimental manipulation of lead levels in great tit (*Parus major*) nestlings revealed few effects on growth, physiology (*i.e.*, glucocorticoid metabolites, aminolevulinate dehydratase activity, hematocrit, heat shock proteins), and survival (Eeva et al., 2014; Rainio et al., 2015) and only minor effects on oxidative status or phagocytosis (Rainio et al., 2015). However, great tits exhibited strong effects on growth and physiology of being in a nest near a smelter that were not duplicated when birds were dosed with lead, suggesting secondary effects of pollution on the food supply (Eeva et al., 2014). These secondary effects are difficult to replicate in a laboratory and warrant further investigation.

### *Mercury*

Mercury is naturally found in coal and heavy-metal rich geologic deposits and released by humans intentionally through mining

operations, and unintentionally through fossil-fuel combustion. Global mercury releases have increased steeply since the 16th century and today are dominated by fossil-fuel combustion, especially by coal-fired power plants, and artisanal gold mining operations in developing countries (Krabbenhoft and Sunderland, 2013). Once released from natural deposits, environmental mercury is readily converted by bacteria to methylmercury (MeHg; Paris et al., 2018). MeHg is highly bioavailable, can cross cell membranes and the blood–brain barrier, and can biomagnify at higher trophic levels (Paris et al., 2018). Historically, MeHg was thought to primarily impact piscivorous species. However, it is also widespread in terrestrial food webs via emergent aquatic insects that are consumed by birds (Ackerman, et al. 2016). Changes in temperature and hydrology due to climate change are also predicted to alter mercury biogeochemical cycles (Krabbenhoft and Sunderland, 2013). Increased precipitation is expected to increase deposition of mercury from terrestrial to aquatic environments; increased frequency, scale, and intensity of wildfires is expected to mobilize mercury stores in soils; finally, changes to ocean productivity, circulation and oxygen minimum zones is expected to alter methylmercury formation (Krabbenhoft and Sunderland, 2013). Generally, studies indicate that methylmercury production and bioaccumulation in aquatic systems will be accelerated under climate change predictions (Krabbenhoft and Sunderland, 2013). Mercury concentrations in blood and organs can vary throughout avian development due to changes in sequestration, mass dilution, maternal deposition, and diet. For birds with both precocial (*i.e.*, American avocets, *Recurvirostra americana,* and black-necked stilts, *Himantopus mexicanus*) and semi-precocial young (*i.e.*, Forster's terns, *Sterna forsteri*), mercury concentration in internal tissues follows a U-shaped pattern with highest concentrations occurring at hatching and fledging (Ackerman et al., 2011).

*Pre-hatching exposure to mercury*

*In ovo*, methylmercury has similar accumulation patterns to that of adult birds, accumulating in the liver, kidneys, and feathers. This sequestration of methylmercury is advantageous by preventing the toxin from accumulating in other vital tissues. By embryonic day 19, chicken embryos appear to be able to demethylate methylmercury in the liver, an additional protective mechanism for embryonic exposure (Rutkiewicz and Basu, 2013). Despite these mechanisms, mercury appears to accumulate in the brain tissue of exposed embryos and hatchlings, at comparable levels to those found in adult birds following mercury exposure through diet. Thus, neurotoxicity may be an important effect of mercury for embryos, as well as adults (Rutkiewicz et al., 2013). *In ovo* exposure to ecologically relevant high levels of methylmercury is also correlated with long-lasting increases in telencephalon size, indicating neuro-inflammation in zebra finches, although male courtship behaviors or song quality were unaffected (Yu et al., 2017).

Mercury concentrations in tissues rapidly increase after embryonic day 16 until hatching, most likely because the yolk is absorbed at this point. Thus, embryotoxicity may be most important at the pipping and hatching stages (Rutkiewicz et al., 2013). Methylmercury and total mercury in eggs decreases hatchability (Heddle et al., 2020) and in Forster's terns this occurs at least in part through embryo malpositioning. Embryo malpositioning may occur as a direct result of maternal transfer leading to impaired embryonic motor development, and/or impaired parental care due to parental mercury levels (Herring et al., 2010). Embryo malpositioning appears to be a dose-dependent effect, as malpositioning was not observed in American avocets or black-necked stilts with lower natural levels of total mercury (Herring et al., 2010). Mercury in downy feathers at hatching (reflective of maternal transfer *in ovo*) is also associated with increased erythrocyte nuclear abnormalities and decreased pre-fledging body condition (Santos et al., 2020). However, no significant histopathological or neurochemical changes have been observed in chicken embryos dosed with methylmercury, no behavioral changes were noted in chicks exposed in *ovo* (Rutkiewicz et al., 2013), and embryonic mercury exposure does not appear to correlate with eggshell thickness (Peterson et al., 2020), or later reproductive success of offspring (Paris et al., 2018).

*Post-hatching exposure to mercury*

Post-hatching mercury exposure can alter the hypothalamic–pituitary–adrenal (HPA) axis, although the direction of change is inconsistent across studies. For example, wild Forster's tern chicks with high blood mercury concentrations exhibit lower fecal glucocorticoid metabolite concentrations (Herring et al., 2012), suggesting that chronic mercury exposure may suppress baseline glucocorticoids. Similarly, common loon (*Gavia immer*) chicks show a reduction in the HPA axis stress response following post-hatching mercury dosing (Franceschini et al., 2017). However, wild red kite (*Milvus milvus*) nestlings and juvenile common blackbirds (*Turdus merula*) with high mercury concentrations exhibit elevated corticosterone concentrations in feathers, which is reflective of stress during feather development (Meillère et al., 2016; Powolny et al., 2020). This apparent discrepancy in the direction of glucocorticoid change may be due to sampling differences, species-specific differences in sensitivity or gastro-intestinal metal absorption, or interactions between mercury and other contaminants, or other environmental factors. For example, for red kite nestlings, the best statistical model predicting feather corticosterone also included an interaction between blood mercury and lead concentrations, suggesting that these two heavy metals interact synergistically to affect HPA axis function (Powolny et al., 2020).

When mercury is present at high levels in the nesting environment, young birds would most likely be exposed at both pre-hatching through maternal transfer, and post-hatching through dietary exposure. Thus, several studies have examined the combined long-term effects of these two exposures routes, and have found significantly reduced reproductive success later in life (Paris et al., 2018; Heddle et al., 2020), at least among altricial zebra finches. Developmentally exposed finches hatched 32 % fewer eggs and fledged 50 % fewer juveniles than control birds (Paris et al., 2018). This effect may be sex-dependent, as at least one study has found that combined pre-hatching and post-hatching mercury exposure more strongly affects survival and reproductive success in females than males (Heddle et al., 2020). Additionally, elevated corticosterone concentration was negatively correlated with telomere length, in these same nestlings. This suggests that heavy metal exposure of nestling may lead to accelerated telomere attrition, a signal of biological aging, through an interaction with glucocorticoids (Powolny et al., 2020).

*Copper*

Copper (Cu) was one of the first metals extracted and used by humans. Currently, it is used in building construction, electricity generation and transmission, electronic products, and vehicle manufacturing (Doebrich, 2009). Cu is a component of agrochemicals like fertilizers and pesticides that are used to improve yields and control pests, which contributes to soil contamination (Ab Hamid et al., 2022). Commercial antifouling paints can release high levels of Cu into water (Adeleye et al., 2016). Global production of copper has increased dramatically in recent years and was estimated to be 22 million metric tons in 2023, up from 16 million metric tons in 2010 (Statista Research Department, 2024). Cu is an essential micronutrient and is an additive in commercial poultry and animal feeds, but the bioavailability of copper sulfate (CuSO4), the main supplement form, is low due to the presence of other ingredients that can inhibit absorption (Scott et al., 2016). Therefore, animals can excrete high levels of Cu contaminating soil and water. In humans, acute ingestion of excess Cu can cause gastrointestinal disturbance, including nausea and vomiting, while chronic ingestion can cause liver or kidney damage (United States Environmental Protection Agency, 2009). The increase of Cu compounds in water, sediment, and soils is an emerging environmental concern. In addition, our exploration of toxicological causes of avian mortality in the WHISPers database

revealed that Cu was a major component of deaths attributed to heavy metals.

*Pre-hatching exposure to copper*

Cu has been used to promote growth and health of domestic poultry and commercial feeds often contain high levels of this micronutrient (Scott et al., 2016). As a result, poultry producers have become increasingly interested in using Cu nanoparticles (Cu-NP) to enhance growth of embryos. However, studies that experimentally injected Cu-NP into eggs have had mixed results, with some finding enhanced metabolic rates (*e.g.*, Scott et al., 2016) and others finding reduced metabolism (*e.g.*, Pineda et al., 2013). In addition, some studies found no effect of Cu-NP on organ growth (*e.g.*, Scott et al., 2016) and others found reduced growth of the embryo's vital organs (*e.g.*, Pineda et al., 2013). Growers have also been interested in using various forms of Cu (*e.g.*, copper sulfate or acetate) as a substitute for injection of antibiotics into eggs (Arafat et al., 2019). In general, injection of copper sulfate or acetate into eggs increased hatching weight (Arafat et al., 2019; Hassan et al., 2023). However, these experiments in poultry did not examine high Cu concentrations. Injection of 5 ppm copper sulfate into chicken eggs induced oxidative damage and necrosis of hepatocytes, increased malondialdehyde (a product of polyunsaturated fatty acids peroxidation), and decreased glutathione levels (Oguz et al., 2010).

Most studies of the toxicological effects of Cu on avian embryos have looked at the combined effects of Cu and another environmental pollutant. For example, Lehel et al. (2014) examined the combined effects of CuSO4 and chlorpyrifos on chicken embryos. Injection of 0.05 % CuSo4 into the egg on day 0 of incubation had no effect on early (day 3) embryo mortality but increased mortality (50 %) of late stage (day 19) embryos over that of controls (5 %). When injected with chlorpyrifos on day 0, the combination increased late-stage embryo mortality relative to the control, CuSO4 alone, and chlorpyrifos alone treatment groups. Only one living embryo was found in the combined treatment group, so statistical tests of effects on growth abnormalities could not be performed. Lehel et al. (2021) examined the effects of CuSO4 and glyphosate on chicken embryos. Injection with CuSO4 on day 0 of incubation increased day 19 mortality and reduced body mass over that of controls, while injection with CuSO4 and glyphosate increased mortality over that of either contaminant by itself. Abdomen and leg deformities as well as reduced growth were also found in the combined group on day 19. Immersion of mallard eggs in water contaminated with CuSO4 did not increase mortality or anomalies in embryonic development over that of controls, while immersion in Pb and CuSO4 increased mortality and the malformation rate of embryos over that of controls and treatment with Pb alone (Kertész and Fáncsi, 2003).

*Post-hatching exposure to copper*

Domestic chickens fed a diet supplemented with 800 mg/kg CuSO4 from day 9 post-hatching exhibited reduced growth and significant Cu accumulation in their livers. However, when half of the protein in their casein diet was replaced with soybeans, Cu tissue accumulation was reduced, suggesting that other diet components can mitigate Cu toxicity (Funk and Baker, 1991). Liver and GI tract damage, anemia, and increased mortality was seen in > 3 day old broiler chicks fed a starter ration supplemented with 2140—2393 ppm tribasic Cu chloride (Malinak et al., 2014). The growth of the bursa of Fabricius was inhibited in domestic ducklings fed > 400 mg/kg Cu from day 1 post hatching, suggesting that exposure early in life to high copper concentrations could inhibit humoral immune function (Yang et al., 2009). One day old chickens fed 300 mg/kg CuSO4 also had reduced overall bursa growth, in addition to follicular atrophy, reduced lymphocyte production, and increased inflammation and oxidative damage to the bursa (Guo et al., 2020; Liu et al., 2020). Few studies have examined the effect of copper alone on the growth and health of wild bird nestlings, but Cu was associated with reduced cell-mediated immune response in nestling white storks (*Ciconia ciconia*) four years after a toxic mining spill, but not in the years immediately following the spill (Baos et al., 2006). Given the evidence of negative effects of early-life Cu exposure in domestic birds, and the increased risk of soil and water contamination from animal feeds and human activities (Xiong et al., 2010), some wild birds are likely exposed to high Cu. More research in this area is needed.

## Plastics

Plastic pollution is of growing concern in the Gulf of Mexico region (Grace et al., 2022). Here, we use the recommendations of Grace et al. (2022) for categorizing plastic particles by size. To avoid confusion, we recategorized plastics to match the scale presented in Table 1 of Grace et al. (2022) if a published paper used a different categorization scheme. Entanglement in macro- and megaplastic debris can kill or injure adult birds, the vast majority of which are seabirds (reviewed in Battisti et al., 2019) and entanglement was a leading cause of mortality in our WHISPers search. Birds also incorporate plastics into nesting material which can also entangle and kill adults and nestlings (*e.g.*, Restani, 2023; Votier et al., 2011). Birds may ingest plastics purposefully by mistaking them for edible food items, indirectly through trophic transfer, or incidentally (Grace et al., 2022). Ingestion of plastics by birds can be problematic due to their largely non-digestible nature. Macroplastics are well known to cause physical blockages, damage, or a false sense of satiety in a variety of taxa (Wright et al., 2013). Plastic-induced fibrosis or "plasticosis" was identified in flesh-footed shearwaters (*Ardenna carneipes*), raising concerns about the possibility of this occurring in other species as well as potentially affecting the efficiency of nutrient absorption (Charlton-Howard et al., 2023).

Besides physical damage and obstruction, microplastics pose an ecotoxicological concern for wildlife because they contain chemicals associated with plastic production and can readily adsorb chemicals from the environment at later time points (Grace et al., 2022). These chemicals can leach from plastics following ingestion by wild birds (Tanaka et al., 2019). Many of these chemicals of concern are discussed elsewhere in this review, therefore we do not discuss them further here, but note that the concentration of pollutants can be many times greater on these plastic particles than in the surrounding environment (Yu et al., 2019). However, one study found no relationship between ingested plastic burden and several plastic associated chemicals in the tissues of fledgling northern fulmars (*Fulmarus glacialis*; Collard et al., 2024).

Finally, plastics cannot be regarded as a singular pollutant entity; rather, they represent a diverse array of polymer types, each with distinct chemical compositions and additives. Furthermore, the extent and rate of degradation vary among different polymer types and the degradation process is influenced by environmental factors such as sunlight, temperature, and microbial activity. In addition to degradation, plastic polymers possess varying degrees of adsorption capacity, and through adsorption and desorption processes, can act as vectors for the transport and distribution of harmful substances across ecosystems (Grace et al., 2022). The multifaceted nature of plastics as pollutants underscores the complexity in understanding their effect on wildlife health and addressing plastic pollution comprehensively.

*Pre-hatching exposure to plastics*

Microplastics or larger plastics are unlikely to be deposited into eggs from females, but nanoplastics were transferred into eggs after female laying hens were orally dosed with radioactive micro- and nanoplastics (Shelver et al., 2024). Although only a small percentage (<0.3 %) of ingested plastics were transferred (Shelver et al., 2024), this suggests that nanoplastics can be deposited into the eggs of other avian species. Nanoplastics injected into the vitelline vein of chicken embryos were distributed to many organs but were concentrated in liver and cardiac tissue resulting in heart defects, death of neural crest cells, and widespread malformations of other organs and tissues (Wang et al., 2023).

Wang et al. (2021) recently developed a technique to visually monitor the effects of nanoplastics on the development of quail embryos. More research is needed to understand the implications of the transgenerational effects of nanoplastics, especially in wild birds. Another potential avenue of exposure for bird embryos is through eggshell gas exchange pores. Nanoplastics could be deposited from adult feathers, nesting material, or from the surrounding air. This potential avenue remains largely unexplored. In addition, coastal microplastics increase the temperature of sand in a dose dependent manner (Lavers et al., 2021; Fuentes et al., 2023). This has the potential to increase heat stress in developing embryos of beach-nesting birds in an already warming world.

*Post-hatching exposure to plastics*

Chris Jordan's series photographs of dead seabird chicks with stomachs full of plastic litter from Midway Atoll are well known (Jordan, 2024). Whether these plastics were the direct cause of death is debatable and many researchers have begun looking for potential detrimental effects of plastic ingestion by seabird chicks as well as young of other species. Lavers et al. (2014) found that plastic ingestion can significantly reduce body mass and other morphometric measurements like wing chord length and head-bill length in shearwaters. While others found no association between plastic ingestion and body condition in pre-fledgling shearwaters (Cousin et al., 2015; Verlis et al., 2018), or association with mortality of chicks in waved albatross (*Phoebastria irrorata*; Anderson et al., 2008). Such equivocal results may be due to reliance on simplistic physiological measures like body mass or morphometrics to assess impacts.

Plastics can impact individuals at multiple scales, from nm to cm, so more nuanced physiological indicators may be needed to understand sublethal impacts of plastics on otherwise superficially healthy wildlife. This can be difficult to accomplish in wild species because these techniques are more invasive. Several blood analytes (calcium, uric acid, cholesterol, and amylase) corresponded with the number and mass of ingested plastics in fledgling flesh-footed shearwaters (Lavers et al., 2019). Although few data exist on the blood chemistry of wild birds (Maness and Anderson, 2017), changes in these analytes and blood cell counts can provide information about the health of individuals and threats to populations (Maness and Anderson, 2017; Ottinger et al., 2019; Maness et al., 2023). A recent study examining the tissues of euthanized flesh-footed shearwaters that had failed a fledging attempt found widespread damage and inflammation in GI tract tissues (Rivers-Auty et al., 2023). Plastic burden corresponded with tissue damage in the proventriculus including a reduction in the size and number of tubular glands, reduction in the number of rugae present, and an increase in water content (*i.e.*, edema) indicating inflammation. None of these effects were seen with other ingested hard materials such as squid beaks or pumice. The macroplastic burden in the proventriculus corresponded with the number of ultrafine plastics embedded in the tissues of the proventriculus and spleen, indicating digestive fragmentation of plastics and transfer into the tissues of the GI tract. The embedded ultrafine plastics were associated with tissue damage and inflammation. A mediation analysis found that damage to the proventriculus from the plastics was associated with kidney damage independent of the number of ultrafine plastics embedded in the tissue. This suggests kidney damage from malabsorption, nutritional stress, and dehydration. Together, the results of this study suggest that ingestion of a single macroplastic particle can have long lasting effects on the health of young birds through fragmentation and shedding of smaller plastics that then damage tissues and cause a cascade of downstream pathologies (Rivers-Auty et al., 2023).

## Conclusions

Overall, compelling evidence demonstrates that early-life exposure to these widespread contaminants significantly impacts both the physiology and behavior of birds. In some cases, these sublethal effects can negatively impact hatching and fledging success or have long-term negative effects on longevity and/or reproductive success. Scaling up, these effects may result in declining populations, and/or increased sensitivity to additional stressors (*i.e.*, decreased resilience), especially for resident species and in a more transient manner for migratory species. For example, early-life contaminant exposure often impacts immune function and neuroendocrine organization, which may increase susceptibility to future disease and negatively affect future fecundity and mating/parental behavior, endangering the viability of avian populations. Ultimately, the fitness of the population will be adversely affected. Structured approaches, such as Adverse Outcomes Pathways (Ankley et al., 2010) provide an approach to link mechanistic information to outcomes for individuals and more broadly for populations. Understanding both lethal and sublethal effects of environmental contaminants is critical for management, restoration, and mitigation to reverse the steep decline in wild avian populations.

## Future directions

This review has focused on the phase of avian life history that is least understood, yet most at risk for high extrinsic mortality. Early life is a highly vulnerable transitional period involving rapid anatomical, physiological, neurological, and behavioral changes. Toxicant exposure can disrupt these developmental processes, resulting in long-term alterations to the phenotype with implications for later reproductive success and longevity, and thus population productivity. At the population level, toxicant exposure may act synergistically with developmental vulnerability by increasing general mortality or may act antagonistically by most strongly affecting birds with lower predicted intrinsic fitness. Thus, more basic research on post-hatching and post-fledging survival and their interactions with toxicant exposure in wild birds is needed to better understand the potential risks of exposure during early life (see Custer et al., 2018; Doering et al., 2018). Considering the many gaps in current knowledge regarding early-life exposure to contaminants for wild birds, we recommend the following directions for future research in this field:

(1) Contaminant investigations using ecologically relevant concentrations and exposure routes. Much of our current knowledge of early-life effects to contaminants involve unnatural exposure routes (*e.g.*, submersion of eggs in contaminants), or very high concentrations beyond what is found typically in nature. Ecological relevance is needed to accurately evaluate the potential threat sublethal exposures pose to individuals and populations.
(2) Increased diversity of study organism life histories. Such studies will allow for the determination of species-specific sensitivities and increase our understanding of the factors underlying differential sensitivities to contaminants. Most contaminant exposure research involves domestic precocial birds (*e.g.* chickens, Japanese quail), with few studies conducted in altricial birds for which critical exposure windows may be very different. Such research would allow for differential sensitivities between species to be integrated into predictive models to ascertain potential risk based on bird species and/or life history.
(3) Assessment of the effects of exposure to common chemical mixtures early in life. Early-life effects are often sensitive to compounding effects of multiple stressors and events (*i.e.*, "allostatic load"; McEwen & Wingfield, 2003), such that effects are magnified when multiple stressors are present (Tung et al., 2016). For example, a degraded habitat where heavy metal exposures are high in combination with pesticide exposures may increase the risk of disease in comparison to either exposure, alone.

(4) Naturalistic scenarios involving early-life exposure to contaminants and additional common stressors. Early-life effects of contaminants are typically studied in a laboratory setting, where the timing, duration, and magnitude of exposure can be strictly controlled and where other conditions can be held constant. However, wild organisms do not encounter contaminants and other stressors in a vacuum. In the wild, a hatchling is confronted with many potential stressors at once, for example unpredictable food availability, predators, extreme weather events, parasites, and contaminants.
(5) Evaluation of early-life effects of contaminant exposure across life stages, especially impacts to fitness (*e.g.,* survival and reproductive success). Most currently published studies of early-life exposure track individuals only until shortly after hatching or just before fledging. While long-term studies are logistically difficult, it is imperative to understand the risk of sub-lethal contaminant exposure to population dynamics and persistence.
(6) Mitigation measures beyond reduction of environmental contaminant load should be considered. For example, exposure to organophosphate pesticides can impair foraging behavior (Grue et al., 1997) and decrease prey availability. Supplemental feeding may thus alleviate the impact of these effects on individuals and populations.

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## CRediT authorship contribution statement

**Jacquelyn Grace:** Conceptualization, Writing – original draft, Writing – review & editing. **Elena Duran:** Conceptualization, Writing – original draft, Writing – review & editing. **Mary Ann Ottinger:** Conceptualization, Writing – original draft, Writing – review & editing. **Terri Maness:** Conceptualization, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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