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## Chapter 13

# Environmental influences on hormones and reproduction in reptiles

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## ABBREVIATIONS

ActRII	activin type II receptor	PII	plasma inorganic iodide
AHR1	aryl hydrocarbon receptor 1	PCB	polychlorinated biphenyl
AHR1	aryl hydrocarbon receptor 2	PCNA	proliferating cell nuclear antigen
AR	androgen receptor	PDYN	prodynorphin
AMH	anti-Müllerian hormone	POMC	proopiomelanocortin
BPA	bisphenol A	PRLH	prolactin-releasing hormone
BrdU	bromodeoxyuridine	RBC	red blood cell
CYP11A1	cytochrome P450 11A1	SVL	snout-to-vent length
CYP19A1	aromatase	SOX9	SRY-Box transcription factor 9
CYP1A	cytochrome P450 1A	SF-1	steroidogenic factor-1
DDD	1,1-dichloro-2,2-bis( <i>p</i> -chlorophenyl)ethane	StAR	steroidogenic acute regulatory protein
DDE	1,1-dichloro-2,2-bis( <i>p</i> -chlorophenyl)ethylene	T	testosterone
DDT	dichlorodiphenyltrichloroethylene	T <sub>3</sub>	triiodothyronine
DEG	differentially expressed gene	T <sub>4</sub>	thyroxine
DES	diethylstilbestrol	TGFβ	transforming growth factor β
DHT	dihydrotestosterone	TH	thyroid hormone
E <sub>2</sub>	estradiol-17β	TR	thyroid receptor
EDC	endocrine-disrupting chemical	TRE	thyroid response element
ER	estrogen receptor	TSD	temperature-dependent sex determination
ERα	estrogen receptor alpha	Vtg	vitellogenin
ERβ	estrogen receptor beta		
FSH	follicle-stimulating hormone		
FST	follistatin		
GBR	Great Barrier Reef		
GDF9	growth differentiating factor 9		
HSD3B1	hydroxy-Δ <sup>5</sup> -steroid dehydrogenase, 3β- and steroid 8-isomerase 1		
INHBA	inhibin βA subunit		
INHBB	inhibin βB subunit		
IPCC	Intergovernmental Panel on Climate Change		
IUCN	International Union for Conservation of Nature		
KissIR	kisspeptin		
LWNWR	Lake Woodruff National Wildlife Refuge		
MINWR	Merritt Island National Wildlife Refuge		
MNO	multinucleated oocyte		
MOF	multioocytic ovarian follicle		
MT	methyl thiophanate		
OC	organochlorine		
P <sub>4</sub>	progesterone		
PE	polyethylene		
PFAA	perfluorinated alkyl acids		

## 1 INTRODUCTION

Extant reptiles, excluding birds, include nearly 12,000 species (Uetz et al., 2023) consisting of turtles (Testudines), crocodilians (Crocodylia), lizards, snakes, and amphisbaenians (Squamata), and tuatara (Rhynchocephalia). Along with birds and mammals, reptiles are amniotes, thus they are not directly dependent on access to aquatic environments for reproduction and are found in a wide variety of habitats across broad geographic ranges. Globally, reptiles are most diverse and abundant at lower latitudes, and have higher species richness in arid and semiarid regions than other tetrapods (Roll et al., 2017). Reptiles exhibit diverse life histories and reproductive strategies. For instance, many lizards are relatively small, mature within a year or two, and rarely survive beyond a few years. In contrast, most crocodilians and many species of turtles are large-bodied, take years to reach maturity, and may remain reproductively active for decades. Additionally, reptiles feed at a variety of trophic levels. Some species maintain either a primarily herbivorous

or carnivorous diet throughout their life, whereas others are omnivorous or exhibit an ontogenetic transition between carnivory and herbivory (Cooper & Vitt, 2002; Reich et al., 2007). Reptiles exhibit considerable variation in their modes of reproduction. Although most reptiles are oviparous, viviparity has evolved independently in many lineages of snakes and lizards, with the relative contribution of lecithotrophy versus placentotrophy highly variable among those lineages (Blackburn, 1998). Many oviparous species exhibit temperature-dependent sex determination (TSD) in which primary sex is determined by egg incubation temperature (see Chapter 1 in this volume). The diversity of reptiles and the variation of life histories within and among lineages make reptiles an attractive group for studying environmental influences on hormones and reproduction.

The threats to, and loss of, reptile biodiversity has not received as much attention as other vertebrate classes, but approximately 21% of all species of reptiles are listed as vulnerable, endangered, or critically endangered by the International Union for Conservation of Nature (IUCN) (Cox et al., 2022). Leading threats to reptiles include various forms of habitat destruction and disturbance, and causes not directly related to habitat, such as invasive species and hunting (Cox et al., 2022). Among the threats less likely to cause acute mortality but known or suspected to affect hormone signaling and reproduction are climate change and pollution. As ectotherms, the rates of development, growth, and metabolism, as well as reproductive seasonality of reptiles are highly sensitive and responsive to changes in ambient temperature in ways that may differ from endothermic amniotes. Additionally, oviparous species are potentially at risk of reduced egg viability and/or skewed sex ratios in TSD species if they are unable to adjust nesting behavior in a way that accommodates an unprecedented rate of warming and sea level rise. Although widespread, environmental contaminants pose locally unique problems based on the nature of the contaminants, routes of exposure, and the sensitivity of the affected species. Field-based studies supported by experimental treatments provide strong evidence of altered hormone signaling, disruption of hormone-regulated processes, and impaired reproductive success in reptiles exposed to sublethal concentrations of a variety of anthropogenic chemicals. This chapter examines environmental factors that affect reproduction and hormone signaling in reptiles, with an emphasis on anthropogenic climate change and environmental contamination.

## 2 EFFECTS OF CLIMATE CHANGE ON HORMONES AND REPRODUCTION

All organisms respond to fluctuations in the environment, and predictable, seasonal changes in environmental conditions that affect reproductive success serve as powerful

forces of natural selection. Most reptiles exhibit annual patterns of morphological, physiological, and behavioral variation in reproductive activity. Reproductive cycles of major reptilian lineages are discussed in detail in Chapters 9–12 of this volume. As ectotherms, reptiles are reliant upon ambient temperature and sunlight for achieving body temperatures that are permissive of feeding, growth, maintenance, and reproductive activity. In temperate regions, reproductive activity in reptiles is highly correlated with seasonal changes in temperature and photoperiod (Licht, 1972). Studies involving the manipulation of temperature and photoperiod suggest that temperature is the more dominant factor governing gonadal recrudescence (Licht, 1973; Marion, 1970, 1982; Mendonça, 1987; Mendonça & Licht, 1986). Less is known about the factors affecting the timing of reproduction in tropical regions. Precipitation serves as the most conspicuous abiotic factor that is likely to affect temporal variation in general activity and the timing of reproduction in tropical environments with distinct wet/dry seasons or seasonal monsoons. Seasonal precipitation patterns are associated with reproductive activity in many tropical reptiles, and rainfall affects population density in aquatic species, suitability of nesting areas and nesting substrate for egg incubation, and the availability of prey for some species (Brown et al., 2002; Brown & Shine, 2006; Platt et al., 2008; Shine & Brown, 2008; Thorbjarnarson, 1994; Thorbjarnarson et al., 1993). Although the mechanisms for the transduction of environmental stimuli to hormone signaling and reproductive activity are not fully understood, clearly reptiles coordinate the timing of reproduction with climatic stimuli.

On a global scale, anthropogenic climate change poses a direct challenge to reptiles that have adapted to historical climatic patterns to initiate and synchronize reproductive activity with other environmental factors to maximize embryo and offspring survival. According to the Intergovernmental Panel on Climate Change (IPCC, 2021), global surface temperatures have increased by an average of  $\sim 1^{\circ}\text{C}$  since the second half of the 19th century, with the temperature increase over land averaging  $1.5^{\circ}\text{C}$ . Surface temperatures are projected to continue to increase another  $0.5^{\circ}\text{C}$ – $3.5^{\circ}\text{C}$  by the end of the 21st century, depending on continued greenhouse gas emission. Since 1901, mean sea level has increased by 20 cm and the rate of sea level rise has increased from 1.3 to 3.7 mm/yr. The frequency of extreme weather events, such as heat waves, droughts, heavy precipitation events, and major tropical cyclones has increased from the 1950s to present. This section provides an overview of the literature and documents the impacts and predicted impacts of climate change on reptiles. In keeping with the theme of this volume, the review focuses on impacts related to sex determination, hormone signaling, and reproduction in reptiles.

## 2.1 Increasing temperature

Reproduction in oviparous reptiles is particularly susceptible to increasing environmental temperatures because of the thermosensitivity of developing embryos and the inability to relocate embryos after oviposition (Noble et al., 2017; While et al., 2018). Models based on projected soil temperatures and thermal tolerance in lizard embryos (*Sceloporus* spp.) suggest that simulations accounting only for adult tolerances severely underestimate the frequency of lethal events in North American lizards by 2100 (Levy et al., 2015). Urban heat islands may disproportionately affect cosmopolitan species. Hall and Warner (2018) incubated crested anole (*Anolis cristatellus*) eggs under variable thermal regimes that included heat spikes that mimicked conditions recorded in wild nests located in urban heat islands. Eggs exposed to the most extreme heat spikes had lower hatch rates and longer incubation periods. These effects were independent of whether the females that laid the eggs were collected from forest populations that have relatively cool, wet, and thermally stable nests or city populations that have warmer, drier, and thermally variable nests (Tiatragul et al., 2019). Embryos subject to the warmer and more variable city incubation regime had a lower egg survival rate following heat spikes than embryos experiencing forest-like incubation conditions, indicating that embryonic acclimation to elevated temperatures does not protect against thermal extremes (Hall & Warner, 2018).

Populations of reptiles that exhibit TSD are uniquely vulnerable to sublethal temperatures that have the potential to severely skew sex ratios. Direct documentation of regional warming patterns resulting in skewed sex ratios is logically challenging due to the need to acquire data over lengthy periods of time; however, several studies have made compelling cases that warrant continued monitoring, if not mitigation planning. In three-lined skinks (*Bassiana duperreyi*), a regional increase in air temperature of  $\sim 1.5^{\circ}\text{C}$  over a 10-year period was associated with a similar increase in nest temperatures, despite earlier nesting dates and deeper nests (Telemeco et al., 2009). Elevated nest temperatures toward the later years of the study period exceeded the threshold at which temperature is likely to affect sex ratios. In loggerhead sea turtles (*Caretta caretta*) near the northern limit of their nesting range, average incubation duration decreased by 7 days over a 25-year period during which nesting season air temperatures increased (Reneker & Kamel, 2016). Based on multiple models of the relationship between incubation duration and primary sex ratios, the estimated percentage of females increased from 55% to 88%. Sex ratios in green sea turtles (*Chelonia mydas*) hatching from northern Great Barrier Reef (GBR) rookeries are more female biased than green sea turtles from southern GBR rookeries. Among green sea turtles from the northern GBR rookeries, sex ratios are more skewed in hatchling

and subadult turtles than adult turtles, as would be predicted by increasing estimated sand temperatures since 1960 (Jensen et al., 2018). Female-biased sex ratios may result in higher recruitment when the availability of males is not constraining fecundity. However, male limitation could have stronger negative impacts on population size than a modest increase in embryonic mortality under warmer temperatures by negating the recruitment advantages of over production of females (Boyle et al., 2014).

Intraspecific variation along latitudinal and elevational gradients in response to temperature is evidence of adaptive response and/or phenotypic plasticity to local conditions. Numerous studies suggest that nesting phenology and nest site characteristics vary according to local climatic conditions (reviewed in Du et al., 2023). For example, the common snapping turtle (*Chelydra serpentina*) exhibits latitudinal variation in nest site selection. Females from higher latitudes tend to nest in locations that receive more sunlight than conspecifics from lower latitudes and embryos from northern latitudes exhibit a broader range of temperatures that result in male development (Ewert et al., 2005). In painted turtle (*Chrysemys picta*) populations examined across a broad geographic range, females selected nesting sites nonrandomly, resulting in similar constant temperature equivalents in nests across varying latitudes (Bodensteiner et al., 2023). Whether or not there is adequate phenotypic plasticity and/or capacity for evolutionary adaptation to accommodate increasing temperatures is subject to further study and will likely vary by taxa and environmental heterogeneity.

In a survey of nine species of freshwater turtles in the United States, Janzen et al. (2018) detected phenological shifts in first nesting date, spring emergence, or first basking date in most of the populations studied. Trends of warmer spring temperatures over periods of 10–36 years coincided with earlier emergence and date of first nesting, suggesting considerable phenotypic plasticity in nesting behavior. Likewise, earlier hatch dates in American crocodiles (*Crocodylus acutus*) are correlated with increasing sea surface temperatures in south Florida, USA (Cherkiss et al., 2020). In three-lined skinks, a phenological shift in nesting dates and deeper nests resulted in historically similar nest temperatures in the first week postoviposition, but did not compensate for the seasonal increase in air temperature occurring as incubation proceeded (Telemeco et al., 2009). Although phenotypically plastic, nesting phenology in painted turtles does not appear to be highly responsive to selection, as the date of first nesting is largely dependent on winter temperatures prior to each nesting season but is not predictably repeatable for individual females (Schwanz & Janzen, 2008). Latitudinal variation in the range of pivotal temperatures between female- and male-biased sex determination in common snapping turtles

indicates that sex determination threshold temperature is a heritable trait (Ewert et al., 2005). However, the thermal homogenization resulting from maternal nest site selection in turtles is likely to limit rapid selection for thermoresponsive traits in embryos (Bodensteiner et al., 2023). American alligator (*Alligator mississippiensis*) nest temperatures from northern and southern populations do not differ by location despite warmer temperatures in the southern population (Bock et al., 2020). Microclimatic factors related to nest site selection explain some of the temperature variation among nests; however, the strongest predictor of annual variation in mean nest temperature is mean daily maximum temperature. Projected increases in air temperatures under modest to severe greenhouse gas emission scenarios are likely to result in nest temperatures that produce strongly male-biased sex ratios in American alligators by mid-century. By the end of the century, nest temperatures are expected to exceed the upper male-to-female pivotal temperature resulting in female-biased sex ratios and possibly increased embryonic mortality (Bock et al., 2020). Collectively, these studies suggest that long-lived, TSD species that are slow to mature are likely at risk if local temperature increases exceed phenotypic plasticity in compensatory nesting behaviors.

In general, the activity of reptiles in temperate regions increases in the warmer months, suggesting warmer ambient temperatures are favorable in these environments. Increasing temperatures over an 18-year period in the Massif Central region of France were associated with a 28% increase in yearling body size in the common lizard, *Zootoca vivipara*, (Chamaillé-Jammes et al., 2006). Average adult female snout-to-vent length (SVL) increased by ~8 mm over the study period, resulting in an increase in clutch size and clutch mass in three of the four populations that were monitored. In the near term, increasing temperature appears favorable to fitness in this species. However, warming temperatures are expected to decrease the availability of suitable habitat (peat bogs and heath lands), thus further restricting and fragmenting existing populations (Chamaillé-Jammes et al., 2006). Additional studies examining common lizards from the same region found an association among high temperatures, rapid growth, shortened telomere length, and elevated population extinction risk (Dupoué et al., 2017, 2022). It is unclear if shortened telomere length brought about by exposure to warmer temperatures has direct impacts on reproductive physiology in reptiles, but intraspecific variation in telomere length is associated with tradeoffs between investment in self-maintenance and reproductive effort in morphotypes of Australian painted dragons, *Ctenophorus pictus* (Rollings et al., 2017). Cool winter temperatures may be particularly important to species that are native to temperate regions. Chinese alligators (*Alligator sinensis*) overwintering in artificially warmed environments exhibit alterations in ovarian mRNA and microRNA expression,

and DNA methylation in association with reduced folliculogenesis in comparison to alligators overwintering in naturally cool environments (Lin et al., 2020).

Correlations between temporally increasing environmental temperatures and endocrine phenotypes in reptiles is lacking, but lab-based studies provide evidence that egg incubation temperature affects posthatching hormone concentrations and gene expression related to hormones and sexual differentiation independent of gonadal sex. Male red-eared sliders (*Trachemys scripta*) from eggs incubated at 26°C had higher plasma progesterone (P<sub>4</sub>) concentrations than males from 28.6°C, and females from 28.6°C had higher plasma testosterone (T) than females from 31°C (Rhen et al., 1999). Juvenile female leopard geckos (*Eublepharis macularis*) from eggs incubated at 34°C have lower estradiol-17 $\beta$  (E<sub>2</sub>) and higher dihydrotestosterone (DHT) levels but similar plasma T in comparison to females incubated at 30°C (Rhen et al., 2005). Egg incubation temperature has lasting effects on plasma concentrations of DHT, T, and P<sub>4</sub>, but not E<sub>2</sub>, in adult leopard geckos after controlling for reproductive stage. However, changes in hormone concentrations associated with reproductive stage are more influential on behavior than incubation temperature (Rhen et al., 2000). Incubation temperature also affects responsiveness to hormone stimulation. When treated with exogenous T, castrated male leopard geckos from male-biased temperatures exhibit more scent marking than males from female-biased temperatures, whereas males from female-biased temperatures courted and mounted females more frequently than their counterparts from male-biased temperatures (Rhen & Crews, 1999). Within sexes, mRNA expression of anti-Müllerian hormone gene (*AMH*) is positively correlated with incubation temperature during the thermosensitive period of sex determination of American alligators. In addition, the magnitude of sexually dimorphic expression of *SOX9* and *AMH* is associated with incubation temperature, with males from high temperatures that produce both sexes (34.5°C) having higher expression than males from low temperatures that produce both sexes (32°C) (McCoy et al., 2015). Additional research is needed to resolve the long-term consequences of altered endocrine function brought about by different egg incubation temperatures.

## 2.2 Sea level rise and extreme weather events

Sea level rise and extreme weather events, such as tropical cyclones, affects nesting habitats of reptiles inhabiting marine and coastal environments. For instance, current nesting habitats used by saltwater crocodiles (*Crocodylus porosus*) in the Northern Territory, Australia, are likely to be lost due to sea level rise and saltwater intrusion; however, new nesting habitats could be created by increased rainfall under some emission scenarios (Fukuda et al., 2022). In sea turtles, species-specific nesting phenology and nesting

behavior influences the vulnerability of nests to increasing frequency of tropical cyclones. Leatherback sea turtles (*Dermochelys coriacea*) nest relatively early with respect to peak tropical cyclone occurrence on the Atlantic coast of Florida, USA, and nests are rarely flooded during storm surges. In contrast, loggerhead and green sea turtles nest later in the year when tropical cyclones are most likely, with green sea turtles nesting latest and experiencing the highest rates of nest flooding (Pike & Stiner, 2007).

A hurricane followed by months of drought in Louisiana, USA, that resulted in a prolonged period of elevated salinity in coastal marshes provides insight into the potential effects of saltwater inundation on species inhabiting coastal areas but not fully adapted to saltwater environments, such as American alligators. Approximately 9 months after the hurricane, there were no nests recorded during the nesting season in an area that typically had several hundred nests (Bagwill et al., 2009). Additionally, alligators sampled while salinity was highest had elevated plasma electrolytes, cortisol, and heterophil/lymphocyte ratios (Lance et al., 2009). These findings are supported by controlled studies in which juvenile alligators exposed to brackish water (12‰) exhibit signs of dehydration characterized by increased electrolyte, glucocorticoid, and plasma protein concentrations (Faulkner et al., 2018, 2019). Interestingly, both short-term (7 days) and long-term (5 weeks) exposure to brackish water suppressed indices of the renin-angiotensin-aldosterone system and altered plasma sex steroid concentrations. Exposure to brackish water for only 7 days led to an absence of discernable ovarian follicles and a reduction in the number of Sertoli cells and germ cells in testes in comparison to alligators maintained in freshwater (Faulkner et al., 2019).

Increased salinity also appears to influence thyroid development and thyroid hormone (TH) secretion in alligators, which unlike many species of crocodiles, do not have extra-renal salt glands. Neonatal American alligators hatched from eggs collected from an estuarine barrier island population exhibited thyroid hyperplasia and higher triiodothyronine ( $T_3$ ) concentrations than neonates from an inland population (Boggs et al., 2013). Although these differences do not persist in hatchlings maintained in freshwater conditions, juvenile alligators from the barrier island population have higher TH concentrations and lower plasma inorganic iodide ( $\text{pI}^-$ ) in comparison to the inland population (Boggs et al., 2011). Inland alligators exhibit a positive relationship between  $\text{pI}^-$  concentration and THs, whereas there is no correlation between  $\text{pI}^-$  concentration and THs in alligators from the barrier island. One might expect higher  $\text{pI}^-$  in the estuarine population due to the greater availability of  $\text{I}^-$  in marine environments, but that is not what was observed. Perhaps the osmotic stress of the estuarine environment leads to a higher rate of  $\text{I}^-$  clearance, but this explanation is not entirely congruent with the observation of elevated

TH concentrations in alligators from the estuarine population. An alternative explanation is that excess  $\text{I}^-$  is sequestered by the thyroid in reptiles that are not well adapted to marine environments, resulting in thyroid hyperplasia and hyperthyroidism. Though much remains to be learned about  $\text{I}^-$  and thyroid homeostasis in reptiles in general, these findings suggest that the osmotic stress of sea level rise and saltwater inundation is likely to affect  $\text{I}^-$  metabolism and thyroid function in coastal species that are primarily adapted to freshwater habitats.

Overall, the biodiversity of reptiles is asymmetric. That is, phylogenetic diversity is not spread evenly among the lineages. For instance, nonsquamate reptiles (turtles, crocodilians, and tuatara) comprise less than 4% of all reptile species, and within the squamates, adaptive radiations have led to species diversity within some genera (e.g., *Anolis* and *Liolaemus*) that outnumber the species diversity of most families (Pincheira-Donoso et al., 2013). A better understanding of how anthropogenic climate change will affect specific lineages of reptiles will be required if we are to effectively conserve reptilian biodiversity. Furthermore, the global distribution and distribution of diversity hotspots for some reptilian lineages, particularly lizards and turtles, does not follow the same patterns as other vertebrate tetrapods and congruence between reptilian endemism hotspots and endemism in other nonreptilian tetrapods is low (Roll et al., 2017). Taken together, effective mitigation of the loss of reptilian biodiversity is dependent upon (1) accurate forecasting of regional changes in temperature, sea level rise, and precipitation patterns, and (2) a better understanding of taxa-specific susceptibility to anticipated climate changes.

### 3 ENDOCRINE DISRUPTION IN REPTILES

The endocrine system controls nearly every aspect of vertebrate life and is instrumental in regulating physiological processes such as metabolism, development, reproduction, tissue function, and behavior. It is a highly integrated system requiring proper signals (hormones) of the right magnitude, reaching the intended receiver (receptor) at the appropriate time. Hormones affect cells through their interactions with receptors. Often these receptors are either transcription factors that directly govern expression of gene pathways, or they initiate signaling cascades that then direct cellular functions. The endocrine system is tightly regulated and uses appropriately timed and dose-dependent signaling to drive physiological and developmental processes. An exogenous chemical that changes these signals can have considerable impacts on animal health and reproductive success.

For decades, we have been aware that xenobiotics, or chemicals originating outside the body, can disrupt the

endocrine system (e.g., phytoestrogens), and our appreciation of the wide array of man-made chemicals capable of altering endocrine function became widely known in the early 1990s (Colborn & Clement, 1992). Such chemicals are now commonly called endocrine-disrupting chemicals (EDCs). Endocrine-disrupting chemicals act as hormone analogs or interfere with the synthesis, transport, storage, or clearance of hormones (Guillette Jr. et al., 2007; Milnes & Guillette Jr., 2008) and include compounds such as pesticides, plasticizers, fungicides, heavy metals, and pharmaceuticals (Davey et al., 2008; Guillette Jr. et al., 2007; Guillette Jr. & Iguchi, 2003).

### 3.1 Mechanisms of endocrine disruption

The physiological consequence of EDC exposure depends greatly on the timing of exposure. Organizational disruption can occur during distinct periods of development—windows of vulnerability—when tissues are dependent on hormonal cues for proper formation (Guillette Jr. et al., 1995). The length and timing of these critical windows can vary depending on the ontogenetic profile of the species. Organizational changes are potentially irreversible and usually related to disruption during organogenesis (Guillette Jr. et al., 1995). Occasionally, effects due to embryonic exposure are not manifest until another major organizational event such as puberty occurs. For example, hypothyroid male children develop large but normal testes, yet after puberty fibrosis of the seminiferous tubules occurs causing infertility (Jannini et al., 1995). Therefore, although a neonate could appear physiologically normal, the second wave of major hormonal cues can trigger deleterious physiological changes, including the failure of the hormone target to respond appropriately.

Alternatively, exposure to EDCs outside of critical windows of vulnerability can still result in considerable health consequences. Endocrine disruptions in juvenile and adult animals can reduce growth and fertility, alter metabolism, change hormone concentrations, and affect hepatic function, and reduce sperm count (Gray Jr. et al., 2006; Guillette Jr. et al., 1995; Trokoudes et al., 2006). These disruptions, which do not necessarily result in permanent changes to the structure and function of the organism, are termed activational disruptions. Environmental contaminants can disrupt the endocrine system through several mechanisms including interfering with hormone-hormone receptor interactions, up- or downregulation of hormonal synthesis, altering hormone binding to plasma proteins, modifying clearance or hepatic biotransformation of hormones, and changing the expression or number of hormone receptors (Fig. 1).

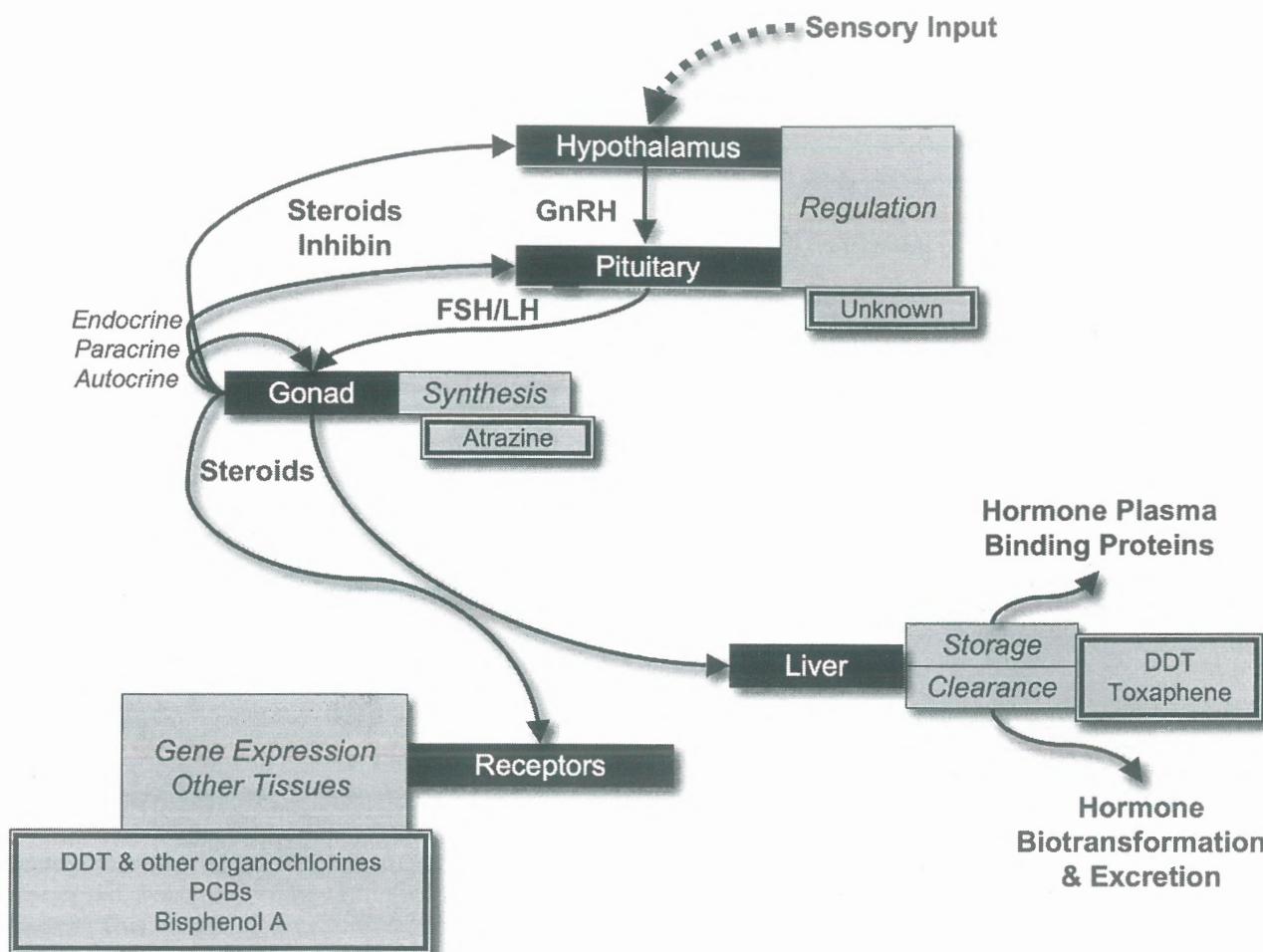
Contaminants can disrupt hormone signaling by direct interference with the hormone receptors (Fig. 2). Endocrine-disrupting chemicals can bind to the receptor, triggering

the normal response of the natural ligand (agonist) or can bind the receptor and block binding of the natural ligand without activating it and thus prevent transcription (antagonist). A wide array of chemicals (e.g., pesticides and plasticizers) bind to vertebrate estrogen receptors (ERs) and can act as either an agonist or antagonist (Rooney & Guillette Jr., 2000; Soto et al., 1995). Additionally, there is a growing list of chemicals (e.g., fungicides and phthalates) that can alter androgen receptor (AR) functioning with many acting as antiandrogens (Gray Jr. et al., 2006; Miyagawa et al., 2015).

Hormone production can be altered by modifying the enzymes and other molecules involved in biosynthesis, inactivation, and transport. One example involves the upregulation of aromatase (CYP19A1), the enzyme that converts T to E<sub>2</sub>, by the pesticide atrazine (Fan et al., 2007; Hayes et al., 2002). Atrazine induces the steroidogenic factor-1 (SF-1) pathway, which increases the production of CYP19A1, leading to a decrease in androgens and an increase in estrogens (Fan et al., 2007). Unbound lipophilic hormones such as steroids are insoluble in blood plasma and are rapidly modified by the liver and removed from circulation for excretion in feces or urine. Hydrophilic carrier or binding proteins, found in the circulatory system, protect hormones from hepatic degradation and excretion, and allow for longer retention time in circulation. Therefore, altering the synthesis of carrier proteins or the affinity of a carrier protein for its hormone ligand can change the hormone's availability and rate of clearance (Cheek et al., 1999).

The upregulation of metabolic enzymes and increased excretion following EDC exposure is part of the body's natural defense. Within the liver, steroids and other compounds are chemically modified prior to excretion. Xenobiotics are detected by promiscuous receptors, such as SXR (steroid and xenobiotic receptor), that upregulate metabolic pathways to remove the invading chemical (Blumberg et al., 1998). Because these receptors are not highly specific, they can also increase clearance of endogenous steroids, resulting in an overall reduction of circulating steroid concentrations. Indeed, some EDCs are known to bind SXR and alter the expression of metabolic enzymes, thereby altering retention or clearance of both endogenous steroids and EDCs alike (Gunderson, Oberdorster, & Guillette Jr., 2004; Li et al., 1995; Milnes, Garcia, et al., 2008).

The complexities surrounding EDC modes of action are further compounded by mixtures. Environmental contamination is rarely due to a single EDC, but rather to a milieu of EDCs of varying concentrations and potency. Whereas the traditional toxicological approach considered the additive effects of mixtures, the study of endocrine disruption has challenged this approach by demonstrating the synergistic effects of some EDCs. Polychlorinated biphenyl (PCB) congeners studied in combination can display synergistic effects on



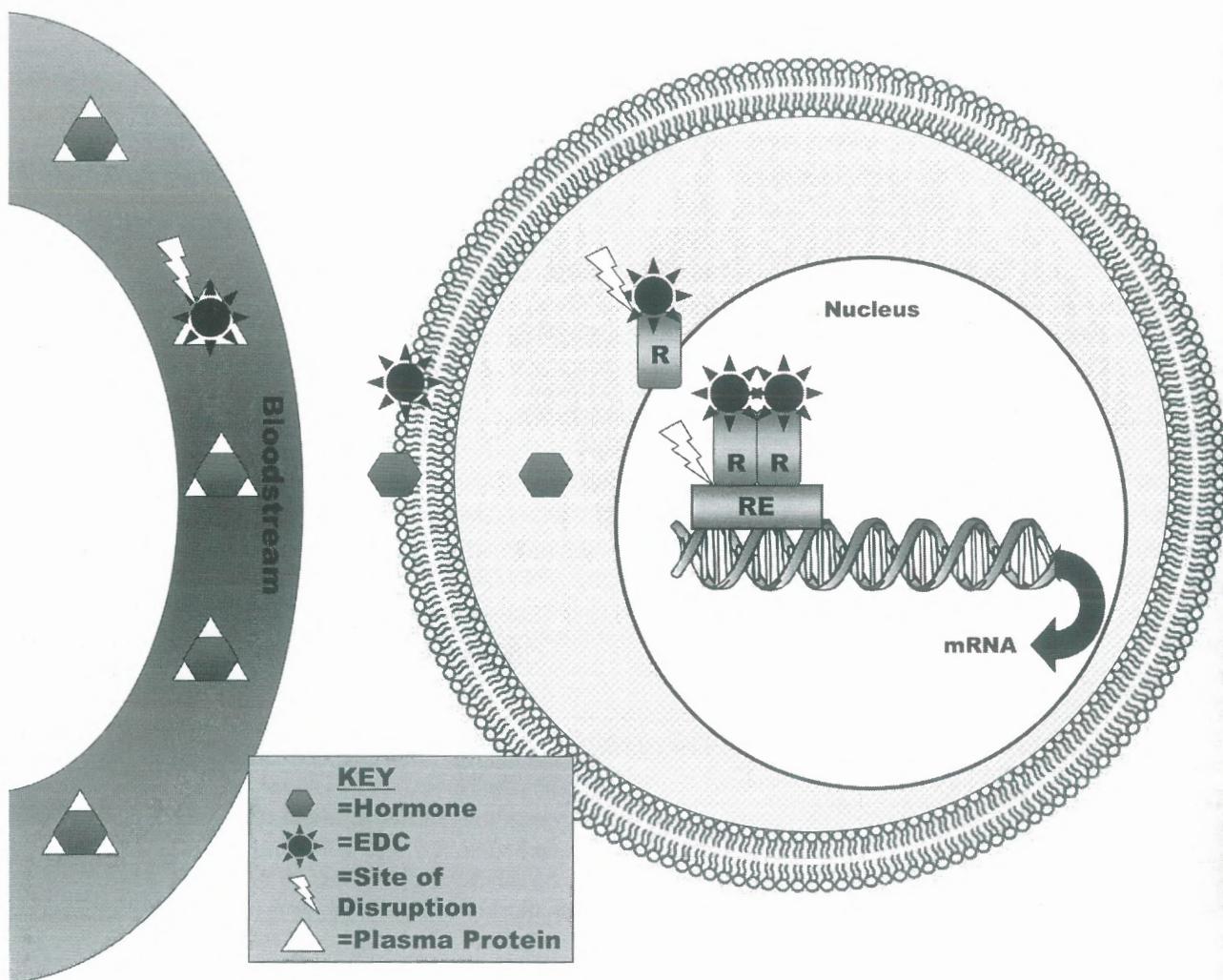
**FIG. 1** Schematic representation of the hypothalamus-pituitary-gonadal (HPG) axis. Steroid hormones interact with receptors in target tissues, altering gene expression profiles. Plasma steroid hormone concentrations are affected by plasma binding proteins synthesized by the liver as well as by hepatic biotransformation and clearance. To date, a number of environmental contaminants have been identified that can alter hormonal synthesis, storage, clearance, and receptor binding (examples are given in the double line boxes). Potentially, contaminants also could alter hypothalamic and pituitary regulation of gonadal steroids, as observed in mammals, but there are no data for reptiles.

estrogenic activity through increased potency above an additive effect (Bergeron et al., 1994). A possible mechanism for this response could be due to different pathways of disruption such as combination of an estrogen mimic and an androgen antagonist to produce a larger feminizing effect than an estrogen mimic alone. Other experiments have demonstrated a decreased effect of mixtures, possibly due to competition for a similar pathway among the compounds in the mixture (Carpenter et al., 1998). Thus, when designing experiments and assessing data, one should account for the potential of confounding factors introduced by mixtures.

### 3.2 Reptiles as models of endocrine-disrupting contaminant exposure

Over the past 30 years, reptiles have received increasing attention as biomonitoring of contaminant-induced endocrine disruption and reproductive toxicology. Reptiles' persistence in a wide variety of habitats and their diversity of life histories

provides for a variety of physiological responses to contaminant exposure, making them valuable subjects for studies of endocrine disruption. Additionally, many reptiles exhibit high site-fidelity (McNease & Joanen, 1974), permitting a unique opportunity to follow individuals through different life stages in their local environment. Reptiles occupy varying dietary niches, allowing research on the effects of trophic level and accumulation of toxicants. Many reptiles are long-lived scavengers or top tier predators and are excellent models for the study of bioaccumulation and biomagnification of contaminants (Selcer, 2006). Common reptilian diets include fishes, which have the potential to be highly exposed to EDCs transported by runoff, or insects, which are the targets of many pesticides. Additionally, reptiles are poikilotherms, a characteristic that affects their ability to metabolize and clear contaminants (Selcer, 2006). This is evidenced by the bioaccumulation and biomagnification of contaminants in reptiles to levels equal to or greater than those demonstrated in mammals and birds (Hall & Henry, 1992).

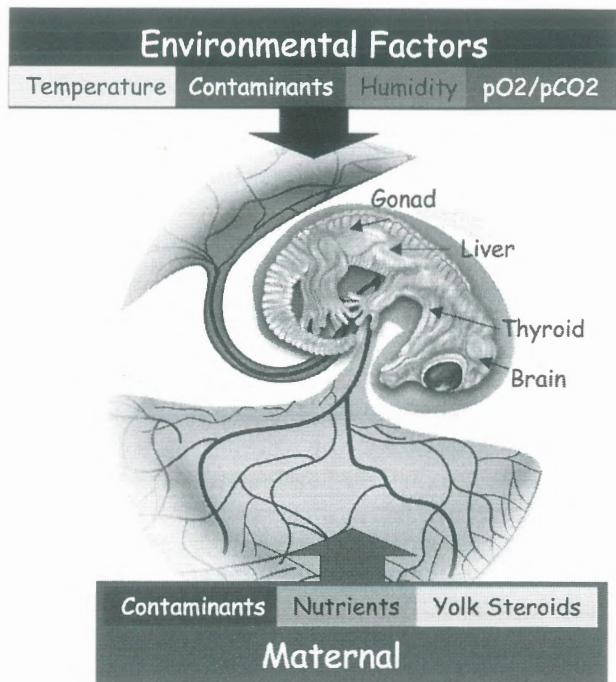


**FIG. 2** Endocrine disruption can occur at various points of hormone signaling but many contaminants have been shown to act as exogenous estrogens or antiandrogens. Hormones travel through the blood stream attached to plasma proteins. Steroids, such as estradiol- $17\beta$  and testosterone, leave the blood-stream and cross the lipid bilayer to enter the cell. Once inside the nucleus, a hormone attaches to its receptor (R). The hormone-receptor complex then attaches to the hormone response element (RE) on the DNA to begin transcription of mRNA. Endocrine-disrupting chemicals can cause disruption by binding to plasma transport proteins or the receptors preventing binding of the hormone. They also can disrupt the linkage of the receptors to the response element in the promotor. All these processes can alter or halt transcription.

As previously mentioned, the sex of many reptiles is determined by the incubation temperature of the egg. Reptiles that commonly demonstrate TSD, may be more susceptible to endocrine disruption because of the suggested increased role of estrogens and androgens during development of the gonad compared to GSD species (Crews, 2003; Crews et al., 1995). The effects of EDCs on sex determination, particular in species that exhibit TSD is examined in detail by Carter et al. (Chapter 1, this volume); therefore, discussion of the impacts of EDCs resulting from embryonic exposure focuses on effects related to hormone signaling and reproductive endpoints beyond sex determination.

Oviparous animals, such as most reptiles, liberate their fat stores to generate yolk nutrients; thus, lipophilic contaminants that bioaccumulate in the mother can be transferred to the yolk (Rauschenberger et al., 2007; Rauschenberger, Sepulveda,

et al., 2004; Rauschenberger, Wiebe, et al., 2004). Contaminants present in the egg at oviposition are absorbed throughout embryonic development and affect development in combination with other biotic and abiotic factors (Fig. 3). Lipoproteins in the egg of birds, turtles, and other oviparous vertebrates often contain contaminants such as 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE; a metabolite of dichlorodiphenyltrichloroethane, DDT), PCBs, dioxins and dibenzofurans at concentrations higher than in the ambient environment due to maternal concentration of these contaminants (Fox, 1992). Because reptiles have thick and poorly permeable skin, topical exposure of EDCs to adult reptiles is presumed to be limited. However, the composition of reptilian eggshells permits effective topical application of EDCs to the embryo, making embryonic exposure scenarios possible (Kern & Ferguson, 1997). In some viviparous



**FIG. 3** The developing embryo is subject to both environmental and maternal influences during development in oviparous reptilian species. Endocrine-disrupting chemicals from the environment and the mother (via her diet and deposition in the yolk) can alter embryonic development.

reptiles, embryonic exposure to contaminants could be a continuous and dynamic process facilitated through placental transfer. This range of reproductive strategies provides numerous experimental approaches to studying endocrine disruption of embryonic development.

Much of our knowledge concerning the impact of EDCs on reptiles comes from descriptive studies of wild populations that are subject to environmental exposure of known or suspected EDCs. In many instances, there are no historical data to establish what is functionally or physiologically normal, in terms of the endpoints of interest (e.g., egg viability, hormone concentrations, etc.). To determine if EDC exposure is causing an effect, investigators rely on one or more reference populations that are presumed to be relatively unaffected due to lower environmental exposure to the EDCs of interest in comparison to the contaminated population(s). In taking the descriptive approach, one must acknowledge that wild populations and natural ecosystems are inherently complex and potential confounding factors that vary among contaminated and reference populations are likely to be present. Potential confounding factors may include, but are not limited to, differences in population genetics, demographics, food availability, habitat disturbance, and contaminants other than those that have been quantified. Therefore, observed differences between contaminated and reference populations are considered associative rather than causative. That is, biological

differences between contaminated and reference populations cannot be exclusively attributed to differences in ambient or tissue concentrations of the environmental contaminants of interest. However, observed differences between contaminant-exposed populations and reference populations serve as a valuable guide for generating hypotheses concerning the biological effects of EDCs that can be tested under more controlled conditions.

Testing EDC-related hypotheses generated by descriptive comparisons of reptiles obtained from wild populations usually takes one of two routes—experimental treatments or common garden experiments. In this context, experimental treatments involve the exposure of animals or eggs from a reference population to environmentally relevant concentrations of EDCs hypothesized to be responsible for the observed differences between the reference and contaminated populations. When a specific mechanism of action of one or more EDC is hypothesized (e.g., environmental estrogen), hormones or pharmaceutical reagents are used as complimentary positive controls. Common garden experiments involve the rearing of animals from contaminated and reference sites under identical conditions. Experimental treatments and common garden experiments are powerful tools to support or refute cause-effect hypotheses generated by descriptive studies of wild populations. Additionally, when conducted on embryos or neonates, they have the potential for differentiating organizational disruption from activational effects, as previously discussed.

### 3.3 Crocodilians and environmental contaminant exposure

Crocodilians are perhaps the most thoroughly studied lineage of reptiles in the context of environmental exposure to anthropogenic contaminants. As long-lived, apex predators, crocodilians are subject to the bioaccumulating nature of contaminants that are persistent in the environment, and many contaminants are passed on to offspring by nutritional provisioning of eggs (Rauschenberger, Wiebe, et al., 2004). Organochlorine (OC) contaminants are present in eggs and/or various tissues of several crocodilian species including the American alligator, American crocodile, Morelet's crocodile (*Crocodylus moreletii*), and the Australian freshwater crocodile (*Crocodylus johnstoni*) (Pepper et al., 2004; Rauschenberger, Sepulveda, et al., 2004; Sepulveda et al., 2004; Wu et al., 2000, 2006; Yoshikane et al., 2006). A positive relationship between maternal body size and egg yolk concentrations of OC pesticides are found in American crocodiles (Charruau et al., 2013), and mercury (Hg) in American alligators (Nilsen et al., 2020). Similarly, Hg concentration in the blood of black caiman (*Melanosuchus niger*) was positively correlated with body size and trophic position based on stable isotope analysis

(Lemaire et al., 2021), and perfluorinated alkyl acids (PFAAs) concentrations are positively correlated with body size in American alligators (Bangma et al., 2017).

Much of what we know regarding the effects of environmental contaminants in crocodilians, stems from complimentary field and laboratory studies of American alligators. Since the early 1990s, researchers have investigated the adverse effects of environmental contaminants on alligators inhabiting Lake Apopka, Florida, USA. Lake Apopka, subject to nearly 40 years of agricultural and pesticide runoff from adjacent agricultural operations, became further contaminated by a large pesticide spill in 1980 that consisted primarily of the insecticide dicofol and sulfuric acid. Dicofol contains several DDT analogs including DDE and 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane (DDD). In the years following the spill, juvenile alligator population density declined and alligator egg viability rates (the average percentage of eggs from a clutch that hatch under controlled conditions) recorded from Lake Apopka were considerably lower than egg viability rates from nearby lakes (Woodward et al., 1993). Yolk samples from Lake

Apopka alligator eggs revealed contamination from several organochlorine pesticides and their metabolites, including DDT, DDE, DDD, toxaphene, dieldrin, trans- and cis-chlordane and trans-nonachlor, providing evidence for direct contaminant transfer to offspring (Heinz et al., 1991). Additional studies of Lake Apopka alligators have examined contaminant levels in muscle, blood, and liver and have noted elevated levels of many OC contaminants in these tissues in comparison to a relatively pristine and ecologically similar site in Florida—Lake Woodruff National Wildlife Refuge (LWNWR) (Delany et al., 1988; Garrison et al., 2010; Guillette Jr., Brock, et al., 1999) (Table 1).

Several of the contaminants identified in alligator tissues from Lake Apopka can bind alligator ER and displace [<sup>3</sup>H]-E<sub>2</sub> in competitive binding assays. The contaminants with the highest affinity for alligator ER in a cytosolic preparation from alligator oviducts are *o,p'*-DDD and *o,p'*-DDT, which are metabolites of *p,p'*-DDT, the active ingredient of technical grade DDT (Vonier et al., 1996). In all cases in which DDT metabolites were able to displace 50% of the [<sup>3</sup>H]-E<sub>2</sub>, they did so only at concentrations two to three

**TABLE 1** Concentrations of contaminants in alligator samples from Lake Apopka, FL, from different years.

Pesticides	Lake Apopka alligator eggs				Lake Apopka alligator muscle		Lake Apopka alligator livers	
	1984		1985		1985		2001	
	Detections <i>n</i> =3	Average conc. ppb	Detections <i>n</i> =23	Average conc. ppb	Detections <i>n</i> =1	Average conc. ppb	Detections <i>n</i> =12	Average conc. ppb
<i>o,p'</i> -DDE	—	—	4	7	0	ND	1	1.9
<i>p,p'</i> -DDE	3	5800	23	3500			12	114
<i>o,p'</i> -DDD	—	—	—	—	1	30	2	1.6
<i>p,p'</i> -DDD	3	820	22	370			12	2
<i>o,p'</i> -DDT <sup>a</sup>	—	—	—	—	1	160	1	2.3
<i>p,p'</i> -DDT	—	—	6	20			2	11.3
<i>trans</i> -Nonachlor	3	110	23	150	—	—	12	6.9
<i>cis</i> -Nonachlor	—	—	—	—	—	—	11	3.2
Oxychlordane	—	—	22	30	—	—	3	10
<i>trans</i> -Chlordane	—	—	2	6	—	—	2	16
<i>cis</i> -Chlordane	1	70	22	60	—	—	1	1.7

<sup>a</sup>Chiral pesticides.

Data from Delany et al. (1988), Guillette Jr., Brock, et al. (1999), and Garrison et al. (2010). See text for explanation of the contaminants. Chiral pesticides include both enantiomers.

(—), not tested; ND, nondetected.

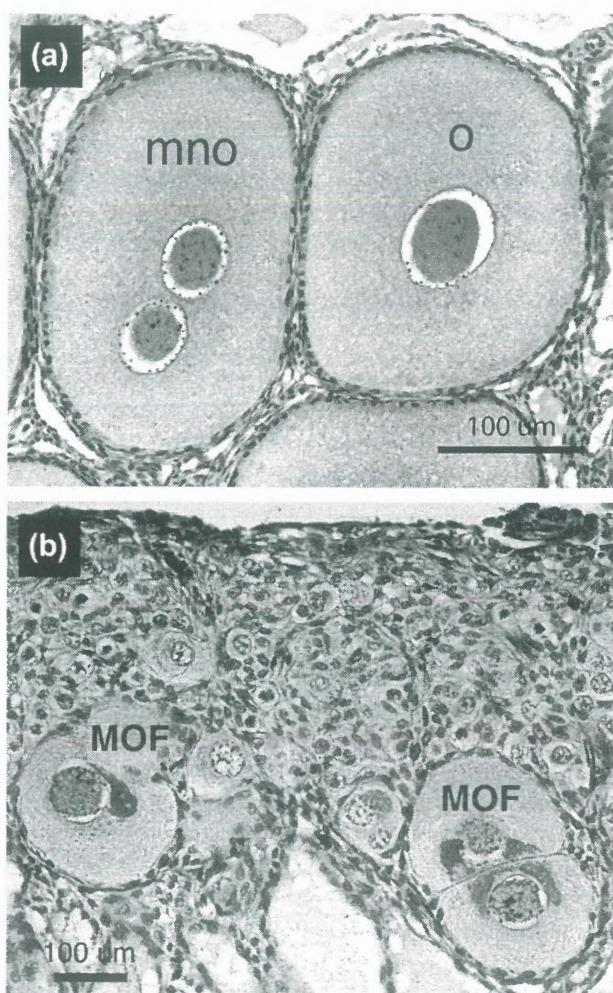
Muscle analysis reports a combined value for 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane (DDD), and dichlorodiphenyltrichloroethane (DDT).

orders of magnitude greater than the concentration required of nonlabeled E<sub>2</sub>; however, mixtures of DDT metabolites at concentrations similar to what has been reported in Lake Apopka alligator tissues were able to displace [<sup>3</sup>H]-E<sub>2</sub> in an additive fashion (Vonier et al., 1996). Although dicofol has a low affinity for alligator ER in the cytosolic competitive binding assay in comparison to some of the DDT metabolites, it is the most potent Lake Apopka contaminant at displacing the synthetic progestin [<sup>3</sup>H]-R5020 from alligator progesterone receptor in the cytosolic competitive binding assay system (Vonier et al., 1996).

In a cell-free binding assay, the Lake Apopka contaminants with the highest affinity for recombinant alligator ER $\alpha$  are *o,p'*-DDT and *p,p'*-dicofol, whereas *o,p'*-DDD is not capable of displacing 50% of the [<sup>3</sup>H]-E<sub>2</sub> in this assay system (Rider et al., 2010). Differences in the relative binding affinity of individual contaminants between the two competitive binding assays (e.g., dicofol and *o,p'*-DDD) are possibly due to the absence of alligator ER $\beta$  in the recombinant receptor binding assay. In both the cytosolic and cell-free assay systems, the most prevalent DDT metabolite in Lake Apopka alligator tissues, *p,p'*-DDE, has very low affinity for alligator ER, but is able to inhibit T-induced transcriptional activity following transfection of HepG2 cells with alligator AR (Miyagawa et al., 2015). These binding affinity studies suggest that complex mixtures of contaminants, such as the mixture present in Lake Apopka, are likely to affect endocrine signaling via multiple pathways simultaneously and in an additive fashion. A multitude of experimental treatment studies, especially in American alligators and broad-snouted caiman (*Caiman latirostris*) further explain some of the observed differences reported in crocodilians from contaminated and reference sites (reviewed in Durando et al., 2023; Milnes & Guillette Jr., 2008).

### 3.3.1 Reproductive organ abnormalities

Although the proximate cause of low egg viability on Lake Apopka is still unknown, observations of multiocytic ovarian follicles (MOFs) and multinucleated oocytes (MNOs) in juvenile alligators from Lake Apopka suggested endocrine disruption as a contributing factor (Guillette Jr. et al., 1994) (Fig. 4). Similarly, broad-snouted caiman experimentally exposed *in ovo* to either E<sub>2</sub> or bisphenol A (BPA) have a greater frequency of MOFs than caiman from untreated eggs (Stoker et al., 2008). The plasticizer BPA increased the frequency of MOFs at a concentration five orders of magnitude greater than the concentration required of E<sub>2</sub>, which is consistent with BPA's relative binding affinity for alligator ER $\alpha$  in comparison to E<sub>2</sub> (Rider et al., 2010). The MOFs and MNOs observed in wild and laboratory treated crocodilians are similar to observations of female mice exposed *in utero* to diethylstilbestrol (DES), a synthetic estrogen (Iguchi, 1992). These



**FIG. 4** Photomicrographs of ovarian follicles from juvenile American alligators. Normal and multi-nucleated oocytes (A) and multi-ovular (polyovular) follicles (B) are shown. Multi-ovular (polyovular) follicles have been reported from female alligators from Lake Apopka, FL, as well as female caiman treated with various estrogenic contaminants. *o*, oocyte; *MOF*, multi-ovular follicle; *mno*, multi-nuclear oocyte.

modifications in ovarian morphology provide a potential explanation for the reduced clutch viability seen in Apopka animals. Studies in mice demonstrate that fertilized ova from MOFs are significantly less likely to develop to implantation stage embryos than uniovular follicles (Iguchi et al., 1991).

Disruption in the gonadotropin-estrogen-inhibin-activin signaling pathway via estrogenic contaminants could be responsible for the MOF occurrence seen in Apopka females (Guillette Jr. & Moore, 2006). Although the etiology of MOF formation is still unclear, one hypothesis is that they arise from a failure of primary follicular cells, i.e., granulosa cells, to differentiate and surround primordial oocytes during early development (Guillette Jr. & Moore, 2006). This activity is partially regulated by the presence

of activin A, one isoform of activin. Activin action is regulated in two ways: through the actions of inhibin, which competitively binds the activin type II receptor (ActRII) and through the actions of follistatin, an activin-binding protein that sequesters activins for degradation (Martens et al., 1997; Pangas & Woodruff, 2000). Follicle-stimulating hormone (FSH) can stimulate production of inhibin  $\alpha$  and follistatin (Tuuri et al., 1996). Perhaps an exogenous estrogenic signal, potentially acting at multiple points, is capable of prematurely initiating this delicate pathway, resulting in the formation of MOFs. If follistatin and inhibin  $\alpha$  are upregulated due to a premature FSH signal or an inappropriate estrogen signal, activin A activity will decline. This will result in altered follicular formation due to a lack of granulosa cell proliferation.

Ovaries from neonatal alligators do not possess follicles because their assembly occurs slowly over several months posthatching (Moore et al., 2008; Moore, Hamlin, Botteri, Lawler, et al., 2010). During germ cell nest breakdown and subsequent follicle assembly, an activin-dominated signaling milieu appears critical in alligators as it does in mammals (Moore, Hamlin, Botteri, & Guillette Jr., 2010). Profiles of sexually dimorphic mRNA expression of the transforming growth factor  $\beta$  gene ( $TGF\beta$ ) and for signaling factor genes, such as those for inhibin  $\beta$  subunits (*INHBA*, *INHBB*), follistatin (*FST*), and growth differentiation factor 9 (*GDF9*) in the gonads of neonatal and five-month-old American alligators from LWNWR are similar to gene expression profiles established in other vertebrates with genetic sex determination (Moore, Hamlin, Botteri, & Guillette Jr., 2010). However, hatchling alligators collected as eggs from Lake Apopka had lower expression of *INHBA* and *FST* mRNA in comparison to LWNWR hatchlings (Moore, Kohno, Cook, Alvers, et al., 2010). In 13-month-old alligators collected from Lake Apopka and LWNWR as eggs and raised under identical conditions, Lake Apopka alligators exhibited a lack of sexually dimorphic mRNA expression and/or lower mRNA expression for *INHBB*, *FST*, and *GDF9* (Moore et al., 2011). The loss or reduction of sexually dimorphic mRNA expression involved in  $TGF\beta$  signaling provides initial evidence for EDC-induced MOFs and supports the hypothesis that altered activin, inhibin, and steroid signaling are likely involved in the development of this pathology.

In addition to MOFs and MNOs, a phenotype resembling primary ovarian insufficiency is reported for crocodilians exposed naturally and experimentally to EDCs. Experimental egg treatment studies in *C. latirostris* found that prenatal exposure to doses of  $E_2$  and BPA that resulted in ovarian development at male-producing temperatures led to the absence of the most advanced-stage follicles found in vehicle-treated, neonatal females (Stoker et al., 2008). Similarly, alligators collected as eggs from Lake Apopka

and alligators from LWNWR exposed *in ovo* to  $E_2$  exhibited a lower density of advanced-stage follicles in the ovarian cortex 5 months after hatching in comparison to vehicle-treated females from LWNWR (Hale et al., 2022; Hale & Parrott, 2020). Interestingly, neonatal caiman from eggs treated with low doses of  $E_2$  and BPA and incubated at female-producing incubation temperatures had a greater percentage of stage III follicles (as defined by Calderon et al., 2004; Uribe & Guillette Jr., 2000) than vehicle-treated females from the same temperature, whereas the higher doses of  $E_2$  and BPA did not affect the percentage of stage III follicles (Stoker et al., 2008). The contradictory findings between the two species could be due to differences in the age of examination of the ovaries (neonates vs. 5 months post hatching) or the applied dosages. The nominal dose of  $E_2$  used in the alligator study was between the two doses used in the caiman study. Additional research on the ontogeny of folliculogenesis in crocodilians and the timing of EDC-induced impacts on follicular dynamics will be required to further explain these findings.

Structural and developmental abnormalities in male crocodilian reproductive structures occur in association with contaminated environments or are induced by experimental egg treatment studies. For instance, juvenile alligators living in Lake Apopka show disorganized seminiferous tubule development (Guillette Jr. et al., 1994), as do broad-snouted caiman exposed *in ovo* to  $E_2$ , BPA, the triazine herbicide atrazine, and the OC insecticide endosulfan (Durando et al., 2013, 2015; Rey et al., 2009). Caiman exposed *in ovo* to BPA have reduced seminiferous tubule cross-sectional area at 10 days after hatching, and juveniles approximately 15 months in age and with a body mass of 2 kg have a higher intratubular cellular proliferation rate than untreated males (Durando et al., 2015). Interestingly, *in ovo* endosulfan exposure resulted in an increase in intratubular proliferation in neonates as determined by bromodeoxyuridine (BrdU)-positive cells (Rey et al., 2009), whereas three-month-old caiman exposed to endosulfan *in ovo* exhibited a decrease in intratubular cellular proliferation as determined by cells staining positive for proliferating cell nuclear antigen (PCNA) (Durando et al., 2015). The percentage of intratubular cells staining positive for PCNA was shown to change over time in control caiman, supporting the contention that the manifestation of contaminant-induced alterations and/or the likelihood of detecting alterations varies ontogenetically (Durando et al., 2015).

In addition to disruptions in testis development, juvenile male alligators from Lake Apopka have smaller penises than similar size males from LWNWR (Guillette Jr. et al., 1996). A similar pattern was observed in a comparison of neonatal alligators hatched from eggs collected from Lake Apopka and LWNWR (Milnes et al., 2005). Reduced

phallus size in alligators from Lake Apopka suggests that contaminants in Lake Apopka interfere with androgen signaling, which is consistent with the presence of *p,p'*-DDE in Lake Apopka eggs and body tissues and/or inhibition of androgen-dependent signaling through some other means in developing alligators from Lake Apopka.

### 3.3.2 Alterations in hormone concentrations, synthesis, and metabolism

Sex steroids are essential for normal reproductive activity in both male and female vertebrates and play integral roles during sex determination in reptiles (see Chapter 1, this volume). Alterations in egg yolk steroid concentrations during critical developmental windows have the potential to cause sex-reversal and altered sex ratios (Lance & Bogart, 1994; Wibbels & Crews, 1995). In a comparison of three sites in central Florida, USA, Hamlin et al. (2010) found variation in alligator egg yolk P<sub>4</sub> and E<sub>2</sub> concentrations among sites and differences in the reduction of yolk E<sub>2</sub> between early and late incubation stages. Among eggs sampled at embryonic stage 12 (staging based on Ferguson (1985)), yolk P<sub>4</sub> concentrations were lower in eggs from Lake Apopka and Merritt Island National Wildlife Refuge (MINWR) than eggs collected from LWNWR, and E<sub>2</sub> concentration at stage 12 and between stages 12 and 24 was lower in eggs from MINWR than the other two sites. MINWR is located on a barrier island along the Atlantic coast of Florida. Alligator plasma samples from MINWR exhibited higher concentrations of PFAAs than any of the other 12 sites sampled across the southeastern United States, including LWNWR and Lake Apopka (Bangma et al., 2017). Alligators from MINWR experience significant differences in salinity and contaminant exposure in comparison to alligators from Lake Apopka and LWNWR, and these differences complicate interpretation of differences among the study sites.

Hatching and juvenile alligators obtained from eggs collected from Lake Apopka and reared in the laboratory exhibit differences in endocrine function in comparison to hatchlings and juveniles from LWNWR. For example, six-month-old male alligators from Lake Apopka show depressed plasma T concentrations, threefold lower than LWNWR males but comparable to Lake Apopka females. Lake Apopka females have elevated plasma E<sub>2</sub> concentrations in comparison to six-month-old LWNWR females raised under similar conditions (Guillette Jr. et al., 1994). In similarly designed experiments, female Lake Apopka alligators raised to 9 months of age display twofold depression in plasma T concentrations and no difference in E<sub>2</sub> concentrations compared to the females from LWNWR, despite reduced ovarian aromatase activity in females from Lake Apopka (Crain et al., 1997). Another study in which male and female alligators from both sites

were raised from the time of hatching for 13 months under similar conditions showed no difference in plasma T for males and no difference in plasma E<sub>2</sub> concentrations in females. However, a loss of sexually dimorphic steroidogenic gene expression was found in the animals from Lake Apopka (Milnes, Bryan, et al., 2008). Taken together, these studies suggest complex alterations in steroid synthesis and/or clearance in neonatal and juvenile alligators that change with age.

Studies analyzing hormone concentrations in wild-caught juveniles display a different pattern to those of juveniles examined in captivity where animals were raised under similar conditions. Juvenile male alligators from Lake Apopka show depressed concentrations of plasma T and elevated concentrations of plasma E<sub>2</sub> compared to animals of the same age and size living in LWNWR. Similarly, juvenile female alligators from Lake Apopka show elevated plasma E<sub>2</sub> concentrations when compared to reference populations (Guillette Jr. et al., 1997; Guillette Jr., Woodward, et al., 1999; Milnes et al., 2002). Subsequent studies of Florida alligator populations from Lakes Griffin and Okeechobee, also contaminated with complex mixtures of agricultural pesticides and excess nutrients, exhibit similarly altered plasma sex steroid hormone concentrations (Guillette Jr., Woodward, et al., 1999; Gunderson, Bermudez, et al., 2004). Thus, without a depuration period such as that found in captivity, normal plasma T and E<sub>2</sub> concentrations in juvenile alligators from contaminated sites continue to be altered and show a consistent pattern.

Contaminant-induced changes in the expression of genes regulating steroidogenesis and steroid metabolizing enzymes provide a molecular basis for the altered sex steroid concentrations seen in animals from Lake Apopka. In 13-month-old alligators hatched from eggs collected from Lake Apopka and LWNWR and raised under controlled conditions, differences in mRNA expression related to steroidogenesis were found between animals from the two sites. Specifically, males from LWNWR had higher expression of *SF-1* and steroidogenic acute regulatory protein (*StAR*) mRNA than males from Lake Apopka. Additionally, LWNWR alligators exhibited sexually dimorphic mRNA expression, with higher expression in males than females for *SF-1*, *StAR*, and the steroidogenic enzymes cytochrome P450 11A1 (*CYP11A1*), and hydroxy- $\Delta^5$ -steroid dehydrogenase, 3 $\beta$ - and steroid  $\delta$ -isomerase 1 (*HSD3B1*), whereas alligators from Lake Apopka were not sexually dimorphic for expression of those genes (Milnes, Bryan, et al., 2008). Likewise, juvenile alligators collected from LWNWR exhibit patterns of steroid metabolizing enzymes in the liver that differ from juvenile alligators from Lake Apopka and several sites located adjacent to agricultural operations in the Lake Okeechobee and Everglades region of south Florida (Gunderson et al., 2001). Most notably,

testosterone hydroxylase and oxido-reductase activity in the liver was sexually dimorphic in alligators from LWNWR, with metabolizing enzyme activity higher in females. Juvenile alligators from Lake Apopka as well as several sampling sites located adjacent to agricultural operations in the Lake Okeechobee and Everglades region of south Florida did not exhibit sexual dimorphism for those enzymes. Hepatic enzyme activity varied among sites to different degrees, depending on enzyme and sex, but not in a manner that could be attributed to specific patterns of contaminant exposure or previously reported plasma steroid concentrations (Gunderson et al., 2001). Collectively, descriptive studies of alligators from contaminated populations suggest that gonadal steroidogenesis and hepatic steroid metabolism are potential targets of endocrine disruption. Additional studies in which changes in patterns of enzyme expression are modeled against plasma steroid concentrations are needed to fully understand the consequences of alterations in the steroidogenic and steroid metabolizing enzymes.

Although endpoints related to reproduction and sex steroid signaling have dominated EDC research, chemically induced alterations in thyroid function are gaining recognition as possible outcomes of exposure to environmental contaminants. Thyroid hormone signaling is potentially susceptible to disruption in the same ways as steroid signaling in addition to mechanisms unique to the thyroid gland and TH synthesis. For instance, some hydroxylated PCBs inhibit the binding of T<sub>3</sub> to rat thyroid receptors (TRs) and stimulate TH-dependent growth hormone secretion in a rat pituitary cell line (Kitamura et al., 2005). Other studies suggest that some PCB congeners can decrease thyroxine (T<sub>4</sub>) concentrations by increasing hepatic metabolism (Kato et al., 2010), and alter the binding of the TRs to the thyroid response element (TRE) in the promotor of TH-responsive genes (Miyazaki et al., 2004). Additionally, perchlorate blocks the sodium iodide symporter of the thyroid gland, leading to hypothyroidism and goiter (Hooth et al., 2001).

Differences in plasma TH concentrations and thyroid morphology in alligators have been noted among several locations in Florida that vary regarding historical environmental contamination. Juvenile alligators from LWNWR show a negative relationship between body size and plasma T<sub>3</sub> and T<sub>4</sub> concentrations (Crain et al., 1998). In contrast, there was no relationship between body size and T<sub>3</sub> concentrations in juvenile females collected from lakes Apopka and Okeechobee, nor for body size and T<sub>4</sub> for males from Lake Apopka or females from Lake Okeechobee. Furthermore, male alligators from Lake Okeechobee had elevated concentrations of plasma T<sub>4</sub> in comparison to LWNWR (Crain et al., 1998). In a separate study, juvenile alligators from the Belle Glade area of Lake Okeechobee, the site most proximal to large-scale agricultural operations, had larger thyroid follicular cell height and smaller follicular

colloid space than alligators from two other areas within or immediately adjacent to Lake Okeechobee (Hewitt et al., 2002). Among these three study sites, plasma T<sub>4</sub> concentration was highest in alligators from the site of intermediate OC contamination (Wildlife Conservation Area 3A), whereas plasma T<sub>4</sub> concentration did not differ between the Belle Glade and Moonshine Bay areas of Lake Okeechobee (Gunderson et al., 2002). The triazine herbicides ametryn, simazine, hexazinone, and two atrazine metabolites (atrazine desisopropyl and atrazine desethyl) were detected in water or sediment in Wildlife Conservation Area 3A but were not detected in one or both of the other sites. Although experimental evidence of EDC exposure affecting TH concentrations in crocodilians is lacking, female juvenile caiman exposed prenatally to atrazine exhibit larger thyroid follicular cell height and follicular hyperplasia in comparison to atrazine-treated males and vehicle-treated caiman (Galoppo et al., 2020). In addition, atrazine exposure was associated with an increase in the percentage of ER immunopositive follicular cells in male caiman and a reduction in the percentage of AR immunopositive cells caiman of both sexes in comparison to their respective vehicle controls (Galoppo et al., 2020).

### 3.4 Turtles and environmental contaminant exposure

Like crocodilians, many species of turtles are long-lived and all are oviparous; thus, they are likely to accumulate and transfer environmental contaminants to their eggs. Muñoz and Vermeiren (2020) provide an extensive review of the detection of persistent organic pollutants in sea turtle eggs. Species of sea turtles that generally feed at higher trophic levels (e.g., loggerhead sea turtles) tend to have higher contaminant concentrations in their eggs than other species. However, significant temporal trends and regional variation in concentrations of OC pesticides and pesticide metabolites and PCBs are apparent and reflect variation in usage, production, and release. Because all species of sea turtles are listed as threatened or endangered, contaminant exposure studies are not permitted, but some field-based studies have shown relationships between contaminant concentrations and altered endocrine-related endpoints. For example, plasma concentrations of persistent organic pollutants tend to be higher in loggerhead sea turtles from the Adriatic Sea than the Atlantic Ocean (Bucchia et al., 2015). Polycyclic aromatic hydrocarbons naphthalene and benzo[g,h,i]perylene are positively correlated with red blood cell (RBC) expression of cytochrome P4501A (CYP1A) and ER $\alpha$  mRNA respectively, in loggerhead sea turtles from the Adriatic sea (Coccia et al., 2018).

Additional field studies suggesting a relationship between environmental contaminant exposure and reduced

reproductive success or altered endocrine function in turtles come from several freshwater species. Adult painted turtle populations living in Moody Pond near the Massachusetts Military Reservation, a Superfund site in Cape Cod, Massachusetts, USA, exhibit alterations in reproductive indices that could be related to exposure to volatile organic compounds from fuel spills, pesticides, PCBs, and heavy metals, including cadmium (Cd) found in the surface water and sediment. Cadmium interacts directly with mammalian ERs and causes proliferation of human breast cancer cells and promotes uterine enlargement and growth of mammary glands in rats (Garcia-Morales et al., 1994; Johnson et al., 2003). Female turtles from Moody Pond have lower plasma E<sub>2</sub> and vitellogenin (Vtg) levels and fewer large ovarian follicles compared to turtles from a nearby reference site, Washburn Pond (Rie et al., 2005). Females from both sites are equally responsive to E<sub>2</sub>-induced Vtg synthesis, but females from Moody Pond are nonresponsive to injections of ovine FSH, whereas Washburn Pond females respond to ovine FSH with a transitory rise in E<sub>2</sub> (Kitana et al., 2006). Male turtles from Moody Pond exhibit longer precloacal tail length; reduced testicular weight, reduced seminiferous tubule diameter, and reduced epididymal sperm counts as well as elevated germ cell apoptosis in comparison to males from Washburn Pond (Kitana et al., 2007).

Gonadal structure and the number of proliferating germ cells do not differ between neonatal turtles hatched from eggs from Washburn Pond and Mood Pond, but oocyte apoptosis is higher in neonates from Moody Pond (Kitana & Callard, 2008). Complimentary *in ovo* exposure of red-eared slider (*T. scripta*) embryos to Cd resulted in an increase in oocyte apoptosis and a decrease in the number of germ cells in embryos and hatchlings up to 3 months old (Kitana & Callard, 2008). Additional studies in which red-eared slider hatchlings were reared in enclosures that contained Moody Pond soil resulted in elevated mRNA expression of hepatic ER $\alpha$  and gonadal aryl hydrocarbon receptor 1 (*AHRI*) and a decrease in brain *AHR2* (Marquez et al., 2011a, 2011b).

Multiple studies have documented regional variation in persistent organic pollutants in tissues and eggs of common snapping turtles (*C. serpentina*) in the Great Lakes region of North America (Ashpole et al., 2004; Bishop et al., 1991; Dabrowska et al., 2006; de Solla & Fernie, 2004). One study (Bishop et al., 1991) found associations between egg contaminant concentrations, especially PCBs, and hatch rates and hatchling deformities. A more recent study found several “Areas of Concern” to have the lowest hatching success and highest rates of hatchling deformities in comparison to less polluted reference sites, but weak associations between contaminant burdens and developmental outcomes (de Solla et al., 2008). Hatchling snapping turtles fed pellets spiked with the PCB mixture Aroclor 1254 exhibited

dose-dependent PCB concentrations in the liver, but no evidence of bioaccumulation after a depuration period (Colson et al., 2021). Turtles fed the highest concentration of Aroclor 1254 responded with elevated hepatic *CYP1A* expression in relation to controls, suggesting the ability to metabolize PCBs at low to moderate concentrations.

Whereas maternal transfer of contaminants to eggs is regarded as the most significant mechanism for embryonic exposure to many lipophilic contaminants, de Solla and Martin (2011) found that snapping turtle eggs can absorb commercial formulations of pesticides directly from the soil. Pesticides with relatively higher water solubility, such as atrazine, are absorbed most readily. An experimental study in which snapping turtle eggs were incubated in soil treated with atrazine did not result in any effects on sex determination or thyroid morphology (de Solla et al., 2006). However, topical application of atrazine to snapping turtle eggs resulted in increased mRNA expression of androgen receptor (*AR*), kisspeptin receptor (*Kiss1R*), and proopiomelanocortin (*POMC*) in both sexes at hatching, and increased expression of *CYP19A1* and prodynorphin (*PDYN*) in females (Russart & Rhen, 2016). Expression of *CYP19A1* and prolactin-releasing hormone (*PRLH*) was elevated in females 6 months after hatching in comparison to vehicle-treated controls, providing evidence that a single exposure during early development can have lasting effects on endocrine function.

Among heavy metal pollutants, mercury (Hg) may be of particular concern for long-lived oviparous species, such as turtles, due to its widespread occurrence, ability to bioaccumulate, and thyroid disrupting effects in other vertebrates. For instance, chronic exposure to Hg reduces growth, increases time to metamorphosis, decreases type II iodothyronine deiodinase, and decreases TR mRNA in Chinese toads (*Bufo gargarizans*) (Shi et al., 2018). In a study of common snapping turtles in Virginia, USA, Hopkins et al. (2013), found that total Hg in muscle was positively related to carapace length in female snapping turtles from a contaminated river. Female body burdens of total Hg were positively correlated to egg concentrations and egg total Hg concentrations were negatively correlated with hatching success. In western pond turtles (*Emys marmorata*) sampled across a broad latitudinal gradient in California, USA, body size and site were the strongest predictors of total Hg in RBCs, with larger turtles having higher total Hg after accounting for site (Meyer et al., 2014). Total Hg concentration was negatively correlated with plasma T<sub>3</sub> and positively correlated with plasma T<sub>4</sub>, suggesting that Hg may disrupt deiodinase activity that is required for the conversion of T<sub>4</sub> to the more biologically active T<sub>3</sub>. Further research is needed to verify this mechanism of action of Hg toxicology in reptiles, and to determine the point at which the effect becomes biologically relevant.

### 3.5 Squamates and environmental contaminant exposure

Squamates are easily the most speciose lineage of reptiles, with more than 11,500 species (Uetz et al., 2023). Yet in comparison to their diversity and abundance, squamates have received relatively little attention in the study of reproductive toxicology and endocrine disruption despite their potential vulnerability. For instance, watersnakes (*Nerodia* spp.), bioaccumulate and biomagnify Hg through their diet (Drewett et al., 2013; Haskins et al., 2021). In northern watersnakes (*Nerodia sipedon*), transfer of Hg to offspring is proportional to maternal tissue total Hg concentration (Chin et al., 2013). Interestingly, no relationship was observed between total Hg in litters and offspring survival in snakes from a site historically contaminated with Hg, suggesting that northern watersnakes are tolerant of relatively high Hg concentrations in the context of reproductive success.

Unlike watersnakes, the majority of squamates are terrestrial, and many species inhabit or live along the periphery of agricultural fields, industrial sites, and urban areas. In these settings, contaminant exposure can occur through ingestion of contaminated prey, such as invertebrates that are often the targets of pesticides or consumers of contaminated vegetation or substrate, inhalation of aerosolized chemicals, or direct contact with contaminated substrate (reviewed in Silva et al., 2020). Multiple studies have documented DNA damage, decreased global DNA methylation, or upregulation of enzymatic biomarkers associated with environmental exposure to pesticides and heavy metals in lizards (Aguilera et al., 2012; Mingo et al., 2017; Moltedo et al., 2023; Sargsyan et al., 2019; Simbula et al., 2021). In a study of Bocage's wall lizard (*Podarcis bocagei*), lizards from corn fields historically treated with herbicides had alterations in thyroid follicle and seminiferous tubule morphology and upregulation of TR in comparison to lizards from organic agricultural fields with no history of pesticide application (Bicho et al., 2013). None of these field-based studies looked at associations between environmental contamination and reproductive success; however, a number of treatment studies in the Italian wall lizard (*Podarcis sicula*) have revealed contaminant-induced alterations that affect hormone signaling and are likely to reduce fitness.

The effects of glyphosate, an organophosphorus herbicide, have been examined in the wall lizards. Following 3 weeks of glyphosate exposure by oral gavage, lizards exhibited multiple signs of hepatotoxicity and increased ER $\alpha$  and Vtg mRNA expression in the liver, consistent with estrogenic action (Verderame & Scudiero, 2019). In males, glyphosate exposure led to altered seminiferous tubule morphology, reduced spermatogenesis, and increased ER $\alpha$  and ER $\beta$  mRNA expression in the testes (Verderame et al.,

2022). Glyphosate exposure in females increased the percentage of prefollicular oocytes that had advanced to the diplotene stage and the percentage of follicles that had advanced to the previtellogenesis stage in comparison to controls (Rosati et al., 2023). Additional follicular alterations in glyphosate-treated females included increased thecal fibrosis and collagen deposition, reduction in peripheral E-cadherin and premature apoptosis in follicular pyriform cells, and altered interactions between the follicular epithelium, zona pellucida, and oocyte cytoplasm, and increased ER $\alpha$  and ER $\beta$  mRNA expression (Rosati et al., 2023).

The fungicide methyl thiophanate (MT) altered adrenal, thyroid, and gonad function in wall lizards. Lizards exposed to MT through contaminated water, food, and terrarium substrate exhibited increased plasma corticosterone and hypertrophied steroidogenic adrenal tissues despite decreased plasma adrenocorticotropic hormone. Exposure to MT also led to elevated plasma epinephrine and decreased plasma norepinephrine concentration in comparison to untreated controls (De Falco et al., 2007). Intraperitoneal injection of MT resulted in decreased thyroid follicle epithelial cell height, retraction of colloid, and decreased plasma T<sub>3</sub>, T<sub>4</sub>, and thyroid-stimulating hormone concentrations (Sciarrillo et al., 2008). Males injected over a period of 3 weeks exhibited fewer primary spermatocytes, germ cell apoptosis, and decreased expression of ER and AR mRNA (Cardone, 2012). Although highly speculative, the decrease in thyroid and gonad activity is suggestive of MT-induced inhibition of hypothalamus and pituitary.

Lastly, the effects of alkylphenols, persistent chemicals used in pesticide formulations and numerous industrial processes, have been investigated in male wall lizards. Experimental exposure to nonylphenol through treated drinking water and food during the breeding season resulted in apoptotic germ cells, reduced testicular expression of ER $\alpha$ , ER $\beta$ , and AR, and reduced epididymal secretions in comparison to untreated males (Verderame & Limatola, 2015). Intraperitoneal injections of nonylphenol and octylphenol in wall lizards similarly altered testis morphology and reduced expression of steroidogenic enzymes in the testes (DiLorenzo et al., 2021). Collectively, the results of these lab-based studies in the Italian wall lizard provide baseline data for endocrine-disrupting effects in squamates.

## 4 FUTURE DIRECTIONS AND CONCLUSIONS

### 4.1 Microplastic particle pollution

Microplastics, which are defined as pieces of plastic smaller than 5 mm along the longest dimension, are broadly classified as either primary microplastics or secondary

microplastics (Cole et al., 2011). Primary microplastics are manufactured at microscopic or near microscopic size to be used as scrubbing or exfoliating agents in a variety of personal care products and industrial scouring applications. Secondary microplastics are formed from the fragmentation of discarded plastic in the environment. Due to the small size and variable buoyancy of microplastics, a wide variety of organisms are susceptible to ingestion of microplastics, especially in aquatic environments (Miller et al., 2020). In marine environments, the highest body burdens of microplastics are found in tetrapod vertebrates (Parolini et al., 2023).

Among reptiles, documentation of microplastic contamination is limited to sea turtles, but the phenomenon appears widespread. Synthetic particles, as diverse as elastomers associated with tire wear and microbeads associated with cosmetics, were found in the digestive tracts of every one of 102 sea turtles examined, representing all seven species of sea turtles sampled across three ocean basins (Duncan et al., 2019). Additional studies have found microplastics in the digestive tracts of green sea turtles from the GBR (Caron et al., 2018) and loggerhead sea turtles from the North Atlantic (Pham et al., 2017), with polyethylene (PE) and polypropylene being the most common polymers. Additional studies suggest that microplastics are ingested by neonatal sea turtles (Rice et al., 2021) and passed on to eggs via maternal transfer (Curl et al., 2024). Egg yolk and livers from loggerhead sea turtle embryos collected from nests along the Tuscany Coast of Italy contained microplastic spheres and fragments less than 5 µm, with PE, polyvinyl chloride, and acrylonitrile butadiene accounting for more than 65% of the polymers (Chemello et al., 2023).

Although the biological effects of microplastic contamination are largely unknown, experimental feeding trials in the European pond turtle (*Emys orbicularis*) suggests that microplastic ingestion affects the physiology of turtles. Pond turtles fed PE-contaminated food at doses of 250, 500, and 1000 mg PE/kg food for 30 days exhibit a variety of differences in serum enzyme activity and serum biochemistry in comparison to pond turtles fed a standardized control diet (Banaee et al., 2021). All doses of PE resulted in higher creatinine phosphokinase and alkaline phosphatase activity and lower lactate dehydrogenase activity and serum Mg<sup>2+</sup> concentration in comparison to controls. Exposure to 500 and 1000 mg PE/kg food led to increased alanine and aspartate aminotransferase activity in serum, and higher serum cholesterol, glucose, creatinine, urea, and Ca<sup>2+</sup> in comparison to controls. Whereas gamma-glutamyl transferase activity and serum protein, albumin, total immunoglobulins, and phosphorus was lower in the same treatment groups in comparison to controls. Pond turtles fed the highest dose of PE had lower serum triglyceride concentration than controls. In addition to direct effects that

microplastics might have on reptiles, microplastics bind lipophilic compounds such as PCBs, thus making microplastics a potential vehicle for exposure to a variety of EDCs (Besseling et al., 2013). Lastly, EDCs, such as nonylphenol, can leach out of plastics and enter the food chain by ingestion or absorption, as has been shown in fish (Hamlin et al., 2015). Although the impact of microplastics on hormone signaling and reproduction in reptiles has not been assessed, this is an emerging area of concern that warrants investigation.

## 4.2 Epigenomics and transcriptomics

Recent efforts aimed at understanding the effects of anthropogenic activities on hormone signaling and reproduction in reptiles involve investigations of epigenomic and transcriptomic responses. For instance, Guillette Jr. et al. (2016) found differences in the RBC DNA methylome among American alligators from LWNWR, Lake Apopka, and MINWR. There was very little overlap between comparisons of LWNWR to either Lake Apopka or MINWR, signifying site-specific differential DNA methylation regions, which is consistent with observed phenotypes related to endocrine function. Similarly, variation in the RBC DNA methylome of hatchling alligators reflects phenotypic sex and egg incubation temperature (Bock et al., 2022). If the signature of past incubation temperature persists in older animals, these findings provide a potential mechanism for monitoring sex ratios in response to past incubation temperatures in TSD species.

Like the DNA methylome, a comparison of the ovarian transcriptome of five-month-old alligators from LWNWR and Lake Apopka revealed site-specific differences (Hale & Parrott, 2020). Remarkably, *in ovo* exposure of LWNWR embryos to E<sub>2</sub> resulted in greater than 75% overlap in the differentially expressed genes (DEGs) observed in Lake Apopka alligators and E<sub>2</sub>-treated LWNWR alligators in comparison to untreated LWNWR alligators. Follicle density was higher in untreated LWNWR alligators than either Lake Apopka or E<sub>2</sub>-treated LWNWR alligators, validating the biological significance of the transcriptome (Hale & Parrott, 2020).

Although epigenomic and transcriptomic approaches are not without their challenges, particularly as it pertains to cost and interpretation of the large data sets that are generated by such work, they have some advantages over more traditional approaches. One of the primary advantages is that the approach yields a more holistic phenotype at the molecular level, free of biases inherent in the conventional gene-by-gene approach. As more of these large data sets are generated under different conditions and annotated against sequenced genomes, unexpected relationships between molecular and anatomical or physiological phenotypes are

likely to emerge. These emergent relationships will generate new hypotheses regarding environmental influences on hormone signaling and reproduction, ultimately further informing us of the consequences of our decisions.

## 5 CONCLUSIONS

The research reviewed in this chapter makes it clear that reptiles are threatened by anthropogenic activities, including climate change and environmental pollution. Some effects are overt, reasonably well-documented, and involve easily recognizable threats to the persistence of affected populations, such as altered nesting phenology and skewed sex ratios in response to warmer temperatures and reduced egg viability in association with environmental contamination. Other effects are subtle and require further study to fully understand their biological significance regarding population-level impacts, such as changes in steroid receptor or steroidogenic enzyme expression. Although much has been learned since the publication of the first edition of this volume, much remains to be learned about hormone signaling and reproduction in reptiles so that we can more readily recognize perturbations in development and reproduction in the face of growing threats to wild populations.

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# Species Index

Note: Page numbers followed by *f* indicate figures and *t* indicate tables.

## A

- Acanthodactylus boskianus*, 143  
*Acanthodactylus erythrurus*, 143  
*Acris crepitans*, 223–224  
*Acrochordus granulatus*, 319, 321  
*Agama agama*, 75–77, 216–217t  
*Agama stellio*, 168  
*Agkistrodon contortrix*, 179, 180f, 181, 221, 221t, 320, 326–327  
*Agkistrodon piscivorus*, 122f, 225, 320, 328  
*Ahaetulla prasina*, 216–217t  
*Aldabrachelys gigantea*, 245–246, 254  
Alligator lizard. *See Gerrhonotus coeruleus principis*  
*Alligator mississippiensis*, 14, 17–18t, 19, 70–71, 74, 76–77, 91, 98, 125f, 126, 139, 171f, 172–173t, 174, 181, 183–184t, 187–188t, 221t, 271–283, 277f, 279–282f, 343–344  
*Alligator sinensis*, 212–213, 276–279, 281–283, 344  
Alligator snapping turtle. *See Macrochelys temminckii*  
Amazonian river turtle. *See Podocnemis expansa*  
*Amblyrhynchus cristatus*, 39, 142, 169–170, 183–184t, 187–188t, 189–191, 214, 216–217t, 219, 222, 301–302  
American alligator. *See Alligator mississippiensis*  
American crocodile. *See Crocodylus acutus*  
*Amphibolurus caudicinctus*, 221t  
*Amphibolurus maculosus*, 216–217t  
*Amphibolurus muricatus*, 9, 12, 15, 22–24, 297  
*Amphibolurus nuchali*, 221t  
*Amphibolurus ornatus*, 123  
*Amyda japonica*, 121  
*Anelytropsis*, 301  
Anguid slow worm. *See Anguis fragilis*  
*Anguis*, 297  
*Anguis fragilis*, 146  
*Aniella pulchra*, 297  
*Anolis*, 7–8, 36, 38, 41–42, 144–145, 222, 290, 298, 304, 307, 345  
*Anolis acutus*, 293  
*Anolis aplopeltatus*, 216–217t  
*Anolis carolinensis*, 15, 35–37, 36f, 42–43, 49, 51t, 53, 72–73, 75, 99–101, 104–105, 107, 122–124, 128, 167–171, 175–179, 181–182, 183–184t, 184, 212–213, 216–217t, 222–224, 292–293, 295, 295t, 298–299, 303

## B

- Anolis cristatellus*, 343  
*Anolis distichus*, 216–217t  
*Anolis equestris*, 42–43  
*Anolis limifrons*, 293–294  
*Anolis opalinus*, 293–294  
*Anolis pulchellus*, 107, 176  
*Anolis sagrei*, 36, 39, 48, 53, 76, 172–173t, 177–179, 183–184t, 214, 216–217t, 219, 221–222, 221t, 293, 295t, 298  
*Anops kingii*, 297  
*Antaresia childreni*, 319, 328, 330–331  
*Apalone spiniferus*, 17–18t  
Argus monitor lizard. *See Varanus panoptes*  
*Arizona elegans*, 325  
Ascincid lizard. *See Eulamprus heatwolei*  
Aspic viper. *See Vipera aspis*  
*Aspidoscelis*, 37  
*Aspidoscelis burri*, 306  
*Aspidoscelis inornatus*, 41, 46–47, 49, 52, 221t, 222, 224, 295t, 306  
*Aspidoscelis lineattissimus*, 144  
*Aspidoscelis uniparens*, 15, 41, 46–47, 49, 52, 219, 224, 306  
*Astatotilapia burtoni*, 223–224  
*Astrochelys radiaceta*, 254–255  
*Astrochelys radiata*, 254–255  
*Astrochelys yniphora*, 241, 243f, 248, 254, 260, 261f  
Augrabies flat lizard. *See Platysaurus broadleyi*  
Australian flatback turtle. *See Natator depressus*  
Australian freshwater crocodile. *See Crocodylus johnstoni*  
Australian jacky dragon. *See Amphibolurus muricatus*  
Australian skink. *See Bassiana duperreyi*  
Australian snapping turtle. *See Elysia dentata*  
Australian tree skink. *See Egernia striolata*

## C

- Blanus cinereus*, 139–140, 139f, 297  
Blood python. *See Python curtus*  
Blotched blue-tongued lizard. *See Tiliqua nigrolutea*  
Blue-tongued skink. *See Tiliqua nigrolutea*  
*Boa imperator*, 321  
*Boiga irregularis*, 150–152, 167, 172–173t, 174, 175f, 326–327, 329–330  
*Bothrops jararaca*, 92–93, 222–223, 322–323  
*Bradyopidion pumilum*, 300  
Brazilian skink. *See Mabuya heathi*  
Broad-headed skink. *See Eumeces laticeps*  
*Brookesia* spp., 300  
Brown anole. *See Anolis sagrei*  
Brown tree snake. *See Boiga irregularis*  
*Bufo gargarizans*, 355

*Chelydra serpentina*, 10f, 11–12, 15, 17–18t, 73t, 107, 119, 125–126, 129, 172–173t, 173–174, 176, 247–251, 343, 355  
*Chersine angulata*, 74, 255  
*Chersobius signatus*, 241–242, 255  
 Chinese cobra. *See Naja naja*  
 Chinese green tree viper. *See Viridovipera stejnegeri* (*Trimeresurus stejnegeri*)  
*Chrysemys dorsigni*, 250–251  
*Chrysemys picta*, 11–12, 15–19, 17–18t, 73t, 92, 96, 102–103, 116–119, 117f, 121–122, 124–125f, 127–129, 129f, 137, 172–173t, 173, 181, 209, 221t, 247–248, 250–251, 343  
*Cnemidophorus*, 307  
*Cnemidophorus burti*, 306  
*Cnemidophorus inornatus*, 221t, 306  
*Cnemidophorus lemniscatus*, 169  
*Cnemidophorus nativo*, 293–294  
*Cnemidophorus sexlineatus*, 76, 183–184t, 186, 187–188t  
*Cnemidophorus tigris*, 75  
*Cnemidophorus uniparens*, 94–95, 183–184t, 219, 306  
*Coleonyx variegatus*, 76  
 Collared lizard. *See Crotaphytus collaris*  
 Common chameleon. *See Chamaeleo chamaeleon*  
 Common gecko. *See Hoplodactylus maculatus*  
*Conolophus* spp., 142  
 Copperhead snake. *See Agkistrodon contortrix*  
*Cordylis nigra*, 74  
*Cordylus cordylus*, 142  
*Cordylus giganteus*, 142, 300  
*Cordylus polystoma*, 300  
*Corucia zebra*, 304–305  
 Cottonmouth snake. *See Agkistrodon piscivorus*  
 Crocodile lizard. *See Shinisaurus crocodilurus*  
*Crocodylus acutus*, 343–344  
*Crocodylus johnstoni*, 187–188t, 272, 275–276, 349–350  
*Crocodylus moreletii*, 275–278, 349–350  
*Crocodylus niloticus*, 74, 275–276, 278–280  
*Crocodylus palustris*, 275–277  
*Crocodylus porosus*, 74, 272–276, 278, 282–283, 344–345  
*Crocodylus siamensis*, 275–276  
*Crotalus adamanteus*, 320  
*Crotalus atrox*, 183–184t, 185f, 319–320, 322–323  
*Crotalus durissus*, 118–119  
*Crotalus durissus terrificus*, 319  
*Crotalus helleri*, 330  
*Crotalus horridus*, 320, 329  
*Crotalus molossus*, 320  
*Crotalus oreganus*, 320, 330–331  
*Crotalus scutulatus*, 320  
*Crotalus tigris*, 322–323  
*Crotaphytus bicinctores*, 142  
*Crotaphytus collaris*, 39, 126, 171–173, 221, 301  
*Cryptoblepharus*, 293  
*Ctenophorus*, 9  
*Ctenophorus decresii*, 216–217t, 219  
*Ctenophorus maculosus*, 216–217t  
*Ctenophorus modestus*, 216–217t

*Ctenophorus pictus*, 129, 216–217t, 344  
*Ctenosaura pectinata*, 98  
*Ctenotus*, 293  
*Ctenotus decresii*, 214  
*Cyrtodactylus malyanus*, 293–294

**D**

*Dermochelys coriacea*, 194, 242f, 247, 251–252, 344–345  
 Desert iguana. *See Dipsosaurus dorsalis*  
 Desert tortoise. *See Gopherus agassizii*  
 Diamondback turtle. *See Malaclemys terrapin centrat*  
*Dibamus*, 301  
*Diploglossus*, 297  
*Diporiphora*, 293  
*Dipsosaurus dorsalis*, 141–142  
*Draco melanopogon*, 293–294  
*Dromicodryas bernieri*, 327–328  
*Dromicodryas quadrilineatus*, 327–328  
 Dwarf chameleon. *See Bradypodion pumilum*

**E**

Earless monitor lizard. *See Lanthanotus borneensis*  
 Eastern fence lizard. *See Sceloporus undulatus*  
 Eastern hermann's totoise. *See Testudo hermanni boettgeri*  
 Eastern three-lined skink. *See Bassiana duperreyi*  
*Egernia* spp., 214, 228–229  
*Egernia stokesii*, 144, 146  
*Egernia striolata*, 144, 146  
*Egernia whitii*, 169–170, 172–173t, 186, 187–188t, 228–229  
*Elaphe climacophora*, 322  
*Elaphe quadrivirgata*, 323  
*Elysa dentata*, 247, 257  
*Emydura*, 257  
*Emydura krefftii*, 258  
*Emys marmorata*, 355  
*Emys orbicularis*, 137, 357  
*Eretmochelys imbricata*, 17–18t, 172–173t, 185–186, 187–188t, 245–246, 251–252, 261–262

*Erymnochelys madagascariensis*, 245, 258–259, 258t, 259f  
*Eublepharis*, 290, 299, 307  
*Eublepharis macularius*, 14, 37, 50, 74, 94, 96, 103, 140, 145, 170, 207f, 208–209, 222, 295t, 299–300, 344  
*Eulamprus heatwoli*, 187–188t  
*Eulamprus tympanum*, 9  
*Eumeces* spp., 305  
*Eumeces fasciatus*, 76–77  
*Eumeces laticeps*, 144, 146  
*Eumeces oboletus*, 305–306  
 European adder. *See Vipera berus*  
 European common lizard. *See Lacerta vivipara*  
 European pond turtle. *See Emys orbicularis*  
 European wall lizard. *See Podarcis muralis*  
*Eutropis longicaudata*, 225

**F**

Fan-throated lizard. *See Sitana ponticeriana*  
*Farancia abacura*, 323  
 Flying lizard. *See Draco melanopogon*  
*Fowlea piscator*, 325  
*Furcifer labordi*, 290, 300  
*Furcifer verrucosus*, 300

**G**

Galapagos marine iguana. *See Amblyrhynchus cristatus*  
 Galapagos tortoise. *See Geochelone nigra*  
*Gavialis gangeticus*, 74, 275–276, 283  
*Gekko gecko*, 144, 222–223  
*Gekko japonicus*, 9, 299–300  
*Geochelone carbonaria*, 137  
*Geochelone denticulata*, 137  
*Geochelone nigra*, 73t, 104, 183–184t, 247, 260  
*Geoclemys reevesii*, 75  
*Gerrhonotus coeruleus*, 98  
*Gerrhonotus coeruleus principis*, 297  
*Gerrhosaurus nigrolineatus*, 144, 301  
 Gila monster. *See Heloderma suspectum*  
 Girdle-tailed lizard. *See Cordylus niger*  
 Glass snake. *See Ophiodes fragilis*  
*Glyptemys insculpta*, 2–7  
*Gonatodes rozei*, 216–217t  
*Goniurosaurus lichtenfelderi*, 222  
 Gopher tortoise. *See Gopherus polyphemus*  
*Gopherus* spp., 137, 255–256  
*Gopherus agassizii*, 76, 129, 137, 183–184t, 247–248, 250–251, 255–256, 259–260  
*Gopherus berlandieri*, 137  
*Gopherus polyphemus*, 137, 183–184t, 221t, 247–248, 255–256, 260  
*Graptemys flavimaculata*, 250–251  
*Graptemys pseudogeographica kohnii*, 68–69  
 Great plains skink. *See Eumeces oboletus*  
 Green anole. *See Anolis carolinensis*  
 Green iguanax. *See Iguana iguana*  
 Green sea turtle. *See Chelonia mydas*  
*Gymnophthalmus underwoodi*, 297

**H**

Hardwick's spiny-tailed lizard. *See Uromastyx hardwickii*  
*Heloderma horridum*, 301  
*Heloderma suspectum*, 301  
*Hemidactylus*, 299  
*Hemidactylus brooki*, 72–73  
*Hemidactylus flaviviridis*, 66, 66–68f, 70–73, 79, 80f, 81–82, 96, 102–103, 121, 142, 299–300  
*Hemiergis decresiensis*, 294–295  
*Hemiphyllodactylus*, 299  
 Hermann's tortoise. *See Testudo hermanni*  
*Heteronotia*, 299  
*Heteronotia binoei*, 142  
*Holbrookia propinqua*, 301, 304  
*Homonota darwini*, 293–294  
*Hoplodactylus*, 299  
*Hoplodactylus maculatus*, 128, 169, 183–184t, 186, 187–188t, 191–193, 293–294

- I**
- Iberian rock lizard. *See Iberolacerta spp.*; *Lacerta monticola*
  - Iberian wall lizard. *See Podarcis hispanica*
  - Iberian worm lizard. *See Blanus cinereus*
  - Iberolacerta* spp., 143
  - Iberolacerta cyreni*, 141f, 143–150, 146–147f
  - Iberolacerta monticola*, 150
  - Iguana iguana*, 92, 123, 140–142, 149–150
  - Imbricate alligator lizard. *See Barisia imbricata imbricata*
  - Indian chequered water snake. *See Natrix piscator*
  - Indian keeled lizard. *See Mabuya carinata*
  - Indian wall lizard, indian house lizard. *See Hemidactylus flaviviridis*
  - Italian wall lizard. *See Podarcis sicula; Podarcis sicula sicula*
- J**
- Japalura mitsukurii formosensis*, 297
  - Japanese grass lizard. *See Takydromus tachydromoides*
- K**
- Karoo girdled lizard. *See Cordylus polyzonus*
  - Karusasaurus polyzonus*, 300
  - Keelback. *See Tropidonophis mairii*
  - Keeled earless lizard. *See Holbrookia propinqua*
  - Kemp's ridley turtle. *See Lepidochelys kempii*
  - Kinosternum* spp., 137
  - Kinosternum odoratum*, 136–137
  - Komodo dragon. *See Varanus komodoensis*
- L**
- Lacerta*, 7–8, 11, 307
  - Lacerta agilis*, 143, 147
  - Lacerta monticola*, 37
  - Lacerta monticola cyreni*, 143
  - Lacerta monticola monticola*, 150
  - Lacerta schreiberi*, 143
  - Lacerta sicula*, 94
  - Lacerta viridis*, 143, 147–148
  - Lacerta vivipara*, 90, 94, 96–97, 102, 118–121, 120f, 143, 146, 169–170, 183–184t, 191–193, 207f, 210, 214, 216–217t, 227–228, 295t, 298, 302
  - Lampropholis guichenoti*, 126
  - Lanthanotus borneensis*, 302–303
  - Laticauda* spp., 150
  - Laticauda colubrina*, 319, 321
  - Leatherback turtle. *See Dermochelys coriacea*
  - Leioheterodon madagascariensis*, 327–328
  - Leioheterodon modestus*, 327–328
  - Leioploisma laterale*, 100
  - Leopard gecko. *See Eublepharis macularius*
  - Lepidochelys*, 245–246
  - Lepidochelys kempii*, 246–247, 251–252, 260
  - Lepidochelys olivacea*, 74, 186, 187–188t, 246–247, 251, 261–262
  - Lepidodactylus*, 299
  - Liford's wall lizard. *See Podarcis lilfordi*
  - Liolaemus* spp., 100–101, 135–136, 141–142
  - Liolaemus chilensis*, 144
  - Liolaemus fabiani*, 142
  - Liolaemus fitzkaui*, 216–217t
  - Liolaemus monticola*, 37
  - Liolaemus pictus*, 293–294
  - Liolaemus sarmientoi*, 216–217t
  - Liolaemus tenuis*, 145
  - Liolaemus wiegmannii*, 142
  - Lissemys punctata*, 128–130
  - Lissemys punctata punctata*, 118–119, 168–169, 250–251, 262
  - Little striped whiptail lizard. *See Cnemidophorus inornatus*
  - Lizard. *See Agama stellio*
  - Loggerhead turtle. *See Caretta caretta*
- M**
- Mabuya* spp., 96, 101
  - Mabuya bistrigata*, 101
  - Mabuya brachypoda*, 101
  - Mabuya capensis*, 74
  - Mabuya carinata*, 76, 99–100, 118, 169–170, 172–173t, 174, 176–178
  - Mabuya heathi*, 101, 305
  - Macrochelodina oblonga*. *See Chelodina oblonga*
  - Macrochelys temminckii*, 11–12
  - Malaclemys terrapin centrata*, 247–248, 251
  - Mauremys leprosa*, 137–138, 138f, 241
  - Mauremys mutica*, 78–79
  - Mauremys rivulata*, 247–248
  - McCann's skink. *See Oligosoma maccanni*
  - Melanosuchus niger*, 349–350
  - Menetia* spp., 304–305
  - Merolia spilota*, 214
  - Mexican beaded lizard. *See Heloderma horridum*
  - Mexican gecko. *See Phyllodactylus lanei*
  - Microlophus albemarlensis*, 216–217t
  - Microlophus delanonis*, 216–217t
  - Mojave rattlesnake. *See Crotalus scutulatus*
  - Monopeltis anchetae*, 297
  - Morelet's crocodile. *See Crocodylus moreletii*
  - Morelia spilota spilota*, 327–328
  - Morelia spilota variegata*, 327–328
  - Morethia*, 293
  - Mountain lizard. *See Japalura mitsukurii formosensis*
  - Mountain spiny lizard. *See Sceloporus jarrovii*
  - Mud turtle. *See Kinosternum odoratum*; *Stenotherus odoratus*
  - Musk turtle. *See Kinosternum odoratum*; *Stenotherus odoratus*
  - Myuchelys*, 257
- N**
- Nactus*, 299
  - Naja naja*, 76, 94, 319–320, 322, 325
  - Natator depressus*, 251–252
  - Natrix maura maura*, 169
  - Natrix piscator*, 325
  - Natrix sipedon pictiventris*, 106
  - Naultinus*, 299
  - Nerodia* spp., 96–97, 127–128, 323, 356
  - Nerodia rhombifer*, 325
  - Nerodia sipedon*, 213, 320, 322–323, 331, 356
  - Nile crocodile. *See Crocodylus niloticus*
  - Nile monitor. *See Varanus niloticus*
  - Niveoscincus*, 305, 307
  - Niveoscincus coventryi*, 294–295
  - Niveoscincus metallicus*, 100, 106f, 294–295, 305
  - Niveoscincus microlepidotus*, 106, 146, 305
  - Niveoscincus microlepidus*, 146
  - Niveoscincus ocellatus*, 9, 90, 294–295, 305
  - Northern fence lizard. *See Sceloporus undulatus hyacinthinus*
- O**
- Oligosoma* spp., 305
  - Oligosoma maccanni*, 305–306
  - Olive ridley turtle. *See Lepidochelys olivacea*
  - Opheodrys aestivus*, 320
  - Ophidiomyces ophiodiicola*, 331
  - Ophiodes fragilis*, 297
  - Ophisaurus*, 297
  - Oriental garden lizard. *See Calotes versicolor*
- P**
- Painted turtle. *See Chrysemys picta; Trachemys picta*
  - Pantherophis guttatus*, 322–323
  - Paroedura picta*, 221t, 222
  - Pelodiscus maackii*, 76–77
  - Pelodiscus sinensis*, 63–65, 67–70, 78–79
  - Pelomedusa*, 259
  - Pelomedusa galeata*, 259
  - Pelomedusa subrufa*, 259, 259f
  - Peltcephalus* spp., 258–259
  - Pelusios castanoides*, 259, 259f
  - Philomachus pugnax*, 231
  - Phrynosoma*, 290, 304
  - Phrynosoma cornutum*, 183–184t, 186, 187t, 298, 304–306
  - Phrynosoma cornutum blainvilliei*, 304
  - Phyllodactylus lanei*, 293, 299–300
  - Phymaturus antofagastensis*, 293–294
  - Phymaturus patagonicus*, 293–294
  - Phymaturus punae*, 293–294
  - Plasmodium mexicanum*, 188
  - Platysaurus broadleyi*, 216–217t, 301, 307
  - Plestiodon septentrionalis*, 225
  - Podarcis* spp., 143, 307
  - Podarcis bocagei*, 76, 216–217t, 356
  - Podarcis erhardii*, 143–144, 216–217t
  - Podarcis gaigeae*, 216–217t
  - Podarcis guadarramae*, 143, 145, 148–150, 148f
  - Podarcis hispanica*, 37, 123
  - Podarcis lilfordi*, 145
  - Podarcis liolepis*, 37, 149, 216–217t
  - Podarcis melisellensis*, 39, 214, 216–217t
  - Podarcis muralis*, 70–71, 148–149, 214, 216–217t, 231

*Podarcis sicula*, 70–79, 81–82, 96, 98–103, 105, 127–128, 216–217t, 223, 295t, 298, 302, 305–306, 356  
*Podarcis sicula campestris*, 75  
*Podarcis sicula sicula*, 67–68, 73t, 74, 76–78, 106–107, 172–173t, 177, 182, 183–184t  
*Podarcis vaucheri*, 216–217t  
*Podarcis waglerianus*, 216–217t  
*Podocnemis*, 247, 258–259  
*Podocnemis expansa*, 247  
*Pogona barbata*, 91–92, 102, 183–184t, 187t, 297  
*Pogona vitticeps*, 10–11  
*Protobothrops flavoviridis*, 323  
*Psammobates tentorius tentorius*, 255  
*Psammodromus algirus*, 143–144, 148–149, 216–217t, 302  
*Pseudemoia entrecasteauxii*, 294–295  
*Pseudemydura umbrina*, 245, 247–248, 258  
*Pseudemys scripta*, 72–73, 169  
*Pseudemys scripta elegans*, 169  
Pygmy monitor lizard. *See Varanus brevicaudus*  
*Python bivittatus*, 151–152  
*Python curtus*, 326  
*Python regius*, 222–223

**Q**

*Quedenfeldtia trachylepharus*, 216–217t

**R**

Rainbow whiptail lizard. *See Cnemidophorus lemniscatus*  
Rat snake. *See Elaphe climacophora*  
Red-eared slider. *See Pseudemys scripta elegans; Trachemys scripta; Trachemys scripta elegans*  
Red-sided garter snake. *See Thamnophis sirtalis parietalis*  
Red-spotted garter snake. *See Thamnophis sirtalis concinnus*  
Reeve's turtle. *See Geoclemys reevesii*  
*Rhacodactylus*, 299  
Rough greensnake. *See Opheodrys aestivus*  
Ruin lizard. *See Podarcis sicula campestris*

**S**

Sagebrush lizard. *See Sceloporus graciosus*  
*Salvator merianae*, 144, 146, 221t  
San diego coast horned lizard. *See Phrynosoma cornutum blainvilliei*  
Sand lizard. *See Lacerta agilis*  
*Sceloporus* spp., 7–8, 37, 142, 228, 231, 290, 293, 303–304, 307, 343  
*Sceloporus cyanogenys*, 104  
*Sceloporus formosus*, 294–295  
*Sceloporus graciosus*, 37  
*Sceloporus grammicus*, 216–217t, 294–295  
*Sceloporus jarrovii*, 103–104, 128, 145, 169, 222, 224, 292–293, 295, 295t, 298, 304  
*Sceloporus malachiticus*, 294–295  
*Sceloporus minor*, 216–217t  
*Sceloporus mucronatus*, 294–295

*Sceloporus occidentalis*, 76–77, 177–178, 183–184t, 188  
*Sceloporus poinsetta*, 11  
*Sceloporus pyrocephalus*, 214–217, 303  
*Sceloporus torquatus*, 98  
*Sceloporus torquatus torquatus*, 98  
*Sceloporus undulatus*, 48, 90, 101, 169, 181, 182f, 183–184t, 231, 295t, 298, 303  
*Sceloporus undulatus erythrocheilus*, 216–217t  
*Sceloporus undulatus hyacinthinus*, 303  
*Sceloporus virgatus*, 48, 107, 140, 142, 231, 303, 305–306

*Sceloporus woodi*, 126  
Sea snakes. *See Laticauda* spp.  
*Seminatrix pygaea*, 118–119  
Sharp-mouthed lizard. *See Anolis pulchellus*  
Shingleback skink. *See Tiliqua rugosa*  
*Shinisaurus crocodilurus*, 306–307  
Side-blotched lizard. *See Uta stansburiana*  
*Sistrurus miliarius*, 224, 319–320, 328–331  
*Sitana ponticeriana*, 116–119, 117f, 121  
Six-lined race runner. *See Cnemidophorus sexlineatus*

*Smaug giganteus*, 300  
Snapping turtle. *See Chelydra serpentina*  
Snow skink. *See Niveoscincus microlepidus*  
Soft-shelled turtle. *See Lissemys punctata punctata*

Solomon island skink. *See Corucia zebra*  
South African giant girdled lizard or sungazer.

*See Cordylus giganteus*

South American red-footed tortoise.  
*See Geochelone carbonaria*

South American yellow-footed tortoise.  
*See Geochelone denticulata*

Spanish terrapin. *See Mauremys leprosa*

*Sphenodon* spp., 139

*Sphenodon punctatus*, 63–65, 102, 117, 138, 172–173t, 173–174, 183–184t, 187–188t, 221t

*Sphenomorphus*, 293

*Sphenomorphus indicus*, 9

Spiny-footed lizard. *See Acanthodactylus erythrurus*

Spotted snow skink. *See Niveoscincus ocellatus*

*Stenotherus odoratus*, 73t, 74, 119, 172–173t, 247–251, 249–250f, 255–256

Steppe's tortoise. *See Testudo horsfieldii*

Stoke's skink. *See Egernia stokesii*

Striped plateau lizard. *See Sceloporus virgatus*

**T**

*Takydromus tachydromoides*, 75, 212–213

Tasmanian skink. *See Niveoscincus metallicus; Niveoscincus ocellatus*

*Terrapene carolina carolina*, 256

*Testudo*, 255–256

*Testudo hermanni*, 117, 137, 247

*Testudo hermanni boettgeri*, 255–256

*Testudo hermanni hermanni*, 255–256

*Testudo horsfieldii*, 247, 256, 256f

Texas horned lizard. *See Phrynosoma cornutum*

*Thamnophis* spp., 122–123

*Thamnophis elegans*, 127, 330

*Thamnophis sirtalis*, 119, 121–122, 214, 221t, 320, 322–323, 325, 329

*Thamnophis sirtalis concinnus*, 172–173t, 183–184t, 186, 189, 329–330

*Thamnophis sirtalis parietalis*, 37, 41, 91–94, 98–99, 127, 150–153, 152f, 171, 172–173t, 174, 179–181, 180f, 183–184t, 185–186, 187t, 189, 216–217t, 317–318, 321–327, 329–332

*Tiliqua*, 305

*Tiliqua nigrolutea*, 74, 91–92, 94, 97, 99f, 101, 221t, 293–294, 305–306

*Tiliqua rugosa*, 72–73, 94, 97, 128, 146, 172–173t, 221t, 305–306

*Timon lepidus*, 143

*Trachemys picta*, 168

*Trachemys scripta*, 14–16, 17–18t, 19, 21, 65f, 68, 70–74, 77–78, 121–122, 124f, 127, 138f, 170, 216–217t, 222–223, 344, 355

*Trachemys scripta elegans*, 50, 72–73, 138, 168

Tree lizard. *See Urosaurus ornatus*

*Trionyx sinensis*, 128–129

*Trogonophis wiegmanni*, 140

*Tropidonophis mairii*, 331–332

*Tropidonotus natrix*, 116

*Tropidurus semitaeniatus*, 216–217t

Tuatara. *See Sphenodon punctatus*

*Tupinambis merianae*, 221t

**U**

*Uromastix hardwickii*, 76–77, 106, 142

*Uromastyx acanthinura*, 96, 170

*Uromastyx aegyptia microlepis*, 142

*Urosaurus*, 37, 221, 228, 304

*Urosaurus graciosus*, 216–217t

*Urosaurus ornatus*, 38, 40, 47, 49, 53, 53f,

103–104, 169–173, 172–173t, 186, 187–188t, 189–190, 192, 206–208, 207f, 214, 216–217t, 218, 221, 224–225, 226f, 227, 295t, 304

*Uta*, 225, 227–228, 304

*Uta palmeri*, 214

*Uta stansburiana*, 38–39, 52–53, 76, 100–101,

170–171, 172–173t, 178–179, 183–184t,

190–192, 206–209, 207f, 212–214,

216–217t, 218–219, 221–222, 225,

227–231, 304

**V**

*Varanus*, 306–307

*Varanus albigularis*, 221t, 306–307

*Varanus brevicaudus*, 306–307

*Varanus komodoensis*, 301, 306–307

*Varanus niloticus*, 290

*Varanus panoptes*, 306–307

Veiled chameleon. *See Chamaeleo calyptratus*

*Vipera* spp., 101

*Vipera aspis*, 102, 221t, 319–321, 329–331

*Vipera berus*, 22, 122–123, 214, 216–217t, 244,

320, 325–327

*Viridovipera stejnegeri* (*Trimeresurus stejnegeri*), 319

**W**

Wall lizards. *See Podarcis* spp.  
 Water snake. *See Natrix maura maura; Nerodia sipedon*  
 Western swamp tortoise. *See Pseudemydura umbrina*  
 Western banded gecko. *See Coleonyx variegatus*  
 Western diamond-backed rattlesnake.  
*See Crotalus atrox*  
 Western fence lizard. *See Sceloporus occidentalis*

**Y**

Western hermann's tortoise. *See Testudo hermanni hermanni*  
 Western whiptail. *See Cnemidophorus tigris*

Whiptail lizard. *See Cnemidophorus natus*  
 White-throated savannah monitor lizard.  
*See Varanus albigularis*

**X**

Xantusia vigilis, 72–73  
*Xenosaurus platyceps*, 297

**Z**

Zaocys dhumnae, 71–72, 77–78  
*Zonosaurus boettgeri*, 301  
*Zonosaurus maximus*, 301  
*Zootoca vivipara*, 207f, 210–211, 216–217t, 223, 225, 227, 229, 344  
*Zygaspis quadrifrons*, 297



# Subject Index

Note: Page numbers followed by *f* indicate figures and *t* indicate tables.

## A

- Accessory sex organs
  - excurrent duct system, 116–117
  - femoral glands, 123
  - infundibulum, 124
  - isthmus, 125–126
  - oviduct, 127–128
  - renal sexual segment, 122–123, 122*f*
  - reproductive cycle and variation, 119
  - uterine tube, 124–125, 124–125*f*
  - uterus, 126
  - vagina, 126
- ACTH. *See* Corticotropin
- AGBGM. *See* Androgen-glucocorticoid-binding globulin
- Aggression
  - Hawk-Dove* interactions, 227
  - social groups, monogamy, filiative behaviors, and aggression suppression, 227–229
- Alkylphenol contaminations, 16–19
- Allostasis, definition, 166
- AmbX. *See* Nucleus ambiguus
- Amh, sex determination, 63–65
- γ-Aminobutyric acid (GABA), stress circuits, 168
- Amygdala, reproductive behavior regulation, 46–49, 51–52, 330
- Androgen-glucocorticoid-binding globulin (AGBG), corticosterone binding, 169–170, 189, 227
- Androgen receptor (AR)
  - female function, 96
  - muscle expression and reproductive behavior, 44
- Androstenedione, steroidogenesis, 71, 93–94, 93*f*
- Anterior hypothalamus-preoptic area (AH-POA), reproductive behavior regulation, 306
- Anterior preoptic area of hypothalamus (APOA), 324
- Anti-Müllerian hormone. *See* Müllerian-inhibiting substance
- AR. *See* Androgen receptor
- Arginine vasotocin (AVT)
  - corticotropin-releasing hormone colocalization, 169
  - crocodile oviposition role, 282–283
  - fitness correlation in males, 219, 220*f*
  - oviposition control, 128
  - reproductive behavior regulation, 222–224

## B

- Behavior, reproductive
  - ecological context of displays
    - anolles, 36–37
    - sex differences, 37–39
  - evolution of hormones and, 41–42
  - hormonal control
    - alternative reproductive strategies, 40
    - anolles, 39–40
    - leopard geckos, 41
    - red-sided garter snakes, 41
    - turtles, 41
    - whiptail lizards, 41
  - neural control
    - anolles, 42–46, 43*f*
    - leopard geckos, 47–48
    - red-sided garter snakes, 47
    - whiptail lizards, 46–47
  - overview, 35–36, 36*f*
  - reptiles (*see* Reproductive behavior, reptiles)
  - season and hormonal manipulation
    - anolles, 51–52, 51*f*
    - leopard geckos, 52
    - red-sided garter snakes, 52
    - side-blotched lizards, 52–53
    - tree lizards, 52–53, 53*f*
    - whiptail lizards, 52
  - stress effects, 178–181, 180*f*
  - trait development
    - anolles and whiptail lizards, 48–49
    - reptiles with alternative reproductive morphs, 49–50
    - reptiles with temperature-dependent sex determination, 50
- Bisphenol A (BPA), 16, 17–18*t*, 19
- Body length. *See* Snout-to-vent length
- BPA. *See* Bisphenol A
- Bradykinin
  - ovarian synthesis, 92
  - vitellogenesis role, 103
- Bully genotype, 227

## C

- CBG. *See* Corticotropin-binding globulin
- Charnov-Bull model, sex differentiation and adaptation, 22–23
- Chlordane, 17–18*t*, 19
- Cholesta-5,7-dien-3-ol, 147–149
- Cis-Nonachlor, 17–18*t*, 19
- CL. *See* Corpus luteum
- Climate change, 342–345
- Cloacal gland, pheromone secretion
  - lizards, 144
  - snakes, 151
- Clutch size, determinants, 100
- CNS neuroendocrine hormones, interactions with, 224
- Constant temperature equivalent (CTE), models, 20
- Cooperation
  - Hawk-Dove* interactions, 227
  - social groups, monogamy, filiative behaviors, and aggression suppression, 228
- Corpus luteum (CL)
  - hormone production
    - relaxin, 106–107
    - steroids, 106
  - life span, 105
  - morphological changes, 105–106, 106*f*
  - prostaglandin F<sub>2α</sub> and luteolysis, 107
- CORT. *See* Corticosterone
- Corticosterone (CORT). *See also* Stress
  - androgen level correlations, 171–174, 175*f*, 177
  - behavior effects, 178–181, 180*f*, 209
  - binding proteins, 169–170
  - endocrine network theory, 213–214
  - fitness correlation in males, 219, 220*f*
  - fitness effects of stress during reproduction
    - adults, 189–191
    - mothers, 191–192
    - offspring, 192–193
  - lizard reproduction regulation, 300
  - pulsatile secretion, 169
  - reproductive behavior regulation, 40–42, 53
- seasonal changes
  - baseline levels, 181–182, 182*f*
  - prebreeding, breeding, and postbreeding periods, 182–184, 183–184*t*, 185*f*
  - stress levels, 181–182, 182*f*
- snake reproduction, 319, 323, 326–331
- stress response modulation during reproduction, 185–186, 187–188*t*, 189

- Corticosterone (CORT) (*Continued*)  
 testicular function, 76  
 turtle reproductive cycles, 260–262, 261f  
 yolk, 103–104
- Corticotropin (ACTH)  
 hypothalamic-pituitary-adrenal axis, 169–170  
 offspring fitness, 193
- Corticotropin-binding globulin (CBG), 96–97
- Corticotropin-releasing hormone (CRH),  
 hypothalamic-pituitary-adrenal axis, 169
- CRH. *See* Corticotropin-releasing hormone
- Crocodiles  
 development of reproductive system  
 gonadal development, 272–274  
 juvenile growth and peripubertal  
 seasonality, 276  
 key events, 272–276, 273t  
 secondary sex characteristics, 274–275  
 urogenital tract differentiation, 274–276  
 overview, 271–272
- parental care, 225
- pheromones, 138–139
- reproductive cycle  
 females  
 ovulation, gravidity, and oviposition, 280–283, 281–282f  
 vitellogenesis and oocyte maturation, 279–280, 280f  
 seasonality, 276–278
- males, 279, 279f
- Crocodilians  
 and environmental contaminant exposure, 349–354, 349f, 350t  
 hormone concentrations, alterations in, 353–354  
 reproductive organ abnormalities, 351–353, 351f  
 parental care, 225
- CTE. *See* Constant temperature equivalent
- Cyproterone acetate, male reproductive behavior  
 impact, 39
- D**
- D-aspartic acid (D-Asp), 78–79
- DAX1, sex determination, 13–14, 13t
- DDE. *See* 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)ethylene
- DDT. *See* Dichlorodiphenyltrichloroethane
- Deception, Hawk-Dove interactions, 227
- Dehydroepiandrosterone (DHEA),  
 steroidogenesis, 71, 93–94
- Dewlap structure  
 color, 206  
 polymorphism in tree lizard, 44, 206  
 reproductive behavior regulation, 42–44
- DHEA. *See* Dehydroepiandrosterone
- DHT. *See* Dihydrotestosterone
- 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)ethylene  
 (DDE), endocrine disruption, 348–349
- Dichlorodiphenyl dichloroethylene (DDE),  
 16–19, 17–18t
- Dichlorodiphenyltrichloroethane (DDT), 19
- Dihydrotestosterone (DHT)
- corticosterone level correlations, 171–173  
 lizard reproduction regulation, 296, 298, 300,  
 302, 306  
 reproductive behavior regulation, 39–42, 48  
 sex determination, 13t, 16  
 snake reproduction  
 females, 319, 321  
 males, 320  
 testicular function, 76–77, 80
- Dmrt1, sex determination, 13–14, 13t, 63–65
- Dopamine  
 aggression studies, 224  
 stress circuits, 168–169, 171
- Dove genotype, 225, 227
- Ductus deferens, anatomy and histology,  
 118–119
- E**
- EDCs. *See* Endocrine-disrupting chemicals
- Eggshell, formation of, 126
- ELISA. *See* Enzyme-linked immunosorbent  
 assay
- Endocrine-disrupting chemicals (EDCs), 16–19  
*See also specific chemical*  
 effects on sex determination, 16, 17–18t  
 estrogenic, 17–18t, 19  
 nonestrogenic, 17–18t, 19  
 signals, 16
- Endocrine-disrupting contaminants, snake  
 reproduction, 331
- Endocrine disruption  
 environmental contaminant exposure  
 crocodilians and, 349–354, 349f, 350t  
 squamates, 356  
 Turtles, 354–355  
 mechanisms, 346–347, 347–348f  
 in reptiles, 345–356
- Endocrine regulation, of testicular function, 81f
- Environmental influences  
 on hormones and reptiles reproduction  
 climate change, 342–345  
 crocodilians, 349–354, 349f, 350t  
 epigenomics and transcriptomics, 357–358  
 extreme weather events, 344–345  
 microplastic particle pollution, 356–357  
 overview, 341–342  
 sea level rise, 344–345  
 squamates, 356  
 temperature, 343–344  
 turtles, 354–355
- Environmental stressors, 178
- Enzyme-linked immunosorbent assay (ELISA),  
 hormone assays, 244
- Epididymis  
 anatomy, 116–117, 117f  
 histology, 117–118, 117f  
 secretory granule formation and  
 regulation, 119–122, 120f  
 sperm storage, 121–122
- Epinephrine, turtle reproductive cycles, 262
- ER. *See* Estrogen receptor
- Ergosterol, 147–148
- Estradiol, 208  
 corpus luteum production, 106
- crocodile reproduction  
 ovulation, 281–282  
 seasonality, 277f  
 vitellogenesis, 280  
 estrogen forms, 91–92  
 lizard reproduction regulation, 296–307  
 reproductive behavior regulation, 40–41  
 reproductive cycles and secretion,  
 126–127  
 sex determination, 13t, 16  
 snake reproduction role in females, 319, 321,  
 323, 327, 329  
 steroidogenesis, 71–72, 94, 95f  
 stress response in females, 174, 175f  
 testicular function, 77–78  
 turtle reproductive cycles, 250–252,  
 254–255  
 vitellogenesis role, 102–103
- Estrogen receptor (ER)  
 forms, 94–95  
 oviduct, 127
- Estrogen receptors alpha (ER $\alpha$ ), 44–45
- Estrogen receptors beta (ER $\beta$ ), 44–45
- 17 $\alpha$ -Ethyneestradiol (EE $_2$ ), 17–18t, 19
- F**
- Female-male-female pattern, temperature-dependent sex determination, 3–6t, 10f, 11–12, 20
- Female-male pattern, temperature-dependent sex determination, 11–12, 20
- Female mimicry, snakes, 152–153, 152f, 327
- Female reproductive system, 123–128, 124f
- Femoral gland  
 behavioral assays, 123  
 lipids in, 142  
 pheromone secretion, 140–144, 141f  
 regulation, 123
- Flutamide  
 male reproductive behavior impact, 39  
 sexual behaviour control, 222
- Follicles. *See also* Corpus luteum; Ovaries;  
 Ovulation  
 atresia, 100–101  
 clutch size determinants, 100  
 development, 98–101, 99f  
 hormonal regulation, 98–99  
 recruitment, 98
- Follicle-stimulating hormone (FSH),  
 351–352  
 clutch size determination, 100  
 crocodile juvenile growth and peripubertal  
 seasonality, 276  
 functional overview, 170–171  
 lizard reproduction regulation, 296,  
 298–299  
 ovarian function, 92–93  
 ovulation control, 104  
 reproductive behavior regulation, 40  
 snake reproduction, 322–323  
 testicular function, 75, 80  
 turtle reproductive cycles, 249–251
- Freshwater turtles, 137–138, 138f
- FSH. *See* Follicle-stimulating hormone

**G**

GABA. *See*  $\gamma$ -Aminobutyric acid  
 Geckos. *See* Lizards  
 Genotypic sex determination (GSD)  
   gonadal differentiation and gene expression, 12–15, 13*t*, 14*f*  
   phylogenetic distribution of patterns, 2–11  
 GH. *See* Growth hormone  
 Ghrelin, turtle reproductive cycles, 262  
 Glucocorticoids, testicular function, 76  
 Glyphosate, 356  
 GnIH. *See* Gonadotropin-inhibiting hormone  
 GnRH. *See* Gonadotropin-releasing hormone  
 Gonadotropin-inhibiting hormone (GnIH), 74–75, 170  
   snake reproduction, 323, 332  
 Gonadotropin-releasing hormone (GnRH)  
   endocrine network theory, 211–212  
   hypothalamic-pituitary-gonadal axis, 170–171  
   lizard reproduction regulation, 296, 303  
   ovarian function, 92  
   ovulation control, 104  
   snake reproduction, 322–323  
   testicular function, 73–75  
   types, 170  
   vitellogenesis role, 103  
 Gonadotropins. *See* Follicle-stimulating hormone; Luteinizing hormone  
 Growth hormone (GH), vitellogenesis role, 103  
 GSD. *See* Genotypic sex determination

**H**

Hawk-Dove system, 225, 227  
 Histamine, testicular function, 79–80  
 Homeostasis, definition, 166  
 HSD. *See* Hydroxysteroid dehydrogenase  
 Hydroxysteroid dehydrogenase (HSD)  
   corpus luteum expression, 106  
   steroidogenesis, 71, 72*f*

IGF-1. *See* Insulin-like growth factor-1  
 Immune system, 170  
 Infundibulum  
   anatomy and histology, 124  
   sperm storage, 128–129  
 Insulin-like growth factor-1 (IGF-1), crocodile reproduction, 281–282  
 Isthmus, anatomy and histology, 125–126

**K**

Kin recognition, pheromones, 146  
 K-strategist, 225, 227

**L**

Leptin, turtle reproductive cycles, 262  
 Leydig cell  
   secreted factors in testicular function, 80–82  
   structure and function, 67–68, 69*f*  
 LH. *See* Luteinizing hormone  
 Lizards  
   classification, 291, 291–292*t*

## pheromones

  agonistic interactions and dominance between males, 149–150  
   chemosensory recognition, 144–146  
   kin recognition, 146  
   scent trails, 146  
   sex and individual recognition, 145–146, 146*f*  
   evolutionary mechanisms, 148–149, 148*f*  
   feces, 144  
   iguanas, 141–142  
   in mate choice, 146–149, 147*f*  
   secretory glands  
     cloacal gland, 144  
     femoral gland, 140–144, 141*f*  
     preanal gland, 140–144  
     precloacal gland, 140–144  
     skin, 140–144  
     urodeal gland, 144

## rationale for study

  environmental and conservation considerations, 291  
   evolutionary considerations, 289–290  
   practical considerations, 289

## reproductive cycles

  prospects for study, 307–308  
   seasonality, 292–294  
   types, 294–296

## reproductive cycles, hormonal control

  Agamidae, 296–297  
   Alopoglossidae, 297  
   Anguidae, 297  
   Anolidae, 298–299  
   Carpodactylidae, 299–300  
   Chamaeleonidae, 300  
   chameleons, 307  
   Cordylidae, 300–301  
   Crotaphytidae, 301  
   Dibamidae, 301  
   Diplodactylidae, 299–300  
   Diploglossidae, 297  
   Eublepharidae, 299–300  
   Gekkonidae, 299–300  
   Gerrhosauridae, 301  
   glass lizards, 297  
   Gymnophthalmidae, 297  
   Helodermatidae, 301  
   Iguanidae, 301–302  
   Lacertidae, 302  
   Lanthanotidae, 302–303  
   overview, 296–307

  Phrynosomatidae, 303–304

  Phyllodactylidae, 299–300  
   Pygopodidae, 299–300  
   Scincidae, 304–306  
   Shinisauridae, 306  
   skinks, 304–306  
   Sphaerodactylidae, 299–300  
   Teiidae, 306  
   Varanidae, 306–307  
   whiptail lizards, 306  
   worm lizards, 297  
   Xantusiidae, 307  
   Xenosauridae, 297

## Luteinizing hormone (LH)

  functional overview, 170–171  
   lizard reproduction regulation, 296  
   ovarian function, 92–93  
   ovulation control, 104  
   snake reproduction, 322–323  
   testicular function, 75  
   turtle reproductive cycles, 249–250, 252

**M**

Macrophage, testicular  
   secreted factors in testicular function, 79  
   ultrastructure, 67–68, 70*f*  
 Male-female pattern, temperature-dependent sex determination, 11–12  
 Male reproductive system, 116–123, 116*f*  
 Melatonin  
   snake reproduction role, 325  
   testicular effects of photoperiod, 72–73  
   turtle reproductive cycles, 262, 262*f*  
 Mercury (Hg), 355–356  
 Metabolic hormones, turtle reproductive cycles, 259–262  
 Methyl thiophanate (MT), 356  
 Microplastic particle pollution, 356–357  
 MIS. *See* Müllerian-inhibiting substance  
 Monogamy, hormonal control, 227–229  
 Müllerian-inhibiting substance (MIS)  
   crocodile secondary sex characteristics, 274–275  
   sex determination, 13, 13*t*, 63–65

**N**

Nasal gland, pheromone secretion, 151  
 Nesfatin-1, 78–79  
 Nesting, cyclicity in turtles, 245–249, 246–247*f*  
 Neurophysin (NP), turtle reproductive cycles, 253  
 NMDA. *See* N-Methyl-D-aspartate  
 N-Methyl-D-aspartate (NMDA), brain receptors, 168  
 Norepinephrine  
   ovarian function, 170  
   stress circuits, 168, 171  
   turtle reproductive cycles, 262  
 Nucleus ambiguus (AmbX), reproductive behavior regulation, 42–43  
 Nucleus sphericus. *See* Amygdala

**O**

Ovaries. *See also* Corpus luteum; Follicles; Ovulation  
   development, 89–91, 90*t*  
   endocrinology and conservation, 107  
   postovulatory, 105–107  
   regulation by pituitary hormones, 92–93  
 steroids  
   overview, 91–92  
   peripheral metabolism, 97  
   plasma binding proteins, 96–97  
   receptors, 94–96  
   steroidogenesis, 93–94, 93*f*  
   stress effects on function, 175–177  
   structure, 89

- Oviduct  
hormonal regulation, 127  
sperm storage, 128–129
- Oviparity, 115. *See also* Viviparity
- Oviposition  
crocodile, 282–283  
hormonal control, 128
- Ovulation  
hormonal control, 104–105  
mechanisms, 104–105  
oocyte maturation, 105
- P**
- P<sub>4</sub>.* *See* Progesterone
- Paracrine regulation, of testicular function, 81f
- PCBs. *See* Polychlorinated biphenyl compounds
- Persistent organic pollutants (POPs), 19
- Pheromones  
Amphisbaenians, 139–140, 139f  
behavioral assays, 136  
crocodiles, 138–139  
lizards  
agonistic interactions and dominance between males, 149–150  
chemosensory recognition, 144–146  
kin recognition, 146  
scent trails, 146  
sex and individual recognition, 145–146, 146f  
evolutionary mechanisms, 148–149, 148f  
feces, 144  
iguanas, 141–142  
in mate choice, 146–149, 147f  
secretory glands  
cloacal gland, 144  
femoral gland, 140–144, 141f  
preanal gland, 140–144  
precloacal gland, 140–144  
skin, 140–144  
urodele gland, 144  
overview, 135  
prospects for study, 153  
Rhynchocephalia, 138  
snakes  
chemosensory recognition  
female mimicry, 152–153, 152f  
mate assessment, 152  
sex discrimination and trailing, 151–152  
secretory glands  
cloacal gland, 151  
nasal gland, 151  
skin, 150–151  
turtles  
freshwater turtles, 137–138, 138f  
functional overview, 136–137  
sea, 138  
sources of pheromones, 136–138  
terrestrial tortoises, 137  
vomeronasal organ, 135–136
- Pineal gland. *See* Melatonin
- Pituitary adenylate cyclase-activating polypeptide (PACAP), 78–79
- POA. *See* Preoptic area
- Polychlorinated biphenyl compounds (PCBs), 17–18t, 19
- PR. *See* Progesterone receptor
- Preanal gland, pheromone secretion, 140–144
- Precloacal gland, pheromone secretion, 140–144
- Pregnancy. *See* Viviparity
- Pregnenolone, steroidogenesis, 71, 93, 93f
- Preoptic area (POA), reproductive behavior regulation, 42, 46–49, 51–52
- PRL. *See* Prolactin
- Progesterone (P<sub>4</sub>), 206, 207f  
corpus luteum, production, 106  
crocodile ovulation role, 281–282  
lizard reproduction regulation, 296–307  
metabolism, 97  
oocyte maturation role, 104  
oviposition control, 128  
reproductive behavior regulation, 40–41  
reproductive cycles and secretion, 126–127  
snake reproduction role, 319, 321, 323, 328  
steroidogenesis, 71, 93–94  
stress response  
females, 173–174, 175f  
males, 173
- Turtle reproductive cycles, 250–251, 254–255
- Vitellogenesis role, 103  
yolk, 103–104
- Progesterone receptor (PR)  
overview, 96  
oviduct, 127–128
- Prolactin (PRL), behavior regulation, 229–231, 230f
- Prostaglandins  
crocodile oviposition role, 282–283  
ovarian synthesis, 92  
ovulation control, 105  
prostaglandin F<sub>2α</sub>  
luteolysis role, 107  
oviposition control, 128  
reproductive behavior regulation, 40  
snake reproduction role, 321, 326  
snake reproduction role, 321  
turtle reproductive cycles, 253
- R**
- Relaxin, corpus luteum production, 106–107
- Renal sexual segment (RSS), secretory granules, 122–123
- Reproductive behavior, reptiles  
developmental effects of hormones on behavior, 206–210, 207f
- Endocrine network theory  
natural, sexual, and social selection, 214–225, 216–217f  
overview, 211–214, 213f, 215f  
prolactin as master regulator, 229–231, 230f
- Fitness correlations  
arginine vasotocin, 219, 222  
overview, 222  
parental care by crocodiles, 225
- Hormonal control  
activation events, 211, 212f  
viviparous species, 210–211
- Hormone modulation, male, 218–219
- Life history, 219
- Neuroendocrine systems, 224
- Overview, 205–214
- Sexual selection, 219
- Social groups, monogamy, filiative behaviors, and aggression suppression, 227–229
- Social networks and endocrine networks, 225–231, 226f
- Testosterone  
aggression and territoriality, 219–221  
colors and badges, 219  
courtship and copulation, 221t, 222  
territory size, 222
- Reptilian sex determination, endocrine signals role in, 16–19
- Retractor penis magnus (RPM) muscle, reproductive behavior, 44, 45f
- RPM. *See* Retractor penis magnus
- RSS. *See* Renal sexual segment
- R-strategist, 225, 227
- S**
- Scent trails  
lizards, 146  
snakes, 151–152
- SDM. *See* Sex determining mechanisms
- Sea turtles, 138
- Seminiferous tubules  
development, 66  
number, 116
- Septum, reproductive behavior regulation, 324
- Serotonin  
aggression studies, 224  
stress circuits, 168, 171
- Sertoli cell  
histology, 66–67, 66–68f  
secreted factors in testicular function, 79
- Sex allocation theory, 22
- Sex determining mechanisms (SDMs)  
chelonian and squamate, 2–9  
diversity, 1–2, 9–12, 10f  
adaptive significance, 21–24, 23t  
ecological relevance, temperature-dependent sex under natural temperatures, 19–21, 21f  
evolutionary transitions, 24
- Family comparisons, 2–9, 3–6t  
genotypic sex determination patterns, 9–11  
Overview, 1–2  
Prospects for study, 24–25  
proximate mechanisms, 12–16  
taxonomic and phylogenetic distribution of patterns, 2–9, 7–8f  
temperature-dependent sex determination patterns, 11–12
- Thermosensitive period, 19–21, 21f
- Sex hormone-binding globulin (SHBG), 96–97  
stress response modulation during reproduction, 189
- Sex-hormone binding protein (SHBP), 96
- Sex steroids, biosynthetic pathway of, 72f
- Sfl*, sex determination, 13–14, 13t, 63–65
- SHBG. *See* Sex hormone-binding globulin

- She-male. *See* Female mimicry
- Snakes**
- female mimicry, 152–153, 152*f*, 327
  - gonadotropins in reproduction, 322–324
  - neuroendocrinology of reproduction, 324
  - overview, 317
  - pheromones
    - chemosensory recognition
    - female mimicry, 152–153, 152*f*
    - mate assessment, 152
    - sex discrimination and trailing, 151–152
  - secretory glands
    - cloacal gland, 151
    - nasal gland, 151
    - skin, 150–151
  - prospects for study, 331–332
  - reproductive cycles
    - attractivity, courtship and copulation, 326
    - body condition and energetics, 328–329
    - brown tree snakes, 326
    - embryonic influences, 330
    - endocrine-disrupting contaminants (EDCs), 331
    - environmental influences, 324–325
    - hormones, environment, and conservation, 330–331
    - male-male interactions, 326–327
    - matting aggregations, 327–328
    - overview, 317–324
    - parental care, 328
    - physiological influences, 328–330
    - posterior pituitary neuropeptides, 328
    - social influences, 325–328
    - stress, 329–330
  - steroids and reproduction
    - females, 321
    - males, 321–322
    - red-sided garter snakes, females, 321
    - red-sided garter snakes, males, 321–322
  - Snout-to-vent length (SVL)
    - crocodile juvenile growth, 276
    - maternal stress effects on offspring, 193
  - Sox9*, sex determination, 13–14, 13*t*
  - Spermatogenesis**, 81*f*
    - patterns and androgen levels, 71, 71*f*
    - postnuptial cycle, 116
    - prenuptial cycle, 116
    - species comparison, 68–71, 71*f*
  - Sperm storage**
    - epididymis, 121–122
    - female reproductive tract, 128–130, 129*f*
    - implications of, 129
    - long-term, 130
  - Squamates**
    - and environmental contaminant exposure, 356
    - sex determining mechanisms, 2–9
  - Sry*, sex determination, 13–14, 13*t*
  - Steroid-binding proteins (S-BPs)**, in plasma, 96–97
  - Steroidogenesis**, 71–72, 72*f*, 73*t*
  - Steroid synthesis**, 93–94, 93*f*
  - Stress**
    - corticosterone seasonal changes
      - baseline levels, 181–182, 182*f*
    - prebreeding, breeding, and postbreeding periods, 182–184, 183–184*f*, 185*f*
    - stress levels, 181–182, 182*f*
  - definitions, 165–166
  - fitness effects during reproduction
    - adults, 189–191
    - mothers, 191–192
    - offspring, 192–193, 330, 332
  - hormones, turtle reproductive cycles, 259–262
  - prospects for study, 193–195
  - reproductive function relationship
    - behavior, 178–181, 180*f*
    - neurotransmitters, 171
    - ovarian function, 175–177
    - overview, 167–168
    - reproductive hormones, 171–174, 171*f*
    - testicular function, 177–178
  - reptile study importance, 166–167
  - response mediation
    - brain, 168–169
    - hypothalamic-pituitary-adrenal axis, 169–170
    - hypothalamic-pituitary-gonadal axis, 170–171
    - immune system, 170
  - response modulation during reproduction
    - evidence, 184–188
    - mechanism, 188–189
    - snake reproduction, 329–330
  - SVL. *See* Snout-to-vent length
- T**
- TCDD**. *See* 2,3,7,8-Tetrachlorodibenzodioxin
  - Temperature-dependent sex determination (TSD)**
    - adaptive significance for, 22–24
    - aromatase role, 91
    - ecological relevance, 19–21
    - phylogenetic distribution of patterns, 2–9, 11–12
    - proximate mechanisms, 12–16
      - gonadal differentiation and gene expression, 12–15, 13*t*, 14*f*
      - steroid signaling, 15–16
    - reproductive trait development, 50
    - thermosensitive period, 19–21, 21*f*
  - Terrestrial tortoises**, 137
  - Testes**
    - development, 63–65, 64–65*f*
    - functional regulation
      - androgens, 76–77
      - environmental factors, 72–73
      - estrogens, 77–78
      - histamine, 79–80
      - hypothalamic hormones, 73–75
      - immune function, 80, 80*f*
      - Leydig cell-secreted factors, 80–82
      - model, 81*f*
      - pituitary hormones, 75
      - Sertoli cell-secreted factors, 79
      - stress hormones, 76
      - testicular factors, 78–79
      - testicular macrophage-secreted factor, 79
      - thyroid hormone, 76
  - spermatogenesis**, 68–71, 71*f*
  - steroidogenesis**, 71–72, 72*f*, 73*t*
  - stress effects on function**, 177–178
  - structure**
    - interstitial compartment, 67–68, 69–70*f*
    - tubular compartment, 66–67, 66–68*f*
  - Testosterone**
    - corpus luteum production, 106
    - corticosterone level correlations, 171–174, 172–173*t*, 177–178
    - crocodile reproduction**
      - gonadal differentiation, 274
      - hypothalamic-pituitary regulation, 278–279
      - juvenile growth and peripubertal seasonality, 276
      - male cycles, 279
      - seasonality, 276–278, 277–278*f*
      - secondary sex characteristics, 275–276
      - vitellogenesis, 279*f*
    - fitness correlation in males
      - aggression and territoriality, 219–221
      - colors and badges, 219
      - courtship and copulation, 221*t*, 222
      - territory size, 222
    - lizard reproduction regulation, 295–307
    - metabolism, 97
    - organizational role in behavior, 206, 207*f*
    - ovarian synthesis, 92–93, 93*f*
    - reproductive behavior regulation, 39–42, 48–49, 51–53, 219
    - reproductive cycles and secretion, 127
    - sex determination, 13*t*, 16
    - snake reproduction
      - females, 319, 321
      - males, 319–322
    - spermatogenesis patterns and androgen levels, 71, 71*f*
    - steroidogenesis, 71
    - turtle reproductive cycles, 249–252, 254–258
    - yolk, 103
  - 2,3,7,8-Tetrachlorodibenzodioxin (TCDD)**, 17–18*t*, 19
  - Thermosensitive period (TSP)**, 19–21, 21*f*
  - Thyroid hormone**
    - forms, 259
    - snake reproduction role, 325
    - turtle reproductive cycles, 259–260
  - Tongue flick**, pheromone detection assay, 135–136
  - TPN muscle**. *See* Transversus penis muscle
  - Transcortin**. *See* Corticotropin-binding globulin
  - Trans-Nonachlor**, 17–18*t*, 19
  - Transversus penis (TPN) muscle**, reproductive behavior, 44, 45*f*
  - TSD**. *See* Temperature-dependent sex determination
  - TSP**. *See* Thermosensitive period
  - Turtles**
    - behavior hormonal control, 41
    - cyclicity of reproduction, 244–247
    - clutch number variability, 247
    - nesting, 245–249, 246–247*f*

*Turtles (Continued)*

prenuptual and postnuptual cycles, 244, 245f  
 sexual maturation, 244–245  
 timing of reproduction, 247–249  
 and environmental contaminant exposure, 354–355  
 gonadal cycle assessment, 242–243, 242–243f  
 hormonal and gonadal reproductive cycles  
 catecholamines, 262  
 corticosterone, 260–262, 261f  
*Cryptodira*, 249–256  
*Cryptodira*, freshwater turtles, 249–251, 249–250f  
*Cryptodira*, sea turtles, 251–253, 252–253f  
*Cryptodira*, tortoises, 253–256, 256f  
 ghrelin, 262  
 leptin, 262  
 pineal hormones and annual cycles, 262, 262f  
*Pleurodires*, 256–259  
*Pleurodires*, *Chelidae*, 257–258, 257f  
*Pleurodires*, *Pelomedusidae*, 259, 259f  
*Pleurodires*, *Podocnemididae*, 258–259, 258t  
 thyroid hormone, 259–260

hormone assays, 244  
 overview, 241–242, 242f  
 pheromones  
 freshwater turtles, 137–138, 138f  
 functional overview, 136–137  
 sea turtles, 138  
 sources of pheromones, 136–138  
 terrestrial tortoises, 137

**U**

*Urodeal gland*, pheromone secretion, 144  
*Uterine tube*  
 anatomy and histology, 124–125, 124–125f  
 sperm storage tubule in, 129f  
*Uterus*  
 eggshell formation, 126  
 epithelium, 126

**V**

*Vagina*, anatomy, 126  
 Vasoactive intestinal peptide (VIP), 78–79  
*Ventromedial hypothalamus (VMH)*,  
 reproductive behavior regulation, 42, 46–49, 51–52, 306, 324

**Vitamin D**, provitamins as pheromones in lizard mate choice, 147–148

**Vitellogenesis**  
 crocodiles, 279–280, 280f  
 hormonal regulation, 102–103  
 mechanisms, 101–102  
 overview, 101

**Vitellogenin**  
 function, 102  
 sequestration, 102  
**Viviparity**, behavior hormonal control, 210–211  
**VMH**. *See Ventromedial hypothalamus*  
**VNO**. *See Vomeronasal organ*  
**Vomeronasal organ (VNO)**, functional overview, 135–136

**W**

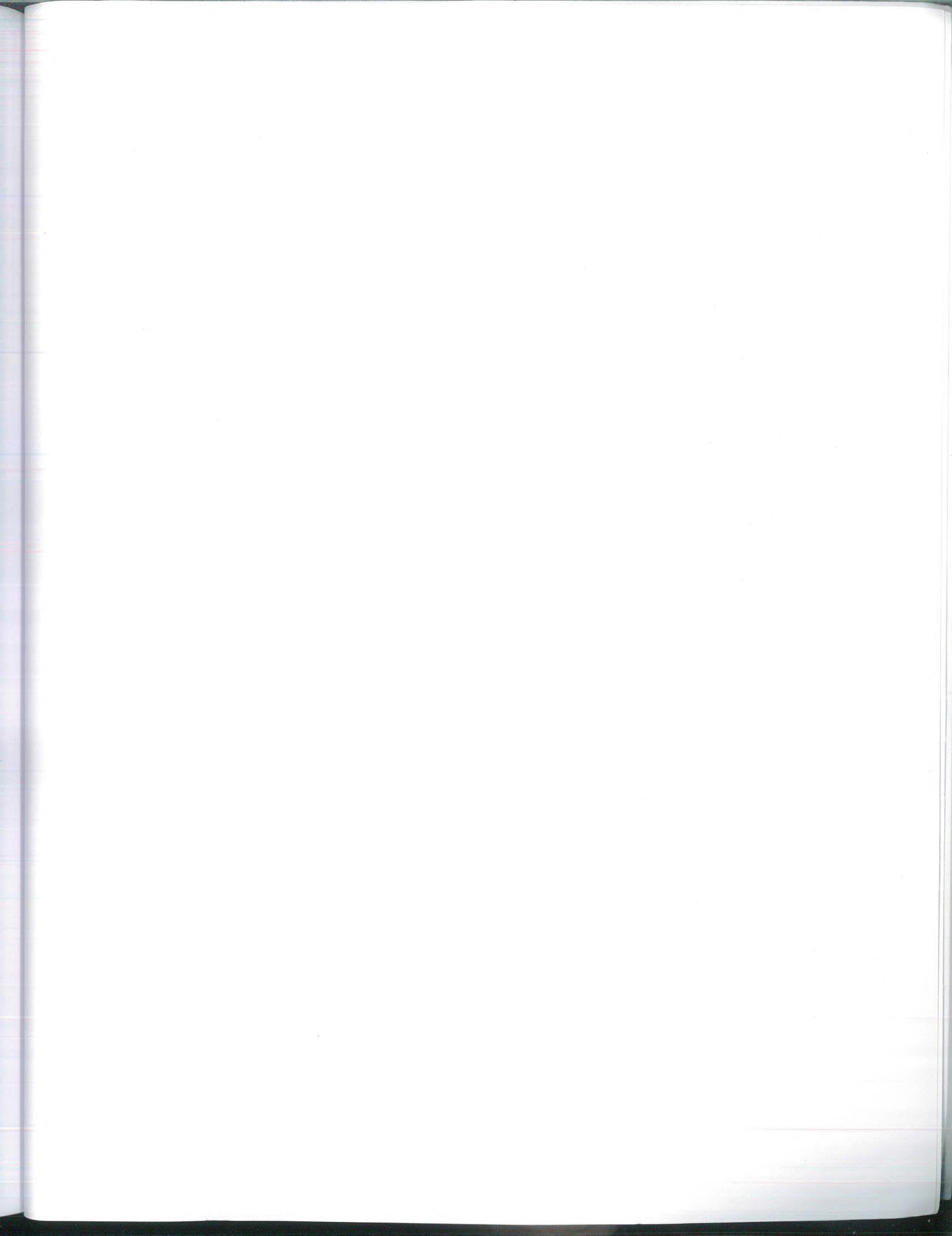
*Wt1*, sex determination, 13–14, 13t, 63–65

**Y**

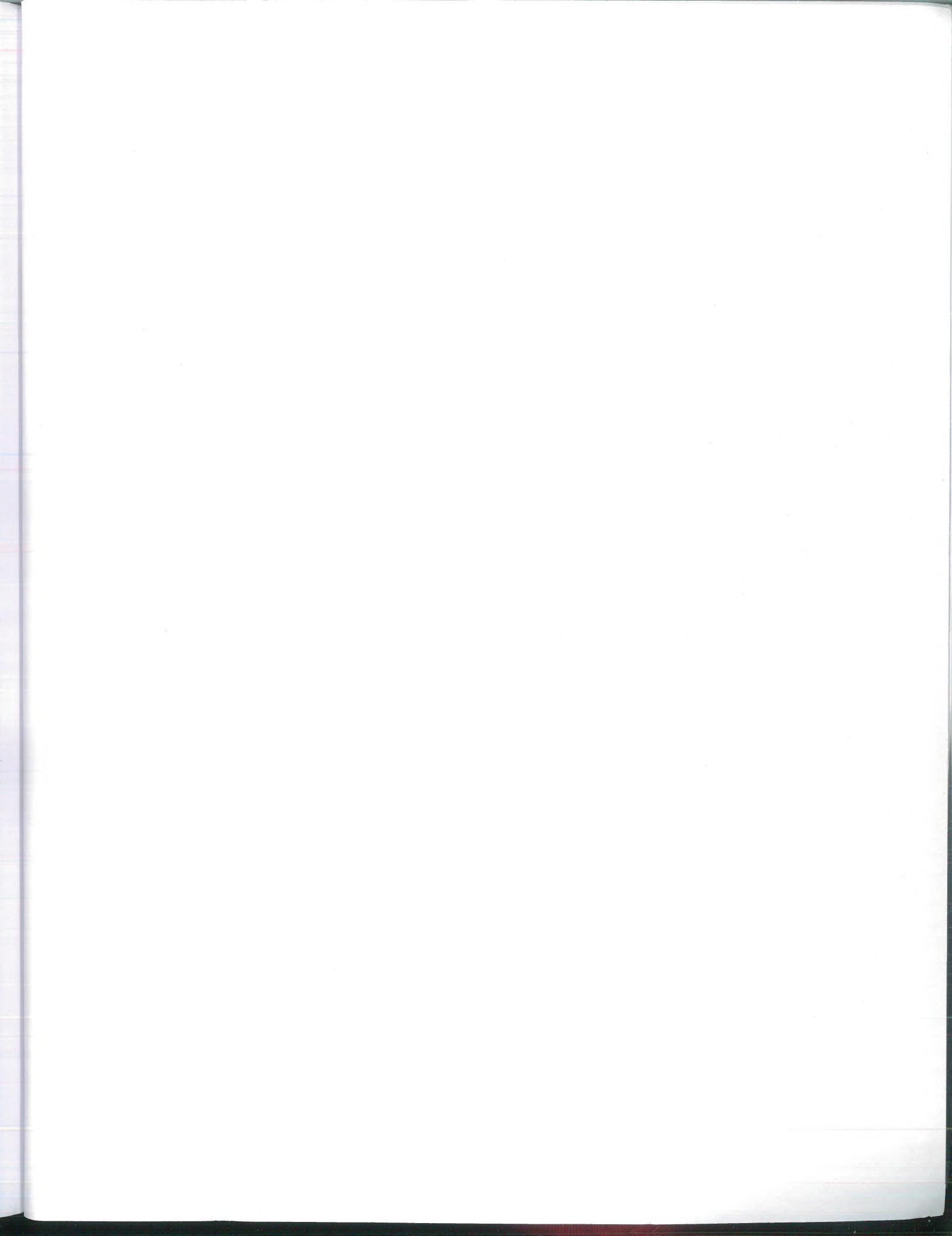
**Yolk**. *See Vitellogenesis*  
**Yolk steroids**, 103–104

**Z**

**Z chromosomes**, sex determination, 14





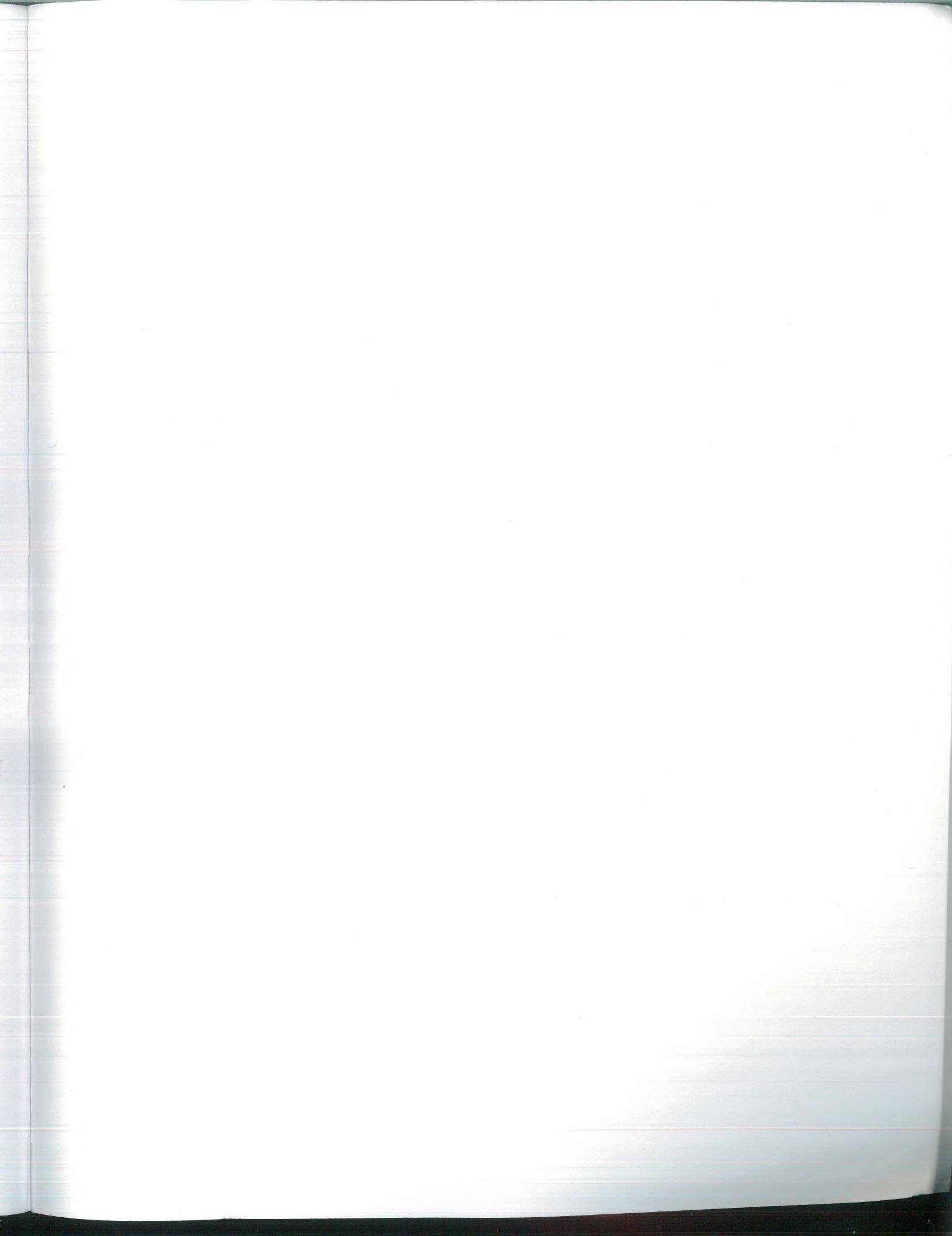


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Jil 2024

Printed in Poland  
by Amazon Fulfillment  
Poland Sp. z o.o., Wrocław



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# HORMONES AND REPRODUCTION OF VERTEBRATES

## Volume 3: Reptiles, Second Edition

Edited by David O. Norris and Kristin H. Lopez

*Provides a complete, essential, and up-to-date reference for herpetologists studying hormones and reproduction of reptiles*

*Hormones and Reproduction of Vertebrates, Volume 3: Reptiles* is the third of five second-edition volumes representing a comprehensive and integrated overview of hormones and reproduction in fishes, amphibians, reptiles, birds, and mammals. The book covers endocrinology, neuroendocrinology, physiology, behavior, and anatomy of reptilian reproduction. It provides a broad treatment of the roles of pituitary, thyroid, adrenal, and gonadal hormones in all aspects of reproduction, as well as descriptions of major life history events. New to this edition is a concluding assessment of the effect of environmental influences on reptiles.

The initial chapters in this book broadly examine sex determination, reproductive neuroendocrinology, stress, and hormonal regulation as they relate to testicular and ovarian function. Subsequent chapters examine hormones and reproduction of specific taxa, including turtles, crocodilians, lizards, and snakes. The book concludes with an examination of endocrine disruption of reproduction in reptiles.

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- Covers endocrinology, neuroendocrinology, physiology, behavior, and anatomy of reptile reproduction
- Includes pituitary, thyroid, adrenal, and gonadal hormones
- Focuses on turtles, crocodilians, lizards, and snakes
- Provides new coverage on endocrine disruption in reptiles

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ACADEMIC PRESS

An imprint of Elsevier  
[elsevier.com/books-and-journals](http://elsevier.com/books-and-journals)

ISBN 978-0-443-16022-6



9 780443 160226