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Editorial

Introduction to Special Issue: Disruption of thyroid, sex steroid, and adrenal hormone systems and their crosstalk in aquatic wildlife

"The Greeks call it *lygos*, sometimes *agnos*, because the Athenian matrons, preserving their chastity at the Thesmophoria, strew their beds with its leaves".

Pliny the Elder, referring to leaves of the chasteberry tree (*Vitex agnus-castus*) (Riddle, 2010).

1. Background

There is no precise way of telling how far back in history people have intentionally used various naturally growing herbs, such as chasteberry, for their ability to disrupt normal reproduction and pregnancy. Based on the written works of ancient scholars such as Hippocrates, Dioscorides, and Pliny the Elder (Riddle, 1994) the practice goes back at least a few thousands of years. The idea that we might be unintentionally exposed to chemicals in the environment with similar disruptive potential, however, is relatively recent and can be traced back to the 1930s–1940s. Observations by Walker and Janney (1930), Dodds et al. (1939), and Emmens (1941) indicated that many natural and anthropogenic compounds have estrogenic properties in laboratory animals. Work by these investigators was supplemented by published accounts of livestock exhibiting reproductive abnormalities such as infertility, and the determination that the cause of these observations was the presence of natural xenoestrogens in certain pasture plants (Biggers and Curnow, 1954). Accounts of endocrine disruption caused by anthropogenic chemicals were not restricted only to effects on reproduction or to agriculturally important livestock. In the late 1970s, John Leatherland and colleagues (Moccia et al., 1977) revealed a puzzling increase in thyroid problems of salmonids from the Laurentian Great Lakes, which was likely due to exposure to still undefined (Carr and Patiño, 2011) environmental endocrine-disrupting chemicals (EDCs).

Despite the earlier published observations, it was not until a conference organized by the World Wildlife Federation in 1991 produced an influential "Consensus Statement" (Bern et al., 1992) that the then loosely-organized research of EDCs was transformed into a well-defined area of scientific inquiry covering health concerns of both humans and wildlife (Matthiessen, 2003). The broader context of research in endocrine disruption is the field of environmental endocrinology, which in turn derives from studies in comparative endocrinology (Denver et al., 2009). Classical comparative endocrinology has been concerned with adaptive and evolutionary features of endocrine mechanisms (Gorbman, 1988) and has been based on either laboratory or field studies, while environmental endocrinology has come to focus on endocrine measurements and mechanisms in nature (Bradshaw, 2007). Research in endocrine disruption grew at a remarkable pace during the first decade after publication of the Consensus Statement, as indicated by the increasing number of published articles that included the terms "endocrine" and "disrupt*" in their titles, abstracts, or keywords (Matthiessen, 2003). We have updated the status of EDC publications using the approach of Matthiessen (2003). The database we used was Web of Science™ Core Collection, which contains articles published since 1981. Although the search terms used may capture some out-of-context articles, results obtained can still be useful for comparative purposes. The first article containing the search terms appeared in 1986, and as of the end of 2014 there was a cumulative total of 15,959 publications. Trend analysis was conducted using results since 1996 because values were low and variable in the earlier period. From 1996 to 2014, the rate of increase was steady at about 88 publications year^{-1} (Fig. 1). Many of these articles, however, describe the results of laboratory studies with limited ecological applications (Marty et al., 2011). We added the term "population" to the search to estimate the fraction of articles with self-described ecological/population-level implications. The resulting subset was relatively small and showed a rate of increase of about 10 publications year^{-1} (Fig. 1) but, when expressed as percentage, it remained steady at an average of about 11% of total EDC articles published each year. A closer look at the 198 studies with reference to populations that were published in 2014 revealed that 70 (35%) dealt with wildlife, mostly fish or amphibian species. These observations numerically confirm what is already evident to practitioners, namely, that endocrine disruption has matured as a distinct area of research within environmental endocrinology. They also suggest that while EDC studies with overt population or ecological context are only a small fraction of the total, wildlife is well represented among them.

Anthropogenic EDCs are widely dispersed around the globe and also found in places distant from population centers regardless of latitude (AMAP, 2002; Caroli et al., 2001) or altitude (Wang et al., 2006). Their long-range transport can occur not only via physical (e.g., atmospheric and oceanic currents) but also biological vectors (Blais et al., 2007). The ubiquitous presence of EDCs arguably has made their consideration as potential explanatory variables for biological phenomena a requirement of field studies, whether or not their influence on biological condition is a primary target of investigation. The geographic distribution of specific EDCs and their concentrations can vary widely, however, depending on their sources and environmental persistence, thus making knowledge of

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regional and local EDCs an important variable to consider for proper assessment of corresponding biological impacts. But even when this information is available, the complexity of biotic and abiotic interactions that exist in nature makes the evaluation of endocrine disruption as a mechanism linking EDC exposures to individual or population responses a daunting task. This is especially notable in cases where EDCs are present at concentrations that are not overtly toxic to organisms. It is not surprising, therefore, that conclusive evidence pointing to endocrine disruption as primary driver of wildlife population declines is limited to a handful of examples (Jobling et al., 2013). Laboratory experimentation under controlled conditions is thus necessary to establish and characterize cause-effect relationships. Exposure concentrations or dosages used in laboratory studies, however, must in turn be justified on the basis of known or anticipated exposure levels in the field. In addition, because EDCs are typically present in the environment as complex mixtures whose effects on organisms may not represent the simple sum of individual EDC effects, laboratory studies should be based on environmentally relevant mixtures and concentrations. Further progress in our understanding of ecologically relevant wildlife endocrine disruption will thus require field and laboratory studies with mutually informed objectives and designs.

While research into disruption of thyroid, reproductive, and adrenal axes in aquatic wildlife has been ongoing for decades, it is only within the last 20+ years that scientists have identified specific targets of EDCs within these endocrine axes. This research has been facilitated by several factors including (1) the development of model systems or assays for quantifying impacts on hormone production, development and reproduction, (2) heterologous expression systems for examining EDC-receptor interactions, and (3) tools for identifying histopathologies in endocrine tissues of non-model animal species (Hontela, 1998; Carr and Patiño, 2011). Studies of EDC effects in aquatic environments present their own set of unique circumstances because, depending upon life history, animals may be directly exposed to (submerged in) EDCs for their entire or large parts of their life cycle and therefore have a correspondingly higher risk of non-dietary exposure to anthropogenic chemicals than most terrestrial species. Some terrestrial species are in close proximity to water and their food chain often begins in, or is closely integrated with aquatic habitats, and thus can also be exposed to aquatic EDCs via their trophic transfer.

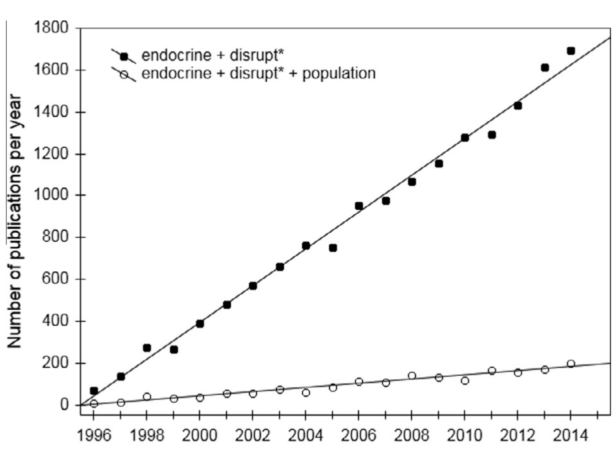

Fig. 1. Time-series plot of the number of published articles in the area of endocrine disruption. The topical search terms initially used were "endocrine" and "disrupt*." The results obtained were searched again using the term "population." Both sets of results were analyzed using simple linear regression to estimate the annual rate of growth: 88 and 10 articles year^{-1}, respectively ($r^2 \geqslant 0.96$, $p < 0.0001$). The cumulative total for the period between 1996 and 2014 is 15,834 articles.

Strong interest in particular circumstances surrounding exposures of aquatic animals to EDCs has been driven, in part, by news and media accounts of reproductive abnormalities in fishes (e.g., Blazer et al., 2012) and amphibians (e.g., Skelly et al., 2010), and the mysterious loss of amphibian populations around the globe.

Given the growth in the EDC literature related to wildlife, and the need for scientists, regulators, environmentalists, and other stakeholders to have ready access to research results, it is perhaps surprising that there is not a single peer-reviewed journal dedicated to the comparative study of EDCs. Although there are several environmental toxicology journals that feature studies of EDCs, non-mammalian models, and wildlife, these journals are not focused on and thus do not normally provide a view from the comparative endocrinology perspective. The late Howard Bern, one of the early pioneers in the field of EDCs, was a founding member of the Editorial Board for *General and Comparative Endocrinology* when it launched in April of 1961. *General and Comparative Endocrinology* was the first journal to provide a prominent forum for studies of comparative endocrinology and its first Editor-in-Chief, the late Aubrey Gorbman, authored with Bern the first textbook of comparative endocrinology (Gorbman and Bern, 1962). *General and Comparative Endocrinology* is therefore a fitting venue for a special edition focusing on the impact of EDCs on wildlife endocrine systems. In this special edition we bring together sixteen articles authored by scientists working at the forefront of EDCs and their effects on the thyroid, reproductive, and adrenal axes in aquatic wildlife and other species associated closely with aquatic habitats. Although a major goal for this volume is to publish articles reflecting state-of-the-art research and synthesis in the field of EDCs, we also hope to attract new readers to this journal with interests in the areas of toxicology, environmental science, and regulation but who may not have been fully aware of the link between comparative endocrinology and the history of EDC research. The collection of papers not only provides a glimpse of how far the area of wildlife endocrine disruption has come since the Consensus Statement was published (Bern et al., 1992), but many of the papers also illustrate how non-mammalian models can provide information to identify new modes of EDC action. In addition, the articles provide a foundation from which to plan future work designed to fill in data gaps and identify research needs for a better understanding of the risk that EDCs pose to the sustainability of aquatic wildlife. While not all articles include the term "population" in their searchable fields, we can assure readers that all have considered the environmental relevance of experimental designs and findings, and three of the articles report observations in the context of exposures of wild populations to complex contaminant mixtures.

2. Special Issue articles

The consequences of endocrine disruption on organisms and populations reside in the impact that this disruption has on organismal physiology, and ultimately on survival and reproduction. The collection of papers in this volume addresses a number of processes affected by EDC action on the thyroid, reproductive or adrenal axes including iodide homeostasis, somatic growth, metamorphosis, gonadal development and gametogenesis, stress and reproductive physiology, disease resistance, and reproduction.

Amphibian metamorphosis has long been considered a model for studying disruption of the thyroid axis during development (Carr and Patiño, 2011), and its use as an assay for assessing the crosstalk of this axis with other endocrine systems dates back at least to the mid-1940s (Sluczewski and Roth, 1948). In their contribution to this issue, Hammond et al. (2015) show that the personal care products and EDCs, ibuprofen (a nonsteroidal anti-inflammatory compound) and triclosan (a biocide) disrupt

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