Introduction: The Ecological Relevance of Chemically Induced Endocrine Disruption in Wildlife

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Environ Health Perspect 114(suppl 1):7–8 (2006).
doi:10.1289/ehp.8046 available via *http://dx.doi.org/* [Online 17 April 2006]

Over the last two decades, there has been increasing scientific concern and public debate regarding the adverse effects of chemical pollutants in the environment that can interfere with the normal functioning of the endocrine system in wildlife and in humans (the so-called endocrine-disrupting chemicals, EDCs). These concerns have been fueled primarily by reports of disrupted reproductive function and development in certain wildlife—mammals, birds, fish, amphibians, and mollusks—and by the increased incidence of certain diseases of the endocrine system in humans. Investigators hypothesize that EDCs are the cause. Some of the adverse effects observed in wildlife species are strongly associated with exposure to chemicals that mimic or interfere with hormone function, particularly estrogen function, but in many cases, the causal link between exposure to EDCs and endocrine disruption is unclear. Because of the diverse effects of EDCs on the thyroid, retinoid, androgen, estrogen, and corticosteroid systems of a wide range of animals, it is imperative that research continues to address the extent of the risk posed by EDCs to wildlife. The ecological relevance of endocrine disruption in wildlife is, however, difficult to quantify, as there is limited understanding of how physiological changes affect the individual animal and how individual responses affect population and community. Furthermore, a major challenge faced by environmental biologists is the need to place endocrine disruption into context with other environmental pressures faced by our wildlife populations, for example, global warming.

In July 2004 an international workshop was convened at the University of Exeter in the United Kingdom to provide a forum for the dissemination and discussion of the most recent data on the ecological relevance of chemical-induced endocrine disruption in wildlife. The workshop was organized by the COMPRENDO Project (Comparative Research on Endocrine Disruption; COMPRENDO 2006). COMPRENDO is one of four projects [COMPRENDO, EDEN (Endocrine Disrupters: Exploring Novel Endpoints, Exposure, Low-Dose and Mixture-Effects in Humans, Aquatic Wildlife and Laboratory Animals), EURISKED (Multi-organic Risk Assessment of Selected Endocrine Disrupters), FIRE (Risk Assessment of Brominated Flame Retardants As Suspected Endocrine Disrupters for Human and Wildlife Health)] that form the research laboratory core (comprising 60 laboratories) of the CREDO (Coordinating European Environmental and Human Research into Endocrine Disruption) cluster for research, technological development, and demonstration activities in the European Community (CREDO 2006). CREDO is funded by the European Commission's Fifth Framework Programme. One hundred-eighty delegates attended the meeting from 20 countries spanning Europe, the United States, Japan, India, and South Africa and representing many stakeholders including academia, government agencies, industry, and nongovernment agencies. The meeting proceedings are available on the World Wide Web (COMPRENDO 2004).

This monograph contains a synthesis of papers presented at the Exeter meeting and presents novel research data and new thoughts and approaches on the ecological relevance of endocrine disruption in wildlife. The first article by Guillette (2006) discusses how the issue of endocrine disruption has developed in complexity, as we now appreciate that a plethora of chemicals are capable of altering hormonal function through a wide range of mechanisms of action. Understanding the effects of EDCs on wildlife populations requires carefully conducted field studies spanning a number of years. Such studies are unfortunately few and far between. Exceptions to these limited studies are those on the effects of organotin compounds on populations of marine mollusks and estrogenic disruption in marine and freshwater fish living in the coastal and riverine waters of the United Kingdom. The latest findings and hypotheses in these studies are presented by Horiguchi et al. (2006), Hagger et al. (2006), Scott et al. (2006), Jobling et al. (2006), Hayes et al. (2006a), Veeramachaneni et al. (2006), and Hall et al. (2006). These case studies illustrate some of the challenges encountered when establishing cause–effect relationships between chemical exposures and physiological function in diverse species. Hagger et al. (2006), in particular, consider the associated genotoxic effects of endocrine-disrupting chemicals on mollusks, perhaps expanding the mechanisms by which EDCs induce harm in wildlife, while Jobling et al. (2006) and Hall et al. (2006) use modeling approaches to delineate the relative risks posed by different EDCs on wildlife populations and to identify likely causative agents. Hayes et al. (2006a) rise to the ultimate challenge and address the likelihood that EDCs are responsible for the widespread population declines in amphibian populations worldwide. Veermachanei et al. (2006) describe testis and antler dysgenesis in Sitka deer on the remote Kodiak Island of Alaska and draw on this as further evidence to support the endocrine disruption hypothesis linking testicular dygenesis in men with reproductive dysfunction in other male wildlife. Finally, in this section on field studies, Durhan et al. (2006) take the reader beyond the dogma surrounding estrogens in the environment and present powerful evidence for the presence of androgenic contaminants in runoff from beef feedlot. The authors identify the causative agents as metabolites of the growth promoter trenbolone acetate.

Most laboratory studies on chemical effects have been conducted on single chemicals, but in the wild, animals are often exposed to complex mixtures that potentially have interactive effects. The next two articles are derived from field studies and provide evidence for interactive effects of EDCs with other environmental factors. Edwards et al. (2006) examine interactive effects of water quality on reproduction in mosquito fish, and Jenssen (2006) discusses the potential for interaction of EDCs with climate change in Arctic marine mammals and birds. The following two articles on mixture effects are laboratory-based studies. Liney et al. (2006) consider the integrative effects of estrogenic effluents from wastewater treatment works on roach health (spanning sexual function, immunotoxicity, hepatotoxicity, and genotoxicity). Thorpe et al. (2006) assess the ability of the model of concentration addition to predict the interactive effects of estrogenic chemicals in a complex mixture (wastewater treatment works effluent) and conclude that end-pipe analysis may be the preferred approach for assessing the effects of these complex mixtures.

Human toxicology studies focus on the protection of the individual, but studies in ecotoxicology wildlife protection are directed principally

This article is part of the monograph "The Ecological Relevance of Chemically Induced Endocrine Disruption in Wildlife."

In addition to employment at Brunel University, S. Jobling is also employed by Beyond the Basics Ltd., an independent consultancy. C. Tyler declares he has no competing financial interest.

Received 28 February 2005; accepted 1 November 2005.

at the population level. Nevertheless, assessments of chemical effects in wildlife are conducted at the biochemical (biomarker), tissue, and individual organism levels. A wide range of end points for effects of endocrine-active substances in wildlife species has been identified, but their ecological relevance is not yet fully understood. A major challenge for investigators conducting studies into endocrine disruption in wildlife is to better harmonize laboratory-based studies on chemicals and the end points used with effects occurring in wildlife populations.

Developing the theme that we should not be trapped by the dogma in research into endocrine disruption is set in the opening article by Guillette (2006). The authors of the next five articles discuss new approaches in determining the ecological relevance of endocrine disruption in wildlife. Schulte-Oehlmann et al. (2006) present the COMPRENDO research program, detailing how comparative phylogenic approaches can be used to develop our understanding of the effects of antiandrogenic chemicals and also to determine commonalities in mechanisms between taxa. Japan is a world leader in the field of ecotoxicogenomics, and the article by Iguchi et al. (2006) reveals how molecular approaches are helping to unravel the mechanisms of action of EDCs in a wide range of animals from *Daphnia* to mammals. This article emphasizes the need to link molecular responses with cellular and tissue level responses to establish pathways of effects for EDCs. In the next article, Hutchinson et al. (2006) provide insight into how we might best use biomarkers for endocrine disruption and emphasizes the need to use biomarkers as "signposts" rather than "traffic lights" in assessing the risk of EDCs. Chemical testing guidelines for endocrine disruption include very few species, thus limiting the investigator's ability to assess the ecological relevance of contamination of the environment by EDCs. An exception for research into antiandrogens in fish has been the development of the three-spined stickleback model; the latest research into the use of this model is presented by Katsiadaki et al. (2006). Gurney et al. (2006) present a fresh view that relatively simple models can provide a useful framework within which to consider the expression of altered individual characteristics at the population level. The objective of such consideration, as Gurney et al. stated, is "to identify those individual changes that are likely to be critical in the population context, so that experimental effort can be appropriately focused."

The effects of bisphenol A in mollusks and of the herbicide atrazine on frog populations in the United States have received much attention and have caused considerable controversy. The articles by Oehlmann et al. (2006) and Hayes et al. (2006b) provide further evidence for effects of these chemicals at concentrations in the submicrogram per liter range.

A key question is "how do we assess the risk posed by EDCs, and indeed should our approach differ from that for any other group of chemicals?" Here, it seems opinions differ in both the scientific and regulatory communities. Two articles are included on this subject. In the first, Gross-Sorokin et al. (2006) describe the U.K. Environment Agency's approach for a management strategy for chemicals causing feminization of fish in U.K. rivers. The U.K. Environment Agency recognizes the threat posed by EDCs and is implementing policy changes to combat possible effects on the U.K. freshwater fishery. Lyons (2006) continues this theme and marks the potential threat posed by EDCs and identifies some required policy changes. In the final paper, Gee (2006), of the European Environment Agency, argues that scientific methods need to better reflect the realities of multicausality, mixtures, timing of dose, and system dynamics that characterize the exposures and effects of EDCs. This improved science could provide a more robust basis for the wider and wise use of the precautionary principle in the assessment and management of the threats posed by endocrine disruptors.

Over the next decade, we must address major issues regarding the adverse effects of EDCs on wildlife. This will necessitate collaboration and cooperation on an international scale in order to identify populations likely to be at risk. Furthermore, we must dedicate resources to address the critical knowledge gaps that exist. Finally, it is the personal view of the editors of this monograph that we must communicate the results of our studies effectively so that the risks posed by EDCs are understood and that policy decisions concerning the protection of wildlife species from the effects of endocrine disruptors are based on the best available scientific knowledge.

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