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Bridging epidemiology and model organisms to increase understanding of endocrine disrupting chemicals and human health effects☆

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ABSTRACT

Concerning temporal trends in human reproductive health has prompted concern about the role of environmentally mediated risk factors. The population is exposed to chemicals present in air, water, food and in a variety of consumer and personal care products, subsequently multiple chemicals are found human populations around the globe. Recent reviews find that endocrine disrupting chemicals (EDCs) can adversely affect reproductive and developmental health. However, there are still many knowledge gaps. This paper reviews some of the key scientific concepts relevant to integrating information from human epidemiologic and model organisms to understand the relationship between EDC exposure and adverse human health effects. Additionally, areas of new insights which influence the interpretation of the science are briefly reviewed, including: enhanced understanding of toxicity pathways; importance of timing of exposure; contribution of multiple chemical exposures; and low dose effects. Two cases are presented, thyroid disrupting chemicals and anti-androgens chemicals, which illustrate how our knowledge of the relationship between EDCs and adverse human health effects is strengthened and data gaps reduced when we integrate findings from animal and human studies.

1. Introduction

Concerning temporal trends in human reproductive health has prompted concern about the role of environmentally mediated risk factors. Studies report increases in reproductive diseases and decline in reproductive function since the mid-20th century among certain locations and populations (primarily in the developed world), previously reviewed and illustrated in Table 1 [1].

The relatively short time frame over which decline in reproductive health and function has been observed cannot be explained by genetic changes. Environmental chemicals have been identified as one of the potential risk factors that may be contributing to observed changes in reproductive health [2–4]. Over roughly the same period, manufacture and use of both natural and synthetic chemicals has increased by over 20 fold [5]. In the US, there are approximately 87,000 chemical substances registered for use in commerce as of 2006, and about 3000 chemicals manufactured or imported in excess of 1 million pounds each [6].

The population is exposed to chemicals present in air, water, food and in a variety of consumer and personal care products [48–51]. In the United States, nationally representative samples of population through the National Health and Nutrition Examination Survey find that every individual has measured levels of multiple environmental chemicals in his/her body [7,8]. There are similar findings from studies in Europe [9], and populations in the Arctic far from pollution sources [10]. Thus it is expected that all human populations are exposed to some level of synthetic chemicals.

Previous studies have demonstrated environmental chemicals can adversely impact human health. Poisoning incidents with mercury in Japan and polychlorinated biphenyl (PCB) in Taiwan, produced neurological, reproductive, and developmental effects, even when the mother was asymptomatic [11–13]. Occupational exposures to 1,2-dibromo-3-chloropropane (DBCP), produced male infertility [14]. Science has evolved to study health effects of lower level exposures among the population. For example, reviews of the epidemiological evidence find that contemporary exposures to PCBs are associated with a decrease in semen quality, specifically reduced sperm motility [2] and prenatal exposures to methylmercury and PCBs at contemporary concentrations can increase risk of neurological deficits in children [15–18].

Environmental contaminants can adversely affect reproductive health through diverse biological mechanisms. Historically, much of the scientific inquiry focused on genotoxic or mutagenic chemicals and cancer effects [19,20]. Since the latter part of the 20th century there has increased emphasis on an important class of chemicals called endocrine disrupting chemicals (EDCs) that interfere with the production, release, transport, metabolism, binding,

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Table 1
Examples of recent trends in select reproductive disease, disorders and function[a].

Reproductive diseases/disorders	Increase	Period	Location	Reference
Testicular cancer	1–6%	1953–1999	Europe	[115]
Testicular cancer	60%	1973–2003	USA	[116]
Certain childhood cancers	20–24%	1976–2005	USA	[117]
Autism	57%	2002–2006	USA	[118]
Attention deficit hyperactivity disorder	3% per year	1997–2006	USA	[119]
Birth defects				
Cryptorchidism	200%	1970–1993	USA	[120]
Gastroschisis	300%	1978–2005	California	[121]
Congenital hypothyroidism	138%	1987–2003	New York	[122]

Reproductive function		Time	Location	Reference
Reported difficulty conceiving and maintaining pregnancy				
All ages	60% more women	1982; 2002	USA	[123,124]
<25 years old	200% more women	1982; 2002	USA	[123,124]
Prematurity	2.9% shorter gestation	1992–2002	USA	[125]
Pre-eclampsia	19–36%	1968-2002	Norway	[126]
Gestational diabetes	122%	1989-2004	USA	[127]
Premature puberty				
Age at onset of breast development	1–2 years younger	1940–1994	USA, Denmark	[3,128]
Age at onset of menstruation	2.5–4 months younger	1940–1994	USA	[3]
Sperm count	~1% decline per year	1931–1994	Western countries	[129,130]
Serum testosterone	1% decline per year	1987–2004	Boston, USA	[135]

[a] Updated from Woodruff et al. [1].

action, or elimination of natural hormones in the body and are responsible for maintenance of homeostasis and regulation of developmental processes and their potential effects on reproductive and developmental effects [2]. Recent reviews and scientific consensus statements find that "the evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong, and there is mounting evidence for effects on other endocrine systems, including thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis." [2].

However, there are still many gaps in our understanding of the relationship between EDC exposures and reproductive and developmental effects. First, the number of chemicals that have been evaluated for effects on human health remains limited [6]. Second, many reproductive and developmental health conditions, such as female reproductive effects (e.g. fibroids, endometriosis), male reproductive effects (e.g. cryptorchidism, prostate cancer), and childhood diseases (e.g. obesity, cancer), have not been fully evaluated for the likely contribution of EDCs as a risk factor. As new efforts are initiated to address knowledge gaps the relationship between EDCs and reproductive and development outcomes, understanding how findings from human and model organisms can each contribute to filling the gaps is critical. Findings from human observational studies provide direct evidence of the relationship between exposure to environmental chemicals and subsequent adverse health effects. However, limitations in the epidemiologic data, both scientific and ethical, require the use of findings from mammalian and other model organisms to compliment human epidemiologic evidence. This paper reviews some of the key scientific concepts relevant to integrating information from human epidemiologic and model organisms to understand the relationship between EDC exposure and adverse human health effects. This is followed by two cases studies: first on thyroid disrupting chemicals; and second on anti-androgens chemicals, illustrating how the interplay between the findings from two disciplines can enhance our understanding of the relationship between exposure and disease.

2. Key concepts and new science

2.1. Sources of scientific information

Our understanding of potentially harmful effects of exposure to environmental contaminants comes from a variety of sources