

## Estrogenic compounds – endocrine disruptors

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**Endocrine disruptors** (polychlorinated biphenyls, dichlorodiphenyl-trichloroethane [DDT], dioxin, and some pesticides) are estrogen-like and anti-androgenic chemicals in the environment. They mimic natural hormones, inhibit the action of hormones, or alter the normal regulatory function of the endocrine system and have potential hazardous effects on male reproductive axis causing infertility. Although testicular and prostate cancers, abnormal sexual development, undescended testis, chronic inflammation, Sertoli-cell-only pattern, hypospadias, altered pituitary and thyroid gland functions are also observed, the available data are insufficient to deduce worldwide conclusions.<sup>[1]</sup>

The development of intra-cytoplasmic sperm injection (ICSI) is beyond doubt the most important recent breakthrough in the treatment of male infertility, but it does not necessarily treat the cause and may inadvertently pass on adverse genetic consequences. Many well-controlled clinical studies and basic scientific discoveries in the physiology, biochemistry, and molecular and cellular biology of the male reproductive system have helped in the identification of greater numbers of men with male factor problems.<sup>[1]</sup>

Newer tools for the detection of Y-chromosome deletions have further strengthened the hypothesis that the decline in male reproductive health and fertility may be related to the presence of certain toxic chemicals in the environment. Thus the etiology, diagnosis, and treatment of male factor infertility remain a real challenge. Clinicians should always attempt to identify the etiology of a possible testicular toxicity, assess the degree of risk to the patient being evaluated for infertility, and initiate a plan to control and prevent exposure to others once an association between occupation/toxicant and infertility has been established.<sup>[1]</sup>

Endocrine disruptors are chemicals that interfere with endocrine (or hormone system) in animals, including humans. These disruptions can cause cancerous tumors, birth defects, and other developmental disorders. Specifically, they are known to cause learning disabilities, severe attention deficit disorder, cognitive and brain development problems, deformations of the body (including limbs); sexual development problems, feminizing of males or masculine effects on females, etc.

Any system in the body controlled by hormones, can be derailed by hormone disruptors. The critical period of development for most organisms is between the transition from a fertilized egg, into a fully formed infant. As the cells begin to grow and differentiate, there are critical balances of hormones and protein changes that must occur. Therefore, a dose of disrupting chemicals can do substantial damage to a developing fetus (baby). Whereas, the same dose may not significantly affect adult mothers.

Endocrine disruptors are substances that "interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for development, behavior, fertility, and maintenance of homeostasis (normal cell metabolism)."<sup>[2]</sup> They are sometimes also referred to as hormonally active agents,<sup>[3]</sup> endocrine disrupting chemicals,<sup>[4]</sup> or endocrine disrupting compounds (EDCs).<sup>[5]</sup>

EDC studies have shown that endocrine disruptors can cause adverse biological effects in animals, and low-level exposures also cause similar effects in human beings.<sup>[6]</sup> The term *endocrine disruptor* is often used as synonym for xenohormone although the latter can mean any naturally occurring or artificially produced compound showing hormone-like properties (usually binding to certain hormonal receptors).

The term *endocrine disruptor* was coined at the Wingspread Conference Centre in Wisconsin, in 1991. One of the early papers on the phenomenon was by Theo Colborn in 1993.<sup>[7]</sup> In this paper, she stated that environmental chemicals disrupt the development of the endocrine system, and that effects of exposure during development are often permanent. Although the endocrine disruption has been disputed by some,<sup>[8]</sup> work sessions from 1992 to 1999 have generated consensus statements from scientists regarding the hazard from endocrine disruptors, particularly in wildlife and also in humans.<sup>[9]</sup>

The Endocrine Society released a scientific statement outlining mechanisms and effects of endocrine disruptors on “male and female reproduction, breast development and cancer, prostate cancer, neuroendocrinology, thyroid, metabolism and obesity, and cardiovascular endocrinology,” and showing how experimental and epidemiological studies converge with human clinical observations “to implicate EDCs as a significant concern to public health.” The statement noted that it is difficult to show that endocrine disruptors cause human diseases, and it recommended that the precautionary principle should be followed.<sup>[3]</sup> A concurrent statement expresses policy concerns.<sup>[10]</sup>

Endocrine disrupting compounds encompass a variety of chemical classes, including drugs, pesticides, compounds used in the plastics industry and in consumer products, industrial by-products and pollutants, and even some naturally produced botanical chemicals. Some are pervasive and widely dispersed in the environment and may bio-accumulate. Some are persistent organic pollutants (POP's), and can be transported long distances across national boundaries and have been found in virtually all regions of the world, and may even concentrate near the North Pole, due to weather patterns and cold conditions.<sup>[11]</sup> Others are rapidly degraded in the environment or human body or may be present for only short periods of time.<sup>[12]</sup>

Health effects attributed to endocrine disrupting compounds include a range of reproductive problems (reduced fertility, male and female reproductive tract abnormalities, and skewed male/female sex ratios, loss of fetus, menstrual problems<sup>[13]</sup>); changes in

hormone levels; early puberty; brain and behavior problems; impaired immune functions; and various cancers.<sup>[14]</sup>

One major objection to the theory of endocrine disruptors is the dosage effect. There is a large gap between high exposures seen in a laboratory experiment versus the relatively low levels found in the environment.<sup>[16][17]</sup>

Critics argue that dose-response relationship data suggest that the amounts of the chemicals actually in the environment are too low to cause an effect. A consensus statement by the Learning and Development Disabilities Initiative rebuts this criticism arguing “The very low-dose effects of endocrine disruptors can not be predicted from high-dose studies, which contradicts the standard ‘dose makes the poison’ rule of toxicology. Nontraditional dose-response curves are referred to as nonmonotonic dose response curves.”<sup>[15]</sup> Furthermore, endocrine disrupting effects have been noted in animals exposed to environmentally relevant levels of some chemicals. For example, researchers have found that a common flame retardant, PBDE-47, affects the reproductive system and thyroid gland of female rats in doses of the order of those to which humans are exposed.<sup>[18]</sup>

The dosage objection could also be overcome if low concentrations of different endocrine disruptors were synergistic, which was asserted in a paper by Arnold.<sup>[19]</sup> This paper was published in *Science* in June 1996, and was one reason for the passage of the Food Quality Protection Act of 1996.<sup>[20]</sup> The results could not be confirmed with the same and alternative methodologies,<sup>[21]</sup> and the original paper was retracted,<sup>[22]</sup> with Arnold found to have committed scientific misconduct by the United States Office of Research Integrity.<sup>[23]</sup> Subsequent papers by other authors demonstrated that low concentrations of endocrine disruptors can have synergistic effects in amphibians, but it is not clear that this is an effect mediated through the endocrine system.<sup>[24]</sup>

The conventional relationship (more exposure equals higher risk) has been challenged by some studying endocrine disruptors. For example, it has been claimed that Tamoxifen and some phthalates have fundamentally different (and harmful) effects on the body at low doses than at high doses.<sup>[25]</sup>

Food is a major mechanism by which people are exposed to pollutants.

Diet is thought to account for up to 90% of a person's PCB and DDT body burden.<sup>[26]</sup> In a study of 32 different common food products from three grocery stores in Dallas, fish and other animal products were found to be contaminated with PBDE.<sup>[27]</sup> Since these compounds are fat soluble, it is likely they are accumulating from the environment in the fatty tissue of animals we eat. Some suspect fish consumption is a major source of many environmental contaminants. Indeed, both wild and farmed salmon from all over the world have been shown to contain a variety of man-made organic compounds.<sup>[28]</sup>

With the increase in household products containing pollutants and the decrease in the quality of building ventilation, indoor air has become a significant source of pollutant exposure.<sup>[29]</sup>

Residents living in homes with wood floors treated in the 1960s with PCB-based wood finish have a much higher body burden than the general population.<sup>[30]</sup> A study of indoor house dust and dryer lint of 16 homes found high levels of all 22 different PBDE congeners tested for in all samples.<sup>[31]</sup> Recent studies suggest that contaminated house dust, not food, may be the major source of PBDE in our bodies.<sup>[32]</sup> One study estimated that ingestion of house dust accounts for up to 82% of our PBDE body burden.<sup>[33]</sup>

Research conducted by the Environmental Working Group found that 19 out of 20 children tested had levels of PBDE in their blood 3.5 times higher than the amount in their mothers' blood.<sup>[34]</sup> It has been shown that contaminated housedust is a primary source of lead in young children's bodies.<sup>[35]</sup> It may be that babies and toddlers ingest more contaminated housedust than the adults they live with, and therefore have much higher levels of pollutants in their systems.

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