

# Are we disrupted?

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The subject of endocrine disrupting chemicals (EDCs) and their effects on mammalian health and especially human health is somewhat contentious.

As scientists, we are trained to prove a concept by the gathering of unequivocal evidence to support a hypothesis. If there is insufficient evidence or no compelling proof of concept, the hypothesis is not supported. This approach to the subject of EDCs and their effects on mammalian health has led to controversy, especially when considering the adverse rather than beneficial effects.

A central issue for discussion is the need to have unequivocal proof of EDCs as being the agents of cause rather than effect. The challenge is to show how EDC exposure directly leads to adverse effects in later life even though the intervening period between exposure and outcome can be years or decades in mammalian life. Herein lies the difficulty and the reason that many studies are correlative and associative. Nevertheless, we live in a society where EDC exposure occurs and there is a legitimate need to investigate how the chemicals to which we are exposed in daily life have potential to harm us or our offspring.

In this special issue of *Endocrine-Related Cancer*, we present three reviews of the actions of EDCs on mammalian health. Many actions of EDCs are considered to occur during development when modification of normal endocrine processes renders the developing organs, tissues and cells particularly vulnerable. The integrity of stem cells and the effects of endocrine modification on such a critical cell population are a new and emerging focus for developmental biologists and cell toxicologists. *Kopras et al. (2014)* review the targeted actions of EDCs on relatively minor populations of stem or progenitor cells and how cell fate and differentiation can be driven down abnormal pathways. It is clear that stem and stem progenitors respond to environmental cues and are

particularly susceptible to disruption in early life when cell fate and differentiation occur. Stem cells are also important in the maintenance of tissues and organs during adult life, and in repair. If there is a change in the sequential differentiation of stem cells or if their pattern of self-renewal is perturbed, the outcomes are not normal and are likely to be abnormal. Altered programming of stem/progenitor cells is an area of future lively debate and this review summarises the current state of knowledge from which new challenges to the field arise. In the era of targeted testing of drug therapies for a wide variety of diseases, the regulatory bodies might take into account the possibility that EDCs adversely alter programmes of stem/progenitor differentiation or self-renewal. How would routine regulatory testing paradigms pinpoint these effects?

The second article by *Gibson & Saunders (2014)* reviews the effect of EDCs on the female reproductive tract, especially the uterine endometrium. This is considered with respect to the potential development of cancer. The issue of attribution of causality arises again in this review, as it is particularly difficult to directly demonstrate that EDCs cause cancer in humans when the intervening period between exposure and malignancy is subverted by lifestyle modifications such as obesity, smoking, etc. These authors also emphasise that the notion of exposure to 'one EDC' generating 'one disease' is limiting. Accordingly, focus on the action of a single EDC may underestimate the risk posed from total exposure to mixtures of EDCs. Whereas individual EDCs might have no effect, combinations may cause adverse outcomes. In summary, this review emphasises the need for more accurate measurements of body-wide concentrations of EDCs and endogenous steroids, using up-to-date methodology based on mass spectrometry, and to measure combinatorial outcomes more appropriately.

The third review by [Knower \*et al.\* \(2014\)](#) considers the effect of EDCs on the epigenome and the implications for breast cancer risk. Epigenetic change in response to the environment provides another way to subvert normal function and, in this case, increases the risk of breast cancer. Another significant feature of epigenetic effect is the transgenerational outcome and the implication with respect to prostate cancer. This profound and controversial effect certainly stimulated debate about the adverse outcomes of EDCs in both the research and public arena, but it remains largely unresolved in terms of breast cancer.

In the reading of these reviews, I was further stimulated to consider how our hypothesis is so critical to proving concept. I was prompted to think about the effects on stem/progenitor populations and how risk of breast cancer might be related to action on breast stem/progenitor cells. The difficulty of proving such an idea as it relates to human health is challenging, but worthy of investigation. I hope that this issue stimulates your thinking to provide answers to the challenges and

keeps the debate active on exactly how EDCs might impact on mammalian health and disease.

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