

# Environment and health:

## 6. Endocrine disruption and potential human health implications

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**D**uring the past 50 years, tens of thousands of chemicals have been synthesized and released into the general environment. Some of these chemicals inadvertently interfere with hormone function in animals and, in some cases, humans. The public health implications of these so-called endocrine disruptors have been the subject of scientific debate, media interest and policy attention over the past several years. The current scientific debate centres on whether there is evidence of significant risks to the general human population.<sup>1</sup>

The health care community should be familiar with this issue because it is increasingly a subject of the popular press and is a topic of concern to patients, who may present with questions. But health policy decisions are currently being made with little input from the medical and public health community. In this article we review the history of environmental endocrine disruption, the mechanisms of action of endocrine disruptors and the current evidence of effects on reproduction, infant development and neurobehavioural function. Finally, we discuss health policy activities worldwide that are relevant to endocrine-disrupting chemicals in the environment.

### Historical background

Endocrine disruption is not a new phenomenon. In the 1930s studies involving laboratory animals demonstrated estrogenic properties of a number of industrial chemicals including bisphenol A, now widely used in plastics, resins and dental sealants.<sup>2</sup> The feminizing effect of the pesticide DDT (dichlorodiphenyltrichloroethane) in roosters was reported in the 1950s.<sup>3</sup>

Although hormonally active chemicals are widely used for beneficial medical purposes, adverse effects have also occurred. In 1971 clinicians traced an epidemic of vaginal clear cell carcinoma in young women to maternal use of a synthetic estrogen, diethylstilbestrol (DES), during pregnancy. Daughters of these women have an increased risk of reproductive and immunologic abnormalities, and sons are at risk of genital anomalies and abnormal spermatogenesis.<sup>4</sup> In animals, and possibly in humans, DES alters male- and female-typical behaviour patterns.<sup>5</sup> The example of DES indicates that the fetus may be at greatest risk from the adverse effects of hormonal disruption.

### Mechanisms of action and fetal vulnerability

Numerous assays have reproducibly shown that some pesticides and other industrial chemicals can directly bind to, or block, hormone receptors, thereby initiating or blocking receptor-activated gene transcription.<sup>6</sup> Other exogenous chemicals act indirectly on hormonal homeostasis by altering steroidogenesis, hormone transport on binding proteins, receptor numbers on target organs or hormone metabolism.<sup>7</sup> For example, polychlorinated biphenyls (PCBs) interfere with thyroid function through a variety of mechanisms, including increased metabolism of T<sub>4</sub> (thyroxine), interference with T<sub>4</sub> delivery to the developing brain by displacement from the carrier protein, and interference with the conversion of T<sub>4</sub> to T<sub>3</sub> (triiodothyronine).<sup>8</sup>

During development the fetus is particularly sensitive to hormonal fluctuations. Exposures to low levels of exogenous hormones or toxicants may result in permanent physiologic changes that are not seen in adults exposed at similar levels.<sup>9</sup> For example, mild hypothyroidism in an adult is not expected to have long-term effects

*Review*

*Synthèse*

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on the brain. In contrast, subtle hypothyroidism during fetal and neonatal life causes disruption of neurotransmitters, neurotrophins, axonal growth and normal mitochondrial function in the developing brain, resulting in retarded cognitive and neuromotor development.<sup>10</sup>

## Potential health implications

Reported abnormalities in laboratory animals and wildlife exposed to endocrine-disrupting chemicals include feminization of males, abnormal sexual behaviour, birth defects, altered sex ratios, decreased sperm density, decreased size of testes, breast cancer, testicular cancer, reproductive failure and thyroid dysfunction (Table 1).<sup>11,12</sup>

Epidemiologic studies involving workers have found associations between exposure to specific pesticides or industrial chemicals and levels of thyroid stimulating hormone (TSH), testosterone and prolactin in adults.<sup>28-30</sup> Some of these studies have also found significant associations with other relevant end points, including diminished sperm

quality, impaired sexual function and testicular cancer.<sup>31,32</sup> Numerous studies have found associations between occupational exposure to solvents or pesticides and subfertility or adverse effects on offspring such as hypospadias or cryptorchidism, but it is unclear whether these effects are due to endocrine mechanisms.<sup>33,34</sup>

Population-based epidemiologic studies relevant to endocrine disruption are few and are limited by the time lag between exposure and clinical disease, the difficulty in defining exposed and control populations, and poor retrospective assessment of exposures during the prenatal period. Moreover, limited understanding of the role of gene-environment interactions increases the likelihood that susceptible subpopulations may remain unidentified. Perhaps as a result, epidemiologic data concerning the relation between breast cancer and tissue levels of certain organochlorines, such as DDT, its by-product DDE, PCBs or dieldrin, are conflicting.<sup>35,36</sup>

Surveillance-based studies in the general population show increases in some potentially hormone-related condi-

**Table 1: Examples of endocrine-disrupting chemicals**

Chemical	Use	Mechanism	Health effect	References
DES	Synthetic estrogen	Estrogen receptor agonist	Humans (prenatal exposure): vaginal cancer, reproductive tract abnormalities (females); cryptorchidism, hypospadias, semen abnormalities (males)	4
Methoxychlor	Insecticide	Metabolite is an estrogen receptor agonist	Rodents: accelerated puberty, abnormal ovarian cycling (females); aggressive behaviour (males)	7,13
DDT	Insecticide	Metabolite (DDE) is an androgen receptor antagonist	Rodents (males): delayed puberty, reduced sex accessory gland size, altered sex differentiation	14
Vinclozolin	Fungicide	Androgen receptor antagonist	Rodents (males): feminization, nipple development, hypospadias	15
PCBs	No longer manufactured; still in electrical transformers, capacitors, toxic waste sites, food chain	Accelerated T <sub>4</sub> metabolism, decreased T <sub>4</sub> levels, elevated TSH levels (high doses: thyromimetic)	Humans (in utero exposure): delayed neurological development; IQ deficits	16,17
Atrazine	Herbicide	Reduces gonadotropin-releasing hormone from hypothalamus, reduces pituitary LH levels, interferes with metabolism of estradiol, blocks estrogen receptor binding	Rodents (females): mammary tumours, abnormal ovarian cycling Humans: some evidence of breast and ovarian tumours	18-22
Dioxin	By-product of industrial processes including waste incineration; food contaminant	Aryl hydrocarbon receptor agonist; increases estrogen metabolism, decreases estrogen-mediated gene transcription, decreases estrogen levels, decreases testosterone levels by interfering with HPG axis	Rodents (in utero exposure): delayed puberty, increased susceptibility to mammary cancer (females); decreased testosterone, hypospadias, hypospermia, delayed testicular descent, feminized sexual behaviour (males) Humans: decreased T <sub>3</sub> and T <sub>4</sub> levels, decreased testosterone levels,* cancer*	23-27

Note: DES = diethylstilbestrol, DDT = dichlorodiphenyltrichloroethane, PCBs = polychlorinated biphenyls, T<sub>4</sub> = thyroxine, TSH = thyroid stimulating hormone, IQ = intelligence quotient, LH = luteinizing hormone, HPG axis = hypothalamic-pituitary-gonadal axis, T<sub>3</sub> = triiodothyronine.  
\*Exposures in adults.

tions (Table 2). These increases are not completely explained by improved detection or reporting.<sup>49,50</sup> Although behavioural and nutritional factors are potential explanations for some of these observations, it is biologically plausible, and consistent with laboratory and wildlife evidence, that fetal exposure to endocrine-disrupting chemicals may play a role. Cancers and other health effects may manifest many years later as steroid hormones continue to stimulate cell growth and proliferation.<sup>51,52</sup>

## Hormones and neurobehavioural effects

Prenatal or early postnatal exposure to certain environmental pollutants has been associated with learning and behavioural abnormalities. In some cases, there is evidence that these neurologic abnormalities may be due to an endocrine mechanism. For example, a single low dose of dioxin during the development of the hypothalamic-pituitary-gonadal axis in the rat has been shown to produce a feminizing effect on the behaviour of male offspring, reflecting altered sexual differentiation of the brain.<sup>53</sup>

Thyroid hormone is known to affect development of the fetal brain.<sup>10</sup> Thyroid disruption, including goiter and neurobehavioural abnormalities, has been found in wildlife and laboratory animal populations feeding on the organochlorine-contaminated food chain of the Great Lakes.<sup>54-56</sup> In utero and lactational exposure of non-human primates to environmentally relevant levels of PCBs has been shown to cause impaired learning.<sup>57</sup> In humans, higher levels of PCBs in breast milk have correlated with higher TSH levels in nursing infants.<sup>58</sup> Blood levels of certain PCBs have posi-

tively correlated with TSH levels and negatively correlated with free T<sub>4</sub> levels in children aged 7-10.<sup>59</sup> In addition to the antithyroid effects of PCBs, animal studies have revealed evidence of altered neurotransmitter and neuroreceptor levels, which may be primary or secondary to the thyroid effects.<sup>60</sup>

Cohort studies involving children environmentally exposed to PCBs in utero through maternal consumption of Great Lakes fish have revealed delayed psychomotor development and increased distractibility in those most highly exposed.<sup>61,62</sup> In one study, at age 11, the most exposed children were more than 3 times as likely to perform poorly on intelligence quotient (IQ) tests and more than twice as likely to be at least 2 years behind in reading comprehension as the least exposed children in the study.<sup>16</sup> Some entire population groups, such as the Inuit in Canada, currently have body burdens of PCBs that exceed levels known to affect cognitive functioning.<sup>63</sup>

## Beyond endocrine disruption: other signalling pathways

Although much attention has focused on the endocrine system, disruption of other biological signalling pathways is an important related issue. The structural and functional development of the brain is dependent on the integration of hormones, neurotransmitters, neurotrophins and locally produced steroids.<sup>64</sup>

Chemicals that interfere with neurotransmitters, such as the organophosphate pesticides, have many similarities to

**Table 2: Trends in human health effects potentially related to endocrine function**

End point	Region	Trend	Degree of change	Reference
Hypospadias	Canada	Increasing incidence	4.3% per year	37
	US		3.3% per year	
Cryptorchidism	Canada	Increasing incidence	3.5% per year	37
	US		1.6% per year	
Sperm count	Canada	Decreasing	-0.7%/mL per year*	38
	US		-3%/mL per year	39
	Europe		-5.3%/mL per year	39
Testicular cancer	Canada	Increasing incidence	2.1% per year	40
	US		2.3% per year	41
	Europe		2.3%-5.2% per year†	42
Prostate cancer	Canada	Increasing incidence‡	3% per year	43
	US		5.3% per year	44
Breast cancer	Saskatchewan	Increasing incidence	3.3% per year	45
	US		1.9% per year	46
Sex ratio	Canada	Shift toward females	-1.0 males/10 000 per year	47
	US		-0.5 males/10 000 per year	
Age at breast development	US	Shifting earlier	11.2-9.96 years in white population	48

\*This trend disappears when data from before 1984 are included.

†Range is dependent on country, with Sweden at the lower and the former East Germany at the upper end of the range.

‡International trends in prostate cancer are complicated by the introduction of the prostate specific antigen screen, but prostate cancer mortality also increased (by about 1% per year through 1995 in the US and Canada), implying that improved diagnosis may not fully explain the rising incidence trends.

chemicals that interfere with hormones. Toxic effects are generally reversible in adults. In the developing brain, however, effects may be permanent and result in functional deficits. For example, rodents exposed to a single low dose of an organophosphate pesticide in a critical period of neonatal life have been found to have permanently decreased brain density of muscarinic receptors and hyperactive behaviour when tested as adults.<sup>65</sup> Recent research has demonstrated that, in the developing brain, neurotransmitters perform growth regulatory and morphogenic functions.<sup>66</sup> For example, inhibition of acetylcholinesterase results in reduced axonal outgrowth and accumulation of neurofilaments *in vitro*.<sup>67</sup> It appears that immature neurologic systems, like immature endocrine systems, are sensitive to low doses of exogenous agents that have no apparent effect on adults.

### Implications and ongoing activities

Hormones act at extremely low levels (parts per trillion); therefore, in theory, even exposures to low levels of hormonally active agents may be of concern, particularly during sensitive periods of fetal development. Furthermore, endocrine-mediated effects may be subtle and manifest primarily in populations rather than in individuals. For example, slight overall declines in sperm density or IQ may have little relevance for an individual but important adverse implications for the population.<sup>68</sup>

Low-level exposures to endocrine-disrupting chemicals are ubiquitous in today's environment. Persistent chemicals such as DDT, PCBs and dioxins are detectable in nearly 100% of human blood samples, and even some of the shorter-lived potential endocrine disruptors are frequently detected in general population surveys of residues in blood or urine.<sup>69,70</sup> The ubiquitous nature of the exposures combined with the nontrivial potential health effects justifies further research, education and preventive action to reduce human exposures to endocrine disruptors.

A great deal of work on endocrine disruptors is under way in government agencies, nongovernment organizations and international organizations (Table 3). The Interna-

tional Joint Commission (IJC), created by treaty between the United States and Canada in 1909 to prevent or resolve disputes over lake and river systems along the border, has taken a leadership role in defining a "persistent toxic substance" and targeting such chemicals for elimination. Many of the chemicals targeted by the IJC are also endocrine disruptors and some are still in commercial use today. In its tenth biennial report, issued in 2000, the IJC reiterated a commitment to virtual elimination and zero discharge of persistent toxic substances, but cautioned that

Every delay in achieving this purpose carries a price. With time the price will grow heavier, and the line between delay and outright failure will be stretched thinner. Governments need to show a new sense of urgency and a commitment to action in restoring and protecting the Great Lakes.<sup>72</sup>

Improved monitoring of disease and exposure is essential for tracking trends in subtle, delayed effects of environmental exposures. Birth defect registries that acquire data through active case ascertainment rather than passive reporting can provide important data on structural birth defects. Neurodevelopmental abnormalities are exceedingly difficult to monitor, yet the evidence suggests that further investigation of time trends and causes is urgently needed. Ongoing efforts around the world to develop accurate biological monitoring of blood and urine for numerous chemical toxicants will improve exposure assessment in epidemiological studies and may eventually provide tools for physicians to assess risks to individuals.<sup>73</sup> As these tests become standardized and widely available, they will be useful clinically, just as blood lead testing has helped facilitate a range of interventions that have resulted in a major reduction in lead poisoning.

Finally, the topic of endocrine disruption has brought to the surface an underlying debate about the nature of scientific proof and decisions about whether to take action in the face of scientific uncertainty. Some argue that there is no proof of human health effects caused by endocrine disruption at current exposure levels in the general population. Others point to suggestive evidence and warn that the consequences of inaction may be significant to future genera-

**Table 3: Some science and policy activities concerning endocrine disruptors**

Activity	Lead organizations	Web site
Screening and testing chemicals for endocrine effects	US Environmental Protection Agency Organization for Economic Cooperation and Development	<a href="http://www.epa.gov/scipoly/oscpendo">www.epa.gov/scipoly/oscpendo</a> <a href="http://www.oecd.org/ehs/endocrin.htm">www.oecd.org/ehs/endocrin.htm</a>
Research on mechanisms, wildlife effects and human epidemiology	Environment Canada US government <sup>71</sup>	<a href="http://www.ec.gc.ca/eds/fact/index.htm">www.ec.gc.ca/eds/fact/index.htm</a> <a href="http://www.epa.gov/endocrine">www.epa.gov/endocrine</a>
Global phase-out of persistent organic pollutants (POPs)	UN Environment Program International POPs Elimination Network	<a href="http://irptc.unep.ch/pops">http://irptc.unep.ch/pops</a> <a href="http://www.ipen.org">www.ipen.org</a>
Education and advocacy for action on endocrine disruptors	World Wildlife Fund Canadian Association of Physicians for the Environment	<a href="http://www.wwfcanada.org/hormone-disruptors/index.html">www.wwfcanada.org/hormone-disruptors/index.html</a> <a href="http://www.cape.ca">www.cape.ca</a>



tions. Medicine and public health have traditionally favoured a science-based precautionary approach aimed at preventing adverse health effects through education and practical exposure reduction whenever feasible.<sup>74</sup> In the case of endocrine disruptors, such an approach will require the medical community to play a critical role in evaluating the science, educating the public and recommending steps to protect the next generation.

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