Endocrine disruption

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Understanding the risks that endocrine disrupters pose to human health is limited by inadequate knowledge of the effects of chronic, low-level and early-life exposures in adult life

Environmental pollutants may exert adverse physiological effects by disrupting normal endocrine function. Chemicals with this capacity, designated endocrine disrupters (EDs), are defined as exogenous substances that alter the function(s) of the endocrine system, thereby producing adverse health effects in an intact organism or its progeny or (sub)populations.

The endocrine disruption hypothesis was originally developed for chemicals that affected the oestrogen-signalling pathway. Thus, most research on endocrine disruption to date has been focused on oestrogenic effects. However, it is now becoming generally accepted that several types of compounds can interact with components of cell-regulatory systems, including steroid and thyroid hormone-receptor families. Endocrine disruption via nuclear receptors in cells of many organs of the body could affect the development and functioning of brain, cardiovascular, skeletal and urogenital systems.

Considerable progress has been made in the identification and quantification of a wide array of chemicals with endocrine disrupting properties. Research efforts have been centred on compounds that persist and bioaccumulate in organisms and their environment. Exposure to less persistent compounds has only recently been addressed. The existing safety assessment framework for chemicals is, unfortunately, poorly equipped to deal with EDs; tests and bioassays used take no account of the effects of simultaneous exposure to multiple chemicals, and may lead to a serious underestimation of the risks.

The vulnerability of a given species to EDs is determined by numerous factors: the intrinsic properties of the chemical; the magnitude, duration, frequency and route of the exposure; the ability of the species to absorb, distribute, transform and eliminate substances; and the sensitivity of specific organs at different stages of development. The direct adverse effects of exposure to EDs on wildlife are well documented, representing an early

warning of possible effects in humans that are yet to be recognised.

Although frequent exposure to some EDs has been documented in humans, evidence of human vulnerability to EDs is weak. Our understanding of the risks that EDs pose to human health is limited by our inadequate knowledge of the effects of chronic exposure to low levels and mixtures of chemicals, and of the relationship between early-life exposure and its impact on adult life. Concerns about this relationship have been heightened by indications from laboratory animal studies that early life stages may be especially sensitive to the effects of EDs and by observations of non-monotonic dose-response curves.

There may be a long latency period between exposure and observed response. Thus, in utero exposure may have developmental effects that become manifest only when the offspring reaches sexual maturity. Human maternal-infant exposure during pregnancy is of special importance as a likely window of high susceptibility associated with severe and irreversible effects during critical developmental periods.

To date, the conflicting results of epidemiological studies have failed to effectively test the hypothesis that endocrine disruption is associated with adverse health effects in humans. Published studies have focused on narrowly defined groups of chemicals, without considering combined exposures, genetic polymorphisms or lifestyle factors. Ongoing European research focuses on building up databases on reproductive effects in males and exploring the mechanistic basis of male disorders, with a view to developing improved biomarkers and screening tools. Human epidemiological studies have only recently been conducted with sufficient rigour to adequately address cause-and-effect relationships between exposure to EDs and disease—that is, by using well-designed biomarkers of the combined effect of oestrogenic chemicals.

Conditions potentially related to exposure to EDs in females include cancers of

breast and reproductive organs, fibrocystic disease of breast, polycystic ovarian syndrome, endometriosis, uterine fibroids, pelvic inflammatory diseases, osteoporosis, precocious puberty and declining sex ratio. In males, exposure to ED may be related to poor semen quality (low sperm count, low ejaculate volume, high number of abnormal sperm, low number of motile sperm), testicular cancer, reproductive organ malformations (undescended testes, small penis size, hypospadias), prostate disease and other abnormalities of male reproductive tissues. Other potential effects include impaired behavioural/mental, immune and thyroid function in developing children.

WHAT WOULD BE WORTH INVESTIGATING?

More research is required to address the remaining uncertainties in this field. Given the dynamic nature of the endocrine system, greater focus is warranted on the timing, frequency and duration of exposure to EDs. A major obstacle to the comparison of study findings is that researchers have considered different exposure assessment methods, exposure times and study populations, and have applied different clinical diagnostic criteria.

Challenges to the assessment of exposure include: (1) the highly heterogeneous chemical classes that have been identified as EDs; (2) the complex pathways between source of ED and exposure; and (3) the coexistence of non-persistent and persistent, or bioaccumulative, EDs. Epidemiology must address several issues related to exposure assessment before any conclusions can be drawn about the endocrine disruption hypothesis: (1) exposure should be classified by direct measurements rather than crude proxies; (2) estimation of exposure should take account of the highly heterogeneous chemical classes involved; (3) biomarkers need to be developed that allow investigators to quantify exposure to mixtures of EDs and to differentiate their effects from those of endogenous hormones; and (4) complex non-monotonic dose-effect relationships need to be interpreted appropriately.

Mechanistic research has focused on receptor-mediated events, whereas horizontal integration with basic cancer research has been neglected and warrants future attention. Carcinogenesis-related issues that need to be addressed include the effects of endocrine-active compounds on genomic instability, stromal/epithelial interactions, and cellular differentiation as a result of faulty programming early in fetal life. The potential

contribution of DNA array and chip technologies is welcome, although interpretation of the emerging data often remains unclear in the context of health-risk assessment. Genomics must be linked to physiological and phenotypic data relevant to disease processes in order to trace gene expression to gene function.

The challenges posed by EDs require a long-term commitment to the monitoring and characterisation of human and wildlife exposure, and to research into the mechanisms of action and interaction. Because of uncertainty about the possible effects of chronic, low-level exposure to a number of chemicals with endocrine disrupting potential and the key role of the endocrine system in maintaining homeostasis, investigation of the potential effects of exposure to these chemicals is an evident international priority. The following research areas will help to resolve uncertainties and should be given high priority:

- Identification of air, water, soil and food contaminant chemicals, persistent and non-persistent, naturally occurring and anthropogenic, that are the most likely candidates for high-impact effects in populations at environmentally relevant concentrations.
- Development of more specific and sensitive biomarkers for detecting endocrine-mediated effects in individuals and populations, including

research into mechanisms of hormonal carcinogenesis.

- Monitoring of trends in relevant human health outcomes to provide information that can be compared across regions and over time, improving global data collection on trends in environmental contamination, exposure and health outcomes, and establishing biobanks with suitable human reference material.
- Focus on populations/subgroups that are most likely to be vulnerable to EDs, including systematic exploration of the effects of exposure time, dose and mixtures.
- Integrated assessment of the role of EDs in the health of populations in relation to other environmental stressors, lifestyle factors and sex.
- Enhancement of international coordination between countries and stakeholders in sharing the information on exposure and effects of endocrine disruption.

In the meantime, given the complexity of the ED hypothesis, the paucity of information, the compelling data gathered from animal studies, the consequent uncertainty about cause-effect relationships and the slow pace of government testing and decision-making, the precautionary principle should underlie policies and decision-making criteria to expedite

prevention-oriented public health strategies. The precautionary principle represents a courageous but necessary approach to weighing scientific evidence and making decisions in the face of uncertainty.

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APHORISM OF THE MONTH

Public health is an art, but it should also be a science

Learn to separate assumptions from hypotheses. Subjective beliefs dressed up as facts are as likely to be found among those who think of themselves as scientists as among the laity. Transparency, openness, and a willingness to listen to other views of the world go both ways.

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