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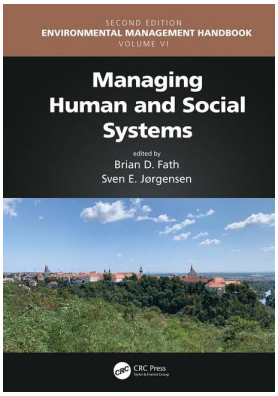

Managing Human and Social Systems

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Human Health: Endocrine Disruption

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3

Human Health: Endocrine Disruption

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Evamarie Straube and Sebastian Straube

Introduction

In general, endocrine disruption in humans can result from genetic disorders,[1] diseases,[2] medical treatments, mental and physical[3] stress, and chemical exposures. Endocrine disruption through chemical agents forms the focus of the present chapter.

Substances relevant for such endocrine-disrupting chemical exposures include pesticides (organochlorines such as DDT,[4] other organohalogens such as dibromochloropropane,[5] some organophosphates, carbamates, dithiocarbamates, phthalates), polychlorinated biphenyls,[6] some solvents,[7] metals such as cadmium, lead, and manganese,[8] phytoestrogens, and isoflavonoids.[9] Furthermore, endocrine disruption can be caused by smoking and alcohol use,[3] and by certain drugs, for example, glucocorticoids, hypnotics, antihypertensives, neuroleptics, and H_2-antihistaminies.[2]

Endocrine disruption can affect various endocrine systems. For example, thyroid hormone inhibition has been reported in humans after occupational exposure to amitrol and mancozeb.[10] Insulin levels can be affected by streptozotocin, which is toxic to pancreatic beta cells.[11]

Arguably the most extensive knowledge exists for chemical exposure affecting the reproductive system, which is discussed in further detail below.

Of note, for some endocrine-disrupting chemicals, non-monotonic dose–response relationships have been described with hormonal disruption occurring at relatively low levels of exposure.[12]

Mechanisms of Endocrine Disruption

Diverse mechanisms of endocrine disruption by chemical agents have been described. Endocrine disruption can be caused by xenohormones. Xenoestrogens, such as endosulfan, toxaphene, dieldrin, DDT, bisphenol A, nonylphenols, and dibutylphthalates,[7] mimic the physiological effects of estrogens. Xenoantiestrogens have effects opposite to those of xenoestrogens. For example, dioxin exerts its inhibitory effect by enhancing the expression of enzymes that degrade the estrogen receptors.[13] Antiandrogenic effects may result from competitive antagonism at androgen receptors. This was demonstrated for

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vinclozolin and DDE, the stable metabolite of the DDT.[7] Sometimes a xenobiotic and its metabolite (such as DDT and DDE) can exert their effects at different targets in the organism.

Pesticide-induced enzymes such as UDP-glucuronyl transferase and monooxygenases can degrade hormones (e.g., testosterone). Furthermore, the pesticides endosulfan, mirex, and DDT can increase the elimination of androgens by stimulating cytochrome P450.[14,15] Pesticide exposure can also disrupt hormonal status by inhibiting enzymes. For example, inhibition of the aromatase system can lead to an increase in testosterone levels and a decrease in the formation of estradiol from testosterone.[16] Inhibitors of the aromatase system include prochloraz, imazalil, propiconazole, fenarimol, triadimenol, triadimefon, and dicofol.[17]

Endocrine disruption can furthermore involve hormone transport proteins: for example, polychlorinated biphenyl can induce thyroid disruption, and this may involve its sulfated metabolites which bind to the thyroid hormone transport protein transthyretin with high affinity.[18]

Moreover, recent research demonstrates that endocrine disruption can involve epigenetic alterations, which may be preserved into the third generation, as has been shown for DNA methylation changes that are associated with lead exposure.[19]

Endocrine Disruption with Occupational Exposure in Women

Pesticide exposure has been linked with reproductive difficulties and menstrual abnormalities. For example, prolonged time to pregnancy, reduced fecundability, reduced fertility as well as infertility have been described for pesticide-exposed women and for women working in agriculture and greenhouses, presumably related to pesticide exposure.[20–24] Furthermore, pesticide exposure has been associated with long cycles, missed periods, and intermenstrual bleeding.[25]

Endocrine Disruption with Occupational Exposure in Men

In men, pesticides may adversely affect sperm count and quality as well as impacting the levels of testosterone, follicle-stimulating hormone, and luteinizing hormone.[26]

We have found changes in sex hormone concentrations after low-dose occupational exposure to pesticides (mainly pyrethroids, carbamates, and organophosphates). With chronic occupational pesticide exposure, we found a higher level of testosterone in comparison to control persons. There also was a reduction in estradiol levels during and after the application season in pesticide applicators.[16] Another study[27], however, found an increase in estradiol concentration in pesticide-exposed men; it may be that variations in the nature and timing of the exposure can account for these differences.

Endocrine Disruption with *In Utero* Exposure

Historically, diethylstilbestrol (DES) was the first recognized example of a xenobiotic eliciting a hormonal effect. This now very well-described paradigm serves to illustrate the potential consequences of *in utero* exposure to endocrine-disrupting chemicals. The treatment of pregnant women with DES leads to an increase in the incidence of adenocarcinoma of the vagina in their daughters[28] and malformations of the external genitals in their sons[29] and grandsons.[30] The risk of breast cancer after age 40 was also increased in women with prenatal DES exposure, as were the risks for spontaneous abortions, premature births, and ectopic pregnancies in later pregnancies of women exposed *in utero*.[31–33] Treatment with DES has, furthermore, been reported to have an effect on sexual orientation[34] and handedness.[35]

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