Int. J. Environ. Res. Public Health **2006**, *3(2)*, 180-184

International Journal of
Environmental Research and Public Health
ISSN 1661-7827
www.ijerph.org

Are Endocrine Disrupting Compounds a Health Risk in Drinking Water?

Ian R. Falconer*

Department of Clinical and Experimental Pharmacology, University of Adelaide Medical School and Cooperative Research Centre for Water Quality and Treatment, Adelaide, South Australia 5005
*Correspondence to Dr. Ian R. Falconer. Email: ian.falconer@adelaide.edu.au

Received: 31 August 2005 / Accepted: 31 May 2006 / Published: 30 June 2006

Abstract: There has been a great deal of international discussion on the nature and relevance of endocrine disrupting compounds in the environment. Changes in reproductive organs of fish and mollusks have been demonstrated in rivers downstream of sewage discharges in Europe and in North America, which have been attributed to estrogenic compounds in the effluent. The anatomical and physiological changes in the fauna are illustrated by feminization of male gonads. The compounds of greatest hormonal activity in sewage effluent are the natural estrogens 17β-estradiol, estrone, estriol and the synthetic estrogen ethinylestradiol. Androgens are also widely present in wastewaters. Investigations of anthropogenic chemical contaminants in freshwaters and wastewaters have shown a wide variety of organic compounds, many of which have low levels of estrogenic activity. In many highly populated countries the drinking water is sourced from the same rivers and lakes that are the recipients of sewage and industrial discharge. The River Thames which flows through London, England, has overall passed through drinking water and sewage discharge 5 times from source to mouth of the river. Under these types of circumstance, any accumulation of endocrine disrupting compounds from sewage or industry potentially affects the quality of drinking water. Neither basic wastewater treatment nor basic drinking water treatment will eliminate the estrogens, androgens or detergent breakdown products from water, due to the chemical stability of the structures. Hence a potential risk to health exists; however present data indicate that estrogenic contamination of drinking water is very unlikely to result in physiologically detectable effects in consumers. Pesticide, detergent and industrial contamination remain issues of concern. As a result of this concern, increased attention is being given to enhanced wastewater treatment in locations where the effluent is directly or indirectly in use for drinking water. In some places at which heavy anthropogenic contamination of drinking water sources occurs, advanced drinking water treatment is increasingly being implemented. This treatment employs particle removal, ozone oxidation of organic material and activated charcoal adsorption of the oxidation products. Such processes will remove industrial organic chemicals, pesticides, detergents, pharmaceutical products and hormones. Populations for which only basic wastewater and drinking water treatment are available remain vulnerable.

Keywords: Endocrine disruptors, estrogens, feminization, wastewater, drinking water

Introduction

During the last decade considerable amounts of scientific and financial resources have been employed to clarify the potential risk to human health of endocrine disrupting compounds (EDCs) in food and drinking water. The topic has been subject to a multi-pronged attack, including epidemiological studies of human and wildlife populations, development of test assays for hormonal compounds at very low concentrations, chemical analysis of surface waters, and identification of endocrine activity of anthropogenic and natural chemical compounds. More recently attention has focussed on wastewater from sewage treatment and industry as sources of potential endocrine disrupting compounds, and the treatment of wastewaters.

There are many complexities in this field of research, ranging from the difficulties inherent in human epidemiology, to the many thousands of chemicals that have potentially endocrine disrupting activity. A consistent difficulty is that the environment carries complex mixtures of suspect chemicals, whereas assay methodologies are best undertaken on pure, characterized material. Few firm conclusions have been drawn from research on EDCs in the environment, apart from the ecological studies on aquatic organisms downstream of sewage discharges, tanneries or paper mills. Metabolic have shown clear, concentration related, changes in gonads and secondary sexual characteristics as will be discussed later.

While the concentrations of potentially EDCs in surface waters are very low in most instances, the increasing shortage of high quality water for the drinking water supply has resulted in increased interest in the use of wastewater. In most North American and European inland cities wastewater from sewage treatment is indirectly re-used, through discharge into rivers which are also a source of drinking water. Dilution by river flow and breakdown by microbial processes greatly reduces the concentrations of EDCs in rivers. Direct re-use of wastewater is in operation in Singapore and Windhoek, Namibia, and under active discussion in Australia. This process raises the question of the risks from EDCs more acutely, and requires evaluation of wastewater treatment and drinking water treatment for EDC removal, and establishment of Guideline Values or Reference Doses of EDCs in drinking water.

EDCs and Aquatic Ecology

The earliest and the best defined ecological effects of EDCs are on aquatic fauna. In the United States the impact of an insecticide spill containing DDT metabolites on alligators and turtles in Apopka Lake in Florida was severe. Abnormal development of the reproductive system, reduced egg hatching and low juvenile survival were recorded [1, 2].

Adverse effects on fish populations have been frequently recorded downstream of sources of aquatic contamination. Masculinization of female fish was one of the first recorded effects, when mosquito fish downstream of a pulp and paper mill were found to have male secondary sexual characteristics [3]. This has been reported since in Sweden, under similar circumstances, with the observation that the progeny of a viviparous fish are biased towards male offspring [4].

Perhaps the most powerful directly adverse effect on aquatic wildlife was that exerted by tributyltin, formerly widely used as an anti-fouling agent on ships hulls. This was very effective in preventing growth of barnacles and other marine organisms on ships, by its toxic action. Unfortunately contamination of ports and estuaries by tributyltin resulted in local extinction of some species of mollusc, with major endocrine changes in shellfish at low concentrations. Initial observation was of a penis-like structure with an associated vas deferens in female gastropod molluscs, with resulting infertility. This change in morphology was termed imposex, and has been found widely in molluscs in marine environments heavily used by shipping [5] . The use of tributyltin paints on ships hulls has been partially banned as a result of the adverse environmental impact.

The converse effect has been frequently reported in freshwaters downstream of wastewater treatment plants, where feminization of male fish and molluscs through estrogen contamination in the effluent has a pronounced effect. Feminization of reproductive ducts in male fish, appearance of oocytes in male gonads and the characteristic production of the female egg protein vitellin (or its precursor vitellogenin) in male fish exposed to wastewater from sewage treatment plants has been recorded [6]. Feminization of fish in English rivers is widespread, attributed to estrogens in sewage effluent [7]. Molluscs living in the St. Laurence Estuary downstream of Quebec in plumes of wastewater from the city have been shown to exhibit a range of toxicologically relevant changes, including estrogen-like stimulation of vitellogenin production, and changes of biochemical and neurochemical activity [8, 9]. These Canadian studies emphasize that sewage effluent may have diverse toxic effects which show as injury and stress responses in aquatic organisms, among which endocrine disruption may be relatively minor.

Little is currently known about endocrine effects that do not result in physical changes to the aquatic organisms, though studies of adverse biochemical changes in molluscs are showing complex metabolic effects which require further investigation [9]. Detergents are widespread in effluents and are currently under investigation for endocrine disruptive and toxic effects [10]. Invertebrates including insects, and all vertebrates, have endocrine systems controlling metabolism as well as reproduction and morphological characters. It can be expected that disruption of these systems will also occur on exposure of the organisms to wastewater. Only population-level studies will clarify whether these effects have significant ecological consequences.

EDCs, Human Benefit and Human Injury

Reproductive Hormones

The pharmacological effectiveness of estrogens and progestins has been studied for almost one hundred years, and employed to both assist and block fertility. Estrogens and progestins are naturally secreted in women as integral components of the menstrual cycle, and excreted in urine as conjugated molecules. These conjugates are released as the original steroids in microbial sewage treatment. The major recent pharmacological addition to the natural steroid hormone excretion in women has been the oral contraceptives, particularly the synthetic estrogen ethinylestradiol, which is similarly excreted in the urine. Androgens and progestins are also excreted in urine in quantities comparable to the estrogens, but have sofar received little attention as components of wastewater. Androgen concentration in sewage effluent may be greater than estrogen, though of lower physiological potency. Progesterone and related steroids are also of lower human potency than estrogen, though aquatic life may be more sensitive [11].

To evaluate the potential for human injury from ingestion of steroid hormones in drinking water, it is necessary to quantify the likely intake, and to identify the most sensitive possible effects. If the likely daily intake from drinking water is a minute fraction of the normal endogenous secretion of steroids, it can be expected that any effects will be undetectable.

Pharmacological Uses

Large doses of the synthetic estrogen diethylstilbestrol, administered to many women in the past for pharmacological reasons such as prevention of miscarriage, the inhibition of lactation or stunting of growth in tall girls, have been associated with a variety of adverse outcomes [12, 13]. The dose regime applied in these pharmacological treatments employed very substantial amounts of estrogen. Karnaky in 1948 recommended doses up to 100mg diethylstilbestrol daily for long periods to control endometriosis [14] and in 1975 quoted doses of 300grams yearly as not showing toxic symptoms and recommended stilbestrol as a contraceptive[15]. Unfortunately both girl and boy infants of mothers given diethylstilbestrol showed reproductive abnormalities [16, 17]. These and other effects led to the banning of this compound from use in pregnancy (but not for other uses) by the USFDA in 1971. The implication from the adverse reactions to diethylstilbestrol was that it exerts a specific pathological response, not occurring with natural estrogen. Recent experiments however showed that there did not appear to be any difference in the uterine cell response to diethylstilbestrol, genistein (a plant estrogenic compound) or the natural hormone 17β-estradiol, when they were administered at physiologically equivalent doses. The *in vivo* potencies of these compounds in mice were compared by diethylstilbestrol used at 2μg/kg/day, 17β-estradiol 2.5μg/kg/day and genistein 50mg/kg/day over 3 days, each of which approximately tripled uterine weight [18]. This research implies that the adverse reactions to stilbestrol were dose-dependent rather than compound dependent.

The prevalence of use of estrogen in treatment of post-menopausal women is considerable. In the USA in 1995 about 40% of the relevant population were taking regular hormone replacement therapy. This decreased by 1999 to 24% of all women of 40 years and older [19]. Pharmacological use of 17β-estradiol at 1mg/day in post-menopausal women, given over two years, raised serum estradiol to 59pg/ml with control women at 14pg/ml. This can be compared to the normal estradiol concentration in the follicular phase of the menstrual cycle of about 170pg/ml [20]. Other clinical uses of estrogen employ estradiol up to 2mg/day.

The normal secretion of 17β-estradiol in reproductive women is approximately 100 to 250 μg/day, depending on the phase of the menstrual cycle. Because of internal metabolism of estrogens by the liver, urinary excretion includes estrone and estriol, which are the major components, in conjugated form, in the urine. Total daily urine excretion of estrogens is about 70μg/day in non-pregnant women and higher in pregnancy. The estrone and estriol in urine are appreciably less potent estrogens than estradiol [21]. All of these compounds are found in sewage effluent.

The oral contraceptives that are currently in wide use contain ethinylestradiol, which is less easily metabolized than 17β-estradiol, and hence requires lower doses to exert biological effects. Contraceptive formulations frequently contain 20μg/day ethinylestradiol, together with a synthetic progestin. Other 'low dose' oral contraceptive formulations contain 5μg/day ethinylestradiol. Depot injectable contraceptives use estradiol valerate at 5mg/monthly injection. This ethinylestradiol is excreted in urine without degradation.

Thus there is very wide pharmacological use of natural and synthetic estrogen in the female population, pre and post menopausal. There is also substantial natural secretion and hence excretion of estrogens. Men also excrete estrogen, but at one fifth or lower concentrations than women. Most of these endogenous and exogenous estrogenic compounds then appear in raw sewage effluent.

Estrogen in Wastewaters

Considerable attention has recently been paid to estrogen activity in wastewater, as a result of evidence for feminization of aquatic fauna. Analysis of estrogen in treated sewage effluent in the UK provided mean concentrations of 17β estradiol, 11ng/L; estrone 17.3ng/L and ethinylestradiol 0.73ng/L [22]. In Canada, mean influent concentrations of 17β-estradiol were 15.6ng/L (range 2.4-26ng/L), estrone 49ng/L (range 19-78ng/L). In final effluents these were reduced to mean concentrations of 1.8ng/L (range 0.2-14.7ng/L) and 17ng/L (range 1-96ng/L), indicating a wide extent of variability of removal in different sewage treatment plants [23]. An Australian study showed the advantages of tertiary sewage treatment in removing estrogens from wastewater, when influents ranging from 18 to 32ng/L of 17β-estradiol were processed to less than 5 to 19 ng/ml by clarification and to less than 7ng/L by ozone or UV. Chlorination of secondary effluent was without effect [24].

In wastewater treatment plants in the Paris region, the percentage removal of natural estrogens from influent sewage ranged from 44% to 67 %, whereas ethinylestradiol was more resistant and only 38 to 45% was removed. All river samples showed both natural and synthetic estrogens, at concentrations of 1.0 to 3.2 ng/L, with 35 to 50% of the estrogenic activity in the form of ethinylestradiol [25].

Detailed chemical analysis of estrogenic compounds in German rivers and drinking water provided basic data on other compounds than natural and synthetic estrogens. Bisphenol A was found at 0.5 to 16ng/L, 4-nonylphenol at 6 to 135ng/L and the steroid hormones from 0.2 to 5ng/L. In drinking water bisphenol A was 0.3 to 2ng/L, 4-tert-octylphenol was at 0.15 to 5ng/L and the steroid hormones 0.1 to 2ng/L [26]. The phenols arising as detergent breakdown products have estrogenic potencies 10^4 to 10^6 times lower than estradiol, with the plant estrogens about 10^4 times less active [24].

Thus a picture can be assembled of possible estrogen consumption from water, endogenous estrogen production and pharmacological estrogen consumption. Assuming 2L of water are drunk by adults daily, then drinking unprocessed wastewater may supply 40ng of estradiol (or equivalent estrogens) per day. Drinking treated effluent may provide half of this intake or less. River water may supply 10ng of estrogen, and drinking water 4ng or less per day. This can be compared to endogenous secretion of (say) 100-200μg/day in women or one tenth of this in men. Pathological effects with stilbestrol were seen with doses of 100mg/day to 1g/day. A further contribution to ingested estrogen comes from food, in which milligrams of phytoestrogens may be consumed daily [27].

A conservative estimate is that approximately one thousandth to one ten-thousandth of the estrogen available to the body may be contributed from drinking water. When pharmacological treatment is in progress, less than one hundred thousandth of the estrogen used in hormone replacement therapy may be consumed from drinking water. The conclusion is that any physiological effects of estrogen from drinking water will be undetectable in people.

Pesticides and Industrial Contamination

Other compounds in the environment with potentially adverse consequences to individuals have been identified from occupational exposures, at much higher levels of exposure than likely from water supplies. This particularly applies to pesticides. Some of the adverse effects of pesticide contamination appear to be EDC effects, rather than direct toxicity. An extensive study of birth defects among children in an agricultural community in Minnesota has shown an excess of children born with defects in agricultural, as compared to urban, communities. The highest rates of defects were found in children conceived in spring as compared with conception in the other three seasons. Spring coincided with maximum pesticide use. Exposure to fungicides in the same population appeared to affect the sex ratio of children born, with an excess of female births [28].

Pesticides that have been associated with adverse human consequences include atrazine, one of the most widely used herbicides and ketoconazole one of the most used fungicides. Interpretation of epidemiological studies of these and other compounds have been reviewed by the International Committee for Chemical Safety of the World Health Organization, with the general conclusion that environmental exposures have not been proved to result in adverse effects, whereas occupational exposures may do so [29] .

Legislation by state and national governments controls the reference doses or guideline levels of agricultural chemicals and organic toxicants allowed for safe drinking water supply. Water utilities therefore monitor concentrations in drinking water, and report to health authorities. Currently little monitoring is done of these compounds in sewage effluent. A detailed analytical monitoring of US waterways for anthropogenic contaminants showed low concentrations of a large number of compounds, derived from sunscreens, insect repellants, detergents and over-the-counter pharmaceuticals [30].

Drinking water treatment is increasingly using advanced oxidation techniques for the removal of undesirable organic compounds, including cyanobacterial toxins and anthropogenic contaminants [31]. These processes employ a combination of particle removal, ozone oxidation and activated carbon adsorption to greatly reduce organic contaminants in drinking water. Recent studies on estrogen removal have shown greater than 99% removal with ozone [32].

Effective monitoring and treatment of drinking water will continue to be required for public health and safety in developed nations, and this may in future be extended to potential endocrine disrupting compounds. Unfortunately many of the world's population continue to drink contaminated surface water without any treatment, and therefore will remain at risk.

References

1. Guillette, L. J. J., et al.: Alligators and endocrine disrupting contaminants: a current perspective. *American Zoologist*, **2000**, *40*: 438-452.
2. USEPA, Special report on endocrine disruption. An effects assessment and analysis. *USEPA, Washington*, **1997**.
3. Howell, W. M.; Black, D. A.; Bortone, S. A.: Abnormal expression of secondary sex characters in a population of mosquitofish, Gambusia affinis holbrookii: evidence for environmentally induced masculinization. *Copeia, 1980,* **1980**: 676-681.
4. Larsson, D. G.; Forlin, L.: Male-biased sex ratios of fish embryos near a pulp mill: temporary recovery after a short-term shutdown. *Environmental Health Perspectives*, **2002,** *110(8)*: 739-742.
5. Matthiessen, P.: An historical perspective on endocrine disruption in wildlife. *Pure and Applied Chemistry*, **2003**, *75:* 2197-2206.
6. Rodgers-Gray, T. P., et al.: Exposure of juvenile roach (Rutilus rutilus) to treated sewage effluent induces dose-dependent and persistent disruption in gonadal duct development. *Environmental Science and Technology*, **2001**, *35(3):* 462-470.
7. Jobling, S., et al.: Widespread sexual disruption in wild fish. *Environmental Science and Technology,* **1998***, 32:* 2498-2506.
8. Gagne, F., et al.: Biomarker study of a municipal effluent dispersion plume in two species of freshwater mussels. *Environmental Toxicology,* **2002***, 17(3):* 149-159.
9. Gagne, F.; Blaise, C.; Hellou, J.: Endocrine disruption and health effects of caged mussels, Elliptio complanata, placed downstream from a primary-treated municipal effluent plume for 1 year. *Comparative Biochemistry and Physiology C Toxicology and Pharmacology*, **2004**, *138(1)*: 33-44.
10. Quinn, B., et al.: Evaluation of the lethal and sub-lethal toxicity and potential endocrine disrupting effect of nonylphenol on the zebra mussel (Dreissena polymorpha). *Comparative Biochemistry and Physiology C Toxicology and Pharmacology,* **2006***, 142(1-2):* 118-127.
11. Sumpter, J. P.: Endocrine disrupters in the aquatic environment: an overview. *Acta hydrochimica hydrobiologica,* **2005***, 33(1)*: 9-16.
12. Swan, S. H.: Intrauterine exposure to diethylstilbestrol: Long-term effects in humans. *APMIS*, **2000**, *108(12)*: 793-804.

13. Milhan, D.: DES exposure: implications for childbearing. *International Journal of Childbirth Education*, **1992**, *7(4):* 21-28.
14. Karnaky, K. J.: The use of stilbestrol for endometriosis. *Southern Medical Journal*, **1948**, *41:* 1109-1110.
15. Karnaky, K. J.: Development of the oral contraceptives. *American Journal of Obstetrics and Gynecology*, **1975**, *123(7):* 771-772.
16. Herbst, A. L.: Diethylstilbestrol and other sex hormones during pregnancy. *Obstetrics and Gynecology*, **1981**, *58(5 Suppl.)*: 35S-40S.
17. Sharpe, R. M.; Skakkebaek, N. E.: Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet*, **1993**, *341:*1392-1395.
18. Moggs, J. G., et al.: The need to decide if all estrogens are intrinsically similar. *Environ Health Perspect,* **2004***, Aug; 112(11):*1137-42.
19. Brett, K. M.; Reuben, C. A.: Prevalence of estrogen or estrogen–progestin hormone therapy use. *Obstetrics & Gynecology,* **2003**, *102(6):* 1240-1249.
20. Hwang, J., et al.: Long-term effect of estrogen replacement on plasma nitric oxide levels: results from the estrogen in the prevention of atherosclerosis trial (EPAT). *Atherosclerosis*, **2005**, *181(2)*: 375-380.
21. Sawin, C. T.: The Hormones: Endocrine Physiology, *London: J. & A. Churchill*, **1969**, *308.*
22. Desbrow, C., et al.: Identification of estrogenic chemicals in S.T.W. effluents. 1: Chemical fractionation and in vitro biological screening. *Environmental Science and Technology*, **1998**, *32:* 1549-1558.
23. 23. Servos, M. R., et al.: Distribution of estrogens, 17ß-estradiol and estrone, in Canadian municipal wastewater treatment plants. *Science of The Total Environment*, **2005**, *336(1-3)*: 155-170.
24. Falconer, I. R. et al.: Review of endocrine disruptors in the context of Australian drinking water. *Cooperative Research Centre for Water Quality and Treatment: Salisbury, South Australia*, **2003**: 40.
25. Cargouët, M., et al.: Assessment of river contamination by estrogenic compounds in Paris area (France). *Science of The Total Environment,* **2003**. *324(1-3)*: 55-66.
26. Kuch, H. M.; Ballschmiter, K.: Determination of Endocrine-Disrupting Phenolic Compounds and Estrogens in Surface and Drinking Water by HRGC-(NCI)-MS in the Picogram per Liter Range. *Environmental Science and Technology*, **2001**, *35(15)*: 3201-3206.
27. Safe, S. H.: Endocrine disruptors and human health - is there a problem? An update. *Environmental Health Perspectives*, **2000**, *108(6)*: 487-493.
28. Garry, V. F., et al.: Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. *Environmental Health Perspectives*, **2002,** *110(Supplement 3)*: 441-449.
29. WHO International Programme for Chemical Safety (IPCS), Global assessment of the state of the science of endocrine disruptors, *Geneva***: 2002**.
30. Kolpin, D. W., et al.: Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance. *Environmental Science & Technology,* **2002,** *36(6):* 1202-1211.
31. Falconer, I. R.: Cyanobacterial toxins of drinking water supplies: cylindrospermopsins and microcystins, *Boca Raton: CRC Press*, **2005**, *279.*
32. Alum, A., et al.: Oxidation of bisphenol A, 17-estradiol, and 17-ethynyl estradiol and byproduct estrogenicity. *Environmental Toxicology,* **2002**, *19(3):* 257-264**.**