Endocrine Disruptors in Drinking Water and Associated Health Effects

A Knowledge Synthesis

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Summary

- Endocrine disrupting compounds refer to any exogenous compound that is capable of interfering with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body, and can be either natural or synthetic
- Some of the most common endocrine disrupting compounds in drinking water include estrogen, progesterone, androgen, ethinylestradiol, bisphenol A, and polychlorinated biphenyl
- The classification and toxicology of endocrine disrupting compounds is complicated and there are many gaps in our knowledge
- Progestagens and androgens are the most resistant to water treatment methods
- Endocrine disrupting compounds are often present in drinking water but at very low levels (ng/L)
- It is proposed that endocrine disruptors act by attaching to endogenous hormone receptors and either mimicking natural hormones or inhibiting them from binding to the receptor
- There is insufficient evidence that low levels of endocrine disrupting compound exposure are a risk to human populations
- Given the amount of uncertainty surrounding the issue, the precautionary principle should be considered

Introduction

Endocrine disrupting compounds (EDCs) are an emerging public health concern, as we learn more about their potential harmful effects on humans. These compounds are so-named because of their ability to disrupt endogenous hormone activity, in particular steroid, estrogen, and androgen activity.[1] They can include hormone mimics, hormonally active agents, endocrine disruptors, and endocrine toxicants.[1] It is well-known that in high doses, these compounds can cause morphological and functional effects in every system in the body that is regulated by hormones, including the nervous, immune, reproductive, and urogenital systems, among others. High doses can also cause infertility and abnormal prenatal and childhood development as well.[2]

It is not well-known, however, what the effects of these compounds are with low-dose, chronic exposure. There are thousands of potential EDCs that can enter our drinking water sources as sewage effluent or pollution, but there is very little data available concerning the detection of these compounds in our final drinking water.[3] Many of these compounds are quite stable and resistant to water treatment methods and there is a concern that they may pass through into drinking water in relatively large concentrations.[2] Present data indicates that there is very little evidence to support a hypothesis that exposure to EDCs from drinking water poses a risk to human health, but there is a great deal of uncertainty surrounding chronic exposure.

Methods

A literature review of English peer-reviewed articles published between 2006 and 2011 was conducted. The search was conducted in PubMed, Primo (University of Guelph) and Google Scholar using MeSH terms: "endocrine disruptor AND drinking water" OR "endocrine disruptor AND health effects" OR "endocrine disruptor AND health effects AND water" OR "endocrine active compound AND health AND drinking water". Six articles were found to be relevant and were chosen for review. Pertinent information such as author, publication date, and type of study was extracted from each article. Refer to Table 1.

Endocrine Disruptors in Drinking Water and Associated Health Effects Evidence Review

A systematic review performed by Falconer et al. (2006) investigated the most common types of EDCs found in drinking water and sewage effluent, as well as their average concentrations and possible health effects. According to the review, estrogens and progestins are secreted naturally by women as part of the menstrual cycle as well as in urine, however with the growing popularity of

oral contraceptives, which contain the synthetic estrogen ethinylestradiol, the concentrations of steroid hormones excreted by women has increased dramatically. Androgen and progesterone have also been found in relatively high concentrations in sewage effluent but have lower potencies. Other compounds with endocrine disrupting effects that have been found in drinking water sources include some agricultural chemicals such as atrazine (a herbicide) and ketoconazole (a fungicide), as well as bisphenol A, which is used to make plastics and epoxy resins.

Falconer et al. note that previous studies have shown evidence for adverse health effects, including reproductive abnormalities, of large doses of the synthetic estrogen diethylstilbestrol when administered to women for pharmacological reasons, or when administered to rats. However, these effects were deemed to be dose-dependent and only detectable at 100 mg/day to 1 g/day, and the concentrations of EDCs found in water sources are far less than this. Some agricultural communities have seen higher birth defect rates surrounding seasons with unusually high pesticide and herbicide use, which may indicate drinking water contamination with agricultural EDCs, although no causation has been confirmed. According to the review, the percentage removal of natural estrogens from influent sewage typically ranges from 44% to 67%, leaving levels of bisphenol A, steroid hormones, synthetic estrogens, and other EDCs well within the ng/L range, and far below any concentration that has been previously linked to adverse health effects. Falconer et al. estimates that approximately one thousandth to one ten-thousandth of the estrogen available to the body comes from drinking water, and concludes that any health effects of estrogen from drinking water will be undetectable in humans. The authors suggest invoking the precautionary principle with constant monitoring and treatment of drinking water, and increased use of ozone in water treatment to prevent any possible health effects of chronic exposure to these low doses of EDCs.[2]

Phillips et al. (2008) conducted a risk assessment quantifying EDC hazard identification, mechanisms of action, and dose-response. For the purpose of this study, some EDCs of particular interest were identified, including natural and synthetic hormones, the pesticide DDT, bisphenol A, and polychlorinated biphenyl (PCB) compounds, used in a variety of industrial processes. The authors identified potential adverse health effects of EDCs to include infertility (decreased fecundity and semen quality and endometriosis), abnormal prenatal and childhood development (spontaneous abortions, reproductive-tract abnormalities, altered sex ratios, precocious puberty, and other birth defects) and cancers of the prostate, breast, ovaries, or testes. It is proposed that EDCs interact with nuclear receptors by either mimicking hormones or inhibiting them from reaching the same receptor. In this way they affect gene expression and thereby modulate the endogenous endocrine system. It is because of this that the potential scope of health effects of EDCs is so large, because they have the potential to interfere with whichever systems are mediated by the hormone that they are mimicking or inhibiting. For estrogens, this includes the nervous, immune, reproductive, and urogenital systems, as well as processes such as sexual differentiation, development, and maturation. Some EDCs can even be nongenomic, and interfere with steroid actions such as activation of sperm, electrolyte and fluid transport in the efferent duct of the testis. Disruption of thyroid hormone formation is yet another suggested effect of EDCs, and has been evidenced by reduced T3 and T4 levels following exposure to high doses of PCBs. This effect can lead to glandular lesions in the thyroid, further reducing T4 levels by inhibiting its release. Phillips et al. proposes that EDCs are able to cause these effects by using three mechanisms of action; inhibition of hormone synthesis, transport, or metabolism, activation of hormone receptors, and release of cellular complexes that are necessary for hormonal action.

However, despite all of these known potential health effects of EDCs, there is still a large amount of uncertainty surrounding them. It is unknown what doses are required to cause these

effects, and it the extent of human exposure to the compounds is also largely unknown. Phillips et al. went on to describe the dose-response curve for EDCs, and found it to be the shape of an inverted "U". This may be explained by human homeostatic feedback loops, but there is a great amount of uncertainty regarding this, and Phillips et al. notes that more research is necessary. Phillips et al. conclude that large doses of EDCs will cause adverse health effects, but exposure from drinking water is minimal, and overall there is insufficient evidence to fully characterize the risks to human health posed by any toxicant that can be described as an endocrine disrupting compound. The authors suggest that a risk characterization be determined for each individual toxicant, education and communication of potential risks to the public, and the maintenance of sustainable development practices to minimize pollution, invoking the "polluter pays" principle.[1]

A weight-of-evidence review by Goodman et al. (2009) focuses on the health effects of bisphenyl A (BPA) from drinking water. They examined low-dose rodent BPA studies focusing on morphological effects on reproductive organs and functional effects on reproduction and development using a structured framework incorporating study rigor, power, corroboration, universality, proximity, relevance, and coherence, with evidence from studies scoring higher in these areas worth a higher weight. According to the review, BPA is a demonstrated weak estrogenic, with a no observable adverse effect level of 50 mg/kg-d. According to this review, estimates of human daily intake of BPA were consistently below 0.1 μg/kg body weight, which is far lower than the doses used in these low dose studies. However, these measurements are taken from urine samples, which represent recent exposure, not cumulative, so there remains some uncertainty as to the effects of chronic exposure. The authors also note that rodents do not tolerate estrogen levels as high as humans experience during pregnancy, and thus what is toxic to a rat may not be toxic to a human. The review found some studies with statistically significant findings showing adverse health effects of EDCs, however they were countered by more numerous studies showing no observable effect for

similar endpoints. Goodman et al. notes that if low doses of BPA do indeed cause endocrine disrupting effects, then study results should be consistent, repeatable, and affect all biological areas that the endogenous hormones would affect. However, this is not what is seen in the review. The article concludes that exposure levels in most of the low-dose animal studies that do show adverse effects are much higher than what the most at-risk populations are exposed to, and therefore the weight of evidence does not support the hypothesis that low doses of BPA are associated with developmental or reproductive health outcomes in humans.[4]

A systematic review by Tourauda et al. (2011) found highly variable types and concentrations of endocrine disruptors in water sources. It was found that progestagens were the most abundant of the EDCs detected in rivers, having entered the aquatic environment in sewage effluent after being excreted by humans and animals in urine and feces. However, although concentrations of EDCs in these water sources vary both geographically and seasonally, they were overall very low, in the ng/L level before water treatment. Tourauda et al. described the main exposure route of environmental EDCs is through contaminated food and water, and concluded that progestagens and andandrogens are the most resistant to water treatment methods. Regarding the adverse human health effects of these compounds, Tourauda et al. found no consensus among scientists and no firm evidence of risk to human health. However, it was noted that education initiatives to increase public awareness of the impact of EDCs and pharmaceuticals in the environment would be a good first step to a more responsible approach to the use of EDCs in the environment.[3]

A cross-sectional study of French drinking water treatment plants conducted by Vulliet et al. (2011) found concentrations of levonorgestrel (a synthetic progestagen found in some hormonal contraceptives), progesterone, estradiol, and testosterone ranging from 1 ng/L to 10 ng/L in treated water. According to the study, progestagens and androgens seem resistant to most drinking water treatments, with concentrations in the ng/L range in final treated water samples not uncommon.

However, no EDCs were found to have concentrations higher than 11.6 ng/L. According to Vulliet et al., when compared to the amount of estrogens, progestagens, and androgens that we produce endogenously, these EDC concentrations have no detectable effects in humans. Vulliet et al. also notes, however, that the hormone contraceptive ingredient norethindrone was detected in 66% of final treated waters, with a median concentration of 2 ng/L but not exceeding 6.8 ng/L, and that a daily consumption of 10 ng/L of this compound may cause harmful effects. In light of this evidence, Vulliet et al. concludes that the risk of harmful health effects on adult humans from ingestion of EDCs in drinking water is very low, but that the relatively high proportion of norethindrone found in many samples may be a concern for public health and is worth monitoring.[5]

The French Agency for Food, Environmental and Occupational Health and Safety (Anses) hosted a two-day workshop on EDC exposures and potential impact on consumer health, and the report, written by Rousselle et al. (2013), outlines their recommendations. Some of the studies that were reviewed at this workshop showed EDC effects below the no observable adverse effect level of 5 mg/kg-d, while most studies showed no risk of harmful effects at low doses. The authors of the report declared that there is a need to enhance our knowledge of the pathways of toxicity that are involved in endocrine system disturbances. The authors recommend, for future hazard identification and risk assessment, the creation of a central database for surveillance and biomonitoring data for the European Union, a larger number of doses, covering lower dose regions, in future EDC toxicity studies, and the development of models for carcinogenic effects of EDCs. Additionally, they recommend that all risk assessments be based on weight-of-evidence reviews, and be wholly transparent to the public, and further collaboration and knowledge-sharing between countries and experts.[6]

Discussion

A thorough review of the scientific literature related to the risks of adverse health effects associated with endocrine disrupting compounds (EDC) in drinking water was conducted. Based on the evidence of this review, it is apparent that there is a significant lack of awareness of EDC-associated health effects at low, chronic doses, both among the public and the scientific community. In particular, these compounds need to be categorized and their toxicology examined independently in order to identify the hazards and exposure. EDCs are not uncommon in drinking water, but occur in very low concentrations, and present data suggests that this level of contamination is unlikely to result in detectable adverse health effects in humans.[2]

This evidence review has some limitations, however. There are significant gaps in the literature regarding endocrine disruptors in drinking water specifically, and none of the studies evaluated contained a complete list of EDCs found in water. Each study focused on a small number of compounds, and there are many more that populations are exposed to, but have not been studied. Additionally, some of these chemicals may have synergistic effects, amplifying physiological effects, and these interactions need to be studied to gain a full understanding of how these substances affect our bodies. Many of the studies reviewed in this document utilize urine samples as a means to measure exposure to EDCs, but this represents recent exposure only, and gives no insight into the effects of chronic exposure. The method of action of EDCs, especially those that modulate gene expression, can mean long latency at low doses, which makes them difficult to study. Categorization, toxicological studies, and studies with low-level, chronic exposure need to be conducted for each EDC in order for us to have a full understanding of their potential effects. The level of uncertainty surrounding this issue and the obvious potential for undesirable health outcomes from chronic exposure calls for use of the precautionary principle in public health.

Recommendations

Given the uncertainties surrounding EDC hazard and exposure data, and the severity of potential health effects from chronic exposure, it is recommended that a precautionary approach be implemented to prevent any unnecessary morbidity or mortality. More collaborative research efforts should be made to fill in exposure gaps, provide surveillance data, and make use of existing and proposed birth cohort studies. Exposure at critical periods of development also needs to be researched, in particular the perinatal period, where sexual differentiation is particularly sensitive to endocrine disruption.[1] These research initiatives should be undertaken while surveillance and testing of water sources and drinking water continues. Additionally, studies regarding health effects of EDCs should be done using the oral transmission route, as that is how humans are exposed to the compounds, and will take into account the effects of First Pass metabolism.

It has been shown that basic drinking water treatment will not eliminate all EDCs from water, especially estrogens and androgens, which are particularly resistant to treatment.[2] Some facilities have incorporated advanced water treatment methods, utilizing particle removal, ozone oxidation, and activated charcoal adsorption of the oxidation products. This has proven quite successful in the removal of industrial organic chemicals, pesticides, pharmaceuticals, and hormones[2], and should be implemented wherever there is a high-risk population, such as agricultural communities. Additionally, education initiatives should be implemented to raise public awareness of the potential health effects as a first step toward more responsible production, utilization, and disposal of EDCs in the environment.

Conclusion

As the use of EDCs in pharmaceuticals, agriculture, and industrial processes continues, public health will continue to face challenges associated with endocrine disrupting compounds and their potential health implications. Preventive strategies such as more collaborative research to fill in knowledge gaps for more accurate hazard identification, more advanced water treatment methods including ozone oxidation for at-risk populations, and education initiatives must be implemented to ensure that the risk of these health effects and their impact on the population are prevented.

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Appendix

Table 1. Summary Review Table of All Papers

Reference	Type of Study	Comments
Falconer et al. (2006)	Systematic Review	- Estrogens & progestins naturally secreted in women as part of their menstrual cycle and excreted in urine as conjugates - Major recent addition to EDCs excreted by women attributable to hormone contraceptives, particularly estrogen ethinylestradiol (excreted in urine) - Androgen concentrations in sewage effluent higher than estrogens, but lower potency - Large doses of diethylstillbestrol, administered to many women in the past for pharmacological reasons has been associated with adverse outcomes o Both girl and boy infants of mothers given this contraceptive showed reproductive abnormalities - Study on mice showed adverse reactions to stillbestrol were dose-

		dependent - Most ethinylestradiol more resistant to waste water treatment andonly 38-45% was removed - BPA found in German rivers from 0.5-16 ng/L - Steroid hormones found in German rivers from 0.2-5 ng/L - Drinking water supplies 4 ng or less per day of estradiol and equivalent estrogens - Pathological effects of stillbestrol seen at doses of 100 mg/d minimum - Conservative estimate that appr. one thousandth to one ten-thousandth of estrogen available to the body comes from drinking water - Concluded that any physiological effects of estrogen from drinking water will be undetectable in humans - Pesticides with EDC effects: o Atrazine (herbicide), ketoconazole (fungicide) o Infants born in agricultural communities with birth defects surrounding high pesticide use times - Remediation Recommendations: o Drinking water treatment increasingly using advanced oxidation o Combined particle removal, ozone oxidation, activated carbon adsorption o >99% of estrogen removed with ozone - Effective monitoring & treatment of drinking water will continue to be important for public health & safety
Phillips et al. (2008)	Risk Assessment	- Potential adverse effects in humans: 1) Infertility (fecundity, semen quality, endometriosis) 2) Abnormal prenatal & childhood development (spontaneous abortions, male repro.-tract abnormalities, altered sex ratios, precocious puberty, other birth defects) 3) Cancers of the prostate, breast, ovaries, endometrium, or testes - EDC: exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body - Eg. DDT, BPA, PCB - Physiological systems related to estrogen & sensitive to EDCs: o Brain & central nervous system o Cardiovascular system o Immune system o Reproductive & urogenital system (incl. sexual differentiation, development, & maturation) - Act by binding to hormone receptors & either mimicking hormones or inhibiting them from binding - Modify gene expression, long latency - Nongenomic steroid action also important in repro. processes like sperm activation & electrolyte fluid & transport in efferent duct of testis - Disruption of thyroid hormone another pathway for EDCs o Reduce T3/T4 production, release, binding to serum, decreases bioavailability of T4, glandular lesions - Other mechanisms of action of EDCs: 1) Inhibition of hormone synthesis, transport, metabolism 2) Activation of receptor through phosphorylation 3) Release of cellular complexes necessary for hormonal action - 2 major areas of uncertainty for EDCs: 1) Unknown adverse health effects 2) Extent of human exposure - Inverted U-shaped dose-response curve o Multiple hormone receptor subtypes, endogenous feedback loops o Represents net contribution of all cells involved in the process - Agricultural practices can cause water contamination with EDC pesticides or hormones to enhance livestock production (growth hormone) - Industrially generated EDCs are major involuntary exposure source, incl. BPA and PCB, and contaminate water - Cosmetic, pharmaceutical, and pesticide EDCs can find way into water via sewage or disposal & seepage or run-off - Identification & classification of EDCs difficult because many different types & classes

		o Risk characterization should be determined for each individual one - Insufficient evidence to fully characterize the risks posed to human health by any EDCs - Risk characterization limited by missing exposure data & focus in literature on persistent chemicals - Education & communication of potential risks important for implementation of precautionary principle - CEPA (1999) focuses on sustainable development and environmental protection, using precautionary principle & polluter pays principle as foundation for policy
Goodman et al. (2009)	Weight-of-Evidence Review	- long acknowledged that BPA could interact with human estrogen receptors - Recently BPA has been shown to act as an antagonist for the human androgen receptor - BPA has been demonstrated to be weakly estrogenic - early studies demonstrated a NOAEL of 50 mg/kg-d - no effects on reproductive or developmental endpoints that were consistently and repeatedly observed following low-dose BPA exposure in rodents - recent review of human biomonitoring studies found that urine levels are consistently low across studies o Estimates of typical total daily BPA intake were less than 0.1 µg per kilogram of body weight o Represent recent exposure, not cumulative - even the low-dose animal studies are generally examining levels of exposure many times those experienced by even the most-exposed people in the general population - rodents don't tolerate estrogen levels as high as we have during pregnancy - statistically significant findings in rodent studies exist, but are outnumbered and outweighed by studies that find no evidence for health effects of BPA on humans at low doses, and findings not consistent or repeatable - Lack of reproducability, robustness, and relevant exposure route strains the credibility of some studies showing health effects - need better design, oral exposure, & reproducability to elevate our concerns about EDC health effects - Weight of evidence does not support the hypothesis that low doses of BPA are associated with reproductive or developmental effects in humans
Tourauda et al. (2011)	Systematic Review	- Endocrine disruptors include: o Natural/synthetic hormones excreted from humans & animals, eventually reach water o Progestagens, androgens, some pesticides - 30-40% of potable drinking water comes from rivers - Pharmaceuticals & EDCs range from ng/L to low g/L in effluents & surface waters - Exposure concentrations variable with geography & season - Exposure route: consumption of contaminated water - Progestagens & andandrogens are most resistant to treatments - Hormones detected in low concentrations in drinking water (ng/L) - Levonorgestrel was detected at concentrations above the human therapeutic plasma level o But no firm evidence of risk to human health - Long-term retrospective study of high concentrations of synthetic estrogen diethylstilbestrol given to women in 1950s for therapies o Abnormalities in structure & function of reproductive organs - To date, no consensus among scientific community on what risk, if any, EDCs pose to human health Strategies to enhance public awareness of pharmaceutical & industrial impact on environmental health to stimulate more responsible production, use, and disposal of EDCs
Vulliet et al. (2011)	Cross-Sectional Study	- Levonorgestrel, progesterone, & testosterone found in treated water at concentrations from 1 ng/L to 10 ng/L

		- Progestagens & androgens seem resistant to most drinking water treatments - Contraceptive ingredient ethinylestradiol found in final drinking water with mean concentrations above 0.3 ng/L & max. conc. of 2.1 ng/L in Southern Germany - Natural hormones also detected in some drinking waters - Compared to what we produce, sampled concentrations of EDCs have no detectable effects - Risk for adult populations is low - Contraceptive ingredient norethindrone detected in 66% of drinking water sampled, with median conc. of 2 ng/L - Daily consumption of 10 ng/L of norethindrone may cause harmful effects o This may be a public health concern
Roussellea et al. (2013)	Meeting Report	- French Agency for Food, Environmental and Occupational Health and Safety (Anses) hosted a two day workshop on Endocrine Disruptors: Exposure and Potential Impact on Consumers Health - Some studies reviewed showed effects below the NOAEL (5 mg/kg-d) - there a need for obtaining a better knowledge of the pathways of toxicity involving endocrine perturbations - All evidence used for decision-making should be reviewed in a weight-of-evidence review - In the future, exposure studies should be done during critical windows, such as prenatal. - Risk assessment must be transparent - Recommendations: o the creation of a central database for surveillance and biomonitoring data o larger number of doses and especially covering lower dose regions in future toxicity studies o development of models for carcinogenic effects of EDCs o hazard and risk assessment across different critical time windows of sensitivity o more international collaboration and knowledge sharing