

REVIEW

CME CREDIT **EDUCATIONAL OBJECTIVE:** Readers will counsel their patients who are pregnant or of childbearing age about the risks associated with endocrine-disrupting chemicals

BELLA HARUTY, MPH, REHS
Los Angeles County Department of Public Health, Environmental Health Division
South Los Angeles District,
Los Angeles, CA

JULIE FRIEDMAN, MPH, CHES
Director, Iris Cantor-UCLA Women's Health Education and Research Center,
Los Angeles, CA

STEPHANIE HOPP, MHS, MS
Massachusetts General Hospital,
Department of Anesthesia, Critical Care and Pain Medicine

RYANE DANIELS, MPH
Tulane University,
New Orleans, LA

JANET PREGLER, MD
Director, Iris Cantor-UCLA Women's Health Center,
Los Angeles, CA

Reproductive health and the environment: Counseling patients about risks

ABSTRACT

Endocrine-disrupting chemicals (EDCs) are associated with reproductive complications such as infertility, pregnancy complications, poor birth outcomes, and child developmental abnormalities, although not all chemicals of concern are EDCs. Pregnant patients and women of childbearing age need reasonable advice about environmental contaminants and reproductive health.

KEY POINTS

Although EDCs primarily affect sex steroid hormone pathways, some can affect adrenal, thyroid, and other endocrine pathways.

Human-produced EDCs vary widely in their properties. Many, but not all, concentrate in fat, and some have a very long half-life.

Because it would be impossible to perform randomized, controlled trials of the health effects of the thousands of manufactured EDCs encountered in daily life, physicians should follow the precautionary principal when counseling patients: ie, tell them to avoid chemicals when possible, especially those that have proven or plausible health risks.

On the other hand, physicians need to keep in mind the economic hardships patients may face in switching to potentially safer products or foods and unavoidable exposures at work and at home.

A 28-YEAR-OLD WOMAN presents for routine follow-up of asthma. She has a 1-year-old son and is considering a second pregnancy. She says she read on the Internet that the US Food and Drug Administration recently banned baby bottles and “sippy” cups that contain bisphenol A (BPA), as recommended by the American Medical Association. She wonders if there are other sources of BPA and if they pose a health risk to her, her son, and possible future children.

Environmental toxins have been linked to pregnancy complications and poor birth outcomes. The past several decades have seen a significant rise in reproductive disorders such as early onset of puberty, low sperm count, and birth defects such as cryptorchidism and hypospadias.¹⁻⁴ These changes may be partly explained by other trends over time, such as older maternal age, rising incidence of obesity and maternal diabetes, and demographic changes that exacerbate health disparities. However, these well-recognized factors explain only some of the wide range of reproductive health problems that have been identified.

This review focuses on emerging evidence of the adverse reproductive effects of human-produced endocrine-disrupting chemicals (EDCs).

■ ENDOCRINE-DISRUPTING CHEMICALS ARE UBIQUITOUS

EDCs are exogenous substances that alter normal functioning of the endocrine system and consequently have the potential to cause adverse health effects in an intact organism and its progeny.^{2,3,5} Substances classified as EDCs are divided into two groups:

doi:10.3949/ccjm.83a.14070

TABLE 1

Information for patients: Tips for avoiding endocrine-disrupting chemicals

Endocrine-disrupting chemicals may affect how hormones work in our bodies. They are found throughout the environment, and cannot be completely avoided.

To reduce bisphenol A (BPA) exposure for infants

Breastfeed infants for at least 12 months when possible for overall health. If breastfeeding is not an option, it is important to use the formula recommended by your healthcare provider. But be aware of the following:

Liquid formula in cans contains BPA. A government study showed that powdered formula mix did not contain measurable amounts of BPA.

Use BPA-free containers to prepare infant formula.

As of 2009, the six major makers of infant bottles and feeding cups have not used BPA when manufacturing for the US market. Avoid older bottles and cups if possible.

BPA is found in many items made of plastic, including baby toys. Look for “BPA-free,” although this is not a guarantee, since in some cases BPA has been replaced by similar chemicals. Some but not all plastics marked with recycle code 7 may be made with BPA.

Do not heat foods in containers made with BPA. Hot or boiling liquids can transfer traces of BPA. When possible, avoid microwaving foods in plastic containers.

Liners of canned food containers are made with BPA. Rinse canned food well, and substitute fresh foods or food in other types of containers when possible.

Do not use cracked or scratched plastics to prepare or contain liquids or solid food. Cracked or scratched plastics that contain BPA are more likely to transfer BPA to liquids and foods.

To minimize pesticide exposure at home

Reduce or eliminate pests through cleaning, home repair, and trapping. Avoid chemical pesticides.

Eating fruits and vegetables is important for health

It is more important for health to eat fruits and vegetables than to avoid pesticides by not eating any. To minimize pesticide exposure:

Buy organic for foods with the highest levels of pesticides when grown nonorganically. These include apples, celery, bell peppers, peaches, strawberries, imported nectarines, grapes, spinach, lettuce, cucumbers, domestic blueberries, and potatoes.

Eat foods that are low in pesticides when conventionally grown, including onions, sweet corn, pineapples, avocado, cabbage, sweet peas, asparagus, mangoes, eggplant, kiwi, domestic cantaloupe, sweet potatoes, grapefruit, watermelon, and mushrooms.

Avoid phthalates

Phthalates are found in many personal-care products. Diethyl phthalate, dimethyl phthalate, and dibutyl phthalate are commonly used in deodorants, fragrances, hair sprays, hand and body lotions, and nail polish. Unfortunately, not all products that contain them may list them as an ingredient on the label. Read the label and avoid products containing phthalates. Look for “phthalate-free.”

Plastics with recycle code 3 may contain phthalates.

Avoid flame-retardant chemicals

Fire retardants are often used in polyurethane foam found in items such as couches, upholstered chairs, futons, car seats, crib mattresses, and nap pads.

Endocrine disruption is linked to compounds such as tris (1,3-dichloro-2-propyl) phosphate (TDCPP, also known as chlorinated tris and Firemaster) found in household products, including furniture, appliances, electronics, and baby products.

Reproductive difficulties and developmental delays are linked to some flame retardants.

Older foam products (ie, made before 2005) may be more hazardous.

Buy products without flame retardants.

Based on information in references 24–26.

- Human-produced compounds, such as pesticides, industrial solvents and lubricants, plastics (eg, BPA), and plasticizers (eg, phthalates)
- Phytoestrogens, which are naturally occurring plant compounds that bind to estrogen receptors. The major dietary source of phytoestrogens is soy.⁶ Many human-produced EDCs are lipid-

soluble. Some bioconcentrate in fat. The dietary route of exposure is the most common, primarily from fat-containing foods such as meats and seafood. Common predatory fish such as tuna and swordfish, as well as other large fish, are more likely to have high levels of EDCs accumulated from contaminated water.⁷ Water, air, soil, and dust in communities, schools, and workplaces may also carry EDCs.⁸

Some human-produced EDCs have a very long half-life and can remain in the environment for years or even decades. Because of their long half-life, some EDCs can “travel” and become part of the food chain, even in “pristine” areas where manufactured substances are not normally found.²

Women of childbearing age and pregnant women come in contact with EDCs on a daily basis. According to the Fourth National Report on Human Exposure to Environmental Chemicals, conducted by the US Centers for Disease Control and Prevention (CDC) in 2009, nearly all pregnant women in the United States have detectable serum levels of EDCs, including BPA, perchlorates, phthalates, polybrominated diphenyl ethers, and pesticides.⁹ Furthermore, BPA was found in more than 90% of the urine samples tested from random subsamples of 2,500 participants in the 2009 National Health and Nutrition Examination Survey report.¹⁰

■ EDCs AFFECT MULTIPLE PATHWAYS

Laboratory and animal research suggests that both manufactured and naturally occurring EDCs primarily affect sex steroid hormone pathways. However, some EDCs can affect adrenal, thyroid, and other endocrine pathways.

EDCs can potentially alter normal endocrine functioning by several mechanisms. They can bind to nuclear hormone receptors such as estrogen receptors, androgen receptors, progesterone receptors, thyroid hormone receptors, and peroxisome proliferator-activated receptor gamma. They can also bind to nonnuclear steroid hormone receptors (membrane estrogen receptors), nonsteroid receptors such as those for dopamine, serotonin, and norepinephrine, and orphan receptors such as aryl hydrocarbon receptor. In addition, some affect enzymatic pathways involved in steroid biosynthesis and metabolism and disrupt centralized endocrine pathways through positive and negative feedback.² There is also evidence that EDCs have epigenetic and transgenerational effects, as they seem to be able to influence DNA methylation and histone acetylation.¹¹

■ EVIDENCE OF HARM, LIMITATIONS OF EVIDENCE

In 2009, the Endocrine Society found convincing evidence that EDCs affect the male and female reproductive systems, breast health, oncogenesis, neuroendocrine function, thyroid function, metabolism, and cardiovascular health.² The first evidence of harm from EDCs came from long-term follow-up of randomized trials of diethylstilbestrol, a synthetic estrogen used as a pharmacologic agent between 1938 and 1971 to prevent miscarriage.¹²

In 2013, the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine issued a joint opinion report on exposure to toxic environmental agents. The report acknowledged that environmental toxins are ubiquitous and that they can negatively affect health from preconception through adult life. “[We] join leading scientists and other clinical practitioners in calling for timely action to identify and reduce exposure to toxic environmental agents while addressing the consequences of such exposure.”¹³

Because the effects of endocrine disruption can occur during fetal and embryonic development, EDC exposure before and during pregnancy is of special concern.¹⁴ Long-term effects of exposure to hazardous chemicals such as cadmium, lead, and mercury in breast milk can lead to negative consequences in adulthood.^{15,16}

Animal studies have pointed to the negative health effects of human-produced EDCs. For example, animals exposed to BPA have aberrant breast and genitourinary development and exhibit abnormal endometrial stimulation and early puberty.²

Despite these suggestive findings, the health effects of environmental toxins on humans are difficult to determine definitively. Evidence comes mainly from epidemiologic studies showing distribution of particular medical conditions based on different levels of exposure. More research is needed on human exposure to environmental toxicants and their effects.^{2,17,18} The National Children’s Study, a cohort collaborative study being conducted by the Environmental Protection Agency, CDC,

Nearly all pregnant women in the United States have detectable serum levels of EDCs, including BPA

TABLE 2

Resources on reproductive health and the environment

Information from professional associations, academic institutions, community organizations, and government agencies

Academic Pediatric Association

Research articles

American Society for Reproductive Medicine

Environment and reproduction special interest group membership information
Research articles
Smoking and infertility

Asian Communities for Reproductive Justice

Safer products and working conditions, specifically in nail salons

Association of Reproductive Health Professionals

Clinical publications
Continuing medical education
Research

California Healthy Nail Salon Collaborative

Improving the health and safety of workers and customers in nail salons

California Teratogen Information Service

Pregnancy risk information
Environmental exposures and reproductive health

Center for Science in the Public Interest

Steps to protect pregnant women from harmful bacteria and parasites in food

Collaborative on Health and the Environment

Chemicals, endocrine disruptors, and reproductive health concerns

Environmental Working Group

Index of chemicals with associated routes of exposure and health effects

March of Dimes

Environmental risks and pregnancy
Mercury and reproductive health

Moms Rising

Pesticides and pregnancy

National Institute of Environmental Health Science

How endocrine disruptors work and their effects

US Centers for Disease Control and Prevention

Effects of tobacco, pesticides, and lead on reproductive health and infertility
Diethylstilbestrol update

US Food and Drug Administration

Advice for parents on bisphenol A

University of California San Francisco Program on Reproductive Health and the Environment

Publications on reproductive health related to exposures at work, food and chemical exposure, and toxins in everyday living

Women for a Healthy Environment

Advice on eating habits, exercising, and avoiding certain chemicals for healthier, environmentally safe pregnancies

Women’s Health and the Environment

Information on avoiding polyvinyl chloride, styrene, and polycarbonate to maintain hormonal health

Women’s Voices for the Earth

Chemicals and reproductive health

and National Institutes of Health, is examining the effects of environmental exposures on more than 100,000 children across the United States, following them from before birth until age 21.¹⁹

THE PRECAUTIONARY PRINCIPLE

The precautionary principle is a fairly new concept in environmental science, although clinicians have been adhering to it for a long time. As proposed in a meeting of scientists, lawyers, policy makers, and environmentalists in 1998, “When an activity raises threats of

harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically.”²⁰

For example, studies show that breast milk in the United States commonly contains many chemicals that do not meet US Food and Drug Administration standards for baby food.^{15,16} Although medical ethics prohibits randomized clinical trials in humans to examine the potential harms of these chemicals, proponents of the precautionary principle advocate that it is reasonable to be concerned that these chemicals may be harmful.^{21–23}

Applying the precautionary principle: Recommendations for patients

Without categorizing all chemicals as toxicants, nor all toxicants as worrisome for reproductive health, physicians can provide access to a growing body of information about reasonable strategies to reduce risk.

Educating patients about potential risks of exposure needs to be tempered with an appreciation of the economic and social barriers to avoiding or reducing risks. Often, people do not make conscious decisions about exposure. Rather, they are unknowingly exposed or have no access to safe, equivalent alternatives. Substituting suspected or known harmful products with potentially safer ones can be financially prohibitive. Where a patient lives and works may result in unavoidable exposure to environmental toxins.

Nevertheless, there are simple, economical alternatives that reduce or eliminate exposure to EDCs (Table 1).^{24–26} These include avoiding plastic and metal containers that are not marked “BPA-free,” eating locally grown fruits and vegetables, controlling pests through frequent cleaning and trapping, and avoiding pesticides.

Additionally, the flame retardant tris (1,3-dichloro-2-propyl) phosphate may be an endocrine disrupter. It is found in numerous products for infants and young children, as well as in dust, automobiles, and furniture. Flame retardants are no longer used in infant clothing but may still be found in foam products such as upholstered furniture, automobiles, and children’s nap pads.^{27,28}

National organizations that provide resources for counseling women about human-produced EDCs as well as patient education materials are listed in Table 2.

CLINICAL CASE RESOLUTION

You counsel the patient that, although more research in humans is needed, because of safety concerns, avoiding exposing herself and her baby to BPA when possible is a reasonable approach. You review recommendations including avoiding BPA-containing plastics for food preparation (recycle code #7) and BPA-containing toys that might be mouthed by the baby, as well as minimizing the consumption of canned foods when possible. You further advise her to avoid products with flame retardants.

REFERENCES

- Sutton P, Giudice LC, Woodruff TJ. Reproductive environmental health. *Curr Opin Obstet Gynecol* 2010; 22:517–524.
- Diamanti-Kandarakis E, Bouguignon JP, Giudice LC, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev* 2009; 30:293–342.
- Friedrich MJ. Endocrine-disrupting chemicals. *JAMA* 2013; 309:1578.
- Schettler T. Environmental exposures, infertility, and related reproductive disorders: an update. October 2011. The Collaborative on Health and the Environment. www.healthandenvironment.org/infertility/peer_reviewed. Accessed March 9, 2016.
- Woodruff TJ, Carlson A, Schwartz JM, Giudice LC. Proceedings of the Summit on the Environmental Challenges to Reproductive Health and Fertility: executive summary. *Fertil Steril* 2008; 89:281–300.
- Cao Y, Calafat AM, Doerge DR, et al. Isoflavones in urine, saliva, and blood of infants: data from a pilot study on the estrogenic activity of soy formula. *J Expo Sci Environ Epidemiol* 2009; 19:223–234.
- Endocrine-disrupting chemicals. The Collaborative on Health and the Environment. Available at www.healthandenvironment.org/initiatives/learning/r/prevention. Accessed March 9, 2016.
- Environmental impacts on reproductive health: clinical proceedings. Association of Reproductive Health Professionals. www.arhp.org/uploadDocs/CPRHE.pdf. Accessed March 9, 2016.
- Fourth national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention (CDC). www.cdc.gov/exposurereport/pdf/FourthReport.pdf. Accessed March 9, 2016.
- Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. *Environ Health Perspect* 2011; 119:878–885.
- Anway MD, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors. *Endocrinology* 2006; 147(suppl 6):S43–S49.
- About DES. Centers for Disease Control and Prevention (CDC). www.cdc.gov/des/consumers/about/index.html. Accessed March 9, 2016.
- Exposure to toxic environmental agents. American Congress of Obstetricians and Gynecologists (ACOG). www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Health-Care-for-Underserved-Women/Exposure-to-Toxic-Environmental-Agents. Accessed March 9, 2016.
- Bergman A, Heindel JJ, Jobling S, Kidd KA, Zoeller RT. United Nations Environment Programme (UNEP). State of the science of endocrine disrupting chemicals: 2012. www.who.int/ceh/publications/endocrine/en/. Accessed March 9, 2016.
- Pohl HR, Hibbs BF. Breast-feeding exposure of infants to environmental contaminants—a public health risk assessment viewpoint: chlorinated dibenzodioxins and chlorinated dibenzofurans. *Toxicol Ind Health* 1996; 12:593–611.
- Abadin HG, Hibbs BF, Pohl HR. Breast-feeding exposure of infants to cadmium, lead and mercury: a public health viewpoint. *Toxicol Ind Health* 1997; 13:495–517.
- Bretveld RW, Thomas CM, Scheepers PT, Zielhuis GA, Roeleveld N. Pesticide exposure: the hormonal function of the female reproductive system disrupted? *Reprod Biol Endocrinol* 2006; 4:30.
- Mendola P, Messer LC, Rappazzo K. Science linking environmental contaminant exposures with fertility and reproductive health impacts in the adult female. *Fertil Steril* 2008; 89(suppl 2):e81–e94.
- National Institute of Health (NIH). National Children’s Study (NCS). www.nationalchildrensstudy.gov/Pages/default.aspx. Accessed March 9, 2016.
- Raffensperger C, Tickner J, editors. Protecting public health and the environment: implementing the precautionary principle. Washington, DC: Island Press; 1999:8.
- Woodruff TJ, Sutton P. The navigation guide systematic review

- methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environ Health Perspect* 2014; 122:1007–1014.
22. **Sutton P, Woodruff TJ.** Risk communication and decision tools for children's health protection. *Birth Defects Res C Embryo Today* 2013; 99:45–49.
 23. **Woodruff TJ.** Bridging epidemiology and model organisms to increase understanding of endocrine disrupting chemicals and human health effects. *J Steroid Biochem Mol Biol* 2011; 127:108–117.
 24. **National Institute of Environmental Health Sciences.** Bisphenol A (BPA). www.niehs.nih.gov/health/topics/agents/sya-bpa/index.cfm. Accessed March 9, 2016.
 25. **Environmental Working Group.** Shoppers guide to pesticides in produce. www.ewg.org/foodnews/. Accessed March 9, 2016.
 26. **Schettler T.** Human exposure to phthalates via consumer products. *Int J Androl* 2006; 29:134–139.
 27. **Betts KS.** Exposure to TDCPP appears widespread. *Environ Health Perspect* 2013; 121:a150.
 28. **Environmental Working Group.** Healthy home tips. www.ewg.org/research/healthy-home-tips/tip-4-avoid-fire-retardants. Accessed March 9, 2016.
-
ADDRESS: Julie Friedman, MPH, Director, Iris Cantor UCLA Women's Health Education and Research Center, 911 Broxton Avenue, Los Angeles, CA 90024; jfriedman@mednet.ucla.edu