

American Medical Women's Association and the Breast Cancer Fund

Position Paper on Endocrine Disruption and Breast Cancer Risk

Overview

The American Medical Women's Association and the Breast Cancer Fund are concerned about the increasing prevalence of endocrine disrupting compounds (EDCs) in consumer products and the environment. EDCs have been linked to health effects as far ranging as reproductive outcomes, breast cancer, obesity, thyroid disease, and neurodevelopmental and behavioral disorders. We explore the rapidly evolving science on EDCs, including concerns about low dose exposures and critical periods of development; approaches to reduce exposures to EDCs among patients and in health care settings; and tips for public education.

Introduction

Chemicals used in everyday products, such as plastics, cleaning products, cosmetics, and in industrial processes can affect human development, growth and hormone balance by mimicking, blocking or disrupting endogenous hormones. Increasingly, research has linked a subset of chemicals to disruption of the endocrine system, with effects on estrogens, androgens, thyroid hormones, and insulin. In many cases, these endocrine disrupting compounds (EDCs) exert their effects at exceptionally low doses—doses often not tested in traditional toxicological tests—and during critical periods including prenatal development, puberty and pregnancy.

In 2011, the American Medical Association adopted a policy recognizing bisphenol A (BPA) as an endocrine disruptor and urging clear identification of consumer products containing BPA, with particular attention to products targeted to sensitive populations.ⁱ In 2013, the AMA adopted a policy calling for Congress to modernize the Toxic Substances Control Act requiring manufacturers to provide safety data on chemicals and granting federal agencies the authority to regulate chemicals.ⁱⁱ The same year, the American Academy of Pediatrics issued a statement recommending that the U.S. chemicals management policy be updated to protect children, pregnant women, and other populations. They further recommended that pediatricians learn about chemicals in the environment and their effects on children's health, and advocate for policies that consider the vulnerabilities of children and pregnant women.ⁱⁱⁱ

In late 2013, the American College of Obstetrics and Gynecology issued a committee opinion stating that "Prenatal exposure to certain chemicals has been documented to increase the risk of cancer in childhood; adult male exposure to pesticides is linked to altered semen quality, sterility, and prostate cancer; and postnatal exposure to some pesticides can interfere with all developmental stages of reproductive function in adult females, including puberty, menstruation and ovulation, fertility and fecundity, and menopause." The committee urged federal and state agencies to take necessary action to ensure the safety of chemicals and called on its members to both address the consequences of exposures and to advocate for policies that identify and reduce exposures.

The State of the Evidence on Endocrine Disrupting Compounds

Endocrine-disrupting compounds (EDCs) are synthetic chemicals developed because of their useful properties in many common products, including plastics, pesticides and herbicides, personal care products, household cleaning products, flame retardants, and stain resistant and non-stick coatings. Secondary, often unanticipated, properties of these chemicals

include dispersal into our soil, dust, water resources and air, and subsequent uptake into wildlife and human bodies, where they exert effects that disrupt the delicate balance of the endocrine system.

How EDCs Work

EDCs can mimic, antagonize or completely disrupt particular endocrine pathways, often interacting with hormone receptors and altering cellular responses.^{iv,v,vi} Although most of the current research on EDCs focuses on mechanisms by which EDCs interrupt the interactions of hormones with traditional steroid receptors (ER, PR, AR), it is important to recognize that there are multiple mechanisms by which the EDCs may exert their effects. Emerging research suggests many EDCs affect more than one of these pathways.

Emerging themes in the research on EDCs

Three characteristics of EDCs distinguish them from many non-endocrine toxicants associated with various disease states: (a) serious effects during critical periods of development;^{vii} (b) low-dose effects;^{viii,ix} and (c) non-monotonic response curves.^x These are critical properties for understanding the scientific literature linking EDCs to disease, including breast cancer. They also are at the center of controversies related to the interpretation of certain studies, especially those that examine low-dose, early-life exposures to EDCs and their subsequent effects on health.

A 2013 report on breast cancer and the environment emphasized the need for an animal-to-human research paradigm to understand the effects of broadly defined environmental exposures on breast cancer, specifically.^{xi} This animal-to-human model is vital for studies of endocrine disruption more broadly as well. Many endocrine systems in humans are well conserved in animals, allowing study of the metabolism and distribution of suspected endocrine disruptors. The committee noted, “The integration of animal and human research offers the best opportunity to understand the contribution of environmental factors to breast cancer risk, the underlying mechanisms, and the potential for prevention strategies.”

Examples of EDCs

Diethylstilbestrol (DES)

One of the most striking examples of an effect of exposure to an EDC is the legacy of diethylstilbestrol (DES), a synthetic estrogen that was prescribed to prevent miscarriage from 1947 to 1970. DES was not effective at preventing miscarriage and it led to an increased incidence of rare vaginal cancers in the daughters.^{xii} Both the mothers who took the drug and their daughters who were exposed to DES in the womb have higher than average rates of breast cancer.^{xiii,xiv,xv,xvi}

Bisphenol A (BPA)

Animal studies also raise concerns about fetal environmental exposures to chemicals found in products we encounter daily. For instance, research suggests that maternal exposures to low doses of the endocrine disruptor BPA — found in household items including the linings of canned foods — can alter fetal mammary gland development.^{xvii,xviii,xix,xx,xxi} These changes

continue through puberty and can predispose female mice to later-life mammary tumors, raising concerns about their effects on human breast tissue.^{xxii}

Chemicals and hormones in food

A number of pesticides have hormone-disrupting properties. Atrazine, used in vast quantities on corn and other grains, contaminates ground water in the Midwest, and significantly alters the reproductive systems in wildlife. High levels of triazines (primarily atrazine) in contaminated waters have been associated with an increased risk of breast cancer,^{xxiii} and application of higher levels of mixed pesticides, including atrazine, has been associated with increased breast cancer in rural communities.^{xxiv} However, not all ecological studies support these associations.^{xxv} Animal studies indicate disrupted mammary gland development, disruptions in the communication between the pituitary and ovaries, and increased aromatase activity.

Hormones are used in dairy cows to increase milk productions and in beef cattle to add weight and fat to the meat. Recombinant bovine growth hormone (rGBH) and recombinant somatotropin (rBST) increase insulin-like growth factor levels,^{xxvi} though the epidemiological research on health outcomes is thus far inconclusive. Zeranol, the hormone given to beef cattle, is nearly as potent an estrogen as estradiol and diethylstilbestrol. It leads to breast tumor cell proliferation,^{xxvii} developmental changes in mammary glands,^{xxviii} and the development of abnormal cells even at levels below FDA allowances.^{xxix}

Mini-toolkit for public education

As the body of evidence continues to accumulate linking endocrine disruption to altered mammary gland development, early puberty, breast cancer, thyroid disease, obesity and infertility, physicians and other health care providers can educate the public and their own patients about ways to avoid chemicals linked to endocrine disruption. EDCs are found in everyday products including personal care products, household cleaners, food and beverage cans and containers, foods, and antibacterial soaps.

Eight tips:

- 1. Avoid synthetic fragrance. Choose personal care and household cleaning products that fully disclose all ingredients, including what's in "fragrance"—that single word on a label can contain dozens of chemicals, some of which, like phthalates, should be avoided.**
- 2. Choose cleaning products that tell you what's in them. Companies are not required to label the ingredients on cleaning products, so look for products made by companies that voluntarily disclose ingredients.**
- 3. Go fresh, organic and hormone-free. When possible, choose organic foods and hormone-free meat and dairy. Buying products grown organically reduces pesticide use, which is good for families, farmworkers and the environment. If organic is not possible, grow your own and look for pesticide-free options. The freezer section may offer less expensive organic options, especially in locations where fresh organics are less common. Hormones are not allowed for use in pork or poultry, so eating less beef and a variety of meats can reduce exposures the**

hormones used in cattle. Look for milk not treated with rBST, which is often available even when organic options are not.

4. **Kick the can. Limit consumption of canned foods until companies replace BPA-based can linings with safer alternatives. Instead, choose fresh or frozen options. Some companies have switched to BPA-free linings in cans and other containers-check labels. Avoiding BPA is especially important for women who are pregnant or nursing, given concerns about prenatal and early-life BPA exposure.**
5. **Limit the use of plastic. Go old-school with metal and glass, and never microwave in plastic. Some plastics are now BPA-free-check labels to find out.**
6. **Avoid antibacterial soaps. These soaps often contain triclosan, a thyroid hormone disruptor.**
7. **Avoid non-stick and stain resistant coatings on pans, furniture and carpeting. These products can contain carcinogenic and endocrine disrupting PFOA.**
8. **Avoid flame retardants. Choose snug fitting children's pajamas and furniture with naturally flame-resistant barrier materials, such as wool and cotton.**

For further information, including detailed references supporting this paper please visit www.breastcancerfund.org/clear-science.

References

ⁱ American Medical Association (2011). AMA adopts new policies at annual meeting. Available online: <http://www.ama-assn.org/ama/pub/news/news/2011-new-policies-adopted.page>. August 26, 2014.

ⁱⁱ American Medical Association (2013). AMA adopts new policies at interim meeting to improve health of nation. Available online: <http://www.ama-assn.org/ama/pub/news/news/2013/2013-11-19-ama-adopts-policies-at-interim-meeting.page>. August 26, 2014.

ⁱⁱⁱ American Academy of Pediatrics (2011). Policy Statement—Chemicals-Management Policy: Prioritizing Children's Health. *Pediatrics*, 127 (3): 983-990.

^{iv} De Coster, S., & van Larebeke, N. (2012). Endocrine-disrupting chemicals: associated disorders and mechanisms of action. *Journal of Environmental and Public Health*, 2012, 713696. doi:[10.1155/2012/713696](https://doi.org/10.1155/2012/713696)

^v Vandenberg L.N., Colborn T., Hayes T.B., Heindel J.J., Jacobs D.R. Jr, Lee D.H., Shioda T., Soto A.M., vom Saal F.S., Welshons W.V., Zoeller R.T. and Myers J.P. (2012). Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocr Rev.* 2012 Jun;33(3):378-455. doi: 10.1210/er.2011-1050.

^{vi} Schug, T. T., Janesick, A., Blumberg, B., & Heindel, J. J. (2011). Endocrine disrupting chemicals and disease susceptibility. *The Journal of Steroid Biochemistry and Molecular Biology*, 127(3-5), 204–215. doi:[10.1016/j.jsbmb.2011.08.007](https://doi.org/10.1016/j.jsbmb.2011.08.007)

^{vii} Barker, D. J. P. (2004). The developmental origins of adult disease. *Journal of the American College of Nutrition*, 23(6 Suppl), 588S–595S.

^{viii} Melnick, R., Lucier, G., Wolfe, M., Hall, R., Stancel, G., Prins, G., ... Kohn, M. (2002). Summary of the National Toxicology Program's report of the endocrine disruptors low-dose peer review. *Environmental Health Perspectives*, 110(4), 427–431. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11940462>

^{ix} Vandenberg L.N., Colborn T., Hayes T.B., Heindel J.J., Jacobs D.R. Jr, Lee D.H., Shioda T., Soto A.M., vom Saal F.S., Welshons W.V., Zoeller R.T. and Myers J.P. (2012). Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocr Rev.* 2012 Jun;33(3):378-455. doi: 10.1210/er.2011-1050.

-
- ^x Vandenberg L.N., Colborn T., Hayes T.B., Heindel J.J., Jacobs D.R. Jr, Lee D.H., Shioda T., Soto A.M., vom Saal F.S., Welshons W.V., Zoeller R.T. and Myers J.P. (2012). Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocr Rev.* 2012 Jun;33(3):378-455. doi: 10.1210/er.2011-1050.
- ^{xi} Interagency Breast Cancer and Environmental Research Coordinating Committee, 2013. Breast Cancer and the Environment: Prioritizing Prevention. Available online: http://www.niehs.nih.gov/about/assets/docs/ibcercc_full_508.pdf. August 28, 2014.
- ^{xii} Giusti, R., Iwamoto, K., & Hatch, E. (1995). Diethylstilbestrol revisited: A review of the long-term health effects. *Annals Intern Med*, 122, 778–788.
- ^{xiii} Colton, T., Greenberg, E., Noller, K., Resseque, L., Van Bennekom, C., Heeren, T., & Zhang, Y. (1993). Breast cancer in mothers prescribed diethylstilbestrol in pregnancy. Further follow-up. *J Am Med Assoc*, 269, 2096–2100.
- ^{xiv} Titus-Ernstoff, L., Hatch, E., Hoover, R., Palmer, J., Greenberg, E., Ricker, W., ... Hartge, P. (2001). Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *Br J Cancer*, 84, 126–133.
- ^{xv} Troisi, R., Hatch, E., Titus-Ernstoff, L., Hyer, M., Palmer, J., Robboy, S., ... Hoover, R. (2007). Cancer risk in women prenatally exposed to diethylstilbestrol. *Int J Cancer*, 121, 356–360.
- ^{xvi} Hilakivi-Clarke, L., & De Assis, S. (2006). Fetal origins of breast cancer. *Trends Endocrinol Metab*, 17, 340–348.
- ^{xvii} Muñoz-de-Toro, M., Markey, C., Wadia, P., Lague, E., Rubin, B., Sonnenschein, C., & Soto, A. (2005). Perinatal exposure to bisphenol-A alters peripubertal mammary gland development in mice. *Endocrinology*, 146, 4138–4147.
- ^{xviii} Vandenberg, L., MV, M., & PH, W. (2007). Exposure to environmentally relevant doses of the xenoestrogen bisphenol-A alters development of the fetal mouse mammary gland. *Endocrinology*, 148, 116–127.
- ^{xix} Markey, C., Luque, E., Munoz-de-Toro, M., Sonnenschein, C., & Soto, A. (2001). In utero exposure to bisphenol A alters the development and tissue organization of the mouse mammary gland. *Biol Reprod*, 65, 1215–1223.
- ^{xx} Soto, A., Vandenberg, L., Maffini, M., & Sonnenschein, C. (2008). Does breast cancer start in the womb. *Basic Clin Pharmacol Toxicol*, 102, 125–133.
- ^{xxi} Ayyanan, A., Laribi, O., Schuepbach-Mallepell, S., Schrick, C., Gutierrez, M., Tanos, T., ... Brisken, C. (2011). Perinatal exposure to bisphenol a increases adult mammary gland progesterone response and cell number. *Molecular Endocrinology*, 25(11), 1915–1923.
- ^{xxii} Murray, T., Maffini, M., Ucci, A., Sonnenschein, C., & Soto, A. (2007). Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol A exposure. *Reprod Toxicol*, 23, 383–390.
- ^{xxiii} Kettles MA, Browning SR, Prince TS, et al. (1997). Triazine herbicide exposure and breast cancer incidence: An ecological study of Kentucky counties. *Environ Health Perspect*, 105:1222-1227.
- ^{xxiv} Muir, K., Rattanamongkolgul, S., Smallman-Raynor, M., Thomas, M., Downer, S., & Jenkinson, C. (2004). Breast cancer incidence and its possible spatial association with pesticide application in two counties of England. *Public Health*, 118(7), 513–520.
- ^{xxv} Hunter, L., Gadbury, G., & Huang, Y. (2008). Atrazine exposure and breast cancer incidence: an ecologic study of Missouri counties. *Toxicol Environ Chem*, 90, 367–376.
- ^{xxvi} Collier, R., Miller, M., McLaughlin, C., Johnson, H., & Baile, C. (2008). Effects of recombinant bovine somatotropin (rbST) and season on plasma and milk insulin-like growth factors I (IGF-I) and II (IGF-II) in lactating dairy cows. *Domest Anim Endocrinol*, 35, 16–23.
- ^{xxvii} Leffers H, Naesby M, Vendelbo B, et al. (2001). Oestrogenic potencies of zeranol, oestradiol, diethylstilbestrol, bisphenol-A and genistein: Implications for exposure assessment of potential endocrine disrupters. *Hum Reprod*, 16:1037-1045.
- ^{xxviii} Sheffield, L., & Welsh, C. (1985). Zeranol (B-resorcylic acid lactone), a common residuous component of natural foodstuffs, stimulates developmental growth of the mouse mammary gland. *Cancer Lett*, 28, 77–83.
- ^{xxix} Liu S, Lin YC (2004). Transformation of MCF-10A human breast epithelial cells by zeranol and estradiol-17B. *Breast J*, 10:514-521.