# Environmental toxicants: hidden players on the reproductive stage

Linda C. Giudice, M.D., Ph.D.

Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, California

A growing body of evidence suggests that environmental contaminants, including natural gas, endocrine-disrupting chemicals, and air pollution, are posing major threats to human reproductive health. Many chemicals are in commonly used personal care products, linings of food containers, pesticides, and toys, as well as in discarded electronic waste, textile treatments, and indoor and outdoor air and soil. They travel across borders through trade, food, wind, and water. Reproductive and other health effects can be incurred by exposures in utero, in the neonatal or adolescent periods, or in adulthood and can have transgenerational effects. Most chemicals do not undergo the level of evaluation for harm that pharmaceuticals, e.g., do, and they are rarely seen or seriously considered as a danger to human health. Herein, the burden of exposures, challenges in assessing data and populations at risk, models for evaluating harm, and mechanisms of effects are briefly reviewed, ending with a call to action for reproductive health care professionals to advocate for further research, education, and chemical policy reform for the health of this and future generations. (Fertil Steril® 2016;106:791–4. ©2016 by American Society for Reproductive Medicine.)

**Key Words:** Reproduction, endocrine disrupting chemicals, environmental toxicants

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The American Society for Reproductive Medicine and other professional societies including the American College of Obstetricians and Gynecologists (ACOG; www.acog.org), Royal College of Obstetricians and Gynecologists (RCOG; www.rcog.org), International Federation of Gynecologists and Obstetricians (FIGO) (1), World Health Organization (WHO)/United National Environmental Programme (UNEP) (www.who.int/ceh/publications/endocrine/en/), and The Endocrine Society (2) have made formal statements that the environment can adversely affect human reproductive health. For this supplement on Environment and Reproduction, I asked colleagues in reproductive medicine, science, and toxicology to think critically about new knowledge accrued over time, as the science continues to unfold about specific environmental contaminants—natural gas, endocrine-disrupting chemicals (EDCs), and outdoor air pollution—posing major challenges to human reproductive health. Herein, the authors have focused on germ cells, gonadal steroidogenesis, sperm quality, female and male fertility, placental function, pregnancy outcomes, polycystic ovarian syndrome, endometriosis, uterine fibroids, and menopause. They found supporting data for adverse impacts on some processes and conflicting data for others, and where possible they describe underlying mechanisms or plausible mechanisms for the results observed. Although nonhuman animal data overwhelmingly support environmental toxicants as detrimental to reproductive tract development and function (2), human data are challenging because of inherent limitations of epidemiologic and clinical studies. To give context to the papers that follow in this supplement, in this preface I present a brief overview of the magnitude of the burden that confronts human reproductive health, insights into EDCs and their mechanisms of action relevant to reproduction, and some challenges in experimental and epidemiologic studies in the reproductive environmental health space. I conclude with an eye to the future and a call for action to protect the reproductive health and capacity of this and subsequent generations.

## GLOBAL HEALTH TRENDS AND ENVIRONMENTAL CHEMICALS

A growing body of scientific evidence suggests that reproductive health and ultimately reproductive capacity are under strain globally. Indicators of such adversity over the past 60 years include increased rates of obesity, cardiovascular disease, hormone-dependent cancers, developmental disorders, chronic childhood diseases, early pubertal onset, poor birth outcomes, altered sex ratios, and longer time to pregnancy (3). Because these changes have occurred in a relatively short time frame, they are unlikely to be explained solely by genetic

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Reprint requests: Linda C. Giudice, M.D., Ph.D., Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, California (E-mail: linda.giudice@ucsf.edu).

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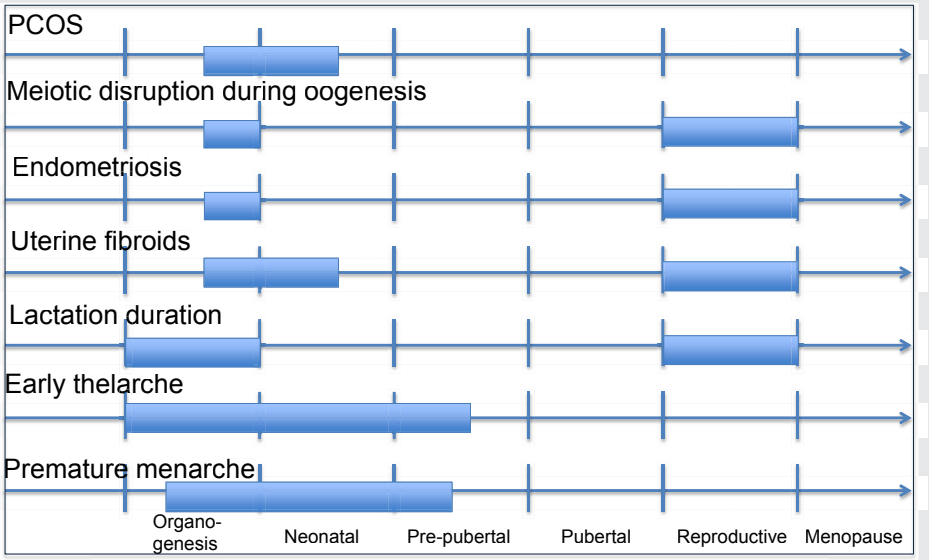
**FIGURE 1**




Sensitive developmental periods when exposures to endocrine-disrupting chemicals greatly increase the risk of female reproductive disorders. Data are derived from studies conducted in mice, rats, lamb, sheep, and humans. Adapted from Crain et al. [3], with permission. PCOS = polycystic ovary syndrome.

*Giudice. Environmental toxicants. Fertil Steril 2016.*

mutations, therefore warranting consideration of other causes, including the environment, i.e., environmental toxicants (chemicals and heavy metals) and indoor and outdoor air pollution (1).

Chemical production increased 23.5-fold from 1947 to 2007, and in 2012 in the U.S. alone, 9.5 trillion pounds of industrial chemicals (e.g., pesticides, plastics, and chemicals in drugs and personal care products) were domestically manufactured or imported, amounting to ~30,000 pounds/person (www2.epa.gov). In the face of limited safety testing and ethically impermissible randomized controlled trials in people to determine the safety of even very low doses (parts per billion) of environmental chemicals, they have been characterized to "act like uncontrolled medicines" for humans (4).

Environmental chemicals cross borders through trade, food, wind, and water, and individuals are exposed through ingestion, transdermally, inhalation, and absorption through mucus membranes. Effects on reproductive (and other health) outcomes of these agents depend on timing of exposures (critical "windows of susceptibility" such as in utero, adolescence, adulthood), dose, duration of exposure, and interactions with other chemicals, as mixtures of chemicals are found in all populations tested (1, 2). In a study of pregnant women representative of the U.S. population, contaminants were ubiquitously found and included environmental tobacco smoke, lead, mercury, phthalates, bisphenol A, perfluorinated compounds, and perchlorate (http://ehp.niehs.nih.gov/wp-content/uploads/119/6/ehp.1002727), underscoring the magnitude of the issue potentially affecting reproductive health. Figure 1 shows windows of susceptibility for several reproductive disorders wherein chemical exposures result in reproductive dysfunction.

## ENDOCRINE-DISRUPTING CHEMICALS

Endocrine-disrupting chemicals have received by far the greatest focus, because of their widespread use and broad exposures (2). EDCs are chemicals or mixtures of chemicals that interfere with any aspect of hormone action at any time of development and/or during the life course. These include pesticides (e.g., dichlorodiphenyltrichloro-ethane [DDT], chlorpyrifos, atrazine, 2,4-dichlorophenoxyacetic acid [2,4-D]), children's products (containing lead, phthalates, cadmium), food contact material (e.g., linings of cans or plastic bottles with bisphenol A, phthalates, phenol), electronics and building materials (e.g., brominated flame retardants), personal care products and tubing (e.g., phthalates), antibacterials (e.g., triclosan), and textiles and clothing (e.g., perfluorochemicals) (2). Emerging evidence supports EDCs as obesogens, diabetogens, reproductive disrupters, thyroid disrupters, and neurodevelopmental disrupters (2).

There is a connection between adult diseases (e.g., obesity, cardiovascular disease, type 2 diabetes, some cancers, neurodevelopmental abnormalities, mental illnesses, impaired fertility, poor pregnancy outcomes, and urogenital abnormalities) and preconceptual, periconceptual, and prenatal environmental exposures (4). Environmental