REPRODUCTIVE TOXICOLOGY

Endocrine disruption and reproductive disorders: impacts on sexually dimorphic neuroendocrine pathways

Heather B Patisaul

Department of Biological Sciences, Center for Human Health and the Environment, North Carolina State University, Raleigh, North Carolina, USA

Correspondence should be addressed to H B Patisaul; Email: hbpatisa@ncsu.edu

This paper forms part of a special section on Reproductive toxicology. The guest editors for this section were Dr Adam Watkins (The University of Nottingham, UK) and Dr Aileen Keating (Iowa State University, IA, USA)

Abstract

We are all living with hundreds of anthropogenic chemicals in our bodies every day, a situation that threatens the reproductive health of present and future generations. This review focuses on endocrine-disrupting compounds (EDCs), both naturally occurring and man-made, and summarizes how they interfere with the neuroendocrine system to adversely impact pregnancy outcomes, semen quality, age at puberty, and other aspects of human reproductive health. While obvious malformations of the genitals and other reproductive organs are a clear sign of adverse reproductive health outcomes and injury to brain sexual differentiation, the hypothalamic-pituitary-gonadal (HPG) axis can be much more difficult to discern, particularly in humans. It is well-established that, over the course of development, gonadal hormones shape the vertebrate brain such that sex-specific reproductive physiology and behaviors emerge. Decades of work in neuroendocrinology have elucidated many of the discrete and often very short developmental windows across pre- and postnatal development in which this occurs. This has allowed toxicologists to probe how EDC exposures in these critical windows can permanently alter the structure and function of the HPG axis. This review includes a discussion of key EDC principles including how latency between exposure and the emergence of consequential health effects can be long, along with a summary of the most common and less well-understood EDC modes of action. Extensive examples of how EDCs are impacting human reproductive health, and evidence that they have the potential for multi-generational physiological and behavioral effects are also provided.

Reproduction (2021) **162** F111–F130

Introduction: reproductive disorders and chemical exposures

Human reproductive health is in trouble. The need for assisted reproductive technology, rates of reproductive cancers, malformations, and similar adversities continue to rise (Swan & Colino 2021). All bodies are also continuously polluted with hundreds if not thousands of chemicals coursing through our tissues and cells every day, including the human placenta and the unborn (Ragusa *et al.* 2021, Wang *et al.* 2021). Are these phenomena related? Extensive evidence from across the globe suggests that they are. Although it can be difficult to explicitly link specific chemical exposures to specific reproductive outcomes in humans, the warning signs that show reproductive health is declining as chemical contamination of our environment and ourselves increases, particularly in the last 20–30 years, are irrefutable and concerning. This chapter summarizes this evidence and explores the potential

mechanisms by which this occurs with a specific focus on the development and function of the reproductive neuroendocrine system.

Adverse reproductive trends potentially linked to chemical exposures are numerous. One of the most highly publicized is reduced sperm counts in men, which have declined by half in the past 40–50 years (Carlsen *et al.* 1992, Swan *et al.* 2000, Geoffroy-Siraudin *et al.* 2012, Mínguez-Alarcón *et al.* 2018, Sengupta *et al.* 2018). Among young Swiss men, only 38% have sperm concentration, motility, and morphology values that meet the WHO semen reference criteria (Rahban *et al.* 2019). A phenomenon first thought confined to Western populations, the multi-decadal decline in sperm count and quality is now also reported in Africa (Sengupta *et al.* 2017). Incidence of testicular germ cell cancer, cryptorchidism and hypospadias are rising (Toppari *et al.* 2010, Manfo *et al.* 2014), particularly in Nordic countries and other Caucasian populations, signifying a multifaceted decline in male reproductive health.

There are also hints that couple fecundity is declining, with an estimated 10–15% of couples experiencing conception difficulties, but it is extraordinarily difficult to identify its causal factors (Snijder *et al.* 2012, Buck Louis 2014). Although birth rates in the United States for women aged 20–34 years are falling, elective postponement is a significant driver of that trend, making impacts of chemical exposures difficult to assess. The industrial chemical TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) has dose-dependently been linked to causing longer time to pregnancy in women living in the heavily polluted community of Seveso, Italy (Eskenazi *et al.* 2010), and there is some evidence that other common pollutants may have similar effects (Wesselink *et al.* 2018, Kim *et al.* 2019). Adverse pregnancy outcomes are also increasing, including preterm birth which, in the United States, has been rising for years and exceeded 10% in 2018 (Martin *et al.* 2019). Disgracefully, it is among the highest in the developed world, disproportionately impacts people of color, and has been linked, at least in part, to air, agricultural and industrial pollution common in low-income communities (Stieb *et al.* 2012, Burris & Hacker 2017, Ling *et al.* 2018).

Female reproductive development, aging, and health is also suffering. According to the American Cancer Society (<https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html>), in the US women, breast cancer rates have risen to one in eight, and it is now the second most common cancer among the US women. A 2000 study of nearly 45,000 pairs of twins from Sweden, Denmark, and Finland concluded that the environment, not genetics, played a principal role in sporadic cancers of the breast, female reproductive system, and prostate (Lichtenstein *et al.* 2000). Exposure to dichloro-diphenyl-trichloroethane (DDT), bisphenol A (BPA), and other pollutants have long been suspected to be contributory to rising rates of breast cancer (Davis *et al.* 1993, Cohn *et al.* 2015, Rodgers *et al.* 2018), and there is growing interest in understanding how combined chemical exposures might heighten breast cancer risk (Calaf *et al.* 2020). It is now irrefutable that aspects of female puberty are advancing (Herman-Giddens 2006, Bourguignon *et al.* 2016, Boeyer *et al.* 2018, Fudvoye *et al.* 2019). In the United States, the median age of breast development and sexual precocity has steadily advanced, especially among minority populations (Herman-Giddens *et al.* 1997, Partsch & Sippell 2001), a phenomenon that has negative long-term effects on sexual health (Ibitoye *et al.* 2017). Similar trends have been noted in Europe and among children adopted from developing countries by Western parents (Proos *et al.* 1991, Parent *et al.* 2003, Aksglaede *et al.* 2009). It is less clear if puberty is also advancing in boys (Ohlsson *et al.* 2019, Reinehr & Roth 2019).

Undoubtedly, the causal factors underlying these and other adverse reproductive health trends for men,

women, and couples are complex and multifaceted, but the rapidity of their increased prevalence unequivocally signifies that the primary drivers are environmental. Of these, because the reproductive system is so heavily dependent on steroid and other hormones to develop and function normally throughout life, of greatest concern are chemicals that have the capacity to act on or disrupt endocrine action, a group collectively called endocrine-disrupting compounds (EDCs) (Gore *et al.* 2015). It was recently estimated that the economic costs of male reproductive disorders and other diseases in men associated with EDC exposure exceed €15 billion annually in the European Union (Hauser *et al.* 2015). Phthalates and flame retardants were identified as particularly problematic. Similar work has estimated that the burden of these and other EDC-related diseases including intellectual disability, obesity, and neurodevelopmental disorders cost the European Union upwards of €160 billion annually (Bellanger *et al.* 2015, Trasande *et al.* 2015). There is also emerging concern that assisted reproductive efforts are compromised in women with higher body burdens of EDCs including phthalates and bisphenols (Al-Saleh *et al.* 2019, Jin *et al.* 2019, Mínguez-Alarcón *et al.* 2019, Shen *et al.* 2020). Thus, EDCs are likely contributing to a wide range of reproductive maladies in both sexes, along with the extensive emotional, physical and monetary health care costs related to them. When, to how many chemicals, and at what dose levels individuals have been exposed matters in terms of long-term reproductive health risks. Unfortunately, since the 1940s, our collective exposures have only steadily increased with no sign of abating.

Our polluted selves

Chemicals are the words of complex conversations in nature. All living things evolved in a stew of exogenous chemicals, many of which have endocrine action and/or toxicity in extant vertebrates. For example, plants and animals generate potent neurotoxins, including venoms and poisons, for both predatory and defensive purposes. CYP enzymes, required for steroid hormone synthesis and to metabolize toxins, appear to have evolved as a defense against botanical poisons and then repurposed over evolutionary history (Gonzalez & Nebert 1990). Even GABA, the primary inhibitory neurotransmitter of the brain, is an ancient molecule and has a role in plant communication, particularly when the plant is stressed (Ramesh *et al.* 2015). Plants produce numerous steroids and sterols, most notably the brassinosteroids and phytoestrogens, for a variety of purposes. Not surprisingly, some are hormonally active in vertebrates, including humans (Bishop & Koncz 2002). Notably, some species, particularly those living in perilous environments, evolved mechanisms to leverage endocrine active plant-produced compounds as potent signals of environmental quality and, therefore, optimal

times to invest in reproduction. In that sense, 'endocrine disruption' could enhance fitness in hard times (e.g. by suppressing ovulation) or (by enhancing puberty, fertility, or similar) in abundant times. Humans also took advantage of the biological activity of botanicals in traditional and ancient medicine for a variety of purposes including manipulation of reproductive health including assisted labor and elective miscarriage (Kamatenesi-Mugisha & Oryem-Origa 2007, Yazbek *et al.* 2016, Mbuni *et al.* 2020). This chemical exchange long conferred evolutionary advantage and heightened fitness. A preliminary form of 'endocrine disruption', in some sense, this evolved interplay also signifies how vulnerable our bodies can be to environmental signals including exposure to exogenous chemicals.

Unfortunately, chemicals of our own making are leveraging those evolved relationships to compromise our reproductive health. We blithely eat, breathe, and absorb thousands of chemicals all day, every day, with little to no awareness of their existence, let alone knowledge about their biological activity or potential toxicity. There is no way to know how many chemicals humans have invented or are in commercial use, but there are over 167 million in the CAS Registry, a database maintained by the American Chemical Society, and close to 90,000 on the Environmental Protection Agency's (EPA) inventory of substances regulated under the Toxic Substances Control Act (TSCA). The vast majority of chemicals in use commercially have not undergone any toxicity testing of any kind. They better our lives in myriad ways and have a wide range of applications including use as plasticizers, surfactants, disinfectants, food preservatives, cleaners, degreasers, fire retardants, solvents, and fragrances. Some have the capacity to interfere with the development and function of the endocrine system and, consequently, reproductive function.

Humans are now born pre-polluted with hundreds to thousands of anthropogenic chemicals (Wang *et al.* 2016). A landmark study, conducted by the Environmental Working Group in 2005, identified 287 industrial chemicals in umbilical cord blood. A follow-up 2009 study focusing on infants of color confirmed the ubiquity of prenatal pollution. Subsequent studies by multiple groups have repeatedly found harmful chemicals including pesticides and biocides, flame retardants, and per- and polyfluoroalkyl substances (PFAS) in maternal serum and cord blood, with levels sometimes higher in fetal than maternal blood (Wang *et al.* 2016, van de Bor 2019, Wang *et al.* 2021). The Centers for Disease Control's (CDC) National Biomonitoring Program (accessible at: <http://www.cdc.gov/nchs/nhanes/index.htm>) regularly assesses more than 300 environmental chemicals in Americans and by 2009 indicated universal exposure to many. Significantly, nearly all pregnant women in the United States have at least 43 chemicals with known toxicity in their bodies including polybrominated

diphenyl ethers (PBDEs) and other brominated flame retardants, some polychlorinated biphenyls (PCBs) and PFAS, organochlorine pesticides including DDT and its metabolites, BPA, perchlorate, and a variety of phthalates (Woodruff *et al.* 2011). All 43 have well-documented experimental evidence of toxicity or endocrine disruption and have repeatedly been linked to human health consequences including adverse birth outcomes, childhood morbidity, reproductive cancer risk, and reproductive abnormalities (Wang *et al.* 2016). Even though some have been phased out of use (e.g. PCBs, DDT, PBDEs), they remain in all of us because their use was so widespread, and they are environmentally persistent. The rapidly expanding catalog of PFAS will also be with us for years and centuries to come. Thus, our 'exposome', which is the totality of our bodily exposures, remains poorly defined and easily contains thousands of chemicals (Wishart *et al.* 2015, Vermeulen *et al.* 2020).

The earliest evidence that EDCs could adversely impact reproduction largely came from wildlife studies in the 1970s and 1980s including seminal work by Charles Broley, Theo Colborn and Louis Guillette Jr., who linked exposure to DDT, PCBs, and other persistent organic pollutants to reduced fertility in birds, genital abnormalities in alligators, and feminization of numerous species of fish (Leatherland 1992, Guillette *et al.* 1994, 1995, Beans 1997, Semenza *et al.* 1997). Around the same time, the clearest evidence that endocrine disruption is plausible in humans emerged from the tragic and misguided use of the potent synthetic estrogen diethylstilbestrol (DES) in pregnancy. Initially prescribed to prevent miscarriage (for which it was ineffective (Reed & Fenton 2013)), it was ultimately dispensed to upwards of 6 million pregnant women in the United States to enhance fetal weight gain (Smith 1948, Karnaky 1953, Kuchera 1971, Palmlund 1996). It was also used as a growth promoter in chicken, cattle, and other livestock, and even used as an ingredient in shampoos, soaps and other personal care products. Human use was suspended in 1971 when prenatal exposure was linked to an extremely rare type of cervicovaginal clear-cell adenocarcinoma (CCAC) in young women (Herbst *et al.* 1970, 1971). Other uses were phased out years later. In women, prenatal DES exposure has subsequently been linked to vaginal dysplasia, vaginal and cervical adenosis, abnormalities of the cervix, vagina, and uterus, reduced fertility, and greater risk of ectopic pregnancy, late spontaneous abortions, and premature delivery (Reed & Fenton 2013). DES sons have elevated rates of urogenital malformations, undescended testes, testicular cancer, and poor sperm quality (Gill *et al.* 1976, Stenchever *et al.* 1981, Wilcox *et al.* 1995, Palmer *et al.* 2005).

These and other examples were detailed in the seminal 1996 book *Our Stolen Future, Are we Threatening Our Fertility, Intelligence and Survival? – A Scientific Detective*

Story written by Colborn and colleagues, that argued EDCs were most certainly impacting the reproductive capability of wildlife and, by extension, humans and could impact reproductive health for generations. The quantity of experimental and epidemiologic evidence linking EDC exposure with compromised human reproductive health has subsequently compounded, leading the WHO and the United Nations Environmental Programme to conclude in its 2012 state of the science report that 'Exposure to EDCs could impair the health of our children and their children (WHO/UNEP 2012)'. The UC San Francisco Program on Reproductive Health and the Environment maintains a database of Professional Statements from health and medical organizations regarding the risks industrial chemicals pose to human health (accessed Oct. 10, 2020; <https://prhe.ucsf.edu/professional-statements-database>) and, as of 2016, had cataloged similarly cautionary statements from the American Congress of Obstetricians and Gynecologists, the International Federation of Gynecology and Obstetrics and the Endocrine Society, among others.

Endocrine disruption defined

There are many working definitions of what constitutes an EDC, some of which are presented in Table 1. The Endocrine Society defines them simply as: chemicals that mimic, block, or interfere with hormones in the body's endocrine system (Diamanti-Kandarakis *et al.* 2009, Gore *et al.* 2015). Others require evidence of an adverse effect on a whole animal. Because our chemical regulatory framework was built decades

ago to detect overt poisons and chemicals that cause lethality or cancer, it has struggled to identify a common working definition. EDCs challenge keystone principles of toxicology, including our understanding of what constitutes an 'adverse' effect and the long-held axiom 'the dose makes the poison'. EDCs are not poisons *per se* (most are not lethal, even at high doses), but rather something else entirely (Schug *et al.* 2016, Demeneix *et al.* 2020). The lack of consensus on how EDCs should be defined (Zoeller *et al.* 2014) has hindered efforts to identify a common list of EDCs. In 2018, the Danish Centre on Endocrine Disruptors published a list (http://cend.dk/files/DK_ED-list-final_2018.pdf) identifying nine chemicals that meet the WHO's definition of an EDC (Table 2) and four others suspected of meeting it (deltamethrin, 2-(4-tert-butylbenzyl)-propionaldehyde, bifenthrin, hexachlorophene). To date, the USA EPA has failed to identify any, while lists published by other governmental and non-governmental groups contain anywhere from 26 to over 1000 (summarized in a 2020 UNEP report: <https://wedocs.unep.org/bitstream/handle/20.500.11822/33807/ARIC.pdf?sequence=1&isAllowed=y>). Some of the most well-studied putative EDCs linked to adverse reproductive outcomes in animals and humans are listed in Supplementary Table 1 (see section on [supplementary materials](#) given at the end of this article). Identified EDCs include numerous pesticides, bisphenols and phthalates, which have multiple applications but are widely used in plastics, and parabens which are often used as preservatives in personal care products. Most identified EDCs that impair reproductive health are

Table 1 EDC definitions currently in use globally.

Agency	Year	Definition	Reference
US Environmental Protection Agency (EPA)	1996	An exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body which are responsible for the maintenance or homeostasis, reproduction, and the regulation of developmental processes.	Kavlock and Ankley (1996), Kavlock <i>et al.</i> (1996)
European Commission Workshop on the Impact of Endocrine Disruptors on Human Health and the Environment	1997	1. An endocrine disrupter is an exogenous substance that causes adverse health effects in an intact organism or its progeny, secondary to changes in endocrine function. 2. A potential endocrine disruptor is a substance that possesses properties that might be expected to lead to endocrine disruption in an intact organism.	European Workshop on the Impact of Endocrine Disruptors on Human Health and Wildlife 1996
US EPA Endocrine Disruptor Screening and Testing Advisory Committee	1998	An exogenous substance that changes endocrine function and causes adverse effects at the level of the organism, its progeny, and/or (sub)populations of organisms based on scientific principles, data, weight-of-evidence, and the precautionary principle	EDSTAC 1998
The World Health Organization (WHO) and the Inter-Organization Programme for the Sound Management of Chemicals (IOMC)	2002	An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations. A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations.	WHO/PCS/EDC/0.2.2 (WHO 20002)
The Endocrine Society	2012	An exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.	Zoeller <i>et al.</i> (2012)

Table 2 A summary of the nine chemicals identified as EDCs by the Danish Center on Endocrine Disruptors in 2018.

EDC	Source	Adverse effects	Mode of action	Citations
Bisphenol AF	Polycarbonate plastics, epoxy resins, food containers, dental fillings, medical devices, eyeglass lenses, thermal paper receipts, electronics	Decreased fertility	Estrogenic	Catenza et al. (2021)
Deltamethrin	Pyrethroid ester insecticide	Malformations of male reproductive organs including the testis	Androgen receptor antagonist	Hodgson and Rose (2007) , Ismail and Mohamed (2012)
Di-n-pentylphthalate (DnPP)	Additive in polyvinylchloride (PVC) and other plastics. No longer in use.	Decreased AGD; increased nipple retention in male rats; decreased sperm count; malformations of male reproductive organs	Anti-estrogenic	Gangolli (1982) , Hannas et al. (2011)
Fenitrothion	Organophosphate insecticide	Decreased AGD; increased nipple retention in male rats; malformations of the testis sperm, and male reproductive organs; reduced testosterone	Anti-androgenic	Curtis (2001)
Isobutyl paraben	Preservatives in personal care products and pharmaceuticals; food preservatives	Decreased sperm count and motility; altered sexually dimorphic behavior	Estrogenic	Kawaguchi et al. (2010) , Gonzalez et al. (2018)
Prochloraz	Imidazol fungicide; not authorized for use in the United States.	Skewed sex ratios in fish and amphibians; disrupted sex determination in fish and amphibians	Aromatase inhibitor; anti-androgenic; anti-estrogenic	Vinggaard et al. (2006)
Salicylic acid	Phenolic acid; aspirin; personal care products	Reduced spermatogenesis	Anti-androgenic	Kristensen et al. (2016)
Triclocarban (TCC)	Antibacterial; soaps, lotions and other personal care products; largely phased out of use	Increased weight of male accessory sex organs	Androgenic	Rochester et al. (2017)
Tris(methylphenyl) phosphate	Organophosphate used as a flame retardant and in lacquers, varnishes and as a plasticizer.	Reduced fertility/fecundity in adult males	Disrupted steroidogenesis; elevates circulating estrogen levels	Reers et al. (2016)

estrogenic, anti-androgenic, or, particularly in the case of the phthalates, decrease gonadal steroid synthesis. Compounds produced in nature rather than by humans, such as the phytoestrogens, behave similarly and thus can also be considered EDCs.

Identifying putative EDCs using our current regulatory framework is challenging because of outdated methodologies and other practical limitations ([Solecki et al. 2017](#)). Historically, assessments made for regulatory and public health decision-making regarding what is 'dangerous' to humans have focused on gross malformations and birth defects such as tumor formation, malformed organs or limbs, severe weight loss, gross motor deficits, fetal loss, and death ([Vogel 2013](#)). As the DES story illuminated, EDCs challenge this method of identifying reproductive toxicants because perturbation of the endocrine system may not necessarily lead to overtly obvious teratogenicity post-exposure but rather can set the body on a path to long-term morbidity. This is particularly likely if exposure occurs during developmental periods when hormones are actively shaping neuroendocrine and other reproductive systems.

A powerfully potent estrogen receptor agonist developed as a pharmaceutical, and there are no anthropogenic EDCs that pose a health risk anywhere near as extreme as DES. Nonetheless, most of the reproductive outcomes of prenatal DES exposure are similar to those elicited in many animal models by early-life exposure to some of the most potent phytoestrogens including coumesterol and genistein ([Patisaul & Jefferson 2010](#), [Patisaul 2017a](#)); a literature dating back to the 1940s ([Bennetts et al. 1946](#)). Additionally, nearly all the human DES outcomes were predicted by or reproduced in animal models ([McLachlan et al. 1982](#), [Newbold & McLachlan 1982](#), [Newbold 2008](#), [McLachlan 2016](#)). As such, this work rapidly established a set of endpoints by which reproductive endocrine disruption could be identified, plus a basic mechanistic understanding of how adverse outcomes arise. Moreover, complementary, fundamental work in neuroendocrinology identified more precisely the critical windows in which specific aspects of the reproductive neuroendocrine system differentiate and undergo sexual differentiation ([Simerly 2002](#), [Wallen 2009](#), [McCarthy 2016, 2020](#)). Thus, by the close of the

20th century, an experimental framework for testing a broader set of compounds for endocrine disrupting activity across a range of reproductive endpoints was firmly established as well as approaches to establish causality between exposure and adverse reproductive outcomes, and probe mechanisms of action. While EDC scientists have embraced these methodologies and developed new ones as -omics tools advanced and concepts like epigenetic inheritance matured, regulatory testing has largely failed to evolve in either their testing strategies or incorporation of new data streams for the purpose of human risk assessment (Vandenberg *et al.* 2016, 2019, Solecki *et al.* 2017, Tweedale 2017, Fritsche *et al.* 2018). Thus, controversy as to how to precisely define what constitutes an EDC unfortunately remains.

Mechanisms of reproductive endocrine disruption

When the term 'EDC' was first coined in the early 1990s, most chemical examples were estrogenic and thought to act via agonism or antagonism of canonical steroid receptor signaling (Hotchkiss *et al.* 2008, McLachlan 2016). Thanks to convergent work in endocrinology, toxicology, and behavioral neuroendocrinology, significant progress has been made identifying potential mechanisms of reproductive endocrine disruption beyond classic steroid hormone receptor agonism/antagonism. These 'key characteristics' (Fig. 1) include changes in steroid metabolism and biosynthesis, receptor degradation and expression level changes, DNA methylation and other epigenetic modifications, interference with signal transduction in hormone-responsive cells and disruption of rapid hormone

signaling via non-canonical pathways (Tabb & Blumberg 2006, Schug *et al.* 2015, La Merrill *et al.* 2020).

While it is beyond the scope of this review to address them all in detail, it is important to note that for each key characteristic, there can be multiple mechanisms of disruption. For example, the earliest identified EDCs were estrogen disruptors. These EDCs were presumed to act by interfering with direct genomic signaling, where an estrogen (17 β -estradiol, estrone, or estriol) binds to either major form of the estrogen receptor (ER α , ER β), and the complex dimerizes and translocates to the nucleus inducing transcriptional changes in estrogen-responsive genes via estrogen response elements (EREs). To this day, most *in vitro* assays that screen for estrogen-disrupting EDCs only test this mechanism of action. It is now known, however, that endogenous estrogens can act via indirect genomic signaling, where another transcription factor mediates DNA binding at a non-ERE site. Additionally, membrane-bound receptors, including a membrane form of ER α , can induce cytoplasmic events such as modulation of membrane-based ion channels, second-messenger cascades, or transcription factors (Fig. 2). Notably, the G protein-coupled estrogen receptor (GPER, also known as GPER1 or GPR30), first discovered in 1996, is expressed in the cell membrane as well as the endoplasmic reticulum and plays an important role in many of the rapid non-genomic estrogen actions including heightened production of cyclic AMP, promotion of intracellular calcium mobilization, and synthesis of phosphatidylinositol 3,4,5-trisphosphate in the nucleus (Filardo & Thomas 2012, Qie *et al.* 2021). EDCs known to bind or interfere with GPER include BPA and other bisphenols, some pesticides including DDT

Figure 1 A summary of the ten 'key characteristics' of endocrine disrupting activity as summarized in a 2020 consensus statement (La Merrill *et al.* 2020). Each of the ten key characteristics is depicted with some example EDCs listed for each one. It is important to note that the way in which EDCs produce the key characteristic can occur via multiple and cell-specific mechanisms.

Figure 2 Examples of canonical and non-canonical estrogen receptor (ER) signaling pathways. The two major nuclear forms of ER are ER α and ER β . Via the classical direct genomic pathway estrogen-bound ERs dimerize, change conformation, are shuttled to the nucleus, bind estrogen response elements (ERE) on the DNA, and recruit coactivators and that promote transcription (denoted by arrow 1). Most regulatory screening in vitro ER assays for EDC activity probe only this mechanism of estrogen signaling. Non-classical genomic signaling (denoted by arrow 2) is also possible via binding with transcription factors (TF) like AP-1 and others to promote transcription through transcription factor response elements (TFRE). ER transcriptional activity can also be activated by kinases via their receptors and is thus estrogen-independent. Finally, GPER and membrane ERs (mER) including membrane forms of ER α and ER β confer many of the rapid effects of estrogen and influence transcription and other cell processes, including ion channel activity, via kinases and other intracellular signaling cascades. This diagram is by no means exhaustive and illustrates that there are myriad ways EDCs can act as ER agonists or antagonists, some of which are just beginning to be elucidated. (E2, estradiol; EGFR, epidermal growth factor/EGF receptor; ERK, extracellular signal-related kinases; IGF1R, insulin-like growth factor receptor; MAPK, mitogen-activated protein kinase; NFKB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase).

and its metabolites, many flame retardants including PBDEs and some organophosphate esters (OPEs), phthalates, and some endocrine active metals such as cadmium (Qie *et al.* 2021). Additionally, ER-independent and estrogen-independent actions are also known to exist and could be impacted by EDCs (Fig. 2). This is why some tissues which primarily express only one form of the estrogen receptor (e.g. ER β in granulosa cells, ER α in thecal cells, and membrane ERs in some brain regions such as the nucleus accumbens) respond differently to endogenous estrogens and, consequently, vary in their vulnerability and response to estrogen-disrupting EDCs (Fucic *et al.* 2012, Hewitt & Korach 2018). Emerging work is also demonstrating that organs other than the gonads can make their own estrogens, most significantly the brain (Barakat *et al.* 2016). Similar receptor signaling complexities exist for androgens (Mittelman-Smith *et al.* 2017) and progestins as well (Piette 2020), with some

ligands binding other receptors including glucocorticoid receptors (Mittelman-Smith *et al.* 2017).

EDCs are now also recognized as being able to induce epigenetic changes, and this is particularly alarming because it provides a mechanistic path to transgenerational effects. When a pregnant woman is exposed to a chemical, she, her unborn child, and the germ cells in that unborn child are all simultaneously exposed. Thus, exposure is to three generations at once and considered multi-generational. The fourth generation, (called F4) or the great-grandchild, is the first to be born not directly exposed. Effects in this F4 generation are considered transgenerational. There is growing evidence that a multitude of EDCs has transgenerational effects on reproductive endpoints including age at puberty, fertility and fecundity, reproductive behavior, and parental behavior (Rissman & Adli 2014, Ho *et al.* 2017, Viluksela & Pohjanvirta

2019). These can occur via a variety of epigenetic mechanisms, most of which are only beginning to be fully understood (Walker & Gore 2011) but include DNA methylation, histone modifications, and long and micro RNAs among others (Perera *et al.* 2020). Although the evidence remains sparse and inconsistent, particularly in humans (Van Cauwenbergh *et al.* 2020), there is pressing interest in the possibility of transgenerational outcomes, particularly in the face of other life challenges, such as prenatal stress or poor nutrition, which could augment adverse generational effects (Sobolewski *et al.* 2020). As such, epigenetic effects and, consequently, the potential for transgenerational inheritance are some of the most intense areas of reproductive EDC research.

The reproductive neuroendocrine system

The neuroendocrine system is essentially the master control system of the body and the primary system responsive to environmental signals. The nervous system component mediates the most immediate and rapid effects, and the endocrine level acts to maintain, modulate, and prolong the response. For example, when frightened, the sympathetic nervous system drives the immediate response (e.g. increased heart rate, sweating and goosebumps) while the endocrine system acts to maintain a stress response (via glucocorticoids and other hormones). The neuroendocrine system, especially the reproductive neuroendocrine system, is exquisitely sensitive to steroids and other hormones throughout life. Itself an endocrine organ, the hypothalamus is the apical coordinator of the neuroendocrine system. This diencephalic, heterogeneous, and sexually dimorphic structure communicates with the rest of the brain, the pituitary and, ultimately, all the endocrine glands including the gonads. The placenta also shapes and controls many neuroendocrine functions in the developing fetus, including the organization of the fetal brain, across pregnancy, beginning well before the hypothalamus is even formed (Behura *et al.* 2019). Thus, it is an ephemeral but critical piece of the neuroendocrine system.

The vertebrate reproductive system is coordinated by the hypothalamic-pituitary-gonadal (HPG) axis, which comprises a complex network of neuronal and endocrine signaling pathways that ultimately centers on the precise control of steroid hormone secretion by gonadotropins (McCarthy *et al.* 2009, Schulz *et al.* 2009, Kaprara & Huhtaniemi 2018). HPG steroid hormone action can be organizational or activational depending on the developmental stage (McCarthy *et al.* 2009, Schulz *et al.* 2009), and over the pubertal transition, there is a little bit of both (Schulz & Sisk 2016). The neural components of the HPG axis span multiple hypothalamic and other brain nuclei, most importantly regions housing discrete populations of kisspeptin-secreting neurons that regulate gonadotropin-releasing hormone (GnRH) secretion. In

humans, a preoptic population coordinates ovulation and steroid positive feedback in females, while the more caudal arcuate (ARC; also called the infundibular nucleus) population regulates pubertal onset and steroid negative feedback in both sexes (Livadas & Chrousos 2016, Barroso *et al.* 2019, Garcia *et al.* 2019). Females have more preoptic kisspeptin neurons than males and estrogen upregulates kisspeptin expression in this region via ER α in both sexes which then, in turn, triggers the pre-ovulatory surge of GnRH release in females (Beltramo *et al.* 2014, Herbison 2020). The ARC population of kisspeptin neurons co-synthesize neurokinin B (NKB) and dynorphin and have thus come to be termed 'KNDy neurons' (Moore *et al.* 2018). Estrogens suppress the kisspeptin expression in KNDy neurons via membrane ER α , and neuron numbers are not sexually dimorphic (Micevych *et al.* 2015). KNDy neurons are also critical for metabolic control and are considered key integrators of reproductive and metabolic signaling pathways (Dudek *et al.* 2018). The network of regulatory inputs from other neural and glial cells in the brain projecting to these kisspeptin populations or to GnRH neurons themselves is diverse, and in many cases, highly sexually dimorphic. Described in detail elsewhere, these pathways are differentiated largely by endogenous gonadal hormones through a series of well-defined, and sometimes very short, gestational, pre- and perinatal critical periods (Simerly 2002, Clarkson *et al.* 2014, Clarkson & Herbison 2016, McCarthy *et al.* 2018) spanning gestation through pre-puberty (Simerly 2002, Schulz *et al.* 2009).

Endocrine disruption of HPG axis sexual differentiation

In humans and other mammals, the fetal testis is steroidogenically active and the secreted testosterone and its metabolites are required to masculinize the brain, genitalia and reproductive tract. Androgens, most significantly dihydrotestosterone, via their action on androgen receptors, are essential for masculinizing the male reproductive organs. By contrast, in rats, mice and some other non-primate species, the masculinizing effect of perinatal androgens in the brain is predominantly conferred by estrogens, derived locally via aromatization, and precisely expressed estrogen receptors (McCarthy 2008, Cao & Patisaul 2011, 2013). Thus, in rodents, estrogen is the 'masculinizing' gonadal hormone of the perinatal brain. In humans, although aromatization occurs, androgen receptors play a far more direct role in brain masculinization, a process that continues after birth (Gooren 2006, Alexander 2014, Savic *et al.* 2017, Puts & Motta-Mena 2018). This is critically important to keep in mind when interpreting and translating effects on rodent hypothalamic sexual differentiation to humans. Estrogenic action in the perinatal brain will be masculinizing in rodents but not

humans or other primates. It is also important to note that the neuroendocrinology of sexual orientation and gender identity remain largely unknown (Roselli 2018).

In many species, the sex-specific organization of GnRH function and feedback can be hormonally manipulated and induce long-term functional consequences. During the perinatal critical period, gonadal steroid hormone exposure can masculinize the female rodent GnRH axis, while neonatal castration can effectively prevent defeminization of the male GnRH axis (Baum 1979, Simerly 2002, Bakker & Baum 2008). Thus, in males castrated as neonates, the potential for estrogen to evoke a GnRH surge is preserved while, conversely, in females neonatally exposed to estrogens, this capacity is diminished or lost. While this critical window is perinatal in rats and mice, it is thought to be entirely prenatal in humans.

Because steroid hormones are essential for the proper organization and sexual differentiation of the perinatal reproductive neuroendocrine system, this process has proven particularly vulnerable to endocrine disruption, especially in males (Kern *et al.* 2017, Graceli *et al.* 2020). For example, in rats, fetal exposure to some phthalates particularly di-(2-ethylhexyl) phthalate (DEHP), genistein, coumestrol and other phytoestrogens, PCBs, as well as BPA and likely other bisphenols perturb programming in multiple hypothalamic and related nuclei including the ARC, anteroventral periventricular nucleus (AVPV) and medial preoptic nucleus (MPN) (Dickerson *et al.* 2011, Jefferson *et al.* 2012, Bell 2014, Gao *et al.* 2018, Patisaul 2020). These disruptions include changes in nuclear volume, expression of steroid hormone and other receptors, the density of projections between brain nuclei, and density of dopaminergic neurons in regions critical for reproductive function (Frye *et al.* 2012, Gao *et al.* 2018, Neubert da Silva *et al.* 2019, Patisaul 2020). EDCs including genistein, BPA and PCBs can be disruptive to the organization and to the function of the GnRH-kisspeptin system (Tena-Sempere 2010, Patisaul 2013). Neonatal genistein, for example, can masculinize the female rat GnRH axis such that capacity for steroid positive feedback is compromised (Bateman & Patisaul 2008). Rat females exposed for only the first 3 days of life have fewer kisspeptin immunopositive fibers in both the AVPV and ARC across the pubertal transition, an effect accompanied by evidence of disrupted ovarian maturation (Losa *et al.* 2011). Genistein and BPA exposure over only the first 48 h after birth is sufficient to alter other aspects of AVPV sexual differentiation including the number of dopaminergic neurons (Patisaul *et al.* 2006). This finding is significant because GnRH neurons express dopamine receptors, and dopamine is a potent modulator of pre- and postsynaptic actions on GnRH neurons (Liu & Herbison 2013, Spergel 2019). Similarly, female mice perinatally exposed to BPA have an early vaginal opening (a marker of rodent puberty), lower circulating levels of LH, and significantly altered

numbers of AVPV and ARC kisspeptin neurons (Ruiz-Pino *et al.* 2019). Perinatal BPA exposure has also been shown to dysregulate the GnRH axis, including kisspeptin neuron numbers, in rats (Bai *et al.* 2011).

In addition to the HPG axis, some EDCs can disrupt the sexual differentiation of other hypothalamic systems. For example, in mice, prenatal exposure to a mixture of common OPEs used as plasticizers and flame retardants eliminates the sex difference in postnatal *Npy* (neuropeptide Y) expression in the mediobasal hypothalamus (MBH) and increases the postnatal expression of ER α and other genes related to sexual differentiation, including *Pparg* (peroxisome proliferator-activated receptor gamma), *Tac2* (tachykinin 2), and *Pdyn* (prodynorphin) in females (Adams *et al.* 2020). Exposed males were also heavier by the second week of life and had higher levels of *Agrp* (agouti-related neuropeptide) in the MBH at birth, supporting other studies identifying them as metabolic disruptors (Farhat *et al.* 2014, Boyle *et al.* 2019). OPEs have also been found to disrupt HPG function and impair reproduction in fish (Liu *et al.* 2013, Saunders *et al.* 2015, Wang *et al.* 2015). There is also evidence from multiple species including quail and monogamous rodent models that BPA, PCBs and some phthalates alter sexually dimorphic aspects of the oxytocin/vasopressin system and their interface with the mesolimbic dopamine system (Sullivan *et al.* 2014, Patisaul 2017b, Gore *et al.* 2019).

In humans, evidence of disrupted hypothalamic sexual differentiation is extremely difficult to detect, but anogenital distance (AGD) has emerged as a potentially useful biomarker of fetal androgen exposure and, consequently, potentially altered the brain defeminization/masculinization (Schwartz *et al.* 2019). Due to prenatal virilization by androgens, AGD is longer in males than females. Although links to specific brain outcomes are not yet well-defined, shorter male AGD is associated with reduced fertility, sperm quality and circulating androgen levels as well as fewer male-typical play patterns (Thankamony *et al.* 2016, Priskorn *et al.* 2019). In addition to shortened AGD, fetal phthalate exposure results in male genital and reproductive organ abnormalities and higher testicular cancer risk in rodent models and humans (Hliseníková *et al.* 2020) which is sometimes termed 'testicular dysgenesis syndrome' (Sharpe & Skakkebaek 2008, Toppari *et al.* 2010). Fetal exposure to acetaminophen (Paracetamol or Tylenol), BPA, DDT and its primary metabolites, dioxins, phthalates, some OPEs, and the dicarboximide fungicides such as vinclozolin can also result in shortening AGD and, consequently, are thought to impair HPG masculinization (Schwartz *et al.* 2019, Adams *et al.* 2020). Similarly, longer AGD in females is considered an indicator of masculinization, the long-term reproductive consequences of which are not entirely clear. Notably, ectopic fetal activation of the progesterone receptor (PR) can masculinize female

genitalia, as can super-physiological doses of potent estrogens, so there are likely multiple modes of action for disrupted AGD length in females. Some EDCs including BPA, paracetamol and a few phthalates have been shown to shorten female rodent AGD, the functional significance of which is unknown. Thus, the relationship between AGD length and HPG sexual differentiation in females has yet to be established. Significantly, AGD measurements have been added to several OECD test guidelines and other regulatory testing strategies for developmental and reproductive toxicity for detecting endocrine-disrupting effects. Its utility for predicting adverse reproductive outcomes in humans is less well-accepted but gaining traction.

Disruption of HPG maturation and adult function

In experimental animals, it is well-established that the administration of steroid hormones during adolescence can accelerate puberty including the premature onset of GnRH pulsatility (Rasier *et al.* 2006, Mueller & Heger 2014, Lucaccioni *et al.* 2020). Disruption of HPG axis maturation and pubertal onset has been observed in rodents following exposure to BPA, phthalates, atrazine, DDT and its metabolites, TCDD, and PCBs (Gore *et al.* 2015). In most cases, female puberty is advanced but high doses of potentially estrogenic compounds can also induce a delay. For example, in female rats, parabens administered during peripuberty delayed puberty and resulted in numerous uterine and ovarian histological changes including decreased corpora lutea, increased incidence of cystic follicles and myometrial hypertrophy (Vo *et al.* 2010).

A far longer list of EDCs including genistein, coumestrol and other phytoestrogens, DDT, atrazine, BPA and other bisphenols, and some PCBs are known to interfere with the activity of the mature HPG axis and thus disrupt GnRH and LH secretion (Gore *et al.* 2015, Rattan *et al.* 2017, Graceli *et al.* 2020). This can occur via direct action on GnRH neurons or other hypothalamic targets but disruption at the level of the pituitary or gonad is more common. In most cases, normal HPG function resumes once exposure is eliminated. For example, a 2009 meta-analysis concluded that isoflavone intake moderately increases cycle length and suppresses luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in adult women (Hooper *et al.* 2009). A 2008 clinical case report described three women (aged 35 to 56) experiencing a suite of symptoms related to excessive soy intake (estimated to exceed 40 g per day) including abnormal uterine bleeding, endometrial pathology and dysmenorrhea, all of which resolved when soy intake was discontinued or reduced (Chandraseddy *et al.* 2008). For couples experiencing fertility challenges, it can be difficult to establish if developmental or current exposures (or both) may have adversely contributed, but assisted reproductive technologies are compromised in

women with high blood levels of BPA, phthalates, and other EDCs (Karwacka *et al.* 2019, Mínguez-Alarcón *et al.* 2019).

Finally, only limited data exist on the impact of EDCs on reproductive senescence and disorders of the aging reproductive system. Estrogenic EDCs including PCBs and phytoestrogens are associated with a higher risk of uterine fibroids, a condition that impacts up to 80% of women in their lifetime and is highly dependent on estrogen and progesterone (Katz *et al.* 2016). Higher blood levels of DDT and its metabolites are associated with an early age at menopause (Akkina *et al.* 2004) while other pesticides have been associated with later age at menopause (Farr *et al.* 2006). There is also some evidence that TCDD and PCBs can advance female reproductive aging (Rattan *et al.* 2017) and BPA heightens the risk of prostate cancer (Prins *et al.* 2014, Gore *et al.* 2015). Effects of phytoestrogens are mixed with conflicting evidence that they are possibly cancer-inducing or protective, most likely depending on dose, the timing of exposure, and other factors (Patisaul & Jefferson 2010). Impacts on other aspects of reproductive aging, including premature depletion of ovarian follicle reserves, are also likely but underexplored (Weiss 2007, Grossman 2014, Johansson *et al.* 2016, Barakat *et al.* 2017).

The placenta

There continues to be growing recognition that the placenta is not an impenetrable barrier but, rather, may be a particularly vulnerable target for endocrine disruption (Wang *et al.* 2016, Gingrich *et al.* 2020). It is now clear that the bulk of EDCs likely reach the developing fetus (Aylward *et al.* 2014). For example, maternal estrogens are effectively sequestered by α -fetoprotein but most structurally similar compounds only weakly or fail to bind to α -fetoprotein and can, therefore, enter fetal circulation relatively unimpeded (Milligan *et al.* 1998, Ikezuki *et al.* 2002, Vandenberg *et al.* 2007). Environmental contaminants known to cross the placenta and reach the fetus include BPA and other phenols, phthalates, heavy metals, pesticides, PFAS, and numerous flame retardants (Leazer & Klaassen 2003, D'Aloisio *et al.* 2013). Some pollutants can accumulate in placental tissue (Esteban-Vasallo *et al.* 2012, Vizcaino *et al.* 2014, Leonetti *et al.* 2016a,b, Phillips *et al.* 2016, Baldwin *et al.* 2017) and appear at higher levels in fetal cord blood than maternal blood (e.g. some metals, brominated flame retardants including TBBPA and many PBDE congeners, and polyaromatic hydrocarbons) (Aylward *et al.* 2014), demonstrating that fetally derived placental tissues and the fetus itself can experience greater exposures than the mother. In the case of some flame retardants, this placental accumulation appears to differ by sex with placentas associated with the male offspring obtaining higher levels, raising the possibility

that fetal exposure may differ by sex (Phillips *et al.* 2016, Rock *et al.* 2018).

The placenta is the site of nutrient exchange between mother and fetus, but it also provides critical support for fetal growth through hormone and neurotransmitter production. Not surprisingly, the placenta has been found to play a unique and critical role in neurodevelopment, and, consequently, dysfunction of the placenta can severely impact neurodevelopment (Myatt 2006, Konkel 2016). There are many examples of situations where stress-induced inflammation can lead to placental dysfunction and altered neurodevelopment (Bronson & Bale 2014, 2016), however, comparatively few studies have tested whether this type of response can occur from exposure to exogenous chemicals (Gingrich *et al.* 2020, Mao *et al.* 2020). Thyroid hormone regulation and transfer are also vital for proper neurodevelopment and highly susceptible to EDCs such as PBDEs and PCBs (Demeneix 2014). Therefore, during the gestational window, neurodevelopment can not only be impacted by direct toxicity to the developing brain, through placental transfer, but can also be impacted indirectly through placental disruption.

Other routes of reproductive endocrine disruption

Endocrine disruption does not have to be direct. Because the neuroendocrine pathways that coordinate reproductive physiology intersect with other organ systems and pathways, even indirect environmental insults can have reproductive consequences. For example, chronic stress including prolonged isolation, parental neglect, starvation, or extreme exercise can itself suppress ovulation, induce miscarriage, reduce sperm count, result in preterm birth, and shift the timing of pubertal maturation. Additionally, dysregulation of the stress axis can contribute to other chronic health conditions including metabolic syndrome, impaired immune function, cardiovascular disease, and cognitive decline (Dirven *et al.* 2017, Joseph & Golden 2017) highlighting the multi-organ system impacts of neuroendocrine disruption. Similarly, the endocrine and immune systems reciprocally influence each other, and hyperinflammation can suppress fertility and reproduction (Belloni *et al.* 2014). Reproductive maturation and function are also under strong metabolic control and highly sensitive to body condition (Bellefontaine & Elias 2014). In combination with stress, chronic illness and other bodily insults, the severity and breadth of EDC-related health effects can be compounded. For accelerated female puberty, for example, commonly ascribed causal factors such as father absence and obesity have turned out to play less of a singular role than once believed (Li *et al.* 2017, Sohn 2017, Reinehr & Roth 2019, Sear *et al.* 2019). However, in combination with other exogenous insults including chemical exposures, the risk of precocious puberty and

other reproductive challenges increase. The degree to which EDCs factor into this complex landscape and influence reproductive outcomes in humans remains difficult to quantify with certainty, but experimental evidence strongly implicates that their impact is likely underestimated and growing.

Finally, many EDCs have the potential to elicit their effects through modes of action that impact other organ systems. The endocrine system has been shown to interact with the immune system, for example, by mediating gene transcription of pro-inflammatory cytokines, and mediators of the innate immune system can feedback on the brain and regulate endocrine signaling (Irwin & Cole 2011, Merrheim *et al.* 2020). PBDEs and PFAS have been associated with inflammation during pregnancy and the postpartum period in women (Zota *et al.* 2018). Additionally, uterine remodeling, driven by immune cells, is critical for preparing the uterus for pregnancy, a process that may be vulnerable to EDCs (Meyer & Zenclussen 2020). In the brain, microglia play an essential role in the execution of sexually dimorphic hypothalamic development (Lenz & McCarthy 2015). Consequently, during development, their densities can be sexually dimorphic in hypothalamic nuclei (Schwarz *et al.* 2012) and environmental exposures, including exposure to air pollution or BPA, can sex-specifically alter their numbers or morphology, particularly in combination with other stressors (Bolton *et al.* 2013, Hanamsagar & Bilbo 2016, Rebuli *et al.* 2016, Bolton *et al.* 2017). Interest in the capacity for EDCs to disrupt the microbiome and the brain-gut axis is also increasing (Roman *et al.* 2019, Kaur *et al.* 2020).

Take-home messages: key concepts of endocrine disruption in the reproductive system

The DES disaster illustrates three core principles of endocrine disruption. First, latency between exposure and effect can be extremely long, even decades. DES-exposed babies were born healthy by all appearance, with no evidence of the reproductive consequences that would ultimately befall them. Pioneering work by Drs Beach, Young, Goy and others exploring the mechanisms by which fetal hormone exposure alters sex behavior and sex-specific neuroendocrine feedback systems (Gorski 1963, Young *et al.* 1964, Goy & Resko 1972, Swaab & Hofman 1984, Balthazart *et al.* 1996, Marler 2005) identified the primary mechanisms underlying this phenomenon in the reproductive system. As such, neuroendocrinologists laid critical groundwork for conceptually understanding how reproductive development and function could be vulnerable to endocrine disruption. This long latency concept is now a cornerstone of the 'developmental origins of health and disease (DoHAD)' framework; a concept born from the Barker hypothesis stating that metabolic adaptations made during early-life scarcity could later heighten the

risk of morbidity in an environment of plenty (Barker 2007, Heindel *et al.* 2015).

The second key principle is that the timing of exposure, perhaps even more than dose, drives the potential and severity of adverse outcomes. In vertebrates, there are critical moments, both for the reproductive organs and the brain, when sensitivity to endogenous hormones and, consequently, EDCs is especially high. Additionally, there are phases in the life trajectory, particularly in prenatal development, where hormones play an organizational role in the formation of reproductive systems. Because interference with those organizational events can result in irreversible injury, they are considered particularly critical windows of EDC vulnerability. For example, the type and severity of disorders common to DES sons and daughters vary substantially depending on the timing of the mother's first exposure, total dose, and length of exposure (Robboy *et al.* 1981, 1984, Faber *et al.* 1990). The vast majority of experimental EDC research on reproduction has used prenatal or early-life exposure paradigms and exposure later in life assessment. By contrast, exposures during puberty, which is an additional, but not as well-characterized period of organizational hormone action, are not as well-studied (Ahmed *et al.* 2008, Schulz *et al.* 2009, Sisk 2016, Herting & Sowell 2017). Also underexplored is the possibility that EDC exposure changes the timing of when and for how long critical windows are open. Thyroid hormones have long been known to open the window for filial imprinting in birds and can reopen that window in some circumstances (Yamaguchi *et al.* 2012). Embryonic exposure to BPA and BPS has been shown to shift the timing of neurogenesis in the zebrafish brain (Kinch *et al.* 2015). Almost nothing is known about how windows of HPG organization can be shifted in the mammalian brain by EDCs.

The third key principle of endocrine disruption is that the dose-response of many hormones and EDCs appears to be non-linear, and adverse outcomes might be different at low vs high doses (Vandenberg *et al.* 2012). The best example of this is thyroid hormone because the effects of abnormally high or low levels are completely different. In adults, symptoms of hyperthyroidism include bulging eyes, weight loss, tachycardia, arrhythmias, goiter, heat intolerance, and anxiety or nervousness, while hypothyroidism can result in weight gain, fatigue, cold intolerance, muscle and joint pain, hair loss, dry skin, depression and menstrual irregularity. This paradigm is anathema to the fundamental toxicological axiom that 'the dose makes the poison' which posits that effects intensify with dose but do not fundamentally change, nor manifest differently, below a certain threshold. Homeostatic adaptation can also produce non-linear dose responses. Our neuroendocrine system evolved to be responsive to environmental signals, both chemical and perceived, including naturally occurring hormonally active compounds. Consequently, we have adaptive

responses to some environmental insults and can make imperceptible adjustments to maintain homeostasis, but only up to a point. For example, the neural components of the HPG axis are constantly responding to numerous external signals simultaneously including day length, hormones, infection, olfactory cues, and glucose levels, among others. Complex feedback loops on the HPG axis maintain physiologically appropriate levels of steroid hormones and rhythmic GnRH pulses. These feedback systems are likely one reason why many EDC dose responses more closely approximate a U-shaped or inverted U-shaped curve (Vandenberg *et al.* 2012, Lagarde *et al.* 2015, Zoeller & Vandenberg 2015). U-shaped dose effects might also reflect an integration of two different mechanisms of action, each of which occurs at a different dose range. For example, DDT interferes with estrogen and androgen action at low doses but is a potent neurotoxin at higher levels (Toppari *et al.* 1996). It should be noted that although some toxicologists have expressed concern that non-linear dose responses are underappreciated, others doubt their existence entirely, and the concept remains highly controversial for some, primarily because it would necessitate changing the way regulatory toxicity testing is conducted (Melnick *et al.* 2002, Vandenberg *et al.* 2012, Lagarde *et al.* 2015, Solecki *et al.* 2017, Demeneix *et al.* 2020). Others have also perturbed this concept and labeled it 'hormesis', a largely debunked hypothesis which purports that low doses of some toxic compounds can actually be beneficial even if high doses are harmful (Thayer *et al.* 2006, Kendig *et al.* 2010).

Concluding thoughts

Human evolution will now occur in a complex chemical landscape of our own making. It is readily evident that exposure to EDCs is already adversely affecting reproductive physiology and behavior in ourselves and our planetary co-occupants and will continue to do so for generations to come. Growing evidence that some EDCs can induce epigenetic reprogramming that may be inherited and impact future generations emphasizes the pressing need to understand how the chemical cocktail inside of us is impacting our reproductive future (Ho *et al.* 2017). Some of the most obvious and potent compounds such as DDT, PCBs, PBDEs and DES, have been phased out of use and, fortunately, global exposure is consequently declining. For others such as BPA and the phthalates, despite an enormous literature documenting their adverse reproductive effects, regulatory inaction persists. The introduction of new chemicals is rapidly outpacing the capacity to understand their potential health effects or the totality of our exposure (Tweeddale 2017). Additionally, even perceived successes are often failures because all too often problematic compounds are replaced by equally problematic cousins, a phenomenon called 'regrettable

substitution' (Scherer *et al.* 2014, Trasande 2017, Blum *et al.* 2019). Collectively, blood levels of many hormonally active compounds can be several fold higher than endogenous estrogen levels, particularly during pregnancy and neonatal development, and are almost always present in both the environment and in tissues as mixtures (Wang *et al.* 2016). Yet, regulatory processes overwhelmingly consider their potential harm in isolation, one chemical at a time. Further efforts to understand the mechanisms underlying EDC effects, particularly complex mixtures of ubiquitous compounds with low hormonal potency, are necessary to adequately develop a public health strategy for preventing or combating their reproductive effects (Bopp *et al.* 2018). That every pregnant woman on the planet is currently carrying a mixture of chemicals during her pregnancy that could affect not only her daughter's reproductive health but also her granddaughter's is a major reason why the topic of endocrine disruption must continue to receive global attention from scientists, governments, and the general public.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/REP-20-0596>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This work was supported by a Department of Defense Autism Research Program, Idea Development Award to H B Patisaul (AR160055), a NIEHS center grant P30ES025128 to R C Smart, and an NIEHS R01ES031419 to H Stapleton (H B Patisaul is a co-PI).

Acknowledgments

This paper forms part of a special section on Reproductive toxicology. The guest editors for this section were Dr Adam Watkins (The University of Nottingham, UK) and Dr Aileen Keating (Iowa State University, IA, USA).

References

- Adams S, Wiersielis K, Yasrebi A, Conde K, Armstrong L, Guo GL & Roepke TA 2020 Sex- and age-dependent effects of maternal organophosphate flame-retardant exposure on neonatal hypothalamic and hepatic gene expression. *Reproductive Toxicology* **94** 65–74. (<https://doi.org/10.1016/j.reprotox.2020.04.001>)
- Ahmed EI, Zehr JL, Schulz KM, Lorenz BH, DonCarlos LL & Sisk CL 2008 Pubertal hormones modulate the addition of new cells to sexually

- dimorphic brain regions. *Nature Neuroscience* **11** 995–997. (<https://doi.org/10.1038/nn.2178>)
- Akkina J, Reif J, Keefe T & Bachand A 2004 Age at natural menopause and exposure to organochlorine pesticides in Hispanic women. *Journal of Toxicology and Environmental Health: Part A* **67** 1407–1422. (<https://doi.org/10.1080/15287390490483845>)
- Aksiglaede L, Sorensen K, Petersen JH, Skakkebaek NE & Juul A 2009 Recent decline in age at breast development: the Copenhagen Puberty Study. *Pediatrics* **123** e932–e939. (<https://doi.org/10.1542/peds.2008-2491>)
- Al-Saleh I, Coskun S, Al-Doush I, Abduljabbar M, Al-Rouqi R, Al-Rajudi T & Al-Hassan S 2019 Couples exposure to phthalates and its influence on *in vitro* fertilization outcomes. *Chemosphere* **226** 597–606. (<https://doi.org/10.1016/j.chemosphere.2019.03.146>)
- Alexander GM 2014 Postnatal testosterone concentrations and male social development. *Frontiers in Endocrinology* **5** 15. (<https://doi.org/10.3389/fendo.2014.00015>)
- Aylward LL, Hays SM, Kirman CR, Marchitti SA, Kenneke JF, English C, Mattison DR & Becker RA 2014 Relationships of chemical concentrations in maternal and cord blood: a review of available data. *Journal of Toxicology and Environmental Health: Part B, Critical Reviews* **17** 175–203. (<https://doi.org/10.1080/10937404.2014.884956>)
- Bai Y, Chang F, Zhou R, Jin PP, Matsumoto H, Sokabe M & Chen L 2011 Increase of anteroventral periventricular kisspeptin neurons and generation of E2-induced LH-surge system in male rats exposed perinatally to environmental dose of bisphenol-A. *Endocrinology* **152** 1562–1571. (<https://doi.org/10.1210/en.2010-1042>)
- Bakker J & Baum MJ 2008 Role for estradiol in female-typical brain and behavioral sexual differentiation. *Frontiers in Neuroendocrinology* **29** 1–16. (<https://doi.org/10.1016/j.yfrne.2007.06.001>)
- Baldwin KR, Phillips AL, Horman B, Arambula SE, Rebuli ME, Stapleton HM & Patisaul HB 2017 Sex specific placental accumulation and behavioral effects of developmental firemaster 550 exposure in Wistar rats. *Scientific Reports* **7** 7118. (<https://doi.org/10.1038/s41598-017-07216-6>)
- Balthazart J, Tlemcani O & Ball GF 1996 Do sex differences in the brain explain sex differences in the hormonal induction of reproductive behavior? What 25 years of research on the Japanese quail tells us. *Hormones and Behavior* **30** 627–661. (<https://doi.org/10.1006/hbeh.1996.0066>)
- Barakat R, Oakley O, Kim H, Jin J & Ko CJ 2016 Extra-gonadal sites of estrogen biosynthesis and function. *BMB Reports* **49** 488–496. (<https://doi.org/10.5483/bmbrep.2016.49.9.141>)
- Barakat R, Lin PP, Rattan S, Brehm E, Canisso IF, Abosalum ME, Flaws JA, Hess R & Ko C 2017 Prenatal exposure to DEHP induces premature reproductive senescence in male mice. *Toxicological Sciences* **156** 96–108. (<https://doi.org/10.1093/toxsci/kfw248>)
- Barker DJ 2007 The origins of the developmental origins theory. *Journal of Internal Medicine* **261** 412–417. (<https://doi.org/10.1111/j.1365-2796.2007.01809.x>)
- Barroso A, Roa J & Tena-Sempere M 2019 Neuropeptide control of puberty: beyond kisspeptins. *Seminars in Reproductive Medicine* **37** 155–165. (<https://doi.org/10.1055/s-0039-3400967>)
- Bateman HL & Patisaul HB 2008 Disrupted female reproductive physiology following neonatal exposure to phytoestrogens or estrogen specific ligands is associated with decreased GnRH activation and kisspeptin fiber density in the hypothalamus. *Neurotoxicology* **29** 988–997. (<https://doi.org/10.1016/j.neuro.2008.06.008>)
- Baum MJ 1979 Differentiation of coital behavior in mammals: a comparative analysis. *Neuroscience and Biobehavioral Reviews* **3** 265–284. ([https://doi.org/10.1016/0149-7634\(79\)90013-7](https://doi.org/10.1016/0149-7634(79)90013-7))
- Beans BE 1997 *Eagle's Plume: The Struggle to Preserve the Life and Haunts of America's Bald Eagle*. Nebraska: University of Nebraska Press.
- Behura SK, Dhakal P, Kelleher AM, Balboul A, Patterson A & Spencer TE 2019 The brain-placental axis: therapeutic and pharmacological relevancy to pregnancy. *Pharmacological Research* **149** 104468. (<https://doi.org/10.1016/j.phrs.2019.104468>)
- Bell MR 2014 Endocrine-disrupting actions of PCBs on brain development and social and reproductive behaviors. *Current Opinion in Pharmacology* **19** 134–144. (<https://doi.org/10.1016/j.coph.2014.09.020>)

- Bellanger M, Demeneix B, Grandjean P, Zoeller RT & Trasande L 2015 Neurobehavioral deficits, diseases, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *Journal of Clinical Endocrinology and Metabolism* **100** 1256–1266. (<https://doi.org/10.1210/jc.2014-4323>)
- Bellefontaine N & Elias CF 2014 Minireview: metabolic control of the reproductive physiology: insights from genetic mouse models. *Hormones and Behavior* **66** 7–14. (<https://doi.org/10.1016/j.yhbeh.2014.04.007>)
- Belloni V, Sorci G, Paccagnini E, Guerreiro R, Bellenger J & Faivre B 2014 Disrupting immune regulation incurs transient costs in male reproductive function. *PLoS ONE* **9** e84606. (<https://doi.org/10.1371/journal.pone.0084606>)
- Beltramo M, Dardente H, Cayla X & Caraty A 2014 Cellular mechanisms and integrative timing of neuroendocrine control of GnRH secretion by kisspeptin. *Molecular and Cellular Endocrinology* **382** 387–399. (<https://doi.org/10.1016/j.mce.2013.10.015>)
- Bennetts HW, Underwood EJ & Shier FL 1946 A specific breeding problem of sheep on subterranean clover pastures in Western Australia. *Australian Veterinary Journal* **22** 2–12. (<https://doi.org/10.1111/j.1751-0813.1946.tb15473.x>)
- Bishop GJ & Koncz C 2002 Brassinosteroids and plant steroid hormone signaling. *Plant Cell* **14** (Supplement) S97–S110. (<https://doi.org/10.1105/tpc.001461>)
- Blum A, Behl M, Birnbaum L, Diamond ML, Phillips A, Singla V, Sipes NS, Stapleton HM & Venier M 2019 Organophosphate ester flame retardants: are they a regrettable substitution for polybrominated diphenyl ethers? *Environmental Science and Technology Letters* **6** 638–649. (<https://doi.org/10.1021/acs.estlett.9b00582>)
- Boeyer ME, Sherwood RJ, Deroche CB & Duren DL 2018 Early maturity as the new normal: a century-long study of bone age. *Clinical Orthopaedics and Related Research* **476** 2112–2122. (<https://doi.org/10.1097/CORR.0000000000000446>)
- Bolton JL, Huff NC, Smith SH, Mason SN, Foster WM, Auten RL & Bilbo SD 2013 Maternal stress and effects of prenatal air pollution on offspring mental health outcomes in mice. *Environmental Health Perspectives* **121** 1075–1082. (<https://doi.org/10.1289/ehp.1306560>)
- Bolton JL, Marinero S, Hassanzadeh T, Natesan D, Le D, Belliveau C, Mason SN, Auten RL & Bilbo SD 2017 Gestational exposure to air pollution alters cortical volume, microglial morphology, and microglia-neuron interactions in a sex-specific manner. *Frontiers in Synaptic Neuroscience* **9** 10. (<https://doi.org/10.3389/fnsyn.2017.00010>)
- Bopp SK, Barouki R, Brack W, Dalla Costa S, Dorne JCM, Drakvik PE, Faust M, Karjalainen TK, Kephelopoulous S, van Klaveren J et al. 2018 Current EU research activities on combined exposure to multiple chemicals. *Environment International* **120** 544–562. (<https://doi.org/10.1016/j.envint.2018.07.037>)
- Bourguignon JP, Juul A, Franssen D, Fudvoye J, Pinson A & Parent AS 2016 Contribution of the endocrine perspective in the evaluation of endocrine disrupting chemical effects: the case study of pubertal timing. *Hormone Research in Paediatrics* **86** 221–232. (<https://doi.org/10.1159/000442748>)
- Boyle M, Buckley JP & Quiros-Alcala L 2019 Associations between urinary organophosphate ester metabolites and measures of adiposity among U.S. children and adults: NHANES 2013–2014. *Environment International* **127** 754–763. (<https://doi.org/10.1016/j.envint.2019.03.055>)
- Bronson SL & Bale TL 2014 Prenatal stress-induced increases in placental inflammation and offspring hyperactivity are male-specific and ameliorated by maternal antiinflammatory treatment. *Endocrinology* **155** 2635–2646. (<https://doi.org/10.1210/en.2014-1040>)
- Bronson SL & Bale TL 2016 The placenta as a mediator of stress effects on neurodevelopmental reprogramming. *Neuropsychopharmacology* **41** 207–218. (<https://doi.org/10.1038/npp.2015.231>)
- Buck Louis GM 2014 Persistent environmental pollutants and couple fecundity: an overview. *Reproduction* **147** R97–R104. (<https://doi.org/10.1530/REP-13-0472>)
- Burris HH & Hacker MR 2017 Birth outcome racial disparities: a result of intersecting social and environmental factors. *Seminars in Perinatology* **41** 360–366. (<https://doi.org/10.1053/j.semperi.2017.07.002>)
- Calaf GM, Ponce-Cusi R, Aguayo F, Muñoz JP & Bleak TC 2020 Endocrine disruptors from the environment affecting breast cancer. *Oncology Letters* **20** 19–32. (<https://doi.org/10.3892/ol.2020.11566>)
- Cao J & Patisaul HB 2011 Sexually dimorphic expression of hypothalamic estrogen receptors alpha and beta and kiss1 in neonatal male and female rats. *Journal of Comparative Neurology* **519** 2954–2977. (<https://doi.org/10.1002/cne.22648>)
- Cao J & Patisaul HB 2013 Sex specific expression of estrogen receptors alpha and beta and kiss1 in the postnatal rat amygdala. *Journal of Comparative Neurology* **521** 465–478. (<https://doi.org/10.1002/cne.23185>)
- Carlsen E, Giwercman A, Keiding N & Skakkebaek NE 1992 Evidence for decreasing quality of semen during past 50 years. *BMJ* **305** 609–613. (<https://doi.org/10.1136/bmj.305.6854.609>)
- Catenza CJ, Farooq A, Shubear NS & Donkor KK 2021 A targeted review on fate, occurrence, risk and health implications of bisphenol analogues. *Chemosphere* **268** 129273. (<https://doi.org/10.1016/j.chemosphere.2020.129273>)
- Chandraseddy A, Muneyirci-Delale O, McFarlane SI & Murad OM 2008 Adverse effects of phytoestrogens on reproductive health: a report of three cases. *Complementary Therapies in Clinical Practice* **14** 132–135. (<https://doi.org/10.1016/j.ctcp.2008.01.002>)
- Clarkson J & Herbison AE 2016 Hypothalamic control of the male neonatal testosterone surge. *Philosophical Transactions of the Royal Society of London: Series B, Biological Sciences* **371** 20150115. (<https://doi.org/10.1098/rstb.2015.0115>)
- Clarkson J, Busby ER, Kirilov M, Schütz G, Sherwood NM & Herbison AE 2014 Sexual differentiation of the brain requires perinatal kisspeptin-GnRH neuron signaling. *Journal of Neuroscience* **34** 15297–15305. (<https://doi.org/10.1523/JNEUROSCI.3061-14.2014>)
- Cohn BA, La Merrill M, Krigbaum NY, Yeh G, Park JS, Zimmermann L & Cirillo PM 2015 DDT exposure in utero and breast cancer. *Journal of Clinical Endocrinology and Metabolism* **100** 2865–2872. (<https://doi.org/10.1210/jc.2015-1841>)
- Curtis LR 2001 Organophosphate antagonism of the androgen receptor. *Toxicological Sciences* **60** 1–2. (<https://doi.org/10.1093/toxsci/60.1.1>)
- D'Aloisio AA, DeRoo LA, Baird DD, Weinberg CR & Sandler DP 2013 Prenatal and infant exposures and age at menarche. *Epidemiology* **24** 277–284. (<https://doi.org/10.1097/EDE.0b013e31828062b7>)
- Davis DL, Bradlow HL, Wolff M, Woodruff T, Hoel DG & Anton-Culver H 1993 Medical hypothesis: xenoestrogens as preventable causes of breast cancer. *Environmental Health Perspectives* **101** 372–377. (<https://doi.org/10.1289/ehp.93101372>)
- Demeneix B 2014 *Losing Our Minds: How Environmental Pollution Impairs Human Intelligence and Mental Health*. Oxford, New York: Oxford University Press.
- Demeneix B, Vandenberg LN, Ivell R & Zoeller RT 2020 Thresholds and endocrine disruptors: an Endocrine Society policy perspective. *Journal of the Endocrine Society* **4** bvaa085. (<https://doi.org/10.1210/jendso/bvaa085>)
- Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT & Gore AC 2009 Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocrine Reviews* **30** 293–342. (<https://doi.org/10.1210/er.2009-0002>)
- Dickerson SM, Cunningham SL & Gore AC 2011 Prenatal PCBs disrupt early neuroendocrine development of the rat hypothalamus. *Toxicology and Applied Pharmacology* **252** 36–46. (<https://doi.org/10.1016/j.taap.2011.01.012>)
- Dirven BCJ, Homberg JR, Kozicz T & Henckens MJAG 2017 Epigenetic programming of the neuroendocrine stress response by adult life stress. *Journal of Molecular Endocrinology* **59** R11–R31. (<https://doi.org/10.1530/JME-17-0019>)
- Dudek M, Ziarniak K & Sliwowska JH 2018 Kisspeptin and metabolism: the brain and beyond. *Frontiers in Endocrinology* **9** 145. (<https://doi.org/10.3389/fendo.2018.00145>)
- EDSTAC 1998 *Endocrine Disruptor Screening and Testing Advisory Committee Final Report: Executive Summary, Vol I and Vol. II*. Washington, DC: United States Environmental Protection Agency. (available at: <https://www.epa.gov/sites/production/files/2015-08/documents/exesum14.pdf>)
- Eskenazi B, Warner M, Marks AR, Samuels S, Needham L, Brambilla P & Mocarelli P 2010 Serum dioxin concentrations and time to pregnancy. *Epidemiology* **21** 224–231. (<https://doi.org/10.1097/EDE.0b013e3181cb8b95>)
- Esteban-Vasallo MD, Aragonés N, Pollán M, López-Abente G & Perez-Gomez B 2012 Mercury, cadmium, and lead levels in human placenta:

- a systematic review. *Environmental Health Perspectives* **120** 1369–1377. (<https://doi.org/10.1289/ehp.1204952>)
- European Workshop on the Impact of Endocrine Disruptors on Human Health and Wildlife** 1996 *Report of Proceedings 1996, Environment and Climate Research Programme of DG XII of the European Commission (Report EUR 17549)* 2–4 December 1996, Weybridge, UK.
- Faber K, Jones M & Tarraza HM** 1990 Invasive squamous cell carcinoma of the vagina in a diethylstilbestrol-exposed woman. *Gynecologic Oncology* **37** 125–128. ([https://doi.org/10.1016/0090-8258\(90\)90320-k](https://doi.org/10.1016/0090-8258(90)90320-k))
- Farhat A, Buick JK, Williams A, Yauk CL, O'Brien JM, Crump D, Williams KL, Chiu S & Kennedy SW** 2014 Tris(1,3-dichloro-2-propyl) phosphate perturbs the expression of genes involved in immune response and lipid and steroid metabolism in chicken embryos. *Toxicology and Applied Pharmacology* **275** 104–112. (<https://doi.org/10.1016/j.taap.2013.12.020>)
- Farr SL, Cai J, Savitz DA, Sandler DP, Hoppin JA & Cooper GS** 2006 Pesticide exposure and timing of menopause: the Agricultural Health Study. *American Journal of Epidemiology* **163** 731–742. (<https://doi.org/10.1093/aje/kwj099>)
- Filardo EJ & Thomas P** 2012 Minireview: G protein-coupled estrogen receptor-1, GPER-1: its mechanism of action and role in female reproductive cancer, renal and vascular physiology. *Endocrinology* **153** 2953–2962. (<https://doi.org/10.1210/en.2012-1061>)
- Fritsche E, Grandjean P, Crofton KM, Aschner M, Goldberg A, Heinonen T, Hessel EVS, Hogberg HT, Bennekou SH, Lein PJ et al.** 2018 Consensus statement on the need for innovation, transition and implementation of developmental neurotoxicity (DNT) testing for regulatory purposes. *Toxicology and Applied Pharmacology* **354** 3–6. (<https://doi.org/10.1016/j.taap.2018.02.004>)
- Frye CA, Bo E, Calamandrei G, Calza L, Dessi-Fulgheri F, Fernandez M, Fusani L, Kah O, Kajta M, Le Page Y et al.** 2012 Endocrine disruptors: a review of some sources, effects, and mechanisms of actions on behaviour and neuroendocrine systems. *Journal of Neuroendocrinology* **24** 144–159. (<https://doi.org/10.1111/j.1365-2826.2011.02229.x>)
- Fucic A, Gamulin M, Ferencic Z, Katic J, Krayner von Krauss M, Bartonova A & Merlo DF** 2012 Environmental exposure to xenoestrogens and oestrogen related cancers: reproductive system, breast, lung, kidney, pancreas, and brain. *Environmental Health: A Global Access Science Source* **11** (Supplement 1) S8. (<https://doi.org/10.1186/1476-069X-11-S1-S8>)
- Fudvoye J, Lopez-Rodriguez D, Franssen D & Parent AS** 2019 Endocrine disruptors and possible contribution to pubertal changes. *Best Practice and Research: Clinical Endocrinology and Metabolism* **33** 101300. (<https://doi.org/10.1016/j.beem.2019.101300>)
- Gangolli SD** 1982 Testicular effects of phthalate esters. *Environmental Health Perspectives* **45** 77–84. (<https://doi.org/10.1289/ehp.824577>)
- Gao N, Hu R, Huang Y, Dao L, Zhang C, Liu Y, Wu L, Wang X, Yin W, Gore AC et al.** 2018 Specific effects of prenatal DEHP exposure on neuroendocrine gene expression in the developing hypothalamus of male rats. *Archives of Toxicology* **92** 501–512. (<https://doi.org/10.1007/s00204-017-2049-z>)
- García JP, Keen KL, Seminara SB & Terasawa E** 2019 Role of kisspeptin and NKB in puberty in nonhuman primates: sex differences. *Seminars in Reproductive Medicine* **37** 47–55. (<https://doi.org/10.1055/s-0039-3400253>)
- Geoffroy-Siraudin C, Loundou AD, Romain F, Achard V, Courbiere B, Perrard MH, Durand P & Guichaoua MR** 2012 Decline of semen quality among 10 932 males consulting for couple infertility over a 20-year period in Marseille, France. *Asian Journal of Andrology* **14** 584–590. (<https://doi.org/10.1038/aja.2011.173>)
- Gill WB, Schumacher GF & Bibbo M** 1976 Structural and functional abnormalities in the sex organs of male offspring of mothers treated with diethylstilbestrol (DES). *Journal of Reproductive Medicine* **16** 147–153.
- Gingrich J, Ticiani E & Veiga-Lopez A** 2020 Placenta disrupted: endocrine disrupting chemicals and pregnancy. *Trends in Endocrinology and Metabolism* **31** 508–524. (<https://doi.org/10.1016/j.tem.2020.03.003>)
- Gonzalez FJ & Nebert DW** 1990 Evolution of the P450 gene superfamily: animal-plant 'warfare', molecular drive and human genetic differences in drug oxidation. *Trends in Genetics* **6** 182–186. ([https://doi.org/10.1016/0168-9525\(90\)90174-5](https://doi.org/10.1016/0168-9525(90)90174-5))
- Gonzalez TL, Moos RK, Gersch CL, Johnson MD, Richardson RJ, Koch HM & Rae JM** 2018 Metabolites of n-butylparaben and iso-butylparaben exhibit estrogenic properties in MCF-7 and T47D human breast cancer cell lines. *Toxicological Sciences* **164** 50–59. (<https://doi.org/10.1093/toxsci/kfy063>)
- Gooren L** 2006 The biology of human psychosexual differentiation. *Hormones and Behavior* **50** 589–601. (<https://doi.org/10.1016/j.yhbeh.2006.06.011>)
- Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J & Zoeller RT** 2015 EDC-2: the Endocrine Society's second scientific statement on endocrine-disrupting chemicals. *Endocrine Reviews* **36** E1–E150. (<https://doi.org/10.1210/er.2015-1010>)
- Gore AC, Krishnan K & Reilly MP** 2019 Endocrine-disrupting chemicals: effects on neuroendocrine systems and the neurobiology of social behavior. *Hormones and Behavior* **111** 7–22. (<https://doi.org/10.1016/j.yhbeh.2018.11.006>)
- Gorski RA** 1963 Modification of ovulatory mechanisms by postnatal administration of estrogen to the rat. *American Journal of Physiology* **205** 842–844. (<https://doi.org/10.1152/ajplegacy.1963.205.5.842>)
- Goy RW & Resko JA** 1972 Gonadal hormones and behavior of normal and pseudohermaphroditic nonhuman female primates. *Recent Progress in Hormone Research* **28** 707–733.
- Graceli JB, Dettogni RS, Merlo E, Niño O, da Costa CS, Zanol JF, Ríos Morris EA, Miranda-Alves L & Denicol AC** 2020 The impact of endocrine-disrupting chemical exposure in the mammalian hypothalamic-pituitary axis. *Molecular and Cellular Endocrinology* **518** 110997. (<https://doi.org/10.1016/j.mce.2020.110997>)
- Grossman E** 2014 Time after time: environmental influences on the aging brain. *Environmental Health Perspectives* **122** A238–A243. (<https://doi.org/10.1289/ehp.122-A238>)
- Guillette Jr LJ, Gross TS, Masson GR, Matter JM, Percival HF & Woodward AR** 1994 Developmental abnormalities of the gonad and abnormal sex hormone concentrations in juvenile alligators from contaminated and control lakes in Florida. *Environmental Health Perspectives* **102** 680–688. (<https://doi.org/10.1289/ehp.94102680>)
- Guillette Jr LJ, Crain DA, Rooney AA & Pickford DB** 1995 Organization versus activation: the role of endocrine-disrupting contaminants (EDCs) during embryonic development in wildlife. *Environmental Health Perspectives* **103** (Supplement 7) 157–164. (<https://doi.org/10.1289/ehp.95103s7157>)
- Hanamsagar R & Bilbo SD** 2016 Sex differences in neurodevelopmental and neurodegenerative disorders: focus on microglial function and neuroinflammation during development. *Journal of Steroid Biochemistry and Molecular Biology* **160** 127–133. (<https://doi.org/10.1016/j.jsbmb.2015.09.039>)
- Hannas BR, Furr J, Lambright CS, Wilson VS, Foster PM & Gray Jr LE** 2011 Dipentyl phthalate dosing during sexual differentiation disrupts fetal testis function and postnatal development of the male Sprague-Dawley rat with greater relative potency than other phthalates. *Toxicological Sciences* **120** 184–193. (<https://doi.org/10.1093/toxsci/kfq386>)
- Hauser R, Skakkebaek NE, Hass U, Toppari J, Juul A, Andersson AM, Kortenkamp A, Heindel JJ & Trasande L** 2015 Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union. *Journal of Clinical Endocrinology and Metabolism* **100** 1267–1277. (<https://doi.org/10.1210/jc.2014-4325>)
- Heindel JJ, Balbus J, Birnbaum L, Brune-Drise MN, Grandjean P, Gray K, Landrigan PJ, Sly PD, Suk W, Slechts DC et al.** 2015 Developmental origins of health and disease: integrating environmental influences. *Endocrinology* **156** 3416–3421. (<https://doi.org/10.1210/EN.2015-1394>)
- Herbison AE** 2020 A simple model of estrous cycle negative and positive feedback regulation of GnRH secretion. *Frontiers in Neuroendocrinology* **57** 100837. (<https://doi.org/10.1016/j.yfrne.2020.100837>)
- Herbst AL, Green Jr TH & Ulfelder H** 1970 Primary carcinoma of the vagina: an analysis of 68 cases. *American Journal of Obstetrics and Gynecology* **106** 210–218. ([https://doi.org/10.1016/0002-9378\(70\)90265-6](https://doi.org/10.1016/0002-9378(70)90265-6))
- Herbst AL, Ulfelder H & Poskanzer DC** 1971 Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. *New England Journal of Medicine* **284** 878–881. (<https://doi.org/10.1056/NEJM197104222841604>)
- Herman-Giddens ME** 2006 Recent data on pubertal milestones in United States children: the secular trend toward earlier development. *International Journal of Andrology* **29** 241–246; discussion 286–290. (<https://doi.org/10.1111/j.1365-2605.2005.00575.x>)

- Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG & Hasemeier CM 1997 Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. *Pediatrics* **99** 505–512. (<https://doi.org/10.1542/peds.99.4.505>)
- Herting MM & Sowell ER 2017 Puberty and structural brain development in humans. *Frontiers in Neuroendocrinology* **44** 122–137. (<https://doi.org/10.1016/j.yfrne.2016.12.003>)
- Hewitt SC & Korach KS 2018 Estrogen receptors: new directions in the new millennium. *Endocrine Reviews* **39** 664–675. (<https://doi.org/10.1210/er.2018-00087>)
- Hlislíková H, Petrovičová I, Kolena B, Šidlovská M & Sirotkin A 2020 Effects and mechanisms of phthalates' action on reproductive processes and reproductive health: a literature review. *International Journal of Environmental Research and Public Health* **17** 6811. (<https://doi.org/10.3390/ijerph17186811>)
- Ho SM, Cheong A, Adgent MA, Veevers J, Suen AA, Tam NNC, Leung YK, Jefferson WN & Williams CJ 2017 Environmental factors, epigenetics, and developmental origin of reproductive disorders. *Reproductive Toxicology* **68** 85–104. (<https://doi.org/10.1016/j.reprotox.2016.07.011>)
- Hodgson E & Rose RL 2007 Human metabolic interactions of environmental chemicals. *Journal of Biochemical and Molecular Toxicology* **21** 182–186. (<https://doi.org/10.1002/jbt.20175>)
- Hooper L, Ryder JJ, Kurzer MS, Lampe JW, Messina MJ, Phipps WR & Cassidy A 2009 Effects of soy protein and isoflavones on circulating hormone concentrations in pre- and post-menopausal women: a systematic review and meta-analysis. *Human Reproduction Update* **15** 423–440. (<https://doi.org/10.1093/humupd/dmp010>)
- Hotchkiss AK, Rider CV, Blystone CR, Wilson VS, Hartig PC, Ankley GT, Foster PM, Gray CL & Gray LE 2008 Fifteen years after 'Wingspread' – environmental endocrine disruptors and human and wildlife health: where we are today and where we need to go. *Toxicological Sciences* **105** 235–259. (<https://doi.org/10.1093/toxsci/kfn030>)
- Ibitoye M, Choi C, Tai H, Lee G & Sommer M 2017 Early menarche: a systematic review of its effect on sexual and reproductive health in low- and middle-income countries. *PLoS ONE* **12** e0178884. (<https://doi.org/10.1371/journal.pone.0178884>)
- Ikezuki Y, Tsutsumi O, Takai Y, Kamei Y & Taketani Y 2002 Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. *Human Reproduction* **17** 2839–2841. (<https://doi.org/10.1093/humrep/17.11.2839>)
- Irwin MR & Cole SW 2011 Reciprocal regulation of the neural and innate immune systems. *Nature Reviews: Immunology* **11** 625–632. (<https://doi.org/10.1038/nri3042>)
- Ismail MF & Mohamed HM 2012 Deltamethrin-induced genotoxicity and testicular injury in rats: comparison with biopesticide. *Food and Chemical Toxicology* **50** 3421–3425. (<https://doi.org/10.1016/j.fct.2012.07.060>)
- Jefferson WN, Patisaul HB & Williams CJ 2012 Reproductive consequences of developmental phytoestrogen exposure. *Reproduction* **143** 247–260. (<https://doi.org/10.1530/REP-11-0369>)
- Jin Y, Zhang Q, Pan JX, Wang FF & Qu F 2019 The effects of di(2-ethylhexyl) phthalate exposure in women with polycystic ovary syndrome undergoing in vitro fertilization. *Journal of International Medical Research* **47** 6278–6293. (<https://doi.org/10.1177/0300060519876467>)
- Johansson HK, Jacobsen PR, Hass U, Svingen T, Vinggaard AM, Isling LK, Axelstad M, Christiansen S & Boberg J 2016 Perinatal exposure to mixtures of endocrine disrupting chemicals reduces female rat follicle reserves and accelerates reproductive aging. *Reproductive Toxicology* **61** 186–194. (<https://doi.org/10.1016/j.reprotox.2016.03.045>)
- Joseph JJ & Golden SH 2017 Cortisol dysregulation: the bidirectional link between stress, depression, and type 2 diabetes mellitus. *Annals of the New York Academy of Sciences* **1391** 20–34. (<https://doi.org/10.1111/nyas.13217>)
- Kamatenesi-Mugisha M & Oryem-Origa H 2007 Medicinal plants used to induce labour during childbirth in western Uganda. *Journal of Ethnopharmacology* **109** 1–9. (<https://doi.org/10.1016/j.jep.2006.06.011>)
- Kapara A & Huhtaniemi IT 2018 The hypothalamus-pituitary-gonad axis: tales of mice and men. *Metabolism: Clinical and Experimental* **86** 3–17. (<https://doi.org/10.1016/j.metabol.2017.11.018>)
- Karnaky KJ 1953 Diethylstilbestrol therapy: long period and high dosage Des therapy. *Medical Times* **81** 315–317.
- Karwacka A, Zamkowska D, Radwan M & Jurewicz J 2019 Exposure to modern, widespread environmental endocrine disrupting chemicals and their effect on the reproductive potential of women: an overview of current epidemiological evidence. *Human Fertility* **22** 2–25. (<https://doi.org/10.1080/14647273.2017.1358828>)
- Katz TA, Yang Q, Trevino LS, Walker CL & Al-Hendy A 2016 Endocrine-disrupting chemicals and uterine fibroids. *Fertility and Sterility* **106** 967–977. (<https://doi.org/10.1016/j.fertnstert.2016.08.023>)
- Kaur S, Sarma SJ, Marshall BL, Liu Y, Kinkade JA, Bellamy MM, Mao J, Helferich WG, Schenk AK, Bivens NJ et al. 2020 Developmental exposure of California mice to endocrine disrupting chemicals and potential effects on the microbiome-gut-brain axis at adulthood. *Scientific Reports* **10** 10902. (<https://doi.org/10.1038/s41598-020-67709-9>)
- Kavlock RJ & Ankley GT 1996 A perspective on the risk assessment process for endocrine-disruptive effects on wildlife and human health. *Risk Analysis* **16** 731–739. (<https://doi.org/10.1111/j.1539-6924.1996.tb00824.x>)
- Kavlock RJ, Daston GP, DeRosa C, Fenner-Crisp P, Gray LE, Kaattari S, Lucier G, Luster M, Mac MJ, Maczka C et al. 1996 Research needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the U.S. EPA-sponsored workshop. *Environmental Health Perspectives* **104** (Supplement 4) 715–740. (<https://doi.org/10.1289/ehp.96104s4715>)
- Kawaguchi M, Morohoshi K, Imai H, Morita M, Kato N & Himi T 2010 Maternal exposure to isobutyl-paraben impairs social recognition in adult female rats. *Experimental Animals* **59** 631–635. (<https://doi.org/10.1538/expanim.59.631>)
- Kendig EL, Le HH & Belcher SM 2010 Defining hormesis: evaluation of a complex concentration response phenomenon. *International Journal of Toxicology* **29** 235–246. (<https://doi.org/10.1177/1091581810363012>)
- Kern JK, Geier DA, Homme KG, King PG, Bjorklund G, Chirumbolo S & Geier MR 2017 Developmental neurotoxicants and the vulnerable male brain: a systematic review of suspected neurotoxicants that disproportionately affect males. *Acta Neurobiologiae Experimentalis* **77** 269–296. (<https://doi.org/10.21307/ane-2017-061>)
- Kim YR, Pacella RE, Harden FA, White N & Toms LL 2019 A systematic review: impact of endocrine disrupting chemicals exposure on fecundity as measured by time to pregnancy. *Environmental Research* **171** 119–133. (<https://doi.org/10.1016/j.envres.2018.12.065>)
- Kinch CD, Ibahazehiebo K, Jeong JH, Habibi HR & Kurrasch DM 2015 Low-dose exposure to bisphenol A and replacement bisphenol S induces precocious hypothalamic neurogenesis in embryonic zebrafish. *PNAS* **112** 1475–1480. (<https://doi.org/10.1073/pnas.1417731112>)
- Konkel L 2016 Lasting impact of an ephemeral organ: the role of the placenta in fetal programming. *Environmental Health Perspectives* **124** A124–A129. (<https://doi.org/10.1289/ehp.124-A124>)
- Kristensen DM, Mazaud-Guittot S, Gaudriault P, Lesné L, Serrano T, Main KM & Jégou B 2016 Analgesic use – prevalence, biomonitoring and endocrine and reproductive effects. *Nature Reviews: Endocrinology* **12** 381–393. (<https://doi.org/10.1038/nrendo.2016.55>)
- Kuchera LK 1971 Postcoital contraception with diethylstilbestrol. *JAMA* **218** 562.
- La Merrill MA, Vandenberg LN, Smith MT, Goodson W, Browne P, Patisaul HB, Guyton KZ, Kortenkamp A, Coglian VJ, Woodruff TJ et al. 2020 Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. *Nature Reviews: Endocrinology* **16** 45–57. (<https://doi.org/10.1038/s41574-019-0273-8>)
- Lagarde F, Beausoleil C, Belcher SM, Belzunces LP, Emond C, Guerbet M & Rousselle C 2015 Non-monotonic dose-response relationships and endocrine disruptors: a qualitative method of assessment. *Environmental Health: A Global Access Science Source* **14** 13. (<https://doi.org/10.1186/1476-069X-14-13>)
- Leatherland J 1992 Endocrine and reproductive function in Great Lakes salmon. In *Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection*, pp. 129–145. Eds T Colborn & C Clement. Princeton: Princeton Scientific Publishing.
- Leazer TM & Klaassen CD 2003 The presence of xenobiotic transporters in rat placenta. *Drug Metabolism and Disposition* **31** 153–167. (<https://doi.org/10.1124/dmd.31.2.153>)
- Lenz KM & McCarthy MM 2015 A starring role for microglia in brain sex differences. *Neuroscientist* **21** 306–321. (<https://doi.org/10.1177/1073858414536468>)

- Leonetti C, Butt CM, Hoffman K, Hammel SC, Miranda ML & Stapleton HM 2016a Brominated flame retardants in placental tissues: associations with infant sex and thyroid hormone endpoints. *Environmental Health: A Global Access Science Source* **15** 113. (<https://doi.org/10.1186/s12940-016-0199-8>)
- Leonetti C, Butt CM, Hoffman K, Miranda ML & Stapleton HM 2016b Concentrations of polybrominated diphenyl ethers (PBDEs) and 2,4,6-tribromophenol in human placental tissues. *Environment International* **88** 23–29. (<https://doi.org/10.1016/j.envint.2015.12.002>)
- Li W, Liu Q, Deng X, Chen Y, Liu S & Story M 2017 Association between obesity and puberty timing: a systematic review and meta-analysis. *International Journal of Environmental Research and Public Health* **14** 1266. (<https://doi.org/10.3390/ijerph14101266>)
- Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A & Hemminki K 2000 Environmental and heritable factors in the causation of cancer – analyses of cohorts of twins from Sweden, Denmark, and Finland. *New England Journal of Medicine* **343** 78–85. (<https://doi.org/10.1056/NEJM200007133430201>)
- Ling C, Liew Z, von Ehrenstein OS, Heck JE, Park AS, Cui X, Cockburn M, Wu J & Ritz B 2018 Prenatal exposure to ambient pesticides and preterm birth and term low birthweight in agricultural regions of California. *Toxics* **6** 41. (<https://doi.org/10.3390/toxics6030041>)
- Liu X & Herbison AE 2013 Dopamine regulation of gonadotropin-releasing hormone neuron excitability in male and female mice. *Endocrinology* **154** 340–350. (<https://doi.org/10.1210/en.2012-1602>)
- Liu X, Ji K, Jo A, Moon HB & Choi K 2013 Effects of TDCPP or TPP on gene transcriptions and hormones of HPG axis, and their consequences on reproduction in adult zebrafish (*Danio rerio*). *Aquatic Toxicology* **134–135** 104–111. (<https://doi.org/10.1016/j.aquatox.2013.03.013>)
- Livadas S & Chrousos GP 2016 Control of the onset of puberty. *Current Opinion in Pediatrics* **28** 551–558. (<https://doi.org/10.1097/MOP.0000000000000386>)
- Losa SM, Todd KL, Sullivan AW, Cao J, Mickens JA & Patissaul HB 2011 Neonatal exposure to genistein adversely impacts the ontogeny of hypothalamic kisspeptin signaling pathways and ovarian development in the peripubertal female rat. *Reproductive Toxicology* **31** 280–289. (<https://doi.org/10.1016/j.reprotox.2010.10.002>)
- Lucaccioni L, Trevisani V, Marrozzini L, Bertoncelli N, Predieri B, Lugli L, Berardi A & Iughetti L 2020 Endocrine-disrupting chemicals and their effects during female puberty: a review of current evidence. *International Journal of Molecular Sciences* **21** 2078. (<https://doi.org/10.3390/ijms21062078>)
- Manfo FP, Nantia EA & Mathur PP 2014 Effect of environmental contaminants on mammalian testis. *Current Molecular Pharmacology* **7** 119–135. (<https://doi.org/10.2174/1874467208666150126155420>)
- Mao J, Jain A, Denslow ND, Nouri MZ, Chen S, Wang T, Zhu N, Koh J, Sarma SJ, Sumner BW *et al.* 2020 Bisphenol A and bisphenol S disruptions of the mouse placenta and potential effects on the placenta-brain axis. *PNAS* **117** 4642–4652. (<https://doi.org/10.1073/pnas.1919563117>)
- Marler P 2005 Ethology and the origins of behavioral endocrinology. *Hormones and Behavior* **47** 493–502. (<https://doi.org/10.1016/j.yhbeh.2005.01.002>)
- Martin JA, Hamilton BE, Osterman MJK & Driscoll AK 2019 Births: final data for 2018. *National Vital Statistics Reports* **68** 1–47. (PMID:32501202)
- Mbuni YM, Wang S, Mwangi BN, Mburi NJ, Musili PM, Walter NO, Hu G, Zhou Y & Wang Q 2020 Medicinal plants and their traditional uses in local communities around Cherangani Hills, Western Kenya. *Plants* **9** 331. (<https://doi.org/10.3390/plants9030331>)
- McCarthy MM 2008 Estradiol and the developing brain. *Physiological Reviews* **88** 91–124. (<https://doi.org/10.1152/physrev.00010.2007>)
- McCarthy MM 2016 Sex differences in the developing brain as a source of inherent risk. *Dialogues in Clinical Neuroscience* **18** 361–372. (<https://doi.org/10.31887/DCNS.2016.18.4/mmccarthy>)
- McCarthy MM 2020 A new view of sexual differentiation of mammalian brain. *Journal of Comparative Physiology: A, Neuroethology, Sensory, Neural, and Behavioral Physiology* **206** 369–378. (<https://doi.org/10.1007/s00359-019-01376-8>)
- McCarthy MM, Wright CL & Schwarz JM 2009 New tricks by an old dogma: mechanisms of the organizational/activational hypothesis of steroid-mediated sexual differentiation of brain and behavior. *Hormones and Behavior* **55** 655–665. (<https://doi.org/10.1016/j.yhbeh.2009.02.012>)
- McCarthy MM, Herold K & Stockman SL 2018 Fast, furious and enduring: sensitive versus critical periods in sexual differentiation of the brain. *Physiology and Behavior* **187** 13–19. (<https://doi.org/10.1016/j.physbeh.2017.10.030>)
- McLachlan JA 2016 Environmental signaling: from environmental estrogens to endocrine-disrupting chemicals and beyond. *Andrology* **4** 684–694. (<https://doi.org/10.1111/andr.12206>)
- McLachlan JA, Newbold RR, Shah HC, Hogan MD & Dixon RL 1982 Reduced fertility in female mice exposed transplacentally to diethylstilbestrol (DES). *Fertility and Sterility* **38** 364–371. ([https://doi.org/10.1016/s0015-0282\(16\)46520-9](https://doi.org/10.1016/s0015-0282(16)46520-9))
- Melnick R, Lucier G, Wolfe M, Hall R, Stancel G, Prins G, Gallo M, Reuhl K, Ho SM, Brown T *et al.* 2002 Summary of the National Toxicology Program's report of the endocrine disruptors low-dose peer review. *Environmental Health Perspectives* **110** 427–431. (<https://doi.org/10.1289/ehp.02110427>)
- Merrheim J, Villegas J, Van Wassenhove J, Khansa R, Berrih-Aknin S, le Panse R & Dragin N 2020 Estrogen, estrogen-like molecules and autoimmune diseases. *Autoimmunity Reviews* **19** 102468. (<https://doi.org/10.1016/j.autrev.2020.102468>)
- Meyer N & Zencius AC 2020 Immune cells in the uterine remodeling: are they the target of endocrine disrupting chemicals? *Frontiers in Immunology* **11** 246. (<https://doi.org/10.3389/fimmu.2020.00246>)
- Micevych PE, Wong AM & Mittelman-Smith MA 2015 Estradiol membrane-initiated signaling and female reproduction. *Comprehensive Physiology* **5** 1211–1222. (<https://doi.org/10.1002/cphy.c140056>)
- Milligan SR, Khan O & Nash M 1998 Competitive binding of xenobiotic oestrogens to rat alpha-fetoprotein and to sex steroid binding proteins in human and rainbow trout (*Oncorhynchus mykiss*) plasma. *General and Comparative Endocrinology* **112** 89–95. (<https://doi.org/10.1006/gcen.1998.7146>)
- Mínguez-Alarcón L, Williams PL, Chiu YH, Gaskins AJ, Nassan FL, Dadd R, Petrozza J, Hauser R, Chavarro JE & Earth Study Team 2018 Secular trends in semen parameters among men attending a fertility center between 2000 and 2017: identifying potential predictors. *Environment International* **121** 1297–1303. (<https://doi.org/10.1016/j.envint.2018.10.052>)
- Mínguez-Alarcón L, Messerlian C, Bellavia A, Gaskins AJ, Chiu YH, Ford JB, Azevedo AR, Petrozza JC, Calafat AM, Hauser R *et al.* 2019 Urinary concentrations of bisphenol A, parabens and phthalate metabolite mixtures in relation to reproductive success among women undergoing in vitro fertilization. *Environment International* **126** 355–362. (<https://doi.org/10.1016/j.envint.2019.02.025>)
- Mittelman-Smith MA, Rudolph LM, Mohr MA & Micevych PE 2017 Rodent models of non-classical progesterone action regulating ovulation. *Frontiers in Endocrinology* **8** 165. (<https://doi.org/10.3389/fendo.2017.00165>)
- Moore AM, Coolen LM, Porter DT, Goodman RL & Lehman MN 2018 KNDy cells revisited. *Endocrinology* **159** 3219–3234. (<https://doi.org/10.1210/en.2018-00389>)
- Mueller JK & Heger S 2014 Endocrine disrupting chemicals affect the gonadotropin releasing hormone neuronal network. *Reproductive Toxicology* **44** 73–84. (<https://doi.org/10.1016/j.reprotox.2013.10.011>)
- Myatt L 2006 Placental adaptive responses and fetal programming. *Journal of Physiology* **572** 25–30. (<https://doi.org/10.1113/jphysiol.2006.104968>)
- Neubert da Silva G, Zauer Curi T, Lima Tolouei SE, Tapias Passoni M, Sari Hey GB, Marino Romano R, Martino-Andrade AJ & Dalsenter PR 2019 Effects of diisopentyl phthalate exposure during gestation and lactation on hormone-dependent behaviours and hormone receptor expression in rats. *Journal of Neuroendocrinology* **31** e12816. (<https://doi.org/10.1111/jne.12816>)
- Newbold RR 2008 Prenatal exposure to diethylstilbestrol (DES). *Fertility and Sterility* **89** (Supplement) e55–e56. (<https://doi.org/10.1016/j.fertnstert.2008.01.062>)
- Newbold RR & McLachlan JA 1982 Vaginal adenosis and adenocarcinoma in mice exposed prenatally or neonatally to diethylstilbestrol. *Cancer Research* **42** 2003–2011.
- Ohlsson C, Bygdell M, Celind J, Sondén A, Tidblad A, Sävendahl L & Kindblom JM 2019 Secular trends in pubertal growth acceleration in Swedish boys born from 1947 to 1996. *JAMA Pediatrics* **173** 860–865. (<https://doi.org/10.1001/jamapediatrics.2019.2315>)

- Palmer JR, Wise LA, Robboy SJ, Titus-Ernstoff L, Noller KL, Herbst AL, Troisi R & Hoover RN 2005 Hypospadias in sons of women exposed to diethylstilbestrol in utero. *Epidemiology* **16** 583–586. (<https://doi.org/10.1097/01.ede.0000164789.59728.6d>)
- Palmlund I 1996 Exposure to a xenoestrogen before birth: the diethylstilbestrol experience. *Journal of Psychosomatic Obstetrics and Gynaecology* **17** 71–84. (<https://doi.org/10.3109/01674829609025667>)
- Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J & Bourguignon JP 2003 The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. *Endocrine Reviews* **24** 668–693. (<https://doi.org/10.1210/er.2002-0019>)
- Partsch CJ & Sippell WG 2001 Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens. *Human Reproduction Update* **7** 292–302. (<https://doi.org/10.1093/humupd/7.3.292>)
- Patisaul HB 2013 Effects of environmental endocrine disruptors and phytoestrogens on the kisspeptin system. *Advances in Experimental Medicine and Biology* **784** 455–479. (https://doi.org/10.1007/978-1-4614-6199-9_21)
- Patisaul HB 2017a Endocrine disruption by dietary phyto-oestrogens: impact on dimorphic sexual systems and behaviours. *Proceedings of the Nutrition Society* **76** 130–144. (<https://doi.org/10.1017/S0029665116000677>)
- Patisaul HB 2017b Endocrine disruption of vasopressin systems and related behaviors. *Frontiers in Endocrinology* **8** 134. (<https://doi.org/10.3389/fendo.2017.00134>)
- Patisaul HB 2020 Achieving clarity on bisphenol A, brain and behaviour. *Journal of Neuroendocrinology* **32** e12730. (<https://doi.org/10.1111/jne.12730>)
- Patisaul HB & Jefferson W 2010 The pros and cons of phytoestrogens. *Frontiers in Neuroendocrinology* **31** 400–419. (<https://doi.org/10.1016/j.yfrne.2010.03.003>)
- Patisaul HB, Fortino AE & Polston EK 2006 Neonatal genistein or bisphenol-A exposure alters sexual differentiation of the AVPV. *Neurotoxicology and Teratology* **28** 111–118. (<https://doi.org/10.1016/j.ntt.2005.11.004>)
- Perera BPU, Faulk C, Svoboda LK, Goodrich JM & Dolinoy DC 2020 The role of environmental exposures and the epigenome in health and disease. *Environmental and Molecular Mutagenesis* **61** 176–192. (<https://doi.org/10.1002/em.22311>)
- Phillips AL, Chen A, Rock KD, Horman B, Patisaul HB & Stapleton HM 2016 Editor's highlight: transplacental and lactational transfer of firemaster(R) 550 components in dosed Wistar rats. *Toxicological Sciences* **153** 246–257. (<https://doi.org/10.1093/toxsci/kfw122>)
- Piette PCM 2020 The pharmacodynamics and safety of progesterone. *Best Practice and Research: Clinical Obstetrics and Gynaecology* **69** 13–29. (<https://doi.org/10.1016/j.bpobgyn.2020.06.002>)
- Prins GS, Hu WY, Shi GB, Hu DP, Majumdar S, Li G, Huang K, Nelles JL, Ho SM, Walker CL *et al.* 2014 Bisphenol A promotes human prostate stem-progenitor cell self-renewal and increases in vivo carcinogenesis in human prostate epithelium. *Endocrinology* **155** 805–817. (<https://doi.org/10.1210/en.2013-1955>)
- Priskorn L, Bang AK, Nordkap L, Krause M, Mendiola J, Jensen TK, Juul A, Skakkebaek NE, Swan SH & Jorgensen N 2019 Anogenital distance is associated with semen quality but not reproductive hormones in 1106 young men from the general population. *Human Reproduction* **34** 12–24. (<https://doi.org/10.1093/humrep/dey326>)
- Proos LA, Hofvander Y & Tuvemo T 1991 Menarcheal age and growth pattern of Indian girls adopted in Sweden. I. Menarcheal age. *Acta Paediatrica Scandinavica* **80** 852–858. (<https://doi.org/10.1111/j.1651-2227.1991.tb11960.x>)
- Puts D & Motta-Mena NV 2018 Is human brain masculinization estrogen receptor-mediated? Reply to Luoto and Rantala. *Hormones and Behavior* **97** 3–4. (<https://doi.org/10.1016/j.yhbeh.2017.07.018>)
- Qie Y, Qin W, Zhao K, Liu C, Zhao L & Guo LH 2021 Environmental estrogens and their biological effects through GPER mediated signal pathways. *Environmental Pollution* **278** 116826. (<https://doi.org/10.1016/j.envpol.2021.116826>)
- Ragusa A, Svelato A, Santacroce C, Catalano P, Notarstefano V, Carnevali O, Papa F, Rongioletti MCA, Baiocco F, Draghi S *et al.* 2021 Placenta: first evidence of microplastics in human placenta. *Environment International* **146** 106274. (<https://doi.org/10.1016/j.envint.2020.106274>)
- Rahban R, Priskorn L, Senn A, Stettler E, Galli F, Vargas J, Van den Bergh M, Fusconi A, Garlantezec R, Jensen TK *et al.* 2019 Semen quality of young men in Switzerland: a nationwide cross-sectional population-based study. *Andrology* **7** 818–826. (<https://doi.org/10.1111/andr.12645>)
- Ramesh SA, Tyerman SD, Xu B, Bose J, Kaur S, Conn V, Domingos P, Ullah S, Wege S, Shabala S *et al.* 2015 GABA signalling modulates plant growth by directly regulating the activity of plant-specific anion transporters. *Nature Communications* **6** 7879. (<https://doi.org/10.1038/ncomms8879>)
- Rasier G, Toppari J, Parent AS & Bourguignon JP 2006 Female sexual maturation and reproduction after prepubertal exposure to estrogens and endocrine disrupting chemicals: a review of rodent and human data. *Molecular and Cellular Endocrinology* **254–255** 187–201. (<https://doi.org/10.1016/j.mce.2006.04.002>)
- Rattan S, Zhou C, Chiang C, Mahalingam S, Brehm E & Flaws JA 2017 Exposure to endocrine disruptors during adulthood: consequences for female fertility. *Journal of Endocrinology* **233** R109–R129. (<https://doi.org/10.1533/JOE-17-0023>)
- Rebuli ME, Gibson P, Rhodes CL, Cushing BS & Patisaul HB 2016 Sex differences in microglial colonization and vulnerabilities to endocrine disruption in the social brain. *General and Comparative Endocrinology* **238** 39–46. (<https://doi.org/10.1016/j.ygcen.2016.04.018>)
- Reed CE & Fenton SE 2013 Exposure to diethylstilbestrol during sensitive life stages: a legacy of heritable health effects. *Birth Defects Research: Part C, Embryo Today: Reviews* **99** 134–146. (<https://doi.org/10.1002/bdrc.21035>)
- Reers AR, Eng ML, Williams TD, Elliott JE, Cox ME & Beischlag TV 2016 The flame-retardant Tris(1,3-dichloro-2-propyl) phosphate represses androgen signaling in human prostate cancer cell lines. *Journal of Biochemical and Molecular Toxicology* **30** 249–257. (<https://doi.org/10.1002/jbt.21786>)
- Reinehr T & Roth CL 2019 Is there a causal relationship between obesity and puberty? *Lancet: Child and Adolescent Health* **3** 44–54. ([https://doi.org/10.1016/S2352-4642\(18\)30306-7](https://doi.org/10.1016/S2352-4642(18)30306-7))
- Rissman EF & Adli M 2014 Minireview: transgenerational epigenetic inheritance: focus on endocrine disrupting compounds. *Endocrinology* **155** 2770–2780. (<https://doi.org/10.1210/en.2014-1123>)
- Robboy SJ, Szyfelbein WM, Goellner JR, Kaufman RH, Taft PD, Richard RM, Gaffey TA, Prat J, Virata R, Hatab PA *et al.* 1981 Dysplasia and cytologic findings in 4,589 young women enrolled in diethylstilbestrol-adenosis (DESAD) project. *American Journal of Obstetrics and Gynecology* **140** 579–586. ([https://doi.org/10.1016/0002-9378\(81\)90236-2](https://doi.org/10.1016/0002-9378(81)90236-2))
- Robboy SJ, Young RH, Welch WR, Truslow GY, Prat J, Herbst AL & Scully RE 1984 Atypical vaginal adenosis and cervical ectropion: association with clear cell adenocarcinoma in diethylstilbestrol-exposed offspring. *Cancer* **54** 869–875. ([https://doi.org/10.1002/1097-0142\(19840901\)54:5<869::aid-cnrc2820540519>3.0.co;2-i](https://doi.org/10.1002/1097-0142(19840901)54:5<869::aid-cnrc2820540519>3.0.co;2-i))
- Rochester JR, Bolden AL, Pelch KE & Kwiatkowski CF 2017 Potential developmental and reproductive impacts of triclocarban: a scoping review. *Journal of Toxicology* **2017** 9679738. (<https://doi.org/10.1155/2017/9679738>)
- Rock KD, Horman B, Phillips AL, McRitchie SL, Watson S, Deese-Spruill J, Jima D, Sumner S, Stapleton HM & Patisaul HB 2018 EDC IMPACT: molecular effects of developmental FM 550 exposure in Wistar rat placenta and fetal forebrain. *Endocrine Connections* **7** 305–324. (<https://doi.org/10.1530/EC-17-0373>)
- Rodgers KM, Udesky JO, Rudel RA & Brody JG 2018 Environmental chemicals and breast cancer: an updated review of epidemiological literature informed by biological mechanisms. *Environmental Research* **160** 152–182. (<https://doi.org/10.1016/j.envres.2017.08.045>)
- Roman P, Cardona D, Sempere L & Carvajal F 2019 Microbiota and organophosphates. *Neurotoxicology* **75** 200–208. (<https://doi.org/10.1016/j.neuro.2019.09.013>)
- Roselli CE 2018 Neurobiology of gender identity and sexual orientation. *Journal of Neuroendocrinology* **30** e12562. (<https://doi.org/10.1111/jne.12562>)
- Ruiz-Pino F, Miceli D, Franssen D, Vazquez MJ, Farinetti A, Castellano JM, Panzica G & Tena-Sempere M 2019 Environmentally relevant perinatal exposures to bisphenol A disrupt postnatal Kiss1/NKB neuronal maturation and puberty onset in female mice. *Environmental Health Perspectives* **127** 107011. (<https://doi.org/10.1289/EHP5570>)

- Saunders DM, Podaima M, Codling G, Giesy JP & Wiseman S 2015 A mixture of the novel brominated flame retardants TBPH and TBB affects fecundity and transcript profiles of the HPGL-axis in Japanese medaka. *Aquatic Toxicology* **158** 14–21. (<https://doi.org/10.1016/j.aquatox.2014.10.019>)
- Savic I, Frisen L, Manzouri A, Nordenstrom A & Lindén Hirschberg A 2017 Role of testosterone and Y chromosome genes for the masculinization of the human brain. *Human Brain Mapping* **38** 1801–1814. (<https://doi.org/10.1002/hbm.23483>)
- Scherer LD, Maynard A, Dolinoy DC, Fagerlin A & Zikmund-Fisher BJ 2014 The psychology of ‘regrettable substitutions’: examining consumer judgements of bisphenol A and its alternatives. *Health, Risk and Society* **16** 649–666. (<https://doi.org/10.1080/13698575.2014.969687>)
- Schug TT, Blawas AM, Gray K, Heindel JJ & Lawler CP 2015 Elucidating the links between endocrine disruptors and future directions. *Molecular Endocrinology* **156** 1941–1951. (<https://doi.org/10.1210/en.2014-1734>)
- Schug TT, Johnson AF, Birnbaum LS, Colborn T, Guillette Jr LJ, Crews DP, Collins T, Soto AM, Vom Saal FS, McLachlan JA *et al.* 2016 Minireview: endocrine disruptors: past lessons and future directions. *Molecular Endocrinology* **30** 833–847. (<https://doi.org/10.1210/me.2016-1096>)
- Schulz KM & Sisk CL 2016 The organizing actions of adolescent gonadal steroid hormones on brain and behavioral development. *Neuroscience and Biobehavioral Reviews* **70** 148–158. (<https://doi.org/10.1016/j.neubiorev.2016.07.036>)
- Schulz KM, Molenda-Figueira HA & Sisk CL 2009 Back to the future: the organizational-activational hypothesis adapted to puberty and adolescence. *Hormones and Behavior* **55** 597–604. (<https://doi.org/10.1016/j.yhbeh.2009.03.010>)
- Schwartz CL, Christiansen S, Vinggaard AM, Axelstad M, Hass U & Svingen T 2019 Anogenital distance as a toxicological or clinical marker for fetal androgen action and risk for reproductive disorders. *Archives of Toxicology* **93** 253–272. (<https://doi.org/10.1007/s00204-018-2350-5>)
- Schwarz JM, Sholar PW & Bilbo SD 2012 Sex differences in microglial colonization of the developing rat brain. *Journal of Neurochemistry* **120** 948–963. (<https://doi.org/10.1111/j.1471-4159.2011.07630.x>)
- Sear R, Sheppard P & Coall DA 2019 Cross-cultural evidence does not support universal acceleration of puberty in father-absent households. *Philosophical Transactions of the Royal Society of London Series B* **374** 20180124. (<https://doi.org/10.1098/rstb.2018.0124>)
- Semenza JC, Tolbert PE, Rubin CH, Guillette Jr LJ & Jackson RJ 1997 Reproductive toxins and alligator abnormalities at Lake Apopka, Florida. *Environmental Health Perspectives* **105** 1030–1032. (<https://doi.org/10.1289/ehp.971051030>)
- Sengupta P, Nwagha U, Dutta S, Krajewska-Kulak E & Izuka E 2017 Evidence for decreasing sperm count in African population from 1965 to 2015. *African Health Sciences* **17** 418–427. (<https://doi.org/10.4314/ahs.v17i2.16>)
- Sengupta P, Borges Jr E, Dutta S & Krajewska-Kulak E 2018 Decline in sperm count in European men during the past 50 years. *Human and Experimental Toxicology* **37** 247–255. (<https://doi.org/10.1177/0960327117703690>)
- Sharpe RM & Skakkebaek NE 2008 Testicular dysgenesis syndrome: mechanistic insights and potential new downstream effects. *Fertility and Sterility* **89** (Supplement) e33–e38. (<https://doi.org/10.1016/j.fertnstert.2007.12.026>)
- Shen J, Kang Q, Mao Y, Yuan M, Le F, Yang X, Xu X & Jin F 2020 Urinary bisphenol A concentration is correlated with poorer oocyte retrieval and embryo implantation outcomes in patients with tubal factor infertility undergoing *in vitro* fertilisation. *Ecotoxicology and Environmental Safety* **187** 109816. (<https://doi.org/10.1016/j.ecoenv.2019.109816>)
- Simerly RB 2002 Wired for reproduction: organization and development of sexually dimorphic circuits in the mammalian forebrain. *Annual Review of Neuroscience* **25** 507–536. (<https://doi.org/10.1146/annurev.neuro.25.112701.142745>)
- Sisk CL 2016 Hormone-dependent adolescent organization of socio-sexual behaviors in mammals. *Current Opinion in Neurobiology* **38** 63–68. (<https://doi.org/10.1016/j.conb.2016.02.004>)
- Smith OW 1948 Diethylstilbestrol in the prevention and treatment of complications of pregnancy. *American Journal of Obstetrics and Gynecology* **56** 821–834. ([https://doi.org/10.1016/0002-9378\(48\)90440-2](https://doi.org/10.1016/0002-9378(48)90440-2))
- Snijder CA, te Velde E, Roelleveld N & Burdorf A 2012 Occupational exposure to chemical substances and time to pregnancy: a systematic review. *Human Reproduction Update* **18** 284–300. (<https://doi.org/10.1093/humupd/dms005>)
- Sobolewski M, Abston K, Conrad K, Marvin E, Harvey K, Susiarjo M & Cory-Slechta DA 2020 Lineage- and sex-dependent behavioral and biochemical transgenerational consequences of developmental exposure to lead, prenatal stress, and combined lead and prenatal stress in mice. *Environmental Health Perspectives* **128** 27001. (<https://doi.org/10.1289/EHP4977>)
- Sohn K. 2017 The null relation between father absence and earlier menarche. *Human Nature* **28** 407–422. (<https://doi.org/10.1007/s12110-017-9299-6>)
- Solecki R, Kortenkamp A, Bergman Å, Chahoud I, Degen GH, Dietrich D, Greim H, Hakansson H, Hass U, Husoy T *et al.* 2017 Scientific principles for the identification of endocrine-disrupting chemicals: a consensus statement. *Archives of Toxicology* **91** 1001–1006. (<https://doi.org/10.1007/s00204-016-1866-9>)
- Spergel DJ 2019 Modulation of gonadotropin-releasing hormone neuron activity and secretion in mice by non-peptide neurotransmitters, gasotransmitters, and gliotransmitters. *Frontiers in Endocrinology* **10** 329. (<https://doi.org/10.3389/fendo.2019.00329>)
- Stenchever MA, Williamson RA, Leonard J, Karp LE, Ley B, Shy K & Smith D 1981 Possible relationship between in utero diethylstilbestrol exposure and male fertility. *American Journal of Obstetrics and Gynecology* **140** 186–193. ([https://doi.org/10.1016/0002-9378\(81\)90107-1](https://doi.org/10.1016/0002-9378(81)90107-1))
- Stieb DM, Chen L, Eshoul M & Judek S 2012 Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. *Environmental Research* **117** 100–111. (<https://doi.org/10.1016/j.envres.2012.05.007>)
- Sullivan AW, Beach EC, Stetzik LA, Perry A, D’Addezio AS, Cushing BS & Patisaul HB 2014 A novel model for neuroendocrine toxicology: neurobehavioral effects of BPA exposure in a prosocial species, the prairie vole (*Microtus ochrogaster*). *Endocrinology* **155** 3867–3881. (<https://doi.org/10.1210/en.2014-1379>)
- Swaab DF & Hofman MA 1984 Sexual differentiation of the human brain. A historical perspective. *Progress in Brain Research* **61** 361–374. ([https://doi.org/10.1016/S0079-6123\(08\)64447-7](https://doi.org/10.1016/S0079-6123(08)64447-7))
- Swan SH & Colino S 2021 *Count Down: How Our Modern World is Threatening Sperm Counts, Altering Male and Female Reproductive Development, and Imperiling the Future of the Human Race*, 1st ed. New York: Scribner.
- Swan SH, Elkin EP & Fenster L 2000 The question of declining sperm density revisited: an analysis of 101 studies published 1934–1996. *Environmental Health Perspectives* **108** 961–966. (<https://doi.org/10.1289/ehp.00108961>)
- Tabb MM & Blumberg B 2006 New modes of action for endocrine-disrupting chemicals. *Molecular Endocrinology* **20** 475–482. (<https://doi.org/10.1210/me.2004-0513>)
- Tena-Sempere M 2010 Kisspeptin/GPR54 system as potential target for endocrine disruption of reproductive development and function. *International Journal of Andrology* **33** 360–368. (<https://doi.org/10.1111/j.1365-2605.2009.01012.x>)
- Thakamony A, Pasterski V, Ong KK, Acerini CL & Hughes IA 2016 Anogenital distance as a marker of androgen exposure in humans. *Andrology* **4** 616–625. (<https://doi.org/10.1111/andr.12156>)
- Thayer KA, Melnick R, Huff J, Burns K & Davis D 2006 Hormesis: a new religion? *Environmental Health Perspectives* **114** A632–A633. (<https://doi.org/10.1289/ehp.114-1665404>)
- Toppiari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillette Jr LJ, Jegou B, Jensen TK, Jouannet P, Keiding N *et al.* 1996 Male reproductive health and environmental xenoestrogens. *Environmental Health Perspectives* **104** (Supplement 4) 741–803. (<https://doi.org/10.1289/ehp.96104s4741>)
- Toppiari J, Virtanen HE, Main KM & Skakkebaek NE 2010 Cryptorchidism and hypospadias as a sign of testicular dysgenesis syndrome (TDS): environmental connection. *Birth Defects Research: Part A, Clinical and Molecular Teratology* **88** 910–919. (<https://doi.org/10.1002/bdra.20707>)
- Trasande L 2017 Exploring regrettable substitution: replacements for bisphenol A. *Lancet: Planetary Health* **1** e88–e89. ([https://doi.org/10.1016/S2542-5196\(17\)30046-3](https://doi.org/10.1016/S2542-5196(17)30046-3))
- Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, DiGangi J, Bellanger M, Hauser R, Legler J *et al.* 2015 Estimating burden

- and disease costs of exposure to endocrine-disrupting chemicals in the European Union. *Journal of Clinical Endocrinology and Metabolism* **100** 1245–1255. (<https://doi.org/10.1210/jc.2014-4324>)
- Tweeddale AC** 2017 The inadequacies of pre-market chemical risk assessment's toxicity studies-the implications. *Journal of Applied Toxicology* **37** 92–104. (<https://doi.org/10.1002/jat.3396>)
- Van Cauwenbergh O, Di Serafino A, Tytgat J & Soubry A** 2020 Transgenerational epigenetic effects from male exposure to endocrine-disrupting compounds: a systematic review on research in mammals. *Clinical Epigenetics* **12** 65. (<https://doi.org/10.1186/s13148-020-00845-1>)
- van de Bor M** 2019 Fetal toxicology. *Handbook of Clinical Neurology* **162** 31–55. (<https://doi.org/10.1016/B978-0-444-64029-1.00002-3>)
- Vandenberg LN, Hauser R, Marcus M, Olea N & Welshons WV** 2007 Human exposure to bisphenol A (BPA). *Reproductive Toxicology* **24** 139–177. (<https://doi.org/10.1016/j.reprotox.2007.07.010>)
- Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs Jr DR, Lee DH, Shioda T, Soto AM, Vom Saal FS, Welshons WV et al.** 2012 Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocrine Reviews* **33** 378–455. (<https://doi.org/10.1210/er.2011-1050>)
- Vandenberg LN, Ågerstrand M, Beronius A, Beausoleil C, Bergman Å, Bero LA, Bornhag CG, Boyer CS, Cooper GS, Cotgreave I et al.** 2016 A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals. *Environmental Health: A Global Access Science Source* **15** 74. (<https://doi.org/10.1186/s12940-016-0156-6>)
- Vandenberg LN, Hunt PA & Gore AC** 2019 Endocrine disruptors and the future of toxicology testing – lessons from CLARITY-BPA. *Nature Reviews: Endocrinology* **15** 366–374 (<https://doi.org/10.1038/s41574-019-0173-y>)
- Vermeulen R, Schymanski EL, Barabasi AL & Miller GW** 2020 The exposome and health: where chemistry meets biology. *Science* **367** 392–396. (<https://doi.org/10.1126/science.aay3164>)
- Viluksela M & Pohjanvirta R** 2019 Multigenerational and transgenerational effects of dioxins. *International Journal of Molecular Sciences* **20** 2947. (<https://doi.org/10.3390/ijms20122947>)
- Vinggaard AM, Hass U, Dalggaard M, Andersen HR, Bonefeld-Jørgensen E, Christiansen S, Laier P & Poulsen ME** 2006 Prochloraz: an imidazole fungicide with multiple mechanisms of action. *International Journal of Andrology* **29** 186–192. (<https://doi.org/10.1111/j.1365-2605.2005.00604.x>)
- Vizcaino E, Grimalt JO, Fernandez-Somoano A & Tardon A** 2014 Transport of persistent organic pollutants across the human placenta. *Environment International* **65** 107–115. (<https://doi.org/10.1016/j.envint.2014.01.004>)
- Vo TT, Yoo YM, Choi KC & Jeung EB** 2010 Potential estrogenic effect(s) of parabens at the prepubertal stage of a postnatal female rat model. *Reproductive Toxicology* **29** 306–316. (<https://doi.org/10.1016/j.reprotox.2010.01.013>)
- Vogel SA** 2013 *Is It Safe?: BPA and the Struggle to Define the Safety of Chemicals*. Berkeley: University of California Press.
- Walker DM & Gore AC** 2011 Transgenerational neuroendocrine disruption of reproduction. *Nature Reviews: Endocrinology* **7** 197–207. (<https://doi.org/10.1038/nrendo.2010.215>)
- Wallen K** 2009 The organizational hypothesis: reflections on the 50th Anniversary of the Publication of Phoenix, Goy, Gerall & Young (1959). *Hormones and Behavior* **55** 561–565. (<https://doi.org/10.1016/j.yhbeh.2009.03.009>)
- Wang Q, Lam JC, Han J, Wang X, Guo Y, Lam PK & Zhou B** 2015 Developmental exposure to the organophosphorus flame retardant tris(1,3-dichloro-2-propyl) phosphate: estrogenic activity, endocrine disruption and reproductive effects on zebrafish. *Aquatic Toxicology* **160** 163–171. (<https://doi.org/10.1016/j.aquatox.2015.01.014>)
- Wang A, Padula A, Sirota M & Woodruff TJ** 2016 Environmental influences on reproductive health: the importance of chemical exposures. *Fertility and Sterility* **106** 905–929. (<https://doi.org/10.1016/j.fertnstert.2016.07.1076>)
- Wang A, Abrahamsson DP, Jiang T, Wang M, Morello-Frosch R, Park JS, Sirota M & Woodruff TJ** 2021 Suspect screening, prioritization, and confirmation of environmental chemicals in maternal-newborn pairs from San Francisco. *Environmental Science and Technology* **55** 5037–5049. (<https://doi.org/10.1021/acs.est.0c05984>)
- Weiss B** 2007 Can endocrine disruptors influence neuroplasticity in the aging brain? *Neurotoxicology* **28** 938–950. (<https://doi.org/10.1016/j.neuro.2007.01.012>)
- Wesselink AK, Hatch EE, Wise LA, Rothman KJ, Vieira VM & Aschengrau A** 2018 Exposure to tetrachloroethylene-contaminated drinking water and time to pregnancy. *Environmental Research* **167** 136–143. (<https://doi.org/10.1016/j.envres.2018.07.012>)
- WHO** 2002 *Global Assessment of the State-of-the-Science of Endocrine Disruptors*. World Health Organization, International Programme on Chemical Safety.
- WHO/UNEP** 2012 *State of the Science of Endocrine Disrupting Chemicals – 2012*. In pp. 296. Eds **A Bergman, JJ Heindel, S Jobling, KA Kidd & RT Zoeller**. World Health Organization, United National Environment Programme.
- Wilcox AJ, Baird DD, Weinberg CR, Hornsby PP & Herbst AL** 1995 Fertility in men exposed prenatally to diethylstilbestrol. *New England Journal of Medicine* **332** 1411–1416. (<https://doi.org/10.1056/NEJM199505253322104>)
- Wishart D, Arndt D, Pon A, Sajed T, Guo AC, Djoumbou Y, Knox C, Wilson M, Liang Y, Grant J et al.** 2015 T3DB: the toxic exposome database. *Nucleic Acids Research* **43** D928–D934. (<https://doi.org/10.1093/nar/gku1004>)
- Woodruff TJ, Zota AR & Schwartz JM** 2011 Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. *Environmental Health Perspectives* **119** 878–885. (<https://doi.org/10.1289/ehp.1002727>)
- Yamaguchi S, Aoki N, Kitajima T, Iikubo E, Katagiri S, Matsushima T & Homma KJ** 2012 Thyroid hormone determines the start of the sensitive period of imprinting and primes later learning. *Nature Communications* **3** 1081. (<https://doi.org/10.1038/ncomms2088>)
- Yazbek PB, Tezoto J, Cassas F & Rodrigues E** 2016 Plants used during maternity, menstrual cycle and other women's health conditions among Brazilian cultures. *Journal of Ethnopharmacology* **179** 310–331. (<https://doi.org/10.1016/j.jep.2015.12.054>)
- Young WC, Goy RW & Phoinis CH** 1964 Hormones and sexual behavior. *Science* **143** 212–218. (<https://doi.org/10.1126/science.143.3603.212>)
- Zoeller RT & Vandenberg LN** 2015 Assessing dose-response relationships for endocrine disrupting chemicals (EDCs): a focus on non-monotonicity. *Environmental Health: A Global Access Science Source* **14** 42. (<https://doi.org/10.1186/s12940-015-0029-4>)
- Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, Woodruff TJ & Vom Saal FS** 2012 Endocrine-disrupting chemicals and public health protection: a statement of principles from the Endocrine Society. *Endocrinology* **153** 4097–4110. (<https://doi.org/10.1210/en.2012-1422>)
- Zoeller RT, Bergman Å, Becher G, Bjerregaard P, Bornman R, Brandt I, Iguchi T, Jobling S, Kidd KA, Kortenkamp A et al.** 2014 A path forward in the debate over health impacts of endocrine disrupting chemicals. *Environmental Health: A Global Access Science Source* **13** 118. (<https://doi.org/10.1186/1476-069X-13-118>)
- Zota AR, Geller RJ, Romano LE, Coleman-Phox K, Adler NE, Parry E, Wang M, Park JS, Elmi AF, Laraia BA et al.** 2018 Association between persistent endocrine-disrupting chemicals (PBDEs, OH-PBDEs, PCBs, and PFASs) and biomarkers of inflammation and cellular aging during pregnancy and postpartum. *Environment International* **115** 9–20. (<https://doi.org/10.1016/j.envint.2018.02.044>)

Received 2 November 2020

First decision 1 December 2020

Revised Manuscript received 21 April 2021

Accepted 30 April 2021