CHAPTER 10

# An Overview of the Effects of Organic Compounds on Women's Reproductive Health and Birth Outcomes

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## ABSTRACT

**Background:** Female reproductive system perturbations may decrease a woman's likelihood of conceiving and carrying her baby to term, influence the future life course of a viable infant, and may also reflect and have an impact on her own gynecological and general health and well-being. This chapter surveys effects of persistent organic compounds (POCs) and other less persistent but often pervasive bioactive organic compounds (BOCs) on these health outcomes.

**Objectives:** To present an overview that highlights evidence gathered from studies and reviews, and to provide readers with background to interpret results of future studies.

**Results:** This chapter provides an overview of human BOC and POC research methods, issues, and findings pertaining to women's reproductive and offspring's developmental effects of exposure. Research gaps and additional information resources are also highlighted.

**Discussion:** Human evidence is mounting for adverse intrauterine exposure effects of (1) polychlorinated biphenyls (particularly estrogenic congeners) on lowered birth weight; (2) phthalates on testicular dysgenesis syndrome; (3) various solvents on fetal loss; (4) smoking on altered reproductive hormone

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levels, lowered fertility, fecundity, birth weights, and menopausal age, and increased stillbirths, cleft lip malformations, and maternal (diastolic) hypertension; and (5) pesticides on childhood leukemia. There are strikingly few studies of other BOCs and POCs and reproductive outcomes, considering how many of these compounds are prevalent and that their potential effects and comorbidities may be severe with impacts across the life span.

**Conclusions:** Evidence of adverse female reproductive and developmental effects is mounting for some BOCs and POCs but is sparse for many others. Well-designed longitudinal human studies are needed.

## INTRODUCTION

Perturbations in the female reproductive system may decrease a woman's likelihood of conceiving and carrying her baby to term, influence the future life course of a viable infant, and impact her own gynecological and general health and well-being.[1] The human research evidence base covering women's and offspring's potential reproductive and developmental harms from exposure to persistent organic (i.e., carbon containing) compounds (POCs) (see the abbreviation list in Table 10.1) and other less persistent but often pervasive bioactive organic compounds (BOCs) is broad but not consistently deep for all the reproductive health outcomes of interest. One objective of this chapter is to provide an overview with a focus on the human evidence of potential effects of BOCs and POCs on the well-being of women and offspring. We limit the emphasis to nonorganometallic POCs and BOCs for which persuasive, suggestive, or conflicting evidence of (primarily) human reproductive or developmental effects was found in research literature, that is, PubMed searches to identify and select key studies and recent review papers (cited herein). Because the evidence base is dynamic, a second objective is to present some general context and caveats for conducting and interpreting studies on the effects of BOC and POC exposures on women and offspring. Current research pertaining to many aspects of women's health is considered, including gynecological dysfunction (i.e., menstrual and reproductive endocrine abnormalities, early/premature menopause, endometriosis, uterine fibroids, and polycystic ovarian syndrome [PCOS]), reproductive function (fertility and fecundity), pregnancy (hypertension, miscarriage, and stillbirth), and neonatal outcomes (i.e., prematurity, fetal growth, sex ratio, immune function, thyroid function, and birth defects). Cancer-related outcomes are discussed only incidentally where fetal origins are suspected since cancer is addressed in other chapters. Because the neuroendocrine axis regulates the healthy as well as the dysfunctional female

[1]The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

**TABLE 10.1. Abbreviation List**

| Exposure Abbreviations | |
|---|---|
| ATZ | Atrazine or 2-chloro-4-(ethylamino)-6-(isopropylamino)-s-triazine |
| BPA | Bisphenol A |
| BPB | Bisphenol B |
| BOC | Bioactive organic compound |
| BFR | Brominated flame retardant |
| Co-PCBs | Coplanar polychlorinated biphenyls |
| DDE | Dichlorodiphenyldichloroethylene |
| DDT | Dichlorodiphenyltrichloroethane |
| DBP | Dibutyl phthalate |
| DEHP | Bis(2-ethylhexyl) phthalate or di(2-ethylhexyl) phthalate |
| DES | Diethylstilbestrol |
| EDC | Endocrine-disrupting compound |
| HAC | Hormonally active compound |
| HCB | Hexachlorobenzene |
| α-HCH | Alpha-hexachlorocyclohexane |
| β-HCH | Beta-hexachlorocyclohexane |
| MBP | Monobutyl phthalate |
| MBzP | Monobenzyl phthalate |
| MEP | Monoethyl phthalate |
| MEHP | Mono(2-ethylhexyl) phthalate |
| OC | Organochlorine |
| OCP | Organochlorine pesticide |
| OH-PCB | Hydroxylated PCB metabolite |
| OP | Organophosphate |
| PBB | Polybrominated biphenyl |
| PBDE | Polybrominated diphenyl ether |
| PCB | Polychlorinated biphenyl |
| PCDD | Polychlorinated dibenzo-*p*-dioxin |
| PCDF | Polychlorinated dibenzofuran |
| PCE | Perchloroethylene, tetrachloroethylene |
| PFC | Perfluorochemical |
| PCP | Pentachlorophenol |
| PFOS | Perfluorooctane sulfonate |
| PFOA | Perfluorooctanoic acid |
| POC | Persistent organic compound |
| POP | Persistent organic pollutant |
| PVC | Polyvinyl chloride |
| TCS | Triclosan (2,4,4′-trichloro-2′-hydroxydiphenyl ether) |
| TCDD | 2,3,7,8-tetrachlorodibenzo-*p*-dioxin |
| TCE | Trichloroethylene |
| THM | Trihalomethane |

(*Continued*)

**TABLE 10.1.** ***(Continued)***

| Other Abbreviations | |
|---|---|
| ADJ | Adjusted for covariates and confounders |
| AGD | Anogenital distance |
| AhR | Aryl hydrocarbon receptor |
| BMI | Body mass index |
| CM | Congenital malformation |
| FR | Fecundability ratio |
| HR, $HR_{ADJ}$ | Hazard ratio, adjusted hazard ratio |
| IUGR | Intrauterine growth retardation |
| MA | Menopausal age |
| (*N*=), (*n*=) | Full study sample size, subgroup sample size |
| NYSA | New York State Angler cohort |
| OR, $OR_{ADJ}$ | Odds ratio, adjusted odds ratio |
| PCOS | Polycystic ovarian syndrome |
| PP | Precocious puberty |
| PR | Prevalence ratio |
| RR, $RR_{ADJ}$ | Relative risk (or risk ratio), adjusted relative risk |
| SA | Spontaneous abortion |
| SGA | Small for gestational age |
| SSIG | Statistically significant |
| SSR | Secondary sex ratio |
| T4 | Thyroxine |
| TD | Testicular dysgenesis |
| TTP | Time to pregnancy |
| Wt | Weight |

reproductive system, special attention is given to publications describing hormonally active compounds (HACs) as potential endocrine-disrupting compounds (EDCs).

## BACKGROUND

### BOC and POCs

The number of organic chemicals in commercial use is substantial, estimated at over 22,000 in 2010 in the United States and Canada alone (Howard and Muir 2010). Potential human health risks associated with the vast majority of these compounds are currently not well characterized, and still less research has focused on women's reproductive health and offspring's developmental risks. Among the features of POCs are varying levels of resistance to degradation and propensity to accumulate in living organisms (i.e., bioaccumulate). In the absence of human data, information on exposure opportunity (e.g., production, use) and certain physical-chemical features of compounds offer clues regarding such attributes. For instance, new compounds of interest for environmental monitoring as potentially bioaccumulative and persistent

have been identified from among those in commerce based on their use and inferred properties (Howard and Muir 2010). Generally, compounds were characterized as more biodegradable if they were straight-chain aliphatics, esters, acids, or had hydroxyl functional groups; bioaccumulative based on octanol–water (log $K_{ow}$) and octanol–air (log $K_{oa}$) coefficients (i.e., bioaccumulative if log $K_{ow} > 3$ or >2, if log $K_{oa} \geq 5$ and ≤12, or if $K_{ow} > 8$ but molecular weights were not very high); whereas more persistent compounds were highly branched, highly halogenated, or nitroaromatic, and many tended to be partially or totally ionic.

Findings from experimental animal, *in vitro*, and *in silico* models can reveal compounds and doses with potentially adverse biological activities (i.e., bioactivities) in humans. However, assumptions about differences due to species, gender, age, and reproductive status are typically required to extrapolate from animals to humans, introducing added uncertainty. Broadly, multiple bioactivities, alone or in concert, have been implicated at various sites and etiologic pathway levels for adverse female reproductive health outcomes in human and (mostly) animal tissues. Some examples include immune alterations, oxidative stress-induced inflammation, altered levels or function of enzymes and other proteins, and endocrine disruption. Genetic and epigenetic mechanisms are frequently implicated. The genomic DNA complement (i.e., throughout the genome) is the inherited template or "instructions" for the structure and function of the entire organism. Alterations in single genes (e.g., point mutations, insertions, deletions) and larger DNA units such as chromosomes (e.g., amplifications, deletions, inversions, translocations) may occur throughout life due to exogenous assaults from genotoxic exposures (e.g., adducts, cross-linkers) or endogenous ones such as inflammation and oxidative damage (which can also result from genotoxicant exposures). These genetic lesions subsequently may or may not be repaired, and the repairs themselves may contain errors or damage that may be promulgated, dormant, or lead to programmed cell death (i.e., apoptosis). Genetic damage during the first few weeks of pregnancy may result in fetal loss, while birth defects may ensue during organogenesis. Throughout the life span, net genetic differences among individuals across their genomes, whether inherited or acquired, are one source of variation in their susceptibility to inherited diseases and responses to environmental agents that exist between individuals and species. Epigenetic differences are another important source of variation. Epigenetic modifications are alterations in gene function (not nucleotide sequence) that occur via DNA methylation, histone modification, and aberrant microRNA expression (Zhang and Ho 2011). In the case of DNA methylation, epigenetic "reprogramming" of gene activation and silencing during developmental windows may produce immediate or latent overt effects. Also, sometimes transgenerational epigenetic transmission is believed to occur in response to environmental influences. The plasticity and reversibility of epigenetic effects are a topic of inquiry and interest from a prevention and treatment standpoint (Zhang and Ho 2011). Altered levels or functions of enzymes and other proteins may ensue downstream from genetic and epigenetic modifications. One such downstream

effect with reproductive and developmental implications is endocrine disruption. An endocrine disruptor is defined as "a compound, either natural or synthetic, which, through environmental or inappropriate developmental exposures alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment" (Diamanti-Kandarakis et al. 2009).

Many BOCs and POCs that are the focus of observational reproductive health studies in women and offspring are those for which nonhuman studies have signaled that possible harm in humans may occur. A heavy reliance on nonhuman sentinels exists because the human *in vivo* evidence base for effects potentially caused by BOC and POC exposure is currently insufficient for many outcomes. One reason is that, unlike *in vitro* experiments and clinical trials where there may be a therapeutic benefit, exposure of humans to potentially harmful compounds such as BOCs and POCs for research purposes is unethical. Other explanations are pragmatic: inadequate numbers of exposed women or offspring for study recruitment and limitations of analyses using data collected for purposes not primarily related to studying female reproduction. Furthermore, each human is exposed to an individual mix of these compounds throughout the life cycle, unlike laboratory animals in which the environment is controlled and effects of a xenobiotic can be measured directly. The exception in humans in which causal links have been more clearly drawn is the case of accidental contamination or incidents when known or unknown population or workplace contamination has occurred in a local or widespread vacuum of human exposure or risk information. Such incidents may result in acute or chronic exposure. Generally, accidental and occupational exposures tend to be higher than those typically encountered by women otherwise, leaving vast data gaps regarding effects of low-dose and dose-rate exposures. Other human reproductive research barriers are often societal, including obstacles to participant recruitment and retention, risks of litigation to producers and users of potentially toxic compounds, and limited funding for reproductive research.

While restrictions and bans on persistent compounds (e.g., certain organochlorine pesticides [OCPs], hexachlorobenzenes [HCBs], polybrominated biphenyls [PBBs], polybrominated diphenyl ethers [PBDEs], polychlorinated biphenyls [PCBs], brominated flame retardants [BFRs], polychlorinated dibenzo-*p*-dioxins [PCDDs]/polychlorinated dibenzofurans [PCDFs], perfluorooctane sulfonate [PFOS]) (Howard and Muir 2010; Muir and Howard 2006) have become more pervasive in some countries, POCs have long half-lives in both humans (O'Grady-Milbrath et al. 2009) and biota in our food chain and so may linger in human bodies, even transgenerationally, long after the compounds have been retired commercially (Quinn et al. 2011). In addition, ongoing exposure to banned compounds may continue for some time from "reservoirs," that is, products with long life cycles that contain POCs (e.g., PBDEs, PFOS), and from environmental contamination (e.g., PBBs, OCPs) (Howard and Muir 2010). While some less persistent compounds remaining in

commerce may be more rapidly eliminated from the body, they may still be bioavailable over long periods of time when exposure is chronic. Thus, possible public health implications ensue, especially when exposure is commonplace and the underlying attributable risk is high.

### Women's and Offspring's Exposures

The impact of potentially toxic exposures is different for women than for men. Differences potentially exist in exposure histories (e.g., historically divergent occupations and smoking habits), toxicant biokinetics (i.e., absorption, transport, metabolism, storage, elimination), exposure effects (e.g., potential targets include both the woman's reproductive system and her offspring during pregnancy and lactation), and the behavioral, hormonal, and other biological factors that modulate toxicant kinetics and risks (Gochfeld 2007). Figure 10.1 illustrates, broadly, the nature and fate of BOC and POC exposures, together with selected female reproductive and developmental exposure effects that have been hypothesized in studies across the course of life. A number of persistent compounds have been detected in body tissues unique to women and their physiologically dependent offspring. This includes dichlorodiphenyldichloroethylene (DDE) and PCBs measured in ovarian follicular fluid (Meeker et al. 2009), PCDDs, PCDFs, and coplanar polychlorinated biphenyls (Co-PCBs) measured in the placenta (Chao et al. 2007; Suzuki et al. 2005), PCDDs, PCDFs, Co-PCBs, dichlorodiphenyltrichloroethane (DDT), DDE, and PBDEs measured in breast milk (Haraguchi et al. 2009; Suzuki et al. 2005), PBDEs, PCDDs, PCDFs, and PCBs, in umbilical cord (i.e., cord tissue) or cord blood (Kawashiro et al. 2008; Suzuki et al. 2005), alpha-hexachlorocyclohexane (α-HCH), and DDE in amniotic fluid (Foster et al. 2000), and PCBs in miscarried fetal tissues (Lanting et al. 1998). Other less persistent BOCs that are currently in use commercially (e.g., bisphenol A [BPA] and phthalates) have also been found in many of the same body compartments (Ikezuki et al. 2002; Maffini et al. 2006; Padmanabhan et al. 2008; Schönfelder et al. 2002; Silva et al. 2004a). Between 99% and 100% of pregnant women in a nationally representative sample of the U.S. population had detectable blood or urine levels of BOCs and POCs including PCBs, OCPs, PFCs, phenols, PBDEs, phthalates, and polycyclic aromatic hydrocarbons (PAHs), as well as other compounds (Woodruff et al. 2011). Among these, DDE was the highest of the lipophilic (i.e., chemical affinity for lipids) POCs in serum, whereas PFOS was the highest of the nonlipophilic POCs.

Many POCs are sequestered in adipose tissue because of their high nonpolarity/lipophilicity. Women have proportionately more adipose versus lean body mass than men and so are thought to generally have higher body burdens of lipophilic compounds (Gochfeld 2007). Stores of stable organic compounds that have accumulated over time in adipose tissue may later be released from storage when body fat is remobilized, such as occurs during weight loss (Lim et al. 2011), pregnancy, and lactation. Other POCs (e.g., PFOS

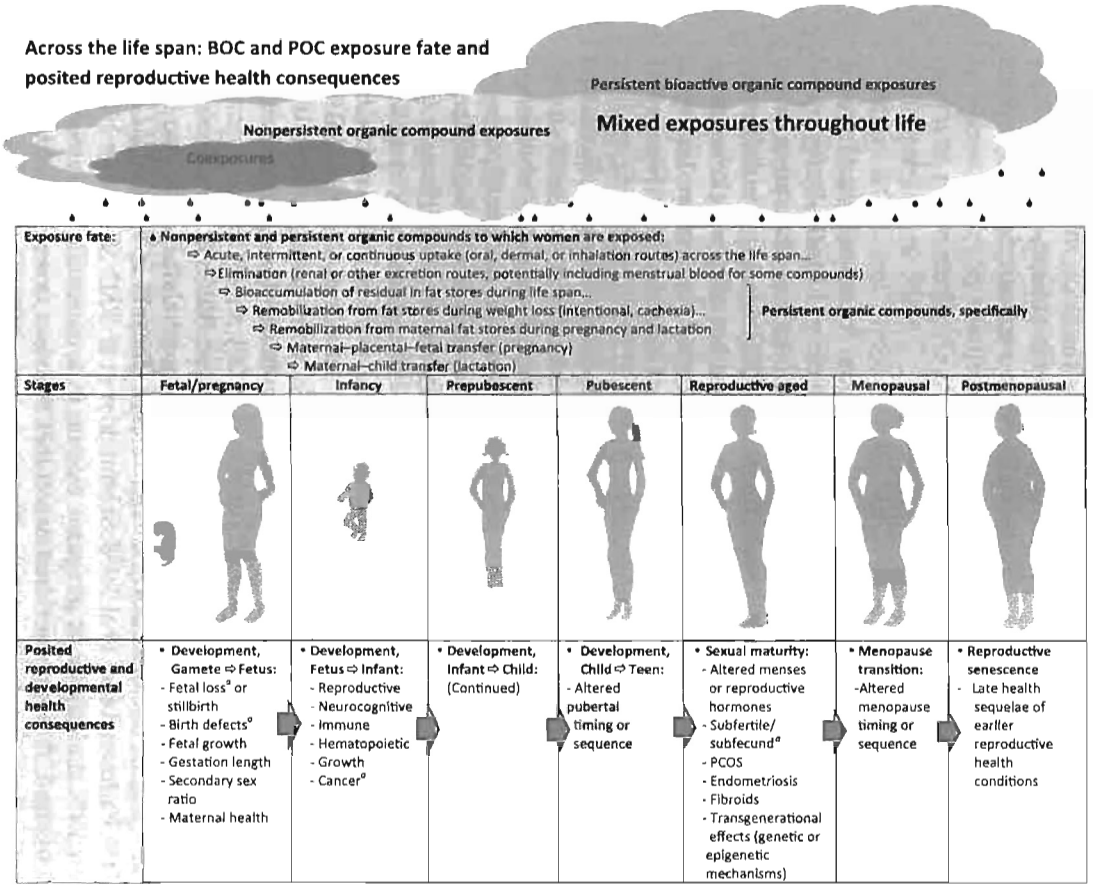


**Figure 10.1.** Across the life span: BOC and POC exposure fate and posited reproductive health consequences.

[a]May involve periconceptual (gametes) and postconceptual (embryo and fetus) exposure susceptibility windows.

**TABLE 10.2. Correlations between Maternal and Fetal BOCs and POCs in Selected Studies**

| Compounds | Correlations | References |
|---|---|---|
| Arochlor | $r_p = 0.78$ | Anda et al. 2007 |
| BPA | $r_s = -0.02$—$r = 0.63$ | Chou et al. 2011; Kuroda et al. 2003 |
| DDE | $r_p = 0.58$—$r_p = 0.94$ | Bergonzi et al. 2009; Sala et al. 2001 |
| DDT | $r_p = 0.76$—$r_s = 0.94$ | Anda et al. 2007; Jaraczewska et al. 2006 |
| HCB | $r_p = 0.49$—$r_p = 0.71$ | Bergonzi et al. 2009; Covaci et al. 2002 |
| HCHs | $r_p = 0.40$—$r_p = 0.71$ | Anda et al. 2007; Sala et al. 2001 |
| PBBs | $r_p = 0.81$ | Jacobson et al. 1984 |
| PBDEs | $r_p = 0.56$—$r_s = 0.91$ | Kawashiro et al. 2008; Wan et al. 2010 |
| PCBs | $r_p = 0.42$—$r_p = 0.99$ | Jacobson et al. 1984; Needham et al. 2011 |
| PCDD/Fs | $r_p = 0.44$—$r_p = 0.85$ | Nakamura et al. 2008; Wang et al. 2004 |
| PCP | $r_p = 0.73$—$r = 0.91$ | Guvenius et al. 2003; Park et al. 2008b |
| PFCs | $r_p = 0.05$—$r_p = 0.91$ | Fromme et al. 2010; Needham et al. 2011 |

$r_p$, Pearson correlation coefficient; $r_s$, Spearman correlation coefficient; $r$, $r_p$ versus $r_s$ unspecified.

and perfluorooctanoic acid [PFOA]) reportedly have an affinity for blood proteins and so it is plausible that their elimination may occur through additional routes specific to women during their reproductive years (i.e., elimination of albumin in menstrual blood and through the placenta to the fetus) (Harada et al. 2005; Thompson et al. 2010). Pregnant women may experience remobilization of compounds, altering bioavailability, redistribution, elimination, or transfer to the placenta and fetus, with potentially harmful fetal exposure. Maternal–fetal transfer of many POCs has been demonstrated in blood, serum, or plasma, usually near pregnancy term, by many investigators. Table 10.2 lists the correlations between maternal and fetal levels for several compounds measured in several studies. Some of these correlations are relatively high. Fetal (cord) levels of these compounds often are an appreciable fraction of levels measured in mothers' circulation and may even exceed levels in mothers. The efficient transfer and high levels of these compounds to the fetus is cause for concern since these tissues are developing and are potentially programmable at a time when fetal tissue targets may be more bioavailable due to immature metabolism, undeveloped barriers (e.g., blood–brain barrier), and undeveloped fetal storage compartments to blunt exposures (e.g., fat) (Jacobson et al. 1984). Cross-study comparisons of maternal–fetal transfer need to account for study differences in, for example, the type of biological sample analyzed (e.g., blood fraction), timing of sample collection (e.g., trimester), and statistical methods employed (e.g., non-normal distributions, imputation of low or undetectable measurements, and lipid adjustment vs. nonadjustment). Circulating lipophilic compounds are often sequestered by blood components including lipids. Accordingly, blood compound levels are often presented with lipid adjustments. Cord blood and placental tissue contain lower lipid levels, and so lipid adjustments are not as universally applied to those matrices.

Some women's health conditions that are associated with altered storage, metabolism, or elimination of compounds have hypothetically plausible effects on the net retention versus elimination of BOCs and POCs from the body. For instance, if appreciable elimination of a compound occurs through menstrual blood, then the rate of that compound's elimination would be dependent on reproductive health conditions that alter the volume of menstrual blood loss (e.g., PCOS, fibroids, menopause). Similarly, conditions sometimes associated with not lactating or reduced parity (e.g., infertility, fetal loss, PCOS, endometriosis) may increase retention of compounds. However, evidence linking parity with reduced body burden is equivocal (Quinn et al. 2011). Much remains to be learned about the variation of kinetics for compounds within and among women across various physiological and health states. Assumptions about kinetic shifts must be tempered by the observation that they are multifactorial and that the inherent variability is not well characterized by current predictive models (Ibarluzea et al. 2011). Investigators have described the potential for reverse causality (Weinberg and Wilcox 2008) such that the level of a compound may have been caused by a reproductive health outcome instead of the converse. This phenomenon must be considered in exposure–disease studies of persistent compounds when causal attribution may be blurred in full or part by underlying biokinetic differences between disease and comparison groups and when the longitudinal timeline of exposures and outcomes (i.e., temporality) is uncertain (e.g., cross-sectional studies). Reverse causation may also be an issue for pregnancy and birth outcome studies since exposure levels measured at the time of conception may differ from those measured later in gestation due to shifts in physiology (e.g., hemodynamic and body composition, fat mobilization) and behavior (e.g., diet, smoking cessation) (Chapin et al. 2004; Glynn et al. 2011; Hansen et al. 2010). Timing of exposure can affect pregnancy outcomes; timing of exposure assessment can affect interpretation of outcome causation.

Other factors, such as lactation history, body mass index (BMI), and age may also be independently related to both the exposure under study (Hsu et al. 2010; Knutsen et al. 2011) and the female reproductive disease of concern, and so may need to be considered as candidate statistical confounders; that is, study participant profiles for such factors may differ systematically between women with and without health outcomes of potential research concern (e.g., subfertility, PCOS, endometriosis, menopause) regardless of their BOC and POC exposure levels. For example, nulliparous women rendered infertile by their conditions will not have eliminated POCs from their bodies by maternal–fetal transfer or breast-feeding routes and so, hypothetically, may have higher POC burdens than parous women. Women with a history of long-term breast-feeding reportedly have lower circulating levels of organochlorine (OC) than those who have never breast-fed (Ibarluzea et al. 2011). Another example is women who are postmenopausal or have PCOS are more prone to obesity with a more abdominal (i.e., visceral and bioavailable) distribution that could, hypothetically, alter their POC uptake, storage, and elimination compared to

unaffected women. Fat mass has been associated with altered circulating persistent organic pollutant (POP) levels; some POPs appear to vary inversely, while others vary directly with fat mass (Rönn et al. 2011). Time-related variables may also act as potential confounders to the extent they are independently associated with both exposure and the occurrence of the health outcome of interest. Examples of time-related variables include current age, time since exposure, exposure duration, exposure latency, age at first exposure, and birth cohort. For instance, an older birth cohort may have had both more time for latent reproductive effects to manifest and more opportunity for exposure to compounds that emerged at earlier or declined (or were banned) at later points in time. Age thresholds and disease latencies also must be considered in analyses when age-related outcomes, such as endometriosis and menopause, manifest only after a certain age threshold or may occur long after exposure.

Given the complexity of human exposure patterns, it is important to control for time-related confounders as well as possible. For example, consider the impact of confounding by time-related variables on conclusions of a large nonrandomized (observational) study of an intentional endocrine exposure, hormone replacement therapy (HRT) in postmenopausal women. The study found cardiovascular benefits from treatment that drove an uptick in prescriptions. A later randomized human clinical trial of this seemingly well-understood endocrine exposure found a contradictory increase in cardiovascular risk from HRT with broad public health implications (Prentice et al. 2005; Smith 2004). Subsequent reanalysis was conducted to reconcile the discrepancy in the cardiovascular disease findings of the observational study versus the randomized trial (Prentice et al. 2005; Willett et al. 2006). Reconciling the results entailed adjustment of observational results for the variables age at first HRT exposure (i.e., initiation) and HRT exposure duration plus attention to the role of disease latency. While this example pertains to a hormonal drug rather than a hormonally active pollutant exposure, it illustrates the importance of collecting and examining appropriate time-related variables as candidate confounders in noninterventional observational BOC and POC exposure studies as well.

## Epidemiological Studies (Special Considerations)

Observational epidemiological studies examine distributions of diseases or physiological conditions in human populations together with factors (e.g., exposures) that influence these distributions (Lilienfeld 1976). They are generally nonexperimental in nature as participants are not randomly preassigned to exposed versus nonexposed groups as they would be in experiments or clinical trials. The body of epidemiological evidence regarding many potential BOC and POC health effects has evolved over time as duration of exposure increases, exposed cohorts mature, and study designs and methods increase in sophistication. The more common epidemiological study designs include cross-sectional, case-control, and cohort designs. Cross-sectional studies offer a

"snapshot" of health effects and exposure(s) of interest concurrently, within one window of time. Cross-sectional studies are often considered exploratory. A purely cross-sectional design does not distinguish new cases of disease that occurred within a given time frame (i.e., incident cases) from all cases including new and preexisting cases (i.e., prevalent cases), nor does it establish whether an exposure occurred before or after the disease (i.e., temporal sequence).

In contrast, cohort studies follow defined groups over time (prospectively or retrospectively) to detect the underlying timeline when health effects arose relative to key exposures. Risks of exposed versus nonexposed cohort members are often reported as point estimates such as relative risks (i.e., risk ratios [RRs]) and, for incidence rate and time-to-event outcomes (e.g., survival analyses), as hazard ratios (HR) (Hernán 2010; Peacock and Peacock 2011). Cohorts in whom reproductive end points and exposures have been characterized across the life span are rare but valuable for several reasons. Exposure profiles and sequences may vary throughout life and many exposures occur as mixtures of individual compounds. Coexposures and other potentially important confounding variables (e.g., age, smoking status, BMI) may also vary across the life span. Cohort studies may potentially capture the temporal sequence of these events. Also, life span cohort studies may capture exposures that happen during critical neuroendocrine and reproductive developmental windows (e.g., fetal stages, puberty). This is important since several lines of evidence suggest such exposures may potentially trigger not only effects that are readily apparent at birth but also latent effects that will not appear until decades later.

Case-control studies compare exposures of those with health effects of interest (cases) with a sample of the population from which the cases arose (controls). Results of case-control studies are typically reported as odds ratios (ORs). The OR is a valid estimate of the relative risk when the sampling frame is properly designed. Nested case-control studies are those in which controls and sometimes cases are drawn from a larger defined cohort. This approach reduces the potential for bias resulting from the use of an inappropriate control group for comparison purposes.

The statistical significance of any individual study result is, among other things, a function of study power and, therefore, a reflection of sample size. Studies with insufficient sample size may not adequately capture human variation (e.g., exposure and biokinetic differences) and may also suggest clinically meaningful risks and yet may be underpowered to demonstrate statistically significant (SSIG) effects beyond chance. In such studies, large between group differences may be accompanied by higher $p$-values or elevated risk estimates may be bounded by wide confidence intervals (CIs). Conversely, studies with a generous sample size and power may detect SSIG effects that are small (e.g., RRs or ORs near one) and potentially so subtle as to not be considered clinically meaningful. Achieving a large sample size is resource intensive, and characterizing suspected interactions (e.g., by age or gender) can inflate sample size requirements. Historical occupational and clinical cohorts often contained few or no women subjects. Therefore, a more frequent challenge in terms of

interpreting studies of women's health risks is insufficient statistical power, as opposed to too much statistical power.

Examining suspected interactions strengthens risk assessments. Additive, multiplicative, or other shades of interaction between different BOCs and POCs or between these compounds and other factors are conceivable considering the range of aggregate effects that might be expressed and since individual compounds may act as agonists, antagonists, or synergists. Further, such interactions could be dependent on dose and on the order of exposure. Findings of SSIG effects together with large risk estimate values, dose–response relationships, and convergent results across different human populations and other models lend evidential weight to epidemiological studies and their conclusions. Synthesis of results across epidemiology studies by "pooled" analysis of data from multiple cohorts or by "meta-analysis," that is, combined analysis of study results, is a tool to aid interpretation of the gestalt of data when sufficient numbers of quality studies permit.

## Endocrine Disruption

Because the reproductive endocrine axis regulates so many aspects of women's health, from fetal development through reproductive senescence and beyond, endocrine disruption hypotheses form the basis for many human studies of reproductive exposures and effects. The view that certain compounds act as endocrine disruptors in humans has in the past been considered controversial by some. While suspected EDCs are hormonally active by definition, their capacity for various physiological disruptions at the doses typically encountered has been the focus of dispute. However, findings linking EDCs to reproductive effects in women and developmental effects in their offspring are mounting (see the following chapter sections). Consensus that EDCs harm various aspects of human health is growing in tandem with burgeoning evidence. It has been argued recently that EDCs do not fit the traditional toxicological "dose makes the poison" paradigm since low-dose EDC health effects "cannot be predicted by the effects observed at high doses" (Vandenberg et al. 2012). Dose–response curves for EDCs are often nonlinear and U or inverted U in shape rather than monotonic, reflecting the cumulative effects of actions on multiple targets (Gore 2010a,b). Multiple authors have, therefore, concluded that traditional methods used to determine the safety of chemicals must be modified in order to characterize EDC health risks. In efforts to consolidate what is suspected and known about EDC risks, in-depth reviews and analyses have been prepared by scientific bodies such as the Endocrine Society and the World Health Organization (WHO) (Diamanti-Kandarakis et al. 2009; World Health Organization (WHO), International Programme on Chemical Safety 2002). Recently, the U.S. Environmental Protection Agency (EPA) released a highly anticipated report on the reproductive and post-birth-related EDC effects of the dioxin 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (U.S. EPA 2012).

One major contention with the paradigm that synthetic estrogens cause endocrine disruption in humans has been the view that the estrogenic activity of dietary phytochemicals (e.g., isoflavones) in soy and other plants greatly exceeded that of commonly encountered synthetic dietary estrogens (e.g., estrogenic pesticides) (Safe 1995, 2004). However, a recent *in vitro* study provided evidence contrary to this view. In that study, investigators reported that the total daily dietary "estrogenicity intake" (estradiol equivalents per kilogram based on the yeast estrogen screen) for a broad panel of foodstuffs was more than 1000-fold lower than previously thought (Behr et al. 2011; Safe 1995). Further, the estimated dietary estrogenic intake for the weak xenoestrogen, BPA (at the European Union's adult maximum tolerable intake limit), was approximately equal to that derived from a normal diet (maximum total daily intake). For infants (at weight 5 kg), the maximum tolerable daily estrogenicity intake from BPA leached from polycarbonate baby bottles was noted to be greater than the estrogenicity expected from the intake of milk-based formula (Behr et al. 2011). Estrogenicity derived from soy formula was 500-fold higher than from milk-based formula. These *in vitro* findings are made against the backdrop of the U.S. National Toxicology Program's (NTP) conclusion that limited health effects have been reported in soy-fed infants (McCarver et al. 2011) with a determination of "minimal concern" for adverse developmental effects in infants fed soy formula. This designation was based on evidence from human and nonhuman models. The human studies considered primarily growth-related parameters. However, the two studies of human infant exposure for which the NTP reported reproductive system outcomes showed associations between soy formula intake and breast bud development in the subset with thelarche onset before age 2 (Freni-Titulaer et al. 1986) and an increased rate of menstrual dysfunction in adulthood among women exposed to soy formula in infancy (Strom et al. 2001). Taken together, the impact of synthetic chemicals is not readily dismissed based on earlier assumptions about dietary estrogenicity intake, as dietary intake appears lower than previously thought. And while infants who consume soy formula have relatively high estrogenicity intakes, and "minimal concern" has been noted based primarily on growth parameter studies, the need for additional study of other developmental and female reproductive end points is evident given the breast bud and menstrual findings.

Potential EDCs are characterized based on their assumed mode(s) of action. Within the realms of the reproductive system, EDCs are classified as estrogenic (e.g., PCB, BPA, BFRs, diethylstilbestrol [DES], genistein), antiestrogenic (e.g., PCB), androgenic (e.g., trenbolone), antiandrogenic (e.g., DDE, dioxin, phthalates, BFR), gestagenic (e.g., control of estrous cycle by melengestrol), antithyroid (e.g., phthalates, PCB, dioxin, BFRs), antisteroidogenesis (PFOA, parabens, dibutylphthalate, di(2-ethylhexyl) phthalate [DEHP]), aromatase inhibiting (phytoestrogens) (Mouritsen et al. 2010), and aromatase inducing (e.g., atrazine [ATZ] in some but not all cell lines) (Simpkins et al. 2011). Various congeners of compounds may, however, exhibit pleiotropic

properties; for example, PCB 138 exhibits both antiestrogenic and antiandrogenic effects (Bonefeld-Jørgensen et al. 2001). Congener groupings for epidemiological studies have been proposed for certain compounds (i.e., PCBs) based on their structural, biological, and pharmacokinetic properties (e.g., persistence, hormonal vs. dioxin-like properties, enzyme induction) (Wolff et al. 1997). Observable effects of endocrine disruptors on women and their offspring represent their diverse and multipathway aggregate effects on cells and tissues, about which much remains to be discovered. Endocrine actions of some compounds (e.g., phytoestrogens) may vary at different dose levels or may depend on the body's hormonal milieu. It has been suggested, for example, that TCDD's activity may vary across the life span since it displays antiestrogenicity when sufficient levels of estrogen are present, but estrogenicity in the absence of estrogen (Boverhof et al. 2006). In some cases, metabolites are more estrogenic or antiestrogenic than the parent compounds themselves (hydroxylated PCBs and hydroxylated PBDEs) (Hamers et al. 2011; Kojima et al. 2009).

Another complexity is that reproductive hormones and EDCs appear to both influence various nonendocrine biological activities and to also be influenced by them. Consider two examples of the interface of reproductive hormones with (1) immunity and, more generally, with (2) epigenetics. The immune system and sex steroids have an interconnected relationship. Estrogens, progesterone, and testosterone are involved in the distribution and function of innate and adaptive immune cells, whereas sex steroids and gender are implicated in a number of immune diseases (Muñoz-Cruz et al. 2011). Accordingly, a small body of evidence suggests human immune function may be impaired by EDC exposures (e.g., PCBs and PFCs developmentally, BPA and triclosan [TCS] among those age 6 through adults) (Clayton et al. 2011; Grandjean et al. 2012; Heilmann et al. 2006; Weisglas-Kuperus et al. 2000, 2004). Epigenetics is a proposed "missing link" between environment, genetics, and hormone function, perhaps accounting for much of the variability and plasticity of the endocrine system. It is thought that epigenetic processes both regulate hormone actions (i.e., synthesis and release, circulating and target tissue levels, and target organ responsiveness) and are also regulated by hormones that activate or repress transcription of different genes (Zhang and Ho 2011). Further, certain EDCs demonstrate epigenetic activity (i.e., DES, TCDD, DDT, PCBs, BPA, PFOA, and vinclozolin) as they alter methylation of various genes in humans and animals. Intriguingly, it has been shown that the potent pharmaceutical drug DES, endogenous estrogen (i.e., physiologic estrogen 17β-estradiol), and the certain exogenous estrogens (i.e., genistein, a phytoestrogen in soy) all alter expression of the same 179 genes in the immature mouse uterus; expression was not examined in the mature uterus in that study (Moggs et al. 2004). *In vivo*, however, other factors, such as biokinetics, and coexposures may come into play. Other EDCs may be relatively more bioavailable to tissues (e.g., uterine) than hormones as they are thought to be less apt than endogenous hormones to bind either blood proteins or the enzymes that

metabolize endogenous hormones (Gore 2010a,b). It has been demonstrated that the activity of compounds considered to be estrogenic differs when considered alone versus as mixtures in the rodent uterus (Tinwell and Ashby 2004). In humans, it is thought that the activities of estrogens from dietary and synthetic sources may be additive (Behr et al. 2011); however, the net bioactivities of these and other mixtures encountered are often currently largely unknown. These uncertainties underscore the need for research on the combined actions and potential reproductive and developmental risks of mixtures commonly encountered by humans. The Endocrine Society has issued recommendations to address gaps in clinical, basic, and epidemiological research, and in clinical practice (Diamanti-Kandarakis et al. 2009).

## SURVEY OF SELECTED BOC AND POC STUDIES

### Gynecological Outcomes

Studies of the reproductive effects of tobacco and alcohol have been a research focus for decades as have, to a lesser extent, specific BOCs (e.g., solvents). The POCs have also garnered growing attention as they have been detected in humans. Some of these agents, including several EDCs described further, have been associated with altered menstrual function or female reproductive hormone levels. Trends in certain reproductive health indicators over time raise questions concerning whether environmental changes adversely affect gynecological health. An expert panel concluded there was sufficient evidence of a temporal trend of earlier breast development and menses onset between 1940 and 1994 among U.S. girls (Euling et al. 2008). Secular trends for most gynecological outcomes are generally less assessable due to the general lack and limitations of female reproductive health surveillance and exposure data.

***Menstrual and Reproductive Endocrine Function*** *Pesticides (general):* Pesticides encompass a broad range of chemical compounds, including organic compounds such as OCs and others (see further). They are used worldwide primarily as insecticides, herbicides, fungicides, and growth regulators (Hanke and Jurewicz 2004). Over 400 pesticide chemicals have been approved for agricultural use, and these may be formulated into thousands of different consumer products. Among 3103 farm women in Iowa and North Carolina (United States, Agricultural Health Study cohort), those who used pesticides had longer menstrual cycles and increased odds of missed periods (OR = 1.5, 95% CI = 1.2, 1.9) compared with women (controls) who never used pesticides. The subset who used pesticides considered probable HACs had 60–100% increased odds of long cycles, missed periods, and intermenstrual bleeding compared with controls (Farr et al. 2004).

*DDT* is an OC that was first used to control malaria and typhus during the latter part of World War II. After the war, DDT was used extensively from

1950 to 1980 in agriculture as an insecticide until it was banned in the United States in 1972. In other countries, such as South Africa, Zambia, and Madagascar, DDT has been reintroduced in recent times with concurrent substantial reductions in malaria morbidity and, likely, mortality (Longnecker et al. 2005). DDE is the primary metabolite of DDT. DDT or DDE affect oocyte maturation, ovulation, and fertilization in several studies of humans or laboratory animals (Tiemann 2008). They have garnered the most attention because of their chemical stability and strong lipophilicity, slow degradation, and bioaccumulation in the food chain. DDE tends to build up in the body throughout life as it is rarely excreted from the body except being excreted in breast milk, thereby transferring the toxicant to the nursing infant.

High serum DDT concentrations in adult Chinese female textile workers were SSIG associated with earlier age at menarche (adjusted trend $p < 0.001$) and shorter menstrual cycles ($OR_{ADJ} = 2.78$, 95% CI = 1.07–7.14) (Ouyang et al. 2005). Windham et al. (2005) reported the mean cycle length of 48 adult, Southeast Asian immigrants with high DDE exposure was not SSIG different from the cycle length for women with low exposure (after adjustment). However, each doubling of DDE levels was linked to a 0.6-day shortening of the luteal phase (−1.1 to −0.2) and a consistent reduction in progesterone metabolite levels (Windham et al. 2005). Perry et al. (2006) found inverse relationships for serum levels of most forms of DDT with estrogen and progesterone metabolites in 287 reproductive-age women. Most SSIG inverse associations with the DDT metabolites were observed for progesterone metabolite during the luteal phase and for estrogen metabolite during the periovulatory phase, suggesting effects of DDT/DDE during the menstrual cycle phases that are crucial for ovulation and early pregnancy maintenance (Perry et al. 2006). In contrast, Chen et al. (2005) failed to detect any association between DDE or DDT levels and menstrual cycle length, duration of menses, or heaviness of menstrual flow in 60 young Chinese women.

*TCDD*, a PCDD, more commonly known as dioxin, is classified as a POP. It is one of the most potent congeners of the PCDDs and binds to the aryl hydrocarbon receptor (AhR), which mediates the effects of many EDCs and contributes to the loss of fertility in polluted environments. Dioxin exerts a multitude of adverse effects on organisms (teratogenesis, tumor promotion, immunosuppression, estrogenic action), mediated primarily by AhR (Baba et al. 2005). It occurs as a by-product in the manufacturing of some OCs or by incineration of chlorine-containing substances such as polyvinyl chloride (PVC). Dioxin contamination occurs mainly through industrial emission and/or accidents.

The Seveso Women's Health Study (SWHS) in Italy assessed subjects with the highest levels of TCDD exposure in this population as a result of a chemical explosion in 1976. A retrospective cohort study of exposed premenarcheal participants revealed no change in the risk of early onset of menarche with a 10-fold increase in TCDD (Warner et al. 2004) and a borderline SSIG association with an increased menstrual cycle length (Eskenazi et al. 2002b).

*ATZ* is notable as the most common herbicide used in the United States, but it is banned in the European Union due to widespread and persistent groundwater contamination. Women in Illinois where ATZ use was "extensive" were SSIG more apt to have irregular menstrual cycle lengths ($OR_{ADJ}$ = 4.69, 95% CI = 1.58–13.95) and more than 6 weeks between bleedings ($OR_{ADJ}$ = 6.16, 95% CI = 1.29–29.38) than women in Vermont where ATZ use was said to be used "sparingly" (Cragin et al. 2011).

*PCBs* were widely used as dielectric and coolant fluids. Due to their toxicities, PCBs have been identified as POPs. Production of PCBs was banned in the United States in 1979 and by the Stockholm Convention of Persistent Organic Pollutants in 2001. PCBs are lipophilic and have long half-lives (8–10 years). PCBs are stable and bioaccumulate in the food web. Human exposure to PCBs occurs via inhalation of contaminated air or through consumption of contaminated food. PCBs are EDCs and interfere with endocrine secretion and actions. The toxicity of PCBs vary among congeners. Co-PCBs tend to have dioxin-like properties, the most toxic of congeners. Certain congeners are known to be estrogenic agonists or antagonists of estradiol. Similar to dioxin, PCBs are thought to mediate by binding the AhR, thereby disrupting cell functions by altering gene transcription (Safe 1984; Safe et al. 1985). PCB exposure and their effects on menstrual cycle characteristics and function have received relatively little attention, and data to date are somewhat contradictory. PCBs affect the endocrine system by a variety of mechanisms. They are known to reduce secretion of the thyroid hormone thyroxine (T4) in animals (Brouwer et al. 1999). In humans, thyroid hormone underproduction (i.e., hypothyroidism) can cause prolonged duration of menses, while overproduction (i.e., hyperthyroidism) reduces menstrual flow and can result in oligomenorrhea (i.e., infrequent menstrual periods).

Total PCB levels measured in the third trimester of the pregnancies of 2314 U.S. women in the Collaborative Perinatal Project were positively associated with reported history of menstrual cycle length (adjusted difference five PCB exposure categories = 0.7 days, trend-test $p$ = 0.02) (Cooper et al. 2005). In 1979, more than 2000 people were poisoned in Taiwan when they ingested PCB-contaminated cooking oil. Two decades later, women from this Yucheng ("oil disease") incident were interviewed and reported abnormally light menstrual bleeding, slightly reduced cycle length ($p$ = 0.03–0.006), and borderline SSIG earlier age of menarche (Yang et al. 2005, 2011; Yu et al. 2000). PCB levels associated with earlier age of menarche were also observed in 138 Native American youth (Denham et al. 2005). Women from the New York State Angler (NYSA) cohort who consumed contaminated fish had moderate to high estimated PCB levels and SSIG cycle length reductions (−1.1 days, 95% CI = −1.87 to −0.35 overall) (Mendola et al. 1997). Women raised in Swedish fishing villages on the east coast off the Baltic sea exposed to contaminated fatty fish (presumably, *in utero*, during breastfeeding and/or through their diet) directly experienced menarche at an older age than women from less contaminated west coast villages (Axmon 2006). Delayed sexual maturation was also

observed in girls living in Antwerp, Belgium, near waste incinerators that may have spewed pollutants including heavy metals and BOCs and POCs including dioxins, dioxin-like compounds, and aromatic hydrocarbons (Den Hond et al. 2002; Staessen et al. 2001).

*PBBs* are used as flame retardants and are added to plastics used in products such as home electrical appliances, textiles, and plastic foams. While PBB manufacturing ceased in 1976 due to slow degradation, the contaminant can still be found in the environment. Similar to PCBs, PBBs bioaccumulate in the food web and exposure is most likely through ingestion of contaminated food and drinks. Over 4000 individuals were exposed to PBB in Michigan in 1973 via accidental contamination of livestock feed. Mothers were exposed by ingestion of contaminated cow's milk and meat. Maternal exposures were passed onto the fetus and infant through the placenta and during breastfeeding (Blanck et al. 2002).

*BPA* is a synthetic compound that is used extensively as a monomer in polycarbonate plastics and in epoxy resins that are used to line food and beverage containers, and in dental sealants. BPA is one of the most omnipresent and high-profile EDCs (Talsness et al. 2009; Völkel et al. 2002), having received much attention from the scientific community and media. Exposure to BPA occurs primarily through the diet, but also by dermal contact and inhalation. BPA metabolites have been detected in more than 90% of people in representative populations in the United States and in Europe (Calafat et al. 2008b; Galloway et al. 2010). However, it is difficult to assess the full impact of human exposure since outcomes of interest manifest latently at later ages.

*TCS* is an antimicrobial and preservative that, for more than two decades, has been added to personal care products (e.g., hand soaps, dishwashing and laundry detergents, mouthwashes, toothpastes, wound disinfection solutions, deodorants) and other commonly encountered items (e.g., toys, facial tissues, textiles [e.g., underwear, socks], plastic kitchen utensils, and medical devices) (Calafat et al. 2008a; Clayton et al. 2011). It is detectable in human breast milk (Allmyr et al. 2006) and, in a population-based U.S. cohort (National Health and Nutrition Examination Survey [NHANES] 2003–2004), was detected in the urine of 75% of people sampled ($n = 2517$) (Calafat et al. 2008b). A recent review of a small number of *in vitro* TCS studies described findings consistent with possible endocrine disruption including weak AhR activity in estrogen and androgen receptors and dependent gene expression, and (human cell) findings of estrogenic and androgenic effects and lowered testosterone-induced transcriptional activity (Dann and Hontela 2011). In one human study, brushing twice daily with TCS toothpaste did not produce an adverse effect on thyroid hormones (Cullinan et al. 2012). No other published epidemiological studies of TCS exposure and reproductive related outcomes were noted.

*Phthalates* are mainly used as plasticizers. They are in consumer items from cosmetics and personal care products to children's toys to cosmetics, shower curtains, wallpaper, vinyl blinds, food packaging, plastic wraps (ATSDR 1995), and intravenous tubing. Phthalates were once used to make pacifiers, soft

rattlers, and teethers, but U.S. manufacturers stopped using phthalates in these products in 1999. Phthalates have been identified as EDCs associated with developmental and reproductive toxicity. Although they do not bioaccumulate in the body like dioxins and other OC chemicals, phthalates are ubiquitous in the environment. They are rapidly metabolized by the body and have a half-life shorter than 24 hours (Koch et al. 2005; Silva et al. 2003). Dietary uptake is a major route of exposure, along with contact (e.g., cosmetics and personal care items) and inhalation (e.g., air spray, nail polish, volatized phthalate from PVC) (Jurewicz and Hanke 2011; Lyche et al. 2009). Phthalate metabolites monoethyl phthalate (MEP) and monobutyl phthalate (MBP) have been detected in virtually all urine samples from a nationally representative U.S. study population (Silva et al. 2004b) and an urban study population in China (Guo et al. 2011). There is increasing concern that phthalates may be harmful to human reproductive health and fertility. Thelarche, the premature development of breast tissue, has a very high occurrence in Puerto Rico. Approximately 68% of early thelarche patients in Puerto Rico had high levels of multiple estrogenic phthalates as opposed to only one control in an analytical chemistry study (i.e., gas chromatography/mass spectrometry) (Colón et al. 2000). In a Chinese study of 210 girls, serum phthalate levels were detected in a higher percentage of precocious puberty (PP) girls than in non-PP girls for both the phthalates dibutyl phthalate (DBP) (27% vs. 4%) and DEHP (22.7% vs. 3%) (Qiao et al. 2007). The PP girls had larger ovaries and uteri with SSIG positive correlations between both DBP and DEHP levels and the sizes of these organs. However, a multicenter cross-sectional study in the United States of 28 girls with PP and 28 age- and race-matched prepubertal females showed no association between any phthalate metabolites and puberty onset (Lomenick et al. 2010).

*Trihalomethane (THM)* is a disinfection by-product that is commonly found contaminating drinking water in the United States and in Europe. In a follow-up study of a cohort of tap water consumers in California, researchers reported a shortened menstrual cycle length and a decreased follicular phase with increasing THM (decrease in cycle and follicular phases by 0.18 days, 95% CI = –0.29 to –0.07 per 10 μg/L increase in total THM) (Windham et al. 2003).

*Perfluorochemicals (PFCs)* are man-made surfactants widely used as water, stain, and grease repellants. Some common uses for PFCs include nonstick cookware, stain-resistant carpets, and fabric. The two most common PFCs are PFOS and PFOA (or C8). PFCs have a relatively long half-life in humans (median of 4.6 years for PFOS and 3.4 years for PFOA) (Olsen et al. 2007). They can generally be found in the soil, sediments, and groundwater. They are not lipophilic and do not break down in the environment.

The C8 health project in West Virginia studied over 69,000 subjects exposed to PFC in drinking water. Average serum levels of PFCs (except PFOS) were higher among C8 participants than in the U.S. population (NHANES 2003–2004), with PFOA levels reported as being 500% higher among the C8 group (Calafat et al. 2007; Frisbee et al. 2009). In one study that investigated the

effect of PFOA and PFOS on serum estradiol and menopause onset, PFOS was negatively (SSIG) associated with serum estradiol levels in the perimenopausal ($p < 0.0001$) and menopausal ($p < 0.007$) women, but an association was not found between PFOA and estradiol (Knox et al. 2011).

*Solvent* exposure is common. Approximately 30% of working women reported regular solvent exposure in a population-based study in Brittany, France (Garlantézec et al. 2009). Solvents are commonly encountered and studied as mixtures. Benzene is an aromatic hydrocarbon solvent that has been widely used in the United States and is formed from both natural processes and human activities. Natural sources of benzene include volcanoes and forest fires; it can also be found in the air from emission from burning coal and oil, car exhaust, and cigarette smoke. Benzene is also widely used in industries producing plastics, resins, synthetic fibers, lubricants, rubbers, detergents, and pesticides. A major source of benzene exposure is tobacco smoke, followed by emissions from gasoline/petrochemical industries (Zhang and Lioy 2002). Exposure to benzene vapors in the workplace has been associated with menstrual irregularity and spontaneous abortion (SA) (Cho et al. 2001; Thurston et al. 2000; Xu et al. 1998). Toluene, an aromatic solvent, is widely used in the manufacturing industries such as shoes, textiles, electronic components, and plastics, and in industrial applications of paints, thinners, adhesives, inks, and pharmaceutical products. Many women are exposed to toluene in occupational settings (long-term, low-level exposure) or by inhalant abuse (intermittent, high-level exposure) (Bukowski 2001; Hannigan and Bowen 2010). Assembly line workers in Singapore reported significant levels of residual toluene in blood after workplace exposure (Foo et al. 1988); however, no significant difference was observed in menstrual cycle frequency or flow of workers (Ng et al. 1992a). In one study, the reproductive hormone profiles of U.S. Air Force women ($n = 63$) were assessed in relation to their occupational exposure to jet fuel (Reutman et al. 2002). Those women whose internal doses (i.e., exhaled breath levels) of total aromatic hydrocarbons (primarily toluene, but also benzene, ethylbenzene, and *m*,*p*,*o*-xylenes) were above the median and had SSIG lower urinary preovulatory luteinizing hormone (LH) levels ($p = 0.007$), suggesting low-level exposure to compounds in fuels, and some solvents may act as neuroendocrine disruptors.

The risk of deleterious effects of toluene exposure in an occupational setting can be greatly reduced in well-regulated workplaces. In contrast, inhalation abuse of toluene and other organic solvents is of greater concern due to repeated high-level exposures (Hannigan and Bowen 2010). Accurate assessment of inhalant abuse is difficult due to the varying contents of toluene in different consumer products. Despite the many case studies on occupational and toluene abuse, the reproductive toxicology of this organic solvent remains underinvestigated.

*Tobacco (cigarette)* smoke contains a mixture of over 7000 chemicals and additives (U.S. DHHS 2010), many of which are considered organic compounds, but also includes inorganics such as heavy metals. The PAHs, nicotine,

and carbon monoxide found in tobacco smoke have been implicated in adverse female reproductive and developmental outcomes. Low levels of several BOCs and POCs described earlier (i.e., benzene, toluene, dioxin, and dioxin-like compounds) (Wilson et al. 2008) have also been detected among the many other compounds in tobacco smoke. Exposure to tobacco smoke occurs through both active and passive smoking, including transplacental fetal exposure during pregnancy (Rogers 2009). The 2010 U.S. Surgeon General Report found "consistent evidence that increases in follicle-stimulating hormone levels and decreases in estrogen and progesterone are associated with cigarette smoking in women, at least in part due to effects of nicotine on the endocrine system." The Report also concluded there was consistent evidence that tobacco smoke diminished oviduct function, which might impair fertilization (U.S. DHHS 2010). Additional reading on smoking-related reproductive and developmental risks is available in other U.S. Surgeon General reports (U.S. Department of Health and Human Services (U.S. DHHS), Office on Smoking and Health (U.S.) 2001; U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health 2004; U.S. DHHS 2006).

***Early/Premature Menopause*** Natural menopause is the conclusion of a developmental transition that marks the end of ovulation and menstruation due to what is widely regarded as the permanent loss of ovarian follicular activity. The WHO defines natural menopause as having occurred after 12 consecutive months of no menstrual periods, given there is no obvious pathological or physiological cause (e.g., pregnancy, lactation) (WHO 1996). In studies of women in industrialized countries, "early" menopause is typically considered cessation of menses before age 46 years, while "premature" menopause is often defined as cessation before age 40 years (NAMS 2012). "Induced" menopause generally refers to both ovarian ablation by agents such as radiation or chemotherapy and removal of both ovaries (i.e., bilateral oophorectomy) with or without hysterectomy (WHO 1996). Women with induced menopause may have different risk profiles than those undergoing natural menopause. This is an important consideration for study design and analysis.

A multitude of factors appear to hasten or delay the timing of natural menopause. Factors consistently associated with earlier menopause include active smoking, hormonal contraceptive use, low parity, and low socioeconomic status (Gold 2011). Diet, body mass, race/ethnicity, physical activity, genetics (Gold 2011), and residence (e.g., country, rural/urban) may also affect menopausal age (MA). Women who are atypically young at menopause may have heightened risks of cardiovascular disease and osteoporosis with attending reductions in overall survival and life expectancy. Concerns about infertility, together with psychological and social complications, have also been reported among those with premature ovarian failure (Nippita and Baber

2007; Singer et al. 2011). Most studies of reproductive toxicant effects compare exposed and reference groups to determine more subtle effects on MA rather than the less frequent outcomes of "premature" or "early" menopause per se. It is not clear if these subtle effects on MA engender the same health risks. Still, the reproductive window will have narrowed perceptibly for some and may impact the subset of women planning pregnancies in the latter reproductive years. Later age at menopause is associated with different risks, including increased ovarian, endometrial, and breast cancers (Gold 2011).

*OCs* The few studies of the effects on MA of other POP compounds measured among U.S. women during adulthood provide inconclusive evidence. TCDD exposure quintiles among the Seveso accident study cohort reportedly followed a monotonically increasing trend with reduced MA up to a dose threshold of 100 ppt ([$n = 616$]: SSIG trend for quintiles 1–4 [$p = 0.04$]) (Eskenazi et al. 2005). Among a cross-sectional sample of naturally menopausal women in the Hispanic NHANES study ($n = 219$), four of seven OCPs measured (serum DDT, DDE, β-HCH, and *trans*-nonachlor) were associated with mean MA reductions of 5.7, 3.4, and 5.2 years, respectively, between women within the highest versus lowest (nondetects) dose categories (Akkina et al. 2004). Similarly, among a subset of women from the North Carolina breast cancer case-control study ($n = 1407$), the median MA of women with the highest DDE levels was 1 year earlier than controls. Accordingly, women with higher serum DDE levels had non-SSIG ($HR_{ADJ} = 1.4$, 95% CI = 0.9–2.1) higher rate of menopause, similar to the rate seen among smokers (Cooper et al. 2002). In contrast, the median MA of farm women ($n = 5013$) who reportedly used and mixed a broad group of pesticides, including ovotoxins and HACs, was approximately 3 months older at menopause than controls overall. The subset that used HAC pesticides was 5 months older at MA. Both findings were SSIG ($HR_{ADJ} = 0.87$, 95% CI = 0.78–0.97 and $HR_{ADJ} = 0.77$, 95% CI = 0.65–0.92, respectively) (Farr et al. 2006). Two analyses examining the timing of menopause relative to levels of PCBs and PBBs (Taiwan Yucheng Study; $n = 118$) and another of PCBs alone (Michigan PCB study; $n = 874$) failed to find an association between exposure and timing of menopause (Blanck et al. 2004; Yu et al. 2000).

*PFCs* Among a cross section of women exposed to PFO-contaminated water, higher PFOS and PFOA levels were SSIG associated with the odds of menopause among both perimenopausal (for PFOS, PFOA: $OR_{ADJ} = 1.4$, 95% CI = 1.1–1.8) and menopausal subgroups (PFOS: $OR_{ADJ} = 2.1$, 95% CI = 1.6–2.8; PFOA: $OR_{ADJ} = 1.7$, 95% CI = 1.3–2.3) (Knox et al. 2011).

*Smoking* The association between smoking and early menopause is considered fairly well established (Parente et al. 2008). Women who smoke have MAs approximately 1–2 years earlier than nonsmokers (Gold 2011).

***Endometriosis*** Endometriosis occurs when tissue that is histologically similar to the inner uterine lining of reproductive-age women becomes ectopic, growing outside the uterus. Adverse endometriosis symptoms may include pelvic pain (particularly during menses or intercourse), infertility, and other possible symptoms and complications. Endometriosis, which occurs in 10–15% of women and requires estrogen to progress, typically presents during the adult reproductive years and subsides with reproductive senescence (Crain et al. 2008). Family history of endometriosis appears to be a risk factor. Altered responses to the extremely common phenomenon of retrograde menstruation are generally believed to be involved in the initiation of this condition, but the reason why progression only occurs in some women and the complete etiologic cascade are not well understood. Tissue samples from women undergoing surgery showed changes in mRNA expression for AhR and aryl hydrocarbon receptor nuclear translocator (ARNT) in diseased uterine tissues (endometriosis and fibroids). AhR and ARNT modify transcription of genes involved in cell differentiation and proliferation (Khorram et al. 2002). Developmental exposures to EDCs such as TCDD under experimental conditions appear to lead to a progesterone-resistant phenotype and hyperactive immune sensitivity to inflammatory stimuli, symptoms observed in women with endometriosis (Herington et al. 2011). Currently posited mechanistic roles of TCDD and other BOCs and POCs in the developmental and adult etiopathology of endometriosis are reviewed in detail elsewhere (Bruner-Tran and Osteen 2010; Crain et al. 2008; Guo 2004; Heilier et al. 2008; Herington et al. 2011; Mendola et al. 2008). Many published epidemiological studies of endometriosis have focused on EDCs.

*OCs* High residential exposure to TCDD, the most potent HAC, occurred in Seveso, Italy, when a chemical plant exploded in 1976. Risk of endometriosis was doubled 20 years after exposure among the 316 women with the highest (>100 ppt) versus lowest (<20 ppt) serum TCDD levels, although the risk and dose–response trend did not reach SSIG ($RR_{ADJ}$ = 2.1, 90% CI = 0.5–8.0) in that historical cohort (Eskenazi et al. 2002a). Female Seveso residents exposed *in utero* and in the youngest age groups were too young for inclusion at the time of that analysis. The authors also noted the results may have presented "an underestimate of the true risk" since the sample was small and misclassification of cases as noncases may have occurred, as surgical or ultrasound confirmation was required for designation as a case. Several authors have reviewed the Seveso study together with results of a combined total of 26 other studies which only captured adult exposures to potential EDCs including mainly dioxin (TCDD), PCDD/DFs, and PCBs (Bruner-Tran and Osteen 2010; Crain et al. 2008; Heilier et al. 2008; Mendola et al. 2008). There was general agreement across the reviews that the lack of developmental data in exposed and longitudinally tracked human populations beyond Seveso limits investigation of the fetal origin EDC exposure endometriosis hypothesis. Also, there was consensus that an association between adulthood OC exposure and endo-

metriosis is currently speculative since findings have been equivocal. However, a possible link was not ruled out. One review stressed that the deep nodular endometriosis phenotype appeared to be related to higher levels of marker PCBs and dioxin-like compounds (Heilier et al. 2008).

*Bisphenols and Phthalates* Few published studies of relationships between other EDCs (i.e., BPA, bisphenol B [BPB], DEHP, MBP, mono(2-ethylhexyl) phthalate [MEHP]) and endometriosis were identified. Findings from two analyses of fertile Italian women evaluated laproscopically suggested a direct association between endometriosis and serum BPA and BPB (Cobellis et al. 2009 [$n = 69$]) and an SSIG ($p = 0.0047$) direct SSIG association with DEHP (Cobellis et al. 2003 [$N = 79$]). In a U.S. (NHANES) study based on self-reported endometriosis, a positive association with MBP and a negative association with MEHP were found to be SSIG, but only when endometriosis or fibroid outcomes were combined ($OR_{ADJ} = 1.71$, 95% CI = 1.07–2.75 and $OR_{ADJ} = 0.59$, 95% CI = 0.37–0.95, respectively) (Weuve et al. 2010 [$n = 238$]). Neither MEP, MEPH, nor monobenzyl phthalate (MBzP) was SSIG in that study when endometriosis was considered alone.

*Dietary Estrogens* In their review, Heilier et al. (2008) hypothesized that phytoestrogens may be linked to endometriosis since one study found them to be associated with endometrial hyperplasia (Unfer et al. 2004) and another demonstrated their ability to stimulate aromatase activity in human endometrial stroma *in vitro* (Edmunds et al. 2005).

Several of the above-mentioned reviewers have speculated methodological dissimilarities such as different comparison groups, exposure profiles, congener groupings, uncontrolled confounders, case versus noncase definitional criteria (i.e., phenotypic and diagnostic), and the potential for reverse causation may hamper individual or aggregate interpretation of EDC endometriosis study results.

***Fibroids*** Uterine fibroids (i.e., leiomyomata) are benign hormonally reactive uterine tumors that originate in the uterus (myometrium) among as many as half of menopausal women (Haney 2008). Fibroid growths may be asymptomatic or can decrease fertility and may cause pelvic pain, including excessive pain and bleeding during menstruation. Infrequently, complications such as blood loss can be life threatening. Risk factors for fibroids include obesity and elevated BMI, but the risk varies inversely with time interval since last delivery. Women in the United States undergo roughly 200,000 hysterectomies and 20,000 myomectomies per year to relieve uterine fibroid symptoms and complications (Haney 2008), and these surgeries also impart health risks.

*Dietary Estrogens* In one review (Crain et al. 2008), dietary phytoestrogens were reported to have been consistently protective against fibroids across

several studies that examined the effects of their consumption by reproductively mature women. More recently, in the National Institute of Environmental Health Sciences (NIEHS) Sister Study breast cancer cohort, fibroids were positively but non-SSIG associated with having been fed soy formula in infancy ($RR_{ADJ} = 1.26$, 95% CI = 0.83–1.89 [$n = 2583$]) (D'Aloisio et al. 2011).

*OCs* Exposure to TCDD has been linked to a lowered risk of fibroids in 410 women in the Seveso cohort 20 years after the explosion (Eskenazi et al. 2007). The investigators proposed that this may reflect antiestrogenic effects in the myometrium. With the paucity of human studies, there are calls for more research on the relationship between BOCs and POCs and fibroids (Crain et al. 2008; Mendola et al. 2008).

*PCOs* Women with PCOS have clinical or biochemical androgen excess and ovarian dysfunction, which manifest as polycystic ovaries and/or infrequent, irregular, or absent ovulation, although there is much heterogeneity in the phenotype, and the definitional criteria are evolving (Azziz et al. 2009). This common condition affects approximately 4–8% of reproductive-age women, although higher prevalences approaching 20% have been reported using broader PCOS criteria (Teede et al. 2010). PCOS is often accompanied by metabolic syndrome symptoms such as abdominal obesity, insulin resistance, and lipid alterations, with elevated risks of diabetes, nonalcoholic fatty liver disease, coronary heart disease, stroke, and endometrial cancer (Crain et al. 2008; de Groot et al. 2011; Hossain et al. 2011). Reproductive risks include premature pubarche, anovulatory infertility, gestational diabetes, pregnancy-related hypertension, and miscarriage (Crain et al. 2008). The pathogenesis is unclear, but genetic predisposition, diet, and other environmental exposures of susceptible individuals during developmental windows are suspected (Crain et al. 2008; Diamanti-Kandarakis et al. 2012).

*Bisphenols* Adult BPA levels have been positively and SSIG associated with PCOS and androgen levels in two clinic-based cross-sectional epidemiology studies ($p < 0.001$ for PCOS and $p < 0.05$ for hyperandrogenism, $n = 171$, Kandarakis et al. 2011; $p < 0.05$ for PCOS and $p < 0.001$ for androgens, $n = 45$, Takeuchi et al. 2004). A positive SSIG relationship between BPA and insulin resistance in the PCOS group was also noted in one study ($p < 0.05$; Diamanti-Kandarakis et al. 2012). Review authors remarked that the potential for reverse causation must be considered when interpreting these study results as the elevated testosterone levels that attend PCOS may decrease BPA clearance (Crain et al. 2008). That few human studies have been published on the effects of BPA and other compounds on PCOS is striking, given the relatively high prevalence and comorbidities associated with this poorly understood condition. Refinements of and consensus on the most relevant phenotypic criteria of PCOS for research will strengthen future research quality.

***Infertility/Subfecundity*** Infertility has been defined by the WHO as failure to conceive after at least 1 year of unprotected intercourse. Infertility rates differ by region (Vayena et al. 2002). Of couples who are at risk for pregnancy (e.g., stop contraception), about 10–15% will take more than 12 months to conceive (Baird and Strassmann 2000). Note, however, that a higher percentage of 30- to 40-year-old women will have experienced at least one infertility episode. Female infertility has been linked to tubal and pelvic factors (40%), ovulatory dysfunction (40%), and cervical and uterine cancers (5%), while 15% of infertility is unexplained (Levens and Decherney 2011). Fetal losses that occur very early in pregnancy are often unrecognized and thus contribute to perceived infertility. Studies of time to pregnancy (TTP) estimate fecundity, or the biological capacity of women, men, or couples to reproduce. A prolonged TTP suggests impaired fecundity (i.e., a reduced probability of conceiving each cycle or fecundability ratio [FR]).

*OCs* Two decades after the 1979 Yucheng PCB-contaminated cooking oil incident, the exposed women reported longer TTP ($p = 0.019$) together with higher odds of infertility ($OR_{ADJ} = 2.34$, 95% CI = 1.23–4.59) (Yang et al. 2008). The NYSA women who consumed fish contaminated with moderate to high levels of PCB later reported shorter menstrual cycles compared with nonexposed women (–1.03 days, 95% CI = –1.88 to –0.19) (Mendola et al. 1997). In addition, a subset of this study population, those who consumed contaminated fish the longest ($n = 732$), reported a small but non-SSIG reduction in fecundity (McGuinness et al. 2001).

*Pesticides (General)* Epidemiological studies of infertility and TTP among agricultural workers have been examined in several reviews, but few of the studies (described further) focused on women's exposures (Hanke and Jurewicz 2004; Sanford et al. 2007). One such study of female agricultural workers and controls ($N = 497$) reported SSIG increased odds of infertility among women in who worked in agriculture before conceiving, in industries associated with agriculture, or who resided on a farm (OR = 11.3, 95% CI = 2.6–48.8; OR = 7.0, 95% CI = 2.3–20.8; and OR = 1.8, 95% CI = 1.2–2.7, respectively) (Fuortes et al. 1997). Another was of 2012 pregnancies among Ontario (Canada) farm couples in whom the TTP was increased for 6 of 13 pesticide exposures during the intervals in which women participated in pesticide activities (as did most of the men) (conditional FR range = 0.51–0.80) (Curtis et al. 1999). A TTP study of 492 female greenhouse workers found SSIG increased TTP only when considering the subset who did not use gloves ($FR_{ADJ} = 0.67$, 95% CI = 0.46–0.98) (Abell et al. 2000). Several later TTP studies of female greenhouse workers did not find SSIG longer TTP (Bretveld et al. 2006; Lauria et al. 2006), although the odds were slightly elevated in one of these analyses (OR 1.9, 95% CI = 0.8–4.4) (Bretveld et al. 2008).

*PFCs* In a study of the Danish National Birth Cohort of 895 women who became pregnant, higher maternal serum concentrations of PFOS and PFOA were associated with SSIG longer TTP ($p < 0.001$), hence reduced fecundity (Fei et al. 2009). Infertility ORs were directly linked to PFOS and PFOA levels in that study ($p = 0.025$ and $p < 0.006$, respectively). In contrast, no SSIG association was found between TTP and exposure to PFCs (at similar levels measured in the Danish National Birth Cohort) among a national study of Danish couples planning a first pregnancy who were recruited from trade union rosters (Vestergaard et al. 2012). A case-control analysis of 910 women from the Norwegian Mother and Child Cohort Study found discrepant relationships between fecundity and serum levels of PFOS and PFOA among those who had been pregnant (prolonged TTP) and those who had never been pregnant (shortened TTP) after age and BMI adjustments (PFOS: $OR_{ADJ} = 2.1$, 95% CI = 1.2–3.8 vs. 0.7, 0.4–1.3, respectively; PFOA: $OR_{ADJ} = 2.1$, 95% CI = 1.0–4.0 vs. 0.5, 0.2–1.2, respectively) (Whitworth et al. 2012). As body burdens of compounds fluctuate with pregnancies and lactation, the authors commented that the analysis of TTP among never-pregnant (i.e., nulliparous) women may be the most informative.

*Solvents* In a study evaluating the relationship between toluene exposure and TTP, male and female employees from 14 different printing companies in Germany were recruited. All women performed jobs that had low-level exposure, while men worked in areas with low, medium, and high exposures to toluene. Results showed a strong association between toluene exposure and reduced fecundity; the FR was 0.48 (95% CI = 0.24–0.97) for these female employees compared to women not in the printing industry (Plenge-Bonig and Karmaus 1999). No association between toluene exposure and male infertility was observed, which suggests that women may be more susceptible to the adverse reproductive effects of toluene. Similar studies on female workers in European shoe manufacturing and laboratory workers exposed to solvents also show reduced fecundity (fertility density $ratio_{ADJ} = 0.55$, 95% CI = 0.40–0.70 for "low" exposure among shoe workers; $FR_{ADJ} = 0.79$, 95% CI = 0.68–0.93 for organic solvent exposure among laboratory workers, respectively) (Sallmén et al. 2008; Wennborg et al. 2001). Also, an SSIG increase in the odds of subfertility was found among the wives of pesticide applicators ($n = 2112$) in the Agricultural Health Study Cohort who were themselves exposed to solvents at least once per month ($OR_{ADJ}$: 1.42, 95% CI = 1.15–1.75) (Sallmén et al. 2006).

*Smoking* A consistent overall association (OR = 1.60, 95% CI = 1.34–1.91) between smoking and increased infertility risk was reported in a meta-analysis of 12 studies and was supported by a concurrent review of nine *in vitro* fertilization studies in which smoking women were also less fecund (Augood et al. 1998).

## Pregnancy and Fetal Development Outcomes

***Fetal Loss*** Fetal loss is a broad term for unintended pregnancy loss, which encompasses very early, often undetected pregnancies as well as clinically recognized miscarriages and stillbirths. Fetal losses are frequent, with most occurring during the early weeks of fertilization and implantation, often before the pregnancy is known. In a given menstrual cycle, it has been estimated that only 36% of attempting women will manifest chemically detectable implantations (i.e., detectable human chorionic gonadotropin levels). The deficit is attributable to fertilization failure and early (i.e., pre- and early postimplantation) pregnancy losses (Baird and Strassmann 2000). It was estimated that another 10% of these early detectable pregnancies will have been lost before 6 weeks after the last menstrual period. Estimates from Western countries indicate 10–20% of clinically recognized pregnancies end in SA (i.e., miscarriage) and 2% end in stillbirth (Baird and Strassmann 2000; Chard 1991). Many maternal and several paternal factors have been linked to fetal loss (e.g., medical and reproductive conditions and history, alcohol, smoking, and drug use, nutritional status, age, job and iatrogenic exposures, genetics, sociodemographic factors) (Reutman and LeMasters 2007). Miscarriages are defined here as losses occurring before 20 weeks of gestation, after which losses are termed stillbirths. However, some studies have used other stillbirth definitions (e.g., ≥28 weeks) (Wigle et al. 2008). The number of stillbirths approached 26,000 in the mid-2000s in the United States (MacDorman and Kirmeyer 2009). Risk factors linked to stillbirths across low-, middle-, and high-income countries include medical (e.g., previous stillbirth, high/low [primi-]parity, multiples, congenital anomalies, infections, AB blood type, intrauterine growth restriction, diabetes, placental pathologies, and eclampsia/preeclampsia), socioeconomic (i.e., no partner or education, lacking prenatal care), lifestyle (smoking or illicit drugs), elevated BMI, race/ethnicity, and advanced maternal age (Faiz et al. 2012; McClure et al. 2011; The Stillbirth Collaborative Research Network Writing Group 2011).

*Pesticides (General)* Studies of parental exposures to pesticides in general and SA or stillbirth have been reviewed elsewhere (Hanke and Jurewicz 2004; Sanborn et al. 2007), and two reviews are of particular interest in that they were focused on maternal occupational (Nurminen 1995) and residential (Shirangi et al. 2011) exposures. Based on positive findings in five of six SA and two of three stillbirth analyses, the Nurminen (1995) review concluded there was evidence to support an association between maternal agricultural occupation and pesticide exposure and SA and stillbirth. Several subsequent studies have been identified, including findings of no SSIG association between stillbirth and pesticides among Indonesian women exposed as spray operators or rice farmers (Murphy et al. 2000). Also, the odds of SA among 973 pregnancies of female greenhouse workers were found to be SSIG elevated among those who reentered within 24 hours of pesticide application ($OR_{ADJ}$ = 3.2, 95%

CI = 1.3–7.7) (Settimi et al. 2008). In a systematic review of birth outcomes among women living near agricultural pesticide applications, two SA studies showed no SSIG associations and four of five stillbirth studies reported suggestive increases RR in one or more subgroups (RR = 1.2–2.0), but none reached SSIG (Shirangi et al. 2011). An SSIG exposure–response gradient was reported in one of the stillbirth studies, however (White et al. 1988).

*OCs* DDT and its metabolite, DDE, are reproductive toxicants associated with fetal loss (Hruska et al. 2000). Among 388 newly married Chinese women in whom preconception serum DDT levels were measured, the subsequent odds of pregnancy loss were higher for the highest DDT tertile compared with those for the lowest ($OR_{adj}$ = 2.12, 95% CI = 1.26–3.57); a 10-ng/g increase in total DDT was accompanied by relative odds of early pregnancy loss of 1.17 (95% CI = 1.05–1.29) in that study (Venners et al. 2005). One recent multicountry study found risks of fetal loss associated with both DDE and PCB 153 exposures, but the investigators cautioned that firm conclusions could not be drawn since there was a lack of dose–response and inconsistencies between countries ($OR_{ADJ}$ = 2.4, 95% CI = 1.1–5.5, $n$ = 678; Toft et al. 2010). During the two decades after the Yucheng PCB mass ingestion poisoning incident, the percentage of reported stillbirths among exposed women was double that of the control group, a finding that approached, but did not reach, SSIG ($p$ = 0.068; 4.2% vs. 1.7%, $n$ = 668; Yu et al. 2000). Other large PCB studies of female cohorts in Boston (827 assisted reproduction cycles; Meeker et al. 2011), Michigan ($n$ = 1344 pregnancies; Small et al. 2007), and Australia ($n$ = 200 pregnancies; Khanjani and Sim 2007) did not detect an association between SA and PCB exposure. Neither did a German clinic-based study of 89 women referred for repeated SA find associations between SA and blood levels of PCP, PCB, DDE, HCHs, and HCB (Gerhard et al. 1998).

*THMs* One U.S. study reported that women consuming large volumes of tap water (≥5 glasses/day) containing high levels of total THMs (≥75 μg/L) had a SSIG higher risk of SA ($OR_{ADJ}$ = 1.8, 95% CI = 1.1–3.0) (Waller et al. 1998).

*Solvents* Occupational exposure of women to solvents during pregnancy is SSIG associated with increased risk of SA, based on a meta-analysis of 19 formaldehyde studies (overall RR = 1.76, 95% CI = 1.20–2.59) (Duong et al. 2011). Subgroups with higher versus lower maternal occupational toluene exposure reportedly had SSIG increased SAs across several individual studies reviewed (Lindbohm 1995; Ng et al. 1992b [$OR_{ADJ}$ = 4.80, 95% CI = 1.01–22.86, $N$ = 173 pregnancies]). A meta-analysis of five studies of various solvents revealed an increase in the odds of SA across those studies that bordered but did not reach SSIG (overall OR = 1.25, 95% CI = 0.99–1.58) (McMartin et al. 1998). The earliest study of SA after exposure to toluene and other solvents

was part of a cross-sectional survey on pregnancy history and occupational exposure by female laboratory workers in Sweden. The study showed a non-SSIG increase in the risk of SA among exposed workers (Axelsson et al. 1984). Subsequent studies reported that female workers and wives of workers exposed to toluene had consistently higher rates of SA compared with control groups (Lindbohm et al. 1990; Ng et al. 1992b; Taskinen et al. 1989, 1994). Adjusted ORs for maternal toluene exposure in these studies were noteworthy and SSIG ranged from 2.79 (95% CI = 1.32–5.88) to 4.80 (1.01–22.86) (Ng et al. 1992b). Xylene ($OR_{ADJ} = 3.1$, 95% CI = 1.3–7.5) and formalin ($OR_{ADJ} = 3.5$, 95% CI = 1.1–11.2) were each SSIG associated with SA in one of these larger studies ($N = 535$) (Taskinen et al. 1994).

In Beijing, a higher percentage of female petrochemical factory production workers than nonchemical plant workers reported SA (8.8% vs. 2.2%; overall $OR_{ADJ} = 2.7$, 95% CI = 1.8–3.9) (Xu et al. 1998). Benzene and gasoline exposure were individually associated with SSIG elevated odds of SA in that study. Similarly, women working at petrochemical plants in Sweden had SSIG heightened odds of miscarriage (OR = 6.6, 95% CI = 2.3–19.2) (Axelsson and Molin 1988). In a subanalysis of chemical workers from that study, SA was SSIG ($p < 0.05$) elevated specifically among the laboratory workers (Axelsson and Rylander 1989).

*Smoking* Smoking is an established risk factor for stillbirths (Rogers 2009). The smoking population's attributable risk has been estimated at 4–7% in high-income countries to as high as 20% in disadvantaged subgroups within those countries in one meta-analysis of 96 population-based studies (Flenady et al. 2011). A 2010 U.S. Surgeon General's Report concluded there was consistent evidence that linked "maternal smoking to interference in the physiological transformation of spiral arteries and thickening of the villous membrane in forming the placenta" and suggested "smoking leads to immunosuppressive effects, including dysregulation of the inflammatory response"(U.S. DHHS 2010). Risk of fetal loss was suggested to be heightened by both of these mechanisms.

***Maternal Hypertension*** Pregnancy-induced hypertension is linked to stillbirths and preterm births (PTBs), and sometimes portents the life-threatening (maternal and fetal) condition, preeclampsia.

*PFCs* A court-appointed scientific panel assessed harm caused by PFOA contamination of six Ohio and West Virginia water districts by manufacturers. They determined that PFOA was "more likely than not" to have caused pregnancy-induced hypertension in that settlement class (Holtcamp 2012). The panel noted data on prematurity, stillbirth, and preeclampsia were insufficient to draw firm conclusions, but that a moderate potential "signal" of a link between PFOA and preeclampsia was suggested.

*Smoking* A 2010 Surgeon General's Report on smoking relayed that maternal smoking during pregnancy transiently raises maternal heart rates and blood pressure (mainly diastolic) (U.S. DHHS 2010).

## Live Birth Outcomes

***Prematurity*** Premature (aka, preterm) births are those occurring before 37 weeks (259 days) of gestation. Infants born prematurely are at near- and long-term risk for adverse outcomes. Those with the shortest gestations are most at risk for infant death and other adverse complications such as cerebral palsy, respiratory problems, intellectual disabilities, vision and hearing loss, and feeding and digestive problems (U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Reproductive Health and National Center for Birth Defects and Developmental Disabilities 2011). Known risk factors include multiple births, previous PTB, black race, uterus or cervical problems, chronic maternal hypertension, clotting disorders or diabetes, certain infections in pregnancy, and lifestyle factors (smoking, alcohol, and illicit drug use).

*OCs* Studies of OC exposures (e.g., PCBs, DDE, DDT, HCB) have demonstrated mixed results, but several of the largest studies we reviewed reported SSIG or near-SSIG direct relationships. Odds of prematurity increased in tandem with increasing DDE exposure quintiles, that is, $OR_{ADJ}$ = 1, 1.5, 1.6, 2.5, 3.1 (SSIG trend, $p < 0.0001$), among eligible U.S. Collaborative Perinatal Project births ($n = 2380$) (Longnecker et al. 2001). Risk of prematurity among 70 neonates born to parents residing near an electrochemical plant in Spain was also directly associated with umbilical cord levels of DDE (2.40 vs. 0.80 ng/mL in prematures and nonprematures, respectively; $p < 0.05$) and PCBs (0.70 vs. 0.14 ng/mL, $p < 0.05$) and approached SSIG for HCB (1.94 vs. 1.10 ng/mL, $p < 0.10$) (Ribas-Fitó et al. 2002). In another study (Wojtyniak et al. 2010), maternal serum DDE levels among women in Kharkiv, Poland ($N = 661$), and Greenland Inuit women ($N = 572$), as well as PCB 153 levels among Inuits only, were SSIG associated ($p < 0.05$) with decreased gestation length but not prematurity. Gestation length was inversely associated with both PCB levels in cord blood ($p < 0.05$) and self-reported maternal consumption of PCB-contaminated fish ($p < 0.01$) for women who delivered in hospitals near Lake Michigan, based on 313 newborns (Fein et al. 1984). Conversely, several studies failed to detect SSIG associations between OCs and shortened gestation (Berkowitz et al. 1996 [$n = 40$]; Farhang et al. 2005 [$n = 420$ male newborns]; Khanjani and Sim 2006 [$n = 200$]; Longnecker et al. 2005 [$N = 1043$]; Torres-Arreola et al. 2003 [$N = 233$]), yet two of these showed elevated ORs or borderline SSIG (Khanjani and Sim 2006; Torres-Arreola et al. 2003). The statistical power of some of these studies was limiting. Future studies with

ample power are indicated to clarify the potential role of BOC and POC exposures on the length of gestation.

*Solvents* In their 2001 review, Scheeres and Chudley (2002) cited clear evidence that toluene abuse during pregnancy increases the risk of prematurity, but low-dose human studies are needed.

*Smoking* One review noted that dose–response relationships between maternal smoking and PTB have been reported across several studies (Rogers 2009). A recent 2010 Surgeon General's Report implicated smoking-induced placental abnormalities and immunosuppressive dysregulation of the inflammatory response (U.S. DHHS 2010) in the relationship between smoking and increased risk of prematurity (Rogers 2009). The report also concluded there was consistent evidence linking genetic variations in metabolizing enzymes (e.g., GSTT1) and prenatal tobacco smoke exposure with increased risk of adverse pregnancy outcomes such as reduced gestation and lowered birth weight.

***Fetal Growth*** Fetal growth is influenced both by genetics and the intrauterine environment. Prenatally, fundal height and ultrasound imaging are applied to estimate gestational age and to clinically monitor fetal growth. Birth size metrics (i.e., birth weight, length, ponderal index as birth weight/length$^3$ $\times$ 100, head circumference) are most often used to characterize fetal growth in epidemiology studies, with birth weight being the most common end point. Head circumference can be altered by molding during vaginal births, as opposed to C-section deliveries (Apelberg et al. 2007). Placental weight is sometimes also considered. Often, gestational age estimates at birth are taken into account in the analysis or interpretation of birth weight studies to isolate the effects of growth (i.e., small for gestational age [SGA] births) versus prematurity. It is important to note that birth weight studies may capture subtle growth shifts; however, the extremes of fetal growth curves are where the greatest risks reside. Broadly, many factors known or suspected to increase the risk of fetal loss also increase the risk of intrauterine growth restriction and SGA births (Reutman and LeMasters 2007). Risks of cardiovascular disease, osteoporosis, and type 2 diabetes are heightened among those who are small at birth and had poor growth during infancy, especially preceded by excessive childhood weight gain (Godfrey et al. 2011).

*Pesticides (General)* Studies of parental exposures to pesticides in general and fetal growth have been reviewed elsewhere (Hanke and Jurewicz 2004; Nurminen 1995; Sanborn et al. 2007; Shirangi et al. 2011). Some of these studies specifically addressed maternal pesticide exposures, most of which were occupational (Dabrowski et al. 2003; Heidam 1984; Lima et al. 1999; McDonald et al. 1988; Murphy et al. 2000; Schwartz et al. 1986; Xiang et al. 2000; Zhang et al. 1992) or residential in proximity to agricultural pesticide applications

(Grether et al. 1987; Levario-Carrillo et al. 2004; Thomas et al. 1992; Willis et al. 1993). Pesticide exposure was associated with SSIG findings, that is, lowered birth weight by 117 g ($p = 0.05$) and low birth weight (RR = 3.6) and ($p < 0.05$, beet crops) in only three of these studies. However, non-SSIG increases in intrauterine growth retardation (RR = 2.3–2.9) and low birth weight (RR = 2.3) were reported in three more of these studies. In more recent studies, early pregnancy maternal exposure to pesticides was not SSIG associated with birth weight in a study of births to 2246 Iowa and North Carolina (United States) farm women (with the exception of carbaryl) (Sathyanarayana et al. 2010). Fetal weight and head circumference were non-SSIG reduced, and placental weight were reported among 4680 infants born to mothers in the Netherlands, and placental weight reduction reached SSIG ($p < 0.05$) (Snijder et al. 2012). Inconsistencies in findings between studies likely reflect differences in exposures (e.g., specific pesticides used, levels, exposure timing in relationship to births, coexposures), study designs (e.g., individual vs. aggregate exposure data), and regional differences, to name just a few.

*OCs* A recent meta-analysis of European studies in which PCBs and DDE were quantified in maternal or cord samples concluded that low-level PCB exposures (or other correlated exposures) are associated with lowered birth weight, whereas DDE exposures were not (Govarts et al. 2012). Birth weight decreased with increasing PCB 153 after confounder adjustment in 12 of the 15 studies examined. This conclusion is consistent with many additional individual PCB birth weight studies (Fein et al. 1984; Halldorsson et al. 2008; Hertz-Picciotto et al. 2005a; Murphy et al. 2010; Patandin et al. 1998; Rylander et al. 1995, 1998; Sonneborn et al. 2008; Wojtyniak et al. 2010) but is inconsistent with several others (Givens et al. 2007; Gladen et al. 2003; Grandjean et al. 2001; Longnecker et al. 2005; Vartiainen et al. 1998). Smaller head circumference was also reported with increasing PCB levels among offspring of fishermen's wives who consumed OC (including PCB)-contaminated fish from the Baltic Sea (Fein et al. 1984; Hertz-Picciotto et al. 2005a; Rylander et al. 1995). Several of these PCB studies also examined DDE, as did a number of other DDE studies described in a recent paper (Lopez-Espinosa et al. 2011). DDE exposure was linked inversely to birth weight and SGA births in a number of these studies, while one study reported an exposure-related birth weight increase. However, consistent with the above-mentioned meta-analysis, most of the studies failed to reveal any DDE effect. Several studies of DDT, HCB, and HCH exposure also failed to find a birth weight effect, with some exceptions (Lopez-Espinosa et al. 2011).

*Organophosphates (OPs)* have been widely used as neurotoxic insecticides in agriculture. They were banned for residential use for over a decade (Williams et al. 2008). Prior to that, they were used extensively for residential use, during which time low-level exposure was ubiquitous. One recent review included studies of four U.S. epidemiological cohorts (i.e., the CCCEH, CHAMACOS, Mt. Sinai CCEHDPR, and a New Jersey cohort) in which associations between fetal growth and prenatal exposure to the OP chlorpyrifos

were examined (Mink et al. 2012). Reviewers evaluated these studies in terms of the potential implications of their findings for risk assessment but concluded that no strong associations with consistent exposure–response patterns were shown. Another review of three of the same cohorts similarly concluded that the study results were not consistent (Koureas et al. 2012).

*ATZ* Potential fetal growth effects of the herbicide ATZ, a highly prevalent drinking water contaminant, were examined across several studies. Borderline (non-SSIG) associations between maternal pregnancy levels of an ATZ metabolite and outcomes of fetal growth restriction and small head circumferences were reported among 579 live births included in a nested case-cohort study in Britanny, France (i.e., PELAGIE Cohort) ($OR_{ADJ}$ = 1.5, 95% CI = 1.0–2.2 and $OR_{ADJ}$ = 1.7, 95% CI = 1.0–2.7, respectively) (Chevrier et al. 2011). Results of two ecological studies of agricultural community drinking water supplies suggest the third trimester of pregnancy might be the most vulnerable exposure window for putted effects of ATZ on SGA. Specifically, SGA was SSIG associated with mean ATZ water concentrations (i.e., above 0.644 μg/L) across all trimesters ($PR_{ADJ}$ = 1.14, 95% CI = 1.03–1.24) among 24,154 Indiana (United States) births. In the same study during the third trimester, exposure to even lower ATZ concentrations was associated with an SSIG increase in SGA prevalence compared to controls ($PR_{ADJ}$ = 1.17, 95% CI = 1.03–1.24) (Ochoa-Acuña et al. 2009). Similarly, based on a subanalysis of 238 SGA births in Finistère, France, when high ATZ water contamination (occurred May–September) coincided with women's entire third pregnancy trimester, the risk of SGA deliveries was elevated ($OR_{ADJ}$ = 1.54, 95% CI = 1.11–2.13) (Villanueva et al. 2005). In that study, however, no relationship was found between ATZ levels measured in municipal water supplies and SGA or low birth weight. Another study of births to mothers in Iowa (United States) reported rural communities with water contaminated with ATZ and other herbicides had SSIG elevated risk of intrauterine growth retardation outcomes compared to control communities (RR 1.8, 95% CI = 1.3–2.7) (Munger et al. 1997). Potential limitations cited by authors of ecological ATZ studies included design constraints, such as aggregate ATZ water measurements and limited confounder data.

*PFCs* PFOA, but not PFOS, in maternal plasma was SSIG associated with lowered birth weight in a nationally representative analysis of 1400 births in Denmark ($\beta_{ADJ}$ = −10.63 g, 95% CI = −20.79 to −0.47 g) (Fei et al. 2007). Increases in exposures to PFOA and PFOS were each associated with SSIG decreases in newborns' ponderal index (in $g/cm^3 \times 100$ units: −0.070, 95% CI = −0.138 to −0.001; and −0.074, 95% CI = −0.123 to −0.025, respectively, after adjustment). Reductions (non-SSIG) in simple birth with increased PFOA and PFOS exposures were also reported in a smaller (293 cord serums) cross-sectional hospital-based study in Maryland (United States) (per 2.7-fold unit cord level increase corresponded to −104 g, 95% CI = −213 to 5 g; and

–69 g, 95% CI = –149 to 10 g, respectively, after adjustment) (Apelberg et al. 2007). Birth weight also was SSIG decreased with PFOS in a hospital-based prospective cohort study of 428 Japanese newborns (10-fold unit PFOS increase associated with –148 g, 95% CI = –297.0 to –0.5 g), which appeared driven by birth weight reductions among females (Washino et al. 2009). Another PFOS analysis of 421 live births to women in an occupational mortality cohort found no association with birth weight (Grice et al. 2007). Head circumference was also SSIG reduced with PFOA and PFOS in adjusted analyses in the U.S. birth weight study (cord blood unit increases of 2.7-fold corresponded to –0.32 cm, 95% CI = –0.56 to –0.07 cm; and –0.41 cm, 95% CI = –0.76 to –0.07 cm, respectively, after adjustment) (Apelberg et al. 2007). A review paper with additional perspectives on the topic of perfluorinated acids, including PFOS and PFOA, has been published by industry experts (Olsen et al. 2009).

*Smoking* Evidence that active and passive maternal smoking represent risk factors for low-birth-weight births has been described as unequivocal (Rogers 2009). It was suggested in the 2010 Surgeon General's Report that smoking-induced placental problems may contribute to low birth weight (U.S. DHHS 2010).

A broad review published in 2008 described evidence (including that cited from the Collaborative on Heath and the Environment) for adverse effects of BOCs and POCs on either fetal growth or gestational age as follows: "limited" evidence for perfluorinated acids, carbon tetrachloride, dioxins/TCDD, perchlorethylene and trichloroethylene in water, phenoxyacetic herbicides, and phthalates; "moderate" evidence for air pollution, herbicides, nicotine, OC and OP pesticides, pentachlorophenol, PCBs, solvents, and water disinfection by-products; and "strong" evidence for carbon monoxide, cocaine, ethanol, and tobacco smoke (Windham and Fenster 2008).

***Sex Ratios*** Secondary sex ratio (SSR) alterations (i.e., altered boy to girl ratios at birth) are thought to be caused by factors that modify the illusive "primary" sex ratio at conception or selectively affect the rate of lethal conditions postconception (e.g., nonviable anomalies) for one gender versus the other. It has been proposed that alterations in SSRs are mediated by "periconception and intrauterine hormone levels, insemination timing relative to ovulation/oocyte maturity, sexual behavior (e.g., family size and age of mate), adaptive responses to environmental stressors, and actions of toxicants" (Pergament et al. 2002). Different formulas are used to derive SSRs, so conversion may be required for comparisons across groups. The contemporary mass rise of selective abortion of females in Asia and elsewhere, contributing to an estimated 160 million "missing girls" (Douthat 2011), may complicate comparisons of SSRs across different time periods or with societies where that practice is widespread (Wilcox and Baird 2011).

*DES* Altered SSRs have been reported in populations where SSR distortions from selective abortions were improbable. Such was the case when an SSIG

excess of baby boys (F2) was born to a subset of 1775 women (F1) exposed *in utero* to DES when their mothers (F0) took that drug to prevent miscarriage. Pregnant women were prescribed DES, a synthetic estrogen, between 1940 and 1971 as it was thought to prevent premature labor and miscarriage. Tragically, DES is now known as a transplacental endocrine disruptor (ED), teratogen and carcinogen. The subset of women whose mothers took their first DES dose earliest in gestation (<13 weeks) at the highest cumulative doses (≥5 g) had SSIG higher odds of a male birth versus unexposed controls ($OR_{ADJ} = 1.24$, 95% CI = 1.04–1.48), but no SSIG SSR effects with DES were described overall (Wise et al. 2007).

*OCs and Polybrominated Compounds* Neither would prenatal sex selection account for the SSIG ($p < 0.001$) excess in females among 74 births to those accidentally exposed to TCDD in Seveso, Italy, who gave birth within 9 months to 7 years after that event. No SSIG alteration in SSR was reported among births occurring in later years (Mocarelli et al. 1996). No association between TCDD levels in breast milk and SSR was apparent in a follow-up analysis of 15 births to a small Kazakhstan cohort exposed to high doses of TCDD (Hooper et al. 1998). In contrast with the female newborn preponderance in Seveso, five of six Kazakhstan newborns with the highest TCDD levels were males. Authors of the Kazakhstan study speculated culturally influenced heightened participation by mothers of sons may have biased their results.

No SSIG SSR effects of accidental PCBs or PCDF ingestion were seen within the F1 generation (children), including 137 children of highly exposed women who accidentally consumed PCBs and PCDF in the Yucheng, Taiwan, tragedy. Nor was there an SSR effect overall among the F1 generation of victims who accidentally ingested PCBs and PCDF in Yusho, Japan (Rogan et al. 1999). However, when the Yusho cohort analysis was restricted to births to parents under age 20 years at the time of the incident, there was a trend toward fewer male births to exposed women in both the F1 and F2 (grandchildren) generations ($p = 0.06$ and $p = 0.02$, respectively) (Tsukimori et al. 2012). Since the most marked sex ratio effect was a reduction in the number of girls born to early-exposed Yusho mothers, the authors posited that there may have been greater female susceptibility and transmission through the female line.

Results of other analyses of PCBs in F1 generations have also found a decline in male births (i.e., more females) in some, but not all, studies. This may not be surprising, given the variety of populations and, thus, PCB congeners likely encountered. Among 99 births to women in the New York Angler Cohort, there was a non-SSIG increase in the number of boys born to women with medium ($OR_{ADJ} = 1.29$) and high ($OR_{ADJ} = 1.48$) serum levels of estrogenic (mostly lower chlorination) PCB congeners. On the other hand, in this study, there was a non-SSIG increase in the number of girls ($OR_{ADJ} = 0.70$) born to women with high levels of antiestrogenic (somewhat higher chlorination) PCB congener (Taylor et al. 2007).

Another analysis of 399 newborns in the San Francisco Child Health and Development cohort also found SSIG more girls ($p < 0.02$) born when exposed *in utero* to (total) PCBs and a non-SSIG increase in the number of girls born when exposed *in utero* to the mostly higher chlorinated individual PCB congeners (Hertz-Picciotto et al. 2008). The authors cautioned the associations could also be due to PCB metabolites or contaminants. Two additional analyses found SSIG larger proportions of girls. Among 208 births to U.S. Great Lake women, more girls were born to mothers within the top quintile of maternal serum PCB levels than were born to mothers within the lowest quintiles (male birth $OR_{ADJ} = 0.18$, 95% CI = 0.06–0.59) (Weisskopf et al. 2003). Similar results were seen among 5054 births to PCB-exposed Baltic Sea mothers compared to those from Sweden's southwest coast ($p = 0.05$) (Rylander et al. 1995). Conversely, an analysis of 865 Michigan long-term PBB cohort births found a non-SSIG trend for more boys born to parents with elevated PBB and PCB levels ($OR_{ADJ} = 1.43$ and 1.53, respectively) (Terrell et al. 2009). No SSIG relationship between cumulative PCBs and SSR was found among 2595 births to women who worked in capacitor plants (Rocheleau et al. 2011).

***Birth Defects*** Birth defects (i.e., congenital disorders or anomalies) are defined by the WHO as "structural or functional abnormalities, including metabolic disorders, which are present from birth." Incidence and mortality estimates for birth defects are uncertain, particularly in regions with less complete surveillance (WHO 2008). In Europe during 2003–2007, "major" congenital anomalies including chromosomal disorders were detected in approximately 2.4% of registered conceptuses (i.e., of all live births, fetal deaths after 20 weeks' gestation, and induced abortions after prenatal detection of fetal anomalies) (Dolk et al. 2010). Similarly, state and local U.S. data on 45 birth defects suggest they occur in approximately 3% of births (CDC 2006). Congenital heart defects, neural tube defects, and Down syndrome are the most common serious "major" anomalies (WHO 2008). "Major" birth defects cause approximately 7% of neonatal deaths worldwide and up to 25% of neonatal deaths in the European Region, where competing causes of neonatal death rates are lower (WHO 2008). "Minor" congenital anomalies (e.g., nevi, angiomas, preauricular tags, cryptorchidism [i.e., undescended testicle{s}]) are collectively very common (these were excluded from the above European and North American anomaly estimates). Later sequelae among survivors with major anomalies may be negligible or range from cosmetic concerns or functional disabilities to heightened disease susceptibility or reduced life expectancy. The specific causes of most birth defects are unknown (CDC 2008), but general causes include genetic disorders (at gene or chromosomal levels), multifactorial inheritance, micronutrient deficiencies, and periconceptual or prenatal exposure to environmental teratogens (WHO 2008). Gene–gene and gene–environment interactions may modify their phenotypic expression. A gene–environment interaction occurs when the combined effect of a particular

gene variant and an environmental exposure exceeds what would be expected on the basis of the effects of the gene and the exposure measured in the absence of the other. Epigenetics also plays a role in several genetic congenital syndromes. The rarity of many birth defects and large sample sizes required to study such interactions are among the research challenges (Kartiko and Finnell 2009).

*Pesticides (General)* Studies of parental exposures to pesticides and birth defects have been reviewed elsewhere (Hanke and Jurewicz 2004; Nurminen 1995; Sanborn et al. 2007; Shirangi et al. 2011; Thulstrup and Bonde 2006). A subset of these studies has focused more specifically on women exposed to pesticides, primarily occupationally (García et al. 1999; Heeren et al. 2003; Hemminki et al. 1980; Lacasaña et al. 2006; McDonald et al. 1988; Medina-Carrilo et al. 2002; Nurminen et al. 1995; Restrepo et al. 1990; Shaw et al. 1999, Zhang et al. 1992) or through domestic application (e.g., garden, field, professional home application) (Loffredo et al. 2001; Shaw et al. 1999). The overall adjusted odds of for birth defects reported in these studies ranged from a slight but non-SSIG increase among offspring of Finnish women exposed through agricultural work versus referents ($N = 2612$) to SSIG among South African women exposed in their domestic gardens and fields ($OR_{ADJ} = 1.4$ [95% CI = 0.9–2.07] and OR = 7.18 [95% CI = 3.99–13.25, matched analysis], respectively) (Heeren et al. 2003; Nurminen et al. 1995). At least marginal or greater SSIG was found in one or more of the above-mentioned studies for nervous system defects (i.e., neural tube [$OR_{ADJ} = 1.6$], anencephaly [$OR_{ADJ} = 4.57$], central nervous system [observed/expected = 7.5]), musculoskeletal defects (OR = 5.0), hemangiomas (RR = 6.66), oral-facial clefts ($OR_{ADJ} = 1.9$), transposition of the great arteries (OR = 2.10), and limb defects (SSIG PR = 2.6 and non-SSIG $OR_{ADJ} = 1.6$). (Engel et al. 2000; García et al. 1999; Hemminki et al. 1980; Lacasaña et al. 2006; Loffredo et al. 2001; Nurminen et al. 1995; Restrepo et al. 1990; Shaw et al. 1999; Zhang et al. 1992). These specific malformations did not reach SSIG in many studies, some of which were likely underpowered statistically. Further, a meta-analysis of 19 studies that applied covariate adjustments found modestly elevated odds of oral-facial clefts among births to female pesticide workers (OR = 1.37, 95% CI = 1.04–1.81) (Romitti et al. 2007). Also, a recent systematic review of 20 studies in which exposure was estimated based on proximity of residence to agricultural pesticide applications suggested an association with congenital malformations (CMs), but the evidence was considered inconclusive, weakened by insufficient exposure and confounder data (Shirangi et al. 2011).

*Solvents* Several studies have linked individual solvents and "solvents" as a broad class to congenital anomalies. A 1998 meta-analysis of five studies of maternal occupational exposure to various solvents found an SSIG increase in the prevalence of major malformations (OR = 1.64, 95% CI = 1.16–2.30) (McMartin et al. 1998). A subsequent review of studies of pregnant women's

exposures to organic solvents provided "no convincing evidence" of a link to birth defects (Thulstrup and Bonde 2006).

Two population-based, prospective occupational studies of solvent-exposed working women were also identified. One of those studies reported a non-SSIG but noteworthy increase in the odds of circulatory and genital malformations among 11,273 offspring of (mostly) painters compared to controls ($OR_{ADJ}$; 95% CI = 2.03; 0.85–4.84; and 2.24; 0.95–5.31, respectively) (Vaktskjold et al. 2011). In the other study, maternal solvent exposure showed positive SSIG associations with oral clefts ($OR_{ADJ}$ = 11.22), urinary malformations ($OR_{ADJ}$ = 2.18–4.11), and male genital malformations ($OR_{ADJ}$ = 1.98–3.47) (Garlantézec et al. 2009). Also, for the highest versus no-solvent exposure category, an SSIG association was reported with major malformations overall ($OR_{ADJ}$ = 2.48–3.48) with an SSIG dose–response trend ($p$ = 0.002–0.005) among offspring of women in solvent-exposed compared to nonexposed jobs ($n$ = 3005). Toluene exposure of women was also associated with increased CMs for their pregnancies in two case-control studies (McDonald et al. 1987; Taskinen et al. 1989). The authors of both papers reported that pregnancies for women with a history of aromatic solvent exposure were at increased risk for CM births, primarily renal-urinary and gastrointestinal defects. Despite the many case studies on occupational and toluene abuse, the reproductive toxicology and the teratogenic effects of this organic solvent remain understudied.

*OC Solvent* Elevated ORs, albeit with wide, non-SSIG CIs, were found between prenatal exposure to tetrachloroethylene-contaminated drinking water near the time of conception and increased neural tube defects (OR 3.5, 95% CI = 0.8 – 14.0), oral clefts (OR 3.2, 95% CI = 0.7 – 15.0), and, among only those in the upper exposure quartile, "all anomalies" (OR 1.5, 95% CI = 0.9 – 2.5) in a Cape Cod, Massachusetts, retrospective cohort study subset of 1658 births (Aschengrau et al. 2009). Authors of a 2006 review of human and nonhuman studies of trichloroethylene-contaminated drinking water and congenital heart defects concluded the literature did not support the notion that TCE is a teratogen at environmentally relevant doses (Watson et al. 2006).

*THMs* Cross-sectional analysis of three studies of the relationships between THM exposure and birth defects showed consistently elevated odds of ventricular septal defects among prenatally exposed groups (summary OR = 1.59, 95% CI = 1.21 – 2.07) (Hwang et al. 2008). THMs are formed as by-products when water is disinfected with chlorine.

*Smoking* Maternal smoking is linked to CMs in the 2010 Surgeon General's Report, which found consistent evidence of an association between periconceptual smoking and cleft lip with or without cleft palate (U.S. DHHS 2010). The report suggests that genetic polymorphisms (e.g., transforming growth factor-alpha variants) may modify maternal smoking-mediated oral clefting risks.

***Reproductive System Development*** The hypothalamic–pituitary–gonadal (HPG) axis feedback loops regulate (among other things) gonadal development and the mature reproductive system. Fetal period development and programming of the HPG axis are thought to render it particularly vulnerable to dysregulation by EDCs, which may result in permanent homeostatic endocrine alterations (Fisher 2004). Some such fetal effects may be readily apparent at birth (e.g., altered gonad morphology), while others may manifest latently after the newborn period through the reproductive years and beyond (e.g., effects on adult female gynecological or male andrological outcomes).

Among newborn boys, signs suggestive of reduced sexual dimorphism may include the fairly common major anomalies hypospadias (i.e., urethra opening on the undersurface of the penis) and cryptorchidism, or relatedy, other more subtle signs such as shortened anogenital distance (AGD). Testicular dysgenesis (TD) syndrome-related (male) newborn outcomes such as hypospadias, cryptorchidism, or later, poor semen quality and testicular germ cell cancer, as well as related non-TD signs such as reduced AGD, have been associated with prenatal EDC exposures. While individual study quality and findings are mixed, the pattern emerging from human and nonhuman studies raises the index of suspicion that certain intrauterine EDC exposures are risk factors for TD-related anomalies. Decades during which the incidence of hypospadias has increased have been documented for many countries (e.g., Norway, Denmark, England, Hungary, Norway, Finland, China) during the last half-century (Li et al. 2012; Toppari et al. 2010). Evidence of such trends is inconclusive, however (Thorup et al. 2010). The large incidence differences between these countries could reflect differences in exposure trends or in registry-based case ascertainment and reporting over time and between counties (Toppari et al. 2010).

*Pesticides (General)* A recent meta-analysis of nine human studies found maternal exposure to pesticides to be SSIG associated with hypospadias risk (Rocheleau et al. 2009).

*OCs* Developmental exposure to the OC TCDD may also produce latent male reproductive effects. The 21 breast-fed sons of TCDD-exposed Seveso cohort mothers, assessed at an average age of 22 years, had reduced sperm concentrations ($p = 0.002$), total counts ($p = 0.02$), progressive motility ($p = 0.03$), and total motile counts ($p = 0.01$), and reduced serum inhibin B levels ($p < 0.02$) and elevated serum follicle-stimulating hormone levels ($p < 0.04$) compared to 36 breast-fed controls and (for hormone outcomes) compared to 18 formula-fed controls (Mocarelli et al. 2011)

*Phthalates* Several review authors have concluded that exposure to phthalates (particularly antiestrogenic phthalates) during male development is implicated in some TD disorders (Chacko and Barthold 2009; Fisher 2004; Kalfa et al. 2011; Main et al. 2009, 2010; Swan et al. 2005; Toppari et al. 2010; Vidaeff

and Sever 2005; Weselak et al. 2007; Wohlfahrt-Veje et al. 2009; Yiee and Baskin 2010).

*BPA* The effects of BPA on reproduction and development in studies of male and female animals were recently reviewed. The authors cited effects on "sex differentiation of exploratory and affective behavior" at lower BPA doses and "gender-differentiated morphology" as key cross-study findings (Golub et al. 2010). The NTP also reported the body animal literature is "sufficiently consistent" to suggest that exposure to "low" doses of BPA during perinatal or pubertal development causes neural and behavior alterations in rats and mice, "especially related to the development of normal sex-based differences between males and females ('sexual dimorphism')" (National Institutes of Health (NIH), National Toxicology Program (NTP) 2008). Observations of BPA wildlife exposure effects and controlled studies of animal models have been extensive, but their relevance to human health continues to be controversial (Maffini et al. 2006).

Among newborn girls who may have more subtle signs of altered sexual dimorphism at birth and in whom reproductive organs are not readily accessible for examination, studies of the effects of prenatal EDC exposure are sparser. Animal studies provide some insights because of the shorter time required for observation of maturational and transgenerational effects, and so more discussion of those studies is included here. For example, developmental exposures (i.e., during gestation through early life) of animals to certain EDCs have been shown to produce lifelong molecular reprogramming of the hypothalamus and premature reproductive aging, which suggests human MA may also be affected by certain prenatal EDC exposures (Gore et al. 2011). Therefore, both human and animal evidence is discussed further.

*DES* Several millions of daughters were exposed to the drug DES *in utero*, with many experiencing adverse reproductive health consequences. Reports of reproductive abnormalities and cancer in DES daughters have evoked the concept that other HAC exposures during pregnancy, particularly at high doses, might be capable of producing adverse reproductive organ and function effects in adults. In addition to developmental genital tract defects associated with prenatal DES exposure, many latent adverse reproductive effects have also been documented. Cumulative risks of functional effects among DES versus non-DES-exposed women reportedly include infertility (HR = 2.37, 95% CI = 2.05 – 2.75), SA (HR = 1.64, 95% CI = 1.42 – 1.88), loss of second trimester pregnancy (HR = 3.77, 95% CI = 2.56 – 5.54), stillbirth (HR = 2.45, 95% CI = 1.33 – 4.54), ectopic pregnancy (HR = 3.72, 95% CI = 2.58 – 5.38), preterm delivery (HR = 4.68, 95% CI = 3.74 – 5.86), and preeclampsia (HR = 1.42, 95% CI = 1.07 – 1.89) (Hoover et al. 2011). DES-exposed daughters also had an 80% higher risk of laparoscopically confirmed endometriosis than nonexposed women in the prospective Nurse's Health Study II cohort ($RR_{ADJ}$ = 1.8, 95% CI = 1.2 – 2.8, $n$ = 767) (Missmer et al. 2004). Contrasting

effects of DES on uterine fibroids were observed in two studies of women exposed prenatally to DES: One study of the NIEHS Uterine Fibroid Study cohort found an SSIG positive association with prevalence and size of uterine fibroids using ultrasound criteria ($n$ = 1323; Baird and Newbold 2005); the other study of the National Cooperative Diethylstilbestrol and Dieckmann cohorts found no association between DES exposure and diagnosis of fibroid using histology ($n$ = 179; Wise et al. 2005). Histological detection, it was noted, requires surgery. Therefore, misclassification would have occurred if fibroids were undetected among controls in the latter study. Further suggestion of influence by early-life exposure on uterine fibroids comes from a recent analysis of black women in the NIEHS Sister Study breast cancer cohort in which intrauterine DES exposure was SSIG linked to early onset of fibroids ($RR_{ADJ}$ = 2.02, 95% CI = 1.28 – 3.18 [$n$ = 2394]). Thus, a possible relationship between women's exposure to DES and fibroids is supported by some, but not consistently all, studies. A combined secondary analysis of four large DES daughter cohorts and the Sister Study cohort of breast cancer found that DES-exposed women were about 50% (SSIG) more likely to go through menopause at any given age compared with nonexposed women (DES cohorts [$HR_{ADJ}$ = 1.49, 95% CI = 1.28 – 1.74; combined $n$ = 6017]; Sister Study [$HR_{ADJ}$ = 1.45, 95% CI = 1.27 – 1.65; $n$ = 19,103]) (Hatch et al. 2006; Steiner et al. 2010).

While cancers are covered in other chapters of this text, it seems important to note here that women exposed to DES *in utero* were shown to have an SSIG latent increase in their risk of breast cancer after age 40 (HR = 1.82, 95% CI = 1.04 – 3.18) and specific reproductive organ cancers. These included clear cell adenocarcinoma of the vagina and cervix in a prospective follow-up study conducted in the Netherlands (standardized incidence ratio = 24.23, 95% CI = 8.89 – 52.47) (Verloop et al. 2010). Animal studies suggest that developmental exposures to other estrogenic EDCs (e.g., genistein, nonylphenol, equivocally BPA) tested at equivalent estrogenic doses produce similar increases in uterine cancer and that DES cancer risk may be transmitted transgenerationally (Newbold et al. 2006). While the mechanisms remain to be clarified, genetic alterations and epigenetic induction of cell proliferation and apoptosis are suggested by animal studies (Newbold et al. 2006; Sato et al. 2004).

*OCs* In one human study, daughters from the California Child Health and Development study cohort had prolonged exposure to PCBs *in utero* (Cohn et al. 2011). Levels of PCB congeners 187, 156, and 99 in the mother's serum were SSIG associated with longer TTP in their daughters, while serum levels of PCB congeners 105, 138, and 183 were SSIG associated with shorter TTP (borderline SSIG for congener 183) (Cohn et al. 2011). The probability of pregnancy fell by 38% and infertility was higher in the group whose mothers had a higher proportion of PCB congeners that are associated with longer TTP; this suggests that exposure to some congeners of PCB *in utero* will affect

human reproduction, either by increasing or decreasing TTP. Animal evidence also suggests that developmental exposure to PCBs, including PCBs having the highest body burden in humans, "profoundly impairs sexual differentiation of the female hypothalamus," causing masculinization/defeminization of the female neuroendocrine system (Dickerson et al. 2011). Pubertal onset was advanced and estrous cyclicity was irregular in PCB endocrine-disrupted females. Developmental exposure to PCB also disrupts reproduction in animals. Rats exposed to PCBs during late pregnancy exhibited compromised reproductive physiology in the exposed female fetuses (F1 generation) and their female offspring (F2 generation) (Steinberg et al. 2008). The exposure skewed liter sex ratios (F1 and F2 considered together) to be females and F1 had significantly altered circulating LH concentrations; more profound effects were observed on F2, with reduced LH and progesterone levels, and correspondingly smaller uterine and ovarian weights in estrus. In another study, F1 rats exposed to PCBs had aberrant estrous cycles and changes in hypothalamic gene and protein expression (Dickerson et al. 2011). Further, in mice, developmental (i.e., intrauterine and lactational) TCDD exposure of either parent results in reduced uterine sensitivity to progesterone and increased risk of PTB (<37 weeks' gestation) in F1 mice exposed *in utero* (Bruner-Tran and Osteen 2011; Ding et al. 2011).

*PBBs* Daughters, exposed to PBB prenatally and during breastfeeding, of PBB-exposed Michigan mothers had SSIG earlier pubic hair staging, while their *in utero* exposures were associated with earlier menarche (Blanck et al. 2000). Recent analyses of data from the Michigan cohort reported that *in utero* PBB exposure was not associated with a change in TTP in women (Small et al. 2011). A recent study reported that *in utero* exposure to PBB of women within the Michigan cohort was associated with an increased risk of SA as adults among their 135 viable and nonviable pregnancies that were not electively aborted ($p = 0.05$ for trend between low-, mid-, and high-exposure ranges) (Small et al. 2011). The respective ORs of 2.75 (95% CI = 0.64 – 11.79) and 4.08 (95% CI = 0.94 – 17.70) for those with moderate and high-level exposure compared to those with low exposure were non-SSIG but noteworthy. A high SA rate (i.e., 35%) was observed among the small subset of female infants in the highest intrauterine exposure group who were also breast-fed ($n = 23$) (Small et al. 2011).

*Bisphenol* Prenatal BPA exposure in various mouse studies has been reported to induce changes long after exposure, such as altered ovarian, uterine, and vaginal morphology, increased estrogen and progesterone positive receptors in the endometrium, altered mammary gland morphogenesis, early sexual maturity, and altered patterns of estrous cyclicity in adulthood (Markey et al. 2001, 2003, 2005; Muñoz-de-Toro et al. 2005; Rubin et al. 2001). Rats exposed to low-dose BPA prenatally developed some similar changes (e.g., altered estrous cyclicity ovarian changes) as well as reduced serum LH levels

after ovarectomy in adulthood, findings suggested to support potential hypothalamus–pituitary–ovarian axis disruption (Markey et al. 2003; Muñoz-de-Toro et al. 2005; Rubin et al. 2001). For example, neonatal exposure to BPA induced PCOS-like alterations in the ovaries and hypothalamic–pituitary–endocrine axis in an animal study (Fernández et al. 2010).

*Solvents* Animal studies provide a controlled atmosphere where subjects are not exposed to "polysolvents." In one study, pregnant Wistar rats were exposed to inhaled 300–1200 ppm toluene for 6 hours each day during gestational days 9–21. The F1 rats exposed prenatally displayed no differences in mating, fertility, or pregnancy compared to control animals (Thiel and Chahoud 1997).

*Smoking* Evidence linking developmental (intrauterine) exposure of daughters to tobacco and lowered fecundity was recently reviewed and reported to be inconclusive. On the other hand, in by far the largest cohort included in that review, a "small to modest" association was reported between Norwegian women's exposure to tobacco smoke *in utero* and reduced fecundity as adults (fecundability $OR_{ADJ} = 0.96, 95\%$ CI $= 0.93 - 0.98, n = 48{,}319$) (Ye et al. 2010). Daughters of women who smoked during pregnancy may also experience earlier MA, suggesting fetal reprogramming, based on SSIG findings within a DES daughters cohort (nonsmoking daughters HR $= 1.38, 95\%$ CI $= 1.10 - 1.74$; overall $HR_{ADJ} = 1.21, 95\%$ CI $= 1.02 - 1.43, n = 1719$) (Strohsnitter et al. 2008).

***Neurodevelopment*** Converging lines of evidence have been proposed to suggest EDCs primarily target the hypothalamic–pituitary axis of the neuroendocrine system with downstream effects across multiple systems and, it is suspected, transmission of transgenerational epigenetic effects (Gore 2010a,b). Prenatal maternal consumption of PCB-contaminated food has been linked to lowered IQ and behavioral outcomes (Stillerman et al. 2008). Prenatal thyroid hormone derangements are a proposed mechanism since normal maternal thyroid levels are important for optimal fetal growth and development, especially neurodevelopment. Even subtle disruption of thyroid gland function during pregnancy may produce adverse fetal outcomes. Concern has been raised regarding potential interactions of EDCs with other susceptibility factors on thyroid homeostasis during pregnancy, particularly in vulnerable subgroups such as those living in areas where iodine deficiency is endemic (Hartoft-Nielsen et al. 2011).

*OCs* The chemical structure of TCDD metabolites is thought to be sufficiently similar to that of thyroxine so as to interfere with the hormone's functions (Hartoft-Nielsen et al. 2011). Studies of the effects of PCBs on thyroid hormone effects in pregnant women, newborns, infants, and adolescents were recently reviewed (Hartoft-Nielsen et al. 2011; Langer 2010). Elevated cord PCB levels were associated with changes in elements of thyroid hormone

secretion and action across several studies (i.e., thyroid-stimulating hormone, thyroid hormone-binding globulin, free thyroxine, total tri-idothyronine, and total thyroxine), while other studies reported no SSIG thyroid effects. Authors of these reviews acknowledged that most current evidence supports a link between human prenatal exposure to certain OCs and adverse developmental and health outcomes among offspring, but with caveats that this generalization applies to higher maternal exposures (Langer 2010) and that conclusions are based on relatively few available studies (Hartoft-Nielsen et al. 2011).

*OPs* Two U.S. studies of prenatal OP pesticide exposure found evidence of neurobehavioral effects including abnormal neonatal reflexes (Young et al. 2005), and at age 3 years, SSIG more delays in psychomotor and developmental plus maternally reported attention problems (Rauh et al. 2006).

*Solvents* *In utero* exposure to toluene, which has structural similarities to BPA, has been linked to developmental delays and neurobehavioral problems in children (Badham and Winn 2010a).

*Smoking* A 2010 Surgeon General's Report on smoking found "consistent evidence that carbon monoxide leads to birth weight deficits and may play a role in neurological deficits (cognitive and neurobehavioral end points) in the offspring of smokers" (U.S. DHHS 2010).

***Immune and Hematopoietic Development*** Immune development begins before birth with hematopoiesis, stem cell migration and progenitor cell expansion, and thymus and bone marrow colonization (Dietert et al. 2000). Mounting evidence suggests certain BOC and POC exposures may alter immune system development, manifesting later as cellular and humoral (i.e., antibody mediated) immune perturbations in neonates and children. The concept of prenatal origin (i.e., initiation) of hematopoietic cancer in childhood is consistent with the observation that specific chromosomal rearrangements associated with childhood leukemia are already present in the blood of newborn infants (Van Maele-Fabry et al. 2011).

*OCs* Prenatal PCB levels have been associated with smaller estimated thymic volume ($p = 0.047$) at delivery, which the investigators suggested may reflect immunologic development impairment (Park et al. 2008a). In another study, prenatal PCB levels were SSIG correlated with the number of lymphocytes ($p = 0.05$), T-cell markers CD3CD8 + ($p = 0.04$), CD4 + CD45RO + ($p = 0.02$) and CD3 + HLA-DR + ($p = 0.005$), T-cell receptor $\alpha\beta$ + ($p = 0.08$), lower antibody levels among preschoolers for measles ($p = 0.03$), and mumps ($p = 0.04$) (Weisglas-Kuperus et al. 2000). Maternal serum levels of PCBs and PFCs during pregnancy and/or lactation have been associated with reduced humoral immune reactions to routine vaccinations in their children (Grand-

jean et al. 2012; Heilmann et al. 2006; Weisglas-Kuperus et al. 2000). Another study found little evidence of such an association with pre- or postnatal PCB exposure (Jusko et al. 2010).

*Pesticides* Prenatal residential exposure to pesticides was associated with childhood leukemia in two separate meta-analyses of 13 and 8 partially overlapping studies (OR = 2.05, 95% CI = 1.80 – 2.32; and meta-RR = 2.19, 95% CI = 1.45 – 2.09, respectively) (Turner et al. 2010; Van Maele-Fabry et al. 2011). The strongest risk signal was for insecticide exposure (prenatal and childhood), which was SSIG in both meta-analyses, herbicides showing a positive SSIG relationship with leukemia in only one of two meta-analyses (Van Maele-Fabry et al. 2011). Similarly, in a meta-analysis of 40 studies of various pesticide exposures (i.e., residential, household, professional), the odds leukemia and lymphoma were SSIG elevated among children exposed prenatally whose mothers used pesticides in the home or garden (OR = 1.48, 95% 1.26 – 1.75 and OR = 1.53, 95% CI = 1.22 – 1.91, respectively) (Vinson et al. 2011). Two other meta-analyses that included studies where mothers were exposed to pesticides occupationally also found associations with childhood leukemia. One of these meta-analyses of 16 studies found SSIG increased odds of childhood leukemia in association with maternal prenatal exposure to pesticides overall (OR = 2.09, 95% CI = 1.51 – 2.88) and, specifically, for exposure to insecticides and to herbicides (Wigle et al. 2009). In the other meta-analysis in which strata of women exposed before (three studies) and during (eight studies) pregnancy were examined, SSIG elevated RRs of childhood leukemia were reported in each exposure strata (RR = 2.24, 95% CI = 1.34 – 3.72 and RR = 2.00, 95% CI = 1.11 – 3.62, respectively), but only the prepregnancy exposure strata studies showed consistency (Van Maele-Fabry et al. 2010).

*Bisphenols* One review of animal studies found consistent effects by BPA on "immune hyperresponsiveness at lower doses" (Golub et al. 2010).

*Solvents/PAHs* Benzene is a carcinogen, genotoxicant, and hematotoxicant (Khan 2007). Long-term or chronic exposure to benzene has been linked to various blood disorders, including aplastic anemia and cancer (leukemia). Benzene also causes several types of malignancies in animals. Prenatal and childhood exposure to benzene has been associated with the development of disorders such as aplastic anemia and leukemia (Badham and Winn 2010a; Shu et al. 1988; Steffen et al. 2004). Researchers found that *in utero* exposure to benzene causes a significant increase in reactive oxygen species (ROS) and significantly altered erythroid differentiation, potentially leading to the development of blood disorders (Badham and Winn 2010b). Prenatal exposure to pollutants (PAH and fine particles) were associated with reduced human cord blood immune cells (T-lymphocyte fractions CD3+, CD4+, CD8+) and increased B-lymphocyte CD19+ cells in a Czech study of 1397 deliveries (adjusted percentage decreases of –3.3% [95% CI = –5.6 to –1.0], –3.1%

[–4.9% to –1.3%], –1.0% [–1.8% to –0.2%], and 1.7% [0.4% to 3.0%], respectively) (Hertz-Picciotto et al. 2005b).

## DISCUSSION AND IMPLICATIONS

The bulk of studies of women's potential reproductive health risks from exposures to the more widespread bioactive and persistent compounds has focused on assessing pregnancy outcomes. Clearly, many such compounds are detectable in pregnant and nonpregnant women, cross the placental barrier, and are excreted in breast milk. Evidence from long-term epidemiological studies of women exposed to the estrogenic drug DES *in utero* also lends support to the concept that latent adverse effects on gynecological, reproductive, pregnancy, and neonatal outcomes could ensue from early exposures to other EDCs. Beyond DES, converging lines of evidence from human and animal studies conducted during the critical fetal development window support emerging conclusions regarding latent adverse health effects for several common pre- and perinatal exposures. Across reviews, documents, and studies surveyed in this chapter, the strength of human evidence is mounting for adverse intrauterine exposure effects of (1) PCBs (particularly estrogenic congeners) on lowered birth weight; (2) phthalates on TD syndrome; (3) various solvents on fetal loss; (4) smoking on altered reproductive hormone levels, lowered fertility, fecundity, birth weight, and MA, stillbirths, cleft lip malformations, and among smokers, increased maternal (diastolic) hypertension; and (5) pesticides on childhood leukemia risk.

Beyond these more established risks, growing evidence was described regarding other biologically active organic compounds and POCs suspected of adversely affecting women's gynecological health or reproductive success or of harming their offspring. In general, major strengths across these studies include the use of biomarkers to characterize exposure and outcomes. A number of positive significant and suggestive findings from epidemiological studies of women and their offspring have been of compounds considered endocrine disruptors, particularly the studies of developmental exposure-related outcomes. To date, however, the potential effects of many of the individual compounds across the full spectrum of women's and offspring's outcomes are understudied, including potential effects of those found in foods, homes, schools, and workplaces. These, to mention a few, include BPA, pesticides such as ATZ, phthalates, flame retardants, and perfluorinated acids. Published studies of gynecological outcomes are particularly rare. This lack of human studies for many outcomes is striking considering the prevalence of some exposures and outcomes, their possible severity and comorbidities, and the potential for adverse impacts across the life span. Infertility, for example, affects many couples. Accordingly, the Centers for Disease Control and Prevention (CDC) has drafted the specific needs for research and policies favoring improved understanding of environmental compound effects on fertility

(i.e., final Federal Register Notice at this writing) (U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Reproductive Health 2012).

It seems reasonable that, given awareness and resources, some individuals may be able to reduce their personal BOC and POC exposures by taking preventative or protective precautions. For some women, avoidance of known external sources of these compounds—especially during vulnerable developmental windows—may be achievable. The evidence base for prevention at the individual level is incipient, but there are some findings that modifiable lifestyle factors influence exposure risk. For instance, a systematic review of dietary habits showed they influence POP levels in humans (Gasull et al. 2011); results of a dietary intervention study demonstrated that consumption of an organic diet provides a dramatic and immediate reduction in children's organophosphorus pesticide levels (Lu et al. 2006). Organic produce is, however, relatively expensive. Women with fewer resources, awareness, or options to reduce their exposures from their diets, occupations, or residences may not take such precautions, even during their pregnancies.

Further, many women are not aware they are pregnant during the critical window of fetal organogenesis. Women with fewer social and economic resources may be particularly vulnerable for other potentially tractable reasons such as poor nutrition, a lack of prenatal care and education, and poorer general health. Other women may be more susceptible genetically or disproportionately affected due to confluence of adverse outcomes in individuals and families, just as multiple adverse health effects may manifest in one unfortunate individual from exposure to smoking or DES exposure.

There is a clear risk identification and educational role for women's advocates, such as health-care providers, who are positioned to offer preventive or intervention outreach and support. This illustrates the need to expand efforts to identify if, when, and where bioactive and persistent exposure engender the greatest exposure and health risks, and how to best mitigate risks from both population and individual health standpoints. It also demonstrates the importance of training the trainers (doctors, nurses, others) to routinely assess work and environmental exposures and to intervene to help women avoid potential harm. Broad application of succinct clinical queries for environmental exposures (e.g., the "environmental and occupational health history profile") (Chalupka and Chalupka 2010) coupled with tools that provide clinicians with guidance based on consolidated and scientifically vetted evidence (e.g., the "Navigation Guide") (Sutton et al. 2010) are also indicated. Development of a deeper toolkit of evidence-based preventive interventions is also critical to effective preventive education and intervention. Many agencies and organizations maintain web-based information resources that may provide valuable assistance to women and advocates seeking to determine individualized risk profiles and preventive strategies. Table 10.3 lists a number of these resources with current links.

**TABLE 10.3. Current Web-Based Resources for Additional Information on Women's Reproductive Health**

| Source | Comments | Website |
|---|---|---|
| Collaborative on Health and the Environment | Environmental health-related information resource on fertility, children's health, learning and developmental disabilities, and so on | http://www.healthandenvironment.org/index.php |
| Environmental Working Group (EWG) | Information on environment and health (including reproductive and developmental) from documents, studies and EWG laboratory tests—chemical index site is available | http://www.ewg.org |
| La Leche League | Searchable index with science and opinion on breast-feeding benefits given breast milk contaminants | http://www.llli.org/resources.html |
| Lact-Med | Peer-reviewed database of drugs to which breast-feeding mothers could be exposed | http://toxnet.nlm.nih.gov/cgibin/sis/htmlgen?LACT |
| March of Dimes | Birth defect prevention information | http://www.marchofdimes.com |
| Motherisk | Program created by the Hospital for Sick Children in Toronto to provide evidence-based content and guidance concerning potential risks to the developing fetus or infant, from exposure to chemicals, drugs, and other environmental agents | http://www.motherisk.org/women/index.jsp |
| National Library of Medicine (NLM), Toxicology Data Network (Toxnet) | Contain references and links to toxicology reports, documents, and literature within various databases: Developmental and Reproductive Toxicology Database (DART), Toxic Literature Online (Toxline), Hazardous Substances Data Bank (HSDB), Genetox, IRIS, Household Products Database, and so on | http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE |
| Natural Defense Council Resources Council | "Environmental and Health" section contains information on lowering exposures and touches on reproductive and developmental hazards | http://www.nrdc.org/ |
| Organization of Teratology Information Specialists (OTIS) | Information includes news, research, and resources including fact sheets for patients pertaining to teratogens, including environmental agents | http://www.otispregnancy.org/ |
| Our Stolen Future website | Authors of book by same name provide updates on science and ongoing policy debates on endocrine disruptors and suggest risk minimization strategies | http://www.ourstolenfuture.org/ |

| | | |
|---|---|---|
| Pediatric Environmental Health Specialty Units | Training and resources geared primarily to pediatric health professionals but with some relevance to prenatal prevention | http://aoec.org/PEHSU/index.html |
| Physicians for Social Responsibility | Environment and health site contains information, resource guides, and clinician toolkits relevant to reproductive health | http://www.psr.org/environment-and-health/ |
| Silent Spring Institute website | Primary focus is on breast cancer. Provides information on the research and publications of the institute plus tools such as individual and community action kits | http://www.silentspring.org/ |
| TEDX Endocrine Disruption Exchange | Contains information on low-dose functional and developmental effects of exposure to endocrine disruptors | http://www.endocrinedisruption.com |
| (U.S. CDC) Agency for Toxic Substances and Disease Registry | Reproductive site contains links to ASTDR reports describing reproductive effects of various environmental compounds | http://www.atsdr.cdc.gov/substances/toxorganlisting.asp?sysid=21 |
| (U.S. CDC) National Institute for Occupational Safety and Health (NIOSH) | Occupational reproductive site with a links including NIOSHTIC-2, a searchable database of NIOSH supported health publications, documents, and reports | http://www.cdc.gov/niosh/topics/repro/ |
| (U.S. CDC) National Center on Birth Defects and Developmental Disabilities | Links to information on alcohol exposure and birth defects | http://www.cdc.gov/ncbddd/index.html |
| (U.S. Environmental Protection Agency [EPA]) Endocrine Disruptor Screening Program | Describes the U.S. EPA's approach toward and progress on screening chemicals for endocrine effects | http://www.epa.gov/endo/ |
| (U.S. FDA) Food and Drug Administration's Endocrine Disruptor Knowledge Base | Resources for predicting estrogenic and androgenic activity; for researchers/regulators to "foster the development of computational predictive toxicology models and reduce dependency on slow and expensive animal experiments" | http://www.fda.gov/ScienceResearch/Bioinformatics Tools/EndocrineDisruptorKnowledgebase/default.htm |
| (U.S. NIH) National Institute of Environmental Health Sciences, National Toxicology Program | Information on animal "reproductive assessment by continuous breeding" and links to reproductive toxicology result abstracts | http://ntp.niehs.nih.gov/?objectid=54ADC224-F1F6-975E-7EAD62A55DD96034 |
| University of California, San Francisco | Program on Reproductive Health and the Environment offers bilingual (English and Spanish) pdf patient brochure | http://prhe.ucsf.edu/prhe/toxicmatters.html |

Broader societal awareness and actions are also required to lower the level and ubiquity of these exposures in the population. Many women and developing offspring are unwittingly exposed to low levels of the more common organic compounds. Even those who are aware of their potential exposures may assume chemicals in commerce have been tested for safety with the same diligence as drugs and foodstuffs, but this has rarely been the case, especially for female reproductive-related outcomes including adverse effects in women and development-related sequelae in their infants and children. Failures of effective scrutiny of and protections from common chemical exposures for the past several decades under the U.S. Toxic Substance Control Act system have been well documented with calls for reform or modernization from the American Medical Association, the American Public Health Association, the American Nurses Association, and the American Chemistry Council (Council on Environmental Health, American Academy of Pediatrics 2011). U.S. Farm Bill remediation to protect reproductive health has also been advocated (Sutton et al. 2011). Recent regulatory framework reforms have been sought in the United States with the EPA's Reform of Chemicals Management Legislation (2009) and implemented in Europe under "REACH," the European Community Regulation on chemicals and their safe use (2007).

The American Academy of Pediatrics has published further specific recommendations for government advocacy that would further strengthen protections by, for example, recognizing the special needs of women and children, particularly during critical developmental windows (Council on Environmental Health, American Academy of Pediatrics 2011). While remedies are underway in wealthier nations, public and workplace protections have likely been even less effective in less developed countries where the bulk of manufacturing and waste stream management problems now reside. Inequities in distribution of consumer benefits and exposure risks may exist, therefore, to the extent that fewer consumer benefits of products made from these compounds have accrued to those who experience greater exposures and health effects, with environmental justice implications.

Because many women's reproductive health problems are intimate and perhaps latent—silent for long intervals after their initiation—exposure–disease-related clusters are difficult to identify and characterize and may be less apt to garner attention than nonreproductive health problems. This highlights the importance of surveillance and diligent cross-discipline collaborations to identify present and emerging risks to women's reproductive health. Development and synthesis of the human and experimental evidence base will enhance the quality of future risk assessments of various organic compound exposures, doses, and vulnerable life stages. In an era of diminished reproductive health research funding, much of the women's reproductive health research agenda appears driven by the availability of existing data for secondary analyses. Funding is required to permit a more proactive approach to human studies so that exposures and potential effects can be documented temporally from the periconception period and beyond. Long-term follow-up, while costly, is

essential to track links between early exposures and downstream outcomes that may manifest decades later. One such ambitious effort in the United States is the National Children's Study, in which BOCs/POCs have been measured longitudinally.

Ultimately, one of the major goals of research on BOCs and POCs is to provide valid inferences about health risks so that women, parents, advocates, and policy makers can make informed and astute exposure-related decisions. The BOC and POC human evidence base is currently too small to support robust risk assessments for many women's reproductive and developmental outcomes for which there is at least some preliminary suggestion of risk. This is especially true within the lower-dose ranges that are most relevant to human populations and for interpretation of the nonmonotonic dose–response relationships that are often observed. Thus, the benefits of the products and processes that create opportunities for human BOC and POC exposures are more defined than are the potential health risk costs. Some compounds that may inflict potential harm also confer great benefit (e.g., pesticides control malaria and increase food production while lowering food costs). DDT is one specific example. There is a pressing need to expand the small epidemiological literature base available to predict DDT-related risks of adverse pregnancy outcomes (e.g., pregnancy loss, prematurity) for comparison to established risks of morbidity and mortality from post-DDT ban malaria, malaria being a disease that kills one million annually worldwide (Longnecker 2005).

Clearly, there is a need to reduce data gaps and other sources of uncertainty to permit accurate accounting for exposure-related health costs associated with outcomes such as fetal loss, infertility, prematurity, birth defects, PCOS, endometriosis, and uterine fibroids, and for the sequelae that can result. Studies with ample power to characterize risks among subgroups who may be vulnerable due to endogenous or nonendogenous factors (e.g., genetic makeup, other health conditions) are also needed. The Endocine Society has recommended future epidemiological studies in large, highly exposed, prospectively followed cohorts. Important elements of future epidemiology studies include the use of validated exposure biomarkers, assessment of dose–response relationships, and assessment of effects of mixtures (Diamanti-Kandarakis et al. 2009). In the face of current uncertainty about such health risks, there have been calls for "precautionary principle" centered action from many preeminent organizations including The Endocrine Society, supported by the American Medical Association.

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