4.22 Risk Assessment Studies: Epidemiology

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Glossary

Ascertainment Identification of individuals for inclusion in an epidemiologic study. For example, case ascertainment is the process by which cases are identified for inclusion.

Biomarker A measurable agent in an individual's body (e.g., in blood) whose presence provides information about the exposure or the outcome.

Case Individual in an epidemiologic study who has the outcome of interest.

Case classification The process by which characteristics of cases are reviewed to determine if they are eligible for participation in the study or if they belong to specific subgroups of cases. For example, the review of medical records to determine if a baby with two birth defects has a genetic syndrome or if the birth defects are unrelated.

Exposure A variable that is being investigated in an epidemiologic study as the potential cause of an outcome.

Exposure assessment A collection of methods used to estimate or measure the magnitude, frequency, or duration of exposure. For example, exposure assessment can be performed by asking questions to the study participant, by having an expert exposure assessor review records, or by taking direct measurements of the exposure, among other methods.

Miscarriage See spontaneous abortion.

Outcome A variable that is being investigated in an epidemiologic study as the potential consequence of an exposure.

Prevalence A measure of the frequency of a variable in a population, typically reported as a percentage.

Proxy respondent An individual who provides information on behalf of a study participant because the participant is unable to do so due to death, illness, language, or other reasons.

Spontaneous abortion Pregnancy that ends naturally (spontaneously) at a gestational age when fetuses would not survive outside the womb. The gestational age defining spontaneous abortion varies; in the United States, it is typically defined as prior to 20 gestational weeks.

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Statistical significance Result of a statistical test to determine the likelihood that a result is due to chance or not. If the test concludes that we would have seen the same result (or a result more extreme) in less than a certain percentage of studies conducted in the same way (typically $<5\%$) if there truly was no association, this is typically considered to be a statistically significant result.
Stillbirth Fetal death occurring later in pregnancy than miscarriage, at a gestational age at which fetal survival might be possible. Definitions of stillbirth vary; in the United States, fetal deaths occurring at 20 or more gestational weeks are considered to be stillbirths.
Surveillance Systematic collection, analysis, and interpretation of health data to guide public health practice.
Regression models Statistical methods often used in epidemiology to determine the relationship between variables. The simplest regression model includes one independent variable (exposure) and one dependent variable (outcome). A multivariable model includes more than one independent variable.

4.22.1 Introduction

The goal of animal toxicology studies is often to predict human effects of exposure to a toxicant. However, extrapolating results of animal models to humans in real-life settings can be difficult. Differences in biology may cause effects that are hard to predict, and some reproductive endpoints are particularly difficult to measure in either humans or animals. Simulating the routes, doses, and patterns of exposure a human might experience can be difficult in animal studies. Additionally, human exposure does not occur in isolation—humans may have varying baseline risk factors, differing lifestyles, and can be exposed to many different toxicants over the course of their normal lives. Epidemiologic data, therefore, can play a critical role in identifying human reproductive toxicants.

Epidemiologic studies examine the factors that influence the frequency and distribution of diseases in humans. The underlying tenet of epidemiology is that diseases are not distributed randomly in a population. Epidemiologic studies seek to identify patterns within disease distribution in order to uncover causal relationships. Epidemiologic studies can be experimental, meaning that researchers control exposure to the agent of interest (e.g., clinical trials or intervention studies). However, when experimental trials are unethical or infeasible among humans, observational studies (in which researchers are observers who do not manipulate exposure) are often used. This section will focus on observational epidemiologic studies of reproductive health and the strengths and limitations of these studies.

4.22.1.1 Study Designs in Observational Epidemiology

Observational studies of adverse reproductive outcomes can take a variety of forms. The simplest of these is the case report or case series (a group of case reports). These are typically clinical reports describing a specific case (or cases) of an adverse reproductive outcome, and any other information that might be relevant. Case reports are useful for identifying problems and generating hypotheses about possible causes. For example, in 1941 an Australian ophthalmologist observed unusual congenital cataracts in several patients: "Although one was struck by the unusual appearance of the cataracts in the first few cases, it was only when other similar cases continued to appear that serious thought was given to their causation" (Gregg, 1991). A review of these cases revealed that most mothers had been infected with rubella in a recent epidemic in their first or second trimesters and led to a hypothesis that rubella infection might be the cause (Gregg, 1991). Although this did not prove that rubella was causing the cataracts—some case mothers did not report infection, and it was unknown whether mothers of healthy infants were equally likely to have been infected with rubella during the outbreak—it sounded an early alarm and created a hypothesis that was later confirmed. Relying on this kind of astute clinical observation has disadvantages, however: uncommon outcomes (or uncommon causes of common outcomes) can easily go undetected until they have already affected large numbers of people, and without a comparison group case reports/series can only be used to generate hypotheses, not test them.

Epidemiologists often try to collect case reports systematically over a population by developing surveillance systems. When combined with data on the population, they can be used to calculate and monitor rates for the disease/outcome over time, between demographic groups, and within geographic areas. For example, vital records systems (birth and death certificate data) can be used to identify prevalence and trends in pregnancy-related mortality, preterm birth, or infant mortality. Surveillance systems can be either passive (relying on a patient, physician, or other designated person to report information to the surveillance system) or active (in which trained staff actively search for cases, e.g., by reviewing hospital records routinely to "find" cases). Certain outcomes—including infectious diseases, food-borne illnesses, cancers, and birth defects—are sometimes mandatorily reported to surveillance systems by healthcare providers under state, territorial, or federal law. For example, most states and territories in the United States have both birth defect and cancer registries (Mai et al., 2015; Weir et al., 2003; Wingo et al., 2003); a few also have stillbirth surveillance systems (Azofeifa et al., 2012; Duke et al., 2009).

To facilitate pooling data between surveillance registries and for increased efficiency, national and international efforts have developed standards for case classification and best practices. Examples include the National Birth Defects Prevention Network (NBDPN) in the United States (Sever, 2004), the European Surveillance of Congenital Anomalies (EUROCAT) system (Boyd et al., 2011; Dolk, 2005), and the Latin-American Collaborative Study of Congenital Malformations (ECLAMC) (Castilla and Orioli, 2004). Many registries report data to regional and international surveillance systems, such as the International Clearinghouse for

Birth Defects (Botto et al., 2006; Erickson, 1991). These data are used by public health officials and policy-makers to allocate resources, identify needs, and provide early warnings of rate increases.

Surveillance data are most useful when all (or nearly all) cases are ascertained, or else the included cases are identified in a non-biased manner from a population. Achieving this can be expensive and can even require legislative authority. Conversely, passive surveillance systems that rely on voluntary reports tend to be inexpensive to maintain but tend to provide biased data (Rothman et al., 2008). Although some reproductive endpoints (birth defects, preterm birth, stillbirth, infant death) are amenable to surveillance, other endpoints are not (miscarriage, infertility) because they might not come to medical attention (Wilcox, 2010).

Analytic studies examine the association between exposure to a potentially harmful substance and an adverse outcome. There are three main types of analytic studies: cross-sectional, case–control, and cohort (Rothman et al., 2008). In a cross-sectional study, both the exposure and the outcome are measured at the same point in time—making these studies fairly quick and inexpensive. Prevalence of the outcome of interest among those with or without the exposure or at varying levels of exposure is determined and compared. For example, a study might compare reproductive hormone levels to blood pesticide measurements in women to examine whether pesticides and hormones are correlated. Because exposure and outcome are measured at the same point in time, we do not necessarily know which came first; thus it is difficult to say whether the exposure caused the outcome. For reproductive studies, observation of the outcome (e.g., the occurrence of a birth defect) can only occur after critical and sensitive windows of exposure (e.g., organogenesis) have already passed; therefore an assumption of relatively constant exposure over time must be reasonable. The National Health and Nutrition Examination Survey in the United States is an example of an annual cross-sectional survey (NCHS, 2015).

Case–control studies identify individuals with an outcome of particular interest, choose a comparison (control) group without the outcome of interest, and then compare prior exposure in the two groups. These studies are considered an efficient way to examine an exposure–outcome relationship in a large population by selecting all qualifying cases and a sample of noncases. An example is the National Birth Defects Prevention Study, which identified cases from birth defects registries in 10 states. Controls were selected as a random sample of live-born, nonmalformed infants born in those states (identified from hospital records or birth certificates). Mothers were then interviewed about their health, nutrition, employment, and lifestyle in the period shortly before they conceived the case or control infant and during their pregnancy (Yoon et al., 2001; Reefhuis et al., 2015).

Cohort studies identify groups that differ in amount of exposure (e.g., any vs. none) and follow the groups to identify later differences in the frequency of adverse outcomes. A major advantage to this study design is the ability to examine more than one outcome in the same population. However, rare events require very large sample sizes in order to observe enough outcomes for comparison between exposure groups. Cohort studies may either be retrospective (in which outcomes have already occurred) or prospective (in which the outcomes have not yet occurred) (Rothman et al., 2008). Many studies of suspected workplace hazards utilize a *retrospective* cohort design where the cohort is defined by exposure to a particular agent and investigators collect historical records of exposure. The health or vital status of all cohort members is then ascertained by matching the cohort roster with existing data bases such as the National Death Index or cancer registries, or in the case of suspected reproductive hazards, a questionnaire may be administered to cohort members to ascertain reproductive outcomes (Correa et al., 1996; Crisostomo and Molina, 2002). One reproductive toxicant that has been well studied using a prospective cohort design is lead. Several large prospective studies of low-level lead exposure during pregnancy and early childhood have documented the detrimental effects of lead on cognitive function in children (Bellinger, 2008).

4.22.1.2 Design Considerations in Reproductive Epidemiology

Reproductive studies present many challenges to the epidemiologist (Wilcox, 2010; Weinberg and Wilcox, 2008). Some factors that should be taken into consideration in the design and implementation of reproductive epidemiologic studies are described in subsequent sections.

4.22.1.2.1 Selection and measurement of endpoints

The estimated prevalence of selected adverse reproductive outcomes in the general population in the United States is provided in **Table 1**. Some reproductive endpoints are rare, requiring inclusion of many participants to identify a large enough sample of adverse outcomes to study. With rare outcomes, the case–control study design is often the most cost- and time-effective (e.g., the National Birth Defects Prevention Study described earlier). With rare exposures, the cohort study design is often the most efficient (e.g., an occupational cohort study).

Many reproductive endpoints are difficult to measure. For example, although spontaneous abortion (miscarriage) is a relatively common endpoint, an estimated 22% of pregnancies end before the woman even realizes she is pregnant (Wilcox et al., 1988). Birth Defects studies often capture the prevalence of birth defects at delivery rather than true incidence, because birth defects can cause a pregnancy to ends in miscarriage or stillbirth or—if the defect is prenatally diagnosed—induced abortion (Svensson et al., 2014). As a consequence, these birth defect cases are missing from epidemiologic studies of birth defects observed among live-born infants. (Svensson et al., 2014). Measuring female fertility is difficult, with no consensus on the best method (ASRM, 2015). In addition, adverse birth outcomes are not always independent, and studying multiple outcomes might be warranted. For example, low exposure to a specific chemical might cause birth defects, but high exposure might cause fetal loss (Selevan and Lemasters, 1987). As a result, a dose–response relationship between the chemical and birth defects might not be apparent, and a lower prevalence of birth defects might be seen with higher exposure.

Epidemiologists often have to make compromises, such as using a simpler—but less accurate—endpoint to make the study feasible. For example, a study might include only recognized miscarriages, might ascertain birth defects among live births only,

Table 1 Frequency of selected adverse reproductive outcomes

Reproductive outcome	*Description*	*Estimated prevalence*
Heavy menstrual bleeding	Bleeding lasting 7 or more days, losing four or more tablespoons of blood	20% of menstruating women[a]
Infertility	>12 months of unsuccessful pregnancy attempt	6–7% of married women aged 15–44 who are not surgically sterile[b]
Spontaneous abortion (miscarriage)	Pregnancy loss at <20 gestational weeks	10–15% of reproductive-aged women (clinically recognized pregnancies); 30% of reproductive-aged women (all losses)[c,d]
Fetal death (stillbirth)	Fetal death at ≥20 gestational weeks	1% of births[e]
Preterm birth	Live birth at <37 completed gestational weeks	10% of births[f]
Low birthweight	Live birth born at less than 2500 grams	8% of births[g]
Birth defects	Structural birth defects	3% of births[h]
Premature menopause	Last menstrual period before age 40	1% of women[i]

[a]Centers for Disease Control and Prevention. 2015. Heavy Menstrual Bleeding. (Online) Available at: http://www.cdc.gov/ncbddd/blooddisorders/women/menorrhagia.html (accessed 12.01.16).
[b]Centers for Disease Control and Prevention. 2015. Key Statistics from the National Survey of Family Growth: Infertility. (Online) Available at: http://www.cdc.gov/nchs/nsfg/key_statistics/i.htm#infertility (accessed 12.01.16).
[c]Wilcox, A.J., 2010. Fertility and Pregnancy: an Epidemiologic Perspective. Oxford University Press, New York, p. 151.
[d]Wilcox A.J., Weinberg, C.R., O'Connor, J.F., Baird, D.D., Schlatterer, J.P., Canfield, R.E., Armstrong, E.G., Nisula, B.C., 1988. Incidence of early loss of pregnancy. N. Engl. J. Med. 319(4), 189–194.
[e]Centers for Disease Control and Prevention. 2015. Facts about Stillbirth. (Online) Available at: http://www.cdc.gov/ncbddd/stillbirth/facts.html (accessed 12.01.16).
[f]Centers for Disease Control and Prevention. 2015. Preterm Birth. (Online) Available at: http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm (accessed 12.01.16).
[g]Centers for Disease Control and Prevention. 2015. Birthweight and Gestation. (Online) Available at: http://www.cdc.gov/nchs/fastats/birthweight.htm (accessed 12.01.16).
[h]Centers for Disease Control and Prevention. 2015. Facts about Birthweight. (Online) Available at: http://www.cdc.gov/ncbddd/birthdefects/facts.html (accessed 12.01.16).
[i]Luborsky, J.L., Meyer, P., Sowers, M.F., Gold, E.B., Santoro, N., 2003. Premature menopause in a multi-ethnic population study of the menopause transition. Hum. Reprod. 18(1), 199–206.

or might use self-reported time to pregnancy (number of menstrual cycles of unprotected intercourse before pregnancy) as a marker of female fertility.

4.22.1.2.2 Selection of a comparison group

The choice of an appropriate comparison group in studies of potential reproductive hazards can be difficult. The comparison group should be as similar as possible to the exposed group in the difficult-to-measure health and socioeconomic factors that may be related to exposure and to the outcome under study (i.e., confounders, described in greater detail later in this chapter). For example, in a study of occupationally exposed women, the comparison group should be unexposed women employed outside the home. Women in the workforce are likely different from women out of the workforce with regard to reproductive history as well as socioeconomic factors such as education, income level, and use of medical resources (Savitz et al., 1990; Joffe, 1985).

The choice of a valid comparison group is particularly important in case–control studies. Cases and controls should both be chosen from the underlying source population from which the cases arose. In other words, if any of the controls should experience the disease under study, they should automatically meet the inclusion criteria for cases. For example, if controls are pregnant women living in Paris, cases should not be chosen from pregnant women living in San Diego. In this example, this is a poor choice for a comparison group because if one of the controls (in Paris) experienced the disease under study, she would not be eligible to be a case (because cases were chosen from San Diego). The potential for bias decreases when cases and controls are chosen who are similar to each other.

4.22.1.2.3 Exposure assessment

Unlike laboratory studies in which toxicant exposure is controlled by the investigator, in observational studies the investigator must find ways to measure exposure that might occur over multiple routes (e.g., inhalation, skin absorption, and ingestion in food) and be inconsistent over time (White et al., 2008). Direct measurement of a study participant's exposure (e.g., by using an air sampler in a worker's breathing zone to quantify inhalation exposures over a work shift) or internal dose (as measured by biomarkers in blood or other bodily fluids as exposure occurs) is preferred but can be costly, invasive, and/or impossible to collect in epidemiologic studies (e.g., in retrospective studies where an unmeasured exposure occurred at some time in the past) (Rothman et al., 2008).

In these cases, it is necessary to use a surrogate estimate of exposure. This might include biomarkers of previous exposure, existing data, or self-reported information. Biomarkers can be useful indicators of exposure because they account for actual internal dose from all sources of exposure. Innate characteristics of various biomarkers—such as the bodily fluids from which they came or their half-life in various fluids and tissues—will impact the validity of their use as a proxy for exposure. For example, cotinine (a metabolite of nicotine) can be measured from blood, saliva, or urine and can provide a measurement of nicotine dose. Because the half-life of cotinine is less than a day, it is an excellent biomarker of recent exposure but cannot be used to draw inferences about long-term smoking (Florescu et al., 2009).

Existing records might include employment records, medical records, or environmental records such as contaminant releases or water quality testing. Because these records already exist, they can be inexpensive to gather; however the logistics of obtaining and linking such records can be daunting at times. Because these records were originally collected to satisfy some other purpose, they might not collect all relevant variables that would be useful for estimating exposure to the toxicant(s) under study. This information might be obtainable from self-report by study participants or their proxies (e.g., a family member). Study participants can only report information they know and can remember, so careful design of surveys is critical for accurate exposure assessment. For example, study participants are often unable to accurately report whether they were exposed to specific chemicals at their workplaces. Because of this, studies of occupational exposures might instead ask participants to describe their job title and typical duties and what their companies made or did (information that is known and easily recalled by most people); this information can be used by experts to impute likely exposures to specific toxicants (Teschke et al., 1994; Teschke et al., 2002).

Besides type of exposure and dose, exposure assessments must take into account routes and timing of exposure. Typical exposure routes might include dermal, ingestion, inhalation, or injection. The effects of a toxicant may be different depending on its exposure route and timing. In reproductive studies, identifying routes of exposure is complicated by the fact that there are multiple individuals whose exposure might be relevant to endpoints. For example, a couple's infertility might be due to either male or female factors, or a combination of both. Exposure of a fetus to a toxicant in utero will reflect both maternal exposure and maternal characteristics (such as her genetic variants affecting metabolism of a toxicant) or the ability of a toxicant to cross the placenta. Maternal exposure can also occur via take-home exposure—when other household members take home toxicants into their homes and vehicles on their skin, hair, clothes, and shoes. For chemicals that pass into semen, prior exposures of male sexual partners can cause maternal exposure as well. A given exposure may result in a number of different outcomes, depending on both the dose and timing of the exposure, in addition to individual characteristics (Buck Louis and Platt, 2011).

A challenge in exposure assessment for epidemiologic studies is the situation of mixed exposures. In most real world situations, people are exposed daily to a complex mixture of chemicals from a wide variety of sources. In the occupational setting where workers are exposed to multiple chemicals, effects may be additive or synergistic, even though no single exposure may be above permissible exposure limits. A common misperception is that studies that show associations with mixed exposures but do not identify a single causative agent are weaker than those that do not. Inferences about a mix of exposures can be equally valid as those that pertain to individual agents (Rothman et al., 2008). However, mixed exposures do pose a particular problem in quantitative risk assessment since such assessments are generally used to judge the potential effect of a single chemical or compound.

4.22.1.2.4 Sources of bias

There are two types of errors in epidemiologic studies: random error and systematic error. Random error can be minimized by increasing sample size, which diminishes random variations in the data. Systematic error, more commonly called "bias," must be addressed by either study design or statistical analysis. The three main types of bias in epidemiologic studies are confounding, selection bias, and information bias.

Confounding can be described as a confusion of effects (Rothman et al., 2008). It occurs when studying the association between an exposure and an outcome and failing to take into account a third variable (the confounder), which is a risk factor for both the exposure and outcome. The effects of the third variable are confused with those of the exposure. For example, a study of alcohol and lung cancer might be confounded by smoking; because alcohol and smoking are correlated in the population (people who smoke also tend to drink alcohol), it is difficult to tell if alcohol causes lung cancer or if the effects of alcohol are being confused with the effects of smoking (which is known to cause lung cancer). If not properly addressed in the study design or analysis, confounders can partially or entirely account for an apparent effect of the exposure or mask an underlying true association. Common confounding factors include lifestyle variables such as smoking and alcohol consumption, variables associated with socioeconomic status, or inherent factors such as age. Confounding can be addressed by several methods, including restricting the study population (e.g., only studying females if sex is a confounder) or using multivariable regression models. Randomization of exposure, as done in randomized controlled trials, is another way to minimize confounding; however, depending on the study design, confounding might not be entirely avoided using this method (Hernan et al., 2013).

Selection bias can occur when exposure and outcome are both predictors of selection of participants into or out of the study. The result is that the association between exposure and disease found in the study population is different from the association found in the population from which the participants were selected (Rothman et al., 2008). Another cause of selection bias is "loss to follow-up," which occurs in cohort studies which are conducted over several years, and some study participants cannot be located at the next follow-up time point (Howe et al., 2016). If loss of study participants differs by exposure and outcome status, selection bias can result, distorting or obscuring an association between exposure and disease. Selection bias can be addressed by ensuring appropriate selection of participants into the study, retaining study participants over time, or adjusting for selection bias in the statistical analysis (which is not always possible).

Information bias results from imperfect measurement of exposure, outcome, or confounders. Difficulties in exposure assessment and measuring reproductive outcomes have been discussed in prior sections. The direction and magnitude of bias caused by information bias is difficult to predict, and like other biases can distort or mask the true effect of the exposure on the outcome. Measurement error can be minimized by making the most accurate measurements possible.

Even in the best designed and analyzed epidemiologic studies, biases cannot be completely avoided. Sensitivity analyses can be conducted to determine the potential effects of residual biases on the results of the study (Greenland and Lash, 2008).

4.22.2 Environmental and Occupational Exposures and Adverse Reproductive Effects

Certain environmental and occupational toxicants, such as lead, have long been recognized as having potential adverse reproductive effects (Hamilton, 1925). However, recent decades have seen an increased concern for the potential threat that a wider variety of environmental and occupational exposures pose for reproductive function and the health of offspring. The concern about potential workplace hazards has grown in part because of the steady increase in the number of women in the work force. Over half (55%) of children in the United States were born to working mothers (US Census Bureau, 2010), and in 2010, 57% of employed men and women were of reproductive age (US Census Bureau, 2012). In addition, it is estimated that 68% of working women will become pregnant at least once during their working life (Cleveland et al., 2000).

Many agents (e.g., solvents, metals, pesticides) are found both in occupational and environmental settings. In many studies of reproductive effects of toxicants, exposures have been first studied in occupational settings, where exposure levels tend to be higher. In conducting epidemiologic studies of the reproductive effects of maternal exposure to toxicants, two persons may be at risk—the woman and, if she is pregnant, her developing child. Exposure may result in a wide range of adverse effects to either. Maternal exposure to a reproductive toxicant may cause infertility, changes in menstrual function, early onset of menopause, and suppressed libido. Commonly assessed adverse fetal outcomes include fetal loss, perinatal death, preterm delivery, low birthweight, altered sex ratio, congenital malformations, childhood cancer, and developmental disabilities.

4.22.2.1 Identifying Hazards

Approximately 85,000 chemical compounds are in commercial use today, with new chemicals introduced each year (EPA, 2015). Of these chemicals in use, however, only a small fraction has been evaluated for reproductive toxicity. In addition to chemicals, physical agents such as heat, cold, noise, radiation, biological agents, psychological stress, shift work, and ergonomic factors are also potential hazards to reproduction. Because epidemiologic studies can be labor- and resource-intensive as well as logistically difficult, efforts have been made to develop systematic approaches to select and prioritize agents for study. For example, in the European Union (EU), the regulation known as "REACH" (Registration, Evaluation, Authorization, and Restriction of Chemicals) outlines a process for prioritizing reproductive toxicity testing by annual volume that is produced or imported to the EU (Scialli and Guikema, 2012). In another example, an expert panel evaluated toxicity data linked with information on the extent of human exposure and chemical production data (all available in public databases) to derive a list of high-priority agents for human studies (Moorman et al., 2000). Another approach to identifying research priorities is to evaluate occupations with potential for exposure to reproductive hazards. For example, healthcare workers, including veterinarians and pharmacists, can be exposed to a wide variety of potential hazards, including chemical (hazardous drugs, high-level disinfectants), physical (radiation), biological (infectious agents or blood-borne pathogens), heavy lifting, or work organizational issues, such as shift work and long working hours.

4.22.2.2 Reproductive and Developmental Effects of Selected Exposures

4.22.2.2.1 Heavy metals

Exposure to heavy metals such as lead, mercury, arsenic, and cadmium has been associated with adverse reproductive outcomes. Lead is probably one of the most studied chemical substances known to adversely affect reproduction and development in humans. Over the past 10 years, evidence has indicated that lead may have serious health effects at exposure levels much lower than previously thought to be harmful (Kosnett et al., 2007). Low to moderate levels of maternal blood lead have been associated with elevated risks of miscarriage, pregnancy hypertension, and developmental toxicity to the fetus that may permanently affect neurologic and behavioral development of offspring (Bellinger, 2008; Bellinger et al., 1992; Gomaa et al., 2002). High paternal blood lead levels have been associated with reduced fertility, increased miscarriage, and reduced fetal growth (Bellinger, 2005). This information has given rise to new clinical guidelines in identifying and managing lead exposure in pregnant and breastfeeding women (CDC, 2010).

Other common metals such as arsenic, cadmium, and mercury have not been as well studied in humans but appear to be potential reproductive toxicants. Several studies have associated high arsenic content in drinking water with spontaneous abortion, stillbirth, infant mortality, and reductions in birthweight (Quansah et al., 2015), though these findings are inconsistent, particularly for low to moderate water concentrations (Bloom et al., 2014). Cadmium has been associated with male infertility in some but not all studies (Benoff et al., 2000), and maternal cadmium has been associated with reductions in birthweight (Sun et al., 2014; Salpietro et al., 2002). Despite substantial animal data showing fetotoxicity and teratogenicity as of the early 1980s (Carmichael et al., 1982), few high-quality human studies have been performed of cadmium and fetal loss or birth defects. Mercury has clear neurotoxic effects on a fetus (Solan and Lindow, 2014), leading to outcomes ranging from cognitive disabilities to hearing loss in children exposed *in utero*.

4.22.2.2.2 Pesticides

There is a growing body of evidence suggesting that exposure of pregnant women and fetuses to certain pesticides (chemicals used to eliminate nuisance insects, weeds, rodents, or fungi) may increase the risk of adverse outcomes. Because pesticides are used in

a variety of occupations as well as around homes, and often used in mixtures, accurate assessment of pesticide exposure is a major weakness of many epidemiologic studies of pesticide exposure and reproductive outcomes. To overcome many of these issues, the Agricultural Health Study recruited over 89,000 pesticide applicators and their spouses from North Carolina and Iowa into a prospective cohort study (Alavanja et al., 1996). To date, this study has found associations between pesticide exposure in women and later age at menopause (Farr et al., 2006), alterations in menstrual function (Farr et al., 2004), self-reported gestational diabetes (Saldana et al., 2007), and hypertensive disorders of pregnancy (Saldana et al., 2009). No association was observed between exposure to 27 individual pesticides and low birthweight (Sathyanarayana et al., 2010). Even in this large cohort, however, examination of rare pregnancy outcomes such as stillbirth and birth defects was limited.

Other studies have reported inconsistent findings for maternal pesticide exposure and miscarriage, stillbirth, or birth defects (Arbuckle and Sever, 1998; Nurminen, 1995; Hanke and Jurewicz, 2004; Kielb et al., 2014; Makelarski et al., 2014; Rocheleau et al., 2015; Nurminen, 2001; Restrepo et al., 1990; Rowland, 1995; Rocheleau et al., 2009). In part, this may reflect the difficulty of classifying pesticides accurately as to functional chemical classes, identifying all sources of pesticide exposure (e.g., occupational, residential, dietary, and environmental sources of exposure) and classifying certain reproductive outcomes accurately (e.g., being able to identify early miscarriage or analyze associations with specific birth defect phenotypes) (Arcury et al., 2006). Other long-term consequences of in utero pesticide exposure on children's health outcomes have recently received a great deal of attention, with consistent findings that organophosphate pesticides are associated with adverse cognitive and neurobehavioral outcomes in children (Koureas et al., 2012).

4.22.2.2.3 Organic solvents

A large number of human epidemiologic studies have examined the reproductive effects of solvents. In most studies, however, exposure was to complex mixtures of chemicals at work or in the environment, making it difficult to identify specific solvents as the causal factor in the observed effects. A meta-analysis of five studies reported an increased risk of certain birth defects in women workers exposed to solvents, and a marginally statistically significant association with miscarriage (McMartin et al., 1998). A meta-analysis of 14 studies of paternal organic solvent exposure found an increased risk of neural tube defects (Logman et al., 2005). Further work is needed to clarify which specific solvents might confer excess risk.

4.22.2.2.4 Dioxins and dioxin-like compounds

Dioxins and dioxin-like compounds (including polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs)) were used heavily in industry throughout the world until the late 1970s and 1980s when evidence of their adverse effects on the environment and human health were recognized. Because of their persistence in the environment and continued use in some parts of the world, however, they continue to be a source of concern. Studies of high-exposure events have clarified effects on reproduction.

During the Vietnam War (1962–1971), large amounts of Agent Orange, an herbicide mixture, were used as a defoliant. Though not known at the time, the Agent Orange was contaminated with 2,3,7,8-tetrachlorodibenzodiozin (TCDD), a potent dioxin compound. Studies of veterans exposed to Agent Orange found evidence of a relationship between paternal exposure to Agent Orange and spina bifida in offspring (IOM, 2003). Studies conducted in Vietnam on the populations exposed to Agent Orange—which included both men and women, who were generally exposed to both higher doses of Agent Orange and for longer duration—generally observed even stronger associations with birth defects (Ngo et al., 2006). In a cohort study of women exposed to TCDD after a factory explosion in 1976 in Seveso, Italy, researchers found an increased risk of endometriosis (Eskenazi et al., 2002) but no associations with miscarriage, fetal growth, or gestational length for future pregnancies (Eskenazi et al., 2000; Wesselink et al., 2014). In a study of wives of dioxin-exposed workers, no association was observed between paternal serum dioxin level and spontaneous abortion, sex ratio, low birthweight, or preterm delivery (Lawson et al., 2004; Schnorr et al., 2001).

Likewise, PCBs have not been associated with miscarriage, lowered birthweight, or preterm birth (Khanjani and Sim, 2007; Vartiainen et al., 1998). Maternal PCB exposure has, however, been associated with poorer behavioral and cognitive development in several studies, including prospective longitudinal cohort studies (Jacobson and Jacobson, 1996; Kimbrough, 1995).

4.22.2.2.5 Endocrine disruptors

Endocrine disruptors are chemicals that interfere with normal hormone activity. Animal and laboratory studies have identified endocrine-disrupting effects for a number of chemicals, and inadvertent effects of exposure on wildlife (particularly for aquatic and amphibian species whose aquatic environments have become contaminated). Effects of endocrine disruptors on human reproductive health are less clear, particularly at the low concentrations that most humans encounter in the environment. Phthalates and bisphenol A (BPA) are examples of endocrine disrupting chemicals that have received a great deal of attention and public concern in recent years, but with no consensus reached (McKee et al., 2004; Mikolajewska et al., 2015; Shelby, 2006; Shelby, 2008). Many studies have observed stronger effects for low-dose exposures than high-dose exposure, which is typically considered to be inconsistent with a true effect in epidemiological studies. A recent and somewhat controversial hypothesis, however, argues that endocrine disruption may cause nonmonotonic and low-dose effects without a similar effect at higher doses (Beausoleil et al., 2013).

4.22.2.2.6 Exposures in the healthcare setting

Healthcare workers may encounter a variety of situations which may affect their reproductive health, such as shift work and long working hours, physical demands such as heavy lifting or standing for long periods of time, or exposure to infectious agents.

Healthcare workers may also be exposed to antineoplastic (chemotherapy) drugs, antiviral drugs, anesthetic gases, disinfectants, or radiation. Working at night and working long hours have been related to menstrual disorders, miscarriages, and preterm birth (Stocker et al., 2014). Antineoplastic drugs are known reproductive and developmental toxicants. A recent literature review indicated that healthcare workers with long-term, low-level occupational exposure to these drugs have an increased risk of adverse reproductive outcomes (Connor et al., 2014). Some disinfectants, such as ethylene oxide and formaldehyde, are recognized as carcinogenic and mutagenic, but there have been few studies in humans to evaluate their reproductive toxicity (Lawson et al., 2012). Healthcare workers, dental assistants, and veterinarians can be exposed to radiation via X-rays, CT scans, fluoroscopies, radioactive isotopes, and radioactive implants; these are listed in order of increasing relative biologic effectiveness. Though it is well known that an acute dose of ionizing radiation is a reproductive hazard, the reproductive risks associated with occupational exposure to low-dose radiation throughout pregnancy are not well defined. Anesthetic gases have long been of concern to nurses, dental workers, and veterinarians. Engineering controls, such as scavenging systems, are commonplace in many hospital operating rooms, and recent studies support the idea that the use of these engineering controls has reduced the risk of adverse reproductive outcomes. However, there may be effects on pregnancy in smaller facilities or facilities where pediatric patients or veterinary patients are less cooperative during gas administration procedures.

4.22.2.2.7 Tobacco use and second-hand smoke

The hazards of smoking to reproductive health are well recognized. Smoking prior to pregnancy is associated with lower fertility, and smoking during pregnancy is associated with low birthweight, fetal growth restriction, preterm birth, placenta previa, placental abruption, birth defects, and ectopic pregnancy, among others (USDHHS, 2014). The hazards of second-hand smoke to reproductive health are less clear but are thought to include low birthweight and preterm birth (USDHHS, 2006).

The exact biological mechanisms by which tobacco use causes adverse reproductive health outcomes remain unknown (USDHHS, 2014). Cigarettes and cigarette smoke contain known or suspected reproductive toxicants, including carbon monoxide, polycyclic aromatic hydrocarbons, and heavy metals (FDA, 2012). There is evidence that women who use smokeless tobacco products during pregnancy also experience adverse reproductive outcomes, suggesting a hazardous role for nicotine alone (United States Department of Health Human Services, USDHHS, 2014). Cigarette smoking and exposure to second-hand smoke in pregnant women are growing public health problems, particularly in low- and middle-income countries where smoking prevalence is increasing (CDC, 2012). In countries such as the United States, smoking and second-hand smoke exposure are most common among persons with low socioeconomic status, a group traditionally at higher risk for adverse pregnancy outcomes (CDC, 2011; Homa et al., 2015; Johnson et al., 2015).

4.22.2.2.8 Air pollution

Many epidemiologic studies in recent years have examined health effects of exposure to air pollution, including reproductive effects. There is evidence of an effect of various air pollutants on female infertility (Mahalingaiah et al., 2016), lowered birthweights/small-for-gestational age (Vieira, 2015; van den Hooven et al., 2012; Winckelmans et al., 2015; Dibben and Clemens, 2015), preterm birth (Vieira, 2015; Capobussi et al., 2016), and certain birth defects such as orofacial clefts (Zhu et al., 2015); these findings are not conclusive, however. This might reflect variation in defining air pollution, as well as time period-specific effects.

Air pollution can refer to a number of toxicants (e.g., particulate matter of 10 microns or less, nitrogen dioxide, sulfur dioxide, carbon monoxide, ozone, polycyclic aromatic hydrocarbons). Effects may vary by the particular chemicals under study. For example, a study in Italy found that preterm birth risk increased with second trimester exposure to nitrogen oxides, but exposure to sulfur dioxide and carbon monoxide seemed to delay delivery (Capobussi et al., 2016). Effects can also vary depending on the timing of exposure relative to a pregnancy. Poor fetal growth in early pregnancy might be compensated for later in pregnancy, for example.

4.22.3 Emerging Areas of Study

Despite significant advances in reproductive health research, there remains much to be learned about the influence of exogenous factors on the spectrum of reproductive outcomes.

One area of active study is the relationship between reproductive health and health in later life. The life-course epidemiology approach considers the influence of biological and social exposures throughout the life span on the occurrence of disease (Kuh et al., 2003). For example, a robust evidence base supports the "fetal origins hypothesis" (also called "Barker hypothesis") that low birthweight or impaired intrauterine growth during gestation increases risk for cardiovascular disease in adulthood (Barker and Bagby, 2005). A second, related area of study is use of adverse reproductive events as markers for future disease in the mother. There is growing evidence that mothers who had preterm births are at greater risk for cardiovascular disease in the future, compared to mothers who had term births (Robbins et al., 2014). The mechanisms underlying the impact of physiologic changes during pregnancy on both the long-term health of the fetus and the mother have yet to be elucidated.

One possible mechanism by which maternal or fetal exposures might influence long-term health in offspring is through epigenetic changes. In contrast to genetic changes, which involve alteration of the DNA sequence, epigenetic changes are those that affect how and when genes are expressed. Research is now being conducted to determine if epigenetic changes might affect reproductive health outcomes such as preterm birth or low birthweight (Engel et al., 2014; Burris et al., 2016). Environmental

epigenetics is a related field that focuses on how environmental exposures might cause or influence epigenetic changes. Many of the exposures discussed above, including endocrine disruptors, tobacco smoke, and heavy metals, are thought to be able to cause epigenetic changes (Ho et al., 2012). However, environmental epigenetic research related to reproductive health is still in its infancy.

Nanotechnology, the manipulation of matter on a near-atomic size scale to produce new structures, materials, and devices, promises to revolutionize many industries. However, information about safety and potential hazards is urgently needed. Nanoparticles may have different toxicologic properties than larger particles, so health and safety standards created for larger particles may not be suitable for nanoparticles (Hirano, 2009). What is generally known is that when inhaled, nanoparticles are efficiently deposited in all regions of the respiratory tract; they evade specific defense mechanisms; they can move out of the respiratory tract via different pathways and mechanisms; they can be absorbed through the skin; and when in blood circulation, they can distribute throughout the body (Oberdorster, 2010; Oberdorster et al., 2005). Questions remain about how effectively nanoparticles will cross the blood–brain barrier (Oberdorster et al., 2009) and cross the placenta to affect developing offspring (Juch et al., 2013).

As technology changes and new materials are used in industry, research on health effects of those materials will be needed. Improvements in our understanding of mechanisms of reproductive toxicity, improved sources of epidemiologic data, and new tools to evaluate past exposure promise to transform the study of reproductive epidemiology.

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https://ntp.niehs.nih.gov/pubhealth/hat/index.html—National Toxicology Program.
http://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated—Epidemiology for the Uninitiated.
http://www.niehs.nih.gov/health/topics/conditions/repro-health/—National Institute for Environmental Health Sciences (NIEHS): Reproductive Health.
http://mothertobaby.org/—MotherToBaby: Medications and More During Pregnancy and Breastfeeding.