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To better understand the science linking environmental contaminants exposures with adverse pregnancy outcomes, we reviewed the relevant epidemiologic literature. We searched PubMed (primarily 1995-2006) using the key word combinations for select environmental exposures and pregnancy outcomes. Environmental tobacco smoke is a risk factor for reduced birth weight and preterm delivery. Outdoor air pollution is associated with reduced term birth weight and preterm delivery. Suggestive evidence associates pesticides and polychlorinated biphenyls with decreased fetal growth and length of gestation. Stronger evidence, primarily occupational, links certain birth defects with exposure to organic solvents and chlorophenoxy herbicides. Evidence suggests dichlorodiphenyltrichloroethane and bisphenol-A could be associated with pregnancy loss. Exposures in utero can also increase the risk of developmental delays (ie, impaired neurological function), adult chronic illnesses (ie, heart disease, diabetes, cancer), and next generation effects (ie, reduced reproductive capacity). Further research, education, and improved public health policy are needed to reduce potentially adverse exposures.

KEY WORDS: Adverse pregnancy outcomes, environmental contaminants, preterm delivery, low birth weight, environmental exposures.

INTRODUCTION

The root causes of many adverse pregnancy outcomes are not well understood, but there is growing evidence that the environment can play an important role. ''Environment'' is a broad term that includes familiar contributors such as nutrition, adequacy of prenatal care, smoking and alcohol use, maternal age, and socioeconomic disparities, as well as less familiar contributors including pollution and chemical agents encountered both indoors and outdoors. In many cases, two or more environmental factors may be interrelated or synergistic. Environmental factors may also be magnified or otherwise affected by varying genetic characteristics unique to the individual. Understanding the impact of this broad range of factors on pregnancy outcome requires careful attention to the study design, including approaches used for exposure characterization.

This article focuses on the impact of exposure (maternal both prior to conception and during pregnancy as well as paternal) to certain chemical hazards and other agents in the physical environment on pregnancy outcome. Until recently, these impacts have received less attention from clinicians compared with other factors. However, the body of medical and scientific evidence linking such exposures with adverse pregnancy outcomes is now reaching a point warranting further consideration (from both a clinical and scientific perspective) and preventive action. Outcomes that may be influenced by environmental factors include preterm and low birth weight births, certain congenital defects, and pregnancy loss.

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LOW BIRTH WEIGHT AND PRETERM DELIVERY

The United States is facing an epidemic of prematurity with continuously increasing rates of preterm and low birth weight infants (small for gestational age; SGA).[1] The preterm birth rate has risen steadily in recent years, climbing 8% since 1990[2] and more than 30% since 1981.[3] In 2004, 12.5% of live births were preterm, the highest reported since comparable national data have been available.[3] Although the increase has been mostly in moderately preterm births (32-36 weeks), the very preterm birth rate (less than 32 weeks) has also risen in recent years.

The increase in preterm births has contributed to a rise in the rate of low birth weight[4] as infants born too early are also smaller. However, some infants are born ''too small'' for their gestational age. Various terms are used to refer to infants who are born too small, the most common of which are ''SGA'' and ''intrauterine growth restriction'' (IUGR). (These 2 terms are commonly used interchangeably, however some researchers distinguish between them. For example, one source notes that SGA is appropriate for infants whose birth weight is below the 10th percentile while IUGR should be used to refer specifically to infants that have failed to reach their growth potential due to some insult in utero.) A less frequently used measure is ''light for date,'' defined as a birth weight 1.5 standard deviations below what is considered appropriate for gestational age (AGA).[5] Small for gestational age, IUGR, and ''light for date'' are all terms that provide a measure of growth restriction, as opposed to shorter gestation, both which can contribute to low birth weight. Following declines during the 1970s and early 1980s, the percentage of newborns delivered with low birth weight has risen 16% since 1990 to 8.1% of births in 2004.[2]

Although recent increases in multiple births, which often occur preterm, have influenced to a small extent the rise in preterm and low birth weight births,[1] rates are also rising among singleton infants. The singleton low birth weight rate in 2003 at 6.2% was up 5% over the 1990 level.

Birth weight and length of gestation are important predictors of neonatal and infant health. The risk of mortality for SGA infants at all gestational ages is 4 to 5 times higher than for AGA infants.[6] This risk increases relative to the degree of smallness.[7,8]

Infants born preterm or with low birth weight also experience significantly higher rates of morbidity during the perinatal period than term and normal birth weight infants. Preterm birth is associated with nearly one half of all congenital neurological defects, though preterm birth in this case is not causative of—but reflective of the defect.[3] A recent large, prospective multicenter trial found that singleton liveborn infants with birth defects were more likely to be delivered preterm or very preterm, and more likely to have low or very low birth weight.[9] Low birth weight infants experience longer hospital stays at birth and a greatly increased risk of respiratory distress syndrome. Intrauterine growth restriction has been identified as a significant risk factor for chronic hypertension, heart disease, lung disease, and type 2 diabetes later in life,[10] creating the need to understand the impact of adverse pregnancy outcome across the life course.

Adverse birth outcomes are a financial and emotional burden on families both in the short and long term. Average hospital charges for premature births in 2003, for example, have been estimated to be $18.1 billion, about half the total infant hospital charges for all US births.[11]

CONGENITAL ANOMALIES

Congenital anomalies are the leading cause of infant mortality in the United States, accounting for more than 20% of all infant deaths.[12] They also cause metabolic disorders and disability. Birth defects are typically underreported on birth certificates, in part because not all defects are apparent at birth, and not all states actively assess birth defects up to the first year of life, which is the best method for fully ascertaining birth defects.[3,13] In addition, it is extremely difficult to know whether congenital anomalies are becoming more prevalent in the United States because of a dearth of national population–based prevalence estimates. Nevertheless, the Centers for Disease Control and Prevention (CDC) have collected statistics on rates of certain anomalies. It is estimated that 1 in 33 infants has a congenital anomaly. Among the most commonly reported specific anomalies is cleft lip/palate, reported at a rate of 75.9 per 100 000 births in 2003; together, heart malformations and other circulatory/respiratory anomalies were reported at a rate of 255 per 100 000 births (excluding data from Pennsylvania and Washington).[3]

Recently, the National Birth Defects Prevention Network reported the first national estimates for 18 selected major birth defects during 1999-2001, based on pooled population–based estimates from 11 states.[14] They report that 10 of the defects affected more than 1000 infants each year nationwide. The highest prevalence conditions include orofacial clefts, which affect

approximately 6800 infants annually, and Down syndrome, which affects approximately 5500 infants annually.

PREGNANCY LOSS

Pregnancy loss encompasses a variety of outcomes, including spontaneous abortion (miscarriage), stillbirth (fetal death, ie, more than 20 weeks of gestation), ectopic pregnancy, and the relatively rare condition of molar pregnancy (in which a mass or growth of tissue known as a hydatidiform mole forms inside the uterus after an abnormal conception, and there may be no fetus at all[15]). In 1997 in the United States, an estimated 6.19 million pregnancies resulted in 3.88 million live births and 0.98 million fetal losses.[16]

The risk of fetal death has declined substantially since the 1950s, though racial and ethnic disparities persist.[17] In addition, the rate of 6.4 fetal deaths per 1000 births in 2002 is well above the national health objective for 2010 of 4.1.[18,19]

Our current understanding of the causes of fetal death is limited. Indeed, even the true rate of pregnancy loss is difficult to determine, as researchers have estimated 20% to 40% of all losses may occur before clinical detection.[20,21] Nevertheless, there is emerging evidence that certain environmental exposures may influence fertility and interfere with successful pregnancy outcomes.

POLLUTION, ENVIRONMENTAL CHEMICALS, AND THE FETAL ENVIRONMENT

The physical environment encompasses air, water, food, soil, and a myriad of consumer products and other substances that individuals come into direct contact with each day. The latter include environmental tobacco smoke, air pollutants from motor vehicles and industrial facilities, pesticides, heavy metals, plasticizers, and flame retardants, chemical byproducts of drinking water disinfection, and pharmaceuticals that are incompletely removed from drinking water. The fetus shares this same environment. The placenta was at one time thought to offer a highly effective barrier minimizing contaminant exposure, although research in recent decades has documented that it is far from impenetrable.[22,23] In some cases, the placenta may actually magnify maternal exposures, depending on mechanism of transport across the placenta, protein binding of the chemical in maternal and fetal serum and physicochemical characteristics of the agent. Cord blood levels of methyl mercury, for example, have been shown to be nearly 2 times higher than corresponding maternal levels.[24]

Concern about fetal exposures to environmental hazards comes from an increasing understanding that the fetus is extremely sensitive during certain critical windows of development, and windows of sensitivity exist for many systems—respiratory, immune, reproductive, nervous, cardiovascular, and endocrine—as well as general growth and later outcomes such as childhood and adult-onset cancers.[25] Exposures to environmental contaminants during these times can increase risk of subsequent adverse health effects.

Although fetal exposures to environmental hazards are often assumed to result from maternal exposures during pregnancy, fetal exposures to certain environmental chemicals can also be concurrent or nonconcurrent with the maternal exposure.[26] For certain persistent and bioaccumulative chemicals such as dioxin and organochlorine pesticides, for example, the fetal exposure can occur from maternal body burdens resulting from many years of preconceptional exposures. Paternal preconceptional exposures may also contribute to fetal risk through a mutagenic mechanism involving the sperm, and in some instances the chemical can also be carried in the semen and exposure to the fetus occur following intercourse.[27]

Herein, we have reviewed available evidence linking certain pregnancy outcomes in humans (and occasionally in experimental animals) with selected environmental factors. Because of the broad subject matter and the difficulty in comparing studies, we did not attempt a systematic review. Rather these should be viewed as case studies illustrating the strength or weakness of the evidence base and improvements in studies needed to fully understand these potential associations. For this general review, we searched the PubMed database for studies and review articles published in English using various combinations of key words and search terms, such as ''environmental exposure,'' ''pregnancy outcomes,'' ''spontaneous abortions,'' ''birth defects,'' and ''air pollution,'' primarily focusing on the period from 1995 to 2006, though we include relevant references from 2007 where pertinent. In addition to summarizing the conclusions of relevant existing reviews, we discuss some of the strongest, most representative, or most groundbreaking investigations on this topic. Table 1 gives an overview of the findings from the literature, and identifies the methods used—including exposure characterization.

Table 1. Selected Studies Showing Environmental Links to Adverse Birth Outcomes

Birth Outcome	Pollutant	Author and Year Published	Study Type	Exposure Characterization[a]	Sample Size
Fetal growth	Particulates	Wang et al[28]	Retrospective cohort	Ambient monitoring	n = 74 671
		Bobak[29]	Retrospective cohort	Ambient monitoring	n = 73 148
		Dejmek et al[30]	Retrospective cohort	Ambient monitoring	n = 4883
		Ha et al[31]	Time series	Ambient monitoring	n = 276 763
		Wilhelm and Ritz[32]	Retrospective cohort	Ambient monitoring	n = 498 235
		Parker et al[33]	Retrospective cohort	Ambient monitoring	n = 18 247
		Dugandzic et al[34]	Retrospective cohort	Ambient monitoring	n = 74 284
	SO_2	Lin et al[35]	Retrospective cohort	Ambient monitoring	n = 92 288
	CO	Maisonet et al[36]	Retrospective cohort	Ambient monitoring	n = 101 153
		Salam et al[37]	Retrospective cohort	Ambient monitoring	n = 3901
	NO_2	Liu et al[38]	Retrospective cohort	Ambient monitoring	n = 229 085
	Polycyclic organic compounds	Dejmek et al[30]	Retrospective cohort	Ambient monitoring	n = 4883
		Vassilev et al[39]	Retrospective cohort	Modeled exposure	n = 214 493
		Perera et al[40]	Prospective cohort	Personal air monitors	n = 329
	Organophosphate insecticides	Perera et al[41]	Prospective cohort	Serum levels	n = 263
		Levario-Carrillo et al[42]	Case–control	Residential history	n = 371
	Triazine herbicides	Munger et al[43]	Cross sectional	Drinking water monitoring	n = 9551
		Dabrowski et al[44]	Case–control	Residential and occupational history	n = 494
		Villanueva et al[45]	Retrospective cohort	Municipal drinking water monitoring	n = 9721
	PCBs	Hertz-Picciotto et al[46]	Prospective cohort	Serum levels	n = 399
Preterm birth	Particulates	Xu et al[47]	Retrospective cohort	Ambient monitoring	n = 25 370
		Bobak[29]	Retrospective cohort	Ambient monitoring	n = 73 148
		Wilhelm and Ritz[32]	Retrospective cohort	Ambient monitoring	n = 498 235
		Sagiv et al[48]	Time series	Ambient monitoring	n = 187 997
		Huynh et al[49]	Matched case–control	Ambient monitoring	n = 42 692
	SO_2	Bobak[29]	Retrospective cohort	Ambient monitoring	n = 108 173
		Liu et al[38]	Retrospective cohort	Ambient monitoring	n = 229 085
	CO	Liu et al[38]	Retrospective cohort	Ambient monitoring	n = 229 085
Congenital abnormalities	Chlorophenoxy herbicides	Garry et al[50]	Cross sectional	Occupational history	n = 210 723
		Garry et al[51]	Cross sectional	Occupational history	n = 1532[b]
		Basso 1999[52]	Cohort	Occupational history	n = 8671
		Schreinemachers[53]	Ecologic	Pesticide use and proximity	n = 43 634
	Other pesticides	Rull 2006[54]	Case–control	Pesticide use and proximity	n = 1671
	Organic solvents	Tikkanen and Heinonen[55]	Case–control	Occupational history	n = 1628
		Cordier et al[56]	Case–control	Occupational history	n = 650
		McMartin et al[57]	Meta-analysis	–	
		Cordier et al[58]	Case–control	Occupational history	n = 2118
		Garcia and Fletcher[59]	Case–control	Occupational history	n = 522
		Khattak et al[60]	Prospective observational controlled study	Occupational history	n = 125
Pregnancy loss	Disinfection byproducts	Waller et al[61]	Prospective cohort	Exposure history and water utility monitoring data	n = 5144
		Toledano et al[62]	Cohort	Monitored tap water extrapolated to populations	n = 920 571

Table 1. (continued)

Birth Outcome	Pollutant	Author and Year Published	Study Type	Exposure Characterization[a]	Sample Size
	DDT	Korrick et al[63]	Case–control	Serum levels	n = 30
		Longnecker et al[64]	Prospective cohort	Serum levels	n = 1717
		Law et al[65]	Prospective cohort	Serum levels	n = 390
		Cocco et al[66]	Retrospective cohort	Occupational history	n = 105
		Venners et al[67]	Prospective cohort	Serum levels	n = 388
	Bisphenol-A	Sugiura-Ogasawara et al[68]	Case–control	Serum levels	n = 45

[a] Ambient monitoring for the common air pollutants is assumed to be a reasonable surrogate for individual level exposures.
[b] The study evaluated families with children with birth defects, the n is for the number of children in the study.

In this review, we did not attempt to examine specifically the possible cumulative and/or synergistic effects of combinations of pollutants to which people commonly are exposed. There is a growing recognition among researchers in the field that such effects are likely. Documenting such effects, however, can be more difficult than identifying the effects of individual chemicals in epidemiologic studies.[69]

FETAL GROWTH AND LENGTH OF GESTATION AND SELECT ENVIRONMENTAL CONTAMINANTS

Air Pollution and Fetal Growth and Length of Gestation

Environmental Tobacco Smoke

Numerous studies have found that infants born to smokers weigh substantially less than infants born to nonsmokers,[70-72] and exposure to secondhand smoke is a risk factor for reduction in birth weight[70,73] and preterm birth.[73] Cigarette smoke consists of a complex mixture of substances—including polycyclic aromatic hydrocarbons (PAHs), lead, and cadmium—that are also generated as air pollutants by other sources. For this reason, studies of the effects of environmental tobacco smoke are instructive for an examination of the impacts on fetal health of other types of air pollution.

Common Air Pollutants

Air pollution arises from a variety of sources, including motor vehicles, industrial sources, wood burning, and small local sources such as dry cleaners. People may be exposed to air pollution indoors or outdoors, with higher exposures usually—but not always—occurring close to pollution sources. Air pollution contributes to a wide variety of adverse health effects.[74] About 6 of the most common air pollutants—carbon monoxide (CO), lead, ground-level ozone (O_3), particulate matter (PM), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2)—are known as ''criteria'' pollutants because there is widespread exposure and the US Environmental Protection Agency (EPA) uses health-based criteria as the basis for setting permissible levels of these pollutants in the atmosphere.[74]

A large number of epidemiologic studies conducted in several countries have reported relationships between maternal exposure to elevated levels of criteria air pollutants and elevated risks of low birth weight and preterm delivery. Specifically, associations have been found between low birth weight and maternal exposure to PM,[28,31,75-79] SO_2,[28,31,36,38,75,76,78,79] CO,[31,36,75,80] nitrogen oxides (NO_x),[31,75,81] and O_3.[37] These associations remain evident when controlling for other potential risk factors, including gestational age, birth order, maternal demographics, and smoking.

Particulate Matter. Particle pollution (also called PM) is the term for a mixture of solid particles and liquid droplets found in the air. Some particles are emitted directly from a source, such as construction sites, unpaved roads, fields, smokestacks, or fires. Others form from reactions in the atmosphere of chemicals such as sulfur dioxides and nitrogen oxides that are emitted from power plants, industries, and automobiles.

Growth Restriction. Studies conducted in countries with relatively high levels of PM have found suggestive associations with growth restriction. Investigators in the

Czech Republic have found both no relationship between particles and SGA[29] and a positive relationship between PM and IUGR.[30] Although a study in South Korea supports effects from exposures early in the pregnancy,[31] a study in China finds a relationship only from exposures during the third trimester.[28]

Results from North America, where levels of pollution are lower, typically find an association between reduced birth weight and PM, but the findings are variable. Studies in California have found some association with PM, though in southern California studies have found an effect for O_3 after adjusting for PM, but studies of later years find PM effects after adjusting for gaseous pollutants.[32,33,37] There was no association between PM and low birth weight in a study in the northeastern United States,[36] and a study in Canada found a small, but insignificant association with low levels of PM.[34]

Preterm Birth. Studies of preterm birth have found associations between preterm birth and PM in the Czech Republic,[29] China,[47] southern California,[32] Pennsylvania,[48] and California.[49] The associations tend to be relatively small, though typically statistically significant. Although effects are relatively modest, they appear to be slightly more consistent than associations with growth retardation.

SO_2, CO, NO_2, and Ozone. More limited studies have assessed other common air pollutants and low birth weight and preterm delivery. A retrospective cohort study in Taiwan found mothers with high SO_2 exposure throughout their pregnancy had 26% higher risk of delivering a term low birth weight infant than those with low exposure.[35] In a population study of 6 northeastern United States cities, maternal exposure to CO during the third trimester of pregnancy increased the risk of low birth weight among term, singleton infants. The association was most consistent and strongest among African Americans.[36]

A study in southern California found an increase in IUGR among term infants born to women with high, third trimester CO exposure. Another California study, however, found increased odds of SGA and a small difference in mean birth weight between infants with the highest and lowest PM exposures, but no association between CO and birth weight or SGA.[33] Finally, a study of infants born primarily in southern California found an association between O_3 exposure primarily during the third trimester, and CO primarily during the first trimester with reduced birth weight.[37]

The literature on air pollution and pregnancy outcomes is still evolving. If a relationship exists, it appears subtle and not easy to characterize, which may be partly due to influence of other important factors such as timing of exposure, geographic variability and potential influence of other factors.

Other factors may independently influence observed associations, such as socioeconomic factors, which are themselves important for birth outcomes. However, most studies suggested that adjustment for maternal factors and smoking does not substantially alter the associations with birth outcomes. There is some suggestion that social and demographic factors may modify the effect of air pollution. Maternal air pollution exposure differs by race,[82] and birth weight differs by race, but air pollution in these studies has not explained the racial disparity. A study in Los Angeles County found that traffic-related air pollution was associated with preterm birth in low income and middle-income neighborhoods, particularly during the winter, when thermal inversions trap motor vehicle pollutants. No effects were observed in high-income neighborhoods regardless of season, suggesting that higher socioeconomic status acts to insulate against the adverse effects of air pollution.[83]

Although there is variability in the results, in general there appears to be a link between air pollution and fetal growth and length of gestation. Observed effects are generally modest, but because air pollution is ubiquitous, public health implications across entire populations may be significant. A 2005 review concluded that the weight of the evidence suggests a causal relationship between exposure to air pollution and reduced birth weight, while noting potential problems with multiple comparisons and heterogeneity of results.[84] In addition, most studies have evaluated PM air pollution, which is comprised of a mixture of pollutants that can vary from location to location. This variability in PM composition could also contribute to variability in findings. The authors of the 2005 review cautioned that further studies are needed ''to confirm causality, to clarify the most vulnerable periods of pregnancy and the role of individual pollutants, and to examine whether the impaired reproductive outcomes have any long-term consequences on child health.'' The same review found that for preterm birth and IUGR, the evidence is as yet insufficient to infer causality, but the available evidence justifies further studies.

Polycyclic aromatic hydrocarbons and polycyclic organic matter

Polycyclic aromatic hydrocarbons are toxic air pollutants generated by combustion and usually bound to particulate air pollution. Recent studies link exposure to PAHs with reduced fetal growth and preterm birth. One study in the Czech Republic found that increasing PAH levels during the first month of pregnancy increased the risk of IUGR.[30]

Research on nonsmoking pregnant women living within 2 miles of the World Trade Center (WTC) disaster in New York City in 2001,[85] where PAHs were identified as one of the hazards, found an increased risk of delivering infants with reduced birth weight and shorter gestational length. Shorter gestation was linked to exposure in the first trimester regardless of distance from the site (which may indicate a role for maternal stress from the 9/11 events), as well as pollution effects. A follow-up found markers in maternal and umbilical cord blood, representative of PAH exposure, were highest for women residing within 1 mile of the WTC site during the month after the disaster. Higher levels of these markers, in combination with exposure to environmental tobacco smoke, were associated with decreased fetal growth, suggesting that exposure to elevated levels of PAHs among women exposed to environmental tobacco smoke may have contributed to reduced fetal growth in women residing closest to the WTC event.[85] A study of births in New Jersey found a relationship between both term and preterm low birth weight and ambient concentrations of polycyclic organic matter (which includes PAHs).[39]

Pesticides and Fetal Growth and Length of Gestation

The EPA defines a pesticide as ''any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest.''[86] This includes insecticides, herbicides, fungicides, and various other substances. United States pesticide usage in 2001 exceeded 1.2 billion pounds, and accounted for more than 20% of total world pesticide usage. Herbicides, in particular, are relatively heavily used in the United States, with US herbicide usage accounting for more than 25% of the worldwide total.[87]

Pesticides are used in many settings—in agriculture, homes, gardens, workplace, and institutional settings—and pesticide exposures are ubiquitous. The agricultural sector accounts for more than 75% of the nation's total conventional pesticides use, suggesting individuals engaged in agricultural work and/or residing in or near agricultural areas may be at greatest risk of exposure.

Exposure to various pesticides has also been correlated with preterm birth and reduced fetal growth. A recent study on the effect of agricultural organophosphate pesticides found a significant positive association between maternal exposure and the occurrence of IUGR.[42] This finding is supported by a series of studies of inner city and minority populations who are more likely to be exposed to indoor pesticides. In the first study, exposure of the fetus to chlorpyrifos was inversely associated with birth weight.[41] The second study found the inverse association between chlorpyrifos and birth weight was highly significant when limited to the newborns born before the EPA banned residential use of this pesticide in 2000. Newborns born later had much lower exposure levels and thus did not exhibit a significant correlation between chlorpyrifos and birth weight.[88]

Other studies of organophosphate metabolite levels and fetal growth have been less conclusive. For example, a study of multiethnic mothers living in New York City found no relation,[89] and a study of Latina women living in an agricultural area did not generally find an association between intrauterine growth retardation and concentrations of organophosphate pesticides in utero.[42] The latter study did find an association between exposure and preterm birth, most clearly related to increasing exposure levels in the later part of pregnancy. Overall, however, the rate of preterm delivery in this population was lower than in a US reference population.[90]

Exposure to triazine and other herbicides, common contaminants of rural drinking water sources, may also lead to decreased fetal growth. An investigation of women living in a region of Iowa with raised levels of triazine, metolachlor, and cyanazine herbicides in the drinking water found that their offspring were more likely to suffer from IUGR than infants born to women in other parts of the state.[43] A Polish study similarly found that exposure to triazine herbicides in combination with other pesticides resulted in increased low birth weight rates, even when controlling for length of pregnancy.[44] French researchers found that atrazine levels in municipal drinking water throughout pregnancy were not associated with increased risk of SGA birth, but that the risk of SGA birth increased when the third trimester occurred in whole or in part during the period of May through September, when atrazine levels typically peak.[45]

The studies are suggestive, and in most cases a substantial sample size is required prior to observing effects,

suggesting that null results could be from inadequate sample size.

Polychlorinated Biphenyls and Fetal Growth and Length of Gestation

Polychlorinated biphenyls (PCBs) are ubiquitous and persistent organic pollutants historically used in electrical transformers and other industrial applications. Polychlorinated biphenyls accumulate in the fatty tissue of animals and humans. They are known endocrine disruptors, possible carcinogens, and may have other mechanisms of toxicity that are poorly understood. They interfere with thyroid function and can cause delayed neurological development and intelligence quotient (IQ) deficits, in addition to low birth weight.[91] Most PCB exposure occurs through the consumption of contaminated fish, meat, and dairy products, although exposure by inhalation is also possible.[92,93] Additionally, PCBs cross the placenta, and they accumulate in breast milk.[94]

A number of studies have found an association between maternal exposure to PCBs and low birth weight among term and preterm infants for higher exposures to PCBs. For example, a review of Japanese women exposure to PCB-contaminated rice oil during pregnancy found a higher percentage of ''light-for-date'' infants delivered (defined as a birth weight 1.5 standard deviations below what is considered AGA) compared with unexposed women.[95] A related analysis of Japanese women with high concentrations of PCB in their breast milk also found increased rates of light for date birth.[96]

Studies of women exposed to PCBs through fish consumption at lower concentrations in a variety of environments has reached mixed conclusions regarding the association with low birth weight.[97-100] Given that increased fish consumption has been found to extend the gestational period and is beneficial in other domains, the relationship between PCBs and low birth weight may be less evident in these women as the two influences potentially counter one another. Two recent studies analyzing US exposure and birth outcome data from the 1960s came to different conclusions. A study of women in the San Francisco Bay Area found higher total in utero PCB exposure associated with reduced birth weight, smaller head circumference, and reduced weight for gestational age in male infants.[46] Head circumference and shorter gestation effects were present, but merely suggestive in girls. The other study examined births at 12 US study centers and found maternal PCB levels during pregnancy were essentially unrelated to preterm birth, birth weight, or length of gestation.[101] Because PCBs represent a group of multiple individual compounds with varying levels of toxicity, it is possible that the mixtures in the 2 studies differed sufficiently to explain the difference in observations, but further research is warranted.

BIRTH DEFECTS AND SELECT ENVIRONMENTAL CONTAMINANTS

Pesticides, Agricultural Work and Rural Living and Birth Defects

Chlorophenoxy Herbicides

Chlorophenoxy herbicides are a class of weed killers first developed in the 1940s. Perhaps, the best known member of the class is 2,4-D. This class of herbicides is widely used in agricultural regions of the United States, especially in the Midwest. Research has found increased risk of congenital anomalies among offspring born to state-licensed private pesticide appliers, as well as offspring born to the general population residing in regions with high usage rates of chlorophenoxy herbicides and fungicides in western Minnesota.[50] This study also found higher rates of congenital anomalies among infants conceived in spring, when herbicides are typically applied. Rates of combined births with central nervous system, circulatory/respiratory, urogenital, and musculoskeletal anomalies and were significantly increased for all anomalies in high-use areas, and shifts in the male:female sex ratio of offspring with anomalies were observed. In a second study of families in this region, the same research team again found that spring conceptions led to significantly more children with birth defects than conceptions in other seasons.[51] This study also suggested a possible gene–environment interact at work in this agricultural region. A total of 22% of families in which the father was an applier had more than 1 child with a birth defect, whereas a previous population-based study by other investigators found only a 5.5% rate of multiple birth defects in families.[52]

An ecologic study in the wheat-growing states of Minnesota, Montana, North Dakota, and South Dakota, where 85% of the wheat acreage in these states is sprayed with chlorophenoxy herbicides during April to June, found significant circulatory/respiratory malformations in high-wheat counties, an indicator of chlorophenoxy herbicide exposure, compared to low-wheat counties. In addition, there was a stronger effect for infants

conceived in spring. Musculoskeletal/integumental anomalies also increased in the high-wheat counties.[53]

Other pesticides

Other researchers have reported increased rates of congenital anomalies with exposure to mixtures of pesticides through residential proximity. A California study, for example, reported an increase in neural tube defects in offspring of mothers living within 1000 meters of agricultural pesticide applications,[54] with exposures to multiple pesticides likely. Based on evidence in animals, the authors suggest that pesticide mixtures or agents applied in combination may increase the risk.

Other studies of pesticides and birth defects are less conclusive. One investigator reported on case studies and EPA documents showing increased risk of congenital anomalies with maternal exposure to the herbicide chlorpyrifos.[102,103] However, other recent epidemiological investigations of chlorpyrifos and pregnancy outcomes found little evidence of a link to congenital anomalies.[40,41,88,104,105] Another case–control study of orofacial clefts, neural tube defects, conotruncal defects, and limb anomalies among 1987 to 1989 California births and fetal deaths failed to find increased risk for any of the studied anomaly groups among women whose self-reported occupational tasks were deemed likely to involve pesticide exposures, but did reveal elevated risk for 2 of the cleft phenotypes associated with paternal occupational exposure to pesticides. Use of pesticides in and around the home was not associated with anomalies in that study, although women who reported that a professional applied pesticides to their homes, or who lived in close proximity to agricultural pesticide use, had increased risks for neural tube defect–affected pregnancies. For many of the comparisons, data were sparse, resulting in imprecise effect estimation and limited sample size for detection.[106]

Organic Solvents and Birth Defects

The best known teratogenic solvent is ethyl alcohol, where ingestion during pregnancy leads to well-documented adverse effects.[107] Now, there is increasing evidence linking industrial solvents with congenital anomalies, with much of the epidemiological investigation focusing on maternal occupation.

Organic solvents have many uses in manufacturing, service industries such as dry cleaning and printing, and consumer products including stain removers, paint thinners, nail polish removers, and hobby/craft products. Solvents are also ubiquitous contaminants of industrial waste sites and nearby soils and groundwater. As a result of these properties, exposure to low levels of organic solvents is widespread, with higher levels of exposure occurring in individuals in certain occupations. Although organic solvents comprise a variety of chemical groups that may have differing mechanisms of action, they are typically grouped together in discussions of exposure and toxicity because they are so often used interchangeably and in mixtures in industrial settings.

Early studies linked occupational exposures to solvents with central nervous system defects,[108] oral clefts,[56,109] and ventricular septal defects.[55] A 1998 meta-analysis of 5 studies found a statistically significant association between maternal occupational exposure to solvents and major malformations, which the authors indicated warranted further investigation.[57]

More recent examinations have strengthened the evidence base. A large multicenter European case–control study looked specifically at maternal exposure to glycol ethers during the first trimester of pregnancy. Such exposures were associated with neural tube defects, spina bifida, cleft lip, and multiple anomalies.[58] Studies have also linked birth defects to maternal work with solvents in specific industries such as the leather industry.[59]

A 10-year prospective case–control study of pregnant women who sought occupational health advice at a clinic in Toronto revealed a startling 13-fold increase in risk of major malformations in offspring of exposed women compared with controls.[60] The risk appeared to be increased for women who reported symptoms of solvent exposure, including headache and breathing difficulties; 12 of the 13 major defects in the exposed group occurred in offspring of symptomatic women. Organic solvents included in the Toronto study included aliphatic and aromatic hydrocarbons, phenols, trichloroethylene, xylene, vinyl chloride, and acetone.

For some specific solvents and malformations, however, the evidence of teratogenicity can be more difficult to ascertain due to study design limitations. The National Research Council recently reviewed studies of trichloroethylene and birth defects and found that a number of studies find a relationship between trichloroethylene and cardiac birth defects, with a similar effect size across the positive studies of about 2-fold to 3-fold increase.[110] In addition, the report notes that the most frequently observed cardiac defects in the human studies are consistent with those found in animal studies.[110]

There is also evidence that paternal exposure to solvents may be associated with birth defects. A recent

meta-analysis examined studies of paternal exposure to a variety of solvents including aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, aliphatic alcohols, glycols, glycol ethers, and their derivatives, concluding that occupational exposure of fathers is associated with increased risk of central nervous system malformations, in particular neural tube defects including anencephaly.[111]

In general, the evidence is that exposures to solvents are associated with birth defects, with primary evidence from occupational exposures.

Plasticizers and Birth Defects

Recent research suggests in utero exposure to plasticizers known as phthalates may cause subtle developmental effects in the genitalia of male infants. Phthalates are widely used in consumer products to soften plastics, carry fragrances, and act as solvents and fixatives. They are most commonly found in vinyl plastic products (eg toys, medical tubing and fluid bags, and certain building materials), a range of cosmetics and personal care products, and a variety of foods, including baby food and infant formula.

Although most investigations of congenital anomalies have focused on major structural defects, emerging epidemiology finds subtle developmental outcomes are also associated with exposure to environmental contaminants. New research has found that prenatal exposure to phthalates is associated with decreased anogenital distance (AGD) in male infants and children.[112] Anogenital distance is a subtle measure of normal male reproductive tract development, and a sensitive measure of prenatal antiandrogen exposure. The findings support previous studies of antiandrogenic activity of phthalates in rodents, but the low level of exposure in the present study suggests that humans may be more sensitive to these effects.[113,114]

PREGNANCY LOSS AND SELECT ENVIRONMENTAL CONTAMINANTS

Drinking Water Disinfection Byproducts and Pregnancy Loss

A number of drinking water contaminants, including selenium,[115] arsenic,[116-118] and nitrates,[119] have been associated with loss of pregnancy and other adverse birth outcomes. Perhaps, the most common drinking water contaminants to be linked with pregnancy loss in the United States, however, are byproducts of routine chemical drinking water disinfection. Disinfection byproducts (DBPs) form when chlorine or other disinfectants react with organic material (from the decomposition of leaves and other vegetation) naturally found in drinking water sources. They are often found at elevated levels, depending on the disinfection method and other variables, in municipal drinking water supplies, so that broad swaths of the population are exposed daily. Byproducts of chlorine-based treatment include the trihalomethanes (THMs; chloroform, bromoform, bromodichloromethane (BDCM), and dibromochloromethane) and the haloacetic acids (monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, monobromoacetic acid, and dibromoacetic acid). People are exposed to these byproducts through ingestion of drinking water as well as dermal absorption and inhalation from showering and other water usages.

The epidemiological evidence linking DBPs and reproductive effects is growing. In the 1980s, researchers began finding links between ingestion of tap water and spontaneous abortion. Retrospective studies indicated that women who reported drinking tap water were more likely to experience spontaneous abortions than those who reported drinking bottled water, but the potential for recall bias made these studies problematic.[120-124] One population-based case–control study in a Central North Carolina county found an increased risk of miscarriage in the highest sextile of THM concentration, but no overall dose–response association.[125]

More recently, a small number of prospective epidemiological studies have added to our understanding of the suggested links. A prospective cohort study of 5144 pregnant women in California measured water consumption and estimated THM exposure from utility measurements, finding that women who drank 5 or more glasses per day of cold tap water containing elevated levels of total THMs had a significantly increased risk of spontaneous abortion.[61] High BDCM was associated with spontaneous abortion both alone and after adjusting for the other THMs measured.

However, further analysis by Savitz et al, which includes more thorough and advanced measurements of exposure and spontaneous abortions did not, in general, find a relationship between DBPs and spontaneous abortions.[126] There was some suggestion that there were elevated risks from relatively high levels of BDCM, with women who had the highest exposures had a slightly elevated risk of spontaneous abortion.

Although the EPA had recently concluded that there is moderate evidence for associations with spontaneous

abortions, the Savitz study suggests that if there is a risk, it is relatively small for most routine exposures.[127] However, the EPA noted that THMs might also be associated with SGA and neural tube defects.[128]

Although most of the research on this topic has occurred in the United States, a recent population study in 3 regions of England looked at estimates of quarterly THM concentrations and 1 million birth records over a 6-year period. This study, the largest to date, found a significant association between total THMs and stillbirth and a similar association with chloroform alone.[62] The authors found no association with BDCM and total brominated THMs alone.

Recent epidemiological investigations have better estimated exposure to DBPs, but there remains a lack of individual exposure assessment for specific chemicals, leading to the possibility of confounding. Most studies examine single DBPs such as chloroform or BDCM, or groups such as THMs, whereas in reality people are exposed to complex mixtures of many DBPs and other contaminants.

Pregnancy Loss and dichlorodiphenyltrichloroethane

Animal models have found exposure to dichlorodiphenyltrichloroethane (DDT), a persistent chlorinated pesticide used extensively in the United States before 1972, increases fetal resorption or abortion.[129,130] Early epidemiological studies found higher levels of PCBs[131] and a variety of organochlorine pesticides[132] in women with miscarriages compared to women with a normal course of pregnancy. A more recent study analyzed levels of dichlorodiphenyldichloroethylene (DDE; a metabolite of DDT) in serum from 1717 women enrolled in the Collaborative Perinatal Project who had previous pregnancies and found that the odds of previous fetal loss increased in relation to DDE level.[64] Although suggestive of an effect, these results must be considered inconclusive because previous pregnancies ending in fetal loss could result in lower levels of serum DDE than those carried to term. Another analysis by the same investigators found a weak association between higher DDE levels and increased time to pregnancy.[65] An Italian study found the stillbirth rate elevated and the male:female ratio reversed in offspring of male DDT applicators.[66]

A pair of studies of female Chinese textile workers provides stronger evidence of a link between DDT/DDE and early pregnancy loss. A case–control study found an association between elevated levels of DDE in maternal serum and increased odds of spontaneous abortion after adjustment for age and body mass index.[63] A subsequent prospective cohort study focused on loss of pregnancy before clinical detection in newly married, childless, nonsmoking female Chinese textile workers who had never borne children. By assaying human chorionic gonadotropin (a sensitive marker of early pregnancy) in daily urine specimens, this study found that the odds of early pregnancy loss increased among those in the highest tertile of preconception serum DDT, with a linear trend of increasing odds with increasing total DDT.[67]

Other studies have been unsuccessful at finding associations between maternal exposure to DDT and recurrent miscarriage,[133,134] as well as paternal exposure and spontaneous abortion.[135] Overall, the evidence is considered merely suggestive, with more study needed.

Recurrent Miscarriage and Bisphenol-A, Meiotic Aneuploidy

Aneuploidy, a term that refers to chromosomal abnormalities such as Down syndrome, is the most common cause of first-trimester miscarriage. A small number of studies in animals have suggested that bisphenol-A (BPA), an estrogenic compound widely used in the production of polycarbonate plastics, dental sealants, and other applications, might be related to meiotic aneuploidy and recurrent miscarriage; and effects in male reproductive function.[136,137]

In light of the animal data, a small prospective case–control study evaluated measured levels of serum BPA and several antibodies and hormones in women with a history of 3 or more consecutive first-trimester miscarriages. Compared to healthy controls with no history of live birth or infertility, patients had significantly higher BPA levels and antinuclear antibodies.[68]

PRENATAL ORIGINS OF OTHER OUTCOMES AND CONDITIONS

Fetal Origin of Adult Disease

During the last two decades, chronic disease has replaced infectious disease as the major focus of public health concern. The top 4 leading causes of death in the United States are chronic diseases.[138] There remains much unknown about the etiology of many chronic conditions, which in most cases is probably multifactorial. Studies

from the 1990s found that effects on the fetal environment, such as through poor or inadequate nutrition, can result in an increased risk of adult onset of chronic conditions, such as coronary heart disease.[139-141] This has been called the fetal origins hypothesis (also known as the Barker theory), which proposes that external influences on the fetal environment can increase the risk of later disease in adulthood.

Diethylstilbestrol (DES)—a synthetic estrogen given to US women between 1938 and 1971 to prevent pregnancy complications illustrates the fetal origins of later in life disease. In utero DES exposure left mature female offspring at increased risk of clear cell adenocarcinoma of the vagina and cervix, breast cancer, structural reproductive tract anomalies, an increased infertility rate, and poor pregnancy outcomes, while male offspring have an increased incidence of genital abnormalities and a possibly increased risk of prostate and testicular cancer.[142] These observed human effects have been confirmed in numerous animal models, which have also predicted changes later found in DES-exposed humans, such as increased incidence of uterine fibroids, oviductal malformations, and second generational effects such as increased menstrual irregularities and possibly ovarian cancer in DES granddaughters and increased hypospadias in DES grandsons.[143] Diethylstilbestrol shows the adverse effects of fetal exposures to synthetic chemicals may not be apparent at birth or even for many years afterward, and that continued monitoring of this cohort of exposed children and grandchildren is necessary to inform potential effects of prenatal exposures to other contaminants.

Neurodevelopmental Effects

There is extensive evidence that in utero exposure to various environmental agents has adverse effects on fetal brain and neurological development, as the developing fetal brain can be vulnerable to exposures to environmental contaminants,[144,145] with lasting effects on intelligence and behavior.[146]

It has been estimated that about 1 in 6 children has a developmental disability,[147] though there is no tracking system to provide more precise information on trends or prevalence. Most, including attention-deficit/hyperactivity disorder (ADHD), learning disabilities, autism, and mental retardation, affect the nervous system. In 2004, nearly 5 million children ages 3 to 17 (8%) had a learning disability and 7% had ADHD.[148]

Reviews of studies find that several widespread environmental contaminants can damage the developing brain and nervous system, with prenatal exposures being an important window of susceptibility.[146,147] Prenatal exposure to methyl mercury through maternal consumption of mercury-contaminated seafood have found adverse effects on intelligence[149,150] and decreased functioning in the areas of language, attention, and memory in the children.[151] Particularly, high levels of exposure to mercury in the womb have been found to cause mental retardation.[152,153]

There are a number of studies finding that prenatal exposure to PCBs through mother's eating contaminated food is associated with neurodevelopmental effects in the children, including lowered intelligence and behavioral deficits such as inattention and excessive reaction to stimulation (behaviors observed in children with ADHD).[154-159]

Exposure to lead is clearly linked to neurological effects in children, such as learning problems, reduced intelligence, and cognitive development, ADHD,[160] and hyperactivity and distractibility[161-163]; increases the likelihood of dropping out of high school, having a reading disability, lower vocabulary, and lower-class standing in high school[164]; and increases the risk for antisocial and delinquent behavior.[165-168] Most of the studies of lead focus on exposure after birth during childhood, though several studies have evaluated the effects of prenatal exposure to lead. In general, the studies suggest that there is less contribution of prenatal exposure to lead, though it still represents an important preventable source of exposures.[165,169]

Numerous toxicological studies link both prenatal and postnatal exposure to organophosphate pesticides to neurodevelopmental effects.[170] A recent study of brominated flame retardants found that 2 of these compounds caused adverse effects on behavior, learning, and memory in animals.[171]

Parkinson Disease and Pesticides

Parkinson disease, which occurs later in life, ranks among the most common late life neurodegenerative diseases behind Alzheimer's disease, with an estimated prevalence of approximately 1 in 100.[172] The cause of Parkinson disease is unknown, and studies suggest that genetic factors do not play a major role in causing Parkinson's, particularly when the disease begins after age 50.[173]

Evidence is increasingly pointing to an environmental role in the causation of Parkinson's. One area of research has suggested that fetal exposure to certain pesticides may set the stage for later development of Parkinson's.[174]

Studies in animals have found that perinatal exposure to low levels of certain pesticides have led to persistent alterations in neurochemistry in offspring.[175] Some authors have concluded that these alterations induce a ''silent'' state of dopamine dysfunction that may leave the individual vulnerable later in life.[176]

DISCUSSION

Where Does the Evidence Lead?

The available scientific evidence suggests a variety of links between environmental pollutants and a range of adverse birth and pregnancy outcomes. Some links, such as evidence of neurodevelopmental effects of lead, mercury, and PCBs in humans, are established, some are likely, such as occupational exposure to solvents and birth defects, others are likely though some uncertainty remains on the nature and extent, such as air pollution and adverse birth outcomes, and some are suggestive, with further study required, such as water contamination from DBPs and pregnancy lost, what is clear is the developing fetus is exposed to a wide range of potentially toxic environmental contaminants, and that fetal development is vulnerable to insult. Although further research is needed, steps can be taken now to prevent adverse health effects.

We can strengthen the evidence by drawing upon data from the animal literature. This review focuses primarily on epidemiologic studies in humans; space did not allow a thorough review here of the animal evidence. A future review of animal studies would be critical for several reasons. First, there are many chemicals for which we have concerns, but there is insufficient human data to fully assess their impacts, often due to limited exposure data, limited human health effects data, or both. Animal studies provide much needed information on potential adverse effects from environmental chemicals. In addition, they can support a prevention-oriented approach to addressing potentially harmful chemicals, if effects in animals are looked for prior to exposures in the human population.

Finally, animal studies can be a more efficient use of research resources, because of difficultly in obtaining sufficient study size to evaluate environmental contaminants and adverse birth outcomes in humans. Animal research also allows for assessing mechanisms of harm, providing both insights into other chemicals acting through a similar mechanism and into informing future research priorities.

Animal studies showing decreased birth weight and pregnancy loss in mice from exposure to perfluorooctane sulfonate (PFOS) compounds demonstrate the importance of animal data.[177,178] Perfluorooctane sulfonate is present at low levels in the entire US population. Although risks to an individual may be small, ubiquitous exposures over a large population can translate into large numbers of adverse outcomes. Animal studies of PFOS were critical in the announced phase out of these chemicals.[179]

Research

There are several critical areas of research needed to advance this field. We need to better understand particular windows during pregnancy when the fetus is most vulnerable to specific contaminants, and during which prevention measures will be most effective. More attention to preconception exposures—both maternal and paternal—is also needed. In addition, future research should focus on the interaction of environmental factors with known social and behavioral determinants of pregnancy outcome, such as socioeconomic status, nutrition, smoking and alcohol, and delaying pregnancy.

A critical issue identified in this review is the need for support for continued improvements in study design. Many insights have been gained by bringing together data from the environment and health fields (eg, air pollution epidemiology), and further efforts in this area are warranted. In addition, the increasing availability of other ways to measure and characterize exposure, either through modeling efforts, statistical improvements, environmental monitoring efforts, or biomonitoring, should be harnessed to improve exposure assessment methods, which can bolster study design and insights into the role of environment on perinatal health.

Several efforts are now underway that will provide a clearer picture of the impacts of environmental exposures on birth outcome. The National Children's Study is a major prospective study planned to follow the health and development of more than 100 000 children from before birth until age 21, taking into account natural and man-made environmental factors; biological and chemical factors; physical surroundings and geography; social, cultural, and behavioral influences; and genetics.[180] Another related initiative is the CDC's National Environmental Public Health Tracking Program.[181] This program focuses on efforts to gather detailed, nationwide trend data to monitor environmental hazards, human exposures, and health effects for factors relevant to

environmental health. There are some recently available trend data, such as through EPA's America's Children and the Environment.[146] However, current efforts rely on existing data sources, which are limited. For example, there is only limited monitoring of birth defects by geographic location through CDC's birth defects program. Comprehensive national tracking of additional environmentally relevant birth outcomes, and continued support and funding for all these activities, is critical to understanding and addressing the effects of environmental factors on pregnancy.

Prevention: The Health Care Provider's Role

There is an important role for reproductive health care providers in preventing fetal and perinatal exposures to environmental hazards and supporting environmental public health policies to ensure healthy pregnancies. Although there may be some influence of publication bias, which could result in more positive studies being published, considering the state of the evidence in a prevention context suggests that we should err on the side of reducing exposures that may pose a risk to the developing fetus. Part of reaching the public and public health professionals about these issues involves working with prenatal health care providers. Obstetrics/gynecology and other reproductive health professionals have generally not been working on these issues in both clinical and policy settings, likely because of insufficient information, training, and tools. The practice of pediatrics offers a valuable model—and some helpful resources—for greater involvement of reproductive health care providers.

For example, for more than half a century, the American Academy of Pediatrics has had a Committee on Environmental Health (COEH; http://www.aap.org/visit/cmte16.htm) studying environmental issues of concern to children and recommending actions and guidelines for pediatric practice and policy. The COEH has also published a clinicians' desk reference, Pediatric Environmental Health, which contains tools for identifying, treating, and preventing pediatric environmental health hazards. Gynecologic and obstetric associations may want to consider establishing similar committees to make recommendations and develop educational materials for clinicians in reproductive health.

Another need is for professional fellowship training programs designed to train clinicians to specialize in environmental health issues affecting women of child-bearing age. Again, pediatrics provides a model. The Ambulatory Pediatric Association offers a 3-year pediatric environmental health fellowship aimed at individuals who excel in community-based and primary care research.

In the absence of such specialized programs, interested clinicians can take advantage of existing resources related to clinical intervention. Federal agencies have developed some such resources. For example, the Agency for Toxic Substances and Disease Registry offers an online guide to taking an exposure history (http://www.atsdr.cdc.gov/HEC/CSEM/exphistory/index.html), and the EPA offers continuing education in environmental health topics at http://www.epa.gov/ogwdw/healthcare/supp.html.

Finally, health care providers can promote public health policies that will improve birth outcomes at a larger scale. Key needs at the national and state level include increasing the knowledge base about the potential harm of chemicals before exposure occurs in utero, similar to policies which govern introduction of new pharmaceuticals into the market place. Increased testing needs to be coupled with new technologies to achieve faster results on potential toxicity. Some of these new ideas are being incorporated into new legislation in by the European Union through the Registration, Evaluation, and Authorization of Chemicals (REACH), will increase the number of chemicals with basic toxicity information.[182] Similar efforts are underway in some states, for example in a recent white paper commissioned by members of the legislature recommends a similar strategy as REACH in California.[183]

Continued research, education and improved public health policy will help spur public health-oriented evaluation of chemicals within a regulatory and legal framework that promotes prevention will benefit the health of this and future generations.

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