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Environmental influences on reproductive health: the importance of chemical exposures

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Chemical exposures during pregnancy can have a profound and life-long impact on human health. Because of the omnipresence of chemicals in our daily life, there is continuous contact with chemicals in food, water, air, and consumer products. Consequently, human biomonitoring studies show that pregnant women around the globe are exposed to a variety of chemicals. In this review we provide a summary of current data on maternal and fetal exposure, as well as health consequences from these exposures. We review several chemical classes, including polychlorinated biphenyls, perfluoroalkyl substances, polybrominated diphenyl ethers, phenols, phthalates, pesticides, and metals. Additionally, we discuss environmental disparities and vulnerable populations, and future research directions. We conclude by providing some recommendations for prevention of chemical exposure and its adverse reproductive health consequences. (*Fertil Steril*® 2016;106:905–29. ©2016 by American Society for Reproductive Medicine.)

Key Words: Chemical, environmental chemical, environmental exposure, pregnancy, reproductive health

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Scientific evidence has shown the adverse impacts of exposure to toxic environmental chemicals to human reproduction (1). Chemical exposures, especially during critical and sensitive windows of development such as pregnancy, can lead to a myriad of health consequences that can manifest across individuals' lifespan and potentially be transmitted to future generations (1, 2). Chemical exposures that occur during pregnancy can cross the placenta and can accumulate in the fetus (3). Accordingly, the next generations are born "prepolluted" (4) owing to these preconception and prebirth exposures. Preventing

harmful exposures to environmental chemicals is, therefore, a priority for reproductive health professionals around the world (5).

Industrial chemicals are present in our daily life and are ubiquitous in food, water, air, and consumer products. World chemical manufacturing has grown rapidly over the past few decades (6, 7), with a projected 3.4% annual rate in production increase until 2030 (7). Among the estimated 70,000–100,000 commercially available chemicals, almost 5,000 of them are produced in volumes exceeding 1 million tons per year (8). In the United States, the total reported production volume (domestically

manufactured and imported) of industrial chemicals in 2012 was 9.5 trillion pounds (4.31 trillion kg)—equivalent to more than 30,000 pounds (13,000 kg) for every American (5, 9). As of 2016 more than 65,000 chemical substances are listed for use by the US Environmental Protection Agency (10). Approximately 3,000 of these chemicals have annual production and importation above 1 million pounds (11). Unlike pharmaceuticals that require extensive in vitro and in vivo toxicity testing as well as human experimental studies before entering the marketplace and clinic, existing and new synthesized industrial chemicals currently can enter the marketplace, homes, schools, workplaces, and communities with only limited or even no assessment on their reproductive or other related toxic effects (12, 13). Recently (June 2016), President Obama signed the Frank R. Lautenberg Chemical Safety for the 21st Century Act, an amendment to the Toxic Substances Control Act (TSCA), which is the main law by which the government oversees industrial chemicals.

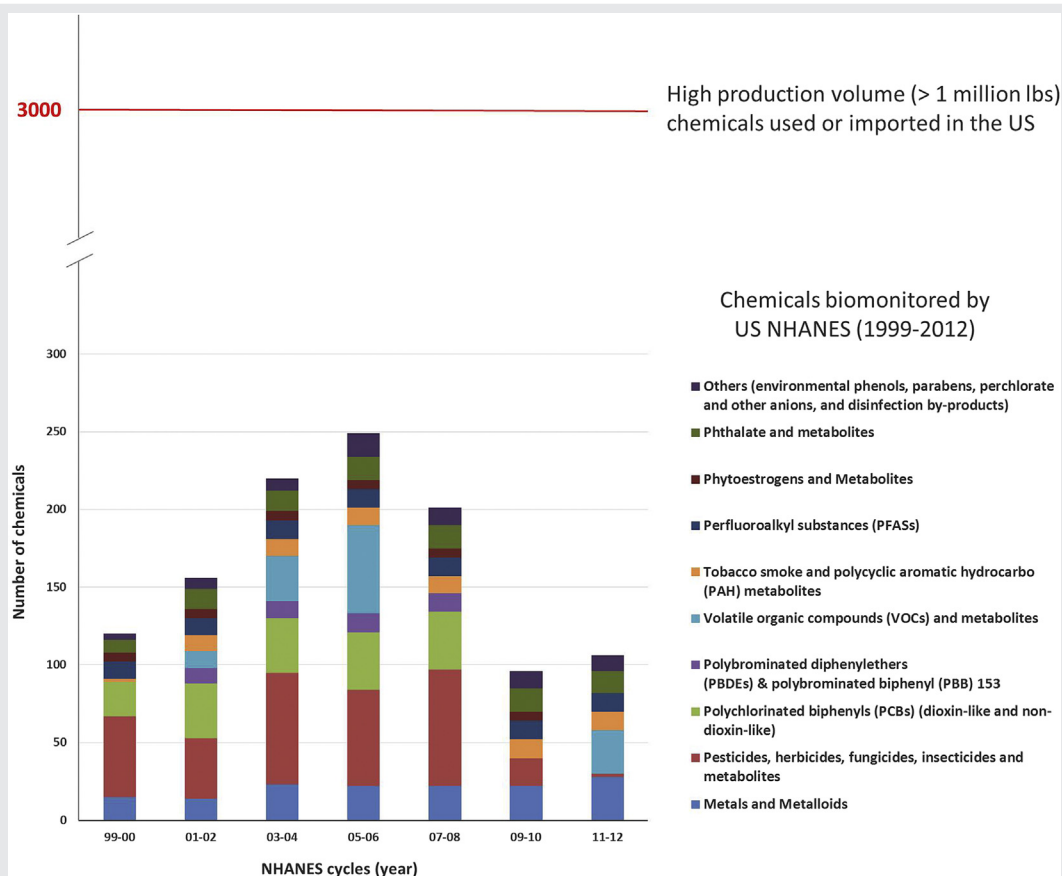
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FIGURE 1



Chemicals that are biomonitored by the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2012 based on the CDC 4th National Report on Human Exposure to Environmental Chemicals (Updated Tables, February 2015) and CDC NHANES website (www.cdc.gov/nchs/nhanes.htm) as of April 2016. Note: There will be more chemicals added for some biannual cycles in the future, especially later cycles, owing to delay in data analyses and releasing. Not all the chemicals currently biomonitored by NHANES are high production volume chemicals.

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While there are significant changes, the law still does not require minimum set of data to be produced by manufacturers for new or existing chemicals, and its effectiveness remains to be evaluated. Further, there are not comprehensive data on where chemicals are used, so it is difficult to identify sources of exposures and the extent of exposures in the population. There are some data sources that allow characterization of certain exposures, such as air pollution monitoring, some monitoring of fish, and some portion of the water and food supply (14). In the United States there is a national biomonitoring program run by the US Center for Disease Control and Prevention (CDC) using the National Health and Nutrition Examination Survey (NHANES), which has increased the number of chemicals biomonitored over the past 15 years (Fig. 1) (15, 16).

Although we have made great progress in understanding the importance of chemicals in reproductive health and understanding exposures to pregnancy, we still have yet to comprehensively understand the full scope of the exposures and outcomes that may affect reproductive health. Understanding exposures is critical to both identify potential health risks and identify opportunities for intervention and preven-

tion of harmful chemical exposures. It is being increasingly recognized in numerous initiatives, including the Exposome (17), Precision Medicine Initiative (18), Genes, Environment and Health Initiative (19), and Children's Health Exposure Analysis Resource (20). Thus, using illustrative examples, this article aims to review the current evidence on environmental chemical exposures, including synthetic chemicals and metals, in pregnant women. We first provide an updated view on the relationship between environmental chemical exposure during pregnancy and potential adverse health consequences. We then summarize the current knowledge on the maternal body burden and fetal exposure to different environmental chemicals. After discussion on environmental disparities and future research directions, we conclude the article with recommendations for prevention of chemical exposure and its adverse health consequences.

HEALTH CONSEQUENCES OF PRENATAL CHEMICAL EXPOSURE

Chemical exposures have been linked to a range of adverse reproductive and developmental outcomes, including fertility-

TABLE 1

Examples of exposure sources and pathways and selected health impacts of prenatal exposure to environmental contaminants.

Chemical	Exposure sources and pathways	Selected health impact (reproduction, poor birth outcome, neurodevelopment, and cancer)
PCBs	Used as industrial insulators and lubricants; banned in the 1970s, but persistent in the aquatic and terrestrial food chains, which results in exposure by ingestion	Decreased semen quality (21) Low birth weight (22) Development of attention deficit–hyperactivity disorder–associated behavior (23) Reduced intelligence quotient (24)
PFAS	Widely used man-made organofluorine compounds with many diverse industrial and consumer product applications; examples are PFOS and PFOA, which are used in the manufacture of nonstick Teflon and other trademark cookware products and in food-contact packaging to provide grease, oil, and water resistance to plates, food containers, bags, and wraps that come into contact with food; persist in the environment; occupational exposure to workers and general population exposure by inhalation, ingestion, and dermal contact	Pregnancy-induced hypertension and preeclampsia (25) Reduced birthweight (26, 27) Reduced fetal growth (28) Increased risk for thyroid disease in children (29)
PBDEs	Flame retardants that persist and bioaccumulate in the environment; found in furniture, textiles, carpeting, electronics, and plastics that are mixed into, but not bound to, foam or plastic	Impaired neurodevelopment (30) Reduction in sustained attention and fine manipulative abilities (31)
Phenols	Examples are BPA, triclosan, and parabens BPA: Chemical intermediate for polycarbonate plastic and resins; found in consumer products and packaging; exposure through inhalation, ingestion, and dermal absorption	Female reproductive toxicity (32) (e.g., recurrent miscarriage [33]) Aggression and hyperactivity in female children (34) Impaired behavioral regulation (anxious, depressive, and hyperactive behaviors) in girls aged 3 y (35) Reduced neonatal thyroid-stimulating hormone in boys (36) Decreased thyroxine concentrations ^a (37, 38)
	Triclosan: Synthetic chlorinated aromatic compound with antibacterial properties; used in many consumer products such as antibacterial soaps, deodorants, toothpastes, cosmetics, fabrics, plastics, and other products; exposure through ingestion, dermal contact, and consumption of contaminated food and drinking water	
	Parabens: Most commonly used preservatives in cosmetic products, including makeup, moisturizers, hair care products, and shaving products; also used in foods and drugs; exposure through dermal absorption and ingestion	Found to have estrogenic activity in vitro (39) but further studies needed for their reproductive and developmental health impacts
Phthalates	Synthetically derived; used in a variety of consumer goods such as medical devices, cleaning and building materials, personal care products, cosmetics, pharmaceuticals, food processing, and toys; exposure occurs through ingestion, inhalation, and dermal absorption	Shortened gestational age (40) Male reproductive tract development (reduced anogenital distance) (41) Impaired neurodevelopment (41) Reduction in executive function at age 4–9 y (42) Alterations of epigenetic signatures in the DNA (DNA methylation) of the placenta and of the newborns (45) Reduced intelligence quotient (46) Increased risk of emotional problems in 7- to 8-year-old boys (47)
Heavy metals	Cadmium: Used in batteries, pigments, metal coatings, and plastics; for nonsmoking public, exposures mainly occur through diet (shellfish, organ meats, grains such as rice and wheat, leafy vegetables, and some root crops such as potato, carrot, and celery) (43, 44); for smokers, exposure mainly occurs through tobacco smoke	
	Lead: Occupational exposure occurs in battery manufacturing/recycling, smelting, car repair, welding, soldering, firearm cleaning/shooting, stained-glass ornament/jewelry making; nonoccupational exposure occurs in older homes where lead-based paints were used, in or on some toys/children's jewelry, water pipes, imported ceramics/pottery, herbal remedies, traditional cosmetics, hair dyes, contaminated soil, toys, costume jewelry	Alterations in genomic methylation (48) Impaired neurodevelopment (decrease in cognitive function, decreased intelligence quotient, increased incidence of attention-related behaviors and antisocial behavior problems, and decreased hearing measured in children, reduced intellectual development) (49, 50)
	Mercury: Coal-fired power plants are largest source in the United States; primary human exposure by consumption of contaminated seafood	Reduced cognitive performance (51, 52) Impaired neurodevelopment (53, 54) Reduced psychomotor outcomes (55) Neurobehavioral deficits (56)
Perchlorate	Used to produce rocket fuel, fireworks, flares, and explosives and can also be present in bleach and in some fertilizers; primary pathway for exposure is through drinking water caused by contaminated runoff	Altered thyroid function in newborns (57)

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TABLE 1

Continued.

Chemical	Exposure sources and pathways	Selected health impact (reproduction, poor birth outcome, neurodevelopment, and cancer)
Pesticides	Applied in large quantities in agricultural, community, and household settings; in 2007, >1.1 billion pounds of active ingredients were used in the United States (58); can be ingested, inhaled, and absorbed by the skin; pathways of exposure include food, water, air, dust, and soil	Impaired fetal growth (59) Impaired cognitive development (60, 61) Impaired neurodevelopment: increased risk of pervasive developmental disorder at age 2 y (62), increase in attention problems and attention deficit hyperactivity disorder behaviors at age 3 y (63), and reduction in working memory capabilities and intelligence quotient at age 7 y (60, 64) Increased susceptibility to testicular cancer (65) Childhood cancers (leukemia [66–68] and brain tumor [69]) Spontaneous abortion and fetal loss (70–75) Decreased fetal and birthweight (76, 77) Congenital malformations (75, 77–81)
Solvents	Liquids or gases that can dissolve or extract other substances; used 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; examples are benzene, gasoline, ethyl alcohol, methanol, phenol, styrene, toluene, trichloroethylene, and xylene; exposure occurs through inhalation, dermal absorption, and ingestion	

Note: Modified from Sutton et al. (82), with permission from Elsevier.
^a Based on animal studies.

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related affects, adverse pregnancy outcomes, and adverse health effects in childhood, such as neurodevelopmental effects (Table 1). A key adverse health impact of concern to human reproduction and development is the endocrine-disrupting property of many chemicals, particularly affecting hormones that are critical to proper development. These chemicals include polychlorinated biphenyls (PCBs), perfluoroalkyl substances (PFAS), polybrominated diphenyl ethers (PBDEs), bisphenol A (BPA), some current-use pesticides, metals, and others (83). Exposure to environmental contaminants, especially during “critical” and “sensitive” periods of development such as during pregnancy, can heighten their potential impact. For example, prenatal exposure to lead and methyl mercury can lead to developmental neurotoxicity of the fetus (Table 1) (84). Sometimes, such negative health impact can be transgenerational and becomes apparent only decades after the initial exposure, as in the case of the drug diethylstilbestrol, a potent synthetic estrogen (5). The daughters of pregnant women who took diethylstilbestrol were found to have higher risks of infertility, poor pregnancy outcomes, and breast cancer (85), whereas the sons of these women have increased the risk of hypospadias (86, 87). Such exposures during a window of vulnerability, even of small quantity, may trigger adverse health consequences that can manifest across the lifespan of individuals and generations (5). Despite these previous studies and discoveries, there is a paucity of studies on the effects of chemicals and reproductive outcomes, especially with regard to the number of chemicals and their potential harm.

MATERNAL CHEMICAL BODY BURDEN

Pregnant women can be exposed to environmental chemicals in food, water, air, and consumer products, as well as soil and dust; such exposure can happen via multiple pathways, including ingestion, inhalation, and dermal contact (Table 1). Biomonitoring of suitable human tissue, such as urine and blood,

has been widely used for examining the chemical burden and providing a measure of the internal doses integrated across different exposure pathways (2, 88). Starting from 1999/2000 the CDC has been biomonitoring several groups of environmental chemicals using NHANES, including metals, pesticides, PCBs, PBDEs, volatile organic compounds, tobacco smoke, polycyclic aromatic hydrocarbon metabolites, perfluoroalkyl substances, phthalate and metabolites, and many others (Fig. 1) (15, 16). The approximately 250 chemicals that we have biomonitoring data on over the years only make up a small fraction of the vast number of chemicals that we may be exposed to every day. In our own previous work we have evaluated chemical exposures among pregnant women using the NHANES 2003–2004 data and found that virtually all pregnant women in the United States are exposed to at least 43 different chemicals (89).

As illustrations, we have collected information on chemical concentrations measured in biomonitoring of pregnant women from more than 30 countries around the world on the most commonly measured chemicals or their metabolites (Tables 2–8). We focused on studies that have mothers’ biospecimens taken during pregnancy or at delivery and cord blood samples collected at delivery unless otherwise noted, and on studies published in the past 5 years for heavy metals because another study has summarized blood cadmium, lead, and mercury levels from studies published from 2000 onward (201). We focus this review on common classes of chemicals and organize the following discussion according to chemical properties: persistent and bioaccumulative halogenated chemicals, less persistent and bioaccumulative chemicals, pesticides, and metals and organometallic chemicals. For each class of chemicals, we first briefly summarize the exposure sources and its health effect and then discuss its concentrations from biomonitoring studies.

TABLE 2

Example studies of concentration of selected PCBs in pregnant women, by location and study years.

Location	Study years	N	Sample	Median concentration (ng/g lipid)		Congeners included in Σ PCBs	First author, year (reference)
				PCB-153	Σ PCBs		
North America							
US	1959–1965	593	MS	1.7 mmol/L	7.9 mmol/L	28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203	McGlynn, 2009 (90)
US (California)	1960–1963	289	MS	0.79 μ g/L			Cohn, 2011 (91)
US (California)	1964–1967	399	MS	133	616	101, 105, 110, 118, 137, 138, 153, 156, 170, 180, 187	James, 2002 (92)
US (Massachusetts)	1993–1998	573	CS		0.19 ng/g	118, 138, 153, 180	Sagiv, 2010 (23)
US (Illinois, Chicago)	1993–1998	252	MS	86			McGraw, 2009 (93)
Canada (Nunavik)	1995–2001	159	MP	105.3 (GM)	313.2 (GM)	28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187	Muckle, 2001 (94)
		98	CP	86.9 (GM)	279.9 (GM)		
Canada (Southwest Quebec)	N/A	39 (1st Tri)	MP	0.07 μ g/L	0.33 μ g/L	28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187	Takser, 2005 (95)
		145 (2nd Tri)	MP	0.08 μ g/L	0.35 μ g/L		
		101 (at delivery)	MP	0.09 μ g/L	0.39 μ g/L		
		92 (CP)	CP	0.02 μ g/L	0.16 μ g/L		
US (New York)	1996–1997	79	MS	0.26 ng/g			Bloom, 2007 (96)
US (California, Salinas)	1999–2001	24	MP	4.4			Bradman, 2007 (97)
US (nationwide)	2003–2004	75	MS	8.8		118, 138 and 158, 153, 180	Woodruff, 2011 (89)
US (Ohio)	2003–2006	175	MS	11.0			Braun, 2014 (98)
Canada	2005–2007	173	MS	4.7–41 (GM)			Curren, 2014 (99)
Canada (Quebec)	2007–2008	349	MP	8.0	18.9		Serme-Gbedo, 2016 (100)
US (California)	2010–2011	77	MS	3.0			Morello-Frosch, 2016 (in preparation)
		63	CS	4.4			
Europe							
The Netherlands and Germany (GRD cohort)	1990–1995	523	CP/CS	150.0 ng/L			Casas, 2015 (101)
Faroe Islands (FAROES2 cohort)	1994–1995	173	MS	394.4 ng/L			Casas, 2015 (101)
Sweden	1994–1995	57	MS	430.0			Fångström, 2005 (102)
Spain (INMA cohort)	1997–2008	868	MS	93.8 ng/L			Casas, 2015 (101)
		1,254	CS	135.2 ng/L			
The Netherlands	1998–2000	97	CS	89.8	290.0	105, 118, 138, 146, 153, 156, 170, 180, 183, 187	Berghuis, 2013 (103)
Germany (Duisburg)	2000–2002	227	MWB	115.2 ng/L			Casas, 2015 (101)
The Netherlands	2001–2002	62	MS	63.0			Roze, 2009 (31)
Belgium (Flanders, FLEHSI cohort)	2002–2004	1,061	CP	60.0 ng/L			Casas, 2015 (101)
Eastern Slovakia	2002–2004	966	MS	143.0	415.0	28, 52, 101, 105, 114, 118, 123, 138, 149, 153, 156, 157, 163, 167, 170, 171, 180, 189	Jusko, 2012 (104)
Greenland	2002–2004	546	MS	126.4 ng/L			Casas, 2015 (101)
Poland	2002–2005	84	CS	43.4 ng/g fat (AM)			Hernik, 2013 (105)
France (Brittany)	2002–2006	396	CS	110.0 ng/L			Casas, 2015 (101)

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TABLE 2

Continued.

Location	Study years	N	Sample	Median concentration (ng/g lipid)		Congeners included in Σ PCBs	First author, year (reference)
				PCB-153	Σ PCBs		
Poland (Warsaw)	2003–2004	199	MS	15.3 ng/L			Casas, 2015 (101)
Ukraine (Kharkiv)	2003–2004	575	MS	28.2 ng/L			Casas, 2015 (101)
Spain (Valencia)	2003–2005	157	MS		137.0	28, 52, 101, 118, 138, 153, 180	Lopez-Espinosa, 2009 (106)
Spain (Valencia)	2004–2006	494	CS	113.0 ng/L	354.0 ng/L	118, 138, 153, 180	Lopez-Espinosa, 2011 (107)
Italy (Brescia)	2006	70	MS	54.0	198.2	28, 31, 52, 74, 99, 101, 105, 114, 118, 123, 128, 138, 146, 153, 156, 157, 167, 170, 172, 177, 180, 183, 187, 189, 194, 196, 201, 203, 206, 209	Bergonzi, 2009 (108)
Greece (RHEA cohort)	2007–2008	1,115	MS	47.4 ng/L			Casas, 2015 (101)
Northern Norway	2007–2009	515	MS	24.8 (GM)			Veyhe, 2015 (109)
Greenland	2010–2011, 2013	207	MS	57.0			Long, 2015 (110)
The Netherlands	2011–2013	51	CP	30.0			Cock, 2014 (111)
Others							
Mexico	2005–2006	240	MP	3.6 (GM)			Adlard, 2014 (112)
Caribbean (10 countries)	2008–2011	438	MS	7.0 (GM)			Forde, 2014 (113)
South Korea	2011	104	MS	8.4	23.5	18, 28, 33, 44, 52, 70, 101, 105, 118, 128, 138, 153, 170, 180, 187, 194, 195, 199 and 206	Kim, 2015 (114)
			CS	10.5	34.7		
China (Wenling, e-waste area)	2011	64	MS	8.3	26.2	28, 99, 118, 138, 153, 180	Lv, 2015 (115)

Note: If several studies included participants from the same cohort, the one with the largest sample size was included. This table is for illustrative purpose and should not be taken as an exhaustive list of relevant biomonitored studies. CP = cord plasma; CS = cord serum; MP = maternal plasma; MS = maternal serum; MWB = maternal whole blood.

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Persistent and Bioaccumulative Halogenated Chemicals

Many chemicals measured and found prevalently in pregnant women are persistent and bioaccumulative halogenated chemicals such as PCBs, PFAS, PBDEs, and organochlorine pesticides (OCPs) such as dichlorodiphenyltrichloroethane (DDT). Because of their chemical properties they persist and can bioaccumulate up the food chain. Thus, they can remain in the environment and can be a source of exposure and pose risk to the health of humans and wildlife for many years. Even after their production and use are discontinued, it may take many years before their concentrations have sufficiently declined to minimal levels that are of less concern to human health (244). For example, despite being banned in the United States after 1979, several PCBs (118, 138 and 158, 153, 180) were still detected in nearly 100% of pregnant women from the NHANES 2003–2004 study (89). Polychlorinated biphenyls had once been used as industrial insulators and lubricants and have been shown to link to low birth weight (22) and poorer neuro-

development outcomes (23) (Table 1). Because they persist in the aquatic and terrestrial food chains, high levels of PCBs were documented among Inuit pregnant women living in Nunavik (Arctic Quebec, Canada), owing to high consumption of fish and marine mammals (94). Fortunately, the maternal concentration of PCB-153, the main contributor of the overall PCB level, has been declining over the years, though with some variability across countries (Table 2).

Perfluoroalkyl substances, especially perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), were used in the manufacture of nonstick cookware products and in food-contact packaging and have been linked to reduced birth weight (26, 27) and fetal growth (28) (Table 1). They are detected in the serum of 90%–100% of pregnant women (3). One study examined the temporal changes in the levels of PFAS among California women over the past 50 years and found a significant drop of PFOS level from the 1960s to 2009, which is consistent with the phase-out of the perfluorooctyl manufacturing practice in the United States in 2002 (245). The

TABLE 3
Example studies of concentration of selected PFAS in pregnant women, by location and study years.

Location	Study years	N	Sample	Median concentration (µg/L)		First author, year (reference)
				PFOA	PFOS	
North America						
US (nationwide)	2003–2004	76	MS	2.6	12.0	Woodruff, 2011 (89)
US (Ohio)	2003–2006	349	MS	5.5 (GM)	13.3 (GM)	Donauer, 2015 (116)
USA (Maryland)	2004–2005	293	CS	1.6	5.0	Apelberg, 2007 (117)
Canada (Ontario)	2004–2005	101	MS (2nd Tri)	2.1	16.6	Monroy, 2008 (118)
			MS (at delivery)	1.8	14.5	
		105	CS	1.6	6.1	
Canada (Alberta)	2005–2006	252	MS	1.5	7.8	Hamm, 2010 (119)
Canada (Ottawa)	2005–2008	100	CS	1.6	5.0	Arbuckle, 2013 (120)
Canada (10 cities)	2008–2011	1,743	MP	1.7	4.7	Velez, 2015 (121)
US (California)	2010–2011	77	MS	0.47	2.4	Morello-Frosch, 2016 (in preparation)
			CS	0.39	2.2	
Europe						
UK (Avon)	1991–1992	447	MS	3.7	19.6	Maisonet, 2012 (122)
Denmark (nationwide)	1996–2002	1,399	MP (1st Tri)	5.6 (AM)	35.3 (AM)	Fei, 2007 (123)
			MP (2nd Tri)	4.5 (AM)	29.9 (AM)	
			CP	3.7 (AM)	11.0 (AM)	
Arctic Russia	2001	7	MB	wb: 0.89	wb: 5.79	Hanssen, 2013 (124)
				pl: 1.61	pl: 11.0	
			CB	wb: 0.49	wb: 1.88	
				pl: 1.00	pl: 4.11	
Uzbekistan	2002	10	MB		wb: 0.24	
						pl: 0.23
Norway (nationwide)	2003–2004	901	MP	2.2	13.0	Whitworth, 2012 (26)
Greenland	2010–2011, 2013	207	MS	1.2	10.2	Long, 2015 (110)
Denmark (Odense)	2011	200	MS	1.8	8.4	Vorkamp, 2014 (125)
The Netherlands	2011–2013	64	CP	1.6	0.9	Cock, 2014 (111)
Others						
Japan (Hokkaido)	2002–2005	428	MS	1.3	5.2	Washino, 2009 (27)
Taiwan	2004–2005	429	CP	1.8 (GM)	5.8 (GM)	Chen, 2012 (126)
China (Guiyu, e-waste recycling area)	2007	108	MS	17.0		Wu, 2012 (127)
China (Chaonan)		59		8.7		
China (Jiangsu)	2009	50	MS	MS: 1.3	MS: 2.9	Liu, 2011 (128)
			CS	CS: 1.1	CS: 1.5	
South Korea (Gyeongbok county)	2011	59	MS	MS: 2.6	MS: 9.4	Lee, 2013 (129)
			CS	CS: 2.1	CS: 3.2	

Note: If several studies included participants from the same cohort, the one with the largest sample size was included. This table is for illustrative purpose and should not be taken as an exhaustive list of relevant biomonitored studies. CB = cord blood; CP = cord plasma; CS = cord serum; MB = maternal blood; MP = maternal plasma; MS = maternal serum; pl = plasma; wb = whole blood.

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TABLE 4

Example studies of concentration of selected PBDEs in pregnant women, by location and study years.

Location	Study years	N	Sample	Median concentration (ng/g lipid)		Congeners included in ∑ PBDEs	First author, year (reference)
				BDE-47	∑ PBDEs		
North America							
US (California, Salinas)	1999–2000	416	MS	15.2	24.6 26.9	47, 99, 100, 153 17, 28, 47, 66, 85, 99, 100, 153, 154, 183	Castorina, 2011 (130)
US (Indianapolis)	2001	12	MS CS	28.0 25.0	37.0 39.0	47, 99, 100, 153, 154, 183	Mazdai, 2003 (131)
US	2001	210	CB	11.2			Herbstman, 2010 (30)
US (Ohio)	2003–2006	349	MS	20.0 (GM)	37.1 (GM)	47, 99, 100, 153	Donauer, 2015 (116)
US (nationwide)	2003–2004	75	MS	23.7			Woodruff, 2011 (89)
Canada (Ontario)	2004–2005	97	MS (24–28 gws; at delivery)	24.2; 23.3	52.1; 50.1	17, 28, 47, 66, 99, 100, 153, 154, 183	Foster, 2011 (132)
Canada	2005–2007	173	CS MS	50.5 1.5–15.0 (GM)	100.0		Curren, 2014 (99)
Canada (Ottawa)	2005–2008	98–114	CB	<LOD			Arbuckle, 2013 (120)
Canada (Quebec)	2007–2008	349	MP	21.2	33.0	47, 99, 100, 153	Serme-Gbedo, 2016 (100)
US (North Carolina)	2008–2010	140	MS	18.9	36.6	47, 99, 100, 153	Stapleton, 2011 (133)
US (Northern and Central California)	2008–2009	25	MS	43.1	82.9	28, 47, 99, 100, 153	Zota, 2011 (134)
US (New York City)	2009–2010	316	MS	7.9			Horton, 2013 (135)
US (California)	2010–2011	77	MS	8.3			Morello-Frosch, 2016 (in preparation)
US (Ohio)	2011	63 20	CS MS	12.4 11.0			Chen, 2013 (136)
Europe							
Sweden	1994–1995	57	MS	1.3			Fangstrom, 2005 (102)
Sweden (Stockholm)	2000–2001	15	MP CP	0.8 1.0	2.1 1.7	17, 28, 47, 66, 99, 100, 153, 154, 183	Guvénus, 2003 (137)
The Netherlands	2001–2002	62	MS	0.9			Roze, 2009 (31)
Poland	2002–2005	84	CS	1.0 ng/g fat			Hernik, 2013 (105)
Spain (Valencia)	2003–2005	174	MS CS	2.3 2.3	9.6 9.6	17, 28, 47, 66, 71, 85, 99, 100, 138, 153, 154, 183, 190, 209	Vizcaino, 2011 (138)
Spain	2003–2008	473 486	MS CS	<LOD 1.7	10.7 7.5	47, 99, 153, 154, 209	Lopez-Espinosa, 2015 (139)
France	2004–2006	91	MS CS	2.8 <LOD			Antignac, 2009 (140)
Sweden	2005–2006	10	MS CS	3.0 pmol/g lipid 3.4 pmol/g lipid			Jakobsson, 2012 (141)
Spain	2007	40	CS	30.0 pg/mL			Grimalt, 2010 (142)
Denmark (Copenhagen)	2007	51 40	MP CP	0.4 <0.07	1.8 1.0	28, 47, 99, 100, 153, 154, 209	Frederiksen, 2010 (143)
Denmark (Odense)	2011	100	MS	3.4	7.7	47, 99, 100, 153, 154, 183, 209	Vorkamp, 2014 (125)

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TABLE 4

Continued.

Location	Study years	N	Sample	Median concentration (ng/g lipid)		Congeners included in Σ PBDEs	First author, year (reference)
				BDE-47	Σ PBDEs		
Others							
China (Guiyu, e-waste recycling area)	2007	75	CS	8.5	57.6	28, 47, 99, 100, 153, 154, 183, 209	Xu, 2013 (144)
China (Chaonan)		45	CS	2.0	8.2		
South Korea (Seoul)	2007	108	CS	6.1	8.2	28, 47, 99, 100, 153, 154, 183	Kim, 2009 (145)
Southern Taiwan	2007–2008	54	CS	0.7	4.6	15, 28, 47, 49, 99, 100, 153, 154, 183, 196, 197	Shy, 2011 (146)
South Korea (Seoul)	2008	21	MS	3.2	7.8	28, 47, 99, 100, 153, 154, 183	Kim, 2012 (147)
			CS	7.7	12.0		
South Korea (Seoul)	2008–2009	90	CS	7.4			Kim, 2011 (148)
Caribbean (10 countries)	2008–2011	438	MS	5.3			Forde, 2014 (113)
Western Australia	2008–2011	164	MP	4.0	10	47, 99, 100, 153, 154	Stasinska, 2014 (149)
Northern China	2010–2012	232	CS	3.7			Ding, 2015 (150)
South Korea	2011	148	MS (at delivery)	1.0	1.8	17, 28, 47, 49, 66, 71, 77, 85, 99, 100, 119, 126, 138, 153, 154, 156, 183, 184, 191	Choi, 2014 (151)
		65	MS (at 6 mo)	1.2	1.9		
		118	CS	2.2	6.6		
China (Wenling, e-waste area)	2011	64	MS	1.0	9.8	28, 47, 99, 100, 153, 154, 183, 209	Lv, 2015 (115)
Southern China (Guangdong)	2012	30	Placenta	6.7	12.7	17, 28, 47, 85, 99, 100, 138, 153, 154, 183, 184, 191, 196, 197, 206, 207, 209	Chen, 2014 (152)
			CS	3.8	9.7		
China (Guiyu, e-waste recycling area)	2012	69	Placenta	1.6	32.3	28, 47, 99, 100, 138, 153, 154, 183, 209	Xu, 2015 (153)
China (Haojiang)		86		0.4	5.1		

Note: If several studies included participants from the same cohort, the one with the largest sample size was included. This table is for illustrative purpose and should not be taken as an exhaustive list of relevant biomonitored studies. CP = cord plasma; CS = cord serum; gws = gestation weeks; LOD = limit of detection; MP = maternal plasma; MS = maternal serum.

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TABLE 5

Example studies of concentration of selected phenols in pregnant women, by location and study years.

Location	Study years	N	Sample	Median concentration (µg/L)		First author, year (reference)
				Bisphenol A	Triclosan	
North America						
US (NYC)	1998–2002	404	MU	1.3	11.0	Wolff, 2008 (154)
US (African American and Dominican women)	1998–2006	568	MU	1.8		Donohue, 2013 (155)
US (California, Salinas)	1999–2000	364	MU	1.3 µg/g Cr		Chevrier, 2012 (36)
US (nationwide)	2003–2004	86	MU	2.7	8.2	Woodruff, 2011 (89)
US (Ohio)	2003–2006	330–363	MU	1.9 µg/g Cr (16 gws, GM) 2.2 µg/g Cr (26 gws, GM) 2.0 µg/g Cr (birth, GM)		Spanier, 2012 (156)
US (Michigan)	2006	40	MS	5.9		Padmanabhan, 2008 (157)
US (New York)	2007–2009	181	MU		7.22 µg/g Cr	Pycke, 2014 (158)
Canada	2008–2011	~2,000	MU	0.9, SG-adj (K-M median)		Arbuckle, 2014 (159)
Canada	2008–2011	1,699	MU		8.3	Velez, 2015 (121)
Canada (Ontario)	2009–2011	80	MU		MU: 25.3	Arbuckle, 2015 (160)
Canada (Ottawa)	2009–2010	66	MU	1.1		Fisher, 2015 (161)
US (nationwide)	2009–2010	506	MU	1.3	15.6	Mortensen, 2014 (162)
US (California)	2010–2012	85	CS (mid-gestation)	0.16 (GM)		Gerona, 2013 (163)
Puerto Rico	2010–2012	105	MU	2.5	26.2	Meeker, 2013 (164)
Europe						
France	2003–2006	520	MU	2.5	30.0	Philippat, 2014 (165)
Spain	2004–2006	402	MU	2.4 µg/g Cr (1st Tri) 2.0 µg/g Cr (3rd Tri)		Valvi, 2013 (166)
Spain	2004–2008	120	MU		6.1	Casas, 2011 (167)
Greece (Crete)	2007–2008	239	MU	1.1 µg/g Cr		Myridakis, 2015 (168)
Denmark (Odense Municipality)	2010–2012	200	MU	1.2 µg/g Cr	0.6 µg/g Cr	Tefre de Renzy-Martin, 2014 (169)
Others						
Mexico (Mexico City)	2001–2003	60	MU	1.4 µg/g Cr		Cantonwine, 2010 (170)
Taiwan	2006–2007	97	MP CP	MP: 2.5 (GM) CP: 0.5 (GM)		Chou, 2011 (171)
South Korea (Seoul)	2007–2010	757	MU	1.6 µg/g Cr		Lee, 2014 (172)
Western Australia	2008–2011	24	MU	2.9 µg/g Cr		Callen, 2013 (173)
China (Nanjing)	2010–2012	567	MU	0.7		Tang, 2013 (174)

Note: If several studies included participants from the same cohort, the one with the largest sample size was included. This table is for illustrative purpose and should not be taken as an exhaustive list of relevant biomonitored studies. CP = cord plasma; Cr = Creatinine-adjusted; CS = cord serum; MP = maternal plasma; MU = maternal urine; gws = gestation weeks; K-M median = Kaplan-Meier median, censored method; SG-adj = specific gravity adjusted.

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TABLE 6

Example studies of concentration of selected parabens in maternal urine of pregnant women, by location and study years.

Location	Study years	N	Median concentration in maternal urine (µg/L)			First author, year (reference)
			Butyl paraben	Methyl paraben	Propyl paraben	
North America						
US (Boston)	2005–2011	148 (1st Tri) 133 (2nd Tri) 97 (3rd Tri)	1.1, SG-adj 0.9, SG-adj 0.8, SG-adj	146.0, SG-adj 141.0, SG-adj 164.0, SG-adj	39.9, SG-adj 37.2, SG-adj 31.8, SG-adj	Braun, 2014 (175)
US (nationwide)	2009–2010	506		105.5	22.3	Mortensen, 2014 (162)
Puerto Rico	2010–2012	105	0.4	153.0	36.7	Meeker, 2013 (164)
Europe						
France	2003–2006	520	2.0	122.0	17.0	Philippat, 2014 (165)
Spain	2004–2008	120	2.4	191.0	29.8	Casas, 2011 (167)
Greece (Crete)	2007–2008	239		121.9 µg/g Cr		Myridakis, 2015 (168)
Denmark (Odense Municipality)	2010–2012	200		20.5 µg/g Cr		Tefre de Renzy-Martin, 2014 (169)

Note: This table is for illustrative purpose and should not be taken as an exhaustive list of relevant biomonitored studies. SG-adj = specific gravity adjusted; Cr = Creatinine-adjusted.

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TABLE 7

Example studies of concentration of selected phthalate metabolite (Monoethyl phthalate [MEP]) in maternal urine of pregnant women, by location and study years.

Location	Study years	N	Median MEP concentration in maternal urine ($\mu\text{g/L}$)	First author, year (reference)
North America				
US (NYC)	1998–2002	404	380	Miodovnik, 2011 (176)
US	1999–2002	180	126.4	Sathyanarayana, 2014 (177)
US	2000–2004	50	68.7 $\mu\text{g/g Cr}$	Buckley, 2012 (178)
US (nationwide)	2003–2004	91	265.7	Woodruff, 2011 (89)
US (Boston)	2005–2011	155	39.5 (1st Tri), SG-adj	Braun, 2014 (175)
		138	48.2 (2nd Tri), SG-adj	
		98	55.1 (3rd Tri), SG-adj	
US (Massachusetts)	2006–2008	482	134.0, SG-adj	Ferguson, 2014 (179)
Canada	2008–2011	~2,000	31.0, SG-adj	Arbuckle, 2014 (159)
Canada (Ottawa)	2009–2010	66	27.0	Fisher, 2015 (161)
Puerto Rico	2010–2012	139	99.2	Cantonwine, 2014 (180)
Europe				
France	2002–2006	287	110.2	Philippat, 2011 (181)
Spain	2004–2006	390	389.1 $\mu\text{g/g Cr}$	Casas, 2016 (182)
Central Poland	2007	150	22.7 $\mu\text{g/g Cr}$	Polanska, 2014 (183)
Greece (Crete)	2007–2008	239	132.6 $\mu\text{g/g Cr}$	Myridakis, 2015 (168)
Sweden	2008–2009	196	60.6	Bornehag, 2015 (168)
Denmark (Odense Municipality)	2010–2012	200	18.9 $\mu\text{g/g Cr}$	Tefre de Renzy-Martin, 2014 (169)
Spain	2011–2012	118	150.8 $\mu\text{g/g Cr}$	Cutanda, 2015 (184)
Others				
Mexico (Mexico City)	1997–2003	135	138.0, SG-adj	Télez-Rojo, 2013 (185)
Taiwan	2000–2001	252 (children loss-to-follow-up)	61.4 $\mu\text{g/g Cr}$	Ku, 2015 (186)
		136 (children followed-up)	65.2 $\mu\text{g/g Cr}$	
Peru (Trujillo)	2004	78	67.4 $\mu\text{g/g Cr}$	Irvin, 2010 (187)
Japan (Tokyo)	2005–2008	149	7.7 $\mu\text{g/g Cr}$	Suzuki, 2010 (188)

Note: If several studies included participants from the same cohort, the one with the largest sample size was included. This table is for illustrative purpose and should not be taken as an exhaustive list of relevant biomonitoring studies. Cr = Creatinine-adjusted; SG-adj = specific gravity adjusted.

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median concentration of PFOA was found to have increased approximately 10-fold from the 1960s to the 1980s but started to decline in 2009 (245). A similar decreasing trend for concentrations of PFOS and PFOA over time during the past two decades can be found in studies across the globe (Table 3). Other PFAS such as perfluorononanoic acid and perfluorodecanoic acid, though at a much lower concentration level compared with PFOS, have a high detection frequency (>90%) among pregnant women (118, 124, 128), and their serum concentrations have increased among California women from the 1960s to 2009 (245) and among Swedish women from 1996 to 2010 (246). The increasing blood levels of perfluorononanoic acid and perfluorodecanoic acid most likely reflect the increased use of their precursors—fluorotelomer chemicals—in commercial products after banning PFOS (247). Perfluorobutane sulfonate—a replacement for PFOS-based chemicals used as stain repellents—is also shown to increase in human blood, with levels doubling every 6 years among Swedish women from 1996 to 2010 (246).

Polybrominated diphenyl ethers are a newer class of persistent chemicals that have been used as flame retardants in furniture, textiles, carpeting, electronics, and plastics and are linked to impaired neurodevelopment and poorer motor, cognitive, and behavioral performance at school age (30, 31) (Table 1). Here we present data for the sum of

different PBDE congeners and 2,2',4,4'-tetrabromodiphenyl ether (BDE-47), one of the major congeners in the commercial mixture because it represents the most often found PBDE (Table 4). Polybrominated diphenyl ethers (e.g., BDE-47) have been measured in populations around the globe (Table 4). BDE-47 is the most abundant PBDE detected in the serum of pregnant women from North America, Europe, and most places around the world, with exceptions in Denmark and China, where the most abundant PBDE is BDE-209 (125) or BDE-153 (115), respectively. The concentration of BDE-47 and sum of PBDEs are also much higher among North American pregnant women compared with women from the rest of the world. The highest maternal serum concentration of BDE-47 was reported among pregnant women from Northern and Central California (134), which was in part due to regulatory standards in California requiring use of flame retardant chemicals in furniture (248). Levels of PBDEs have been shown to decline as a result of them being banned and phased out and the changed regulatory standard for flame retardants (249, 250).

Less Persistent and Bioaccumulative Chemicals

Many chemicals are nonpersistent and tend to be rapidly metabolized and eliminated, with half-lives in the human body within

TABLE 8

Example studies of concentration of blood cadmium (Cd), lead (Pb), and mercury (Hg) in pregnant women published in the past 5 y, by location and study years.

Location	Study years	N	Sample	Median concentration			First author, year (reference)
				Cd ($\mu\text{g/L}$)	Pb ($\mu\text{g/dL}$)	Hg ($\mu\text{g/L}$)	
North America							
Canada (Nunavik)	1995–2001	94	CB		3.5	17.0	Boucher, 2014 (189)
US (Boston)	1998–	50	MRBCs	0.86 (GM)	3.93 (GM)	2.35 (GM)	Chen, 2014 (190)
			CRBCs	0.06 (GM)	2.41 (GM)	3.58 (GM)	
US (nationwide)	1999–2006	1,183	MWB			0.71 (GM)	Razzaghi, 2014 (191)
US (Oklahoma)	2002–2007	476	MB		0.61 (GM)		Karwowski, 2014 (192)
			CB		0.42 (GM)		
US (nationwide)	2003–2004	253	MB	0.2	0.6	0.7 (THg)	Woodruff, 2011 (89)
US (Baltimore)	2004–2005	285	CB		0.66		Wells, 2011 (193)
Canada	2005–2007	16 (foreign-born) 77 (Canadian-born)	MWB	0.59 (GM)	0.78 (GM)	0.88 (THg, GM)	Adlard, 2014 (112)
				0.46 (GM)	0.57 (GM)	0.40 (THg, GM)	
Canada (Quebec)	2007–2008	349	MWB	0.2	0.83	0.6	Serme-Gbedo, 2016 (100)
US (New York City)	2007–2009	78	CB			2.14	Geer, 2012 (194)
Canada (10 cities)	2008–2011	1,260	MWB	0.32	0.88	0.86	Ashley-Martin, 2015 (195)
US (North Carolina)	2009–2011	211	MWB	0.18 (GM)	0.89 (GM)	0.45 (GM)	Sanders, 2012 (196)
US (Tennessee)	2009–2011	98 (2nd Tri) 88 (3rd Tri) 69 (delivery)	MB		0.43 0.43 0.50		Rabito, 2014 (197)
		48	CB		0.37		
US (Hawaii)	2010–2011	107	CB			5.2	Soon, 2014 (198)
US (California)	2010–2011	77	MWB	0.22	0.60	0.46	Morello-Frosch, 2016 (in preparation)
		59	CWB	<LOD	0.39	0.58	
Europe							
Kosovo	1985–1986	147 (Pristina) 144 (Mitrovica)	MB		5.6 20.0		Kahn, 2014 (199)
Faroe Islands	1986–1987	675	CB			23.3 (GM)	Grandjean, 2014 (200)
UK (Avon)	1991–1992	4,285	MB	0.29	3.41	1.86	Taylor, 2014 (201)
Germany	2000–2002	234	MWB		2.0		Neugebauer, 2015 (202)
Poland (Krakow)	2001–2004	379	CB		1.21	0.89	Jedrychowski, 2015 (203)
Spain	2003–2004	140	MB	0.60	1.90	4.61	García-Esquinas, 2013 (204)
		114	CB	0.27	1.38	7.66	
Spain	2003–2008	1,466; 1,407 (Pb; Hg)	CWB		1.1 (GM)	7.7 (GM)	Llop, 2011 & 2015 (205, 206)
Germany	2006	50	MB	0.34	1.15	0.44	Kopp, 2012 (207)
			CB	<LOD	1.03	1.48	
Northeastern Italy	2007–2009	606	MB			2.35 ng/g	Valent, 2013 (208)
		457	CB			3.97 ng/g	
Northern Norway	2007–2009	515	MWB	0.18 (GM)	0.74 (GM)	1.21 (GM)	Veyhe, 2015 (109)
Poland	2007–2011	594	CB		1.1 (GM)		Polanska, 2014 (209)
Slovenia	2007–	446	CB			1.5 ng/g	Miklavcic, 2011 (210)
Belgium	2008						
Poland (Upper Silesia)	2010–2012	40	MB			8.0	Kozikowska, 2013 (211)
			CB			0.008 $\mu\text{g/g}$	
Greenland	2010–2011, 2013	207	MWB	1.2	0.73	4.2	Long, 2015 (110)

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TABLE 8

Continued.

Location	Study years	N	Sample	Median concentration			First author, year (reference)
				Cd ($\mu\text{g/L}$)	Pb ($\mu\text{g/dL}$)	Hg ($\mu\text{g/L}$)	
Turkey	2011	93	CB		2.57 (AM)		Kayaalti, 2015 (212)
Eastern Slovakia	NA	75	MB CB			0.50; 0.22 0.53; 0.32 (THg; MeHg)	Ursinyova, 2012 (213)
Others							
Mexico	1994–2006	217 (1st Tri) 264 (2nd Tri) 248 (3rd Tri) 457; 144 (Pb; Hg, at birth)	MB MB MB CB		5.5	2.9 2.8 2.8 4.1	Basu, 2014 (214) & Zhang, 2012 (215)
Japan	2001–	387	CB		1.0	10.1 ng/g (THg)	Tatsuta, 2014 (216)
Taiwan	2004–2005	230	CWB		1.14	12.27	Lin, 2013 (217)
Mexico	2005–2006	233	MWB	0.36 (GM)	2.5 (GM)	0.86 (THg, GM)	Adlard, 2014 (112)
Saudi Arabia (Al-Kharj)	2005–2006	247	CB			3.1	Al-Saleh, 2014 (218)
China (Shanxi)	2005–2009	215	MB	0.47	2.45	0.26	Jin, 2014 (219)
South Korea	2006–2010	1,131 (<20 gws) 914 (at delivery) 897 (CB)	MB MB CB		1.29 1.27 0.93		Hong, 2014 (220)
South Korea	2006–2010	718–867	MB	1.4 (12–20 gws); 1.5 (28–42 gws)		3.5 (12–20 gws); 3.1 (28–42 gws) 5.2	Kim, 2011 & 2013 (221, 222)
Iran (Tehran)	2006–2011	797 174 (1st Tri) 148 (2nd Tri) 145 (3rd Tri)	CB MB MB MB		4.15 (AM) 3.44 (AM) 3.78 (AM)		Vigeh, 2014 (223)
China (Chengdu)	2007–2008	150 128	CB MB		2.86 (AM) 5.95 (1st Tri) 5.51 (2nd Tri) 5.57 (3rd Tri) 2.79 (AM)		Jiang, 2011 (224)
Mexico	2007–2008	292	MB				La-Llave-León, 2014 (225)
China	2008	1,323	CB			1.8 (GM)	Wu, 2013 (226)
Northeastern China	2008	192	MB			1.24 (THg)	Li, 2014 (227)
		195	CB			2.15 (THg)	
South Africa	2008	350	MWB CWB			0.57 0.80	Channa, 2013 (228)
Caribbean (10 countries)	2008–2011	436 (Hg) 102 (Pb)	MB		1.46	2.09	Forde, 2014 (229)
Western Australia	2008–2011	173	MB	0.38	0.37	0.46	Hinwood, 2013 (230)
Eastern China	2009–2010	213	CB			1.54	Guo, 2013 (231)
Pakistan	2009–2012	150; 120 (industrial area; domestic area)	MB CB		19.0; 9.6 13.6; 8.6		Kazi, 2014 (232)
Northern China	2010–2011	252; 258 (Pb; Hg)	MB CB		3.20 2.52	0.90 1.50	Ding, 2013 (233) & Xie, 2013 (234)
Northern China	2011	45	MB			2.17; 0.94	Ou, 2015 (235)
		46	CB			2.81; 1.85 (THg; MeHg)	
Nigeria (Nnewi)	2011	119; 95 (Pb; Hg)	MWB CWB		5.6 4.3	3.5 4.9	Obi, 2014 & 2015 (236, 237)

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TABLE 8

Continued.

Location	Study years	N	Sample	Cd (µg/L)	Pb (µg/dL)	Hg (µg/L)	First author, year (reference)
China (Guizhou)	2011–2012	17	MB		1.93	3.0 (THg)	Rothenberg, 2013 (49)
China (Wuhan City)	2012	234 (1st Tri) 249 (2nd Tri) 248 (3rd Tri)	MB		1.36		Shen, 2015 (238)
China	NA	209	MB CB	0.48 0.15	4.05 3.23		Sun, 2014 (239)
India	NA	60	MB CB		13.5 (AM) 8.5 (AM)		Reddy, 2014 (240)
Japan (Fukuoka)	NA	81	MRBCs CRBCs	1.97 ng/g (AM) 0.22 ng/g (AM)	26.4 ng/g (AM) 13.2 ng/g (AM)	9.4 ng/g (AM) 15.3 ng/g (AM)	Sakamoto, 2010 (241)
Kuwait	NA	194	MB CB		5.8 (AM) 10.9 (AM)		Rahman, 2012 (242)
Nigeria	NA	349	MB		36.4 (AM)		Ugwuja, 2013 (243)

Note: If several studies included participants from the same cohort, the one with the largest sample size was included. This table is for illustrative purpose and should not be taken as an exhaustive list of relevant biomonitored studies. CB = cord blood; CRBCs = cord red blood cells; CWB = cord whole blood; gws = gestation weeks; MB = maternal blood; MRBCs = maternal red blood cells; MWB = maternal whole blood; THg = total mercury; MeHg = methyl mercury.

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24 hours. Two examples of these chemicals that are widely reported in biomonitoring studies are phenols, a type of carboxylic acid and aromatic compound including BPA, triclosan, and parabens (3, 251), and phthalates (252). In contrast to the persistent chemicals such as PFAS, for which maternal concentrations across pregnancy are highly correlated (123), only low to moderate correlations were found between multiple measurements taken over pregnancy for less persistent chemicals such as BPA (156, 161, 166) and phthalate metabolites (161, 253). Thus, multiple measurements of these chemicals across pregnancy, particularly for studies of small sample size, are recommended (161, 254).

Phenols are (255) widely found in consumer products, packaging, and cosmetic products and are also used in foods and drugs (Table 1). Bisphenol A is a female reproductive toxicant (32) and has been linked to adverse hormonal and behavioral outcomes in childhood (Table 1). There is sufficient nonhuman evidence of an association between triclosan exposure and thyroxine concentration decrements, and triclosan is possibly toxic to reproductive and developmental health (37). Research also suggests that parabens have estrogenic activity (39). Detectable levels across multiple populations of these types of chemicals indicate recent and/or continuous exposure to the chemicals, and have been shown for BPA (Table 5), triclosan (Table 5), and three types of parabens (Table 6). Comparable BPA concentrations were found across different studies and geographic locations (Table 5). Fewer studies have documented the concentration of triclosan and parabens. There are variabilities in maternal triclosan concentration across studies (Table 6). Methyl paraben had a much higher concentration than butyl paraben and propyl paraben, despite the small number of studies (Table 6).

Phthalates are used in a variety of consumer goods, such as medical devices, cleaning and building materials, personal care products, and cosmetics, and have been linked to shortened gestational age (40) and impaired neurodevelopment in girls (256) (Table 1). Phthalate metabolites are detected in more than 90% of the maternal urine samples during pregnancy among North American or European populations (3). Yet there are variations in monoethyl phthalate (MEP) levels across different studies and populations (Table 7).

Pesticides

Pesticides have been used to control a variety of pests, such as insects, weeds, rats and mice, bacteria and mold, and more, and are applied in agricultural, community, and household settings. Different pesticides have been associated with a range of reproductive and developmental outcomes, including poorer birth outcomes, impaired cognitive development and neurodevelopment, and childhood cancers (Table 1). Among pesticides, OCPs such as hexachlorobenzene, DDT, chlordane, and hexachlorocyclohexane have been more widely studied, owing to their earlier use and their persistent and bioaccumulative nature and endocrine-disrupting properties, as well as their adverse health effects (3, 257). Despite being banned in the United States in the 1970s, some OCPs are still detected in US pregnant women (89). Dichlorodiphenyltrichloroethane is still used in some places

around the world, most notably for controlling mosquito-borne diseases, including malaria. As expected, in a study examining the regional difference of DDT exposure in South Africa, the authors found that levels of DDT isomers in plasma of delivering women were the highest in the endemic malaria sites where indoor residual spraying with DDT was taking place, among mining, urban, industrial, Atlantic, and rural sites (258). Women living in Latin America and other regions that use OCPs also have relatively higher maternal OCP levels (99, 259, 260). Current-use pesticides, characterized by shorter half-lives and chemical properties that do not promote bioaccumulation in sediments or organisms, are used to control a wide range of pests and in a variety of applications. For example, 2,4-dichlorophenol, 2,5-dichlorophenol, and 1-naphthol have been detected in more than 50% of pregnant women from the Salinas Valley in California (agricultural region) and with higher median concentrations than that from a US nationwide sample (NHANES study) (261).

Metals and Organometallic Chemicals

Cadmium, lead, and mercury are three metals that have been widely used in a variety of applications over the past 50 years. They are also among the most well-studied industrial pollutants and have been found collectively to have a number of adverse reproductive and developmental effects.

Cadmiums are used in batteries, pigments, metal coatings, and plastics and have been found to alter epigenetic signatures in the DNA of both the placenta and newborns (45), reduce intelligence quotient (46), and increase risk of emotional problems in boys (47) (Table 1). It can accumulate in liver and kidney, has a long half-life of 5–40 years in the body (262), and has been detected in both maternal and cord blood (Table 8).

Lead was widely used in gas, paint, water pipes, and other applications. Although lead use in many applications has been banned for several decades, exposure can still occur in older homes where lead-based paints were used, and in or on toys, costume jewelry, and water pipes. Lead has been linked to alterations in genomic methylation (48) and impaired neurodevelopment (49, 50) (Table 1). In human adults, approximately 94% of the total body burden of lead is found in the bones. During pregnancy the mobilization of bone lead will increase, which contributes to 10%–88% of the lead in blood in pregnant women (263). Environmental policies, including removing lead from gasoline, paint, and water pipes, have led to significant reductions in blood lead levels in the United States. The median level of blood lead among pregnant women from the United States tends to be lower than in women from the rest of the world (Table 8) (201). Similarly, a gradual reduction in blood lead levels over time has been reported in pregnant women from the United Kingdom (UK), which is in accordance with banning lead in petrol and paint, replacing lead water pipes, and reducing cigarette smoking in the UK (201).

Mercury, which comes primarily from coal-burning power plants, combustion of waste, industrial processes that use mercury, and from natural sources such as volcanoes (14), usually gets into the human body through consumption

of contaminated seafood or fresh water fish and can negatively affect cognitive performance and neurodevelopment (Table 1). Maternal blood mercury levels can vary across geographic areas and populations (Table 8). Populations with high fish consumption tend to have higher maternal blood mercury levels during pregnancy, for example pregnant women in Japan (216, 241) and Faroe Islands (200) and the Inuit population in Nunavik (Arctic Quebec, Canada) (189).

Challenges of Biomonitoring Studies

Biomonitoring studies, despite their usefulness, have their own challenges. Cautions should be taken when trying to compare maternal blood levels across biomonitoring studies, owing to differences in sample size, sample preparation and analytical techniques, study period, and gestational ages at which the blood is drawn (201). Additionally, chemical levels measured in biomonitoring studies do not provide information about the sources of exposure but are the sum of exposures through multiple pathways. Environmental monitoring (e.g., air, water, and soil) studies, on the other hand, can provide useful information on exposure sources identification, which is critical for prevention.

PLACENTAL TRANSFER AND FETAL BURDEN

Fetal chemical exposures result from maternal body burden of chemicals during pregnancy due to placental transfer. However, fetal exposure is difficult to measure directly and thus is usually achieved by measuring chemicals in maternal matrices as a surrogate, or by measuring chemicals in cord blood, placental tissue, amniotic fluid, or neonatal meconium (2, 264). The pattern of placental transfer is determined by the specific structure, chemical composition, molecular weight, and relative persistence of xenobiotic chemicals (2). Past literature has documented that most classes of environmental chemicals can cross into the fetal environment. These chemicals include metals, PCBs, PFAS, PBDEs, pesticides, phenols, and phthalates.

Some xenobiotic chemicals can bioaccumulate in the fetus and result in higher fetal exposure than maternal exposure, whereas others are transferred in equal or less proportion (2, 3). For example, studies have consistently found higher mercury concentration in cord blood than in maternal blood across different populations, the former being 1.5 to 3 times that of the latter (190, 207, 214, 221, 236, 241). Polychlorinated biphenyls are widely detected in cord blood (107, 114). Nearly all PCBs are found in higher levels in maternal than cord serum (265), with the exception of only a few congeners (266). One recent study suggested that lower chlorinated PCB congeners have a higher maternal–fetal transfer rate compared with higher chlorinated congeners (267), but this pattern is not supported by a systematic review and other studies (265, 268, 269). As PCB congener molecular weight (267, 269) or lipophilicity (269) increase, placental transfer decreases. However, lipophilicity does not always predict bioaccumulation. Polybrominated diphenyl ethers are lipophilic and also frequently detected in cord blood (3). Though the degree of bromination was suggested to influence placental transport, no apparent trend in ratios of cord:maternal concentration (>1 meaning concentration

higher in cord blood than in maternal blood) was observed (265). The central estimates of this ratio also varied for the same PBDE congener across studies and depended on the measure (i.e., wet-weight basis or lipid-weight basis) (265). Organochlorine pesticides, similar to PBDEs, are also lipophilic chemicals and have been detected in placenta tissues (270) and cord serum (271–274). The majority of the studies included in a recent review reported central estimates of cord:maternal to be near or below 1 for most OCPs, on the basis of both wet-weight and lipid-adjusted concentrations (265).

Other chemicals tend to more evenly distribute between maternal–fetal compartments. For example, phenols, phthalates, and phthalate metabolites can cross the placenta, but evidence suggests that they do not accumulate in the fetus (3). Studies in both human (275) and rats (276) indicated that both active BPA and its inactive form can cross the placenta into the fetus, where most of the active form remains active and some of the inactive forms can be converted to the active form. Moreover, certain forms of the chemicals can distribute disproportionately in maternal vs. fetal environment, owing to immaturity of enzymes that conjugate or metabolize these chemicals. For example, levels of BPA and BPA in sulfate form were two to three times higher than levels of BPA in glucuronide form in cord sera collected during mid-gestation, possibly owing to immaturity of the glucuronidation conjugation enzymes (163). Among the few human studies that have compared concentrations of BPA in fetal and maternal blood sera, the reported mean BPA level is lower in fetal serum in some studies (171, 277–279) but higher in others (280). Phthalate levels in cord blood or newborns' urine were found to be similar to or lower than that in maternal blood or urine, respectively (281, 282). Except for BPA, evidence is limited on placental transfer characteristics of triclosan, parabens, phthalates, and phthalate metabolites, and the transfer patterns of these chemicals need further investigation.

For some chemicals, the levels found in the fetus are lower compared with maternal measurements. For example, lead is generally present in slightly lower levels in the cord blood relative to maternal blood (227, 283). Lower levels of PFAS are also generally found in cord blood compared with maternal blood (118, 124, 128, 129). Placental transfer of PFAS depends on the length of the carbon chain (2, 3): shorter chain PFAS transferred more readily to cord blood than longer chain PFAS (284, 285). Cadmium is another example: the placenta seems to be a barrier, with much lower concentration in the cord blood being detected relative to maternal blood (204, 207, 239, 241).

Studies have reported that PCBs, PFAS, PBDEs, OCPs, phenols such as BPA, TCS, and PBs, phthalates, and phthalate metabolites are detected in breast milk (3). This indicates that prebirth exposures to the above chemicals and metals can continue to affect the offspring postpartum, via breastfeeding.

ENVIRONMENTAL DISPARITIES AND VULNERABLE POPULATIONS

The potential sources and amount of exposure to toxic chemicals are not the same for everyone. Women and men of reproductive age can encounter toxic chemicals at home, in the

community, and in the workplace. Communities and individuals vary in their vulnerability and in their risk for exposure (5). The amount, duration, and cumulative risk of exposure can depend on social, economic, geographic, occupational, medical, and genetic factors (286).

Exposure to toxic environmental chemicals and related health outcomes are inequitably distributed among populations within countries and between countries. In the United States, researchers and policy makers have identified a higher frequency and magnitude of exposures to environmental stressors in communities of color and low-income communities (287, 288). In addition, the consequences of exposure to toxic chemicals—including morbidity and mortality, loss of family income and productivity, and environmental degradation—are disproportionately borne by people with low incomes (289). For example, lower-income, ethnically diverse pregnant women in California were shown to have the highest level of PBDEs among pregnant women worldwide, mainly owing to geography (e.g., California's unique furniture flammability standards) and socioeconomic status (134). This combination and potential interaction of elevated environmental hazard exposures, on the one hand, and socioeconomic stressors, on the other, have been described as a form of “double jeopardy” (287, 288).

Occupation can also add additional risk of exposure to toxic chemicals disparities, which in turn impacts risk. For example, women employed as cosmetologists and manicurists are exposed to higher levels of volatile solvents (e.g., formaldehyde, methacrylates, acetone, and toluene), plasticizers (e.g., dibutyl phthalates), and other toxic substances. Pregnant women who worked as cashiers had the highest urinary BPA concentrations (253). A recent study found that women in the nail and hair care industry were at higher risk of adverse birth outcomes (290). Farm workers and their families are also at higher risk of exposure to pesticides, with potential adverse reproductive and developmental outcomes (Table 1) (291).

Even after decades of basic science research and public health initiatives, disparities in pregnancy outcomes, such as preterm birth, remain relatively unchanged. Factors that underpin the disparity are elusive and likely derived in part from complex interactions between social, biologic, and environmental factors including social inequality, genetics, neighborhood-level exposures, roles of infection and inflammation, and preconception health differentials. Better characterizing exposures has been recognized as a need in health disparities research and will provide important information in understanding the cumulative impacts of environmental and social stressors and promoting targeted policies to address these impacts (292).

FUTURE DIRECTIONS

Nontargeted Screening for Novel Chemicals

The chemicals discussed in the present review are merely the tip of the iceberg. There are tens of thousands of chemicals that we may be in contact with but know little or nothing about. Conventional studies used targeted approaches whereby the list of chemical analytes being measured is

chosen a priori. There is research need to identify the “unknown” chemicals for future biomonitoring that are prevalent in and could potentially pose harm to the human body, using novel methods (293) such as nontargeted screening (publication in preparation).

Cumulative Effects of Multiple Chemical Exposures

Because of the wide application of various environmental chemicals, pregnant women are not exposed to a single chemical or a single class of chemicals, but rather a cocktail of chemicals from different classes. Research finds that simultaneous exposure to multiple chemicals can have an additive or synergistic effect on health, particularly for the same adverse health outcome (294–298). Analysis conducted on one chemical at a time is likely to underestimate its potential health effect in the presence of other chemicals. Thus, an increasing number of studies have measured cumulative exposures to multiple chemical classes. A recent review suggests that among those studies of North American and European populations that had measured multiple chemical classes, few have attempted to capture a complete picture across classes and biological matrices (3). Certain classes are frequently measured simultaneously and in a single matrix (maternal urine or maternal serum): nonpersistent phenols and phthalates are often measured in urine, whereas persistent chemicals such as PFAS, PBDEs, PCBs, and OCPs are commonly measured in serum (3). Epidemiologic studies trying to examine the health effect of joint exposure to different chemicals are limited, possibly owing to a high cost for multiple measurements and limited sample size. Cumulative risk assessment of multiple chemicals and other environmental stressors needs to account for the possible compounded effects on the outcomes of concern, as the appropriate statistical models become available. Meanwhile, more educational efforts are needed to reduce the cumulative chemical exposure load currently experienced by pregnant women (3).

Paternal Exposure

Although the present review focuses on maternal exposure, paternal exposure to environmental chemicals also plays a critical role in the health of next generations. Especially for persistent chemicals like PCBs, PBDEs, and lead, fetal exposure can be a result of parental exposures before conception. Paternal lead exposure was found to affect the development of newborns (299). Paternal exposures may contribute to fetal risk through mutagenic and epigenetic mechanisms involving the sperm; and the chemical could also be carried in semen, leading to fetal exposure after intercourse (300–302).

Interactions between Gene and Environmental Chemicals

Humans can vary in their susceptibility to the adverse effects of toxic chemicals owing to genetic variability (303). For example, one study found that higher maternal blood levels of β -hexachlorocyclohexane, an OCP, is associated with

increased risk of idiopathic preterm delivery in women with *GSTM1* null polymorphisms, because they lack activity of the enzymes responsible for detoxification of xenobiotics (304). Some genetic variant may also modify placental transfer of chemicals, leading to differential levels of fetal exposure. For example, a maternal iron metabolism genotype was found to be a modifier of placental lead transfer in the US population: infants born to mothers with *HFE C282Y* gene variant have lower cord blood level concentrations relative to those born to mothers who were wild-type (prevailing among individuals in natural conditions) (192).

The relation between genetic profile and the external environment in affecting human health is not unidirectional but bidirectional. Toxic environmental exposure could also induce changes in gene regulatory mechanisms that correlate strongly with disease etiology (e.g., cancer and infertility) (305). For example, PCBs may cause mutations in *p53* and *K-ras* oncogenes and represent risk factors for colorectal and pancreatic cancers (306, 307). The inclusion of gene-environmental interaction in risk assessment may help identify and thus safeguard vulnerable populations.

RECOMMENDATION FOR PREVENTION

In clinical settings, obstetricians and gynecologists can provide authoritative and science-based guidance on how to avoid potentially adverse exposures (82). They are also uniquely poised to intervene to prevent harm before and during pregnancy, which is a critical window of human development (308). In 2015 the International Federation of Gynecology and Obstetrics (FIGO) released an opinion article on reproductive health impacts of exposure to toxic environmental chemicals, in which FIGO joins the American College of Obstetrics and Gynecology/American Society for Reproductive Medicine, the Royal College of Obstetricians and Gynecologists, the Endocrine Society, and the Society of Obstetricians and Gynecologists of Canada in “urging reproductive health professionals including obstetricians, gynecologists, midwives, nurses, women’s health nurses practitioners and others to take timely action to prevent exposure to toxic environmental chemicals” (5). Clinicians can adopt several tactics to incorporate environmental health into their patient-centered care, including [1] becoming knowledgeable about toxic environmental agents that are endemic to their specific geographic area, [2] intervening as early as possible (before conception and during pregnancy), [3] taking an exposure history (especially occupational exposures), [4] providing anticipatory guidance on how to make healthier choices and avoid toxic exposures at home, in the community, and at work, and [5] reporting identified hazards. Detailed strategies and useful resources have been summarized elsewhere (1, 82, 308).

The role of reproductive health professionals in preventing harmful environmental exposures extends beyond the clinical setting. Advancing society-wide and prevention-oriented policy actions is essential for reducing toxic exposures to pregnant women and other vulnerable populations because many exposures are beyond individual’s control (i.e., from air and water) (82). To this end, clinicians play a

crucial role in, for instance, initiating institutional-level interventions in support of a healthy food system and engaging in reducing pesticide use in institutional pest-control policies (82) and many more policy settings, including through their own professional organizations.

Understanding the sources and extent of exposures to environmental chemicals is a critical element in the efforts of reproductive health professionals to identify and prevent harmful chemical exposures to their patients and the population. In conclusion, to translate science into healthier pregnancy, healthier children, and healthy future generations, efforts are needed in advancing scientific research on characterizing chemical exposure in pregnant women and its health impact, synthesizing evidence to develop recommendations for prevention using systematic methods (309), and promoting policy change.

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