Cumulative Chemical Exposures During Pregnancy and Early Development

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Abstract Industrial and consumer product chemicals are widely used, leading to ubiquitous human exposure to the most common classes. Because these chemicals may affect developmental milestones, exposures in pregnant women and developing fetuses are of particular interest. In this review, we discuss the prevalence of chemical exposures in pregnant women, the chemical class-specific relationships between maternal and fetal exposures, and the major sources of exposures for six chemical classes of concern: phthalates, phenols, perfluorinated compounds (PFCs), flame retardants, polychlorinated biphenyls (PCBs), and organochlorine pesticides (OCs). Additionally, we describe the current efforts to characterize cumulative exposures to synthetic chemicals during pregnancy. We conclude by highlighting gaps in the literature and discussing possible applications of the findings to reduce the prevalence of cumulative exposures during pregnancy.

Keywords Cumulative exposure · Pregnancy · Phthalates · Phenols · Flame retardants · Perfluorinated compounds · Polychlorinated biphenyls · Organochlorine pesticides

Introduction

Synthetic chemicals are ubiquitous in modern society. As of 2012, more than 80,000 chemical substances are listed for use by the US Environmental Protection Agency, with about 1500 new chemicals manufactured or imported each year [1]. Approximately 3000 of these chemicals are used or imported in volumes greater than 1 million pounds/year and are found in a wide variety of consumer products, including cleaning and personal care products, building materials and home furnishings, electronics, food packaging, pharmaceuticals, and pesticides, leading to widespread human exposure [1, 2•].

Pregnant women's exposures to synthetic chemicals are especially important, because many chemicals may be transferred from mother to child across the placenta and via breast milk [3•, 4]. Furthermore, synthetic chemicals may disrupt development even at low levels [5]. For the fetus and neonate, exposures to environmental toxicants may result in a wide range of adverse health consequences across the life course and potentially be transmitted to the next generation [2•].

Growing interest in the impacts of environmental chemicals on fetal growth and development, coupled with advances in analytical chemistry, has led to a substantial body of scientific literature characterizing exposures to chemicals across the maternal/fetal unit during pregnancy and early postpartum. These studies have largely relied on biomonitoring of human tissue matrices (e.g., serum, urine, and breast milk) to estimate internal exposures to a variety of contemporary and banned chemical classes.

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In this review, we will describe the prevalence and sources of chemical exposures in pregnant women, and the relationships between maternal and fetal exposures, for six chemical classes of interest: phthalates, phenols, perfluorinated compounds, flame retardants, polychlorinated biphenyls, and organochlorine pesticides (see Table 1). We will also discuss the much smaller literature attempting to characterize cumulative exposures to these six classes during pregnancy. We will conclude by highlighting gaps in the literature and discussing possible scientific and public health implications of the findings. To ensure our review is current and focused, we will concentrate on literature from North America and Europe, published in the preceding 5 years.

Phthalates

Phthalates are used for a variety of purposes: as softeners in vinyl plastics, as solvents in personal care products, and as coatings in medications, among other uses [6]. Phthalates are non-persistent chemicals in humans, with half-lives of about 12–24 h, so measured levels reflect recent exposures [7]. Younger age, greater use of cleaning products and personal care products, and a high-fat diet are associated with higher

levels of phthalates in pregnant women [8–10]. Early life exposure to phthalates is associated with the development of allergic diseases, altered neurodevelopment, endocrine disruption including reduced anogenital distance in male infants [11, 12], and preterm birth [13].

Phthalate metabolites are frequently detected in the urine of pregnant women. Most measured metabolites are detected in 90–100 % of maternal urine samples during pregnancy and immediately postpartum (e.g., [8, 14, 15]). Additionally, phthalates or phthalate metabolites can cross the placental membrane. Up to 18 phthalate metabolites have been detected in neonatal urine [16, 17], and phthalate metabolites are also detected at low levels in cord blood and amniotic fluid [18, 19], breast milk [14], and meconium [20]. Although phthalates or their metabolites may cross the placenta, the evidence suggests that they do not accumulate in the fetus. In one study, newborns' urinary phthalate levels were generally similar to or lower than the levels found in their mothers' urine [17]. Similarly, in a second study levels of mono-(2-ethylhexyl) phthalate (MEHP) in maternal and cord blood were highly correlated, though levels in cord were slightly lower than maternal levels [20]. It is unclear whether phthalate metabolism or placental transfer varies during pregnancy. Two studies of maternal

Table 1 Summary of the detection frequency, health effects, and maternal/fetal transfer evidence for six chemical classes (phthalates, phenols, perfluorinated compounds (PFCs), flame retardants, polychlorinated biphenyls (PCBs), organochlorine pesticides (OCs))

Chemical	Detection frequency ^a		Potential health effects from early developmental exposures	Evidence for transfer		Accumulate in fetus? ^b	Persistent?
	Maternal	Fetal/neonatal		Placental	Breastfeeding		
Phthalates	90–100 % in urine	90–100 % in urine	Allergic disease; altered cognitive and behavioral development; altered male reproductive tract development; endocrine disruption; preterm delivery	Yes	Yes	No	No
Phenols	80–100 % in urine	40–60 % in urine	Asthma; altered cognitive and behavioral development; cardiometabolic disorders; endocrine disruption	Yes	Yes	No	No
PFCs	90–100 % in serum	90–100 % in cord serum	Endocrine disruption; reduced fetal growth	Yes	Yes	Yes	Yes
Flame retardants	90–100 % in serum	70–100 % in cord serum	Altered cognitive and behavioral development; thyroid hormone disruption	Yes	Yes	Yes	Yes
PCBs	80–100 % in serum	90–100 % in cord serum	Altered cognitive and behavioral development; thyroid hormone disruption; reduced fetal growth	Yes	Yes	Yes	Yes
OCs	90–100 % in serum	90–100 % in cord serum	Altered cognitive and behavioral development; endocrine disruption; immune suppression	Yes	Yes	Yes	Yes

^a Detection frequency is a general estimate, based on the literature, of the percent of individuals in a North American or European population having detectable levels of at least two congeners from a given class

^b Class is recorded as accumulating in the fetus if there is at least some evidence that fetal transfer is occurring at a rate greater than maternal exposure, e.g., (1) fetal levels exceed maternal levels or (2) maternal levels decrease during pregnancy or breastfeeding

urinary phthalate metabolites reported either no differences by gestational age [8] or results that varied by metabolite [21]. However, two other studies in maternal urine and amniotic fluid suggested that some phthalate metabolite levels may increase with gestational week [18, 22].

Phenols

Phenols are used in a variety of consumer products, including in the lining of food cans, in plastic bottles, in dental sealants, as antimicrobials, and as preservatives [6, 23]. Phenols, including bisphenol A (BPA), triclosan, and parabens, are non-persistent chemicals that are rapidly metabolized and eliminated, with half-lives in the human body between 6 and 30 h [24]. Higher levels of phenols in pregnant women are associated with use of mouthwash and cosmetics, as well as higher body mass index (BMI) and higher education level [23, 25, 26]. Higher prenatal BPA has been associated with younger age, lower socioeconomic status, black race, and consumption of canned vegetables [27]. Early-life BPA exposure is associated with impaired neurodevelopment, endocrine disruption, childhood asthma, and possibly cardiometabolic disorders [12, 28]. Other phenols, such as triclosan and parabens, may also act as endocrine disrupters but their human health effects are less well characterized [29, 30].

BPA is measurable in maternal urine throughout pregnancy and postpartum, frequently in 80–100 % of samples (e.g., [23, 25, 31•, 32, 33]) and is also detected in maternal serum [34, 35] and breast milk [31•, 32]. Triclosan is also frequently detected in maternal urine, serum, and breast milk [23, 25, 31•, 32, 33]. Methyl and propyl parabens are detected in nearly 100 % of maternal urine and breast milk, while butyl and ethyl parabens are detected less frequently [23, 25, 32, 33]. Detection of BPA and triclosan in neonatal urine [31•], cord blood [34–36], placental tissue [37, 38], amniotic fluid [33, 39], meconium [31•] and fetal liver [38] indicates that phenols are able to cross the placenta throughout pregnancy. Triclosan levels in infant meconium are highly correlated with levels in their mothers' urine [31•]. BPA levels in amniotic fluid are weakly correlated with maternal urinary levels [33], and BPA levels in the placenta are correlated with fetal liver levels [38]. However, phenols do not seem to accumulate in the fetus. BPA is typically found at much lower levels in amniotic fluid than in maternal urine [33], and at much lower levels in cord serum than maternal serum [35–37, 40] (with exceptions [34]).

Perfluorinated Chemicals

Perfluorinated compounds (PFCs) are persistent industrial chemicals used to impart water and stain resistance to consumer products [41]. PFCs preferentially bind to proteins such as albumin, and due to their highly stable chemical structure, they bioaccumulate and remain in the human body (and the

environment) long after exposure [42]. In pregnant women, parity and previous breastfeeding duration are inversely associated with PFC level, while age and living in an industrialized environment are positively associated; mixed results have been found for BMI, smoking, and diet [43–48]. Developmental exposure to PFCs is associated with reduced fetal growth [41] and possible endocrine disruption in females [49], but few other neonatal health effects have been strongly linked to PFC exposure.

PFCs, particularly perfluorooctane sulfonate (PFOS), perfluorooctanesulfonic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluorohexane sulfonate (PFHxS), are detected in the serum of nearly 100 % of pregnant women (e.g., [43, 50, 51]); longer-chain compounds are also frequently detected, though sometimes at lower levels [43, 47, 50, 52]. PFCs have also been detected in breast milk [51, 53–55]. Widespread detection of PFCs in cord blood [47, 56], amniotic fluid [18, 52], and placental tissue [57, 58] indicates that PFCs can cross the placenta. The degree of placental transfer varies by the biochemical properties of each congener. Short-chain PFCs and PFCs that bind to fatty blood proteins are the most readily transferred from maternal serum to cord serum [50, 59, 60]. Depending on the congener, maternal PFC levels may be one to six times higher than cord levels [3•, 45, 47, 50, 59]. Although fetal levels remain lower than maternal levels in most cases, placental transfer may occur in excess of maternal exposure. PFC levels in maternal serum decrease more than 10 % during pregnancy, with some congeners decreasing more than a third from pre-pregnancy levels [43, 46, 47, 61]. These trends are likely due to both dilution from increased blood volume during pregnancy and placental transfer [47, 61].

Breastfeeding is additionally thought to be a major source of neonatal PFC exposure. Lipid-adjusted PFC levels in breast milk may be higher than maternal serum levels [57]. Maternal serum [43, 51] and breast milk [62] PFC levels decrease continuously with breastfeeding, and women who have previously breastfed have lower serum PFC levels [46, 54]. Additionally, longer breastfeeding and exclusive breastfeeding are associated with increased infant serum PFC levels [4].

Flame Retardants

Flame retardants are used in upholstered furniture, electronics, and textile products [6]. Most polybrominated diphenyl ether (PBDE) flame retardants are no longer used in the USA, and replacement flame retardants (RFRs) have been developed as alternatives. However, because flame retardants are lipophilic persistent chemicals, with half-lives between a few months to over 10 years in adult human adipose tissue, PBDEs as well as RFRs are still detected by biomonitoring [63]. Greater number of electronic appliances and pieces of stuffed furniture at home, non-Hispanic ethnicity, and longer time living in the USA are associated with higher PBDEs in pregnant women

[64–67]; low income pregnant women in California are very highly exposed, likely due to California furniture flammability standards [64]. PBDE exposure has been associated with reproductive toxicity [12], thyroid hormone disruption in pregnant women and newborns, and poorer mental and psychomotor development including decrements in IQ and poorer attention in children [68, 69], while the health effects of RFRs are not yet fully known.

PBDEs, especially BDE-47 and BDE-153, followed by BDE-28, BDE-99, BDE-100, and BDE-209, are detected in the serum of nearly all pregnant women (e.g., [64, 70–72]). PBDEs are also frequently detected in breast milk [65, 73]. RFRs have also been measured in maternal serum and breast milk [67, 74–76], and RFR metabolites are measurable in maternal urine [77]. Flame retardants are able to cross the placenta throughout pregnancy [72, 78], though maternal levels do not decrease [77, 78]. PBDEs have been measured in cord serum [71, 73], placenta [72, 79], amniotic fluid [80], and colostrum [81]. RFRs have been measured in cord serum and the placenta [76]. PBDE metabolites (OH-PBDEs) are also found, at much lower levels, in both maternal and fetal matrices [55, 64, 70, 82]. The extent of placental transfer and possible accumulation varies by chemical (and is affected by lipid adjustment) [71]. Some PBDEs have consistent transfer patterns: BDE-153 is higher in maternal serum, BDE-99 is higher in cord serum, BDE-100 is similar across matrices [70, 71, 73], and OH-PBDEs may be higher in cord serum [70, 83]. However, others, such as BDE-47 and BDE-28, show a less-consistent pattern [70, 71, 73, 74, 81]. Similarly, some RFRs are higher in maternal serum, but others are higher in cord serum [74, 76]. Several studies suggest that highly brominated PBDEs cross the placenta more readily than lower brominated PBDEs [73, 84], but one systematic review did not support that pattern [3].

PCBs

Polychlorinated biphenyls (PCBs) are industrial chemicals that were once widely used as lubricants and coolants, and now persist in the environment despite being banned [85]. PCBs are highly persistent, lipophilic chemicals that accumulate in humans and the environment and have half-lives of 10–20 years or longer in adipose tissue [86]. Because PCBs bioaccumulate, maternal levels are associated with age and birth year [87–89], and women who eat high quantities of fatty fish and game, such as Inuit and northern Norwegian mothers, are highly exposed [90, 91]. PCBs are reproductive toxicants [12], and developmental exposure to PCBs may adversely affect thyroid hormones, child neurodevelopment, and birth weight [69, 92].

PCB-138, PCB-153, PCB-170, and PCB-180 are the most frequently detected congeners, typically detected in 80–100 % of maternal serum samples [88, 93–97] as well as colostrum

and breast milk [97–102]. PCBs are able to cross the placenta and are widely detected in cord blood [103–105], placenta [106–108], meconium [94], and amniotic fluid [109, 110]. Hydroxylated PCB metabolites (OH-PCBs) are also detected in multiple matrices at lower levels than the parent PCBs [94, 106]. Nearly all PCBs are found in higher levels in maternal than cord serum [103, 111–113], with only a few congeners found at similar levels across both or higher in cord [103, 113, 114]. Two recent studies suggest that lower chlorinated PCB congeners are more readily transferred than highly chlorinated ones [111, 112], though other studies, including an earlier systematic review, did not support that pattern [3, 103, 114]. Placental transfer may decrease as congener molecular weight increases [111] or as congener lipophilicity increases [103]. Parity also may contribute to inter-individual differences in placental transfer: one study reported a higher rate of placental transfer of PCB-157 in primiparous women, though placental transfer rates for other organochlorines were higher in multiparas [114]. Although most studies find that lipid-adjusted PCB levels decrease during pregnancy, the effect is likely due to dilution as blood volume increases [115].

After birth, PCBs are likely transferred to the neonate during breastfeeding. PCB levels are somewhat higher in colostrum than in mature milk [98], and multiparous women have lower serum PCB levels [116]. Two studies found that PCB levels in breast milk significantly decrease over the course of breastfeeding [62, 99], though a third found no decline in serum or milk levels [97].

Organochlorine Pesticides

Organochlorine pesticides (OCs) are persistent lipophilic chemicals that accumulate in adipose tissue [117]. Therefore, despite being banned decades ago, OCs persist in the environment and human tissue [110]. Maternal OC levels are closely associated with recent exposure to pesticides; women who live in Latin America and other regions that use OCs for pest control or agriculture have comparatively higher OC levels [104, 118, 119]. OC exposure may be associated with adverse psychomotor and attention development, immune suppression, and endocrine disruption, among other effects [12, 69, 96, 120].

Dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), and trans-nonachlor are typically detected in over 90 % of samples across matrices, including maternal serum [88, 93, 95, 105], breast milk [97, 100, 101, 121]. Oxychlordane and β -hexachlorocyclohexane (β -HCH) are detected less frequently, but still often present in over half of maternal samples [93, 97, 105]. OCs are able to cross the placenta and are detected in cord serum [104, 122, 123], meconium [94], placenta [124] and amniotic fluid [109, 110]. Using wet weights, OC levels are higher in maternal than cord blood, though the difference is slight for some compounds [113, 114, 125]. Using lipid-adjusted measures, OC levels

are typically slightly higher in cord than maternal serum, though the levels are not different enough to imply fetal accumulation [114, 125, 126]. Additionally, levels of DDE and dichlorodiphenyltrichloroethane (DDT) in maternal serum do not differ across trimesters of pregnancy [116, 127, 128]. Breast milk may also be a vehicle of transfer for OCs. OC levels are higher in breast milk than maternal serum [97, 129], and levels in breast milk fat decline during the first month postpartum [130]. However, it is unclear whether maternal serum OC levels change during breastfeeding [97, 131].

Cumulative Exposures

In addition to the extensive literature measuring single chemical classes in the maternal/fetal unit, some recent studies have measured cumulative exposures to multiple chemical classes. Of studies measuring multiple chemicals, most have measured the chemicals of interest in a single matrix (e.g., maternal urine or maternal serum; Table 2). Certain classes are frequently measured together, for example, non-persistent phthalates and phenols are often measured in urine, whereas persistent chemicals such as PFCs, flame retardants, OCs, and PCBs are commonly measured in serum or breast milk. However, few papers have attempted to capture a complete picture across classes and matrices.

Cumulative exposure studies measuring only non-persistent chemicals typically report that around a third to a half of the measured chemicals is detected in all participants. One study measuring 26 phenol and phthalate metabolites found a median of 16 chemicals in each pregnant woman, with more than half the chemicals detected in the majority of women [132]. Another two studies, both measuring 20 phenol and phthalate metabolites, reported that every woman had detectable levels of seven [133] or eight of the chemicals [134], respectively, while one to two additional chemicals in each study were detected in all but a few women.

Cumulative exposure studies measuring only persistent chemicals have also reported widespread simultaneous exposure to many chemicals. Two studies of placental tissue both reported universal detection of about 20–25 % of measured PBDEs and organochlorine compounds [107, 135]. Studies measuring maternal serum reported simultaneous detection of between 2–5 chemicals in all samples, representing between 11 and 57 % of chemicals measured [82, 95, 118, 135, 136–138], although fewer chemicals were detected in all cord blood samples [135, 139]. Similarly, in breast milk, studies reported the simultaneous detection of at least 20 % of the measured chemicals in every woman's milk, with most studies detecting around a third of the measured chemicals in all samples [100, 101, 140, 141]. One study detected fully half the chemicals it measured in every breast milk sample (16/31 chemicals [97]).

Several studies measuring total cumulative exposure detect a multitude of chemicals from many classes, including both persistent and non-persistent chemicals. In one US study measuring 52 total chemicals, including phthalates, BPA, PFCs, OCs, PCBs, and PBDEs, at least 21 chemicals were detected in every woman; the median number of chemicals measured was 44, and all 52 chemicals were measured in some women [142]. In a nationally representative US study, eight chemicals were detected in every pregnant woman including three PCBs, two OCs, one PBDE, one phenol, and two phthalate metabolites; 15 chemicals were detected in at least 99 % of women [2]. Finally, a Swiss study measuring 39 phenols, phthalate metabolites, PCBs, PBDEs, and pesticides in breast milk found 15 of the chemicals in every sample [121].

Despite widespread exposure to multiple classes of chemicals, chemical levels between classes are not well correlated. PCB and PBDE levels tend to be poorly correlated in maternal serum, breast milk, and placental tissue [82, 107, 137, 138, 143, 144]. Phthalates and phenols are weakly correlated in some studies [134, 145], and more strongly correlated in others [132, 146]. Because exposure to high levels of one class does not appear to be consistently predictive of exposure levels within other classes, modeling (or predicting) cumulative exposures is likely to be complex.

Discussion

Pregnant women are exposed to a large number of synthetic chemicals, including both banned and contemporary contaminants, and existing data form only a partial picture of the prevalence of cumulative exposures. Several chemicals from each class are routinely detected at close to 100 % across studies, suggesting that those chemicals are likely present in all pregnant women or fetuses, even when not explicitly measured. However, few studies with data on multiple contaminants in pregnancy cohorts have conducted cumulative impacts analyses.

Cumulative exposure assessment could be used to understand interactions between chemical classes on a particular health outcome of interest, and to control potential confounding and isolate the effects of a single class of compounds. Individually, many synthetic chemicals have been associated with similar adverse health endpoints, such as altered hormonal action in both the pregnant woman and fetus, and altered behavioral and cognitive development in children [11, 28, 69] (Table 1). Because pregnant women and fetuses are cumulatively exposed to multiple chemicals, these exposures may interact with one another, amplifying health effects. Indeed, the National Academy of Sciences recently recommended that risk assessment of multiple chemicals expand to account for the possibility of compounded effects on the outcomes of concern [147].

Table 2 A selection of recent cumulative exposure studies from populations in North America and Europe, including exposures to six chemical classes (phthalates, phenols, perfluorinated compounds (PFCs), flame retardants, polychlorinated biphenyls (PCBs), organochlorine pesticides (OCs))

Study	Sample size (n)	Location	Years	Matrix ^a	Classes measured				
					Phthalates	Phenols	PFCs	Flame retardants	PCBs and OCs
Maternal serum (MS)									
Abdelouahab et al. [136]	380	Canada	2007–2008	MS				x	x
Adlard et al. [118]	363	Canada, Mexico	2005–2007	MS				x	x
Carmichael et al. [137]	48	USA	2003	MS				x	x
Cheslack-Postava et al. [88]	150	Finland	1991–2000	MS				x	x
Roze et al. [151]	62	Netherlands	2001–2002	MS				x	x
Vafeiadi et al. [95]	1117	Greece	2007–2008	MS				x	x
Vorkamp et al. [138]	100	Denmark	2011	MS			x	x	
Zota et al. [82•]	61	USA	2008–2012	MS				x	x
Maternal urine (MU)									
Arbuckle et al. [152]	2000	Canada	2008–2011	MU	x	x			
Braun et al. [153]	137	USA	2004–2009	MU	x	x			
Braun et al. [154]	177	USA	2005–2011	MU	x	x			
Casas et al. [134]	120	Spain	2004–2008	MU	x	x			
Tefre de Renzy-Martin et al. [132]	200	Denmark	2011	MU	x	x			
Ferguson et al. [155]	107	Mexico	1994–2004	MU	x	x			
Hoepner et al. [145]	375	USA	1999–2006	MU	x	x			
Phillipat et al. [133]	191, 287	France	2002–2006	MU	x	x			
Watkins et al. [156]	116	Mexico	1997–2004	MU	x	x			
Weinberger et al. [157]	72	USA	Not listed	MU	x	x			
Breast milk (BM)									
Alivernini et al. [158]	13	Italy	2005–2007	BM				x	x
Croes et al. [141]	84	Belgium	2009–2010	BM				x	x
Gómara et al. [159]	9	Spain	2005	BM				x	x
Hernik et al. [100]	28	Poland	2002–2005	BM				x	x
LaKind et al. [97]	10	USA	2004–2005	BM				x	x
Lankova et al. [55]	50	Czech Republic	2010	BM			x	x	
Lignell et al. [140]	335	Sweden	1996–2006	BM				x	x
Park et al. [143]	82	USA	2003–2005	BM				x	x
Pratt et al. [160]	109	Ireland	2010	BM			x	x	
Raab et al. [101]	516	Germany	2007–2008	BM			x		x
Schlumpf et al. [121]	54	Switzerland	2004–2006	BM	x	x		x	x
Schuhmacher et al. [144]	15	Spain	2007	BM				x	x
Thomsen et al. [62]	70	Norway	2001–2009	BM			x	x	x
Cord serum (CS)									
Arbuckle et al. [139]	126	Canada	2005–2008	CS			x	x	
Chevalier et al. [19]	180	France	2002–2005	CS	x	x			x
Vizcaino et al. [161]	265	Spain	1997–1998	CS				x	x
Placenta (P) and amniotic fluid (AF)									
Leino et al. [107]	130	Finland	2004–2005	P				x	x
Nanes et al. [162]	42	USA	Not listed	P				x	x
Jensen et al. [18]	300	Denmark	1980–1996	AF	x		x		
Multiple matrices									
Braun et al. [142•]	175	USA	2003–2006	MU, MS	x	x	x	x	x

Table 2 (continued)

Study	Sample size (n)	Location	Years	Matrix ^a	Classes measured				
					Phthalates	Phenols	PFCs	Flame retardants	PCBs and OCs
Brucker-Davis et al. [163]	69, 84	France	2002–2005	BM, CS	x	x			x
de Cock et al. [56]	83	Netherlands	2011–2013	CS, BM	x		x		x
Doucet et al. [164]	52, 60	Canada	1998–2006	P, fetal liver				x	x
Needham et al. [57]	15	Faroe Islands	2000	MS, BM, CS, P			x		x
Porpora et al. [165]	38	Italy	2008–2009	MS, CS			x		x
Vizcaino et al. [135•]	308, 50	Spain	2004–2008	MS, CS, P				x	x
Woodruff et al. [2•]	268	USA	2003–2004	MU, MS	x	x	x	x	x

^a Matrix abbreviations: *MS* maternal serum, *MU* maternal urine, *BM* breast milk, *CS* cord serum, *P* placenta, *AF* amniotic fluid

Another important extension of cumulative exposure assessment is exposure source reduction, both through changes in individual behavior and changes in policy to protect the population on a broader scale. Because the chemical classes described largely come from different sources, small changes in individual behavior are unlikely to reduce overall exposures. However, given the prevalence of phthalates, phenols, flame retardants, and PFCs in some household items, personal care products, and certain foods, pregnant women may consider reducing their exposure to those sources where possible.

Because many of these chemicals are produced and used in high volumes, policy changes may reduce exposures more effectively than individual behavioral changes. For example, the phase out of PBDE flame retardants in the USA and Europe has led to lower exposures in both breast milk [148] and maternal serum levels during pregnancy [82•]. However, in response to the phase out, the chemical industry introduced replacement chemicals, often very similar in structure and with equal or uncharacterized toxicity; these substitutes were soon measured in pregnant women's bodies [67, 75]. Therefore, a meaningful reduction in cumulative chemical exposures will likely entail chemical policy reform that requires more adequate assessment of health and safety concerns before market introduction, as well as a reduction in the overall use of synthetic chemicals in commerce.

Our understanding of chemical exposure during preconception and early- to mid-gestation, as well as longitudinal exposure levels, is somewhat limited by access to relevant study populations and the necessary biological matrices for chemical analysis. For example, although cord blood can provide information about fetal exposure at birth, it may not accurately reflect fetal exposures during early gestation, which may also have profound developmental effects. Additionally, neonatal urine and meconium provide metabolites, rather than parent compounds, for analysis. It can be difficult to determine whether these metabolites resulted from placental transfer or were created in the fetus directly, and in cases where

metabolites are not specific to a parent compound, it may be unclear which parent compound preceded the metabolite. In some cases, the metabolite itself may be found in the environment (e.g., [149]). Finally, amniotic fluid has been used to gather data on gestational exposure, but the relationship between amniotic fluid levels and internal fetal levels is unknown, and amniotic fluid is often contaminated with maternal blood [150]. Fetal exposures throughout pregnancy might be estimated from maternal levels using known placental transfer rates, though some unanswered questions—e.g., whether the transfer rate varies during pregnancy, why certain chemicals are transferred more than others, and whether metabolites are more readily transferred than parent chemicals—currently limit interpretation of maternal levels. Therefore, measuring cumulative exposures during pregnancy and early development may require sequential measurements of multiple matrices beginning in preconception and extending through postpartum.

Conclusions

Although a substantial number of recent studies have collected data on environmental exposures during pregnancy, few have adequately characterized cumulative exposures and their consequent effects on the developing fetus. Future research should focus on characterizing cumulative maternal and fetal exposure from preconception to postpartum and investigating possible additive or multiplicative clinical effects of multiple cumulative exposures using appropriate statistical tools. Moreover, educational materials on chemical exposures should focus on modifiable risk factors, such as diet, that are associated with multiple classes of chemicals, in attempt to reduce the cumulative chemical exposure load currently experienced by pregnant women. Because synthetic chemicals are now global contaminants, it is increasingly important to create opportunities for environmental health prevention through

understanding and ultimately reducing cumulative exposures during pregnancy and early development.

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Compliance with Ethical Guidelines

Conflict of Interest Susanna D. Mitro, Tyiesha Johnson, and Ami R. Zota declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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