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Interactions between Environmental Exposures and the Microbiome: Implications for Fetal Programming

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Abstract

Decades of population-based health outcomes data highlight the importance of understanding how environmental exposures in pregnancy affect maternal and neonatal outcomes. Animal model research and epidemiological studies have revealed that such exposures are able to alter fetal programming through stable changes in the epigenome, including altered DNA methylation patterns and histone modifications in the developing fetus and infant. It is similarly known that while microbes can biotransform environmental chemicals via conjugation and de-conjugation, specific exposures can also alter the community profile and function of the human microbiome. In this review, we consider how alterations to the maternal and or fetal/infant microbiome through environmental exposures could directly and indirectly alter fetal programming. We highlight two specific environmental exposures, cadmium (Cd) and polycyclic aromatic hydrocarbons (PAHs), and outline their effects on the developing fetus and the perinatal (maternal and fetal/infant) microbiome. We further consider how chemical exposures in the setting of natural disasters may be of particular importance to environmental health.

Introduction

Human exposure to environmental chemicals has changed in significant ways in recent decades. These changes broadly include both quantitative disruptions (the number and concentration of environmental chemicals) as well as qualitative variations (the nature, timing and duration of the exposure, largely as a result of prolonged exposures across the lifespan). Epidemiologists, toxicologists, reproductive biologists and clinicians have long studied how environmental exposures influence maternal and fetal/neonatal outcomes, inclusive of both teratogenic and non-teratogenic sequelae. Some exposures, such as that of methylmercury, a known neurotoxin, have been extensively studied [1–4]. However, the

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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effects on fetal outcomes and the potential for fetal programming later in life disease via common and generally non-teratogenic compounds remains largely unknown. Furthermore, determining precise levels and duration or temporality of either maternal or fetal exposures following several routes of exposure to environmental chemicals during pregnancy remains a challenge. Specifically, in the environment, we are exposed to mixtures of chemicals through the air we breathe (*inhalation* exposures), the food and water we consume (*ingestion* exposures), and the specific conditions of the environment where we live and work (largely *absorption* exposures through our skin). In the case of pregnancy, these exposures may be secondarily vertically transmitted to the developing fetus, both as a product of transplacental exposure as well placental deposition. Qualitative and quantitative estimates of these exposures is both understudied and continuously challenging.

In this review we will first provide a very brief overview of environmental chemical biotransformations, which are known to occur both in humans and other vertebrate animals as well as in bacteria. We will then provide a brief overview of key molecular mechanisms which are thought to mediate the adverse effects of environmental exposures in pregnancy. We will consider two specific environmental exposures of interest, cadmium (Cd) and polycyclic aromatic hydrocarbons (PAHs), and consider two possibilities. First, how their disruption of the maternal and perinatal microbiome may subsequently modify risk of later in life disease. Second, we will consider how a disrupted microbiome may limit the biotransformation of these environmental chemicals to similarly modify occurrence of perinatal disease. Finally, we will consider the occurrence of particularly adverse environmental exposures which may accompany natural disasters.

Biotransformation of environmental chemicals occurs in vertebrates and bacteria

Human metabolism and biotransformation of environmental chemicals.

In vitro and *in vivo* studies have highlighted the role of the molecular machinery of the human liver, gut and kidney in the metabolism and elimination of environmental chemicals (Figure 1). It typically involves biotransformation of these chemicals (via Phase I, II and/or III pathways) to form a more hydrophilic compound which can be readily excreted out of the body [5]. We and others have previously published examples of genomic and epigenomic variants which can affect the ability or activity of these biotransformation reactions in pregnancy [6, 7]. However, although genomic structural variations and single nucleotide polymorphisms are known to occasionally alter an individual's susceptibility to disease occurrence resulting from exposures to environmental chemicals, the overwhelming majority of biotransformation reactions are shared among the population at-large. Phase I enzymes belong to the cytochrome P450 (CYP) superfamily and are usually expressed in hepatic cells and some enterocytes. Metabolism through the Phase II pathway mainly involves formation of water soluble products by conjugation of functional groups to the products formed in Phase I pathway. Liver, gut and kidney are the site of the majority of Phase II reactions. Phase III pathways primarily employ cellular and efflux transporters which enable the metabolic products of Phase I and II to be eliminated from the body.

Maternal, placental and fetal metabolism—implications for understanding the potential for fetal harm.

As a result of metabolism and biotransformation reactions, the fetus will not necessarily experience maternal dose levels of environmental chemicals. Compounds which do not undergo first pass metabolism in the maternal liver and are renal excreted and transported across the placenta will hemoconcentrate in the fetus (due to its smaller circulating blood volume). One such example is the commonly used diabetes medication, metformin. Some compounds may be metabolized by the placenta, either generating inert metabolites or metabolites which may cause placental damage. We have previously shown that this occurs with maternal tobacco use, with both Cd and PAHs being implicated as the harmful agents [6,7]. Some environmental chemicals have the potential to directly affect the fetus. In fact, we have previously shown that PAHs from maternal smoking are both associated with histologic evidence of oxidative damage in the placenta and can cause fetal growth restriction when the fetus is missing the Phase II activity of GSTT1 [8]. In this scenario, differential methylation and increased expression of CYP1A1 in the placenta occurs as a result of maternal smoking. This then generates more harmful DNA adducts and intermediates, driving the observed placental oxidative damage [6]. When the fetus lacks the GSTT1 enzyme activity, it cannot excrete these harmful intermediates. This renders relative weight differences in the fetus only when maternal smoking occurs [7]. In sum, fetal harm can occur through multiple mechanisms including via placental damage and/or direct fetal exposure.

Microbial biotransformation reactions: help from our smallest friends.

Classical environmental chemical biotransformation studies on human health largely considered the role of human cells and their molecular machinery on metabolism, catabolism, and elimination of environmental chemicals. However, we have long understood the importance of bacteria in biotransformation reactions and several studies have recently highlighted the importance of both bacteria in the environment and our gut microbes on the biotransformation of environmental chemicals of importance to human health (Figure 1).

Five enzymatic families of gut microbial origin (azoreductases, nitroreductases, β -glucuronidases, sulfatases and β -lyases) have been identified as key players in metabolizing many environmental chemicals (Figure 1) [8, 9]. Although most of our current and working knowledge pertaining to environmental chemicals and actions of microbial enzymes have resulted from studies of drugs at high therapeutic concentrations, several examples of gut-microbiome involvement in metabolism of mutagenic and carcinogenic chemicals has been demonstrated both *in vitro* and *in vivo* [8, 10]. Furthermore, *in vitro* studies of human and rodent gut bacteria show that gut microbiomes can modify bioavailability and toxicity of metals like arsenic, mercury and cadmium, generally by complex and multi-step enzymatic reactions [10]. More than 800 microbial genera have been identified as playing active roles in such biotransformation reactions, which collectively occur via either direct or indirect mechanisms and can modulate the toxicity, absorption and bioavailability of environmental chemicals [9]. Akin to first pass metabolism in the human liver, many chemicals undergo direct binding and/or degradation and deactivation by the gut microbiota. These small molecule intermediates may constitute a more or (ideally) a less toxic compound which can be further transformed in the human liver via Phase II reactions, or form conjugated or

deconjugated products with a varied or altered potential for endocrine or metabolic disruption [11–13]. Indirect mechanisms include up- or down-regulation of human metabolism and biotransformation via phase I and II/III reactions and excretions [8]. This is schematically depicted in Figure 1. While the precise nature of these are outside the scope of the current review, it is important to advance the concept that there are both direct and indirect means by which the presence or absence of a certain strain or species of bacteria in the human gut can alter the molecular capacity of human cells and their molecules to biotransform environmental chemicals (Figure 1).

General importance of biotransformation reactions and their intermediates on pregnancy and perinatal outcomes.

Some of the small molecule intermediates and their related metabolites and compounds formed as a result of microbial biotransformation will ultimately manifest as endocrine disrupting agents [11–13]. As such, these will in turn increase the risk of certain disorders in women, such as miscarriage, pregnancy loss and preterm birth among gravidae, as well as reproductive tract cancers and dysfunction and metabolic, cardiovascular and respiratory disorders (Figure 2) [11]. These exposure risks extend to the placenta and fetus, since certain environmental chemicals or their metabolic byproducts have been found to be transplacentally transported and may enter the fetal circulation [14, 15]. This in turn imparts many similar and often anticipated disorders among the offspring, which can extend throughout the lifespan (Figure 2).

Detection of environmental chemicals in the cells of the placenta [6,16], as well as from maternal and umbilical cord blood in association with preterm birth and developmental disruptions [7, 17, 18] reveal the importance of focused investigations into the level or dose of an exposure, as well as the importance of timing relative to embryogenesis and throughout the developing offspring's lifespan, including critical windows for programming cardiovascular and metabolic health. Rapid growth of organ and physiologic system developments in fetuses and infants make them particularly vulnerable to the effects of organic pollutants, as we and others have previously demonstrated [6, 7, 9–12, 19–35]. The chemical burden circulating through the mother's blood is shared with her fetus or neonate, and the child may, in some cases, be exposed to heavy doses relative to the body weight, which can lead to developmental defects and life-long functional deficits [19].

Environmental exposures in pregnancy: Cd and PAH as two relevant examples

While summarizing decades of research on the effects of environmental exposures in pregnancy is outside the scope of this review, we direct the reader to several excellent recent reviews on this subject [20–23]. Suffice it to say in brief, we and others have demonstrated that epigenomic modifications to critical gene regulatory regions are one key set of molecular mechanism by which environmental exposures parlay an enduring impact on the developing fetus [11, 24–26]. Maternal diet, lifestyle and environmental exposures have all been shown to persistently modulate gene transcription in the offspring via stable epigenomic modifications, including DNA methylation and histone modifications leading to

altered occupancy of critical promoter regions. These stable modifications in the epigenome and/or its molecular machinery render risk of later in life metabolic, respiratory, neurodevelopmental and immunological disorders (Figure 2) [15, 27–29]. However, considerably less attention has generally been given to the role of perinatal microbiome in modulating and mitigating environmental exposures. Nonetheless, there are two good examples (Cd and PAH exposure) where there is emerging evidence to suspect the microbiome may play a role in their transformation and metabolism.

Cadmium (Cd).

Several routes of Cd exposure occurs including ambient *inhalation* (cigarette smoking, fossil fuel combustion and mine tailings) and *ingestion* (bioaccumulation in plant foods like cereals, leafy and root vegetables, and animal products) [30]. In non-pregnant individuals, Cd is toxic to the brain and kidney [31] and has a half-life of 5–40 years [32]. In pregnant women, Cd is known to accumulate in the placenta, and is associated with both necrosis and diminished placental function, presumptively via a reduction in trophoblast cell proliferation with a concomitant permissive apoptosis [33, 34]. Furthermore, Cd exposure is associated with reduced fetal birth weight and a smaller head circumference in newborns [35] and in animal models has been shown to alter fetal central nervous system, liver and kidney end-organ development [36].

Polycyclic aromatic hydrocarbons (PAHs):

Similar to Cd, PAHs are toxic organic chemicals that are found in carbon combustion byproducts including vehicle emissions, ambient air, and cigarette smoke, as well as in plant and animal based foods, soil, and water. They arise from incomplete combustion of fossil fuels, and can contaminate soil and aquatic environments. PAH exposure in pregnancy is associated with preterm delivery, reduced birthweight, small for gestational age infants, an increased risk of neonatal bronchopulmonary dysplasia, higher risks of childhood asthma and lower cognitive test scores [37–43]. PAHs are also able to cross the placenta and are found in measurable quantities above ambient levels in cord blood [17, 18, 44]. Due to their Phase I metabolism, PAHs are converted to electrophilic species which covalently attach to nucleophilic sites on the DNA backbone forming bulky adducts on DNA [45, 46]. These bulky DNA adducts therefore can be mutagenic due to faulty base excision repair of the double helix [45]. It is unsurprising that PAH exposures *in utero* have also been associated with persistent fetal reprogramming to render risk of later in life disease (Figure 2).

Cd and PAH mediated epigenetic modifications—In the non-pregnant individual, Cd bioaccumulates in bones [24, 47–50]. During pregnancy, this Cd is released from bone, increasing the risk of Cd exposure to the developing fetus [51]. Cd is thought to alter DNA methyl transferase activity, which could in turn alter epigenetic marks during development which are crucial for regulation of gene transcription events [52]. While the precise molecular mechanisms underlying Cd-driven associations in adverse pregnancy outcomes is not completely understood, *in utero* Cd exposures are associated with hypo-methylation of repetitive regions of the genome, specifically those of long interspersed nuclear elements (LINE-1) with increased Cd levels [53]. Given that maintenance of methylation levels of repetitive regions is important for genome stability, this may contribute to a number of

pleiotropic measures. Interestingly, one study suggested sex-specificity with sexual dimorphism of altered DNA methylation patterns in the cord blood with *in utero* Cd exposures [54]. Specifically, DNA methylation patterns in male offspring were positively correlated with Cd exposure, while those of female offspring were negatively correlated.

Given that the reactive oxygen species generated from PAH metabolism are able to form bulky adducts to DNA, DNA methylation patterns can be altered during repair of the affected areas of the genome. Studies of epigenetic alterations of PAH exposure in pregnancy have therefore focused specifically on changes in DNA methylation patterns in the exposed offspring. Genomic hyper-methylation in cord blood was found in umbilical cord white blood cells of newborns exposed to PAHs *in utero* [55]. In these same subjects, PAH exposure, DNA methylation levels and neurodevelopmental delays were correlated at age 3 [56]. In a murine model of prenatal PAH exposures offspring revealed behavioral changes not observed in exposed animals and these behavioral changes were accompanied by alterations to DNA methylation patterns in the cortex [57].

Cd and PAH mediated microbiome alterations—Several studies to date have suggested that the microbiome interacts with and alters the end point measures of environmental toxicants like heavy metals (including Cd) and organic pollutants (including PAHs). Perhaps unsurprising given their crucial role in the biotransformation and turnover of small molecule intermediates and metabolites, microbes are key players in xenobiotic and environmental chemical metabolism [13]. Generally commensal microbiota can metabolize such compounds both directly following ingestion or inhalation, or secondarily following their initial conjugation in the human liver [13]. Similarly, ingested xenobiotics are able to interfere with microbial enzymatic activity of the gut, and have been shown to directly induce dysbiosis via alterations in the community profile of the gut niche and its microniches [13]. Thus, environmental chemicals can disrupt the human gut ecology, both at the levels of altering human microbial composition and its encoded metagenomic functions. The net effect of these compositional and functional changes to the gut microbiome is that it's capacity to metabolize or biotransform environmental chemicals and their derivatives either towards human benefit or with risk of human harm occurs. Consequences of these interactions are only beginning to be appreciated and remain largely understudied and poorly characterized.

In developmental animal models, Cd administered through drinking water induced gut dysbiosis of both communities and their functions in the small intestine and distal colon [58]. However and interestingly, having an established gut microbiota (e.g. adult-like) was protective against heavy metal induced dysbiosis, including that of Cd [59]. Specifically, mice lacking a mature or diverse intestinal microbiota are more susceptible to accumulation (5–10 times) of Cd or lead (Pb) in their target organs including blood, liver, kidney and spleen compared to symbiotic control groups.

As one such example, BaP is an interesting organic pollutant with regards to its interaction with microbiome. It has been found that human gut microbiota metabolize BaP creating an estrogenic compound through hydroxylation to 7-hydroxybenzo[a]pyrene (7-OH-BaP), is able to activate human estrogen receptor while its parent compound cannot [60]. Therefore,

the toxicity of ingested, inhaled, or absorbed PAHs may be enhanced through interactions with the human microbiome. In other words, members of the gut microbiome which would retain the capacity to hydroxylate BAP to 7-OH-BaP would be considered “dysbiotic” in this context. Conversely, absence of these microbes would confer potential symbiotic benefit to the human host. Thus, knowing the presence or absence of given microbes capable of not only beneficial but potentially detrimental biotransformation reactions would be crucial to understanding environmental health risks and potential mitigation benefits. At present, how this transformation into estrogenic compounds may affect pregnancy loss, preterm birth, and reproductive health are unknown at present. Clearly an understanding of this association and alterations in pregnancy outcomes and fetal programming remain an unexplored but potentially high impact area of study.

Environmental exposures and fetal programming

The concept of fetal programming proposes that preconception and/or prenatal and postnatal nutrient and environmental chemical exposures (collectively referred to as the perinatal period) have persistent multigenerational and potentially transgenerational adverse effects on the offspring. Over the course of pregnancy, fetal nutrient requirements changes with time, leading to dynamic metabolic adaptations in pregnant women [61]. However, the gut microbiota can modulate the metabolic and physiology of utilization of both macro and micronutrient, parlaying implications on fetal programming across the lifespan [48, 62, 63]. The strategic location of the microbiome at almost all interfaces with external environment (e.g., the lung and nasopharyngeal microbiomes with respect to *inhalation*, the skin with respect to *absorption*, and the oral and gut with respect to *ingestion*). The net effect is that by measuring environmental chemicals and their intermediates alongside functional alterations in the microbiome of multiple body sites in parallel with measures of altered molecular, cellular, organ, and whole systems physiology across the lifespan, reasonable suppositions regarding the capacity to link risk from exposure to the functions of the microbiome can be made [64]. To this end, it is worthwhile to note that the majority of epigenetic modifications which result in detectable gene regulatory events, including alterations in site-specific DNA methylation and histone demarcations, are now correlated with examples regarding predominance or absence of certain microbial taxa and their resultant metagenomic functions [64, 65]. Whether this will hold true across the spectrum of environmental chemicals which have been linked to fetal reprogramming events remains to be seen.

Beyond just direct environmental chemical exposures, it is worthwhile to consider a “two hit” model of modulation in biotransformation of potential toxicants. For example, we and others have shown that the maternal diet has a profound and lasting influence on early developmental processes, including metabolic, behavioral, immune modulatory, and cardiovascular. Similarly, multiple recent publications from our lab in both humans and non-human primates demonstrates the concomitant lasting “footprint” of a high fat maternal diet on both the offspring gut microbiome and biologically relevant histone modifications, which parlay as risk of later in life disease [24, 47–50, 66, 67]. We and others have also correlated increased risks of spontaneous preterm birth with prenatal exposure to environmental PAHs [50, 68, 69]. Although several studies have shown that environmental chemicals can induce microbiome changes [58, 59, 65, 70] and that altered microbial communities contribute to

changes in host phenotypes [48], it is equally possible that common exposures such as a maternal high fat diet can render alterations in the maternal and offspring microbiome which render later susceptibility to environmental chemicals [recently summarized in]. Therefore embracing microbes in exposure science would play a key role in illuminating the relationships among secondary perinatal factors (such as the maternal diet), concomitant or latter environmental chemical exposure, functional alterations in the human microbiome, and fetal programming rendering risk of later in life disease.

Special Considerations: Natural Disasters

As previously noted, where we live and work can significantly determine the burden of environmental exposures we encounter. However, something that can drastically change this burden is the occurrence of a natural disaster which further disrupts environmental chemicals deposition in the environment and renders increased human exposure susceptibility. From disasters such as flooding in urban populations (*i.e.* from Hurricanes Katrina and Harvey) we know that the local microbial ecosystem is drastically modified [71, 72]. Flooded homes become vulnerable to molds and myotoxins [73, 74], which further risk disruption of the microbial community. In parallel with these potential microbial disruptions is the risk of increasing the load and intensity of environmental chemical exposures either as a result of leaching of ground deposits, compromise of mitigation efforts, or increased inhalation, ingestion and/or absorption. Moreover, both immediate and lasting clean-up and remediation efforts may negatively affect air quality increasing the risk of adverse environmental exposure burden via inhalation [75]. The end sequelae of these events have been partially measured in limited studies. For example, otherwise healthy individuals exposed to flood waters are at significant risk for skin infections [76], including those with pathogenic multi-drug resistant bacteria [77]. Exposed children are at an increased risk for upper and lower respiratory infections and reactive airway disease [78]. Whether this is a direct result of increased environmental irritants, the result of disrupted microbiome ecology, or a combination of the two remains to be determined.

With regards to environmental exposures per se, flooding is able to redistribute soil and water contaminants such as PAHs and toxic metals. This was measured as seen in the aftermath of Hurricane Harvey, which flooded the greater Houston area in August of 2017 [79, 80]. During Harvey, 51 inches of rain fell over a span of two days and flash flooding drove over 100,000 evacuees through contaminated floodwaters following unprecedented residential home damage. How exposures to these floodwaters, and their associated contaminants have affected population health are still being studied and remain largely unexplored. However, a study from our lab constituting of over 40,000 deliveries occurring before, during and after Hurricane Harvey revealed that pregnant women and their infants had a higher likelihood of adverse outcomes if they delivered after landfall of the Hurricane [81]. We continue to study a longitudinal cohort to determine specific changes to the maternal and neonatal microbiomes from exposure to the floodwaters of Harvey, and how this is further associated with maternal and neonatal outcomes ([ClinicalTrials.gov Identifier: NCT02392650](https://clinicaltrials.gov/ct2/show/study/NCT02392650)). Suffice it to say, with the ongoing threat of climate change being realized as increased flooding in coastal communities, it is of imminent need to be understood what the

risks are, how and why they are conferred on human health, and what potential mitigations may be of benefit.

Future Directions

We are in an exciting and impactful time in our understanding of the role human play on the environment, and how the environment in turn affects human health. As our working knowledge increases, we are beginning to understand the potential limitations to mitigation efforts. As is only too often the case with respect to these deepening understandings of the role human activity plays on negatively impacting our increasingly fragile environment, the time for focused efforts with a sense of crisis and urgency has arrived. Considering that environmental exposures interact with and modify the microbiome, and that the microbiome interacts and modifies environmental chemicals, we believe that there is no more important opportunity for practical and relevant translational research than perinatal environmental microbial health. We can imagine no more important activity than interrogations which are dedicated and committed to understanding if, how, and when there are opportunities for correcting the health of the current and coming generations in response to environmental exposures. Alternately, if these processes are largely irreversible, then we must ardently undertake large scale efforts to mitigate these exposures at a local, regional and global levels. The very health of not only our species but nearly every living and reproducing species depends on such efforts.

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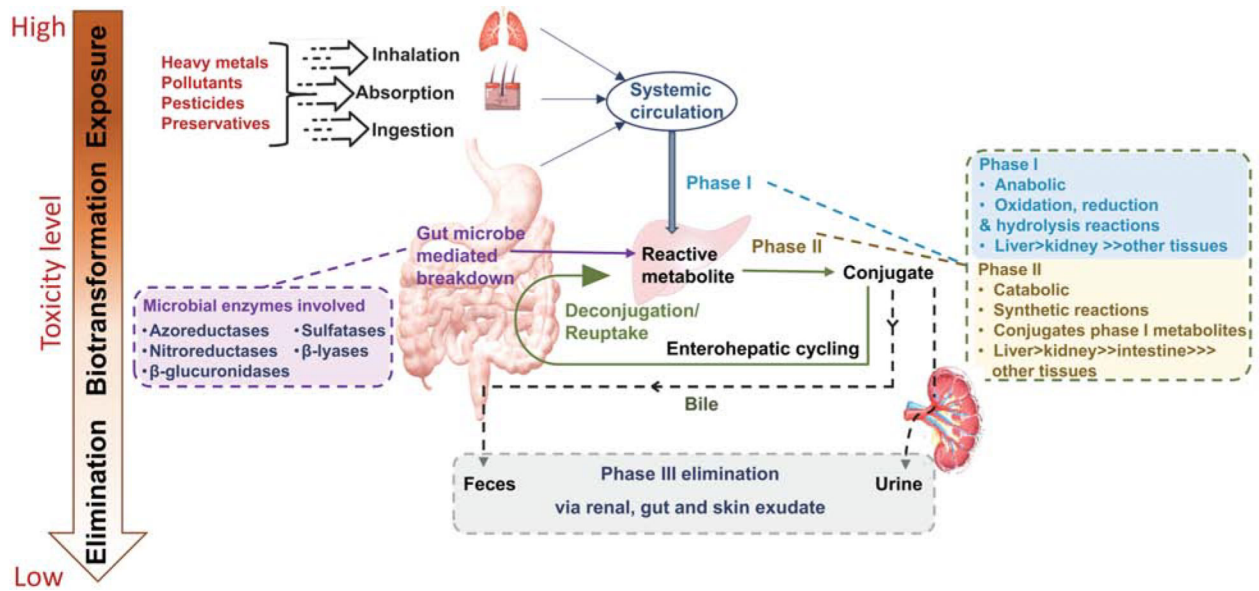


Figure 1.

Diagrammatic representation of environmental chemical exposure routes, human and microbial biotransformation pathways, and elimination of metabolites and small molecular intermediates.

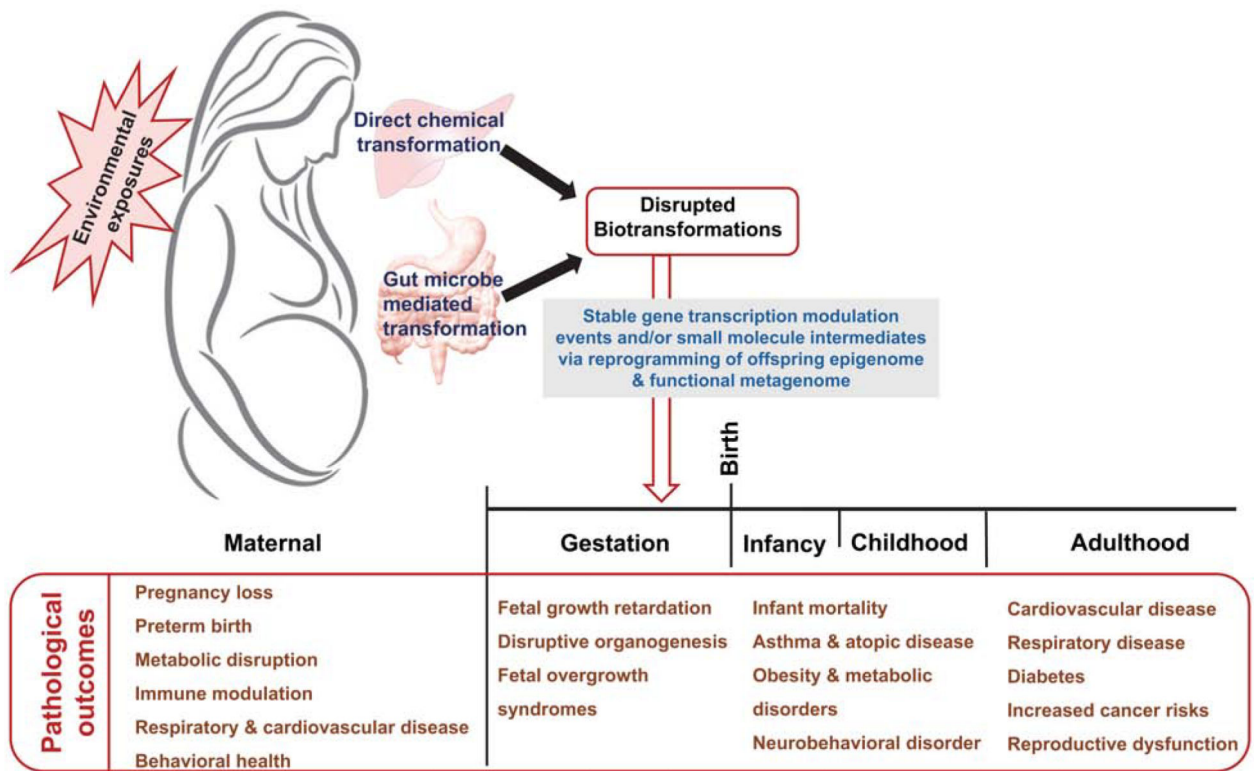


Figure 2. Diagrammatic representation of the outcomes of environmental exposures across the life stage.