Prenatal Pesticide Exposure and Child Health

Monica K. Silver and John D. Meeker

1 Introduction

Fetuses are rapidly developing, making them highly vulnerable to the long-lasting effects of pesticide exposure. Important windows of susceptibility occur in utero and exposure during these highly vulnerable periods, even to low levels that might not affect adults, may have the potential to lead to long-term health effects [1–3]. Fetal susceptibility to pesticides is further augmented by the fact that many pesticides can cross the placenta [4]. Fetuses also have lower levels of detoxifying enzymes to metabolize pesticides [5] and immature metabolic pathways, which results in slow excretion [6].

This chapter provides an overview of the human evidence for associations between prenatal exposure to some common pesticides and adverse impacts on child health and development, focusing specifically on neurodevelopment, obesity, preterm birth (PTB)/fetal growth, congenital abnormalities (CAs), and childhood cancers as the health end points of interest. This chapter is not meant to be an exhaustive review of all health effects that have been associated with early life pesticide exposure, but rather a compilation of some of the most notable findings for common childhood morbidities. Contemporary review and primary research articles are referenced here, and readers are directed toward those for additional details. For further information regarding specific biological mechanisms of prenatal pesticide exposure and child health outcomes, interested readers are encouraged to explore the related toxicology literature.

M. K. Silver · J. D. Meeker (✉)
Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI, USA
e-mail: meekerj@umich.edu

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2 Assessment of Prenatal Pesticide Exposure

Assessment of prenatal pesticide exposure typically falls into one of two categories, biomarker or ecological/environmental assessment (Fig. 1). Exposure assessment using biomarkers is preferred as it can provide a more precise measurement of exposure, as well as capture all routes of exposure. Two examples of biomarkers sometimes used to determine prenatal pesticide exposures are maternal blood during pregnancy and umbilical cord blood. These can provide direct evidence of prenatal exposure during pregnancy, though pesticide levels in blood tend to be low, particularly for the contemporary pesticides with short half-lives, which can make detection difficult [7]. Collection of maternal blood during pregnancy is also invasive and therefore not always the best choice. One of the most common biomarkers for assessing prenatal exposure is the measurement of pesticide metabolites in maternal urine samples taken during pregnancy. Urine collection is simple and noninvasive, making collection at multiple time points more feasible. A disadvantage of using urinary metabolites is that they are often class specific, but not necessarily pesticide specific. For example, the majority of organophosphate pesticides (OPs) are excreted in urine as dialkylphosphate (DAP) metabolites. While DAPs do reflect exposure to OPs, they are not specific to any single pesticide and may also represent exposure to the DAPs themselves, which are nontoxic, as OPs degrade into DAPs naturally in the environment [8]. Other less commonly seen biomarkers include amniotic fluid collection during pregnancy or placental tissue extraction at birth. Meconium, the infant's first stool, can also provide a measurement of prenatal pesticide exposure. It contains materials ingested by the fetus in the last half of gestation and can provide information about fetal exposure for up to 20 weeks. The alternative way of assessing exposure is known as ecological exposure assessment. It tends to be less

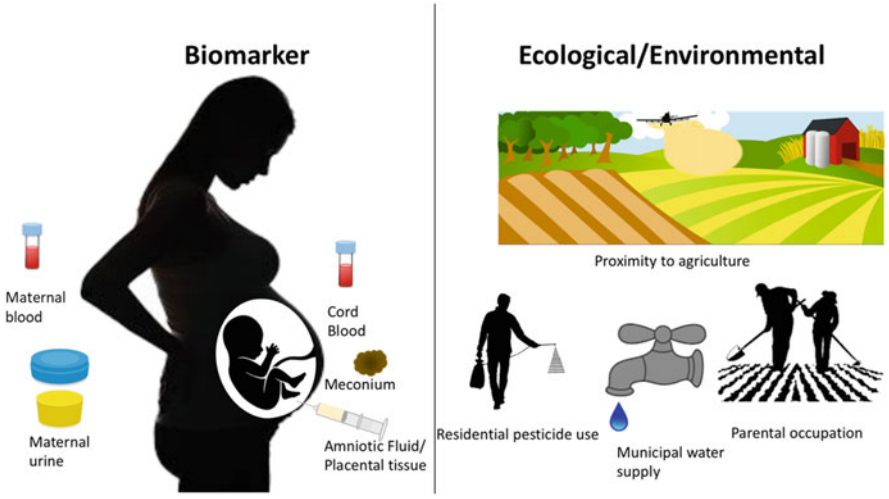

Fig. 1 Most common methods of determining prenatal exposure to pesticides

precise, in general, but is common in studies where biomarkers of exposure are not used.

Common types of ecological/environmental prenatal exposure assessment include residential proximity to agriculture or pesticide use sites during gestation. While pesticide application records may be accurate, it is difficult to determine the level of individual exposure. Living near an agricultural site does not necessarily result in consistent exposure to pesticide spray drift. Parental occupation during pregnancy or around conception is also often used to estimate exposure to certain pesticides, as are residential use surveys. Residential use surveys seek to determine what types of pesticides may have been used in or around the home during pregnancy. While these less precise methods of exposure assessment tend to be much less expensive than a biomarker study because there are no laboratory expenses for analysis or storage, they tend to rely on recall, which can be problematic. Recall bias may occur when parents whose children have a health problem may be more likely to or incorrectly recall using pesticides during their pregnancy than parents of healthy children, thereby potentially biasing study results.

3 Persistent Versus Nonpersistent Pesticides

The vast majority of pesticides in use today are classified as "nonpersistent," meaning that they generally have relatively short half-lives (hours to days) in the environment and the human body. These chemicals are largely believed to be "safer" than their more persistent counterparts, which tend to have much longer half-lives (months to years). Persistent pesticides, such as the organochlorines (OCs) dichlorodiphenyltrichloroethane (DDT), aldrin, dieldrin, and endrin, favored for their broad-spectrum activity and low cost, were heavily used in the 1940s for controlling a wide variety of pests affecting agriculture and human health [9]. Overuse of these pesticides was common and resulted in harmful effects on nontarget species and the development of genetic resistance to pesticides in some target species. Concerns of widespread health effects led many countries to shift to more nonpersistent pesticides in the 1970s. In addition to faster breakdown times, the nonpersistent pesticides also tend to be more "pest specific" and therefore believed to be safer for nontarget species. In 2001, the Stockholm Convention went so far as to mandate a global ban on nine persistent pesticides: aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, hexachlorobenzene (HCB), mirex, and toxaphene [10]. Endosulfan, chlordecone, and lindane have since been added to the banned list as well. Despite the phasing out of these persistent pesticides, exposure remains a public health problem because of their persistence in the environment and continued exempted uses in some countries. For example, while banned for agricultural use, DDT is still used as an effective way to control mosquitos in countries with high malaria prevalence.

Most pesticides in use today are nonpersistent and designed to break down quickly. However, it has been shown that even nonpersistent pesticides can remain

for years after application in homes and other indoor environments where they are protected from moisture, sunlight, and other degradation mechanisms. Common classes of nonpersistent pesticides include OPs, carbamates, and pyrethroids. These pesticides were all considered "safe" when introduced into the market; however, similarities between insect and human nervous systems can lead to shared toxicity [9]. This book chapter largely focuses on the most common nonpersistent pesticides in use today and also touches on the persistent pesticides of the past.

4 Health Outcomes

4.1 Neurodevelopment

Neurobehavioral disorders, such as autism spectrum disorder (ASD) and/or attention-deficit/hyperactivity disorder (ADHD), appear to be on the rise globally [11]. Nearly ubiquitous exposure to pesticides in the environment may play a role in the global uptick of these disorders [11]. Pesticides are neurotoxic by design and rapidly developing fetal brains may be an unintended target. Comprehensive reviews and numerous epidemiologic studies across countries, populations, and settings have reported significant associations between prenatal OP exposures and deficits in cognitive, behavioral, and social development in childhood [12–14]. Affected outcomes include deficits in memory, processing speed, verbal comprehension, perceptual reasoning, and IQ, as well as mental and motor delays, abnormal reflexes, and increased risk of developing ASD and/or ADHD [15]. Recent studies continue to support the notion that early life exposure to OPs is detrimental to the developing brain. Children born to residences in proximity to agricultural fields where OPs are applied have a higher likelihood of ASD diagnosis [16] and a reduction in IQ [17]. Impaired neurodevelopment was greater among children of farmworkers [18]. OP metabolite concentrations in maternal urine during pregnancy were also associated with ASD traits in adolescence [19], while cord blood concentrations were associated with arm tremors in children [20]. While recent studies also report no association between agricultural OPs and developmental delay [16] or maternal OP metabolites with intelligence test scores in urban settings [21, 22], the overall body of evidence that prenatal OP exposure can adversely affect neurodevelopment in children is convincing.

The effects of prenatal exposure to other nonpersistent pesticides, such as pyrethroids, on child neurodevelopment are less well studied. Recent studies have reported that pyrethroid metabolites in maternal urine during pregnancy were associated with ADHD symptoms [23], internalizing difficulties [24], and a variety of behavioral problems and poorer executive functioning deficits [25] in children and mental functioning in infants [26] and poorer social-emotional [27], language [27], and mental development [28] in toddlers. However, other studies have reported no significant associations between prenatal pyrethroid metabolites and motor functioning in infants [26] or cognitive scores in children [29].

Studies of persistent pesticides, such as the OC DDT, are also limited and have mixed results. Cord blood levels of DDT have been associated with deficits in cognitive skills in preschoolers (verbal and memory tests) [30]. DDT and/or its metabolite, dichlorodiphenyldichloroethylene (DDE), measured in maternal serum during pregnancy were also associated with a significant reduction in psychomotor development in infants in one study [31], but not neurodevelopmental deficits in infants [32] or toddlers [27, 33] in three others.

4.2 Obesity

The rapidly increasing prevalence of overweight and obesity worldwide may result from environmental chemical obesogens [34, 35], altering lipid homeostasis to accelerate lipid accumulation and adipogenesis. There have been studies investigating the possible role of prenatal pesticides as environmental obesogens with outcomes in childhood such as obesity and BMI. Unfortunately, there is a dearth of epidemiological research concerning prenatal nonpersistent pesticide exposure and childhood obesity. One study examined the effects of prenatal dialkylphosphate (DAP) metabolites measured in maternal urine during pregnancy on markers of glucose metabolism, adiponectin, and insulin, in umbilical cord blood serum. Insulin levels were associated with higher urinary DAPs, but adiponectin levels were not [36]. A research assessed prenatal nonpersistent pesticide exposure by employment of pregnant women in a greenhouse and found that pregnant women who were the most highly exposed to pesticides may lead to increased skinfold thickness, BMI, and percentage of body fat in children [37].

Most contemporary research about persistent pesticide exposure during pregnancy and childhood obesity and other health outcomes have focused on DDT and/or DDE and few other OCs and have yielded mixed results. Studies have found that DDT and DDE in either maternal serum or cord blood are positively associated with waist circumference, BMI, and risk of obesity (for DDT and DDE) significantly [38] and risk of overweight (for DDT) [39]. Multiple studies have reported that prenatal DDE was associated with overweight [39], increased waist circumference [40], and BMI [40, 41] in girls, while another study reported a decrease in insulin and adiponectin levels in umbilical cord blood with increased levels of DDE, only in girls [36]. One additional study found that prenatal DDT and DDE were associated with adiposity measures and BMI in boys, but not girls [42]. Other studies have reported no associations between prenatal DDT/DDE [43, 44] and other organochlorine pesticides [43] and increased risk of obesity, overweight, or increased BMI in children.

4.3 Preterm Birth/Fetal Growth

Preterm birth (PTB), defined as delivery prior to 37 weeks of gestation, occurs in approximately 10% of pregnancies and is one of the strongest predictors of neonatal mortality and morbidity worldwide [45]. Likewise, extremely low or high birth weight is also a well-known risk factor for neonatal mortality and morbidities in infancy and childhood [46]. Investigations of nonpersistent pesticides and preterm birth (PTB) are limited. Until recently, they have mainly focused on OPs and the herbicide atrazine [47]. No associations were reported between maternal exposure to OPs and PTB [48, 49] and studies of atrazine, measured in drinking water, are similarly inconclusive [50–53]. One additional study similarly found no associations between individual or total urinary pyrethroid levels and length of gestation [54]. A more recent study examined prenatal exposure to 17 agricultural pesticides and three nonpersistent pesticide classes (OPs, pyrethroids, and carbamates) and their associations with PTB. Pesticide exposure that occurred in the first or second trimester of pregnancy and exposure to multiple pesticides (two or more) were associated with an increased risk for PTB; results were strongest for girls [55].

Contemporary review studies examining the strength of evidence for associations between prenatal exposure to nonpersistent pesticides and measures of fetal growth have reported mixed results [46]. The bulk of epidemiological research has been focused on OPs, with exposures typically measured using maternal urinary metabolites during pregnancy [46]. Overall, results were largely null, though a few studies yielded significant findings, particularly in some subpopulations of interest. Maternal urinary DAPs were associated with lower birth weight [56, 57], smaller head circumference [58, 59], and birth length (non-Hispanic black women only) [60], while a metabolite specific to parathion and methyl parathion was also associated with birth length [48]. In addition to OPs, a few studies have also examined maternal urinary metabolites of other nonpersistent pesticides with mixed results [54, 61–63]. 3-Phenoxybenzoic acid (3-PBA), a commonly studied pyrethroid metabolite, has been associated with smaller birth size [61], while total pyrethroid metabolites were associated with birth weight, but not birth length [54]. The herbicide atrazine was similarly associated with decreased birth weight and head circumference, while metolachlor levels were inversely associated with head circumference [52]. An additional study measured nonpersistent pesticides in the umbilical cord and found reduced birth weight in newborns with higher total number of pesticides detected [64]. Several others used less precise methods of assessing exposure, such as maternal occupation during pregnancy [37] and residential proximity to agricultural pesticides during pregnancy [55]. Newborns whose mothers had high occupational exposure during pregnancy had lower birth weights [37], yet residential exposure to agricultural pesticides was not associated with low birth weight for all but one (myclobutanil, a fungicide) of 17 pesticides studied [55].

Current studies of prenatal exposure to persistent OCs and PTB reveal a possible association. Umbilical cord serum levels of hexachlorocyclohexanes (HCHs) [65] and HCB [66], and maternal serum levels of chlordecone [67], were associated with

shortened gestational age. Women who delivered preterm had significantly higher placental levels of HCHs, DDE, and DDT compared to those with term deliveries [68], and total placental OCs were significantly associated with increased risk of PTB [69]. In contrast, another study found no association between a number of OCs in maternal serum and preterm birth [70].

For persistent pesticides, total OCs detected in placental tissues were significantly associated with increased risk of low birth weight [69], while hexachlorobenzene (HCB) measured in maternal serum was inversely associated with indices of fetal growth and higher odds of being small for gestational age [71]. HCB in umbilical cord serum was also associated with reduced abdominal circumference growth in early pregnancy (as a measure of fetal growth), as estimated by ultrasound, though no associations were observed for DDE with any of the longitudinal fetal growth curves [72].

4.4 Congenital Abnormalities

According to the World Health Organization, congenital abnormalities (CAs), sometimes referred to as birth defects, resulted in the death of over 2.5 million infants within their first month of life between the years 2000 and 2015 [73]. Here we discuss the evidence concerning the associations between prenatal exposure to pesticides and CAs of the urogenital, musculoskeletal, and cardiovascular systems, as well as neural tube defects (NTDs).

Cryptorchidism, when one or both testes are undescended, and hypospadias, when the opening of the urethra is on the bottom of the penis instead of the tip, are the most common urogenital CAs. Review studies of the associations between nonpersistent pesticides, measured directly using biomarkers, and urogenital CAs were inconclusive [74]. However, positive associations were observed for persistent OCs measured in breast milk [75] and placental tissue [76] in relation to cryptorchidism [75, 76] and hypospadias [76]. Several studies linked hypospadias and/or cryptorchidism with specific pesticides including mirex and lindane in the placenta [76], hexachlorobenzene [77], and DDT and metabolites [78] in maternal serum, and trans-chlordane in breast milk [75]. When ecological measures of overall pesticide exposure were used to define prenatal exposure, associations with hypospadias and cryptorchidism were largely positive [74]. Studies revealed that county-level estimates of atrazine exposure during pregnancy were associated with the risk of hypospadias and cryptorchidism [79], as well as an increased risk of hypospadias [80, 81] and cryptorchidism [80] in boys whose parents self-reported occupational exposure to pesticides during the pregnancy.

The most common musculoskeletal abnormalities (MSAs), or CAs of the skeletal and muscular system, are gastroschisis and reduction defects of the upper limbs. Studies of associations between these MSAs and prenatal exposure to pesticides appear to be limited to a few studies with only ecological assessments of exposure. Review studies indicate an overall positive association between occupational/

environmental prenatal pesticide exposure and MSAs [74]. Women who worked in the agriculture industry [82], as well as those with self-reported occupational exposure to insecticides, herbicides, and fungicides [83], during pregnancy had an elevated risk of having offspring with limb defects. Environmental atrazine exposure (residential proximity) was also associated with increased risk of gastroschisis [84, 85].

Cardiovascular abnormalities (CVAs) are the leading CA-related cause of death in newborns [86]. Though only a handful of studies have assessed prenatal pesticide exposure and CVAs, a general positive association is observed overall [74]; however, results should be interpreted with caution given the sole use of ecological exposure assessments. Residential proximity to the agricultural application of a variety of pesticides was found to be associated with a number of CVAs [87]. For example, increased odds of pulmonary valve stenosis and ventricular septal defects were observed with exposure to OPs and pyrethroids, respectively [87]. Maternal residential use of herbicides and rodenticides during pregnancy was associated with an increased risk of transposition of the great arteries in their newborns [88], while maternal occupational exposure to insecticides, herbicides, and fungicides was associated with an increased risk for other CVAs, such as tetralogy of Fallot [89].

Neural tube defects (NTDs), CAs of the brain, spine, or spinal cord, occur during the first month of pregnancy. The few available studies are suggestive of a positive association between prenatal pesticide exposure and NTDs, though exposure was assessed indirectly for most of the studies, so results should be interpreted with caution. Maternal exposure to persistent OCs, measured in serum, was associated with an increased risk of NTD occurrence in offspring [90]. Several other studies showed positive associations between parental occupational exposure during pregnancy to unspecified pesticides and anencephaly and spina bifida, the two most common NTDs, as well as others [91–93].

4.5 Childhood Cancers

The overall body of research suggests that prenatal pesticide exposure may be associated to the development of leukemia and brain tumors in childhood, though, in general, these studies tend to be limited by their assessment of prenatal exposure, making it hard to draw definitive conclusions. Review articles [94] and meta-analyses reveal associations between prenatal pesticide exposure and childhood leukemia. For example, several meta-analyses have reported that residential pesticide exposure in the few months before conception [95] and during pregnancy [95–97] was associated with an increased risk of childhood leukemias. Another large meta-analysis found a significantly increased risk of lymphoma and leukemia in children whose mothers were exposed to personal household use or professionally applied pesticides during the prenatal period [98]. Maternal prenatal exposure was also associated with a significantly increased risk of childhood brain tumors (CBTs) among offspring, for both agricultural [99] and residential pesticide exposures

[99, 100]. Interestingly, two meta-analyses have also revealed increased risks of childhood brain tumors (CBT) [99] or brain cancer [98] with paternal prenatal or preconception pesticide exposure.

5 Conclusions

Here we have summarized some epidemiological evidence that prenatal exposure to contemporary-use pesticides may be associated with alterations in infant and child health and development, specifically neurodevelopment, obesity, pre-term birth/fetal growth, congenital abnormalities, and childhood cancers (Table 1). Perhaps the strongest evidence is for the effects of early life exposure to pesticides on neurodevelopment. Pesticides are neurotoxic by design, each with a prescribed mechanism of toxicity and target organism(s). While the effects of high exposures in humans often mirror those seen for target organisms, low-dose effects in humans seem to disrupt alternative pathways, such as through endocrine or thyroid disruption, oxidative stress, interference with signaling pathways, or epigenetic changes.

Table 1 Summary of the health effects in children related to prenatal pesticide exposure and research needs

Health outcome	Summary of findings	Research needs
Neurodevelopment	Nonpersistent OPs adversely impact neurodevelopment; persistent OCs may be associated with neurodevelopment	Additional studies of other common nonpersistent pesticides; additional longitudinal studies and mixture analyses
Obesity	Few studies of nonpersistent pesticides; persistent OCs may be associated with obesity-related health outcomes	Studies of nonpersistent pesticides; longitudinal studies and mixture analyses
Pre-term Birth/fetal growth	Nonpersistent pesticides do not appear to be associated with PTB but may be with reduced fetal growth; persistent pesticides may be associated with PTB/fetal growth	Additional studies of nonpersistent pesticides; longitudinal studies and mixture analyses; measurements of fetal growth using ultrasound
Congenital abnormalities	Persistent pesticides may be associated with urogenital CAs; pesticides may be associated with MSAs, CVAs, and NTDs	Studies of nonpersistent pesticides and urogenital CAs; biomarker studies of specific persistent and nonpersistent pesticides and MSAs, CVAs, and NTDs; longitudinal studies and mixture analyses
Childhood cancer	Pesticides may be associated with childhood leukemia and brain tumors	Biomarker studies of specific persistent and nonpersistent pesticides and leukemia and brain tumors; longitudinal studies and mixture analyses

Perturbation of these pathways at critical times of growth could potentially lead to downstream health effects.

While much of the literature reviewed in this chapter supports a growing body of evidence that pesticides may adversely affect child health and development, more work needs to be carried out before any conclusions regarding causation can be drawn with certainty. The strongest evidence presented here comes from studies where biomarkers of exposure were measured, such as maternal urine or blood or umbilical cord blood, especially those that assessed exposure at multiple time points. Exposure biomarkers, as opposed to more ecological measures of exposure, such as proximity to agriculture, or self-reported residential/occupational exposures, which may be subject to recall bias, provide direct evidence of exposure from any source. Studies that collected exposure biomarkers at multiple time points throughout pregnancy are also preferred over those that collected only measurement. Using only one time point to estimate prenatal exposure may be problematic, especially for nonpersistent pesticides. Exposure at one point in time may not necessarily be representative of exposure over the course of the pregnancy. It cannot capture temporal or intraindividual variability in exposure or allow for identification of the sensitive windows of susceptibility during gestation. Further, epidemiological studies should be used in conjunction with toxicology/animal studies to help establish the causality and elucidate specific biological mechanisms, individual susceptibility factors, and sensitive windows of exposure. Additionally, research exploring the health effects following exposure to multiple pesticides simultaneously is also needed. More studies are beginning to account for multiple exposures to real-life mixtures, though these can make interpretation (e.g., risk assessment, risk management, and regulation) challenging.

Given all these factors and the large variability across epidemiological studies, it is problematic to determine whether there are "safe" levels of gestational exposure to pesticides. Although many of the risk estimates reported in the literature seem small on an individual level, even a seemingly small shift in the population distribution could be important in a public health perspective. Given the nearly ubiquitous exposure to pesticides among the general population, the vulnerability of fetuses, and the potential for long-term effects on health and development, efforts to reduce pesticide exposure as a precaution among pregnant women are warranted.

In conclusion, this chapter presents studies that indicate that prenatal pesticide exposure may adversely affect child health and development. Many of the current studies are limited by nonspecific exposure assessments and cross-sectional study designs that do not account for temporal variability in pesticide exposure, especially for nonpersistent pesticides, or identify sensitive windows of susceptibility during gestation. Additional well-designed longitudinal studies that measure exposure at multiple potentially sensitive time points and exposure to multiple pesticides simultaneously are needed, as well as the development of novel, noninvasive biomarkers for measuring these exposures. Still, given the range of potentially serious developmental effects and widespread exposure in the population, efforts to reduce pesticide exposure as a precaution among pregnant women are likely prudent.

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