REVIEW

Early-life Exposure to Widespread Environmental Toxicants and Health Risk: A Focus on the Immune and Respiratory Systems

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Abstract

Evidence has accumulated that exposure to widespread environmental toxicants, such as heavy metals, persistent organic pollutants, and tobacco smoke adversely affect fetal development and organ maturation, even after birth. The developing immune and respiratory systems are more sensitive to environmental toxicants due to their long-term physical development, starting from the early embryonic stage and persisting into early postnatal life, which requires complex signaling pathways that control proliferation and differentiation of highly heterogeneous cell types. In this review, we summarize the effect of early-life exposure to several widespread environmental toxicants on immune and lung development before and after birth, including the effects on immune cell counts, baseline characteristics of cell-mediated and humoral immunity, and alteration of lung structure and function in offspring. We also review evidence supporting the association between early-life exposure to environmental toxicants and risk for immune-related diseases and lung dysfunction in offspring in later life.

KEY WORDS early-life exposure, heavy metals, tobacco smoke, persistent organic pollutants, immune development, lung

INTRODUCTION

The "developmental origin of health and disease" theory hypothesizes that disease in adulthood has fetal origins.[1] In support of this, it has been shown that environmental signals influence the structure and function of fetal organs, and subsequently affect susceptibility to disease later in life.[2] A series of insightful epidemiologic studies have demonstrated that maternal malnutrition during pregnancy was associated with high susceptibility to cardiovascular disease and obesity in offspring.[3,4] In these studies, maternal malnutrition facilitated fetal adaptation to a nutrition-restricted environment after birth.

However, the mismatch between prenatal malnutrition and a rich postnatal food supply caused suboptimal function of organs and cells, which predisposed offspring to obesity and related diseases later in life. Currently, massive amounts of environmental pollutants are rapidly accumulating in industrializing countries. The widespread environmental pollutants, such as heavy metals, persistent organic pollutants (POPs), and tobacco smoke can be detected in both maternal and cord blood in various areas in the world. Prenatal exposure to these environmental toxicants has been demonstrated to affect immune and lung function in offspring.[5-10] These toxicants may firstly affect the maternal side, which then provides indirect signals to the fetus, or directly affects the fetus to program cell- or tissue-specific functional alterations in offspring. Because development of the immune and respiratory system is still proceeding after birth,[11-13] environmental toxicants could continue to be a threat to maturation of immune and lung function after birth. Developmental exposure to environmental toxicants, which may induce maladaptive alteration in organs or cells, would become an early origin of immune- and lung-based diseases in children or adults in the modern world. It is urgent to better understand how exposure to environmental toxicants in early life affects immune and lung function, and how toxicants alter the risk for diseases later in life.

EARLY-LIFE EXPOSURE TO ENVIRONMENTAL TOXICANTS: IMMUNE STATUS IN OFFSPRING AND IMMUNE-BASED DISEASES LATER IN LIFE

Effect of Prenatal/Early-Postnatal Exposure to Environmental Toxicants on Immune Cell Counts in Offspring. *Heavy metals.* Arsenic (As) and lead (Pb) are common environmental contaminants to which people are primarily exposed from drinking water and diets. In a prospective birth cohort recruited in Bangladesh, maternal exposure to As in drinking water had an exposure-dependent effect on specific T-cell subpopulations in cord blood. Higher As concentrations were associated with an increased percentage of CD8+ T cells and decreased percentage of CD4+ T cells in cord blood.[14] In a study from the United States, maternal urinary As concentrations were inversely related to the absolute total cord blood activated T-cell count (CD45RA+CD69+CD4+) and positively associated with absolute T-helper 2 (CD45RA+CD69-CD294+) cell counts.[14]

Additionally, school children who were exposed to higher As levels had a decreased percentage of CD4+ T cells and reduced ratio of CD4 to CD8.[15] High levels of Pb exposure (mean Pb level: 140.6 μg/L) in children also correlated with a reduced percentage of CD4+ cells,[16] showing that early-life exposure to As or Pb is associated with increased risk for adverse health outcomes later in life.

The dose- and sex-specific effects of heavy metals on immune cell count in offspring was further shown in animal models. In 13-week-old female F344 rat offspring whose mothers were exposed to low levels of Pb (250 ppm in drinking water) during pregnancy, the relative neutrophil numbers were higher, whereas the relative and absolute monocyte numbers and relative basophil numbers were lower in spleen compared with offspring in the control group. Interestingly, the male offspring of the same age did not display any changes in these cell counts.[17] However, in 5-week-old male offspring with maternal exposure to 100 ppm of Pb in drinking water during pregnancy, the relative neutrophil number was higher, whereas the relative lymphocyte number was lower.[17] Prenatal exposure to cadmium (Cd) resulted in a higher percentage of CD4−CD8−CD44+CD25− (double-negative stage 1) thymocytes, spleen B cells, and CD4+ T cells in 20-week-old male and female C57BL/6 mouse offspring. Meanwhile, the percentage of spleen neutrophils and myeloid-derived suppressor cells, natural killer (NK) cells, and granulocytes were both lower in these offspring.[18] Additionally, the percentage of spleen CD8+ T cells was higher in female offspring, but lower in male offspring when compared with the controls.[18] Prenatal Cd exposure also increased percentage of thymus CD4+Foxp3+CD25+ regulatory T cells in both male and female mice offspring at 7 weeks of age, whereas it decreased the percentage of splenic CD4+Foxp3+CD25+ regulatory T cells in female offspring.[5] In contrast, the percentage of splenic CD4+Foxp3+CD25+ regulatory T cells was all decreased in male and female mice offspring at 20 weeks of age in the Cd-exposed group.[18]

Only 1 group evaluated percentage of splenic natural regulatory T cell at multiple time points (7- and 20-week-old) in offspring.[5,19] The percentage of splenic natural regulatory T cell in male offspring with prenatal Cd exposure was not consistent between the 2 time points. The fluctuation in offspring may reflect interindividual variety or differed effects of prenatal exposure to Cd on development and homeostasis of splenic natural regulatory T cell at different stages. Considering that most studies mentioned here only

evaluated cell constituents at one time point, the interpretation of the long-term effects of prenatal exposure to heavy metals on the immune system based on cell count data was not accurate in these studies.

Persistent organic pollutants. Polychlorinated biphenyls (PCBs), a class of typical organochlorine compounds, modulate peripheral immune cell differentiation and maintenance with dose-dependent manner. In children prenatally exposed to PCBs, CD3+ T lymphocytes, B lymphocytes, and activated B lymphocytes were significantly higher in the high-exposure group than in low-exposure group at 6 or 16 months old.[19] Moreover, percentage of memory T lymphocytes (at birth, 6 months, and 16 months), terminally differentiated memory T cells (at birth and at 6 months), and lymphoid dendritic cells (at 6 months) in the high-exposure group were also significantly higher than in the low-exposure group at corresponding ages.[19] Prenatal exposure to environmental background levels of PCBs was associated with an increased number of lymphocytes, T cells, CD8+ T cells, CD4+CD45RO+ memory T cells, TCRαβ+ T cells, and CD3+HLA-DR+ activated T cells in children at 42 months of age.[20]

Prenatal PCB exposure also directly disturbed thymocyte maturation. It caused thymic atrophy in chicken embryos and in neonatal child.[21-24] In chicken embryos, the total number of thymocytes, TCRαβ+ thymocytes, lymphoid cells, CD4+CD8+, and CD4-CD8+ lymphocytes decreased with increasing doses of PCB-126, a PCB congener.[23] Furthermore, for full-term exposure, the dose of the dioxin-like PCB-126 required to cause reduction of live lymphoid numbers in the thymus and bursa was much lower than for exposure only during the late stage of incubation in chicken embryos (since day 13 of incubation).[24]

Exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at an early stage of life also may interfere with the T-cell maturation process in the thymus and subsequently alter cell distribution in human. In one study, prenatal exposure to higher levels of PCB/dioxin was associated with increased numbers of TCRγδ+ T cells at birth, and with increases in total T-cell number and number of CD8+ T cells, TCRαβ+ T cells, and TCRγδ+ T cells at 18 months of age.[25] Similarly, in 10-month-old infants who were exposed to dioxins, PCBs and organochlorine pesticides, higher levels of heptachlor epoxide, chlordane, and dioxins in breast milk were significantly associated with increased percentages of CD8+ T cells and CD3+ T cells, and the CD4+-to-CD8+ ratio, respectively.[26] Additionally, neonates exposed to background levels of dioxin not

only had an increased percentage of CD4+ T cells, but also increased CD45RA+-naive T cells at 8 years of age.[27] Perinatal exposure to dioxins was positively associated with percentages of CD4+ T cells, but negatively associated with percentages of CD8+ T cells in the blood of breast-fed infants.[28] Because T-cell maintenance is supported by thymus emigrant and peripheral homeostasis proliferation in early stages of life, it is not impossible that prenatal exposure to TCDD may affect peripheral T-cell maintenance mechanism to alter T-cell distribution in offspring. Except for effect on T-cell distribution, early postnatal exposure to high levels of PCB/dioxin was associated with lower monocyte and granulocyte counts in infants at 3 months of age.[25]

Animal studies clearly demonstrated that prenatal TCDD exposure is able to directly affect thymocyte maturation. Prenatal TCDD exposure impaired seeding of lymphocyte stem cells in murine fetuses and neonates.[29,30] Gestational exposure of mice to TCDD increased the count of less mature CD4−CD8+J11d+ thymocytes at embryonic day 18 (E18), whereas the more mature CD4−CD8+J11d− was not significantly changed, indicating suppression of thymocyte maturation at the transition phase.[31] The decreased percentages of CD4+CD8+ fetal thymocytes, as well as the increased percentages of CD4−CD8− and CD4-CD8+ fetal thymocytes further suggested inhibition of normal thymocyte maturation by prenatal exposure to TCDD.[32] This impairment of thymocyte maturation persisted into adulthood in both rats and mice that were prenatally exposed to TCDD.[33,34] However, animal studies did not provide further evidence of how prenatal TCDD exposure affect T-cell maintenance in periphery and cannot fully explain the result in human studies.

Tobacco smoke. Increased circulating white blood cells (WBCs) and lymphocyte numbers were observed in neonates from mothers who smoked during pregnancy.[35,36] Additionally, the reduced number of neutrophils in infants from mothers who smoked was associated with maternal smoking during pregnancy.[37] B6C3F1 mice offspring who was exposed in utero to cigarette smoke also had increased numbers of circulating WBCs and lymphocytes at 2.5 months of age.[38] However, no significant difference was found in subpopulations of immune cells from the lymphoid organ in these offspring when compared with sex- and age-matched control offspring.[39] These limited data indicate that maternal smoking may affect the early stage differentiation of immune cells in offspring.

Taken together, exposure to environmental toxicants in early life usually altered profiles of myeloid and lymphoid lineage cell counts through perturbation of thymocyte maturation, or interference with maintenance of immune cells in periphery. The effect was dose and sex dependent. Because most of studies evaluated profiles of immune cell counts in a relatively short period of time since exposure to environmental toxicants occurred, more studies are needed to determine long-term effect of early-life exposure to environmental toxicants on immune cell counts in adulthood.

Effect of Prenatal/Early-Postnatal Exposure to Environmental Toxicants on Status of Cell-Mediated Immunity in Offspring. *Heavy metals.* Prenatal and early-postnatal exposure to heavy metals may alter baseline characteristics of cell-mediated immunity. Rats (35-45 days of age) prenatally exposed to low levels of Pb (0-50 ppm in drinking water) had a suppressed lymphocyte response to mitogen stimulation and a reduced delayed hypersensitivity response.[40] The suppression of delayed type hypersensitivity (DTH) response was also found in 5- or 13-week-old female F344 rat offspring who were prenatally exposed to moderate levels of Pb (250 ppm in drinking water).[17,41] In contrast, a similar suppression was not observed in male rat offspring.[17,42] Additionally, there was no significant alteration in DTH to bovine serum albumin (BSA) in chicken offspring exposed to Pb at E5.[43-45] However, the DTH response to BSA was markedly decreased in chicken offspring exposed to Pb at E12.[44] Except for the decrease in DTH, female rat offspring exposed to 500 ppm Pb during pregnancy had a decrease in interferon (IFN)-γ levels.[41] Similar results were also found in 5- to 6-week-old rat offspring.[17] In adult male Sprague-Dawley rat offspring exposed to Pb during E15 to 21, interleukin (IL)-12 production increased, whereas IL-10 production decreased, in contrast to the increase of IL-10 production in matched female offspring.[42] These data indicate that prenatal Pb exposure generally suppresses cell-mediated immune responses in offspring, even under low levels of exposure. The exposure window and sex are 2 crucial factors to determine the immunotoxicity of Pb exposure in early life.

Prenatal exposure to Cd also resulted in decreased splenocyte production of IL-2 and IL-4 from 2-week-old female C57BL/6 mice offspring.[5] At 7 weeks of age, production of IL-2 decreased in male mice offspring, whereas IFN-γ production decreased in both male and female mice offspring.[5]

Additionally, in male and female Sprague-Dawley rats who were exposed to Cd through breastfeeding, thymocyte proliferation was inhibited when stimulated by concanavalin A (ConA). In contrast, NK cytotoxic activity was suppressed only in female rats at higher levels of Cd exposure.[46] These data again suggest a sex- and dose-dependent effect for Cd exposure on cell-mediated immunity in offspring.

Arsenic exposure at an early stage of life also affected cell-mediated immune response in offspring in a dose-dependent manner. For prenatal exposure to As in humans, maternal urinary As concentrations were positively associated with placental expression of IL-1β.[14,47] Moreover, maternal urinary As at gestational week 30 had a U-shaped association with levels of cord blood cytokines IL-1β, IL-8, IFN-γ, and tumor necrosis factor (TNF)-α.[47] Decreased lymphocyte proliferation and DTH response were found in children exposed to As from an early age.[48,49] Moreover, higher urinary As concentrations in children were associated with lower serum levels of IL-2 and TNF-α,[49] and lower levels of IL-2 production by peripheral blood mononuclear cells (PBMCs) after phytohemaglutinen (PHA) stimulation.[15] Additionally, urinary As concentrations were negatively associated with nitric oxide (NO) and superoxide production from activated monocytes in children exposed to local environmental Pb and As.[50] Urinary inorganic As levels and its metabolites were positively associated with superoxide anion levels in activated monocytes in children.[51] Moreover, urinary inorganic As levels in children who were exposed to As in drinking water positively associated with basal levels of NO and superoxide anion in PBMCs and monocytes. Animal studies evidenced similar suppression of cell-mediated immunity by prenatal As exposure. Peripheral blood and spleen lymphocytes from broiler chickens who were exposed to As from 1 day to 60 days old, had decreased proliferation following stimulation by Ranikhet disease virus antigen and ConA.[52] The DTH response to 2,4-dinitro-1-chlorobenzene or PHA was also suppressed in these chickens.[52]

Persistent organic pollutants. There is limited information about the effect of organochlorine compound exposure in early life on cell-mediated immunity in offspring. Proliferation of cord blood-isolated T cells under mitogenic stimulation was negatively associated with levels of PCBs and 4,4'-dichlorodiphenyl-dichloroethene (4,4'-DDE) in newborns prenatally exposed to organochlorine

compounds and mercury.[53] TNF-α secretion by cord blood mononuclear cells under mitogen stimulation was also negatively associated with prenatal organochlorine exposure.[54] Additionally, T-cell mitogenic responses were significantly lower in free-ranging seal pups from the more PCB-contaminated Baltic than in reference pups from the Atlantic.[55] However, a positive correlation existed between PCB concentration and mitogen-induced lymphocyte proliferation in pups from the Atlantic.[55] There may be a nonlinear dose-response relationship between PCB concentration and T-cell proliferation. Although it is difficult to find direct dose-response relationships in free-ranging animals, this study still suggested an immunomodulatory effect of PCBs on free-ranging pups. In New Zealand rabbit offspring whose mothers were exposed to 250 ppm PCBs during pregnancy, the contact sensitivity response to 2,4-dinitro-1-fluorobenzene (DNFB) was significantly lowered, but no marked difference in lymphocyte proliferation was observed.[56] In general, prenatal or early-postnatal exposure to PCBs may inhibit or promote T-cell proliferation in offspring, based on the dose of PCBs.

TCDD exposure was found to suppress the DTH response in male and female F344 rat offspring (14-17 weeks of age) who were perinatally exposed.[33] Additionally, perinatal exposure to TCDD did not influence lymphocyte proliferation under mitogen stimulation in both genders of offspring, except for suppression of lymphocyte proliferation in female offspring by poke weed mitogen (PWM) stimulation was observed.[33] Exposure to TCDD during gestational days 6 to 14 led to altered thymocyte antigen expression and subsequently decreased cytotoxic T lymphocytes in 8-week-old mouse offspring.[32] Additionally, ConA-stimulated splenocytes produced decreased IL-17 in female SNF1 mice offspring prenatally exposed to TCDD, whereas the male offspring showed increased expression of IL-2 and IFN-γ.[34] However, exposure of human infants to TCDD in breast milk from birth did not cause any changes in immunologic parameters when they were 12 months old, possibly because the concentration of TCDD in breast milk was too low.[57] In summary, perinatal exposure to TCDD suppresses T-cell–mediated immunity through reduction of antigen-specific T-cell numbers and decrease of inflammatory cytokine secretion in offspring.

Tobacco smoke. Whole cord blood cells from smoking mothers during pregnancy had greater uptake of thymidine after PHA stimulation than from nonsmoking mothers.[35] However, lymphocytes isolated from these cord blood cells did not show a difference, suggesting that the suppressor cell function in cord blood was suppressed by maternal smoking during pregnancy.[35] Cord blood mononuclear cells from mothers who smoked during pregnancy produced higher levels of IL-13 after stimulation by house dust mites and ovalbumin, and the higher IL-13 levels were associated with maternal smoking during pregnancy.[58] The expressions of IL-9 mRNA, IL-5 mRNA, IL-6 mRNA and protein tended to be higher in these cord blood mononuclear cells, but the differences were not significant.[58] Cord blood immune response to Toll-like receptor stimulation in infants from smoking mothers was decreased compared with infants from nonsmoking mothers.[59] Additionally, T-lymphocyte proliferation under mitogen stimulation was decreased in 3-week-old B6C3F1 mouse offspring of smoking mothers, whereas the mixed lymphocyte response to mitogen stimulation was increased in 5-week-old pups.[38] These data suggested that prenatal exposure to smoke may suppress innate immune cell-mediated inflammatory response and T-cell proliferation. However, more work is needed to explore the long-term effects of prenatal smoke exposure on lymphocyte proliferation and cytokine responses.

In summary, prenatal or early-postnatal exposure to environmental toxicants were able to affect cell-mediated immune function through modulating DTH, lymphocyte proliferation, and cytokine responses in later life. The modulatory effect depended on time windows of exposure, dose of environmental toxicants and sex of participants.

Effect of Prenatal/Early-Postnatal Exposure to Environmental Toxicants on Status of Humoral Immunity in Offspring. *Heavy metals.* Pb exposure modulates antibody response in early life. Gestational Pb exposure was associated with increased levels of immunoglobulin (Ig)E in cord blood.[60] Postnatal Pb exposure also increased IgE levels among non-Hispanic white children, but not in other child groups.[61] Additionally, postnatal Pb exposure was associated with increased blood levels of IgA, IgG, and IgM in children under the age of 3, but not in older children.[62] Animal studies showed that a single exposure of 5-day-old avian embryos to 10 μg lead acetate caused an increase in anti-BSA IgG levels in male chickens at 6 or 8 weeks of age, whereas no alterations were observed in female chickens at the same age.[43] Similar results

were also found in F344 rat offspring.[41] Moreover, serum IgE levels were increased in female F344 rat offspring prenatally exposed to 100 ppm of Pb in drinking water.[41] These data indicate that sex, genetic background, and age of offspring modify long-term effects of prenatal or early-postnatal Pb exposure on humoral function.

There is limited information about effect on offspring humoral immunity followed by early-life Cd exposure. In children aged 5 to 14 years, urinary Cd levels were associated with dose-dependent suppression of serum IgG, but not IgM, IgA, or IgE.[48] One animal study showed that 20-week-old C57BL/6 mice that were prenatally exposed to low levels of Cd and immunized with heat-killed *Streptococcus pneumoniae* had decreased phosphorylcholine (PC)-specific serum antibody titers (T-cell independent) in females, but increased titers in male mice. Moreover, pneumococcal surface protein A (PspA)-specific serum IgG antibody titers (T-cell dependent) were increased in male and female mice, and PspA-specific serum IgM antibody titers were decreased in female mice.[18] The serum IgM antibody response to sheep red blood cells was increased in female ICR mice offspring of mothers who were exposed to low levels of Cd on day 16 of pregnancy.[63] These limited data suggest again that effect of Cd exposure on specific antibody response is dose and sex dependent. The exposure window is essential for antibody response in offspring.

One human study showed that maternal urinary As adjusted with specific gravity of urine was not significantly associated with cord blood IgG levels.[64] However, for 1-day-old chickens who were administered metalloid As for up to 60 days in drinking water, the response to Ranikhet disease virus vaccination (administered on days 1 and 60) was suppressed compared with the control group.[52] Considering the ability of As exposure to suppress cell-mediated immune function, it is possible that early-life exposure to As would adversely affect humoral function in offspring.

Persistent organic pollutants. Increased perinatal exposure to PCBs usually adversely affects immune responses to vaccination in children.[20,65,66] The sum of the PCBs was positively associated with serum IgM, whereas hexachlorobenzene was negatively associated with serum IgM in children who were exposed to low levels of organochlorine compounds and Pb. Moreover, 4,4′-DDE was associated with IgE, IgG, and IgA levels in these children.[67] In contrast, very high PCB levels in maternal, cord, and 6-month-old infant serum were not associated with total serum IgG, IgA, IgM, or IgE.[68] Association between very high levels of PCB exposure and specific antibody response was not significant in 6-month-old infants.[7] It is possible that a nonlinear relationship existed between PCB concentration and antibody responses in these studies. In general, these data indicate that concentration of PCB is the most important factor when determining the effect of early-life exposure to organochlorine on humoral response in offspring. Additionally, the interaction between organochlorine compounds may determine the net effect on an offspring's humoral response.

Prenatal exposure to TCDD did not alter the antibody response to sheep red blood cells in F344 rat offspring at 14 to 17 weeks of age.[69] Similar results were found in murine offspring exposed to TCDD during pregnancy.[32] Additionally, there was no significant association between neonatal exposure to dioxin through breast milk and levels of antibody in human infants at 12 months of age.[57] Also, there was no relationship between prenatal or postnatal dioxin exposure and antibody levels to mumps, measles, and rubella in 18-month-old infants.[25] Current data indicate that dioxins do not affect antibody response in offspring.

Tobacco smoke. The IgG, IgM, and IgA levels were higher in cord blood serum of children from mothers who smoked during pregnancy.[70] Maternal smoking during pregnancy also caused a significant elevation of IgE and IgD levels in cord blood of newborns.[71] Maternal smoking after birth caused an increase in total salivary IgA levels, rather than levels of specific IgA to common colonizing bacteria (pneumococcal PS serotype 14 and NTHI OMP6) in infants at 12 months of age.[72] These data suggest that maternal smoking stimulates B-cell maturation and antibody production/secretion in fetuses and newborns. However, maternal smoking during pregnancy is associated with decreased immunity and increased risk for airway infections in offspring, indicating that maternal smoking may impair specific antibody responses later in life.

In summary, many environmental toxicants, such as heavy metals, PCBs, and cigarette smoke were able to affect antibody production in a general or antibody-specific manner. Dose of toxicants, sex, age, and genetic background would modify effect of early-life exposure to environmental toxicants on antibody response in later life.

Association of Prenatal/Early-Postnatal Exposure to Environmental Toxicants and Susceptibility to Immune-related Diseases. Cord blood Cd levels were found to be associated with the onset of atopic

dermatitis in infants at 6 months of age.[73] Maternal urinary As concentration during pregnancy is associated with the total number of infections that required a physician visit or prescription medication, as well as lower respiratory infections requiring medication in infants at 4 months of age.[74] Moreover, maternal urine As concentration during pregnancy was positively associated with acute respiratory infections in infants and in male children.[75] Additionally, in utero or early childhood environmental exposure to As was associated with increased death from various cancers in adults (<50 years old).[76,77]

Regarding PCB and dioxin exposure, no relationship existed between pre- or postnatal PCB/dioxin exposure at environmental background levels and upper or lower respiratory tract symptoms in 18-month-old Dutch infants.[25] The increase in cord blood levels of PCBs were not associated with risk for wheezing in 18-month-old infants.[78] In contrast, levels of 4,4′-DDE in cord blood serum positively associated with the risk for wheezing or bronchitis in 18-month-old infants, although no association was found between cord blood levels of 4,4′-DDE or PCB and bronchitis or wheezing in infants >18 months.[78] However, 1 study showed that maternal exposure to PCBs during pregnancy was found to associate with an increased risk for wheezing and more frequent upper respiratory infections in 3-year-old children.[8] Additionally, the postnatal exposure to PCBs associated with higher recurrent middle ear infections in Dutch school children.[79] The discrepancy in these data may stem from different levels of PCBs and the endpoint of the effect that was explored in the studies. Low levels of PCBs might not cause significant dysfunction or persistent effects on the immune system in offspring. Moreover, respiratory symptoms may not be obvious at early age without challenge, but latent effects could appear at older years with challenge. For dioxin-like compounds, relatively high levels of polychlorinated dibenzofuran in maternal blood during pregnancy associated with increased occurrence of otitis media in 18-month-old infants, especially in male infants.[80] High levels of 2,3,4,7,8-pentachlorodibenzofuran in the blood of pregnant mothers were associated with increased risk for otitis media in these infants.[80] In general, these data indicate that prenatal/early-postnatal exposure to environmental POPs associates with susceptibility to infectious diseases in offspring. However, multiple-endpoint studies are needed to determine the stable long-term effect of early-life exposure to POPs on susceptibility to immune-

related diseases in offspring. The dose-response relationship is another question to be explored in developmental immunotoxicity of early-life exposure to POPs.

Maternal smoking during pregnancy has been associated with a lower risk for childhood acute lymphocytic leukemia and a higher risk for acute myelogenous leukemia in offspring.[81] Additionally, maternal smoking was associated with infections,[82-84] sensitization,[72] wheezing,[85] asthma,[86] and allergic diseases[71,87,88] in early childhood, all of which are associated with immune dysfunction in child. In animal models, prenatal exposure to cigarette smoke caused suppression of cytotoxic T-lymphocyte activity, faster tumor cell growth, and greater tumor incidence in murine offspring.[39]

In summary, prenatal or early-postnatal exposure to environmental toxicants were associated with infection and immune dysfunction-related diseases in later life. The levels of environmental toxicants might have a nonlinear relationship with susceptibility to immune-related diseases. Further studies are needed to explore how long the effect of early-life exposure to environmental toxicants would persist on susceptibility to immune-related diseases.

EARLY-LIFE EXPOSURE TO ENVIRONMENTAL TOXICANTS: LUNG DEVELOPMENT IN OFFSPRING AND SUSCEPTIBILITY TO LUNG DISEASES LATER IN LIFE

Prenatal/Early-Postnatal Exposure to Environmental Toxicants and Lung Development. Lung budding starts at about 22 days after fertilization and continues into infancy and early childhood, ending with alveoli maturation.[89] Lung development can be divided into several different stages: embryonic, pseudoglandular, canalicular, saccular, and alveolar,[90] with lung growth continuing until the end of the adolescent stage.[90] The prenatal and early-postnatal periods are the most vulnerable times for lung development because of rapid airway epithelial cell proliferation, differentiation, alveolar formation, and functional maturation. Environmental toxicants, such as As, Cd, dioxins, and tobacco smoke, may disturb progenitor cell differentiation and alter lung structure, resulting in both reduced lung function after birth and high susceptibility to lung disease in adulthood.

Heavy metals. In utero exposure to As has been shown to induce aberrant gene expression, which was relevant to lung adenocarcinoma development

in fetal C3H mice.[91] Prenatal and early-postnatal exposure to As (≤100 ppm in drinking water) also increased lung mRNA expression of smooth muscle actin in a dose-dependent manner in 28-day-old mouse pups, and increased smooth muscle mass around the small airways.[92] Additionally, the increased smooth muscle was associated with increased expression of extracellular elastin and collagen in the pup offspring.[92] In utero As exposure additionally resulted in smaller lungs and impaired lung mechanics in 2-week-old C57BL/6 mice offspring. It induced mucous cell metaplasia as well as more expression of CLCA3 protein in the large airways.[93] Additionally, in utero As exposure led to upregulated expression of genes relevant to mucus production (Clca3, Muc5b, Scgb3a1), innate immunity (Reg3gamma, Tff2, Dynlrb2, Lplunc1), and lung morphogenesis (Sox2) in C57BL/6 mice.[93] These data indicate that prenatal exposure to As disturbs airway epithelial differentiation and normal parenchymal tissue maturation in a manner that may alter lung resilience to stimuli after birth and predispose offspring to lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD).

In utero exposure to Cd levels without affecting fetal viability, body weight, and lung weight was associated with a reduction in the amount of saturated fatty acids containing lecithin, a main component of lung surfactant in fetal rats, when examined at E21.[94,95] Reduced surfactant in airways inhibited elimination of toxic particle matter and microbes on airway epithelial cells and also reduced compliance of airways and plasticity of alveoli, subsequently increasing risk for infection and decreased air flow and gas exchange. Additionally, exposure to 100 ppm dietary Cd from day 1 post-birth caused an enlarged tertiary bronchial lumen in 5-week-old White Leghorn cockerels.[96] Current data suggests that early-life exposure to Cd may impair airflow and increase infection in lungs.

Persistent organic pollutants. There is very limited information about the effects of POPs on lung development. One animal model study demonstrated that gestational exposure to TCDD caused significant decrease in total airspace, wider tissue septa, and dry lung weight-to-body weight ratio in 7-day-old Holtzman rat pups.[97] A study in children showed that dioxin concentration in breast milk was inversely associated with children's forced expiratory volume at 1 second (FEV_1)/forced vital capacity (FVC) ratio.[98] Additionally, perinatal dioxin exposure was associated with chest congestion in the

children.[98] The alteration of lung structure induced by dioxins partly explains why prenatal exposure to dioxins caused lower lung function in offspring.

Tobacco smoke. Prenatal or early-postnatal exposure to tobacco smoke has been widely described to affect fetal lung development and functional maturation after birth. In rat fetuses that were prenatally exposed cigarette smoke, the lung volume at term was reduced and the saccule number decreased, whereas the average saccule volume increased as a result of decreased formation of saccule partitions. Additionally, the internal surface area of saccules also was reduced, as was the total length of parenchymal elastic tissues.[99] In infant monkeys prenatally exposed to environmental tobacco or exposed to environmental tobacco for 6 months after birth, the alveolar number decreased while the alveolar space markedly increased compared with controls.[100] Additionally, the respiratory bronchiole volume increased in the 6-month exposure group.[100] Similar structure alteration was observed in other animal studies. In 21-day-old neonatal guinea pigs exposed to cigarette smoke during gestation, the number of alveolar attachment points to airway walls was decreased. Additionally, both inner and outer airway walls and the smooth muscle area showed a trend to be greater than in non-exposed neonates, although the difference was not significant.[101] Data from our own lab also indicate an effect of prenatal smoke exposure on lung development. One study demonstrated that maternal smoke exposure from 3 weeks before conception to birth, resulted in lower expression of encoding forkhead box a2 (*FOXA2*), frizzled receptor 7 (*FZD-7*), epidermal growth factor (*EGF*), β-catenin (*CTNNB1*), fibronectin (*FN1*), and platelet-derived growth factor receptor α (*PDGFRα*) in neonatal offspring.[102] These genes are members of, or related to the Wnt/β-catenin pathway, which plays an important role in lung-branching morphogenesis. Additionally, a significantly thickened airway smooth muscle layer was observed in Balb/c mice offspring that had been exposed to smoke in utero.[103] Moreover, collagen III deposition and house dust mite-induced goblet cell numbers were also increased in these offspring mice.[102] Because nicotine is known as a main toxicant in smoke, prenatal nicotine exposure also caused significant reduction in proximal airway conductance.[104]

In summary, prenatal or early-postnatal exposure to environmental toxicants disturbed airway epithelial differentiation and gene expressions and altered lung structure through interfering with

alveolar maturation processes and lung parenchymal tissue development, which resulted in malfunction of airway epithelial cells and increased thickness of airway walls while decreased gas exchange in the lung.

Prenatal/Early-Postnatal Exposure to Environmental Toxicants Is Associated With Alteration of Lung Function and Lung Disease Later in Life. Several studies demonstrated the persistent effect of prenatal and early-postnatal exposure to environmental toxicants on lung function and lung diseases in later life. A study with a small sample of Dutch children demonstrated that prenatal or postnatal exposure to environmental background levels of dioxin may inversely associate with child FEV_1/FVC ratios.[98] For prenatal exposure to As, As-induced aberrant estrogen receptor signaling in fetal mice was associated with lung adenocarcinoma and adenoma in adulthood.[91] Although prenatal exposure to heavy metals, such as Cd and As, and organochlorines, such as PCBs and dioxins, has been demonstrated to affect lung development and function in animal studies, there is relatively limited epidemiologic evidence that supports association of early-life exposure to these environmental toxicants with lung function status in children.

Prenatal or postnatal exposure to tobacco smoke had adverse effects on lung function in offspring. However, different effects existed between active and passive smoke exposure, and prenatal and postnatal exposure. Newborn (mean, 2.7 days old) from a smoking mother during pregnancy (active or passive), had significant lower tidal flow volume ratios (time to reach peak expiratory flow to total expiratory time) and compliance. Interestingly, the tidal flow volume ratios and compliance only associated with active maternal smoking during pregnancy.[105] Significant reductions in forced expiratory flow (FEF) rates in infants (mean, 4.92 ± 1.9 weeks) associated with maternal smoking during pregnancy, but were not associated with postnatal environmental tobacco exposure.[106] Similar results were found in infants at different ages after birth, indicating that prenatal exposure to smoke plays a greater role on the lung function of children than does postnatal exposure.[107]

The effect on lung function of maternal smoking during pregnancy can persist into childhood and even longer. One study demonstrated that children from mothers who smoked during pregnancy had FEF between 65% and 75% percent of FVC (FEF65%-75%), FEF25%-75%, and FEF in 3/4

of a second (FEV0.75) at 8 to 12 years of age.[108] Decreased FEV1/FVC, FEF25%-75%, and FEF25%-75%/FVC ratios were found in children from another study who were exposed to smoke in utero.[109] The reduced lung function caused by maternal smoking during pregnancy can persist into adolescence[10] and adulthood.[110]

Prenatal or early-postnatal exposure to smoke is associated with respiratory symptoms or illness in both childhood and adulthood. Maternal smoking during pregnancy is associated with a higher incidence of hospital admission for lower respiratory illness in children.[111] It is interesting to note that mothers who started to smoke after giving birth did not affect the incidence of their children's illness.[111] In contrast, another study demonstrated that children exposed to environmental tobacco smoke were more susceptible to acute respiratory tract illnesses, and maternal smoking during pregnancy exacerbated the condition.[112] Prenatal or early-postnatal exposure to smoke also was associated with increased airway hyperresponsiveness,[113,114] allergic sensitization,[115-117] asthma,[10,117-121] and COPD[122] in later life.

In summary, early-life exposure to environmental toxicants, especially cigarette smoke, altered lung structure and lowered lung function in long term, which elevated susceptibility to various lung diseases later in life.

REMARKS AND CONCLUSIONS

Environmental toxicants act directly or indirectly on immune system and lung development, inducing adaptive response in the immune and lung systems. Early-life exposure to environmental toxicants altered immune cell counts, DTH and cytokine responses, and levels of specific antibody in offspring. Moreover, it disturbed airway epithelial cell differentiation and gene expression, and perturbed normal processes of alveolar maturation and parenchymal tissue development in lung. The alteration in immune and lung structure and gene expression in airway epithelial cells may cause dysfunction in immune and lung systems and result in high risk for infection and lung diseases later in life. The dose of toxicants, exposure windows, and sex are determining factors for long-term effects of early-life exposure to environmental toxicants on immune and lung functioning. The different endpoints selected in the reviewed studies may confound the interpretation of long-term effect of early-life exposure on disease risk in offspring. Further studies are required to find stable molecular markers that can accurately predict

change of cell or tissue function later in life as caused by early-life exposure to environmental toxicants. Additionally, there is relatively limited information about the effect of early-life exposure to POPs on immune and lung development, and their long-term effects in offspring. Considering the accumulation of these pollutants in environment, much more effort is needed to explore association between early-life exposure to POPs and health risk in later life.

REFERENCES

1. Barker DJ. The origins of the developmental origins theory. J Intern Med 2007;261:412–7.
2. Swanson JM, Entringer S, Buss C, Wadhwa PD. Developmental origins of health and disease: environmental exposures. Semin Reprod Med 2009;27:391–402.
3. Barker DJ. In utero programming of cardiovascular disease. Theriogenology 2000;53:555–74.
4. Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. N Engl J Med 1976;295:349–53.
5. Hanson ML, Holaskova I, Elliott M, Brundage KM, Schafer R, Barnett JB. Prenatal cadmium exposure alters postnatal immune cell development and function. Toxicol Appl Pharmacol 2012;261:196–203.
6. Ramsey KA, Larcombe AN, Sly PD, Zosky GR. In utero exposure to low dose arsenic via drinking water impairs early life lung mechanics in mice. BMC Pharmacol Toxicol 2013;14:13.
7. Jusko TA, De Roos AJ, Schwartz SM, et al. A cohort study of developmental polychlorinated biphenyl (PCB) exposure in relation to post-vaccination antibody response at 6-months of age. Environ Res 2010;110:388–95.
8. Stolevik SB, Nygaard UC, Namork E, et al. Prenatal exposure to polychlorinated biphenyls and dioxins from the maternal diet may be associated with immunosuppressive effects that persist into early childhood. Food Chem Toxicol 2013;51:165–72.
9. Ng SP, Silverstone AE, Lai ZW, Zelikoff JT. Prenatal exposure to cigarette smoke alters later-life antitumor cytotoxic T-lymphocyte (CTL) activity via possible changes in T-regulatory cells. J Toxicol Environ Health A 2013;76:1096–110.
10. Skripak JM. Persistent effects of maternal smoking during pregnancy on lung function and asthma in adolescents. Pediatrics 2014;134(suppl 3):S146.
11. Dietert RR. Developmental immunotoxicity (DIT), postnatal immune dysfunction and childhood leukemia. Blood Cells Mol Dis 2009;42:108–12.
12. Scutaru MD. The pre- and postnatal development of the human lung. Rev Med Chir Soc Med Nat Iasi 1998;102:143–9.
13. Holt PG. Postnatal maturation of immune competence during infancy and childhood. Pediatr Allergy Immunol 1995;6:59–70.
14. Nadeau KC, Li Z, Farzan S, et al. In utero arsenic exposure and fetal immune repertoire in a US pregnancy cohort. Clin Immunol 2014;155:188–97.
15. Soto-Pena GA, Luna AL, Acosta-Saavedra L, et al. Assessment of lymphocyte subpopulations and cytokine secretion in children exposed to arsenic. FASEB J 2006;20:779–81.
16. Li S, Zhengyan Z, Rong L, Hanyun C. Decrease of CD4+ T-lymphocytes in children exposed to environmental lead. Biol Trace Elem Res 2005;105:19–25.
17. Bunn TL, Parsons PJ, Kao E, Dietert RR. Gender-based profiles of developmental immunotoxicity to lead in the rat: assessment in juveniles and adults. J Toxicol Environ Health A 2001;64:223–40.
18. Holaskova I, Elliott M, Hanson ML, Schafer R, Barnett JB. Prenatal cadmium exposure produces persistent changes to thymus and spleen cell phenotypic repertoire as well as the acquired immune response. Toxicol Appl Pharmacol 2012;265:181–9.
19. Horvathova M, Jahnova E, Palkovicova L, Trnovec T, Hertz-Picciotto I. The kinetics of cell surface receptor expression in children perinatally exposed to polychlorinated biphenyls. J Immunotoxicol 2011;8:367–80.
20. Weisglas-Kuperus N, Patandin S, Berbers GA, et al. Immunologic effects of background exposure to polychlorinated biphenyls and dioxins in Dutch preschool children. Environ Health Perspect 2000;108:1203–7.
21. Park HY, Hertz-Picciotto I, Petrik J, Palkovicova L, Kocan A, Trnovec T. Prenatal PCB exposure and thymus size at birth in neonates in Eastern Slovakia. Environ Health Perspect 2008;116:104–9.
22. Goff KF, Hull BE, Grasman KA. Effects of PCB 126 on primary immune organs and thymocyte apoptosis in chicken embryos. J Toxicol Environ Health A 2005;68:485–500.
23. Grasman KA, Whitacre LL. Effects of PCB 126 on thymocyte surface marker expression and immune organ development in chicken embryos. J Toxicol Environ Health A 2001;62:191–206.
24. Fox LL, Grasman KA. Effects of PCB 126 on primary immune organ development in chicken embryos. J Toxicol Environ Health A 1999;58:233–44.
25. Weisglas-Kuperus N, Sas TC, Koopman-Esseboom C, et al. Immunologic effects of background prenatal and postnatal exposure to dioxins and polychlorinated biphenyls in Dutch infants. Pediatr Res 1995;38:404–10.
26. Nagayama J, Tsuji H, Iida T, et al. Immunologic effects of perinatal exposure to dioxins, PCBs and organochlorine pesticides in Japanese infants. Chemosphere 2007;67:S393–8.
27. ten Tusscher GW, Steerenberg PA, van Loveren H, et al. Persistent hematologic and immunologic disturbances in 8-year-old Dutch children associated with perinatal dioxin exposure. Environ Health Perspect 2003;111:1519–23.
28. Nagayama J, Tsuji H, Iida T, et al. Postnatal exposure to chlorinated dioxins and related chemicals on lymphocyte subsets in Japanese breast-fed infants. Chemosphere 1998;37:1781–7.
29. Fine JS, Silverstone AE, Gasiewicz TA. Impairment of prothymocyte activity by 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Immunol 1990;144:1169–76.

30. Fine JS, Gasiewicz TA, Silverstone AE. Lymphocyte stem cell alterations following perinatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Mol Pharmacol 1989;35:18–25.

31. Blaylock BL, Holladay SD, Comment CE, Heindel JJ, Luster MI. Exposure to tetrachlorodibenzo-p-dioxin (TCDD) alters fetal thymocyte maturation. Toxicol Appl Pharmacol 1992;112:207–13.

32. Holladay S, Lindstrom P, Blaylock B, et al. Perinatal thymocyte antigen expression and postnatal immune development altered by gestational exposure to tetrachlorodibenzo-p-dioxin (TCDD). Teratology 1991;44:385–93.

33. Gehrs BC, Smialowicz RJ. Alterations in the developing immune system of the F344 rat after perinatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin I. [correction of II]. Effects on the fetus and the neonate. Toxicology 1997;122:219–28.

34. Mustafa A, Holladay SD, Goff M, et al. Developmental exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin alters postnatal T cell phenotypes and T cell function and exacerbates autoimmune lupus in 24-week-old SNF1 mice. Birth Defects Res A Clin Mol Teratol 2009;85:828–36.

35. Paganelli R, Ramadas D, Layward L, Harvey BA, Soothill JF. Maternal smoking and cord blood immunity function. Clin Exp Immunol 1979;36:256–9.

36. Almanzar G, Eberle G, Lassacher A, et al. Maternal cigarette smoking and its effect on neonatal lymphocyte subpopulations and replication. BMC Pediatr 2013;13:57.

37. Harrison KL. The effect of maternal smoking on neonatal leucocytes. Aust N Z J Obstet Gynaecol 1979;19:166–8.

38. Ng SP, Zelikoff JT. The effects of prenatal exposure of mice to cigarette smoke on offspring immune parameters. J Toxicol Environ Health A 2008;71:445–53.

39. Ng SP, Silverstone AE, Lai ZW, Zelikoff JT. Effects of prenatal exposure to cigarette smoke on offspring tumor susceptibility and associated immune mechanisms. Toxicol Sci 2006;89:135–44.

40. Faith RE, Luster MI, Kimmel CA. Effect of chronic developmental lead exposure on cell-mediated immune functions. Clin Exp Immunol 1979;35:413–20.

41. Miller TE, Golemboski KA, Ha RS, Bunn T, Sanders FS, Dietert RR. Developmental exposure to lead causes persistent immunotoxicity in

Fischer 344 rats. Toxicol Sci 1998;42:129–35.

42. Bunn TL, Parsons PJ, Kao E, Dietert RR. Exposure to lead during critical windows of embryonic development: differential immunotoxic outcome based on stage of exposure and gender. Toxicol Sci 2001;64:57–66.

43. Bunn TL, Marsh JA, Dietert RR. Gender differences in developmental immunotoxicity to lead in the chicken: analysis following a single early low-level exposure in ovo. J Toxicol Environ Health A 2000;61:677–93.

44. Lee J-E, Naqi SA, Kao E, Dietert RR. Embryonic exposure to lead: comparison of immune and cellular responses in unchallenged and virally stressed chickens. Arch Toxicol 2002;75:717–24.

45. Lee JE, Chen S, Golemboski KA, Parsons PJ, Dietert RR. Developmental windows of differential lead-induced immunotoxicity in chickens. Toxicology 2001;156:161–70.

46. Pillet S, Rooney AA, Bouquegneau JM, Cyr DG, Fournier M. Sex-specific effects of neonatal exposures to low levels of cadmium through maternal milk on development and immune functions of juvenile and adult rats. Toxicology 2005;209:289–301.

47. Ahmed S, Mahabbat-e Khoda S, Rekha RS, et al. Arsenic-associated oxidative stress, inflammation, and immune disruption in human placenta and cord blood. Environ Health Perspect 2011;119:258–64.

48. Ritz B, Heinrich J, Wjst M, Wichmann E, Krause C. Effect of cadmium body burden on immune response of school children. Arch Environ Health 1998;53:272–80.

49. Ahmed S, Moore SE, Kippler M, et al. Arsenic exposure and cell-mediated immunity in pre-school children in rural bangladesh. Toxicol Sci 2014;141:166–75.

50. Pineda-Zavaleta AP, Garcia-Vargas G, Borja-Aburto VH, et al. Nitric oxide and superoxide anion production in monocytes from children exposed to arsenic and lead in region Lagunera, Mexico. Toxicol Appl Pharmacol 2004;198:283–90.

51. Luna AL, Acosta-Saavedra LC, Lopez-Carrillo L, et al. Arsenic alters monocyte superoxide anion and nitric oxide production in environmentally exposed children. Toxicol Appl Pharmacol 2010;245:244–51.

52. Aggarwal M, Naraharisetti SB, Dandapat S, Degen GH, Malik JK. Perturbations in immune responses induced by concurrent subchronic

exposure to arsenic and endosulfan. Toxicology 2008;251:51–60.

53. Belles-Isles M, Ayotte P, Dewailly E, Weber JP, Roy R. Cord blood lymphocyte functions in newborns from a remote maritime population exposed to organochlorines and methylmercury. J Toxicol Environ Health A 2002;65:165–82.

54. Bilrha H, Roy R, Moreau B, Belles-Isles M, Dewailly E, Ayotte P. In vitro activation of cord blood mononuclear cells and cytokine production in a remote coastal population exposed to organochlorines and methyl mercury. Environ Health Perspect 2003;111:1952–7.

55. Sormo EG, Larsen HJ, Johansen GM, Skaare JU, Jenssen BM. Immunotoxicity of polychlorinated biphenyls (PCB) in free-ranging gray seal pups with special emphasis on dioxin-like congeners. J Toxicol Environ Health A 2009;72:266–76.

56. Thomas PT, Hinsdill RD. Perinatal PCB exposure and its effect on the immune system of young rabbits. Drug Chem Toxicol 1980;3:173–84.

57. Kaneko H, Matsui E, Shinoda S, et al. Effects of dioxins on the quantitative levels of immune components in infants. Toxicol Ind Health 2006;22:131–6.

58. Noakes PS, Holt PG, Prescott SL. Maternal smoking in pregnancy alters neonatal cytokine responses. Allergy 2003;58:1053–8.

59. Noakes PS, Hale J, Thomas R, Lane C, Devadason SG, Prescott SL. Maternal smoking is associated with impaired neonatal toll-like-receptor-mediated immune responses. Eur Respir J 2006;28:721–9.

60. Annesi-Maesano I, Pollitt R, King G, et al. In utero exposure to lead and cord blood total IgE. Is there a connection? Allergy 2003;58:589–94.

61. Wells EM, Bonfield TL, Dearborn DG, Jackson LW. The relationship of blood lead with immunoglobulin E, eosinophils, and asthma among children: NHANES 2005-2006. Int J Hyg Environ Health 2014;217:196–204.

62. Sarasua SM, Vogt RF, Henderson LO, Jones PA, Lybarger JA. Serum immunoglobulins and lymphocyte subset distributions in children and adults living in communities assessed for lead and cadmium exposure. J Toxicol Environ Health A 2000;60:1–15.

63. Soukupova D, Dostal M, Piza J. Developmental toxicity of cadmium in mice. II. Immunotoxic effects. Funct Dev Morphol 1991;1:31–6.

64. Ser PH, Banu B, Jebunnesa F, et al. Arsenic exposure increases maternal but not cord serum IgG in Bangladesh. Pediatr Int 2015;57:119–25.

65. Heilmann C, Grandjean P, Weihe P, Nielsen F, Budtz-Jorgensen E. Reduced antibody responses to vaccinations in children exposed to polychlorinated biphenyls. PLoS Med 2006;3:e311.

66. Barrett JR. Diminished protection? Early childhood PCB exposure and reduced immune response to vaccinations. Environ Health Perspect 2010;118:A445.

67. Karmaus W, Brooks KR, Nebe T, Witten J, Obi-Osius N, Kruse H. Immune function biomarkers in children exposed to lead and organochlorine compounds: a cross-sectional study. Environ Health 2005;4:5.

68. Jusko TA, De Roos AJ, Schwartz SM, et al. Maternal and early postnatal polychlorinated biphenyl exposure in relation to total serum immunoglobulin concentrations in 6-month-old infants. J Immunotoxicol 2011;8:95–100.

69. Gehrs BC, Riddle MM, Williams WC, Smialowicz RJ. Alterations in the developing immune system of the F344 rat after perinatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin: II. Effects on the pup and the adult. Toxicology 1997;122:229–40.

70. Cederqvist LL, Eddey G, Abdel-Latif N, Litwin SD. The effect of smoking during pregnancy on cord blood and maternal serum immunoglobulin levels. Am J Obstet Gynecol 1984;148:1123–6.

71. Magnusson CG. Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. J Allergy Clin Immunol 1986;78(5 Pt 1): 898–904.

72. Noakes P, Taylor A, Hale J, et al. The effects of maternal smoking on early mucosal immunity and sensitization at 12 months of age. Pediatr Allergy Immunol 2007;18:118–27.

73. Kim JH, Jeong KS, Ha EH, et al. Association between prenatal exposure to cadmium and atopic dermatitis in infancy. J Korean Med Sci 2013;28:516–21.

74. Farzan SF, Korrick S, Li Z, et al. In utero arsenic exposure and infant infection in a United States cohort: a prospective study. Environ Res 2013;126:24–30.

75. Raqib R, Ahmed S, Sultana R, et al. Effects of in utero arsenic exposure on child immunity and morbidity in rural Bangladesh. Toxicol Lett 2009;185:197–202.

76. Smith AH, Marshall G, Liaw J, Yuan Y, Ferreccio C, Steinmaus C. Mortality in young adults following in utero and childhood exposure to arsenic in drinking water. Environ Health Perspect 2012;120:1527–31.

77. Smith AH, Marshall G, Yuan Y, et al. Increased mortality from lung cancer and bronchiectasis in young adults after exposure to arsenic in utero and in early childhood. Environ Health Perspect 2006;114: 1293–6.

78. Gascon M, Sunyer J, Casas M, et al. Prenatal exposure to DDE and PCB 153 and respiratory health in early childhood: a meta-analysis. Epidemiology 2014;25:544–53.

79. Weisglas-Kuperus N, Vreugdenhil HJ, Mulder PG. Immunological effects of environmental exposure to polychlorinated biphenyls and dioxins in Dutch school children. Toxicol Lett 2004;149:281–5.

80. Miyashita C, Sasaki S, Saijo Y, et al. Effects of prenatal exposure to dioxin-like compounds on allergies and infections during infancy. Environ Res 2011;111:551–8.

81. Mucci LA, Granath F, Cnattingius S. Maternal smoking and childhood leukemia and lymphoma risk among 1,440,542 Swedish children. Cancer Epidemiol Biomarkers Prev 2004;13:1528–33.

82. Dahal GP, Johnson FA, Padmadas SS. Maternal smoking and acute respiratory infection symptoms among young children in Nepal: multilevel analysis. J Biosoc Sci 2009;41:747–61.

83. Jeppesen DL, Nielsen SD, Ersboll AK, Valerius NH. Maternal smoking during pregnancy increases the risk of postnatal infections in preterm neonates. Neonatology 2008;94:75–8.

84. Nafstad P, Jaakkola JJ, Hagen JA, Botten G, Kongerud J. Breastfeeding, maternal smoking and lower respiratory tract infections. Eur Respir J 1996;9:2623–9.

85. Lannero E, Wickman M, Pershagen G, Nordvall L. Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE). Respir Res 2006;7:3.

86. Hylkema MN, Blacquiere MJ. Intrauterine effects of maternal smoking on sensitization, asthma, and chronic obstructive pulmonary disease. Proc Am Thorac Soc 2009;6:660–2.

87. Tanaka K, Miyake Y, Sasaki S, Ohya Y, Hirota Y. Maternal smoking and environmental tobacco smoke exposure and the risk of allergic diseases in Japanese infants: the Osaka Maternal and Child Health Study. J Asthma 2008;45:833–8.

88. Lee SL, Lam TH, Leung TH, et al. Foetal exposure to maternal passive smoking is associated with childhood asthma, allergic rhinitis, and eczema. ScientificWorldJournal 2012;2012: 542983.

89. Harding R, Maritz G. Maternal and fetal origins of lung disease in adulthood. Semin Fetal Neonatal Med 2012;17:67–72.

90. Miller MD, Marty MA. Impact of environmental chemicals on lung development. Environ Health Perspect 2010;118:1155–64.

91. Shen J, Liu J, Xie Y, Diwan BA, Waalkes MP. Fetal onset of aberrant gene expression relevant to pulmonary carcinogenesis in lung adenocarcinoma development induced by in utero arsenic exposure. Toxicol Sci 2007;95:313–20.

92. Lantz RC, Chau B, Sarihan P, Witten ML, Pivniouk VI, Chen GJ. In utero and postnatal exposure to arsenic alters pulmonary structure and function. Toxicol Appl Pharmacol 2009;235:105–13.

93. Ramsey KA, Bosco A, McKenna KL, et al. In utero exposure to arsenic alters lung development and genes related to immune and mucociliary function in mice. Environ Health Perspect 2013;121: 244–50.

94. Daston GP. Toxicity of minimal amounts of cadmium to the developing rat lung and pulmonary surfactant. Toxicol Lett 1981;9:125–30.

95. Daston GP, Grabowski CT. Toxic effects of cadmium on the developing rat lung. I. Altered pulmonary surfactant and the induction of respiratory distress syndrome. J Toxicol Environ Health 1979;5:973–83.

96. Lefevre M, Heng H, Rucker RB. Dietary cadmium, zinc and copper: effects on chick lung morphology and elastin cross-linking. J Nutr 1982;112:1344–52.

97. Kransler KM, McGarrigle BP, Swartz DD, Olson JR. Lung development in the Holtzman rat is adversely affected by gestational exposure to 2,3, 7, 8-tetrachlorodibenzo-p-dioxin. Toxicol Sci 2009;107:498–511.

98. ten Tuscher GW, de Weerdt J, Roos CM, et al. Decreased lung function associated with perinatal exposure to Dutch background levels of dioxins. Acta Paediatr 2001;90: 1292–8.

99. Collins MH, Moessinger AC, Kleinerman J, et al. Fetal lung hypoplasia associated with maternal smoking: a morphometric analysis. Pediatr Res 1985;19:408–12.

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100. Avdalovic M, Putney L, Tyler N, Finkbeiner W, Pinkerton K, Hyde D. In utero and postnatal exposure to environmental tobacco smoke (ETS) alters alveolar and respiratory bronchiole (RB) growth and development in infant monkeys. Toxicol Pathol 2009;37:256–63.

101. Elliot J, Carroll N, Bosco M, McCrohan M, Robinson P. Increased airway responsiveness and decreased alveolar attachment points following in utero smoke exposure in the guinea pig. Am J Respir Crit Care Med 2001;163:140–4.

102. Blacquiere MJ, Timens W, van den Berg A, Geerlings M, Postma DS, Hylkema MN. Maternal smoking during pregnancy decreases Wnt signalling in neonatal mice. Thorax 2010;65:553–4.

103. Blacquiere MJ, Timens W, Melgert BN, Geerlings M, Postma DS, Hylkema MN. Maternal smoking during pregnancy induces airway remodelling in mice offspring. Eur Respir J 2009;33:1133–40.

104. Sandberg K, Poole SD, Hamdan A, Arbogast P, Sundell HW. Altered lung development after prenatal nicotine exposure in young lambs. Pediatr Res 2004;56:432–9.

105. Lodrup Carlsen KC, Jaakkola JJ, Nafstad P, Carlsen KH. In utero exposure to cigarette smoking influences lung function at birth. Eur Respir J 1997;10:1774–9.

106. Hanrahan JP, Tager IB, Segal MR, et al. The effect of maternal smoking during pregnancy on early infant lung function. Am Rev Respir Dis 1992;145:1129–35.

107. Tager IB, Ngo L, Hanrahan JP. Maternal smoking during pregnancy. Effects on lung function during the first 18 months of life. Am J Respir Crit Care Med 1995;152:977–83.

108. Cunningham J, Dockery DW, Speizer FE. Maternal smoking during pregnancy as a predictor of lung function in children. Am J Epidemiol 1994;139:1139–52.

109. Gilliland FD, Berhane K, Li YF, Rappaport EB, Peters JM. Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function. Am J Respir Crit Care Med 2003;167:917–24.

110. Hayatbakhsh MR, Sadasivam S, Mamun AA, Najman JM, Williams GM, O'Callaghan MJ. Maternal smoking during and after pregnancy and lung function in early adulthood: a prospective study. Thorax 2009;64:810–4.

111. Taylor B, Wadsworth J. Maternal smoking during pregnancy and lower respiratory tract illness in early life. Arch Dis Child 1987;62:786–91.

112. Jedrychowski W, Flak E. Maternal smoking during pregnancy and postnatal exposure to environmental tobacco smoke as predisposition factors to acute respiratory infections. Environ Health Perspect 1997;105:302–6.

113. Wu ZX, Hunter DD, Kish VL, Benders KM, Batchelor TP, Dey RD. Prenatal and early, but not late, postnatal exposure of mice to sidestream tobacco smoke increases airway hyperresponsiveness later in life. Environ Health Perspect 2009;117:1434–40.

114. Joad JP, Ji C, Kott KS, Bric JM, Pinkerton KE. In utero and postnatal effects of sidestream cigarette smoke exposure on lung function, hyperresponsiveness, and neuroendocrine cells in rats. Toxicol Appl Pharmacol 1995;132:63–71.

115. Kulig M, Luck W, Wahn U. The association between pre- and postnatal tobacco smoke exposure and allergic sensitization during early childhood. Multicentre Allergy Study Group, Germany. Hum Exp Toxicol 1999;18:241–4.

116. Tanaka K, Miyake Y. Association between prenatal and postnatal tobacco smoke exposure and allergies in young children. J Asthma 2011;48:458–63.

117. Burke H, Leonardi-Bee J, Hashim A, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics 2012;129:735–44.

118. Dong GH, Wang D, Yang ZH, et al. Gender-specific differences in effects of prenatal and postnatal environmental tobacco smoke exposure on respiratory symptoms in 23, 474 children with and without allergic predisposition: results from 25 districts of northeast China. Int J Environ Health Res 2011;21:173–88.

119. Jaakkola JJ, Gissler M. Are girls more susceptible to the effects of prenatal exposure to tobacco smoke on asthma? Epidemiology 2007;18:573–6.

120. Leung DY, Szefler SJ. In utero smoke (IUS) exposure has been associated with increased prevalence of asthma and reduced lung function in healthy children. J Allergy Clin Immunol 2010;126:481–2.

121. Wang L, Pinkerton KE. Detrimental effects of tobacco smoke exposure during development on postnatal lung function and asthma. Birth Defects Res C Embryo Today 2008;84:54–60.

122. Beyer D, Mitfessel H, Gillissen A. Maternal smoking promotes chronic obstructive lung disease in the offspring as adults. Eur J Med Res 2009;14(suppl 4):27–31.