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Environmental toxicants and the developing immune system: a missing link in the global battle against infectious disease?

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Abstract

There is now compelling evidence that developmental exposure to chemicals from our environment contributes to disease later in life, with animal models supporting this concept in reproductive, metabolic, and neurodegenerative diseases. In contrast, data regarding how developmental exposures impact the susceptibility of the immune system to functional alterations later in life are surprisingly scant. Given that the immune system forms an integrated network that detects and destroys invading pathogens and cancer cells, it provides the body's first line of defense. Thus, the consequences of early-life exposures that reduce immune function are profound. This review summarizes available data for pollutants such as cigarette smoke and dioxin-like compounds, which consistently support the idea that developmental exposures critically impact the immune system. These findings suggest that exposure to common chemicals from our daily environment represent overlooked contributors to the fact that infectious diseases remain among the top five causes of death worldwide.

Keywords

Maternal Exposure; Pollutants; Fetal Basis of Adult Disease; Infectious Disease Susceptibility; Immune Development

1.1 Environmental exposures may impact susceptibility to infectious disease

Infectious disease remains a major global health concern; in fact, respiratory infections are the third most common cause of death worldwide, leading to over four million deaths each year. In low income countries, four of the top five leading causes of death are due to infectious disease [1] (see Figure 1). But perhaps what is even more striking is that in high income countries infectious diseases, in particular lower respiratory tract infections, remain among the top five causes of death. These deaths are occurring even with significant

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advances in medical research and therapeutics, raising the question: what factors contribute to vulnerability to infectious disease? Even when considering the same type of infection, there is a wide spectrum of clinical outcomes for infected individuals, ranging from sub-clinical to mild to severe and, at times, lethal. Genetics and age impact the susceptibility to and severity of infection, but other factors that influence infection rates and disease pathophysiology are not fully understood [2,3]. Several studies have suggested that environmental pollutants, such as pesticides, air pollution and cigarette smoke contribute to poorer clinical outcomes after infection [4–8]. In this review, we explore the emerging idea that maternal and early-life exposures to common environmental contaminants have a critical but underappreciated impact on susceptibility to infection later in life.

1.2 Developmental exposure to environmental agents impacts adult health

The developmental origin of health and disease concept, which is also referred to as the Barker hypothesis and the fetal basis of adult diseases, holds that environmental signals influence development and thereby alter health later in life [9]. Information about the maternal environment is communicated to the fetus transplacentally, and to the infant via lactation, thereby instructing fetal and early-life development. Insults during this period can lead to subtle alterations in development that permanently affect function. This concept has been demonstrated for a number of diseases, as exposure to pollutants or even alterations in the maternal diet have been associated with increased risk of cardiovascular disease, stroke, obesity, and cancer later in life [10–12]. Although it has received less attention, environmental agents also influence the development and programming of the immune system. Proper immune development is critically important, as even slight changes can decrease resistance to infectious disease, reduce vaccine efficacy, and diminish tumor surveillance. Imbalances in immune function can also enhance responsiveness to non-pathogenic antigens, as is the case in autoimmune disease and hypersensitivity reactions. Furthermore, it is now appreciated that immune deregulation underlies the pathophysiology of many chronic diseases; thus, there is tremendous impetus to understand how the early life environment affects the programming of the developing immune system [13].

1.3 Immune system development is an intricate process

Although the length of gestation differs in mice and humans, the process of immune development is quite similar, sharing the same sites of ontogeny, regulatory factors, and requirement for postnatal development. For example, in both species, development of the immune system involves a coordinated series of events beginning early in gestation and continuing into the postnatal period [14–16]. All leukocyte lineages arise from a small population of pluripotent hematopoietic stem cells (HSCs), and the primary site of hematopoiesis changes with developmental stage. HSCs undergo a process of self-renewal, and also differentiate into lineage-specific precursors: common lymphocyte precursors (CLPs) or common myeloid precursors (CMPs). CLPs give rise to T and B lymphocytes and natural killer (NK) cells, whereas macrophages, neutrophils, and other leukocyte lineages are derived from CMPs. Although many details of the development of the immune system have been elucidated, it is not fully known how environmental factors alter immune development. Moreover, due to this long and intricate period of development, early life environmental insults have the potential to alter normal immune development, leading to persistent alterations in function, which are not appreciated until adulthood.

1.4 Proper immune function is critical for fighting infection and preventing cancer

As is the case for immune system development, many aspects of immune function are similar in humans and mice. A well-tuned immune system is required to recognize pathogens and fight infection. In humans and mice, immune cells are continuously made and circulate throughout the body. Working in an orchestrated manner, leukocytes are

responsible for executing an appropriate immune response. Their function can be measured experimentally by assessing their response to antigenic challenge, such as proliferation, trafficking, cytolytic activity, or their ability to produce the appropriate antibodies or cytokines. Deregulation of any one of these aspects of immune function could lead to an impaired ability to mount an immune response, increasing susceptibility to infection. On the other hand, an overactive immune response could exacerbate pathology through the excessive damage of healthy tissue. Clearly, a proper balance of immune function is critical. It is also important to bear in mind that the immune system is responsible for detecting and destroying cancerous cells and preventing tumor growth. Furthermore, infectious agents and infection-associated inflammation are among the major causes of cancer, with as many as 15% of cancer cases resulting from infections [17,18]. Thus, subtle changes in immune regulation that perturb immune function have far-reaching health consequences as they can directly impact susceptibility to infections as well as increase vulnerability to cancer.

1.5 Evidence that developmental exposure to environmental contaminants influences susceptibility to infectious disease

The similarities between immune system development and function in humans and mice make mice an appropriate model for studying the long-term effects of developmental immunotoxicants, as they provide a framework for predicting potential outcomes of developmental exposures in humans [19]. In the following sections, we review human and animal data indicating that early life exposure to pollutants leads to increased susceptibility to infectious disease and cancer later in life. Knowing that pollutants can cross the placenta and be passed to infants via lactation, we present data from epidemiological and animal studies that have investigated the long-term impact of developmental exposure on immune function. Specifically, data from developmental exposures to dioxin, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, cigarette smoke, metals, pesticides and a few agents of emerging concern are presented in the following sections. These examples provide insight into how early life exposure to environmental factors alters immune function later in life. Emerging evidence that epigenetic mechanisms are altered by developmental exposure is explored as a possible mechanism of immune system reprogramming, and gaps in knowledge are identified.

2. TCDD, PCBs and PAHs

Exposure to persistent organic pollutants and their affects on human health continues to be a major health concern. 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), also known as dioxin, is a byproduct of numerous manufacturing processes, and can be released by the incineration of municipal and medical waste. Polychlorinated biphenyls (PCBs) are chemically very stable, and while this property made them useful as coolants and lubricants in electrical equipment, it has led to their continued presence in the environment more than 30 years after their production stopped. Polycyclic aromatic hydrocarbons (PAHs) are formed from the incomplete combustion of many types of organic matter, including fuel, tobacco and garbage. All three of these classes of compounds are ubiquitous environmental contaminants to which humans are regularly exposed. Moreover, these chemicals have been shown to cross the placenta and are excreted into breast milk [20–22], indicating that human exposure occurs during development. Furthermore, TCDD, as well as many other dioxins, PCBs and PAHs are agonists for the aryl hydrocarbon receptor (AhR), an environmental sensor that plays a role in development [23]. TCDD is one of the most commonly used environmental agents for studying the link between AhR and immunotoxicity because of its high affinity and specificity for the AhR. While most of the animal studies use TCDD as a model developmental immunotoxicant, epidemiological data have demonstrated that early life exposure to AhR ligands, including dioxins and PCBs, leads to altered immune function in children [24–31].

2.1 Developmental exposure to TCDD leads to persistent changes in immune function in rodents

Not only is TCDD one of the best studied immunotoxicants, but the theory that maternal and early life exposure to environmental chemicals impacts the developing immune system originated from studies of TCDD conducted over 30 years ago. In these studies, Vos and Moore demonstrated that administering TCDD to pregnant rodents altered immune parameters in their offspring [32]. This work laid the foundation for the concept of developmental immunotoxicology. Subsequent research has further characterized the effects of developmental exposure to TCDD in rodent models, demonstrating that early life exposure to TCDD alters the functional capacity of the offspring's immune system. For example, impaired lymphocyte functions, including reduction in the proliferative response to mitogens, decreased delayed-type hypersensitivity (DTH) responses, and reduced cytotoxic T lymphocyte (CTL) responses have been reported [32–36]. While maternal or perinatal doses with higher levels of TCDD led to thymic atrophy [32–35,37–39] and alterations in subpopulations of lymphocyte maturing in the thymus [34,35,37–39], these effects on cellularity were transient, resolving within a few weeks after birth. In contrast, alterations in immune function are long lasting and detected into adulthood [36,40,41]. Furthermore, persistent functional changes were observed at a maternal dose of TCDD at which no changes in the cellularity of the primary or secondary immune organs were observed [40], suggesting that functional changes are not simply due to altered immune organ cellularity.

Emerging animal data highlight how persistent changes in immune function can increase disease susceptibility. Sugita-Konishi *et. al.* showed that in mice developmentally exposed to TCDD, there was an increased level of bacteria present following infection with *Listeria monocytogenes* [41]. Likewise, exposing pregnant mice to TCDD impaired the offsprings' host responses to influenza virus infection, as demonstrated by a reduction of effector lymphocyte clonal expansion, IFNγ production, and virus-specific antibody production [40,42]. The decreased T lymphocyte response to influenza virus infection could be transferred with bone marrow cells, demonstrating the developmental exposure to TCDD directly affects the hematopoietic cell population [43].

While many PCBs and PAHs have not been as extensively examined for their immunotoxic effects following developmental exposure in animal models, the epidemiological evidence reviewed below highlights their potential to alter immune function. Collectively, these findings suggest that the AhR pathway plays a critical role in the development of the immune system, as inappropriate AhR signaling by these environmental agents alters normal immune development. Further work is needed to elucidate the mechanism by which exposure to these pollutants leads to a persistent alteration in function, and to carefully sort out the contribution of AhR-mediated and non-AhR-mediated impact of these chemicals.

2.2 Increased incidence of infections correlates with children's early life exposure to TCDD, PCBs and PAHs

A growing number of studies have investigated the impact of early life exposure to dioxins and PCBs on children's health, providing evidence that developmental exposure causes alterations in immune function. A few studies suggest that minor changes in relative amounts of peripheral immune cells can result from early life exposures [25,26,28,44–47], and in a cohort of Slovakian children, higher perinatal exposure to PCBs correlated with decreased thymic size, as determined from an ultrasound measurement of thymic index [48]. However, as demonstrated in the animal model of developmental exposure to TCDD, it is the ability of these pollutants to impact immune function that is most striking. Increased incidences of respiratory and ear infections, cough, and sore throat were observed in children with higher early life exposure to dioxins, PCBs and PAHs [25–31]. Further,

studies in the Faroe Islands and the Netherlands demonstrated that increased developmental PCB exposure correlated with reduced antibody response to vaccination [24,30], although no change in antibody response was seen in a cohort of Slovakian infants [49]. Cancer susceptibility may also be increased in offspring of mothers exposed to PAHs, as indicated by the presence of PAH-DNA adducts in cord blood [50–52]. These studies clearly demonstrate the ability of dioxins and related persistent organic compounds to have a long-lasting and deleterious impact on immune function.

3. Cigarette Smoke

Another environmental agent to which developing fetuses and children are frequently exposed is cigarette smoke. While the worldwide rate of smoking during pregnancy is not known, it is estimated that as many as 20% of pregnant women in the United States smoke, and even among those women that quit during pregnancy, two-thirds resume smoking within a year [53,54]. This exposes the fetus and baby to the thousands of chemicals, including over 60 carcinogens, found in tobacco smoke. Some chemicals in cigarette smoke bind the AhR, while others do not; however, the specific contribution of the various constituents of cigarette smoke to adverse health outcomes remains an active area of study. While the precise consequences vary with different cigarette smoke components, the overarching impact is clear: early life exposure to cigarette smoke alters immune responses and may increase the risk of cancer.

3.1 Immune function is altered after early life exposure to cigarette smoke in humans and rodents

Early life exposure to cigarette smoke has been shown to affect infectious disease susceptibility in childhood. Adverse outcomes of prenatal or neonatal cigarette smoke exposure include increased bronchitis, upper respiratory tract infections, ear infections, pneumonia and rate of hospitalizations [55–59]. While the mechanism for this increased susceptibility is not known, human and animal data point to an alteration in immune function. Examining lymphocytes purified from cord blood of exposed neonates, Noakes *et. al.* found altered levels of cytokines after stimulation [60,61], while Devereux *et. al.* observed increased lymphocyte proliferation after stimulation [62]. Peripheral blood lymphocytes collected from children whose parents smoked prenatally and throughout their early lives produced less IFNγ when stimulated [63]. Studies in rodents present a clear picture of reduced lymphocyte responsiveness. For example, Ng *et. al.* observed a decreased lymphocyte response [64,65], while Sing *et. al.* found reduced response of lymphocytes, and decreased antibody production after antigenic challenge [66]. Prenatal exposure to benzo[*a*]pyrene (BaP) [67] or nicotine [68], which are components of cigarette smoke, also suppressed lymphocyte responses, which in the case of BaP persisted to 18 months of age. Interestingly, mice developmentally exposed to cigarette smoke had higher viral burdens when challenged with respiratory syncytial virus (RSV) in early life [69]. As in the case of TCDD and PCBs, further work is needed to elucidate the mechanism by which early life exposure reprograms immune function, especially considering the prevalence of these pollutants.

3.2 Developmental exposure to cigarette smoke may be linked to increased incidence of cancer

A recent review of the epidemiological literature illustrated that there is not a consensus regarding the association between maternal smoking and childhood leukemia, with only a limited number of studies showing a positive association [70]. However, the risk of hepatoblastoma and non-Hodgkin’s lymphoma in children increased with maternal or parental smoking [71–73], and maternal smoking was associated with slightly increased

rates of central nervous system tumors [74–77]. Animal data provide a further link between developmental exposure to cigarette smoke, the incidence of cancer, and the altered function of the immune system. Mice perinatally exposed to dibenzopyrene, a component of cigarette smoke, had increased formation of aggressive lung and liver lymphomas [78]. In separate studies using a mouse model of prenatal cigarette smoke exposure, male offspring presented an increased incidence of tumor formation after challenge with lymphoma cells. Further, cells from these exposed mice exhibited reduced CTL activity and lymphocyte expansion after mitogen stimulation, suggesting that the functional immune changes could underlie the offspring's increased cancer susceptibility [64,65].

4. Metals

There is a great deal of concern about exposures to metals and their adverse affects on human health. Metals such as arsenic and lead are found naturally in the earth's crust, and high levels of arsenic in rocks can lead to contaminated groundwater sources. Lead has had many industrial uses, and although it is no longer an additive in gasoline or paint, it continues to be a widespread pollutant, and is added to certain products despite continued concern about toxicity. The link between metals and immune function has been studied for many years, and as reviewed in Dietert *et. al.*, developmental exposure to lead results in persistent immune alterations in rodents, including reduced antibody levels, altered cytokine production and decreased DTH response [79]. Below we highlight arsenic, another metal of worldwide concern. We explore emerging data that suggest further efforts are warranted to investigate the link between developmental exposure to arsenic and increased susceptibility to infections and cancer.

4.1 Arsenic exposure during development may lead to altered disease susceptibility in children

Data linking early life exposure to heavy metals and altered immune function are emerging, with a growing literature implicating arsenic as a developmental immunotoxicant. Arsenic crosses the placenta [80], but unlike TCDD and other lipophillic pollutants, is not found extensively in breast milk [81]. A cohort of children in Bangladesh who were developmentally exposed to arsenic via contaminated groundwater have increased infant death rates, increased incidence of respiratory infections, and reduced thymic index lasting until 12 months of age [82,83]. Interestingly, children with early life arsenic exposure were less prone to developing the skin lesions that are characteristic of acute exposure [84]. Increased urine arsenic levels in children correlated with decreased proliferation from their isolated lymphocytes [85]. While immune function has not been assessed in an animal model after developmental exposure to arsenic, adult mice acutely exposed to arsenic via drinking water exhibited changes in the expression of genes involved in mounting an immune response, specifically those involved in innate immunity [86,87], and had decreased lymphocyte proliferation [88]. Further, acute exposure of adult mice to arsenic led to an impaired immune response to influenza virus infection, as exhibited by increased morbidity and viral titer, and decreased immune cell infiltrates early during infection [89]. These findings, combined with the epidemiological data of developmental exposure, highlight the need for functional immune assessment in a developmental model of arsenic exposure.

4.2 In rodents, cancer incidence is increased after gestational exposure to arsenic

Only a limited number of epidemiological studies in humans have looked at cancer incidence and early life arsenic exposure. Most have not found an association between arsenic and childhood cancers [90], although early life exposure to high levels of arsenic in a Chilean cohort correlated with increased incidence of lung cancer and nonmalignant airway destruction [91]. In rodents, however, increased cancer susceptibility has been demonstrated

after developmental exposure to arsenic. Mice gestationally exposed to arsenic had increased tumor incidence [92]. Moreover, tumor incidence increased when mice were exposed to arsenic and diethylstilbesterol (DES) or tamoxifen, which are estrogenic compounds [93–95]. While the mechanism for this altered susceptibility has not fully been elucidated, intriguing data implicate a change in epigenetic regulation as an underlying mechanism. Chen *et. al.* found that exposing a rat liver cell line to arsenic led to S-adenosyl methionine (SAM) depletion and DNA hypomethylation [96]. Similarly, treatment of a keratinocyte cell line with arsenic depleted SAM, decreased DNA methylation, and decreased expression of DNA methyltransferases [97]. Interestingly, estrogen receptor-alpha (ERα) activation at gestational day 18 was associated with arsenic induced tumors [98], and arsenic mediated over-expression appears to be due, at least in part, to promoter hypomethylation [99]. Further evidence linking arsenic to epigenetic regulatory machinery is provided by a study in which gestational exposure of mice led to a suppression of genes for methionine metabolism, which could lead to the reduced SAM levels observed *in vitro* [100]. Understanding how developmental exposure to arsenic alters epigenetic regulation may provide a framework in which to evaluate other developmental immunotoxicants.

5. Pesticides

Pesticides represent another class of ubiquitous pollutants, with many different types being used in agricultural applications, in the workplace, and in the home. More than 5 billion pounds of pesticides are used annually worldwide, with about 25% being used in the United States [101]. Pesticide exposure occurs during their application, via their drainage into water supplies, and through the consumption of food. Levels of pesticides detected in amniotic fluid demonstrate that the fetus has direct exposure to at least some pesticides during development [102]. Studies in rodents highlight the potential for developmental exposure to pesticides to impact immune function, and epidemiological evidence suggest a link to increases in childhood cancers.

5.1 In rodents, early life exposure to pesticides leads to altered immune function

Although epidemiological data looking at immune function are lacking, studies in rodents suggest that perinatal exposure to pesticides alters immune function. For example, developmental exposure of rodents to atrazine, one of the most commonly used herbicides, altered proliferative responses in both B and T lymphocytes [103,104]. Alterations in immune function after gestational exposure to chlordane have been well studied, and include decreased killing of tumor cells by macrophages, altered NK cell activity, altered T lymphocyte responses, and enhanced survival to influenza virus infection [105–109]. Further assessment of disease-related immune endpoints is needed in both animal models of developmental exposure and in the human population. Also needed are assessments of the impact of developmental and early life exposure to numerous other pesticides—and combinations of pesticides—on immune function.

5.2 Maternal exposure to pesticides may increase risk of childhood cancer

Two recent meta-analyses have shown that maternal exposure to pesticides, either occupational or residential, was associated with an elevated risk of childhood leukemia [110,111]. Zahm and Ward reviewed the epidemiology literature and found some evidence of elevated risk of leukemia and other cancers in children with early life exposure [112]; these findings were upheld when revisited a decade later [113].

6. Environmental agents for which there is an emerging concern

There are numerous other chemicals to which we are exposed in our daily life. For most, studies to examine whether they adversely impact the developing immune system or alter

susceptibility to infectious disease have not been conducted. Likewise, for many of these chemicals, we do not yet fully understand their mechanism of action as toxicants to complex mammalian development and physiology. Despite these gaps in knowledge, it is increasingly recognized that early life exposures can have a profound impact on the developing immune system, and may thereby contribute to disease later in life. In the following section, we explore the available data for a few examples of ubiquitous pollutants to which many people are continuously exposed, such as perfluorinated compounds, solvents, and plastics.

6.1 PFOS and PFOA

Perfluorooctane sulfonic acid (PFOS) and perfluorononanoic acid (PFOA) are widely used for their non-stick, fire resistant, and stain repellent properties. These chemicals have recently been recognized as a class of potentially harmful pollutants, but few studies have investigated their impact on development or their immunomodulatory properties. In studies of acute administration to adult rodents, PFOS exposure increased NK cell activity and decreased antibody production [114]. Exposure to sulfluramid, another perfluorinated compound used as a pesticide, led to reduced antibody production [115]. Developmental exposure to PFOS led to reduced NK cell activity, antibody production and B lymphocytes numbers [116]. This work suggests that further investigation of immune function after developmental exposure to fluorinated compounds is necessary.

6.2 Solvents

Solvents, such as toluene and trichloroethylene (TCE), are used in paints, adhesives, and cleaners. While the function of the immune system after developmental exposure to solvents has not received extensive attention in humans, maternal and paternal occupational exposure to solvents has been linked to increased incidence of childhood leukemias [117–121], although not all studies found an association [122]. Animal data suggest that solvents can be developmental immunotoxicants. For example, perinatal toluene exposure modulated Th1 and Th2 responses after exposure to peptidoglycan, a toll-like receptor (TLR) ligand [123]. Early life exposure of mice to trichloroethylene decreased antibody production, increased thymic cellularity, and altered lymphocyte responses [124–126]. These data are suggestive, and support the idea that rigorous examination of the impact of maternal and early-life exposure to environmentally relevant levels of solvents on the ability to fight infection and detect and destroy tumor cells is needed.

6.3 BPA and Phthalates

Plastics have widespread use throughout the world, but little is known about the immunomodulatory properties of their chemical components. Two components of plastics that have garnered considerable attention are bisphenol A (BPA) and phthalates. BPA is a monomer used in polycarbonate plastics and epoxy resins, while phthalates are used as softeners in many products. The extent to which humans have been exposed to BPA and phthalates is widespread: 93% of NHANES (National Health and Nutrition Examination Survey) participants had detectable levels of BPA in their urine [127], while 75% had phthalate metabolites present [128]. Furthermore, levels of BPA in amniotic fluid were three to four-fold higher than in maternal serum [129]. Detectable levels of phthalate metabolites were also found in amniotic fluid [130]. Because of these findings, active research is being conducted to determine the health outcomes from early life exposure to these chemicals.

Only one animal study has investigated the impact of developmental exposure to phthalates on immune function, and in that study no change was seen in the DTH response in rats with gestational exposure to the phthalate DEHP [131]. However, epidemiological studies investigating phthalate exposure in children found increased risk of respiratory symptoms

such as wheeze and allergic indications [132]. Due to these findings, and the high levels of exposure in humans, further studies in humans and rodents are critically needed to clearly understand whether and how developmental and early life exposure to phthalates impacts the immune system.

In contrast to scant data on phthalates and immune system, there are several animal studies to support the idea that exposure to BPA alters immune function. In one study, mice with prenatal exposure to BPA showed increased lymphocyte proliferation after *Listeria major* infection, along with increased cytokine production and a reduction in the number of regulatory T cells [133]. Increased lymphocyte proliferation and numbers of splenic T lymphocytes have also been reported, but the consequences of these changes remain unclear [134]. Although there is a dearth of information looking at the immune response to infection, early-life exposure to BPA has been suggested to alter the mechanisms underlying oral tolerance to the model antigen ovalbumin, and enhance the development of an asthmatic phenotype [135,136]. Furthermore, acute exposure of adult rodents to BPA altered the levels of cytokines and antibodies produced, leading to enhanced autoantibody production [137–140]. While these data suggest BPA has the capacity to modulate the developing immune system, more studies are needed to determine if developmental exposure to BPA alters disease susceptibility later in life, and to elucidate the underlying mechanisms.

7. Future Directions

We have presented data from a number of studies demonstrating that developmental exposure to environmental pollutants leads to persistent changes in immune function. When examined, these changes in function contribute to deregulated immune responses following infection. However, even for the best characterized developmental immunotoxicants, animal models examining susceptibility to infectious disease are generally just emerging. In the example of dioxin-like compounds, epidemiological data show that children with developmental exposure have increased susceptibility to infections. While only a few animal models have been developed to address this question, they support the epidemiological data showing defects in multiple facets of the immune response to infection. More research using animal models that faithfully study aspects of host defenses against human pathogens are needed. These models should include viral, bacterial and parasitic infections, and consider pathogens that elicit acute and resolving disease as well as those that result in latent illness. Moreover, studies that seek to better understand how developmental exposures impact innate and inflammatory responses to infection are sorely needed. These studies will, collectively, help to elucidate the mechanisms underlying this increased susceptibility, and will provide an essential foundation on which to test the developmental immunotoxicity of emerging agents. Moreover, the widespread use of these models will become especially important as we move forward to consider the effect of developmental exposure to mixtures of environmental insults.

The studies presented here strongly suggest that early life insults can reprogram normal immune development, leading to persistent functional alterations. The mechanisms for this have not yet been elucidated, but changes in epigenetic regulation are thought to play a large part [141]. Epigenetic mechanisms involve modifications to DNA and chromatin to regulate gene activation and silencing, and play a role in cell proliferation and differentiation [142]. In the cases of arsenic and pesticides, several studies suggest that exposure to these environmental agents alters epigenetic regulatory mechanisms [99,100,143]. Furthermore, changes in epigenetic mechanisms have been linked to early life exposure to BPA, although not in the context of studies of immune function [144–147]. These findings are intriguing, but more research is needed to determine if alterations in epigenetic regulatory mechanisms are directly linked to changes in immune function. The role that epigenetic mechanisms play

in the normal physiological development of the immune system is not fully known; therefore, discoveries about how developmental exposures disrupt epigenetic programming during immune system development will help us to understand the normal programming of the immune system.

While the studies reviewed here focus on how developmental exposure alters vulnerability to infectious disease, early life exposure to environmental insults can lead to a number of adverse health outcomes in adulthood, such as cardiovascular disease, stoke, obesity, and cancer [10–12]. Indeed, to truly appreciate the impact of environmental exposures on health and disease, we need to think very broadly about how environmental exposures influence the etiology of complex diseases. Using infectious diseases as an example shows that this link can be direct, such as a decreased ability to destroy the pathogen. However, the consequences can be indirect too. Developmental exposures that lead to an immune system with a diminished capacity to fight infection may also reduce the body's ability to detect and destroy tumor cells, thereby increasing risk of cancer. The recently released President's Cancer Panel 2008–2009 Annual Report highlights the growing, yet limited body of research linking suspected environmental factors with immune dysfunction and the development of cancer and other disease [148]. Thus, decreases in immune responses not only mean infections persist longer, which has an immediate impact on the overall wellness of society, but there is an increased risk of cancer. Furthermore, some environmental agents may increase inflammatory responses. While this is a normal and important response to infection, deregulated inflammation has been shown to exacerbate infection-associated pathology and increase cancer [18]. Thus, a better understanding of how environmental factors reprogram immune development will lead to a more in depth appreciation of the general mechanisms underlying developmentally-programmed diseases. Additionally, these studies will provide a new framework for considering the developmental impact of other agents, such as alcohol consumption, pharmaceuticals, or even maternal diet and/or stress [149]. As the field moves forward, new findings will also lead to the discovery of novel immunomodulatory strategies and interventions to reduce the impact of environmental factors on human health.

In spite of tremendous improvements in health care, infectious diseases continue to be a substantial burden on human health. As we seek to prevent disease and improve therapeutic treatments, we need to better understand the factors that contribute to the persistence of these agents as threats to global health. Indeed, disease prevention and the translation of basic research into better health, opportunities identified as important efforts for the future by the National Institutes of Health, can be achieved in this field with the continued identification of environmental factors with adverse effects on the developing immune system and the subsequent elimination of those exposures [150]. To accomplish this goal, it is clear that we need to determine precisely how early life exposures to pollutants impact the developing immune system. There are many excellent rodent models in which this endeavor can be successfully accomplished. Moreover, there are numerous opportunities in which these studies can and ought to be integrated with epidemiological studies that include tests of immune function. In this manner, rodent-based, mechanistic studies and population-based epidemiological studies can be woven together and efficiently translated into effective public health and prevention strategies.

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Literature Citations

1. World Health Organization. The global burden of disease: 2004 update. 2008. http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html
2. Hill AVS. The Immunogenetics of human infectious diseases. Annual Review of Immunology. 1998; 16:593–617.
3. Weiskopf D, Weinberger B, Grubeck-Loebenstein B. The aging of the immune system. Transplant International. 2009; 22:1041–50. [PubMed: 19624493]
4. Colosio C, Birindelli S, Corsini E, Galli CL, Maroni M. Low level exposure to chemicals and immune system. Toxicology and applied pharmacology. 2005; 207:320–8. [PubMed: 15992843]
5. Spannhake EW, Reddy SP, Jacoby DB, Yu XY, Saatian B, Tian J. Synergism between rhinovirus infection and oxidant pollutant exposure enhances airway epithelial cell cytokine production. Environmental health perspectives. 2002; 110:665–70. [PubMed: 12117643]
6. Stancek D, Kosecka G, Oltman M, Keleova A, Jahnova E. Links between prolonged exposure to xenobiotics, increased incidence of hepatopathies, immunological disturbances and exacerbation of latent Epstein-Barr virus infections. International journal of immunopharmacology. 1995; 17:321–8. [PubMed: 7672882]
7. Singh V. The burden of pneumonia in children: an Asian perspective. Paediatric respiratory reviews. 2005; 6:88–93. [PubMed: 15911453]
8. Stampfli MR, Anderson GP. How cigarette smoke skews immune responses to promote infection, lung disease and cancer. Nat Rev Immunol. 2009; 9:377–84. [PubMed: 19330016]
9. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science. 2004; 305:1733–6. [PubMed: 15375258]
10. Edwards TM, Myers JP. Environmental exposures and gene regulation in disease etiology. Cien Saude Colet. 2008; 13:269–81. [PubMed: 18813540]
11. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008; 359:61–73. [PubMed: 18596274]
12. Barker DJ. The origins of the developmental origins theory. J Intern Med. 2007; 261:412–7. [PubMed: 17444880]
13. Dietert RR. Developmental immunotoxicology: focus on health risks. Chem Res Toxicol. 2009; 22:17–23. [PubMed: 18783253]
14. Dzierzak E, Medvinsky A. Mouse embryonic hematopoiesis. Trends in Genetics. 1995; 11:359–66. [PubMed: 7482788]
15. Robin C, Ottersbach K, de Bruijn M, Ma X, van der Horn K, Dzierzak E. Developmental origins of hematopoietic stem cells. Oncol Res. 2003; 13:315–21. [PubMed: 12725520]
16. Zhu J, Emerson SG. Hematopoietic cytokines, transcription factors and lineage commitment. Oncogene. 2002; 21:3295–313. [PubMed: 12032771]
17. Kuper H, Adami H, Trichopoulos D. Infections as a major preventable cause of human cancer. Journal of internal medicine. 2000; 248:171–83. [PubMed: 10971784]
18. Worlld Health Organization. World Cancer Report. 2008. http://www.who.int/cancer/publications/en/
19. Holladay SD, Smialowicz RJ. Development of the murine and human immune system: differential effects of immunotoxicants depend on time of exposure. Environmental health perspectives. 2000; 108:463. [PubMed: 10852846]
20. Abraham K, Papke O, Gross A, Kordonouri O, Wiegand S, Wahn U, et al. Time course of PCDD/PCDF/PCB concentrations in breast-feeding mothers and their infants. Chemosphere. 1998; 37:1731–41. [PubMed: 9828301]
21. Guvenius DM, Aronsson A, Ekman-Ordeberg G, Bergman A, Noren K. Human prenatal and postnatal exposure to polybrominated diphenyl ethers, polychlorinated biphenyls, polychlorobiphenylols, and pentachlorophenol. Environ Health Perspect. 2003; 111:1235–41. [PubMed: 12842779]
22. Zanieri L, Galvan P, Checchini L, Cincinelli A, Lepri L, Donzelli GP, et al. Polycyclic aromatic hydrocarbons (PAHs) in human milk from Italian women: influence of cigarette smoking and residential area. Chemosphere. 2007; 67:1265–74. [PubMed: 17258279]

23. Nguyen LP, Bradfield CA. The search for endogenous activators of the aryl hydrocarbon receptor. Chem Res Toxicol. 2008; 21:102–16. [PubMed: 18076143]
24. 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. [PubMed: 16942395]
25. Weisglas-Kuperus N, Patandin S, Berbers GA, Sas TC, Mulder PG, Sauer PJ, et al. Immunologic effects of background exposure to polychlorinated biphenyls and dioxins in Dutch preschool children. Environmental health perspectives. 2000; 108:1203. [PubMed: 11133402]
26. Glynn A, Thuvander A, Aune M, Johannisson A, Darnerud P, Ronquist G, et al. Immune cell counts and risks of respiratory infections among infants exposed pre- and postnatally to organochlorine compounds: a prospective study. Environmental Health. 2008; 7:62. [PubMed: 19055819]
27. Dallaire F, Dewailly E, Muckle G, Vezina C, Jacobson SW, Jacobson JL, et al. Acute infections and environmental exposure to organochlorines in Inuit infants from Nunavik. Environ Health Perspect. 2004; 112:1359–63. [PubMed: 15471725]
28. Dewailly E, Ayotte P, Bruneau S, Gingras S, Belles-Isles M, Roy R. Susceptibility to infections and immune status in Inuit infants exposed to organochlorines. Environ Health Perspect. 2000; 108:205–11. [PubMed: 10706525]
29. Jedrychowski W, Galas A, Pac A, Flak E, Camman D, Rauh V, et al. Prenatal ambient air exposure to polycyclic aromatic hydrocarbons and the occurrence of respiratory symptoms over the first year of life. European journal of epidemiology. 2005; 20:775–82. [PubMed: 16170661]
30. 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. [PubMed: 15093274]
31. Guo YL, Lambert GH, Hsu CC, Hsu MM. Yucheng: health effects of prenatal exposure to polychlorinated biphenyls and dibenzofurans. Int Arch Occup Environ Health. 2004; 77:153–8. [PubMed: 14963712]
32. Vos JG, Moore JA. Suppression of cellular immunity in rats and mice by maternal treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin. International archives of allergy and applied immunology. 1974; 47:777–94. [PubMed: 4154311]
33. Faith RE, Moore JA. Impairment of thymus-dependent immune functions by exposure of the developing immune system to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Journal of toxicology and environmental health. 1977; 3:451–64. [PubMed: 926199]
34. Holladay SD, Lindstrom P, Blaylock BL, Comment CE, Germolec DR, Heindell JJ, et al. Perinatal thymocyte antigen expression and postnatal immune development altered by gestational exposure to tetrachlorodibenzo- p-dioxin (TCDD). Teratology. 1991; 44:385–93. [PubMed: 1683717]
35. 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. [PubMed: 9328223]
36. Gehrs B, Smialowicz R. Persistent suppression of delayed-type hypersensitivity in adult F344 rats after perinatal exposure to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin* 1. Toxicology. 1999; 134:79–88. [PubMed: 10413190]
37. Fine J, Gasiewicz T, Silverstone A. Lymphocyte stem cell alterations following perinatal exposure to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin. Molecular pharmacology. 1989; 35:18. [PubMed: 2783621]
38. Blaylock B, Holladay S, Comment C, Heindel J, Luster M. Exposure to tetrachlorodibenzo-p-dioxin (TCDD) alters fetal thymocyte maturation. Toxicology and applied pharmacology. 1992; 112:207–13. [PubMed: 1531708]
39. Camacho I, Nagarkatti M, Nagarkatti P. Evidence for induction of apoptosis in T cells from murine fetal thymus following perinatal exposure to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicological Sciences. 2004; 78:96. [PubMed: 14718643]
40. Vorderstrasse B, Cundiff JA, Lawrence BP. Potent aryl hydrocarbon receptor agonist 2,3,7,8-tetrachlorodibenzo-p-dioxin impairs the cell-mediated immune response to infection with

Influenza A virus, but enhances elements of innate immunity. J Immunotoxicol. 2004; 1:103–12. [PubMed: 18958643]

41. Sugita-Konishi Y, Kobayashi K, Naito H, Miura K, Suzuki Y. Effect of lactational exposure to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin on the susceptibility to Listeria infection. Bioscience, biotechnology, and biochemistry. 2003; 67:89–93.
42. Vorderstrasse BA, Cundiff JA, Lawrence BP. A dose-response study of the effects of prenatal and lactational exposure to TCDD on the immune response to influenza a virus. Journal of toxicology and environmental healthPart A. 2006; 69:445–63.
43. Hogaboam JP, Moore AJ, Lawrence BP. The aryl hydrocarbon receptor affects distinct tissue compartments during ontogeny of the immune system. Toxicol Sci. 2008; 102:160–70. [PubMed: 18024991]
44. Nagayama J, Tsuji H, Iida T, Nakagawa R, Matsueda T, Hirakawa H, et al. Immunologic effects of perinatal exposure to dioxins, PCBs and organochlorine pesticides in Japanese infants. Chemosphere. 2007; 67:S393–8. [PubMed: 17222440]
45. ten Tusscher GW, Steerenberg PA, van Loveren H, Vos JG, Borne AE, Westra M, 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. [PubMed: 12948893]
46. Weisglas-Kuperus N, Sas TC, Koopman-Esseboom C, Zwan CW, De Ridder MA, Beishuizen A, et al. Immunologic effects of background prenatal and postnatal exposure to dioxins and polychlorinated biphenyls in Dutch infants. Pediatr Res. 1995; 38:404–10. [PubMed: 7494667]
47. Hertz-Picciotto I, Park HY, Dostal M, Kocan A, Trnovec T, Sram R. Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development. Basic & clinical pharmacology & toxicology. 2008; 102:146–54. [PubMed: 18226068]
48. 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. Environmental health perspectives. 2008; 116:104–9. [PubMed: 18197307]
49. Jusko TA, De Roos AJ, Schwartz SM, Paige Lawrence B, Palkovicova L, Nemessanyi T, et al. A cohort study of developmental polychlorinated biphenyl (PCB) exposure in relation to post-vaccination antibody response at 6-months of age. Environmental Research. In Press, Corrected Proof.
50. Kelvin EA, Edwards S, Jedrychowski W, Schleicher RL, Camann D, Tang D, et al. Modulation of the effect of prenatal PAH exposure on PAH-DNA adducts in cord blood by plasma antioxidants. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2009; 18:2262–8.
51. Wang S, Chanock S, Tang D, Li Z, Jedrychowski W, Perera FP. Assessment of interactions between PAH exposure and genetic polymorphisms on PAH-DNA adducts in African American, Dominican, and Caucasian mothers and newborns. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2008; 17:405–13.
52. Perera F, Tang D, Rauh V, Lester K, Tsai W, Tu Y, et al. Relationships among polycyclic aromatic hydrocarbonñDNA adducts, proximity to the World Trade Center, and effects on fetal growth. Environmental health perspectives. 2005; 113:1062. [PubMed: 16079080]
53. National Research Center for Women and Families. Issue Brief: Smoking is a Women's Health Issue. 2004. http://www.center4research.org
54. American Cancer Society. Women and Smoking. 2009. http://www.cancer.org/docroot/ped/content/ped_10_2x_women_and_smoking.asp
55. Jaakkola JJ, Kosheleva AA, Katsnelson BA, Kuzmin SV, Privalova LI, Spengler JD. Prenatal and postnatal tobacco smoke exposure and respiratory health in Russian children. Respiratory research. 2006; 7:48. [PubMed: 16569224]
56. Le Souef PN. Adverse effects of maternal smoking during pregnancy on innate immunity in infants. The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology. 2006; 28:675–7. [PubMed: 17012623]

57. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. Pediatrics. 2004; 113:1007. [PubMed: 15060193]
58. Bradley JP, Bacharier LB, Bonfiglio J, Schechtman KB, Strunk R, Storch G, et al. Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy. Pediatrics. 2005; 115:e7–14. [PubMed: 15629968]
59. Cheraghi M, Salvi S. Environmental tobacco smoke (ETS) and respiratory health in children. Eur J Pediatr. 2009; 168:897–905. [PubMed: 19301035]
60. 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. European Respiratory Journal. 2006; 28:721–9. [PubMed: 16870663]
61. Noakes PS, Holt PG, Prescott SL. Maternal smoking in pregnancy alters neonatal cytokine responses. Allergy. 2003; 58:1053–8. [PubMed: 14510725]
62. Devereux G, Barker RN, Seaton A. Antenatal determinants of neonatal immune responses to allergens. Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology. 2002; 32:43–50. [PubMed: 12002736]
63. Tebow G, Sherrill DL, Lohman IC, Stern DA, Wright AL, Martinez FD, et al. Effects of parental smoking on interferon gamma production in children. Pediatrics. 2008; 121:e1563–9. [PubMed: 18519461]
64. Ng S, Zelikoff J. The effects of prenatal exposure of mice to cigarette smoke on offspring immune parameters. Journal of Toxicology and Environmental Health, Part A. 2008; 71:445–53. [PubMed: 18306092]
65. Ng SP, Silverstone AE, Lai Z-W, Zelikoff JT. Effects of Prenatal Exposure to Cigarette Smoke on Offspring Tumor Susceptibility and Associated Immune Mechanisms. Toxicological Sciences. 2006; 89:135–44. [PubMed: 16207940]
66. Singh SP, Razani-Boroujerdi S, Pena-Philippides JC, Langley RJ, Mishra NC, Sopori ML. Early postnatal exposure to cigarette smoke impairs the antigen-specific T-cell responses in the spleen. Toxicology letters. 2006; 167:231–7. [PubMed: 17113252]
67. Urso P, Gengozian N. Subnormal expression of cell-mediated and humoral immune responses in progeny disposed toward a high incidence of tumors after in utero exposure to benzo [a] pyrene. Journal of Toxicology and Environmental Health, Part A. 1984; 14:569–84.
68. Basta PV, Basham KB, Ross WP, Brust ME, Navarro HA. Gestational nicotine exposure alone or in combination with ethanol down-modulates offspring immune function. International journal of immunopharmacology. 2000; 22:159–69. [PubMed: 10685000]
69. Phaybouth V, Wang SZ, Hutt JA, McDonald JD, Harrod KS, Barrett EG. Cigarette smoke suppresses Th1 cytokine production and increases RSV expression in a neonatal model. American Journal of Physiology- Lung Cellular and Molecular Physiology. 2006; 290:L222. [PubMed: 16126789]
70. Chang JS. Parental smoking and childhood leukemia. Methods in molecular biology (Clifton, NJ). 2009; 472:103–37.
71. Sorahan T, Lancashire RJ. Parental cigarette smoking and childhood risks of hepatoblastoma: OSCC data. British journal of cancer. 2004; 90:1016–8. [PubMed: 14997199]
72. Pang D, McNally R, Birch JM. Parental smoking and childhood cancer: results from the United Kingdom Childhood Cancer Study. British journal of cancer. 2003; 88:373–81. [PubMed: 12569379]
73. Magnani C, Pastore G, Luzzatto L, Terracini B. Parental occupation and other environmental factors in the etiology of leukemias and non-Hodgkin's lymphomas in childhood: a case-control study. Tumori. 1990; 76:413–9. [PubMed: 2256184]
74. Brooks DR, Mucci LA, Hatch EE, Cnattingius S. Maternal smoking during pregnancy and risk of brain tumors in the offspring. A prospective study of 1.4 million Swedish births. Cancer causes & control: CCC. 2004; 15:997–1005.
75. Schüz J, Kaletsch U, Kaatsch P, Meinert R, Michaelis J. Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. Pediatric Blood & Cancer. 36:274–82.

76. Filippini G, Farinotti M, Ferrarini M. Active and passive smoking during pregnancy and risk of central nervous system tumours in children. Paediatric and perinatal epidemiology. 2000; 14:78–84. [PubMed: 10703038]
77. Filippini G, Farinotti M, Lovicu G, Maisonneuve P, Boyle P. Mothers' active and passive smoking during pregnancy and risk of brain tumours in children. International journal of cancerJournal international du cancer. 1994; 57:769–74. [PubMed: 8206670]
78. Yu Z, Loehr CV, Fischer KA, Louderback MA, Krueger SK, Dashwood RH, et al. In utero Exposure of Mice to Dibenzo[a,l]Pyrene Produces Lymphoma in the Offspring: Role of the Aryl Hydrocarbon Receptor. Cancer research. 2006; 66:755–62. [PubMed: 16424006]
79. Dietert RR, Lee JE, Hussain I, Piepenbrink M. Developmental immunotoxicology of lead. Toxicol Appl Pharmacol. 2004; 198:86–94. [PubMed: 15236947]
80. Concha G, Vogler G, Lezcano D, Nermell B, Vahter M. Exposure to inorganic arsenic metabolites during early human development. Toxicological sciences: an official journal of the Society of Toxicology. 1998; 44:185–90. [PubMed: 9742656]
81. Fangstrom B, Moore S, Nermell B, Kuenstl L, Goessler W, Grander M, et al. Breast-feeding protects against arsenic exposure in Bangladeshi infants. Environmental health perspectives. 2008; 116:963–9. [PubMed: 18629322]
82. Raqib R, Ahmed S, Sultana R, Wagatsuma Y, Mondal D, Hoque AMW, et al. Effects of in utero arsenic exposure on child immunity and morbidity in rural Bangladesh. Toxicology letters. 2009; 185:197–202. [PubMed: 19167470]
83. Rahman A, Vahter M, Ekstrom E-C, Rahman M, Golam Mustafa AHM, Wahed MA, et al. Association of Arsenic Exposure during Pregnancy with Fetal Loss and Infant Death: A Cohort Study in Bangladesh. American Journal of Epidemiology. 2007; 165:1389–96. [PubMed: 17351293]
84. Rahman M, Vahter M, Sohel N, Yunus M, Wahed MA, Streatfield PK, et al. Arsenic exposure and age and sex-specific risk for skin lesions: a population-based case-referent study in Bangladesh. Environmental health perspectives. 2006; 114:1847–52. [PubMed: 17185274]
85. Soto-Pena G, Luna A, Acosta-Saavedra L, Conde-Moo P, Lopez-Carrillo L, Cebrian M, et al. Assessment of lymphocyte subpopulations and cytokine secretion in children exposed to arsenic. The FASEB Journal. 2006:05.
86. Kozul, C.; Hampton, T.; Davey, J.; Gosse, J.; Nomikos, A.; Eisenhauer, P., et al. Chronic exposure to arsenic in the drinking water alters the expression of immune response genes in mouse lung. 2009.
87. Andrew A, Bernardo V, Warnke L, Davey J, Hampton T, Mason R, et al. Exposure to arsenic at levels found in US drinking water modifies expression in the mouse lung. Toxicological Sciences. 2007
88. Patterson R, Vega L, Trouba K, Bortner C, Germolec D. Arsenic-induced alterations in the contact hypersensitivity response in Balb/c mice. Toxicology and applied pharmacology. 2004; 198:434–43. [PubMed: 15276424]
89. Kozul, C.; Ely, K.; Enelow, R.; Hamilton, J. Low-dose arsenic compromises the immune response to influenza A infection in vivo. 2009.
90. Engel A, Lamm SH. Arsenic exposure and childhood cancer--a systematic review of the literature. Journal of environmental health. 2008; 71:12–6. [PubMed: 18990928]
91. Smith AH, Marshall G, Yuan Y, Ferreccio C, Liaw J, von Ehrenstein O, et al. Increased mortality from lung cancer and bronchiectasis in young adults after exposure to arsenic in utero and in early childhood. Environmental health perspectives. 2006; 114:1293–6. [PubMed: 16882542]
92. Waalkes MP, Ward JM, Liu J, Diwan BA. Transplacental carcinogenicity of inorganic arsenic in the drinking water: induction of hepatic, ovarian, pulmonary, and adrenal tumors in mice. Toxicology and applied pharmacology. 2003; 186:7–17. [PubMed: 12583988]
93. Liu J, Xie Y, Merrick BA, Shen J, Ducharme DMK, Collins J, et al. Transplacental arsenic plus postnatal 12-O-teradecanoyl phorbol-13-acetate exposures associated with hepatocarcinogenesis induce similar aberrant gene expression patterns in male and female mouse liver. Toxicology and applied pharmacology. 2006; 213:216–23. [PubMed: 16368122]

94. Waalkes MP, Liu J, Ward JM, Diwan BA. Enhanced urinary bladder and liver carcinogenesis in male CD1 mice exposed to transplacental inorganic arsenic and postnatal diethylstilbestrol or tamoxifen. Toxicology and applied pharmacology. 2006; 215:295–305. [PubMed: 16712894]

95. Waalkes MP, Liu J, Ward JM, Powell DA, Diwan BA. Urogenital Carcinogenesis in Female CD1 Mice Induced by In utero Arsenic Exposure Is Exacerbated by Postnatal Diethylstilbestrol Treatment. Cancer research. 2006; 66:1337–45. [PubMed: 16452187]

96. Chen H, Liu J, Merrick BA, Waalkes MP. Genetic events associated with arsenic-induced malignant transformation: applications of cDNA microarray technology. Molecular carcinogenesis. 2001; 30:79–87. [PubMed: 11241755]

97. Reichard JF, Schnekenburger M, Puga A. Long term low-dose arsenic exposure induces loss of DNA methylation. Biochemical and biophysical research communications. 2007; 352:188–92. [PubMed: 17107663]

98. 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. Toxicological Sciences. 2007; 95:313–20. [PubMed: 17077188]

99. Waalkes M, Liu J, Chen H, Xie Y, Achanzar W, Zhou Y, et al. Estrogen signaling in livers of male mice with hepatocellular carcinoma induced by exposure to arsenic in utero. JNCI Journal of the National Cancer Institute. 2004; 96:466.

100. Liu J, Xie Y, Cooper R, Ducharme DMK, Tennant R, Diwan BA, et al. Transplacental exposure to inorganic arsenic at a hepatocarcinogenic dose induces fetal gene expression changes in mice indicative of aberrant estrogen signaling and disrupted steroid metabolism. Toxicology and applied pharmacology. 2007; 220:284–91. [PubMed: 17350061]

101. US Environmental Protection Agency. Pesticides Industry Sales and Usage: 2000 and 2001 Market Estimates. 2004. http://www.epa.gov/oppbead1/pestsales/

102. Bradman A, Barr DB, Claus Henn BG, Drumheller T, Curry C, Eskenazi B. Measurement of pesticides and other toxicants in amniotic fluid as a potential biomarker of prenatal exposure: a validation study. Environ Health Perspect. 2003; 111:1779–82. [PubMed: 14594631]

103. Rowe AM, Brundage KM, Barnett JB. Developmental immunotoxicity of atrazine in rodents. Basic & clinical pharmacology & toxicology. 2008; 102:139–45. [PubMed: 18226067]

104. Rooney AA, Matulka RA, Luebke RW. Developmental Atrazine Exposure Suppresses Immune Function in Male, but not Female Sprague-Dawley Rats. Toxicological Sciences. 2003; 76:366–75. [PubMed: 14514952]

105. Theus SA, Tabor DR, Soderberg LS, Barnett JB. Macrophage tumoricidal mechanisms are selectively altered by prenatal chlordane exposure. Agents and Actions. 1992; 37:140–6. [PubMed: 1456175]

106. Blaylock BL, Soderberg LS, Gandy J, Menna JH, Denton R, Barnett JB. Cytotoxic T-lymphocyte and NK responses in mice treated prenatally with chlordane. Toxicology letters. 1990; 51:41–9. [PubMed: 2315958]

107. Barnett JB, Holcomb D, Menna JH, Soderberg LS. The effect of prenatal chlordane exposure on specific anti-influenza cell-mediated immunity. Toxicology letters. 1985; 25:229–38. [PubMed: 2990071]

108. Barnett JB, Soderberg LS, Menna JH. The effect of prenatal chlordane exposure on the delayed hypersensitivity response of BALB/c mice. Toxicology letters. 1985; 25:173–83. [PubMed: 3159128]

109. Menna JH, Barnett JB, Soderberg LS. Influenza type A virus infection of mice exposed in utero to chlordane; survival and antibody studies. Toxicology letters. 1985; 24:45–52. [PubMed: 2983457]

110. Turner, MC.; Wigle, D.; Krewski, D. Residential Pesticides and Childhood Leukemia: A Systematic Review and Meta-Analysis.

111. Wigle DT, Turner MC, Krewski D. A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure. Environmental health perspectives. 2009; 117:1505–13. [PubMed: 20019898]

112. Zahm SH, Ward MH. Pesticides and childhood cancer. Environmental health perspectives. 1998; 106:893. [PubMed: 9646054]

113. Infante-Rivard C, Weichenthal S. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. Journal of Toxicology and Environmental Health Part B: Critical Reviews, 10. 2007; 1:81–99.

114. Peden-Adams M, Keller J, EuDaly J, Berger J, Gilkeson G, Keil D. Suppression of humoral immunity in mice following exposure to perfluorooctane sulfonate (PFOS). Toxicological Sciences. 2008

115. Peden-Adams M, EuDaly J, Dabra S, EuDaly A, Heesemann L, Smythe J, et al. Suppression of humoral immunity following exposure to the perfluorinated insecticide sulfluramid. Journal of Toxicology and Environmental Health, Part A. 2007; 70:1130–41. [PubMed: 17558808]

116. Keil DE, Mehlmann T, Butterworth L, Peden-Adams MM. Gestational Exposure to Perfluorooctane Sulfonate Suppresses Immune Function in B6C3F1 Mice. Toxicological Sciences. 2008; 103:77–85. [PubMed: 18252804]

117. McKinney PA, Raji OY, van Tongeren M, Feltbower RG. The UK Childhood Cancer Study: maternal occupational exposures and childhood leukaemia and lymphoma. Radiat Prot Dosimetry. 2008; 132:232–40. [PubMed: 18922820]

118. Sung T-I, Wang J-D, Chen P-C. Increased risk of cancer in the offspring of female electronics workers. Reproductive Toxicology. 2008; 25:115–9. [PubMed: 17923386]

119. Colt JS, Blair A. Parental occupational exposures and risk of childhood cancer. Environmental health perspectives. 1998; 106 (Suppl 3):909–25. [PubMed: 9646055]

120. Savitz DA, Chen JH. Parental occupation and childhood cancer: review of epidemiologic studies. Environmental health perspectives. 1990; 88:325–37. [PubMed: 2272330]

121. Buckley JD, Robison LL, Swotinsky R, Garabrant DH, LeBeau M, Manchester P, et al. Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the Childrens Cancer Study Group. Cancer research. 1989; 49:4030–7. [PubMed: 2736544]

122. Infante-Rivard C, Siemiatycki J, Lakhani R, Nadon L. Maternal exposure to occupational solvents and childhood leukemia. Environmental health perspectives. 2005; 113:787–92. [PubMed: 15929905]

123. Yamamoto S, Tin Tin Win S, Yoshida Y, Kunugita N, Arashidani K, Fujimaki H. Children's immunology, what can we learn from animal studies (2): Modulation of systemic Th1/Th2 immune response in infant mice after prenatal exposure to low-level toluene and toll-like receptor (TLR) 2 ligand. The Journal of toxicological sciences. 2009; 34(Suppl 2):SP341–8. [PubMed: 19571489]

124. Blossom SJ, Doss JC. Trichloroethylene alters central and peripheral immune function in autoimmune-prone MRL(+/+) mice following continuous developmental and early life exposure. Journal of immunotoxicology. 2007; 4:129–41. [PubMed: 18958721]

125. Blossom SJ, Doss JC, Hennings LJ, Jernigan S, Melnyk S, James SJ. Developmental exposure to trichloroethylene promotes CD4+ T cell differentiation and hyperactivity in association with oxidative stress and neurobehavioral deficits in MRL+/+ mice. Toxicology and applied pharmacology. 2008; 231:344–53. [PubMed: 18579175]

126. Peden-Adams M, Eudaly J, Heesemann L, Smythe J, Miller J, Gilkeson G, et al. Developmental immunotoxicity of trichloroethylene (TCE): studies in B6C3F1 mice. Journal of Environmental Science and Health, Part A. 2006; 41:249–71.

127. Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003–2004. Environ Health Perspect. 2008; 116:39–44. [PubMed: 18197297]

128. Silva, Mj; Barr, DB.; Reidy, JA.; Malek, NA.; Hodge, CC.; Caudill, SP.; Brock, JW., et al. Urinary levels of seven phthalate metabolites in the US population from the National Health and Nutrition Examination Survey (NHANES). 1999–2000.

129. Inoue K, Kato K, Yoshimura Y, Makino T, Nakazawa H. Determination of bisphenol A in human serum by high-performance liquid chromatography with multi-electrode electrochemical detection. Journal of chromatographyB, Biomedical sciences and applications. 2000; 749:17–23.

130. Silva MJ, Reidy JA, Herbert AR, Preau JL Jr, Needham LL, Calafat AM. Detection of phthalate metabolites in human amniotic fluid. Bull Environ Contam Toxicol. 2004; 72:1226–31. [PubMed: 15362453]

131. Piepenbrink MS, Hussain I, Marsh JA, Dietert RR. Developmental Immunotoxicology of Di-(2-Ethylhexyl)phthalate (DEHP): Age-Based Assessment in the Female Rat. J Immunotoxicol. 2005; 2:21–31. [PubMed: 18958656]

132. Kimber I, Dearman RJ. An assessment of the ability of phthalates to influence immune and allergic responses. Toxicology. In Press, Uncorrected Proof.

133. Yan H, Takamoto M, Sugane K. Exposure to Bisphenol A prenatally or in adulthood promotes T(H)2 cytokine production associated with reduction of CD4CD25 regulatory T cells. Environmental health perspectives. 2008; 116:514–9. [PubMed: 18414636]

134. Yoshino S, Yamaki K, Li X, Sai T, Yanagisawa R, Takano H, et al. Prenatal exposure to bisphenol A up-regulates immune responses, including T helper 1 and T helper 2 responses, in mice. Immunology. 2004; 112:489–95. [PubMed: 15196218]

135. Ohshima Y, Yamada A, Tokuriki S, Yasutomi M, Omata N, Mayumi M. Transmaternal exposure to bisphenol a modulates the development of oral tolerance. Pediatr Res. 2007; 62:60–4. [PubMed: 17515845]

136. Midoro-Horiuti T, Tiwari R, Watson CS, Goldblum RM. Maternal bisphenol a exposure promotes the development of experimental asthma in mouse pups. Environ Health Perspect. 118:273–7. [PubMed: 20123615]

137. Alizadeh M, Ota F, Hosoi K, Kato M, Sakai T, Satter MA. Altered allergic cytokine and antibody response in mice treated with Bisphenol A. J Med Invest. 2006; 53:70–80. [PubMed: 16537998]

138. Sawai C, Anderson K, Walser-Kuntz D. Effect of bisphenol A on murine immune function: modulation of interferon-gamma, IgG2a, and disease symptoms in NZB X NZW F1 mice. Environ Health Perspect. 2003; 111:1883–7. [PubMed: 14644661]

139. Goto M, Takano-Ishikawa Y, Ono H, Yoshida M, Yamaki K, Shinmoto H. Orally administered bisphenol A disturbed antigen specific immunoresponses in the naive condition. Biosci Biotechnol Biochem. 2007; 71:2136–43. [PubMed: 17827700]

140. Yurino H, Ishikawa S, Sato T, Akadegawa K, Ito T, Ueha S, et al. Endocrine disruptors (environmental estrogens) enhance autoantibody production by B1 cells. Toxicol Sci. 2004; 81:139–47. [PubMed: 15166399]

141. Skinner MK, Manikkam M, Guerrero-Bosagna C. Epigenetic transgenerational actions of environmental factors in disease etiology. Trends Endocrinol Metab.

142. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet. 2003; 33 (Suppl):245–54. [PubMed: 12610534]

143. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science (New York, NY). 2005; 308:1466–9.

144. Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc Natl Acad Sci U S A. 2007; 104:13056–61. [PubMed: 17670942]

145. Yaoi T, Itoh K, Nakamura K, Ogi H, Fujiwara Y, Fushiki S. Genome-wide analysis of epigenomic alterations in fetal mouse forebrain after exposure to low doses of bisphenol A. Biochemical and biophysical research communications. 2008; 376:563–7. [PubMed: 18804091]

146. Bromer, JG.; Zhou, Y.; Taylor, MB.; Doherty, L.; Taylor, HS. Bisphenol-A exposure in utero leads to epigenetic alterations in the developmental programming of uterine estrogen response.

147. Prins GS, Tang WY, Belmonte J, Ho SM. Perinatal exposure to oestradiol and bisphenol A alters the prostate epigenome and increases susceptibility to carcinogenesis. Basic & clinical pharmacology & toxicology. 2008; 102:134–8. [PubMed: 18226066]

148. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. President's Cancer Panel: Reducing Environmental Cancer Risk. Annual Report. 2008–2009. http://deainfo.nci.nih.gov/advisory/pcp/pcp.htm

149. Bellinger DL, Lubahn C, Lorton D. Maternal and early life stress effects on immune function: relevance to immunotoxicology. J Immunotoxicol. 2008; 5:419–44. [PubMed: 19404876]

150. Collins FS. Research agenda. Opportunities for research and NIH. Science. 327:36–7. [PubMed: 20044560]

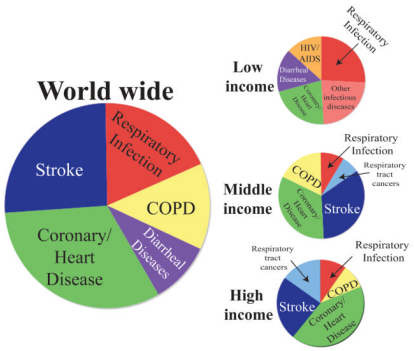

Figure 1. Lower respiratory tract infections are among the top five causes of death worldwide

Data are adapted from a recent WHO report on the global burden of disease [1]. Data are based on information from 2004, in which an estimated 59 million people died, with 4.2 million deaths attributed to lower respiratory tract infections, and at least another 7 million deaths due to other infectious diseases. The primary differences between affluent and poor countries with respect to antecedents of mortality are that in low income countries, the major causes of death are infectious diseases, and over 1/3 of all deaths are children under 14 years of age. In middle income countries, chronic diseases begin to contribute to major causes of death; however tuberculosis remains a major source of morbidity and mortality. In high income countries, nearly half the population lives to 70 years of age and chronic illnesses predominate as major causes of death; although lower respiratory tract infections persist among the top 5 killers even in the world's most affluent nations.