

## TRAINING FOR THE HEALTH SECTOR

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# IMMUNE DISEASES AND CHILDREN

### Children's Health and the Environment

WHO Training Package for the Health Sector

World Health Organization

*www.who.int/ceh*

October 2011

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## **LEARNING OBJECTIVES**

- ❖ **To introduce the complexity of immune system function and the consequences of its impairment**
- ❖ **To explain perinatal immune system vulnerability**
- ❖ **To present some examples of current evidence of associations between environmental risk factors and immune system impairment**

<<READ SLIDE>>

## **OVERVIEW**

- ❖ **Immune system and immune diseases**
- ❖ **Perinatal vulnerability and developmental immunotoxicity**
- ❖ **Environmental risk factors associated with immune adverse effects**
- ❖ **Biomarkers of immune alteration**
- ❖ **Further research – new challenges**

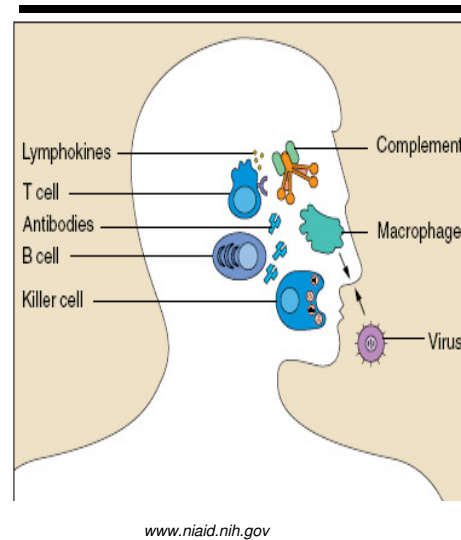
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## Immune diseases and children

### IMMUNITY

❖ Complex, highly regulated, multicellular, physiologic mechanisms designed to accomplish a singular goal:

- *to differentiate self from non self*



Immunity depends on an intricate homeostatic system aimed at maintaining a delicate balance between health and disease.

Its function is maintained by a series of complex, highly regulated, multi-cellular, physiologic mechanisms designed to accomplish a singular goal: to differentiate self from non-self. The healthy immune system has the ability to distinguish between the body's own cells, recognized as "self" and foreign cells, or "non-self."

When the immune system is challenged by a microbe, it has many defense barriers and types of responses to choose.

The immune defenses normally coexist peacefully with cells that carry distinctive self marker molecules. Anything that can trigger this immune response is called an antigen. An antigen can be a microbe, or a part of a microbe such as a molecule. Tissues or cells from another person (except an identical twin) carry non-self markers and act as foreign antigens. In abnormal situations, the immune system can mistake self for non-self and launch an attack against the body's own cells or tissues.

Immunocompetence is maintained by the concert of lymphoid organs, specific and non-specific cellular and humoral factors.

All immune cells begin as immature stem cells in the bone marrow. They respond to different cytokines and other chemical signals to grow into specific immune cell types, such as T cells, B cells, or phagocytes.

Lymphocytes known as T lymphocytes or T cells ("T" stands for "thymus") mature in the thymus and then migrate to other tissues. B lymphocytes, also known as B cells, become activated and mature into plasma cells, which make and release antibodies or immunoglobulins (G, M, A, E and D).

T cells contribute to immune defenses in two major ways: some direct and regulate immune responses, whereas others directly attack infected or cancerous cells. Helper T cells, or Th cells, coordinate immune responses by communicating with other cells, promote activation of cytotoxic T lymphocytes (CTLs) and B cells to become memory cells. CTLs — also called killer T cells directly attack other cells carrying certain foreign or abnormal molecules on their surfaces.

Natural killer (NK) cells are another kind of lethal white cell with granules filled with potent chemicals. NK cells recognize cells lacking self-MHC (histocompatibility) molecules. Thus, NK cells have the potential to attack many types of foreign cells.

Phagocytes or macrophages are large white cells that can swallow and digest microbes and other foreign particles. Monocytes are phagocytes that circulate in the blood.

Dendritic cells are found in the parts of lymphoid organs where T cells also exist. Like macrophages, dendritic cells in lymphoid tissues display antigens to T cells and help stimulate T cells during an immune response.

Cytokines or lymphokines are chemical messengers secreted by immune cells and act on other cells to coordinate appropriate immune responses. Cytokines include a different types of interleukins (IL), interferons (IFN), and growth factors. Chemokines often play a key role in inflammation.

The complement system is made up of about 25 proteins that work together to assist, or "complement," the action of antibodies in destroying microbes.

*Ref and image:*

•National Institutes of Health. Understanding the immune system. How it works .U.S. Department of Health and Human Services. National Institutes of Health National Institute of Allergy and Infectious Diseases, National Institutes of Health Publication No. 07-5423, September 2007

## Immune diseases and children

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### IMMUNITY

- ❖ **Cytokines: hormonal messengers in the immune system**
- ❖ **Cytokines can be proinflammatory or anti-inflammatory**
- ❖ **T lymphocytes: major source of cytokines: antigen specific receptors on their cell surface to allow recognition of foreign pathogens.**
- ❖ **T lymphocytes expressing surface molecule CD4 are also known as helper T cells**
- ❖ **Helper T cells are subdivided into Th1 and Th2, and the cytokines they produce are Th1-type cytokines and Th2-type cytokines.**
- ❖ **Th1-type cytokines tend to produce the proinflammatory responses**
- ❖ **Th2-type cytokines deal with responses in atopy and anti-inflammatory responses.**

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Cytokines: hormonal messengers for most of the biological effects in the immune system (e.g. cell mediated immunity and allergic responses)

Cytokines can be proinflammatory or anti-inflammatory (but that promote allergic responses).

T lymphocytes are a major source of cytokines: antigen specific receptors on their cell surface to allow recognition of foreign pathogens.

There are two main subsets of T lymphocytes, distinguished by the presence of cell surface molecules known as CD4 and CD8. T lymphocytes expressing CD4 are also known as helper T cells, and these are regarded as being the most prolific cytokine producers. This subset can be further subdivided into Th1 and Th2, and the cytokines they produce are known as Th1-type cytokines and Th2-type cytokines.

Th1-type cytokines tend to produce the proinflammatory responses responsible for killing intracellular parasites and for perpetuating autoimmune responses.

Th2-type cytokines deal with responses in atopy and anti-inflammatory responses.

*Ref:*

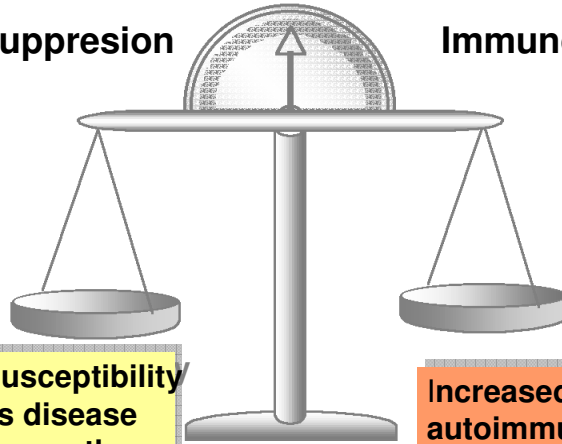
•Berger A. Th1 and Th2 responses: what are they? *British Medical Journal*. 321:424.

## Immune diseases and children

### IMMUNOCOMPETENCE AND IMMUNOTOXICITY

**Immunosuppression**

**Immunostimulation**



**Increased susceptibility to infectious disease and tumour growth**

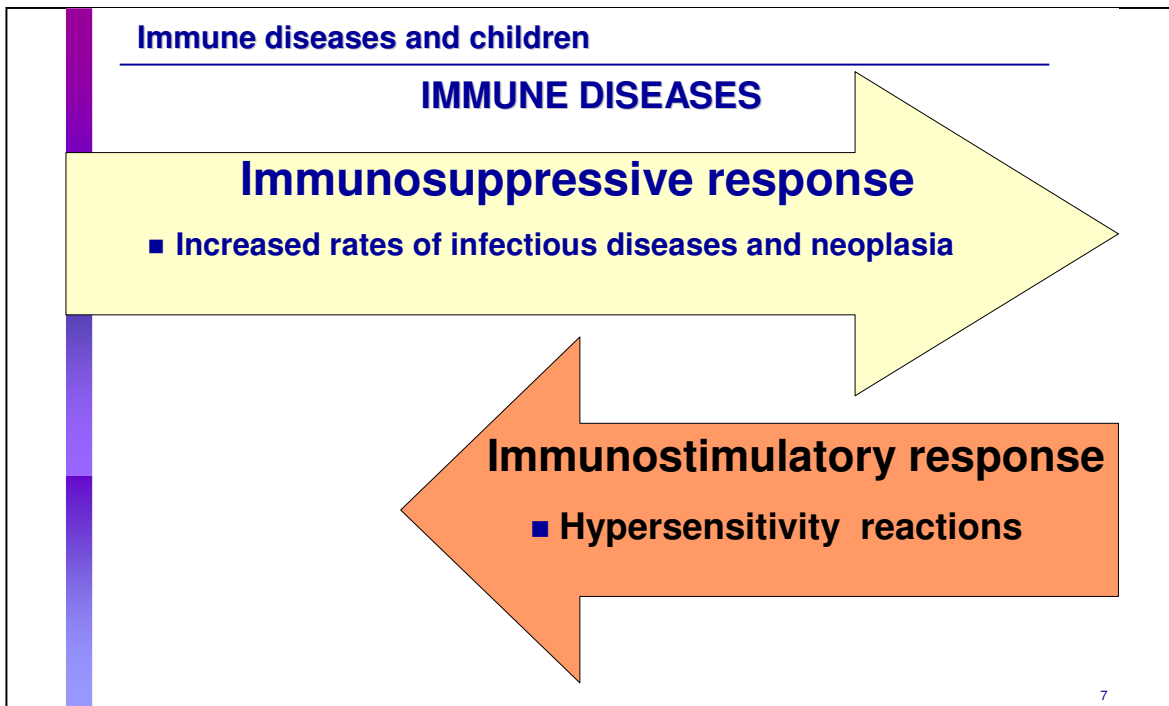
**Increased incidence of autoimmunity & allergy**

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- Immunocompetence is a state of functional immunity that provides effective resistance to infectious agents and neoplastic cells.
- The immune system is designed to respond with the appropriate, non-exaggerated response to non-self biological, chemical or physical stimuli.
- Immunotoxicity is defined as the inappropriate immune response induced directly or indirectly by xenobiotics or physical agents.
- The immune system can be a target for toxic effects caused by a wide variety of environmental, occupational and pharmaceutical agents at one or more points of the physiologic mechanism.
- The adverse effect is generally immunosuppression or immunostimulation. If immunocompetence represents an optimal balanced immune response, then profound immunosuppression or overt hypersensitivity represents the extremes of ineffective and inappropriate immune responsiveness.

*Ref:*

- WHO/IPCS. Principles and methods for assessing direct immunotoxicity associated with exposure to chemicals. Environmental health criteria 180, WHO, 1996.



**Immunosuppression** is a decrease in immune function measured as an effect on cellular, humoral, or non-specific immune parameters. Primary immune response is the more susceptible to suppression (e.g: macrophage phagocytic activity), although a wide range of subtle effects has been described. Heavy metals, polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), certain air pollutants, certain pesticides and drugs may cause significant and persistent immunosuppressive effects. The likely clinical sequels of immunosuppression are increased rates of infectious diseases and neoplasia.

Clinicians agree that susceptible groups are more likely to suffer adverse health consequences from any immune suppression. Children in developing countries may be more susceptible due to malnutrition.

**Hypersensitivity disorders** are the most prominent forms of immunotoxicity recognized in humans. Hypersensitivity is an exaggerated response to an antigenic stimulus, commonly distinguished by a reduced threshold to antigen response. Regardless of their type, all hypersensitivity reactions are induced by recall antigens in or on a host that has previously caused an immune response to the antigen. This type of immunopathology can be antibody-mediated, cell-mediated or a combination of both.

*Ref:*

•Sullivan J , Brooks BO, Meggs JM. Clinical immunotoxicology and allergy. Chap 25. In: Sullivan JB, Krieger GR. *Clinical environmental health and toxic exposures*. 2nd ed. Lippincott Williams & Wilkins, 2001.

## Immune diseases and children

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### Examples:

- ❖ Asthma, rhinitis, eczema, urticaria, anaphylaxis
- ❖ Autoimmune diseases : diabetes 1, rheumatoid arthritis, systemic lupus
- ❖ Allergic alveolitis
- ❖ Contact dermatitis (T lymphocytes-mediated)
- ❖ Hemolytic disease of the newborn
- ❖ Glomerular basement membrane damage

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The most clinically relevant hypersensitivity reactions encountered with chemical hazards are:

- Immediate hypersensitivity reactions (type I -IgE): asthma, eczema, urticaria, anaphylaxis.
- Immunocomplex reactions (type III): autoimmune diseases, such as diabetes 1, rheumatoid arthritis, systemic lupus or farmers lung or allergic alveolitis.
- Delayed hypersensitivity reactions (type IV ): contact dermatitis (T lymphocytes-mediated).
- Antibody dependent cytotoxicity (type II): hemolytic disease of the newborn, glomerular basement membrane damage.

### Ref:

• Sullivan J , Brooks BO, Meggs JM. Clinical immunotoxicology and allergy. Chap 25. In: Sullivan JB, Krieger GR. *Clinical environmental health and toxic exposures*. 2nd ed. Lippincott Williams & Wilkins, 2001.

## IMMUNOTOXICITY

Subtle effects

- ❖ Environmental factors may act years before clinical disease becomes apparent

Latency of effects

- ❖ Clinical diseases may be apparent after the altered immune system is challenged by other risk factors

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The immune system is a multifaceted network that maintains a level of functional reserve. Therefore, a toxic effect on a particular cell or circuit may not necessarily lead to detectable clinical manifestations.

Besides that, environmental factors may act many years before clinical disease becomes apparent and clinical diseases may be apparent after the altered immune system is challenged by other risk factors (eg: viral infection).

Although the immune system and its development have not been completely characterized, there is increasing evidence that immune-associated diseases are dependent upon specific windows of early life exposure, the gender of the exposed offspring, and the genetic background of the offspring.

*Ref:*

•Dietert RR, Piepenbrick MS. Perinatal immunotoxicity: why adult exposure assessment fails to predict risk. *Environ Health Perspect*, 2006, 114: 477-483

## DEVELOPMENTAL IMMUNOTOXICITY

Increasing incidence of immune-related diseases

- Perinatal events are critical for later life host defense
- The maturing immune system is a vulnerable window to toxic effects

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- The developing immune system can be permanently altered or 'programmed' by the early exposure to environmental agents.
- A growing number of childhood diseases such as allergic disorders (e.g. allergic rhinitis, atopic dermatitis, asthma), cancer (e.g. acute leukemia and myeloid leukemia), and others (e.g. type 1 diabetes) have been linked to environmental exposures during prenatal and early postnatal development.
- Because the immune response plays a critical role in each of these diseases, it is important to consider the effects of toxicants on children's developing immune system.

*Ref:*

- Duramad P, Tager IB, Holland NT. Cytokines and other immunological biomarkers in children's environmental health studies. *Toxicol Lett*, 2007, 30, 172(1-2): 48–59.

## Immune diseases and children

### CHILDREN'S IMMUNE SYSTEM INCREASED SENSITIVITY

- ❖ 3 to 12-fold dose sensitivity
- ❖ Different and unpredictable array of alterations
- ❖ Persistence of effects
- ❖ Latency –alteration is unrecognizable until the postnatal immune system is placed under stress

***Predictive methods used to assess the immune function in adults are not adaptable to the developmental model***

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Health risks are significantly increased following early life versus adult immunotoxic exposures. The pre and postnatal periods are particularly sensitive to environmental agents.

There are several examples suggesting that the developing immune system is altered by significantly lower doses of toxicants than those required to produce effects in the adult.

Sensitivity to immunotoxicants may produce a wide spectrum and severity of effects. Different and unpredictable arrays of alterations may be expected when the exposure occurs *in utero* or in the early neonate versus the adult exposure. A number of chemicals produce different ranges or severities of outcomes depending upon age of exposure.

The immunotoxic alterations after early exposure may be persistent and last long after exposure. Diethylstilbestrol (DES) is an example where early xenobiotic exposure results in a greater persistence of effects than would be predicted from adult exposure assessment.

Sublethal exposure to a toxicant may produce an unrecognizable immunotoxic alteration until the postnatal immune system is placed under subsequent stress. This hidden or cryptic state is referred to as "latency". Early exposure to DES is also a classic example, as an apparently innocuous early exposure to DES alters the immune system in such a manner that it responds to a second adult estrogenic exposure (which of itself has no effect) with a completely aberrant cytokine production profile.

Ref :

•Dietert RR, Piepenbrick M. Perinatal immunotoxicity: why adult exposure assessment fails to predict risk. *Environ Health Perspect*, 2006, 114: 477-483

•Dietert RR. Developmental immunotoxicology: focus on health risks. *Chem Res Toxicol*, 2009, 22(1):17-23

## Immune diseases and children

# DEVELOPMENT OF IMMUNOCOMPETENCE BALANCE LESSONS LEARNED FROM NUTRITION

**Breastfeeding  
decreases incidence  
of allergic pathology.**



WHO.

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Lifelong capacity for immunocompetence is determined early in development, during prenatal and early postnatal development.

Early life exposure to environmental agents may play a key role in the immunocompetence balance.

There is a lesson learned from the impact of breastfeeding on immune responses.

The neonatal immune system tends to favor an allergic (Ig E promoting) response to certain environmental allergens (Ig E promoting or Th2 response). As the immune system matures, T cells tends to release a different group of cytokines that favor an IgG promoting or Th1 response.

Early life exposures to environmental contaminants may shift the balance toward Th1 or Th2 responses.

Epidemiologic studies have indicated that breastfeeding is associated with infant health benefits and protects against many diseases.

Children who were exclusively breastfed had significantly higher levels of Th1-type cytokines at 1 month of age in the study cited below. These findings suggest a mechanistic explanation for the observed associations between breastfeeding and a decreased incidence of allergic pathology.

One mechanism to explain the effects of breastfeeding on immune disorders is that breast milk is implicated in aiding the establishment of native gut microbiota (acquired at birth and during the first year of life), which has been demonstrated to be an important modulator of the immune system.

### Ref:

•Figueiredo CA et al. Spontaneous cytokine production in children according to biological characteristics and environmental exposures. *Environ Health Perspect*, 2009, 117:845–849

*Environmental factors are likely to have profound effects on the development of host immune responses, with serious implications for infectious diseases and inflammatory disorders such as asthma. This study was designed to investigate the effects of environmental exposures on the cytokine profile of children. The study involved measurement of T helper (Th) 1 (interferon-gamma), 2 [interleukin (IL)-5 and IL-13], and the regulatory cytokine IL-10 in unstimulated peripheral blood leukocytes from 1,376 children 4-11 years of age living in a poor urban area of the tropics. We also assessed the impact of environmental exposures in addition to biological characteristics recorded at the time of blood collection and earlier in childhood (0-3 years before blood collection). The proportion of children producing IL-10 was greater among those without access to drinking water [ $p < 0.05$ , chi-square test, odds ratio (OR) = 1.67]. The proportion of children producing IL-5 and IL-10 (OR = 10.76) was significantly greater in households that had never had a sewage system ( $p < 0.05$ , trend test). These data provide evidence for the profound effects of environmental exposures in early life as well as immune homeostasis in later childhood. Decreased hygiene (lack of access to clean drinking water and sanitation) in the first 3 years of life is associated with higher spontaneous IL-10 production up to 8 years later in life.*

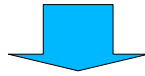
## Immune diseases and children

### DEVELOPMENT OF CHILDREN'S IMMUNOCOMPETENCE BALANCE: LESSONS LEARNED FROM EARLY INFECTIONS



Laborde A.

Early childhood infections,  
are becoming less frequent  
favoring a hypersensitivity  
reaction



The hygiene hypothesis

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Lessons learned from the hygiene hypothesis and its role in the immunocompetence balance are another example of early life exposures as determinant factors of the balance between Th1 and Th2 responses.

According to the hygiene hypothesis, an increased incidence of allergic pathology in westernized societies may be explained in part by a reduced microbial load early in infancy. An inverse relation between the incidence of prototypical infectious diseases and the incidence of immune disorders as been demonstrated.

Allergic diseases are caused by inappropriate immunological responses to innocuous antigens driven by a TH2-mediated immune response. Many bacteria and viruses elicit a TH1-mediated immune response, which down-regulates TH2 responses. Observations of this down-regulation led to the development of the first proposed mechanism of action of the hygiene hypothesis, which stated that insufficient stimulation of the TH1 arm of the immune system lead to an overactive TH2 arm, which in turn led to allergic disease

This hypothesis is quite controversial in the scientific community, as it can not explain by itself the higher risk of African-American children, and the increases in asthma rates seen in developing countries.

#### *Ref:*

- Bach JF The effect of infection on susceptibility to autoimmune and allergic diseases. *N Engl J Med*, 2002, 347(12):911-20.
- Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax*, 2000, 55(1):S2-10.



## Immune diseases and children

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### IMMUNE DISEASES ARE ASSOCIATED WITH A WIDE RANGE OF RISK FACTORS

- ❖ Genetic
- ❖ Stress
- ❖ Microorganisms
- ❖ Radiation
- ❖ Chemicals
  - Pharmaceutical
  - Environmental contaminants

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Immune disorders may have multiple causal factors.

•Decreased immune responsiveness (immunosuppression) may be caused by genetic / congenital disorders (primary immunodeficiency). The acquired immune deficiency syndrome (AIDS) represents the first recognised acquired epidemic chronic immunosuppressive defect caused by a viral infection.

•Functional activation of the immune system (hypersensitivity) may occur associated with chronic stress. Lymphocytes have membrane receptors to catecholamine, particularly NK cells.

•There is increasing evidence to support that infectious agents, radiation, therapeutic agents and chemicals of diverse origins may act as etiologic agents in the induction of both types of immune diseases.

## Immune diseases and children

### ENVIRONMENTAL CONTAMINANTS IMMUNOTOXICITY

- ❖ Ultraviolet radiation
- ❖ Mycotoxins
- ❖ Polycyclic aromatic hydrocarbons
- ❖ Polychlorinated biphenyls / Polybrominated biphenyls
- ❖ Metals
- ❖ Pesticides



**suggestive evidence**

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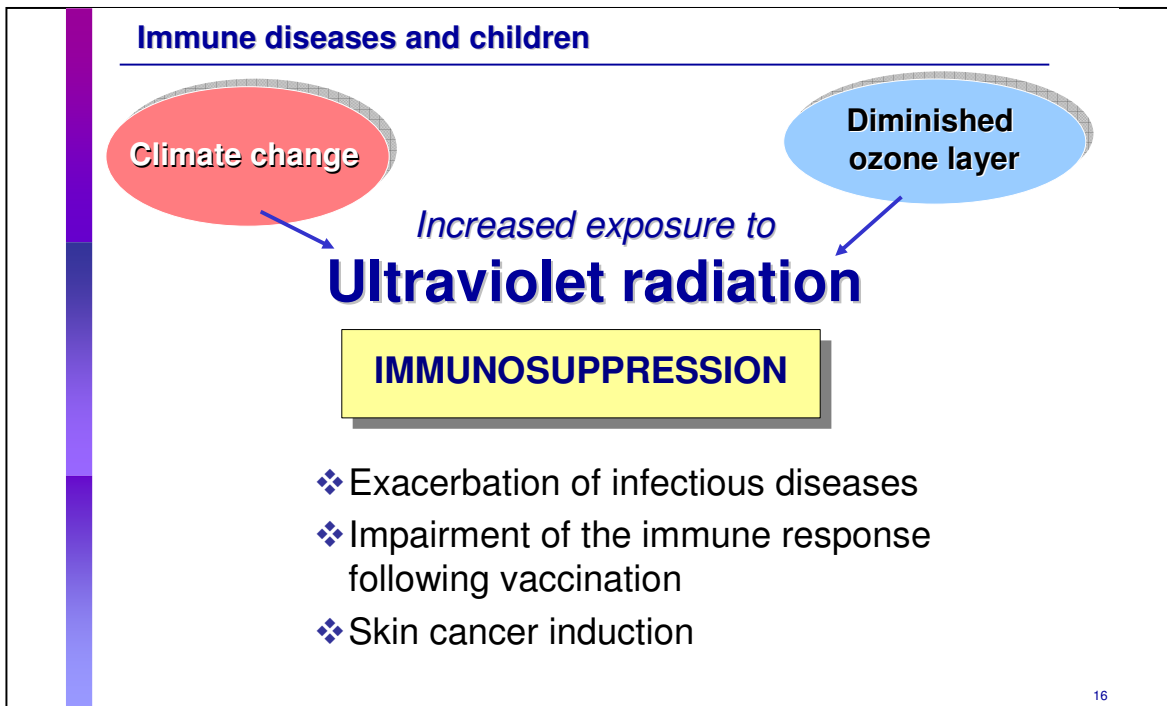
The International Seminar on the Immunological System as a Target Organ for Toxicity recommended that an agent should be considered immunotoxic when there is:

- A direct or indirect action of the xenobiotic (and or biotransformation product) on the immune system.
- An immunologically-based host response to the compound and or its metabolites; or host antigens are modified by the compound or it metabolites.

Most of the evidence regarding immunotoxicity is considered suggestive, because it comes from experimental studies that need a battery of descriptive and function assays to determine the immunological status of the studied population. There are very few studies in children among human studies.

*Ref:*

•Sullivan J , Brooks BO, Meggs JM. Clinical immunotoxicology and allergy. Chap 25. In: Sullivan JB, Krieger GR. *Clinical environmental health and toxic exposures*. 2nd ed. Lippincott Williams & Wilkins, 2001.



Numerous studies have demonstrated that ultraviolet radiation (UVR) is locally and systemically immunosuppressive to animals and humans .

Excessive exposure to UVR causes sunburn, skin cancer, immune suppression and skin aging.

The exacerbation of infectious diseases, particularly those involving the skin (e.g: herpetic lesions and viral warts) is a well recognized clinical effect of sun (UV light) exposure.

The immunosuppressive potential of UVR may be of critical importance in affecting vaccine efficacy as well.

Solar-simulated UV sun radiation (UVA+UVB; 295–400 nm), applied after immunization, suppressed the immunological memory and the elicitation of delayed-type hypersensitivity to a common opportunistic pathogen.

UVA and UVB wavelength were equally effective in immune-suppression activity.

In recent decades, lifestyle changes have resulted in an increasing exposure of people in industrialized nations to ambient UV radiation, and this trend is expected to increase in future decades as a result of stratospheric ozone depletion.

Climate change models predict that human populations may be exposed to increased solar ultraviolet radiation, largely as a result of changing behavioral and clothing patterns, and potentially via an indirect effect of global warming on stratospheric ozone.

In the context of climate change, UVR-induced, immunosuppressive effects could have major public health implications.

UVR from solarium lamps has also shown reversible immunosuppression.

Skin cancer induction and immunosuppression in humans may have similar immunological pathways. It is also possible that a sunscreen that could protect against sunburn, be relatively ineffective in protecting against another effect of UV radiation.

Refs:

•Swaminathan A et al. Climate change and the human immune system: Ultraviolet radiation & immunity study, assessing the impact of ultraviolet radiation on the immune response to primary vaccination in Australian adults. *Earth and Environmental Science*, 2009, 6, 142033

•Ullrich SE, Kripke ML, Ananthaswamy HN. Mechanisms underlying UV-induced immune suppression: implications for sunscreen design *Experimental Dermatology*, 2002, 11 (1)

## Immune diseases and children

### MYCOTOXINS

#### Mold - indoor air pollution

#### HYPERSENSITIVITY

- ❖ Inhalation of antigenic material or mycotoxins associated to respiratory and dermatologic hypersensitivity diseases



Laborde A.

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It is well recognized that molds produce immunotoxic metabolites (mycotoxins) and antigenic materials (spores, hyphae, extracellular polysaccharides and enzymes) that cause immunologic responses (antigens) when they are inhaled.

Fungal fragments occur in indoor air as bio-contaminants.

Epidemiological studies have shown that indoor molds are associated with increased prevalence and exacerbation of respiratory hypersensitivity symptoms.

Inhalation of antigenic material or mycotoxins have a role in the development of acute asthma, allergic rhinitis and urticaria (hives).

Some mycotoxins increase the allergic immune response in mice by modulating the Th1/Th2.

#### Refs:

- Etzel R, Rylander R. Indoor mold and children's health. *Environ Health Perspect*, 1999, 107(3):463.
- Schütze N, et al. Exposure to mycotoxins increases the allergic immune response in a murine asthma model. *American Journal of Respiratory and Critical Care Medicine*, 2010, 181:1188-1199.

**<<NOTE TO USER: Please see modules on indoor air pollution and mycotoxins for more information.>>**

## Immune diseases and children

### MYCOTOXINS



FAO, 1991

### IMMUNOSUPPRESSION

#### Dietary exposure

Chronic ingestion of aflatoxin B<sub>1</sub> and Tricothecenes have potent immunosuppressive effect and are carcinogenic

- Long-term effects of low levels exposure to mycotoxin - aflatoxin B<sub>1</sub> and tricothecenes (ingestion from contaminated food), is a well recognized risk factor for immunosuppressant effect. Tricothecenes impair cell mediated immunity.
- Aflatoxin B is one of the most potent hepatocarcinogens known. There is limited evidence showing that tricothecenes-2 toxin is carcinogenic in animals.
- The ingestion of aflatoxin B<sub>1</sub>-contaminated animal feed, by dairy cattle, for instance, can result in the presence of aflatoxin M<sub>1</sub>, a metabolite of aflatoxin B<sub>1</sub>, in milk. This is an issue of considerable importance to public health, given the frequent consumption of milk and dairy products by infants .
- Other mycotoxins are not transmitted from food to milk. Mycotoxins may be present in cereals (maize, wheat, barley, oats and rice) and groundnuts.

#### *Refs and image:*

- Albert JL. Mycotoxins and food supply. *Food, nutrition and agriculture*. 1, Food and Agriculture Organization (FAO), 1991.
- Proctor DL. Grain storage techniques. The significance of mycotoxins. Chapter 2. *FAO Agricultural services bulletin*. 109, Food and Agriculture Organization (FAO), 1994

## Immune diseases and children

### OUTDOOR AIR POLLUTION POLYCYCLIC AROMATIC HYDROCARBONS (PAHs)

- ❖ Increased incidence of respiratory infections
- ❖ PAHs cause suppression of humoral and cell-mediated immunity
- ❖ Immunotoxic effect linked with carcinogenic effects

#### IMMUNOSUPPRESSION



WHO

Higher risk of cancer

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Air pollution is associated with a higher incidence of respiratory infections.

Polycyclic aromatic hydrocarbons (PAHs) are a group of chemicals emitted by combustion that cause suppression of humoral immunity and cell-mediated immunity.

The PAHs that are carcinogenic (eg: benzopyrenes) also have potent immunosuppressive properties. Those which are not carcinogenic lack marked immunotoxic effects.

*Ref:*

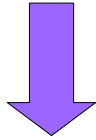
•WHO/IPCS. Principles and methods for assessing direct immunotoxicity associated with exposure to chemicals. Environmental health criteria 180, WHO, 1996.

## Immune diseases and children

### INDOOR AIR POLLUTION SOLID FUEL COMBUSTION- TOBACCO SMOKE

#### IMMUNOSUPPRESSION

- Decreased macrophage activity in the respiratory tract



PNEUMONIA



WHO

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Other indoor and outdoor air pollutants (ozone, nitrogen dioxide, sulfur dioxide) have immunosuppressive effects on the respiratory system, leading to an increasing incidence of infections and inflammation.

There is strong evidence of the association between acute infections of the lower respiratory tract and exposure to indoor pollutants from solid fuel use in children. Pneumonia and hospitalization in the first year of life is 38% more frequent in children whose mothers smoke.

Acute exposure of macrophages to these air pollutants decreases phagocytic activity and IFN (Th1 cytokine) production by macrophages.

The same pollutants are thought to have effects on the exacerbation of existing respiratory diseases, such as asthma and bronchitis. The evidence about air pollutants increasing allergic responsiveness is weak.

#### Ref:

•Sullivan J , Brooks BO, Meggs JM. Clinical immunotoxicology and allergy. Chap 25. In: Sullivan JB, Krieger GR. *Clinical environmental health and toxic exposures*. 2nd ed. Lippincott Williams & Wilkins, 2001.

## Immune diseases and children

# PERSISTENT ORGANIC POLLUTANTS LESSONS FROM ACCIDENTALLY-EXPOSED HUMANS

PCBs – Japan and Taiwan rice oil contamination

TCDD - Missouri sludge oil sprayed on soil

PBBs – Michigan Dairy contamination

IMMUNOSUPPRESSION

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Polychlorinated biphenyls (PCBs) and dioxins like 2,3,7,8-Tetrachlorodibenzodioxin (TCDD) are chlorinated hydrocarbons considered as persistent organic pollutants (POPs).

The main source of exposure to the general population is through food.

There has been accidentally-exposed populations to persistent organic pollutants, that were immunologically studied, and a wide range of immunosuppressive alterations were described.

Contamination of rice oil by PCBs in Japan (1968) and China, Province of Taiwan (1979) resulted in the exposure of a large number of people to PCBs and their congeners polychlorinated dibenzofurans (PCDFs) respectively. People exposed in the Yucheng (1979) incident had low resistance and suffered from a variety of infections. Examination during the first year revealed decreased concentrations of IgM and IgA, decreased percentages of total T-cells, active T-cells and helper T-cells. After 3 years, some, although not all, of the effects had disappeared.

The sludge of a TCDD-contaminated oil sprayed on dirty roads caused long term exposure to TCDD (soil levels from 39 to 1100 ppb). Population exposure was associated with increased incidence of anemia, and decreases in percentages of T cells (CD 3, CD 4 and CD 11).

In 1974, polybrominated biphenyls (PBBs) were accidentally mixed with livestock feed. Dairy farmers exposed to PBBs showed decreased absolute number of T cells, decreased mitogenic response to T cell mitogens and persistent increase on NK cells, which were still present 5 years after the exposure. Other studies did not find immune alterations.

Infants who ingest these compounds through contaminated breastmilk show pronounced immunological deficiencies and elevated risks of infections, including meningitis, and inner ear infections.

### Refs:

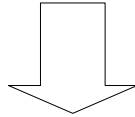
- Bekesi JC, Holland JF, Anderson HA. Lymphocyte function of Michigan dairy farmers exposed to polybrominated biphenyls. *Science*, 1978, 199:1207-1209.
- Hoffman RE et al. Health effects of long term exposure to 2,3,7,8 tetrachlorodibenzo-p- dioxin. *Journal of the American Medical Association*, 1986, 255: 2031-2038
- Lu YC, Wu YC. Clinical findings and immunological abnormalities in Yu-Cheng patients. *Environ Health Perspectives*, 1985, 58:17-29

<<NOTE TO USER: Please see module on Persistent Organic Pollutants for more information.>>

## Immune diseases and children

### POLYCHLORINATED BIPHENYLS

### IMMUNOSUPPRESSION



- Lower immune response to vaccine



WHO/Aphaluck Bhatiajevi

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The potency of diphtheria and tetanus vaccination can be attenuated by children's exposure to polychlorinated biphenyls (PCBs). In study of 587 children, specific antibodies against tetanus were significantly lower in those whose mothers had above average serum PCBs levels during pregnancy (4.61 versus 7.03,  $P=0.035$ ).

Immune response to the diphtheria vaccine was slightly lower for these children who were examined when they were 7 years old (0.60 versus 0.64,  $P=0.82$ ). This suggests that the early postnatal period is the most important in determining PCBs effects on the developing immune system.

#### Ref.

•Heilmann C et al. Serum concentrations of antibodies against vaccine toxoids in children exposed perinatally to immunotoxicants. *Environ Health Perspect*, 2010, 118:1434-8.

*Polychlorinated biphenyls (PCBs) may cause immunotoxic effects, but the detailed dose-response relationship and possible vulnerable time windows of exposure are uncertain. In this study we applied serum concentrations of specific antibodies against childhood vaccines as sentinels of immunotoxicity.*

*The main objective was to assess the possible dependence of antibody concentrations against diphtheria and tetanus toxoids in children with regard to prenatal and postnatal PCB exposures.*

*From a cohort of 656 singleton births formed in the Faroe Islands during 1999-2001, children were invited for examination with assessment of serum antibody concentrations at 5 years (before and after a booster vaccination) and at 7 years of age. Total PCB concentrations were determined in serum from ages 5 and 7 years, and data were also available on PCB concentrations in maternal pregnancy serum, maternal milk, and, for a subgroup, the child's serum at 18 months of age.*

*RESULTS: A total of 587 children participated in the examinations at ages 5 and/or 7 years. At age 5 years, before the booster vaccination, the antidiphtheria antibody concentration was inversely associated with PCB concentrations in milk and 18-month serum. Results obtained 2 years later showed an inverse association of concentrations of antibodies against both toxoids with PCB concentrations at 18 months of age. The strongest associations suggested a decrease in the antibody concentration by about 20% for each doubling in PCB exposure. At age 5 years, the odds of an antidiphtheria antibody concentration below a clinically protective level of 0.1 IU/L increased by about 30% for a doubling in PCB in milk and 18-month serum.*

*CONCLUSIONS: Developmental PCB exposure is associated with immunotoxic effects on serum concentrations of specific antibodies against diphtheria and tetanus vaccinations. The immune system development during the first years of life appears to be particularly vulnerable to this exposure.*

## ARSENIC

### IMMUNOSUPPRESSION

#### Chronic arsenic-contaminated water exposure

- ❖ Compromises the primary immune response to infection
- ❖ Associated with increased mortality due to H1N1 infection .



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Chronic exposure to arsenic from contaminated water is a significant global environmental problem. Arsenic (As) has been identified as a potent immunomodulatory agent in many experimental models and epidemiologic studies.

Chronic As exposure significantly compromises the immune system, and specifically dendritic cells, in response to viral respiratory infection.

Arsenic decreases the cell migration that is a critical component of the initiation of the immune defense against respiratory viral infection. Through this mechanism, infection may be impaired.

An experimental study of water contamination with As levels of 100 ppm, showed a compromise of the immune response to influenza A infection. It has been suggested that altered anti viral response may have played a role in the increased mortality as a result of H1N1 infection in Mexico areas of elevated As contamination, compared with relatively milder cases of the disease in other infected populations.

#### Ref:

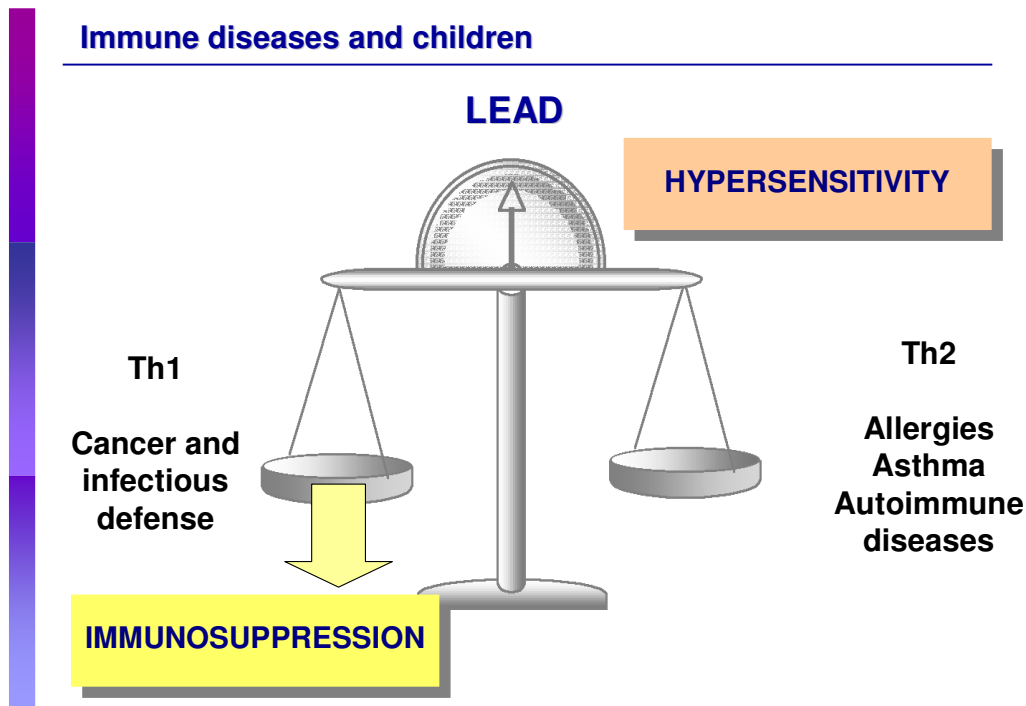
•Courtney D et al. Low-dose arsenic compromises the immune response to influenza A infection in vivo. *Environ Health Perspect*, 2009, 117:1441–1447

*Arsenic exposure is a significant worldwide environmental health concern. We recently reported that 5-week exposure to environmentally relevant levels (10 and 100 ppb) of As in drinking water significantly altered components of the innate immune response in mouse lung, which we hypothesize is an important contributor to the increased risk of lung disease in exposed human populations.*

*We investigated the effects of As exposure on respiratory influenza A (H1N1) virus infection, a common and potentially fatal disease.*

*Methods: In this study, we exposed C57BL/6J mice to 100 ppb As in drinking water for 5 weeks, followed by intranasal inoculation with a sub lethal dose of influenza A/PuertoRico/8/34 (H1N1) virus. Multiple end points were assessed postinfection.*

*Results: Arsenic was associated with a number of significant changes in response to influenza, including an increase in morbidity and higher pulmonary influenza virus titers on day 7 post-infection. We also found many alterations in the immune response relative to As-unexposed controls, including a decrease in the number of dendritic cells in the mediastinal lymph nodes early in the course of infection. Our data indicate that chronic As exposure significantly compromises the immune response to infection. Alterations in response to repeated lung infection may also contribute to other chronic illnesses, such as bronchiectasis, which is elevated by As exposure in epidemiology studies.*



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A hallmark of lead-induced immunotoxicity is a pronounced fetal shift in the balance in T helper cell function toward T helper 2 responses at the expense of T helper 1 functions. This appears as elevated total serum IgE, reduced IFN-gamma production (a benchmark Th1-associated cytokine) and elevated production of IL-4 (a benchmark Th2-associated cytokine).

In vitro studies confirm that lead has the ability to polarize antigen-specific T cells to Th2 cells. Lead also inhibits Th1 effects on humoral and cell-mediated immunity. The lead effect was mainly on dendritic cells, rather than on T cells, and lead's modification of dendritic cells' function appears to be the main cause of lead promotion of type-2-related immunity.

A number of studies illustrating the capacity of lead to impair the immune function and/or host resistance to disease date back to at least the 1960s.

However, it has only been in recent years that lead has been recognized among a new category of immunotoxicants: those that dramatically shift immune functional capacity while producing only modest changes to immune cell populations and lymphoid organs.

Lead is likely to be a risk factor for chronic immune-related disease because it favours atopy and autoimmune diseases. At the same time, the host's defenses against infectious agents and cancer may be reduced.

*Refs:*

- Dietert RR et al. Lead and immune function. *Crit Rev Toxicol*. 2006, 36(4):359-85.
- Gao D, Mondal TK, Lawrence DA. Lead effects on development and function of bone marrow-derived dendritic cells promote Th2 immune responses. *Toxicol Appl Pharmacol*, 2007 222(1):69-79

<<NOTE TO USER: Please see module on lead for more information.>>

## LEAD DEVELOPMENTAL IMMUNOTOXICITY

- Prenatal period is highly sensitive to lead immunotoxicity
- Immunotoxic responses to lead differ across life stages
  - Blood lead levels below 10 microg/dL !
- Early immunotoxic changes are persistent
  - even after lead body burden has been reduced to background levels

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Immunotoxic effects of lead differ across life stages not only quantitatively with regard to dose response, but also qualitatively in terms of the spectrum of immune alterations.

Experimental studies in several laboratory animal species suggest that the latter stages of gestation are a period of considerable sensitivity for lead-induced immunotoxicity.

Age-based exposure studies also suggest that blood lead levels (BLLs) previously thought to be safe (below 10 microg/dL) may be associated with immune alterations later in life .

Even though neonatal exposures to lead shares some immune changes with adulthood, they occur at exposure levels much lower than those immunotoxic to adults. Children's BLLs of 10–20 µg/dL following pre & postnatal lead exposure are associated with immunotoxic detectable changes, compared to BLLs of 40–50 µg/dL, or even greater, which are required in order to produce immune changes in adults.

*Refs:*

- Dietert RR et al. Developmental immunotoxicology of lead. *Toxicol Appl Pharmacol*, 2004, 198:86.
- Dietert RR, Piepenbrink MS. Perinatal immunotoxicity: why adult exposure assessment fails to predict risk. *Environ Health Perspect*, 2006, 114:477-483.

**OTHER METALS ASSOCIATED WITH CHRONIC INFLAMMATORY PROCESSES & AUTOIMMUNE DISEASES**

<b>HYPERSENSITIVITY</b>	<b>Cadmium</b>	<b>Mercury</b>
<b>Nephritis</b>	✓	✓
<b>Autoimmune diseases</b>	✓	✓

Other metals can alter health through modulation of immune homeostasis.

Metals can lead to inadequate or excessive production of inflammation and to an inappropriate activation of lymphoid subsets involved in the acquired immunity to specific antigens. Resultant pathologies may include chronic inflammatory processes and autoimmune diseases

**Cadmium**

Immunostimulation including induction of autoantibodies was found to be the primary immunotoxic effect of cadmium, associated with polyclonal B cell activation (PBA). The PBAs activation is induced by mercury and lead as well. This mechanism has been related to the pathogenics of nephritis and possibly autoimmune diseases.

**Mercury**

There is solid evidence that mercury can induce autoimmune disease both in humans and experimental animals.

In humans, chronic exposure to low doses of inorganic mercury, can induce glomerulonephritis. Human exposure to mercury caused by mercury-containing pills, skin lightening cream, hair-dyeing agents and mercury vapors (during 2 to 60 months), showed elevated urinary mercury concentrations and presented membranous nephropathy with IgG deposit.

*Refs:*

- Lawrence DA, McCabe MJ. Immunomodulation by metals. *Int Immunopharmacol*, 2002, 2(2-3):293-302.
- Li SJ et al. Mercury-induced membranous nephropathy: clinical and pathological features. *Clin J Am Soc Nephrol*. 2010, 5(3):439-44.
- Ohsawa M. Heavy metal-induced immunotoxicity and its mechanisms. *Yakugaku Zasshi*, 2009, 129(3):305-19.

## Immune diseases and children

### PESTICIDES

- May stimulate, suppress or de-regulate the immune system
- Improvement when pesticides are removed from the body !

IMMUNOSUPPRESSION



HYPERSENSITIVITY

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Children who reside in agricultural settings are potentially exposed to higher levels and a wider range of mixtures of pesticides.

Pesticides can stimulate, suppress or de-regulate the immune system. Most can do all three, depending on the concentration and duration of the dose. Evidence on the immunotoxic mode of action and effects is limited.

#### Immunosuppression

Studies have shown that pesticide exposure significantly reduces resistance to bacterial, viral, and parasitic infections and promotes tumor growth in many animal species.

Exposure to many pesticides produces significant changes in immune system structure and function. These changes can be accompanied by increased risks of infectious diseases and cancers associated with immunosuppression.

Improvement in immune parameters also occurs when pesticides are removed from the body

#### Hypersensitivity

Higher-than-usual frequencies of allergies as well as alterations related to autoimmunity have been described. It has also been described that agricultural environment, affect the development of children's Th1/Th2 immune response.

Maternal agricultural work has been associated with increased Th2 in children from agricultural areas.

The simplest change made by pesticides' exposure on the immune system is that proteins are altered and become haptens. Immediate hypersensitivity reactions and contact hypersensitivity reactions are probably the most common immunotoxic effects of pesticides reported.

Infants exposed to herbicides before the age of one were 10 times more likely to develop early persistent asthma.

#### Refs:

- Dewailly E et al. Susceptibility to infections and immune status in Inuit infants exposed to organochlorines. *Environ Health Perspect*, 2000, 108:205
- Duramad P et al. Early environmental exposures and intracellular Th1/Th2 cytokine profiles in 24-month-old children living in an agricultural area. *Environ Health Perspect*. 2006, 114(12):1916-22
- Rea WJ, Hsueh-Chia L. Effects of pesticides on the immune system. *Journal of Nutritional & Environmental Medicine*, 1991, 2(4) 399-410
- Repetto R , Baliga SS . Pesticides and the immune system. The Public Health Risks. *Cent Eur J Public Health*, 1996, 4(4):263-5
- Salam MT et al. Early life environmental risk factors for asthma: findings from the Children's Health Study. *Environmental Health Perspectives*, 2004, 112:760

<<NOTE TO USER: Please see modules on pesticides for more information.>>

## AUTOIMMUNE DISEASES

Cluster of autoimmune diseases suspected to be associated with chemicals

Toxic oil syndrome : scleroderma-like disease

L-tryptophan-induced eosinophilia-myalgia syndrome

*Hydrocarbons and heavy metals in groundwater: lupus and antinuclear antibodies*

The development of autoimmune diseases has been frequently linked to exposure to environmental factors such as chemicals, drugs, or infections.

Two well-recognized syndromes associated to sporadic contamination of foodstuffs, in which auto-antibodies were found, include:

- the toxic oil syndrome with exposure to some contaminant in the denatured rapeseed oil and
- the eosinophilia myalgia syndrome, linked with an unconfirmed contaminant present in samples of L-tryptophan health food products.

There have been reports relating exposure to contaminated groundwater in Arizona, to the appearance of lupus and the development of antinuclear antibodies (ANA). However, this study, has not as yet been confirmed. The chemicals identified were : trichlorethane, benzene, toluene, xylene, perchlorethylene and inorganic chromium.

*Ref:*

- Hess EV. Editorials. Environmental lupus syndromes. *British Journal of Rheumatology*, 1995, 34:597-601

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## Immune diseases and children

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### **LUPUS AND LUPUS-LIKE SYNDROMES (ANA POSITIVE)**

Complex interactions of multiple genes and environmental agents

Potentially connected to

- **Breathable silica**
- **Trichloroethylene (air & water contaminant)**
- **Mercury, gold, cadmium**

ANA: antinuclear antibodies

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A number of chemical exposures have been associated with lupus or related autoimmune phenomena. Chemicals and environmental factors potentially connected to elements identified in the lupus disease pathway include aromatic amines and hydrazines, breathable silica, organic solvents (trichloroethylene - TCE) and heavy metals: mercury, gold and cadmium.

It has been recognized that immune pathology, including the autoantibody production in adult lupus may begin years before the clinical disease is detected. This supports the possibility that environmental factors may have been present during the time of immune system development.

#### *Refs:*

- Edwards CJ, Cooper C. The developmental origins of disease. Early environmental exposure and the development of lupus. *Lupus*, 2006, 15:814-819
- Glinda S et al. Recent advances and opportunities in research on lupus: environmental influences and mechanisms of disease. *Environ Health Perspect*, 2008, 116:695–702

## ALLERGIC-MEDIATED ASTHMA

- The number of children with asthma has more than doubled since 1980 in developed countries
- Increase in sensitivity to triggers or increase in amount of triggers?
- Early exposure to chemicals seems to be a determinant factor of increased sensitivity

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•The number of children with asthma has more than doubled since 1980 in developed countries. Asthma clearly has increased in frequency and severity. Genetic factors, household allergens and the hygiene hypothesis are insufficient to explain the dramatic increase in frequency and severity of asthma. What appears to be happening is that people have become more sensitized to the factors that trigger asthma attacks. The frequency of asthma could go up even if the triggers themselves were decreasing. A growing body of research points towards early exposure (before birth and during infancy) to chemicals as a determinant factor in the dramatic increase of asthma. Lead has been considered as one potential determinant.

•Asthma occurs in all countries regardless of level of development. Over 80% of asthma deaths occur in low and lower-middle income countries. For effective control, it is essential to make medications affordable and available, especially for low-income families.

•Well-known triggers of asthma attack are: dust mite allergen, mold, cockroach, and cat and dog allergens. Sensitizing environmental chemicals and contaminants act as haptens by combining with proteins present in the mucosal surfaces and induce both humoral and cellular immune response. Allergenic metals such as cobalt, arsenic, beryllium, chromium and nickel are recognized as potent sensitizers and may be present in many sources and materials. Some plastic monomers like diisocyanates (TDI, MDI) and plasticizers like phthalic anhydrides are well-known precipitators of allergic asthma. They can be found in paints, adhesive coating and sealant materials.

<<NOTE TO USER: Please see module on respiratory diseases for more information.>>

Ref:

•ATSDR . Environmental triggers of asthma environmental factors. In: *Case studies in environmental medicine (CSEM)*. ATSDR, 2007

•Solomon G. Asthma and the environment. Available at [www.healthyhouseinstitute.com/a\\_962-Asthma\\_and\\_the\\_Environment](http://www.healthyhouseinstitute.com/a_962-Asthma_and_the_Environment) - accessed May 2011.

•Sullivan J , Brooks BO, Meggs JM. Clinical immunotoxicology and allergy. Chap 25. In: Sullivan JB, Krieger GR. *Clinical environmental health and toxic exposures*. 2nd ed. Lippincott Williams & Wilkins, 2001.

•WHO. 10 facts on asthma. Available at [www.who.int/features/factfiles/asthma/en/index.html](http://www.who.int/features/factfiles/asthma/en/index.html) – accessed 10 June 2011

## BIOMARKERS OF IMMUNOTOXICITY RESEARCH NEEDS

- **No single test can accurately demonstrate or predict immunotoxicity**

The most common biomarkers used :

- Cell count
- Cell surface activation markers
- Immunoglobulin levels
- Responses to mitogen
- Expression and secretion of cytokines

Children's unique susceptibility to environmental toxicants has become an important focus of immunotoxicology and the use of immune biomarkers in the molecular epidemiology of children's environmental health is a rapidly expanding field of research.

The endpoints most commonly used to study human immune function include cell counts, cell surface activation markers, immunoglobulin levels, responses to mitogen, and expression and secretion of cytokines.

Limitations exist for all biomarkers currently in use. Incorporation of immune biomarkers could facilitate understanding of the mechanisms that underlie the associations between environmental exposures and immune-mediated disorders.

*Ref:*

•Duramad P, Yager I, Holland N. Cytokines and other immunological biomarkers in children's environmental health studies. *Toxicol Lett*, 2007, 30,172 (1-2): 48-59.

**<<NOTE TO USER: Please see module on human biomonitoring and biomarkers for more information.>>**

## NEW CHALLENGE : NANOMATERIALS

- ❖ Few studies suggest immunosuppression
- ❖ More studies show hypersensitivity
  - “Asbestos –like” inflammation and granuloma formation
  - Allergic reactions

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Nanomaterials have novel physical and chemical properties, and is not known yet what their interactions with biological systems will be. Health and fitness products lead the nanotechnology market.

Most studies focus on inflammatory properties and production of inflammatory cytokines. Several studies have reported cytokine induction by different types of nanomaterials (gold colloids, dendrimers, polymers, lipid nanoparticles, others).

Nanoscale materials are particles that are first picked up by the phagocytic cells of the immune system (e.g. macrophages). Granuloma formation was observed in the lungs, skin, and pleural lining of the animals exposed to carbon nanotubes (CNTs). CNTs exposure resulted in asbestos-like pathogenic effects that included inflammation and granuloma formation.

Immunosuppression studies are sparse for nanoparticles. One of the few studies on immunosuppression has demonstrated that inhalation of CNTs suppresses B cell function and that the TGF- produced by alveolar macrophages is a key element in the mechanism of the observed Immunosuppression.

A few studies linked exposure to nanoparticles to allergic reactions in test animals and humans.

*Refs:*

•Stemp-Morlock G. Research initiatives. What lies ahead for nanotechnology? *Environmental Health Perspectives*, 2009, 117-4:A146

•Zolnik BS et al. Minireview: Nanoparticles and the immune system. *Endocrinology*, 2010, 151: 458– 465

## Immune diseases and children

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### PREVENTION

Protect children, particularly mothers and newborns from exposure to environmental risk factors



Laborde A.

33

<<READ SLIDE>>

<<NOTE TO USER: Please see prevention measures to minimize exposure to air, water, food, soil and products' contaminants from relevant modules.>>



## Immune diseases and children

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### SUMMARY

- ❖ Immune diseases can be caused by genetic, biological, physical and chemical factors.
- ❖ The IMMUNE SYSTEM is a complex and vulnerable system, particularly in early stages of life
- ❖ Early exposure to contaminants could play a role in immune disease development later in child or adult life
- ❖ An increasing body of evidence suggests that persistent organic pollutants, pesticides, air pollution, metals, sunlight, and mycotoxins increase the risk of both reduces defenses or exaggerated immune response.

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<<READ SLIDE>>

**CRITICAL ROLE OF HEALTH AND ENVIRONMENT PROFESSIONALS**

- ❖ Diagnose and treat immune diseases
- ❖ Take the Environmental History of the patient and family
- ❖ Report cases that can be related to environmental exposure, as they may be sentinel cases
- ❖ Promote research on immunotoxicity related to main environmental threats
- ❖ Advocate to protect children and mothers from exposure to contaminants

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<<READ SLIDE>>

**Immune diseases and children**

***We hold our future in our hands  
and it is our children.***



Poster Contest by HRIDAY with support from WHO Regional Office for South East Asia

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I end with this beautiful reminder to us from a child in India. We must recognize the risks to our children and assume our responsibilities of preventing them, because we hold our future in our hands—and it is our children.

Thank you.

## Immune diseases and children

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*Latest update: October 2011*



## Immune diseases and children

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