Endocrine Disruption and Immune Dysfunction

Rodney Dietert
Cornell University

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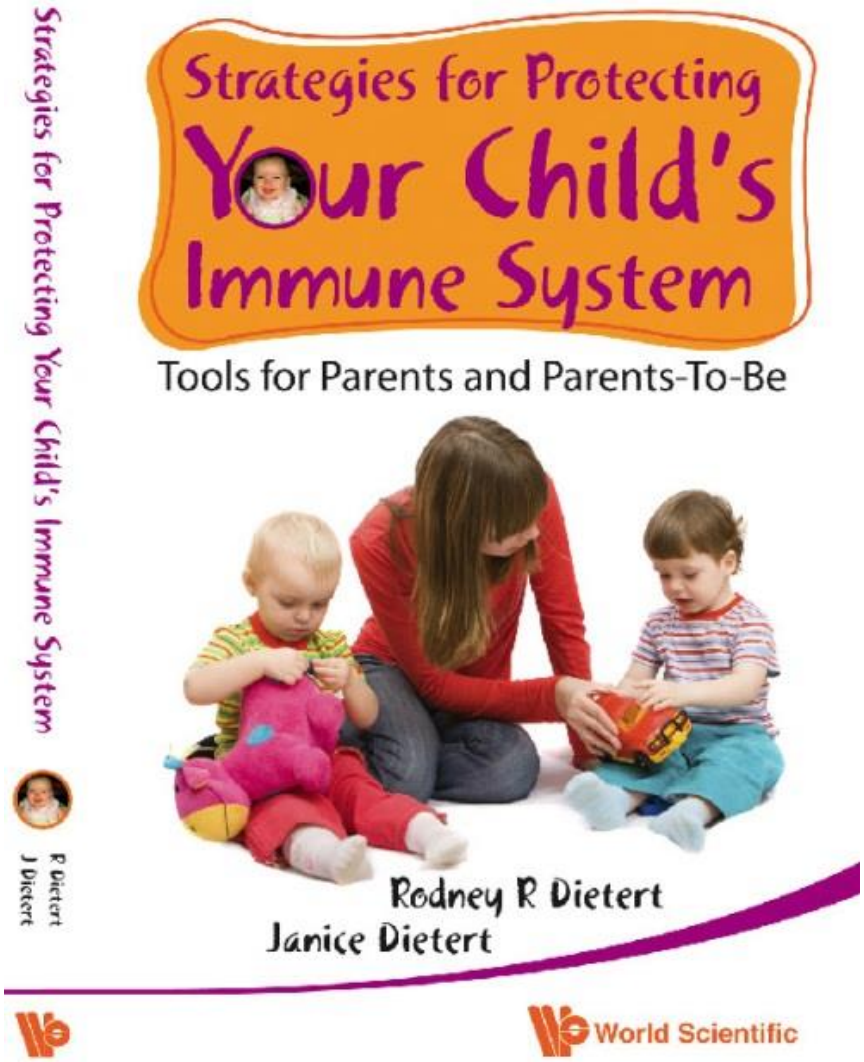
contact: rrd1@cornell.edu

EDCs are a Significant Hazard for the Developing Immune System

EDCs and DIT

Dose sensitivity
Persistence
Spectrum of effects
Latency



The majority of risk factors we discuss in this book are…… EDCs.

Available
Amazon.com
paperback and Kindle

Outline

1. Endocrine disrupting chemicals (EDCs) as a priority health threat for non-communicable diseases (chronic diseases and conditions)
2. The role of EDCs in developmental immunotoxicity (DIT) and immune dysfunction
3. Misregulated inflammation as the foundation bloc that connects EDCs to networks of chronic diseases
4. Inadequacy of current safety testing to protect us from environmentally-induced chronic diseases.

The Landscape of Endocrine Disrupting Chemicals (EDCs)

Endocrine disruptors are chemicals that may interfere with the body's endocrine system and produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife. – (NIEHS, Dec. 2013)

Approximately 1,000 potential EDCs have been identified .

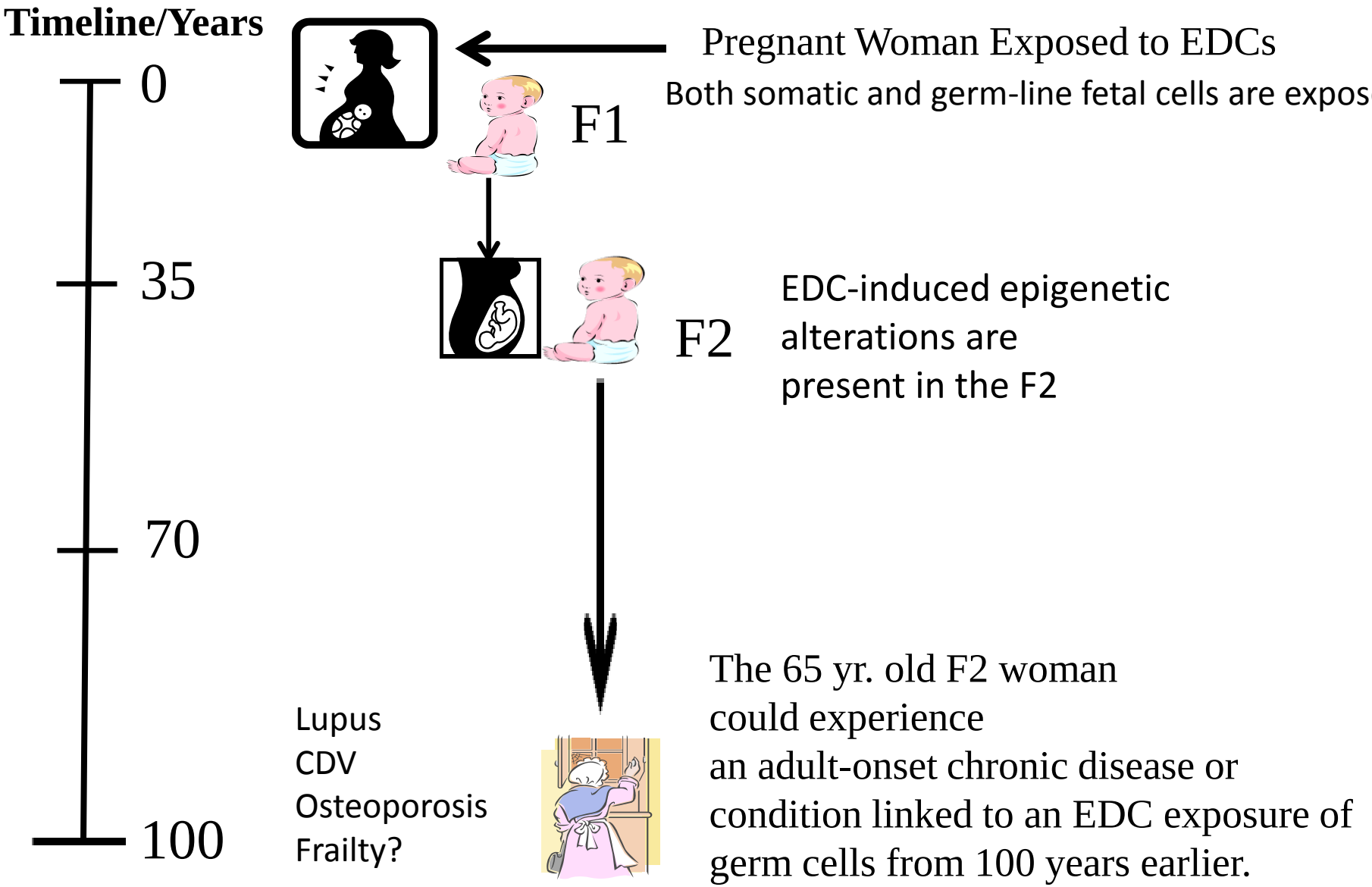
- (The Endocrine Disruption Exchange [TEDX], Dec. 2013)

They can be found among: household products, personal care products, food, flame retardants, pesticides, plastic and rubber products, antimicrobials, metal mixtures, industrial additives, solvents, metabolites of other chemicals, and biogenic compounds. – (TEDX, Dec., 2013)

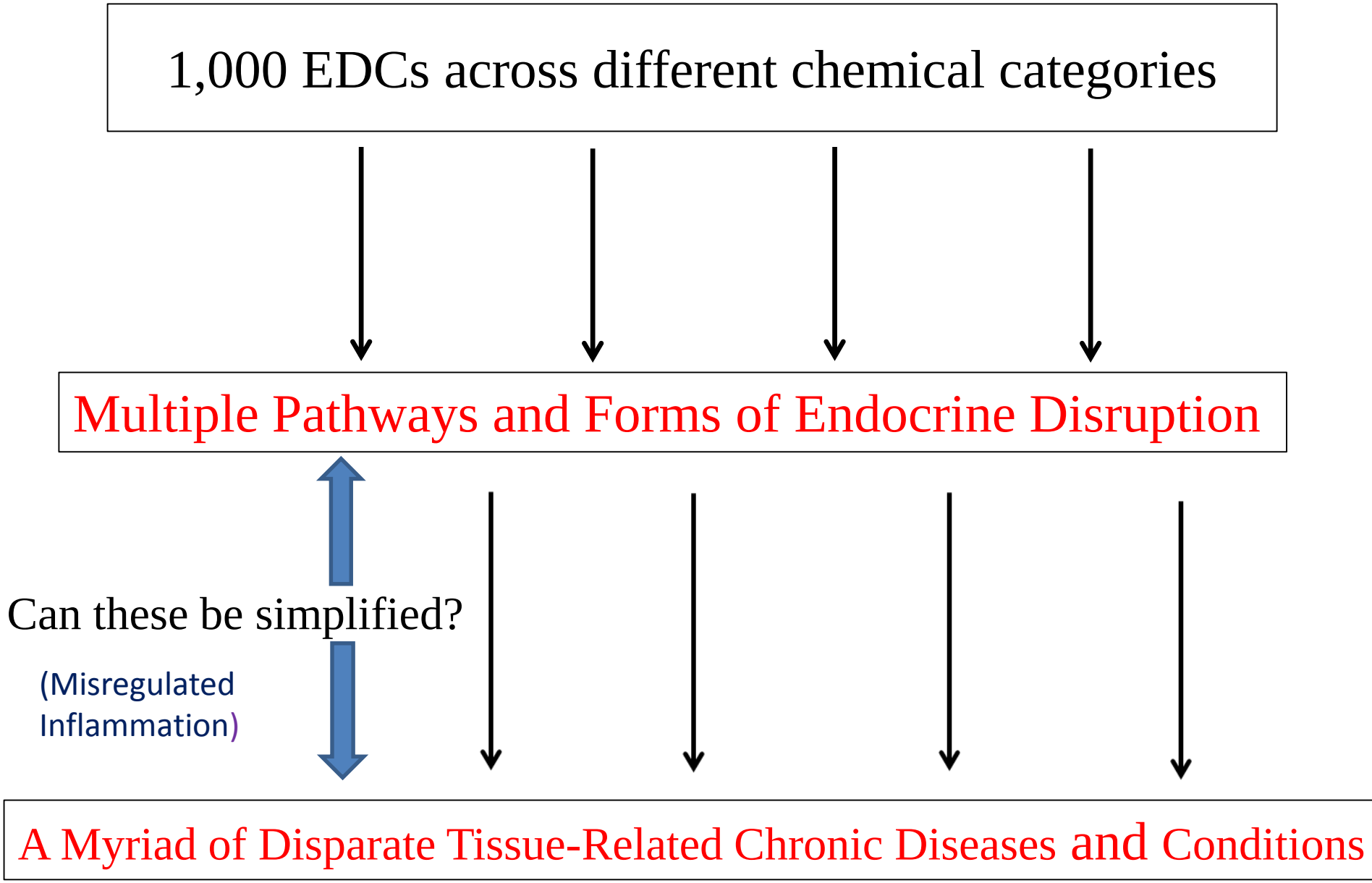
EDCs are active at very low doses (non-monotonic dose-response curves).

EDC-linked dysfunction has been reported for virtually every organ and tissue of the body.

Act Now to Protect Against EDCs: Direct Prenatal Exposure to EDCs Can Produce a Century of Developmentally-Programmed Disease



Adapted from Dietert, Transgenerational Epigenetics of EDCs, in press


1,000 EDCs across different chemical categories
Multiple Pathways and Forms of Endocrine Disruption
Can these be simplified?
(Misregulated Inflammation)
A Myriad of Disparate Tissue-Related Chronic Diseases and Conditions

NIH Examination of the Inflammation-Chronic Disease Link

NIH STEP Forum
STEP - **Inflammation: The Root and Route of Chronic Diseases?**
(HHS Only)
Tuesday, November 15, 2011
Jerry Phelps, Rodney Dietert, Charles Serhan and David Mosser
441 views (276 live, 165 VOD)

NIEHS Partnership for Environmental Public Health
PEPH Webinar - **Connecting Environmental Exposures to Chronic Inflammation and Diseases**
February 28th, 2012 – 12:00 to 1:30 p.m. ET
Webinar Summary (337KB)
NIEHS Calendar

Non-Communicable Diseases (*i.e.*, Chronic Diseases) are the Number One Health Threat and Most Likely Adverse Outcomes Following EDC Exposure

- The Number #1 Cause of Mortality Worldwide (63%)*
- Most Chronic Diseases are Increasing in Prevalence
- They Dramatically Impact Quality of Life
- Estimated to Cost 48% of Global GDPs by 2030*
- 45.3% of all US adults age 65 and above have two or more chronic diseases: a 20% increase from the previous decade.*

*Joint 2011 report: Harvard School of Public Health and World Economic Forum and NCHS Data Brief Number 100, July 2012

Chronic diseases are highly interconnected;
Depression, CVD, tissue-specific cancer,
sleep disorders.
metabolic disease and
sensory loss,
are common to immune
dysfunction-driven disease
patterns

Approximately one quarter
of children in certain developed
countries have
immune-based chronic diseases
Dietert and Zelikoff, 2009
Curr Pediatr. Rev.

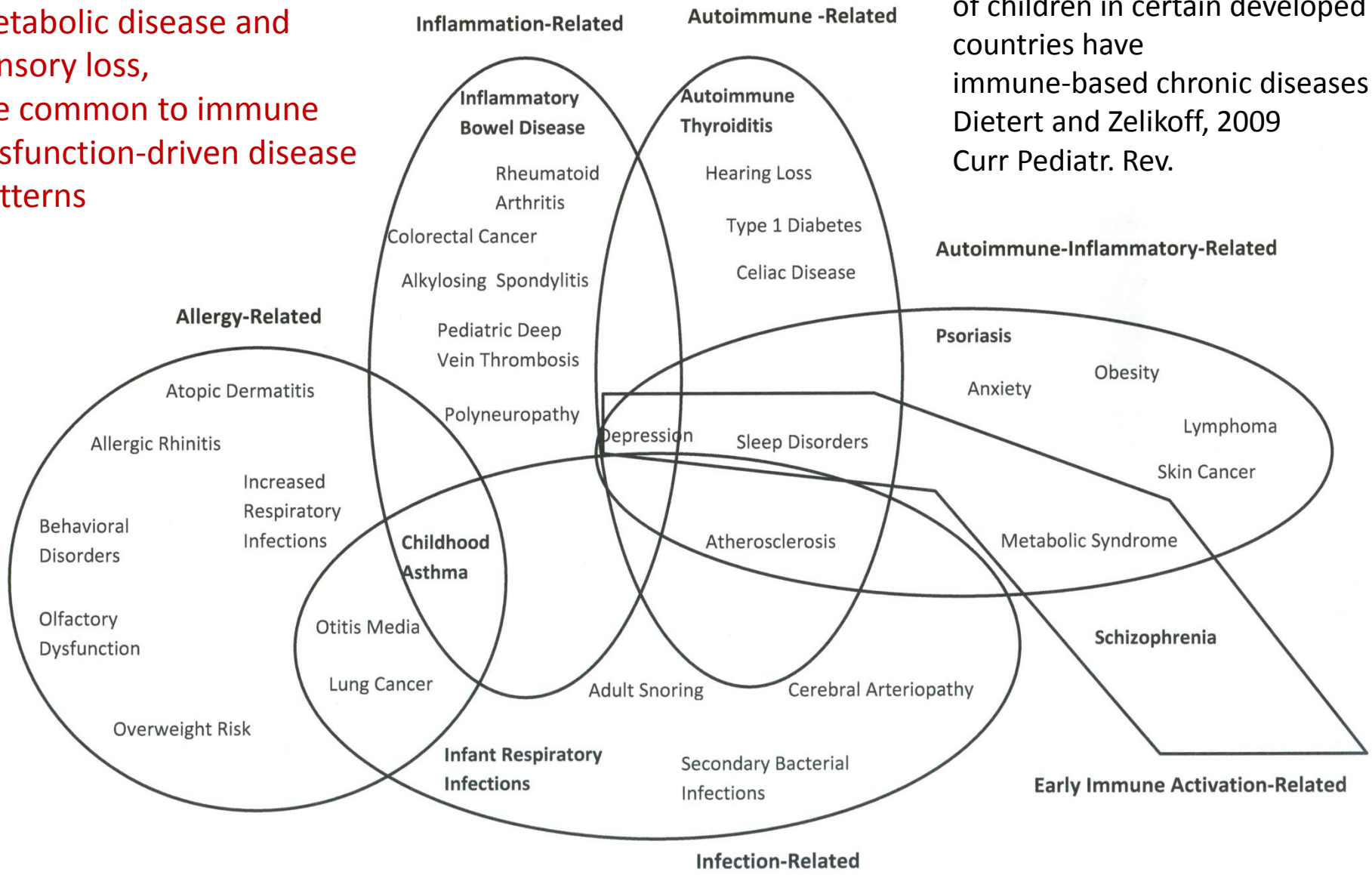


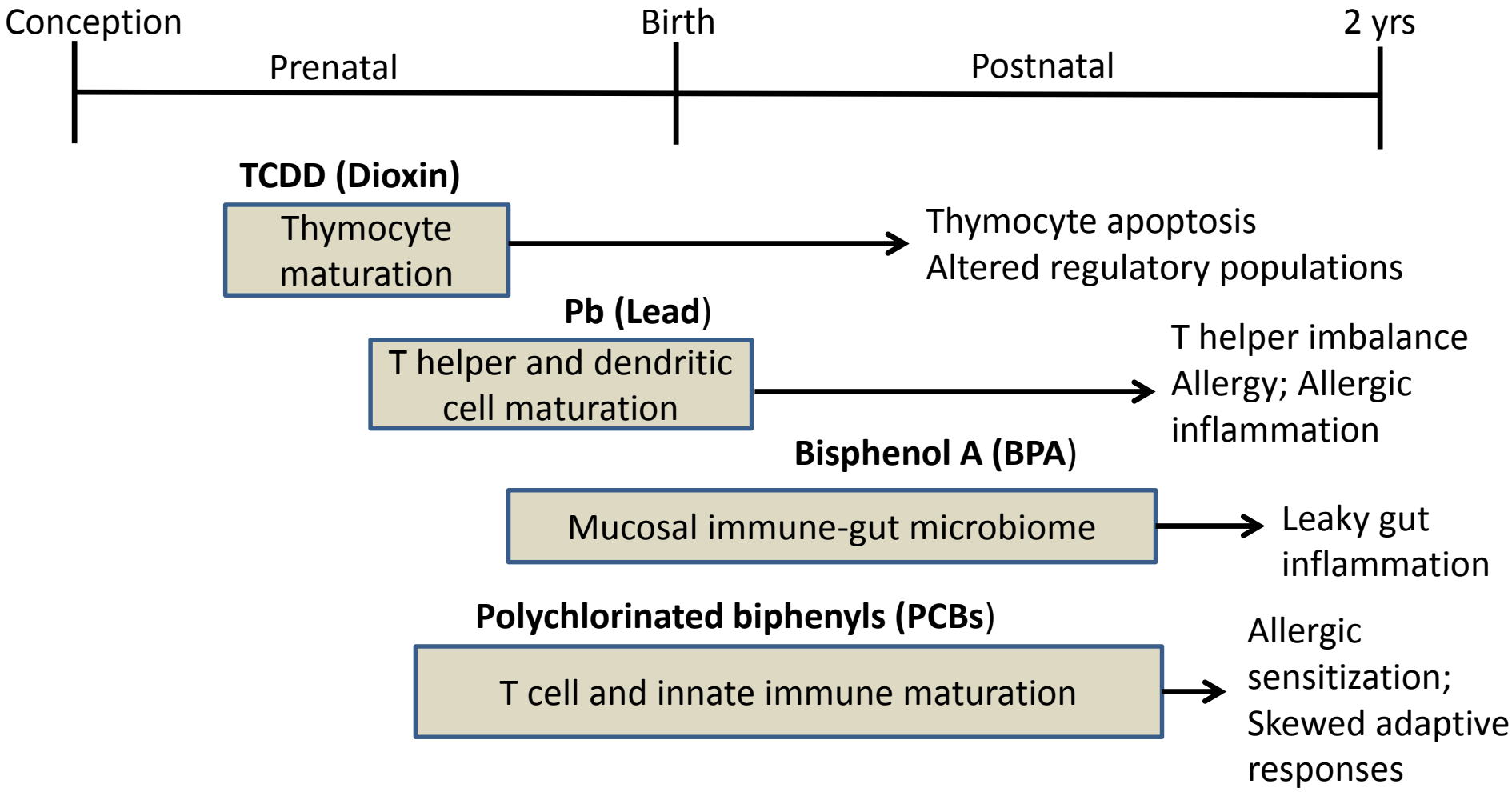
Diagram from: Dietert, DeWitt, Germolec and Zelikoff , Environ. Health Perspect. 118:1091-9, 2010

Two More Immune-Driven Chronic Disease Networks

TYPE 1 DIABETES	CELIAC
Celiac disease	Osteoporosis (& fractures)
Autoimmune thyroiditis	COPD (men)
Endometrial cancer (women)	**Specific G.I. tract cancer**
Depression and anxiety	**Depression (women)**
Hearing loss	**Hearing loss**
Eating disorders	**Eating disorders (women)**
Cardiovascular disease	**Cardiovascular disease**
Hypertension	Sarcoidosis
Osteopenia	Restless leg syndrome
Addison's disease	Liver Cirrhosis
Vitelligo	Recurrent Miscarriage (women)

EDCs and Critical Windows of Immune Vulnerability

(Interference in real-time maturation and/or epigenetically-programmed later-life malfunction)

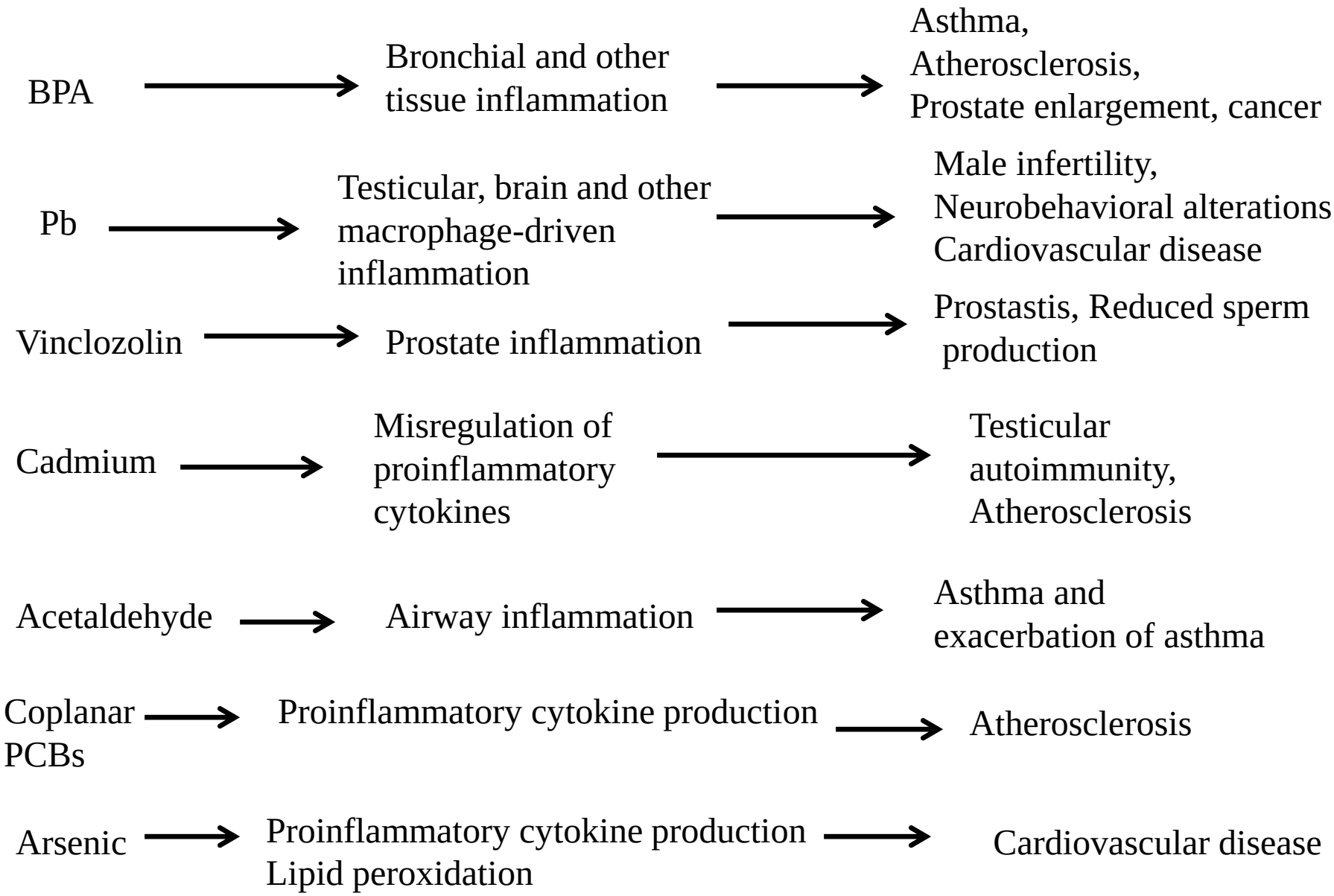


Examples of specialized populations of resident macrophages in different tissues*

Organ or tissue	Population(s)
Liver	Kupffer cells
Lung	Alveolar macrophages
Brain	Microglia
	Astrocytes
Fat	Preadipocytes
Gut	Intestinal macrophages
Kidney	Mesangial phagocytes
Cardiovascular	Monocytes
	Perivascular macrophages
Reproductive organs	Testicular macrophages
	Uterine macrophages
Placenta	Placental macrophages (Hofbauer cells)
Bone	Osteoclasts

* These residents affect tissue homeostasis, dysfunction, and pathology

Most EDCs Produce Problematic Unresolved Inflammation



The Predominate Gene Network Changes for BPA and Phthalate Exposure Involve Inflammation

A recent study of genes altered by both BPA and Phthalates found that 5 of the top 10 gene networks are involved with inflammation.

See: Sher Singh and Steven Shoei-Lung Li ,
Bisphenol A and phthalates exhibit similar toxicogenomics and health effects, Gene 2012, 494(1):85-91.

Inadequate Safety Testing of Chemicals and Drugs

Based on current causes of global mortality, the top priority for regulated safety testing of chemicals and drugs should be to reduce the risk of NCDs (Chronic Diseases). But it is not! In fact, required safety testing has little relevance to risk of chronic disease.

Question Posed to FDA Drug Safety Evaluators: (at a May 2011internal seminar)

What safety data do you require for new drugs that are relevant for the risk of childhood immune dysfunction-based diseases such as

…..Childhood asthma?

….Type 1 diabetes?

Conclusions

- EDCs are a serious threat to health and wellbeing.
- The predominate outcomes of EDC exposure are: NCDs (aka Chronic Diseases and Conditions).
- Chronic Diseases are highly interrelated via comorbidities.
- Misregulated inflammation linked with immune dysfunction is required to produce and/or maintain chronic diseases.
- The developing immune system is a primary target for immune dysfunction-driven chronic diseases.
- Current required safety testing is inadequate to protect against developmental immunotoxicity (DIT) and risk of chronic diseases.