Environmental Factors in Women's Reproductive Health: Impact on Child Health and Development

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Human health problems on the rise

- Over the past 30 years, there has been a significant rise in many childhood disorders as well as in hormonal and reproductive disturbances
- Early life exposure to environmental pollutants is a leading suspect.
- Some chemicals are directly toxic to an exposed child while other chemicals induce a chain of events that may culminate in a diagnosed health problem later in life.

AUTISM	10X	increase early 80's-1996
MALE BIRTH DEFECTS	2X	increase hypospadias, 1970-1993
CHILDHOOD ASTHMA	2X	increase 1982-1993
ACUTE LYMPHOCYTIC LEUKEMIA	62%	increase in children, 1973-1999
CHILDHOOD BRAIN CANCER	40%	increase 1973-1994
PRETERM BIRTH	23%	increase mid 80's-2002
INFERTILITY	5-10%	of couples
BIRTH DEFECTS	3-5%	of all babies
SPERM COUNTS	1%	decrease yearly 1934-1996

Children are More Vulnerable to Environmental Factors

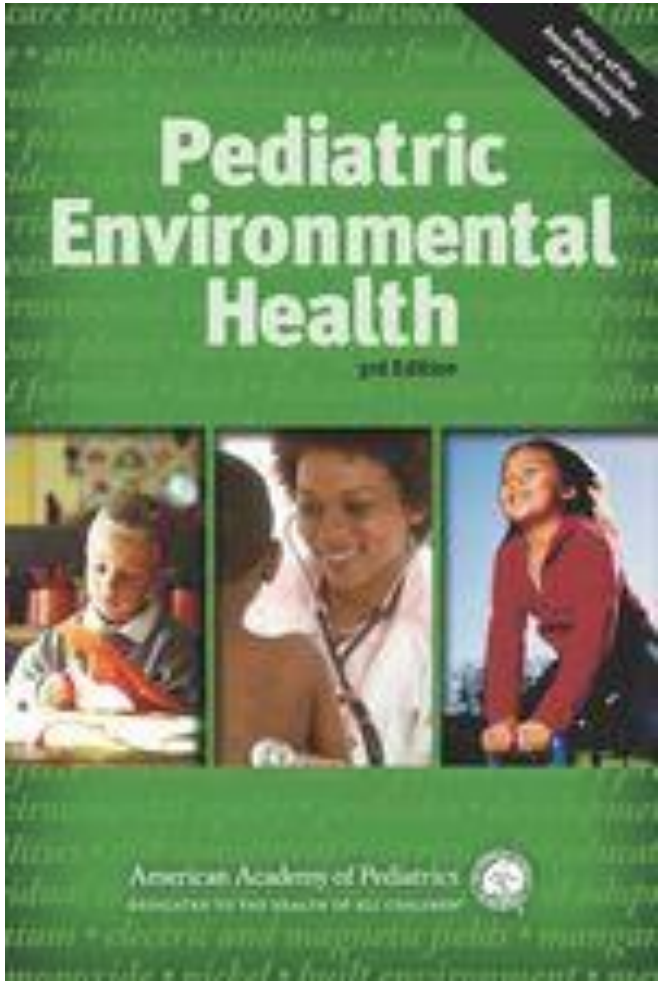
- A developing child's chemical exposures are greater pound-for-pound than those of adults
- Children have lower levels of some chemical-binding proteins, allowing more chemical to reach target organs
- Systems that detoxify and excrete industrial chemicals are not fully developed
- An immature, porous blood-brain barrier allows greater chemical exposures to the developing brain
- Organs and systems are rapidly developing, and thus are often more vulnerable to damage from chemical exposure

National Academy of Sciences 1993

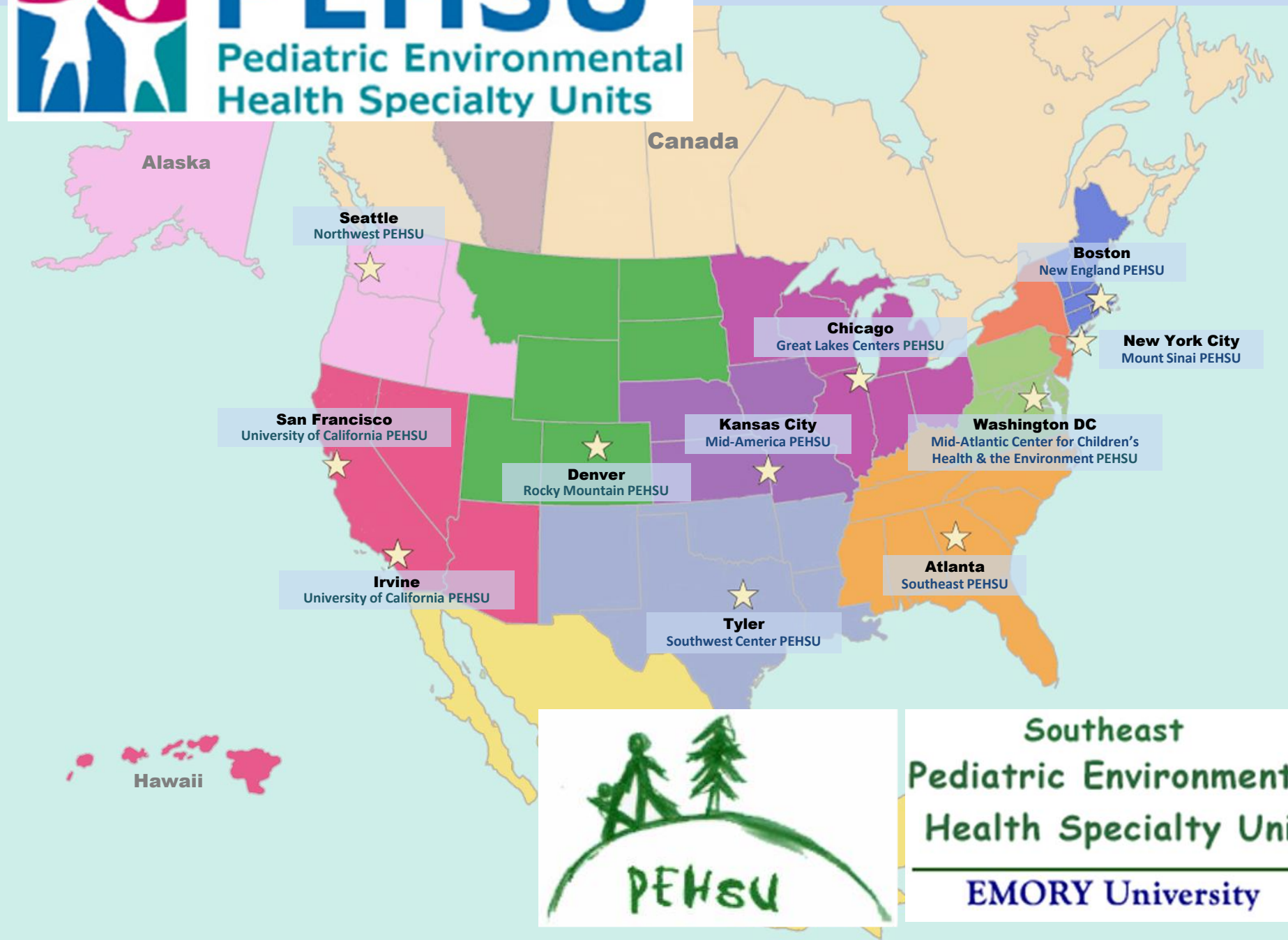
Pediatric Environmental Health

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

- The child's environment as a sum of
  - Chemical
  - Physical
  - Biological &
  - Social Factors
- The environment can impact the child's growth, development, and well-being for better or worse



PEHSU
Pediatric Environmental Health Specialty Units



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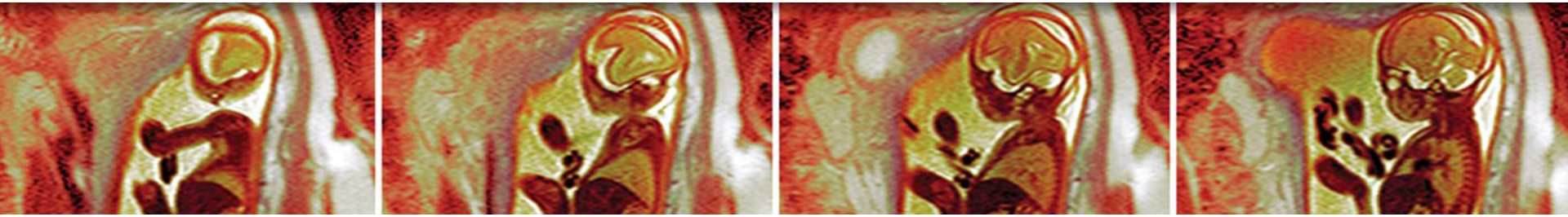
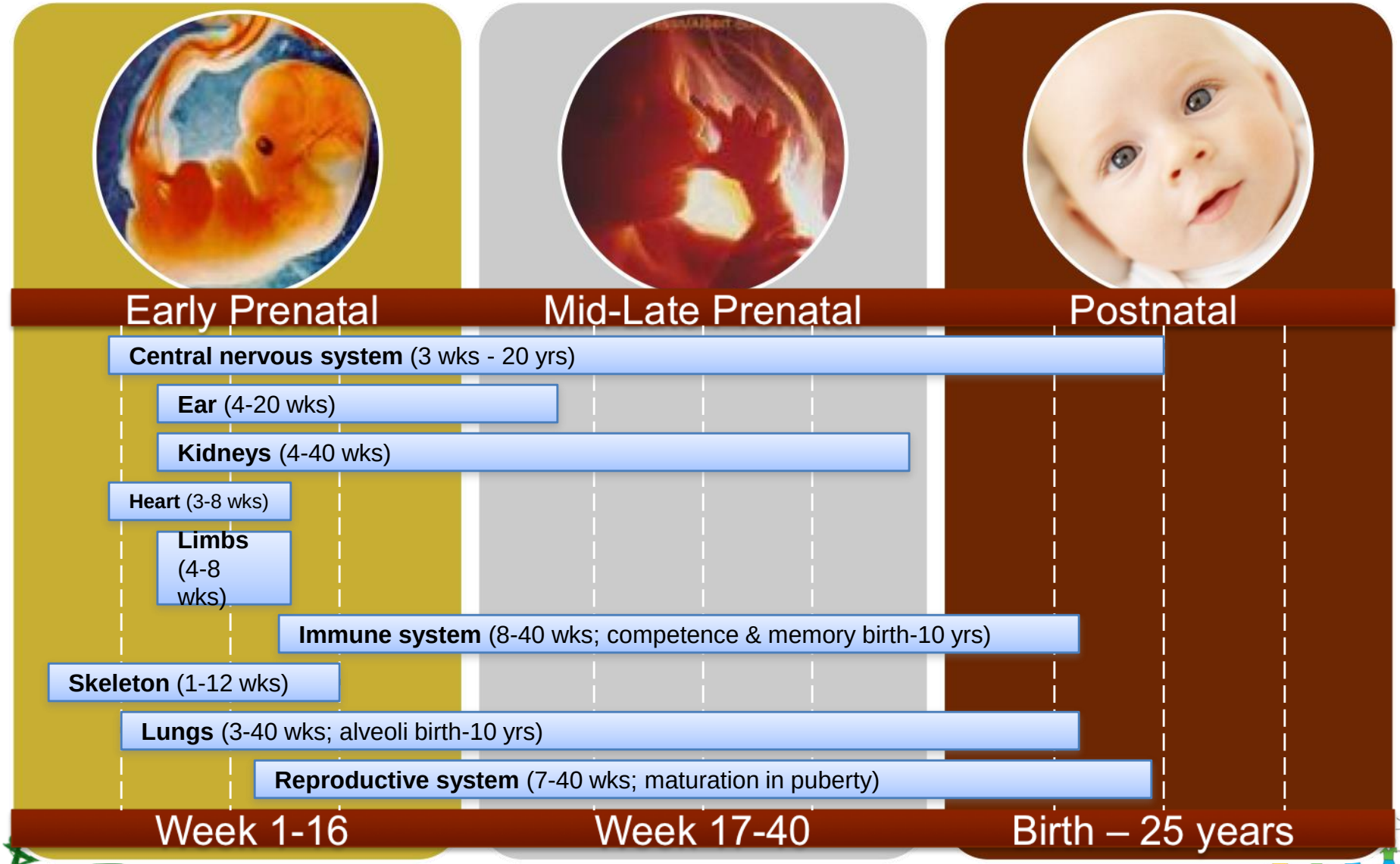
Vulnerability of the Fetus



- However vulnerable a child is to environmental factors, the embryo and fetus are much more sensitive to disruptions even at low doses

Critical Periods in Development



Source: Altshuler, K; Berg, M et al. Children's Health and the Environment, February 2003.

Thalidomide

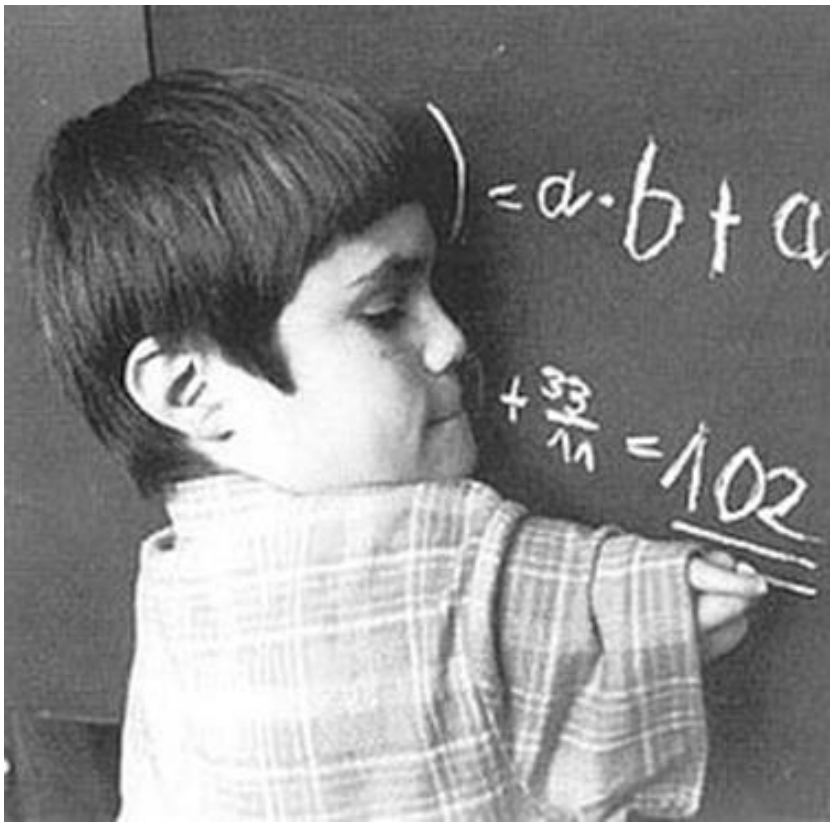
- Thalidomide first entered the German market in 1957 as a sedative, tranquilizer, and antiemetic.
- It was also proclaimed a ***"wonder drug"*** for insomnia, coughs, colds, and headaches.
- It was advertised as ***"completely safe"*** for everyone, including mother and child, "even during pregnancy," as its developers "could not find a dose high enough to kill a rat."
- By 1960, thalidomide was marketed in 46 countries, with sales nearly matching those of aspirin!

Thalidomide

- In 1961, reports began to emerge associating the drug with severe birth defects
- By March of 1962, the drug was banned in most countries where it was previously sold
- An estimated 10-20,000 infants were born with this condition

Thalidomide - Lessons

- The field of Teratology was given a start and research was directed to finding what other drugs caused birth defects
- Regulations became more stringent on testing drugs for safety during pregnancy



Minamata Disease

- On April 21, 1956, a five year-old girl was examined at the Chisso Corporation's factory hospital in Minamata, Japan,
- The physicians were puzzled by her symptoms: difficulty walking, difficulty speaking and convulsions.
- They soon found other family members and many other children with the condition

Minamata Disease

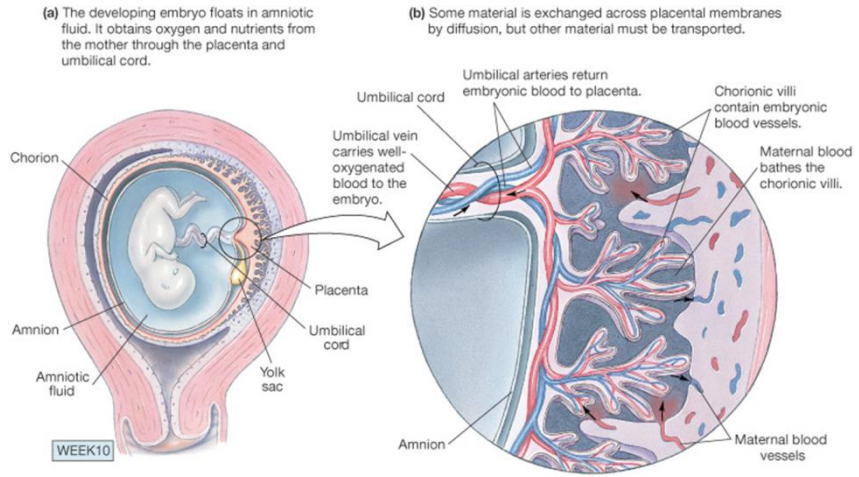
- On May 1, the hospital director reported an "epidemic of an unknown disease of the central nervous system“ - marking the official discovery of ***Minamata disease***
- By the end of the year Minamata disease was considered to be a result poisoning by a ***methyl mercury*** that entered the body through consumption of fish and shellfish from the Minamata Bay

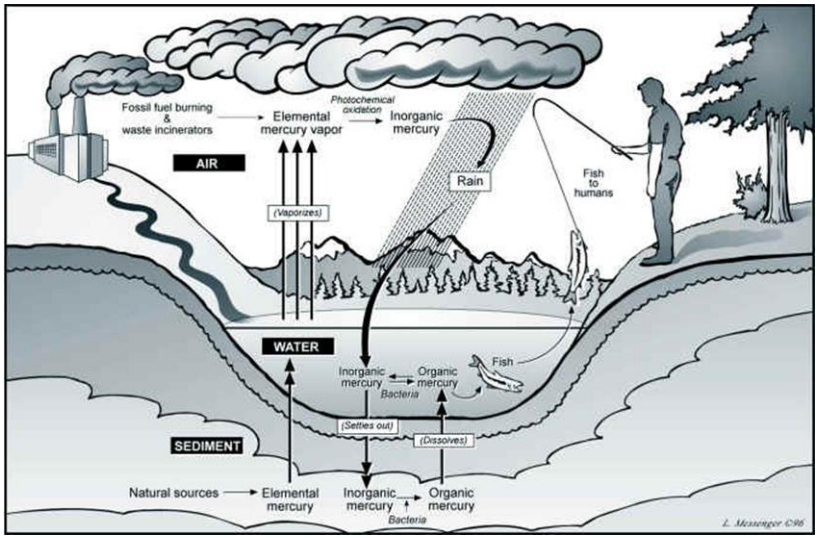
Minamata Disease

- Chisso Corporation, a chemical company located in Kumamoto Japan, had dumped an estimated ***27 tons of mercury compounds*** into Minamata Bay.
- As of March 2001, ***2,265 victims*** had been officially recognized

Lessons Learned

- The placenta does not provide full protection
- Mercury can cause brain damage in the unborn fetus
- Other heavy metals and toxins can do the same
- Toxic chemicals need to be regulated
- We need to monitor the consumption of fish during pregnancy





FDA Guidelines for Children and Pregnant Women

- No more than 12-oz of “low” mercury fish, (e.g. Cod & Canned Tuna) should be consumed weekly.
- “High" mercury fish, (e.g. Sea Bass & Bluefish) should be kept to only three 6-oz servings per month.
- "Highest" mercury fish, (e.g. Marlin & Swordfish) should be completely avoided

Congenital Rubella

- Between 1963 and 1965 a rubella epidemic swept the nation….
- Children were mildly affected, but…
- It caused 30,000 miscarriages and
- 20,000 pregnant women who contracted the disease gave birth to infants with congenital anomalies and neurodevelopmental disorders

Lessons Learned

- Infections in pregnant women (even supposedly mild ones) can have major consequences on their unborn fetus
- Other similar conditions were recognized - ToRCH
- Immunizations against childhood illnesses not only prevents complications in the children but prevents potential effects on the fetus during pregnancy

Fetal Alcohol Syndrome

- In 1973 Jones and Smith published a report on ‘the first reported association between maternal alcoholism and aberrant morphogenesis in the offspring’ – the main features are
  - pre and/or postnatal growth retardation,
  - characteristic facial abnormalities, and
  - central nervous system dysfunction, including mental retardation
- Studies by the CDC report prevalence rates of FAS alone from 0.2 to 1.5 cases per 1,000 births across various populations

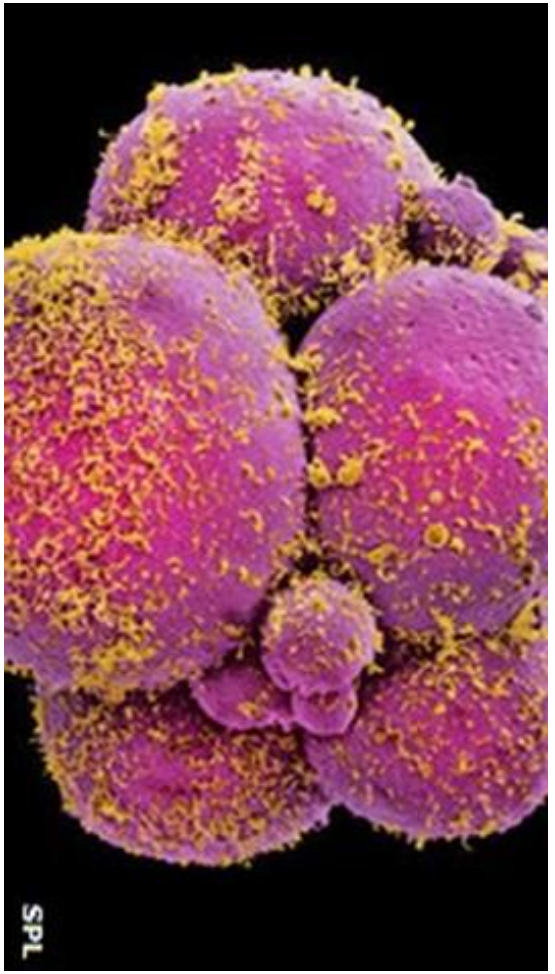
Smith, et al (1973) Lancet i, 1267–1271.

FAS – Lessons Learned

- Alcohol and other drugs taken by the mother during pregnancy can have a deleterious effect on the growth and development of the fetus and child
- Warning labels on bottles of alcohol and education of public

Smoking During Pregnancy

- The embryos of mothers who smoked took 62 hours to reach the eight-cell stage, compared to 58 hours in non-smokers
- Increasing risk of low birth weight, prematurity and other consequences on embryogenesis



Freour et al University of Nantes Presented at ESHRE meeting in Turkey 2012

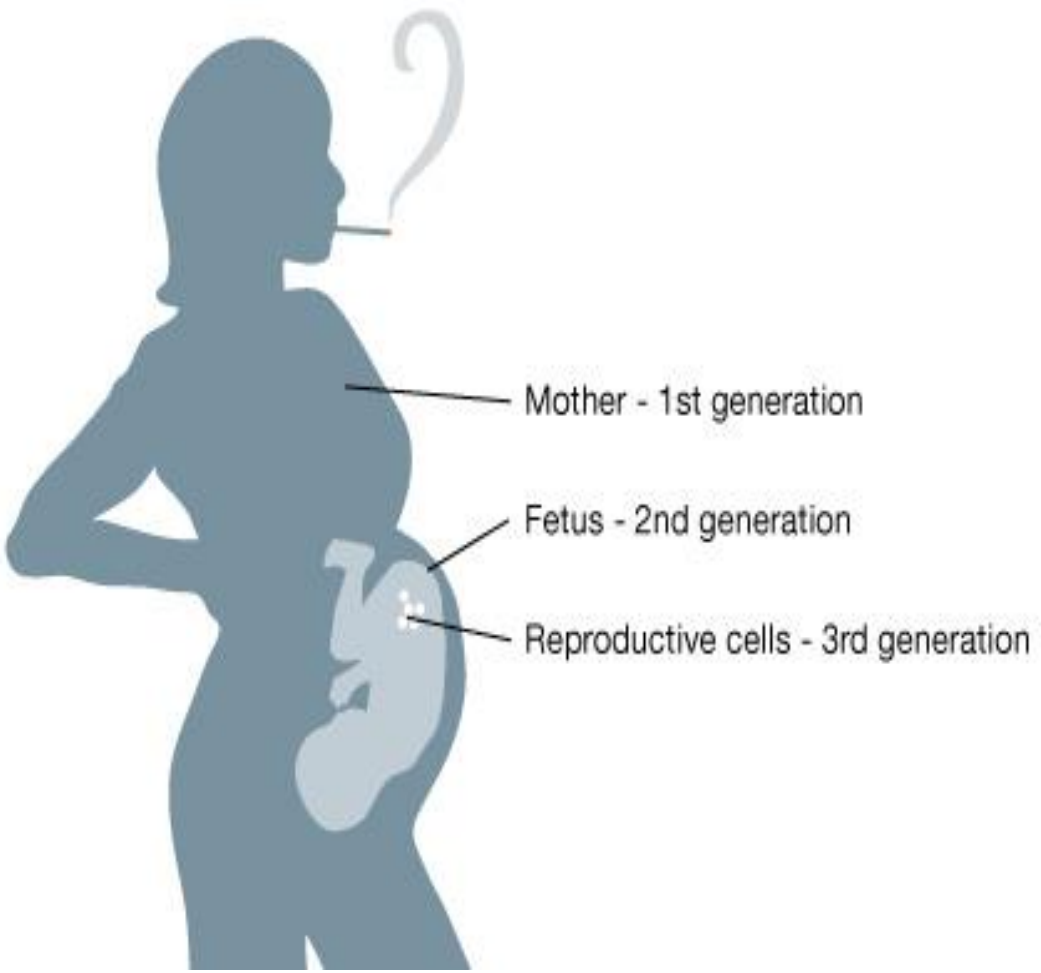
Long-Term Consequences of Fetal and Neonatal Nicotine Exposure

- Studies suggest that nicotine may be a key chemical responsible for many long-term effects associated with maternal cigarette smoking on the offspring, such as
  - hypertension
  - type 2 diabetes, obesity
  - respiratory dysfunction
  - neurobehavioral defects
  - impaired fertility

Bruin et al Toxicological Sciences 116: 364-374 2010

Tobacco – Lessons Learned

- The effects of the toxin not only have a direct effect on the smoker and on the growth of the fetus
- but can have long term health implications for the rest of that child's life
- And for that child's offspring as well



Diethylstilbestrol (DES): The Promise

- Diethylstilbestrol (DES) is a synthetic estrogen that was developed to supplement a woman's natural estrogen production.
- First prescribed in 1938 for women who experienced miscarriages or premature deliveries
- *DES was originally considered effective and safe for both the pregnant woman and the fetus*

Diethylstilbestrol (DES): Alarms!

- In 1971, the FDA issued a Drug Bulletin advising physicians to stop prescribing DES to pregnant women because it was linked to a rare vaginal cancer *in female offspring.*
- An estimated 5-10 million people in the USA were exposed to DES during 1938-1971

Diethylstilbestrol (DES): What we Know Now

- Women prescribed DES while pregnant are at a modestly increased risk for breast cancer.
- Women exposed to DES in utero, are at an increased risk for:
  - clear cell adenocarcinoma (CCA) of the vagina and cervix,
  - reproductive tract structural differences
  - pregnancy complications, and
  - infertility.
- Men exposed to DES in utero are at an increased risk for non-cancerous epididymal cysts.

Lessons Learned

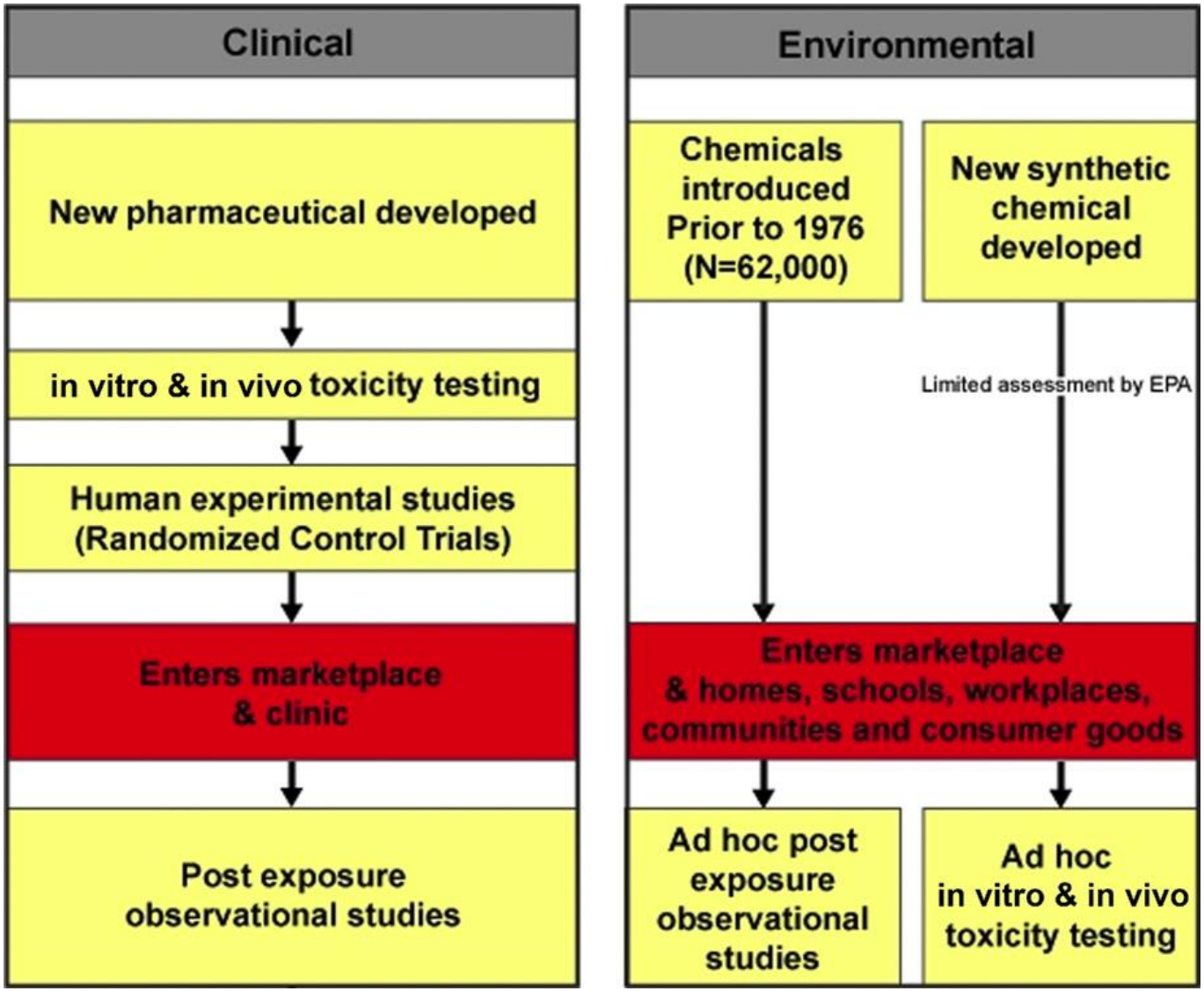
- We cannot assume any drug or chemical is completely safe even if we do not see immediate consequences
- The effect may only manifest later in life or in the next generation
- Therefore we need to adopt the ***precautionary principle***

Chemicals in our Environment

- EPA lists >80,000 chemicals in the USA
- 3,000-4,000 are ‘high volume’ >1million pounds per year
- 700 new chemicals introduced into the USA per year
- The Toxic Substances Control Act (TSCA) authorizes EPA to test <200 chemicals

Sutton et al AJOG 2012

Premarket Testing



Woodruff et al Health Aff 2011 30:931-7

- Researchers at two major laboratories found an average of 200 industrial chemicals and pollutants in umbilical cord blood from 10 babies born in August and September of 2004 in U.S. hospitals.
- Tests revealed a total of 287 chemicals in the group.
- The umbilical cord blood of these 10 children, collected by Red Cross after the cord was cut, harbored
  - pesticides,
  - consumer product ingredients, and
  - wastes from burning coal, gasoline, and garbage.

Environmental Working Group, July 14, 2005

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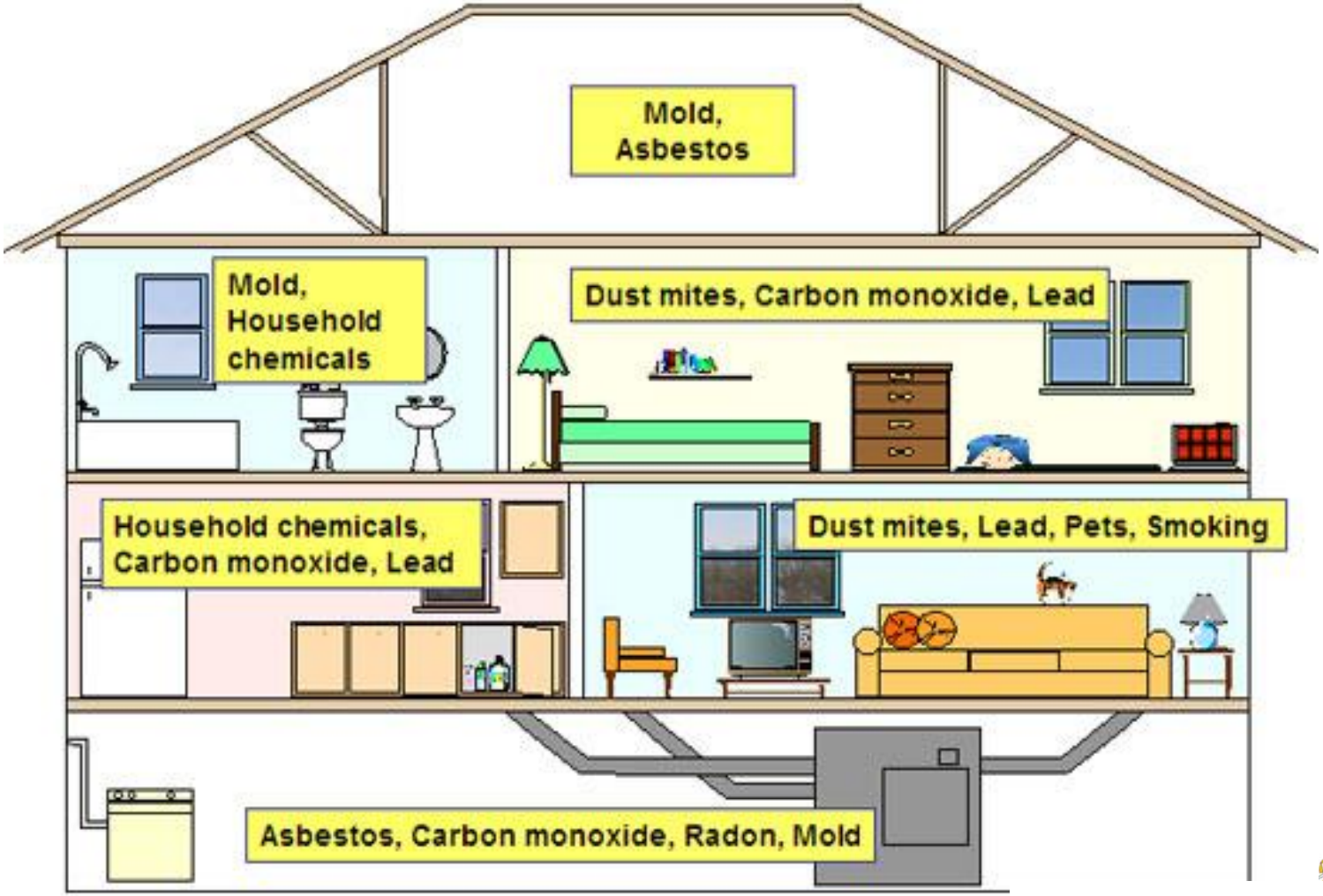
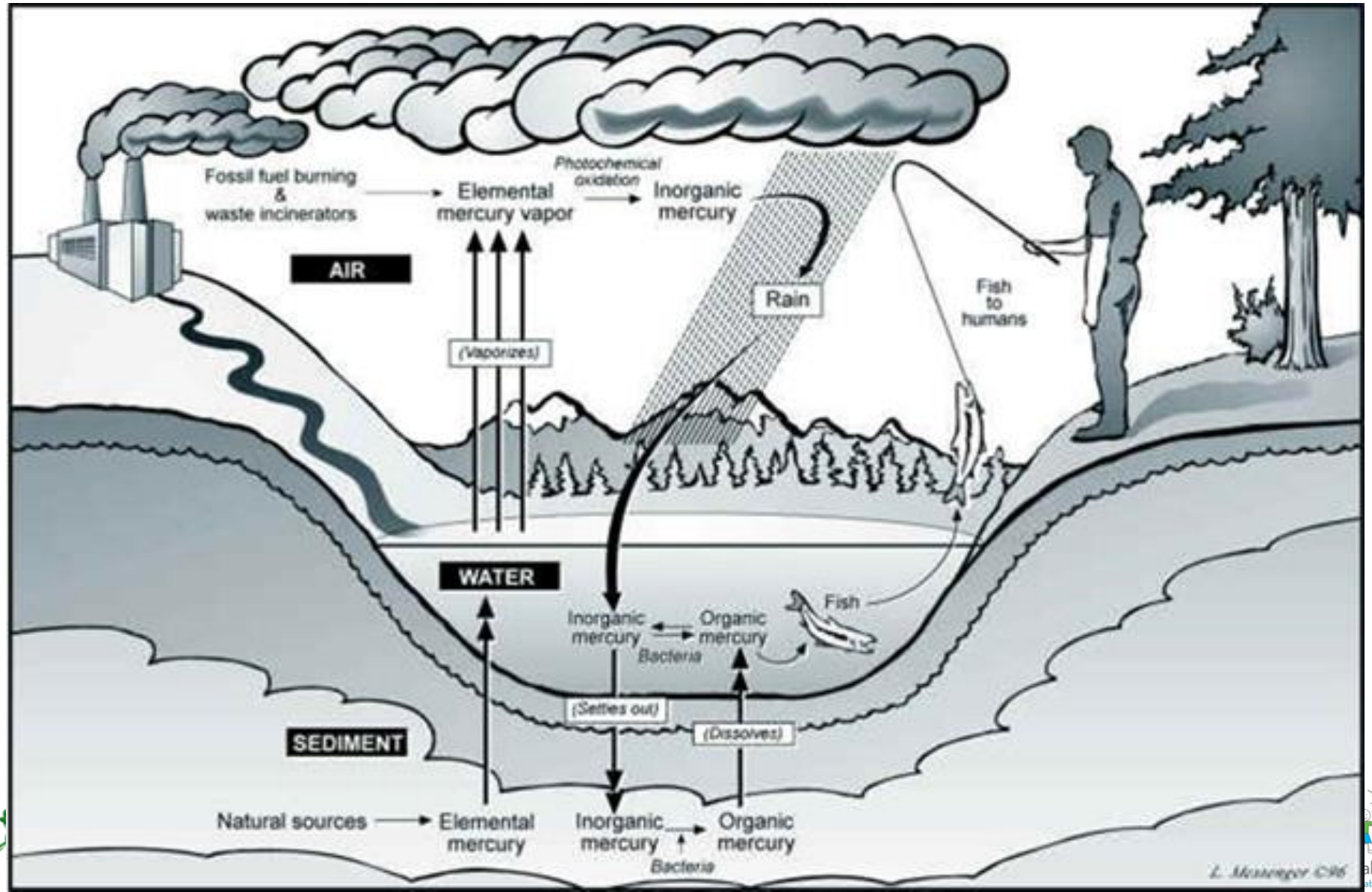
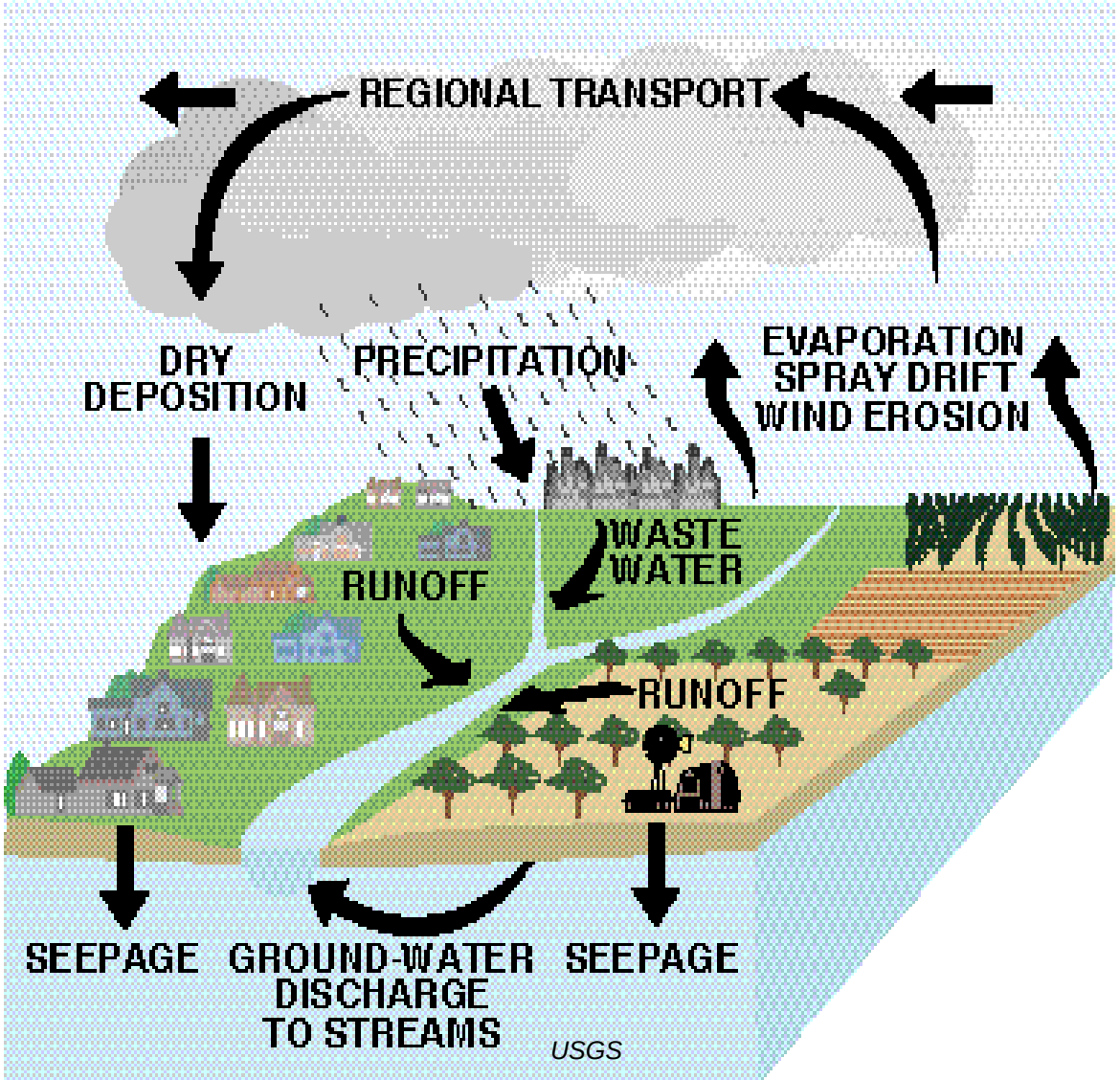
Environmental Toxins in the Home



Industrial Pollution



Pesticides on the Ground, in the Air & in the Water



Neurodevelopmental Scores and Prenatal Exposure to **Chlorpyrifos**

- 265 children in a prospective study
  - measured prenatal Chlorpyrofos exposure using umbilical cord blood plasma and
  - 7-year neurodevelopment using the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV).
- **Results:** On average, for each standard deviation increase in Chlorpyrofos exposure (4.61 pg/g),
  - Full-Scale intelligence quotient (IQ) declined by 1.4% and
  - Working Memory declined by 2.8%!

Rauh et al. 2011 Environ Health Perspect

Agricultural Pesticides and Autism

- Children of mothers living within 500 m of field sites with the highest amount of organochlorine pesticides had a *6x greater chance of having a child with Autism* compared to those with mothers not living near the field sites

Roberts et al Environ Health Perspect. 2007 Oct;115(10):1482-9.

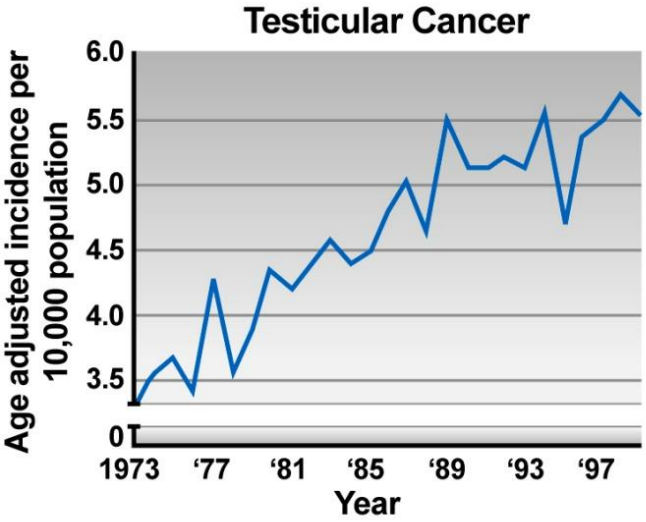
Endocrine disruptors

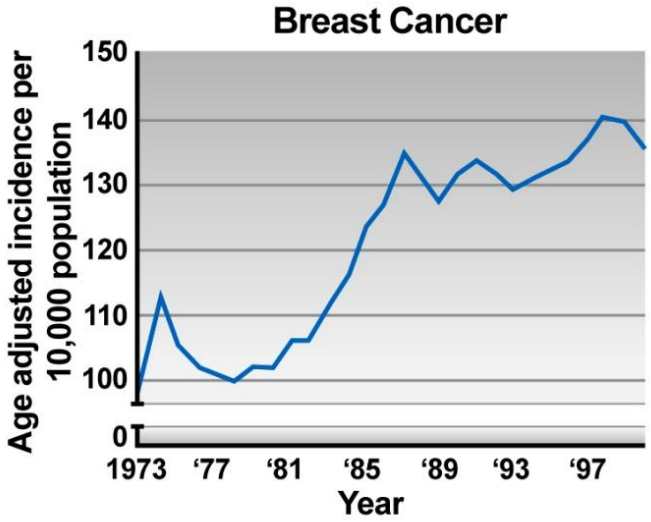
- Chemicals that may interfere with the body's endocrine system
- Endocrine Disruptor Chemicals:
  - pharmaceuticals, dioxins, polychlorinated biphenyls (PCB's), pesticides, and plasticizers such as bisphenol A (BPA)
- Endocrine disruptors may be found in
  - plastic bottles, metal food cans, flame retardants, detergents, food, toys and cosmetics
- Endocrine disruptors pose the greatest risk during prenatal and early postnatal development when organ systems are forming

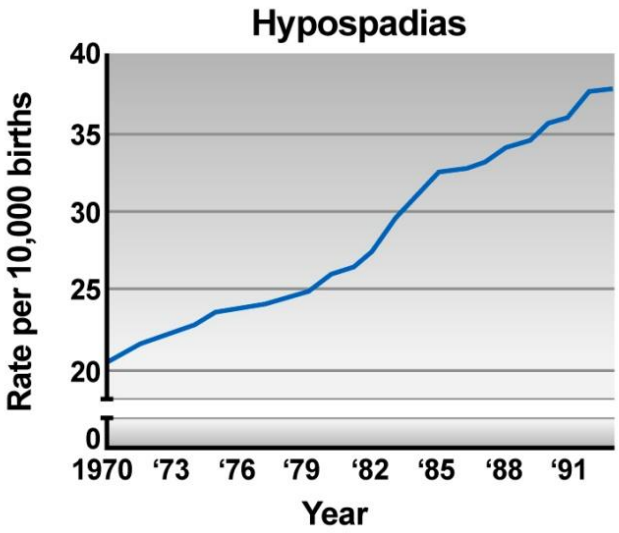
Consequences of Endocrine Disruptors

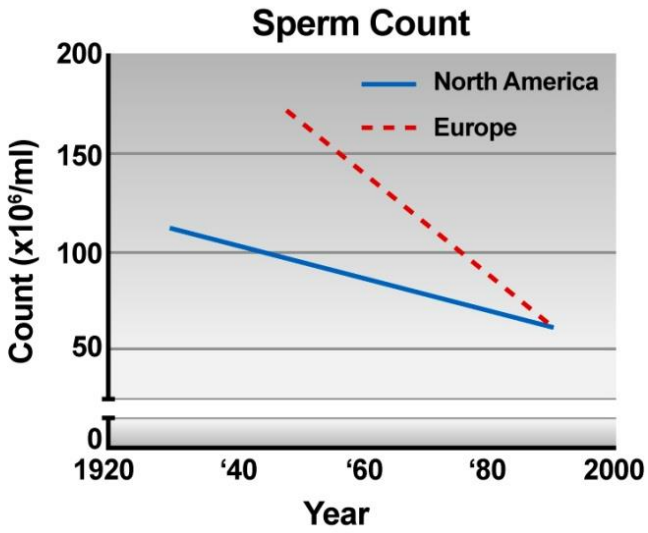
- For women:
  - Breast and reproductive organ tissue cancers, fibrocystic disease of the breast, polycystic ovarian syndrome, endometriosis, uterine fibroids and pelvic inflammatory diseases.
- For men:
  - Poor semen quality (low sperm counts, low ejaculate volume, high number of abnormal sperm, low number of motile sperm), testicular cancer, malformed reproductive tissue (undescended testes, small penis size), prostate disease
- In children:
  - congenital anomalies of genitalia (e.g. hypospadius), neurodevelopmental disorders, immune disorders, thyroid disorders, precocious puberty.

Should We Be Concerned?









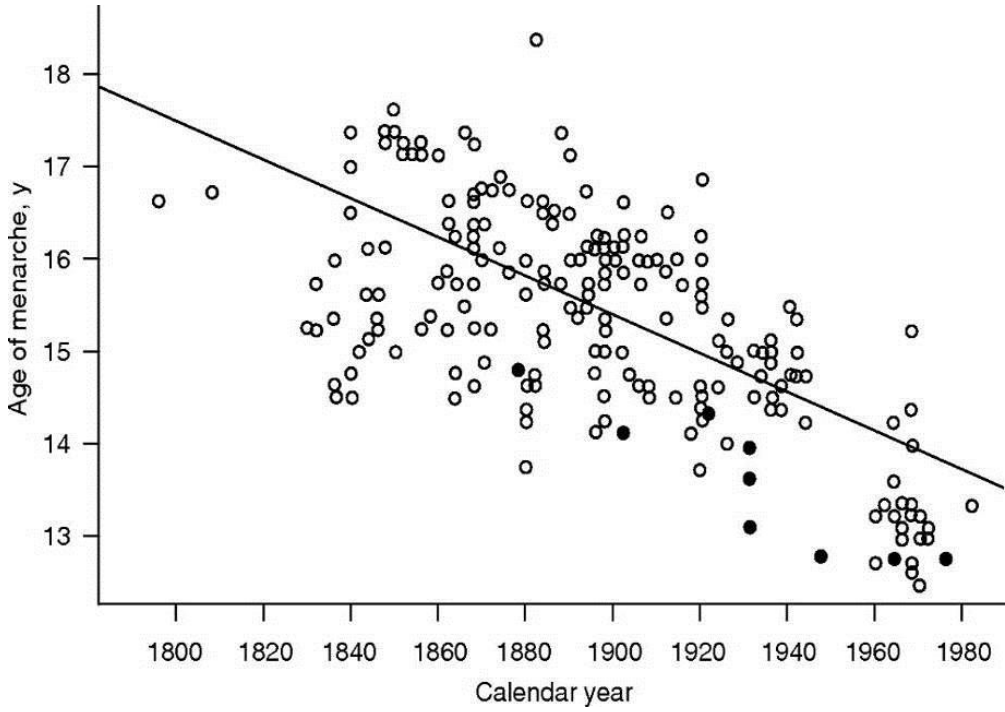
Sharpe and Irvine, 2004 - Slide Curtesy of Linda Birnbaum NIEHS 2012

Decreasing Age of Puberty

US expert panel concluded:

- Earlier breast development and onset of menarche
- “Suggest … endocrine-disrupting chemicals …and body fat are important factors associated” with the change
- African American and Mexican American girls enter puberty earlier than white girls

Age of Menarche in Europe and the US from 1790 to 1980

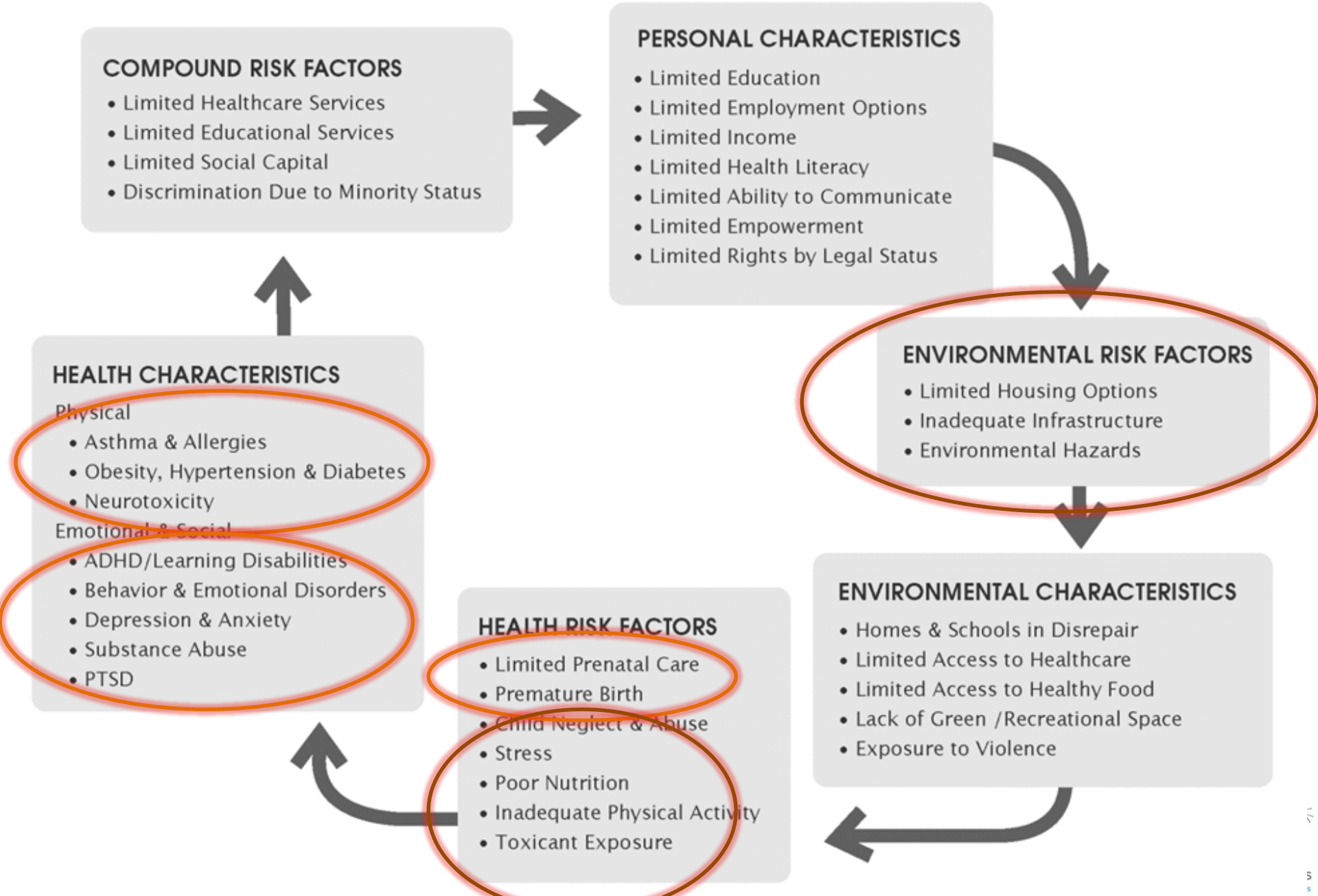


Euling et al. Pediatrics 2008 - *Slide Curtesy of Linda Birnbaum NIEHS 2012*

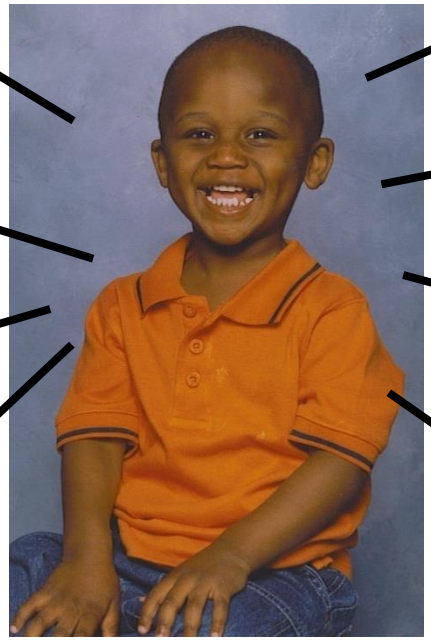
Environmental Living Conditions of Poor Communities

- In old housing with poor indoor air quality, mold and deteriorating lead based paint
- Unsafe Neighborhoods due to: Crime, Traffic Density, Litter & Trash, Poor Lighting Adjacent to major roadways
- More likely to be exposed to a variety of toxins from a variety of sources
- Lack of or limited green space and parks
- Poor quality schools
- Limited access to quality health care

CYCLE OF ENVIRONMENTAL HEALTH DISPARITIES



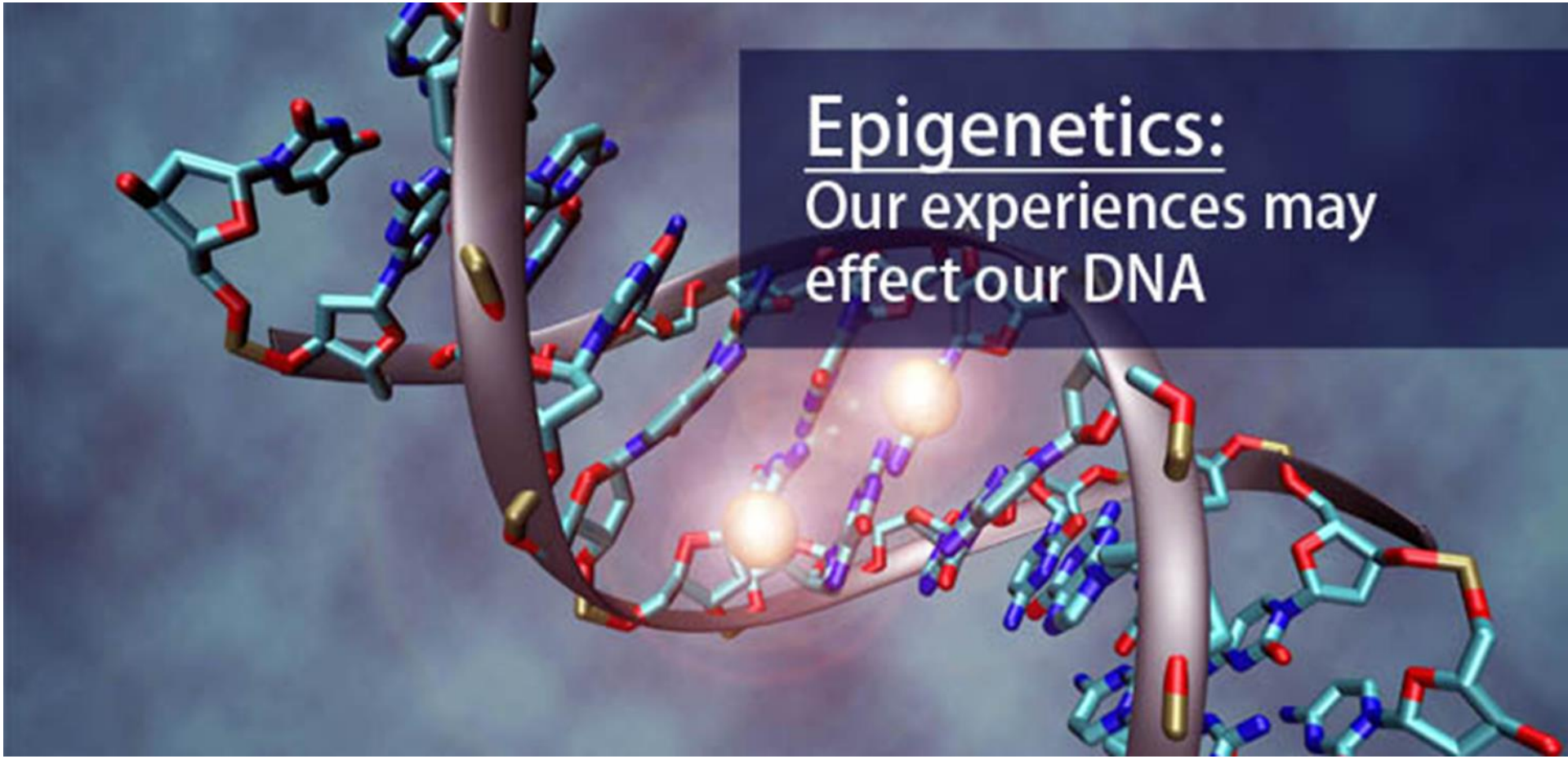
Cumulative risk



- Poverty
- Lead & other toxins
- Allergens
- Poor nutrition
- Stressed mother
- Noise
- Unsafe neighborhood
- No parks

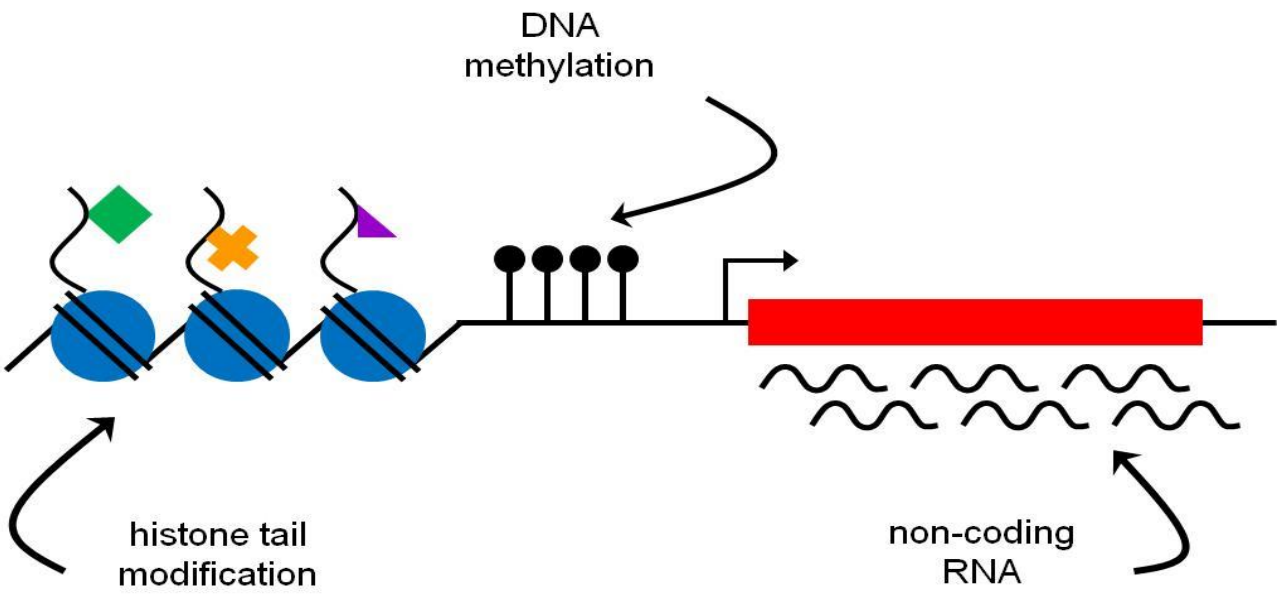
From Lecture by Dr. Howard Frumkin

How does it work?



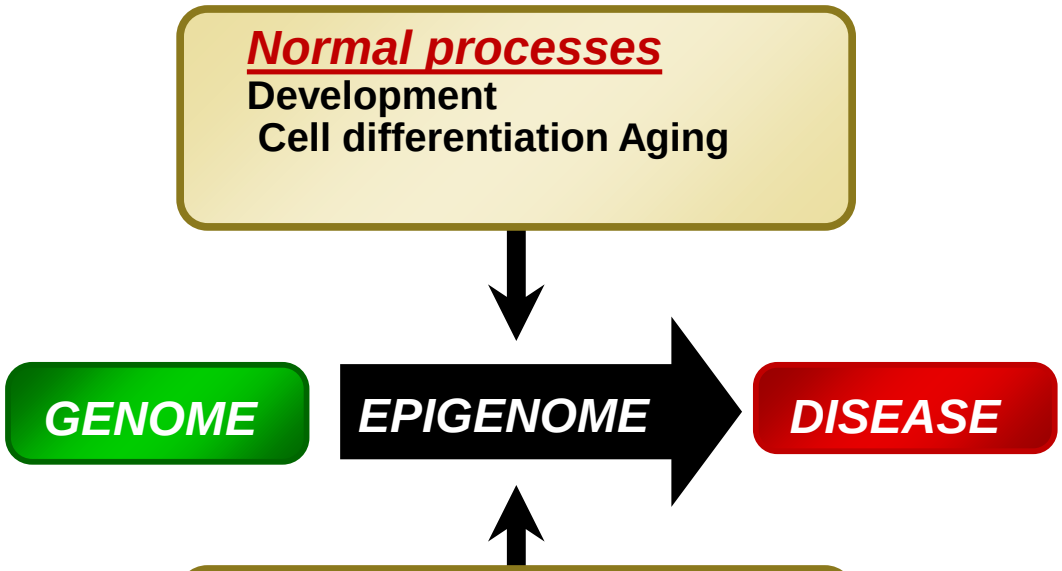
Epigenetics

- Environmental Factors do not change the DNA but change the expression of genes by the process of methylation



Adapted from Linda Birnbaum NIEHS 2012

Epigenetic Changes and Human Diseases

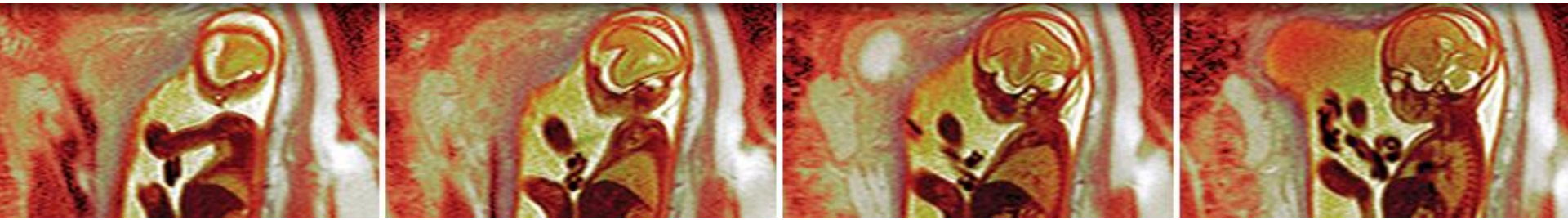


Adverse health outcomes

- Cancer
- Cardiopulmonary disease
- Autoimmune disease
- Obesity
- Diabetes
- Neurodevelopmental disorders
- Schizophrenia
- Addiction
- Depression

Slide Cutesy of Linda Birnbaum NIEHS 2012

Conclusions



- The fetus is exquisitely sensitive to environmental influences
- These influences may cause immediate or long term consequences on the health, growth and development of the child and even on the child's reproductive health and into the next generation
- It is our responsibility to assure that pregnant women are not unnecessarily exposed to environmental factors that could be harmful to them or their fetus

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