

# Toxic chemicals: an ecologic and lifespan perspective

Interstate Chemicals Clearinghouse

NEWMOA

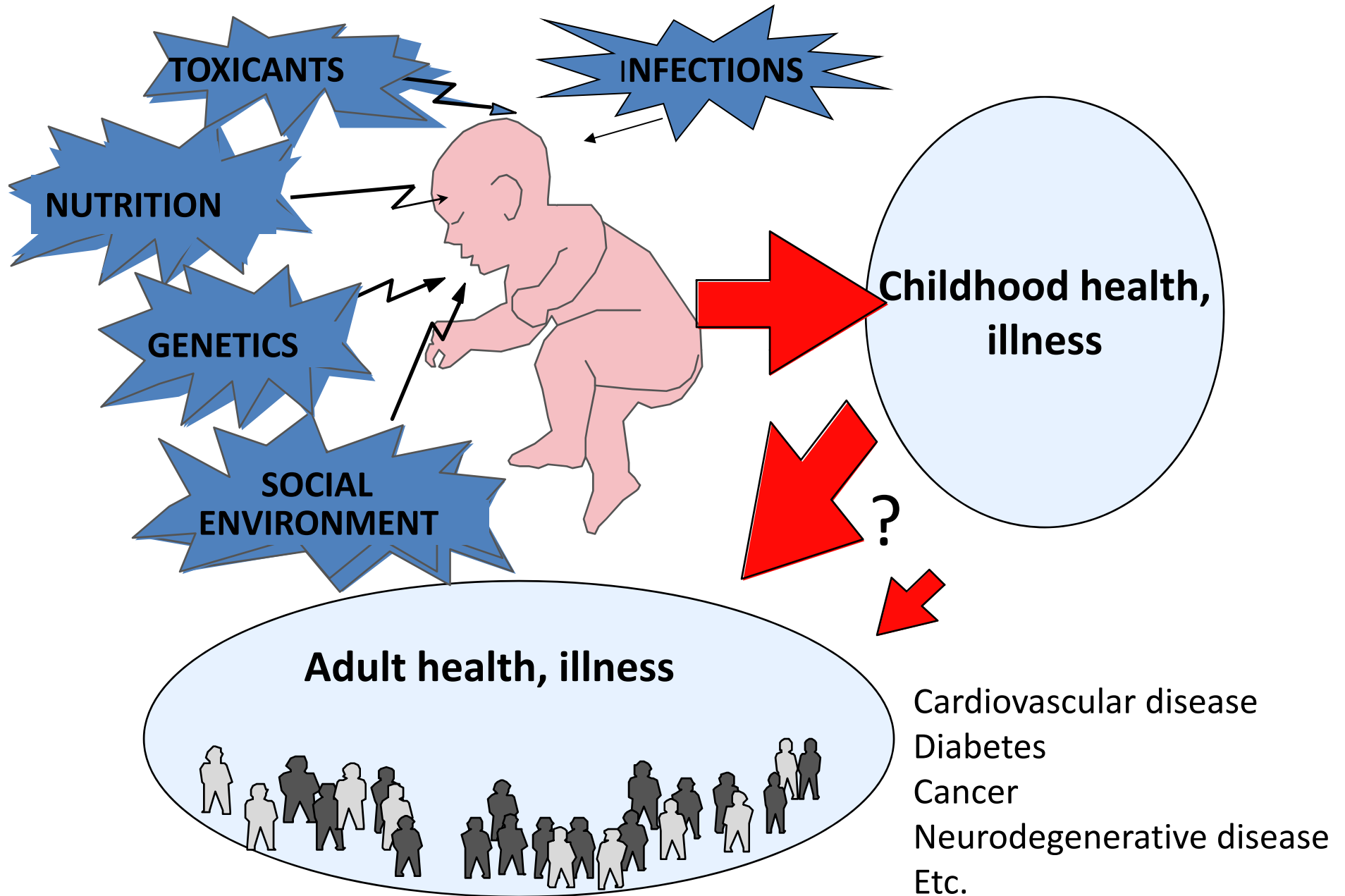
October 4, 2011

Ted Schettler MD, MPH

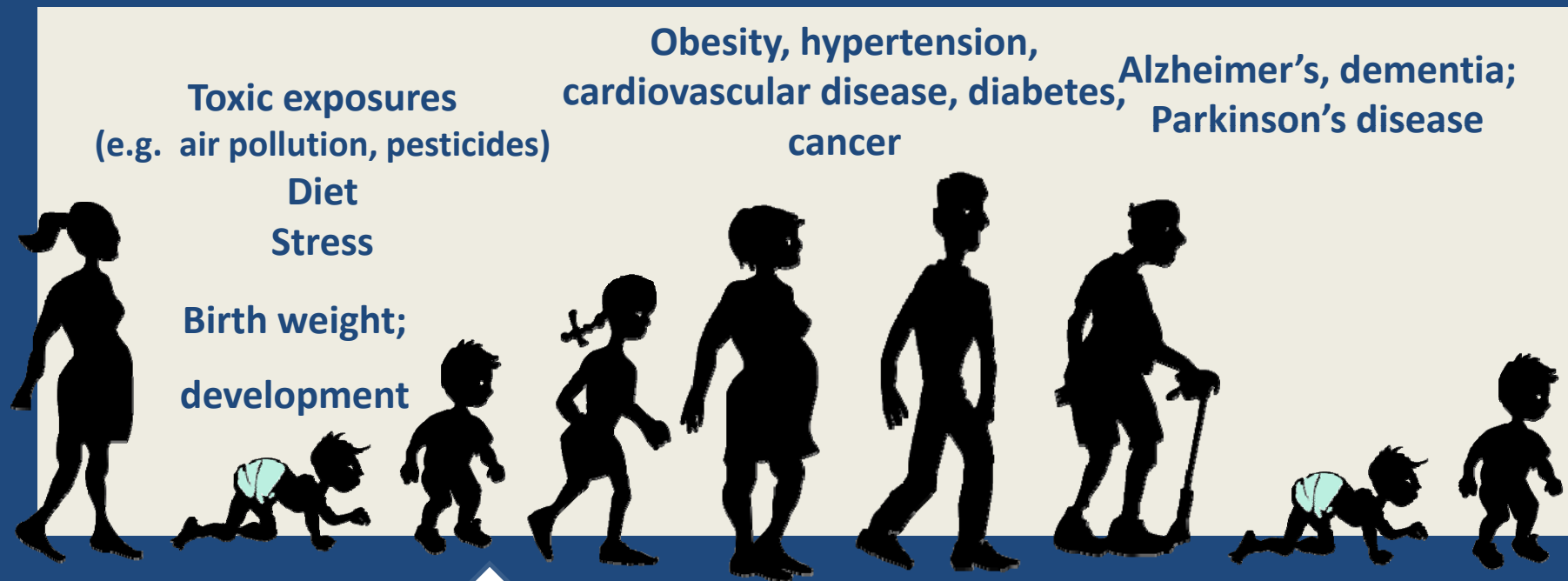
Science and Environmental Health Network

[www.sehn.org](http://www.sehn.org)

# Lifespan perspective



# Earlier life experiences can influence later-life health, disease



DES in utero: ↑ vaginal, cervical, breast cancer risk

Pesticides: organophosphates/neurodevelopmental impacts  
-Parkinson's disease risk

↑ DDT before age 14: ↑ breast cancer risk (Cohn, 2007)

# Developmental exposure to DES and weight gain

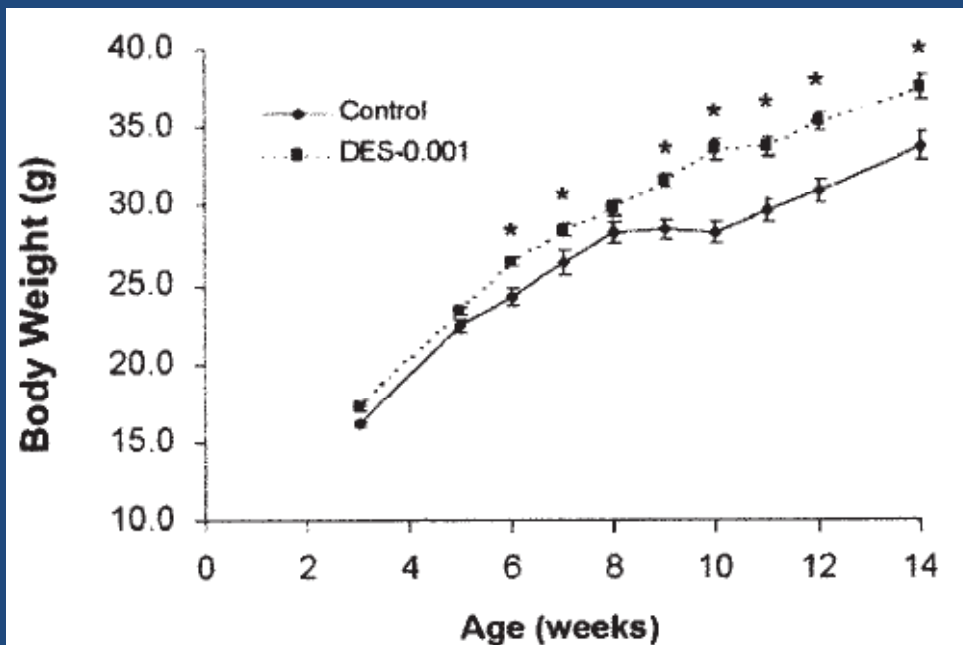


Figure 1. Neonatal exposure to a low dose of DES (0.001 mg/kg/day; DES-0.001) on days 1–5 caused an increase in body weight starting at 6 weeks of age. Each point represents a minimum of 20 mice per dose per age. \*Statistically significant difference from untreated.

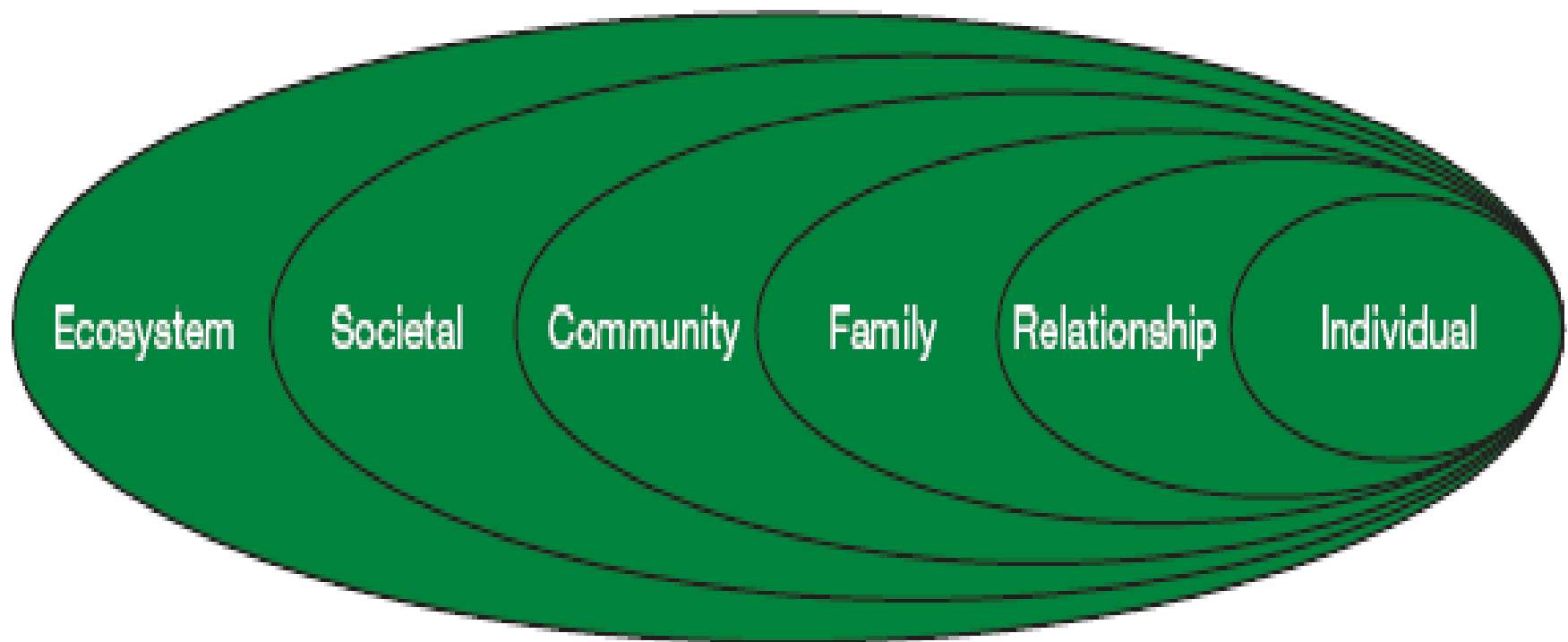


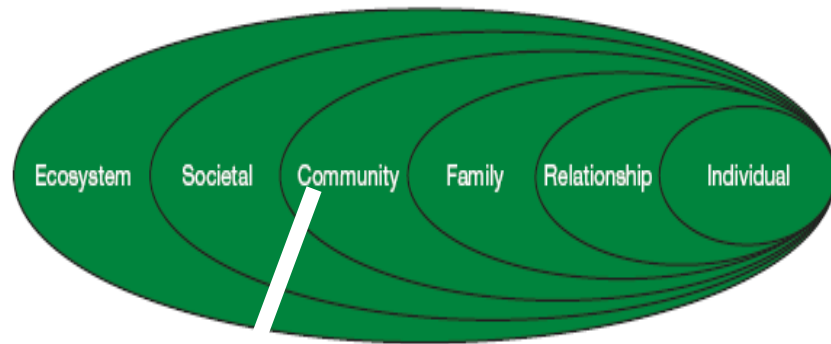
# Epigenetic Effects: Altered gene expression

## Epigenetic effects:

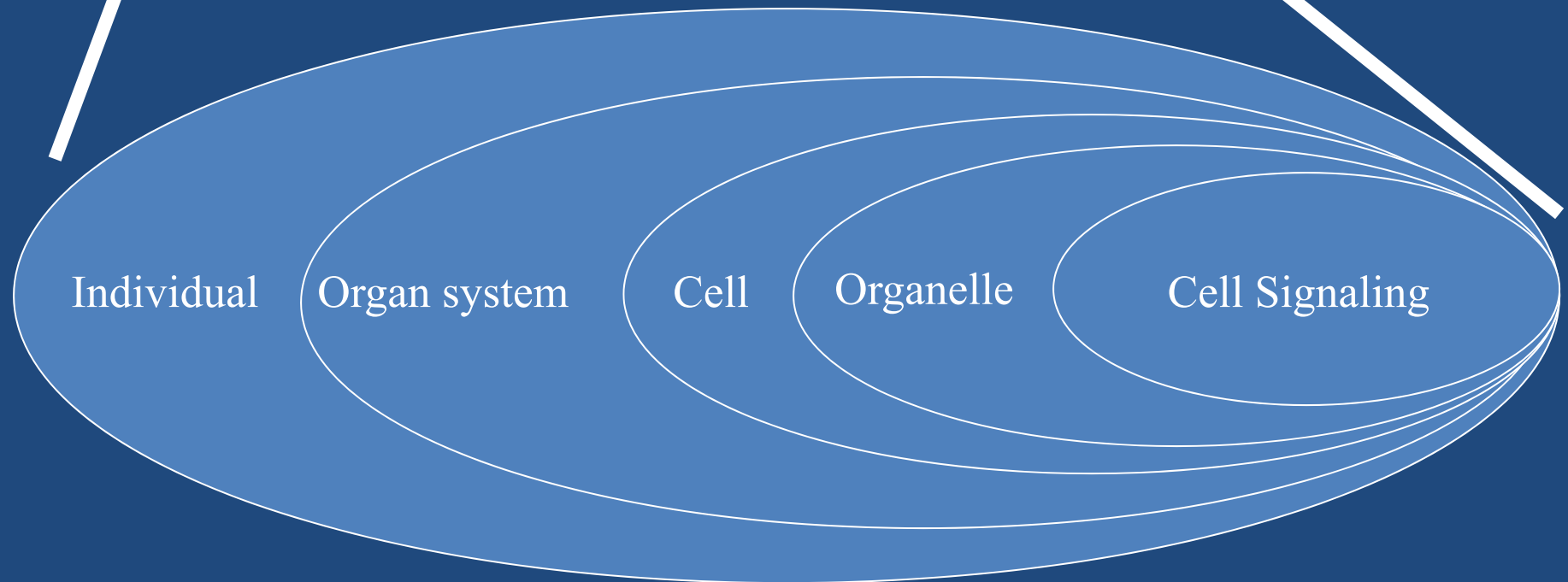
- Not caused by changes in DNA sequence
- May be caused by chemicals, nutrition, stress
- In some cases can be passed to following generations (an emerging concern)

An ecological health framework: the individual  
in the context of family, community, society  
and ecosystem.





The ecological health framework extended to the subcellular level.



# Hazards, exposures, risks

- Hazard—a chemical or physical agent capable of causing harm; the potential to cause harm
- Exposure—the applied dose of a chemical agent
- Risk—the probability of harm. Hazard and exposure together determine risk.



# Exposure

- “The dose makes the poison”.  
Yes but....dose is timing, duration, pattern, as well as amount
- Dose-response curve varies for different endpoints; threshold, non-threshold

# Non-linear dose-response curve with “threshold”

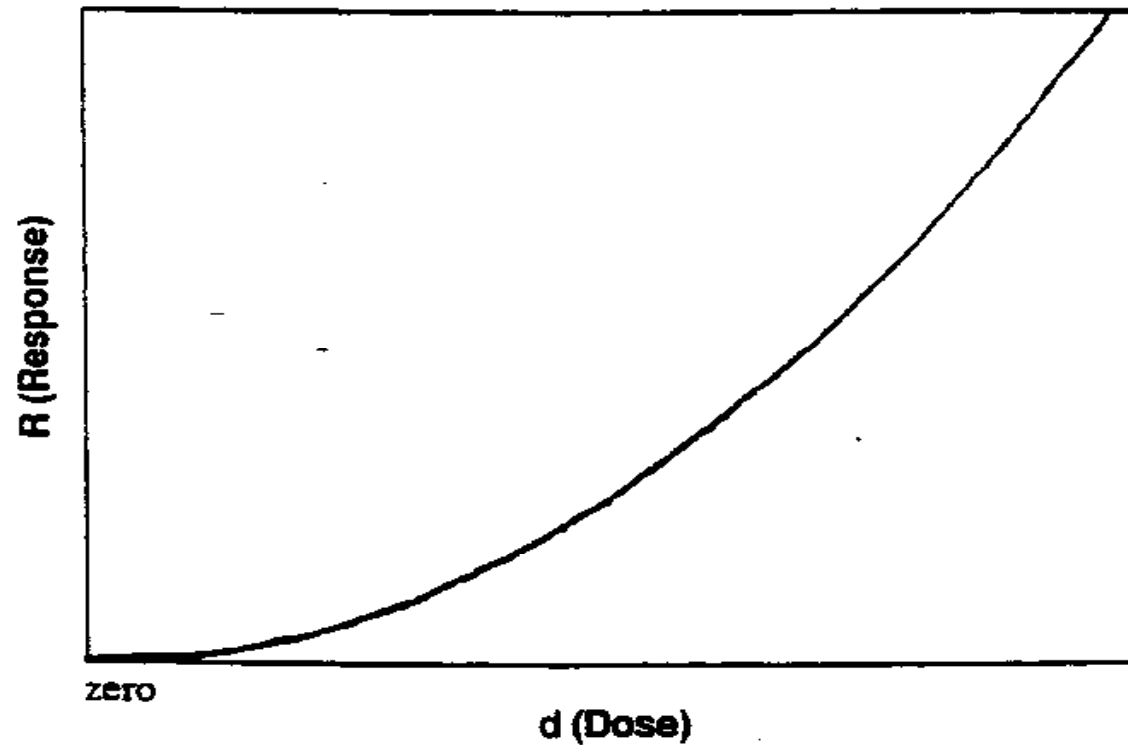
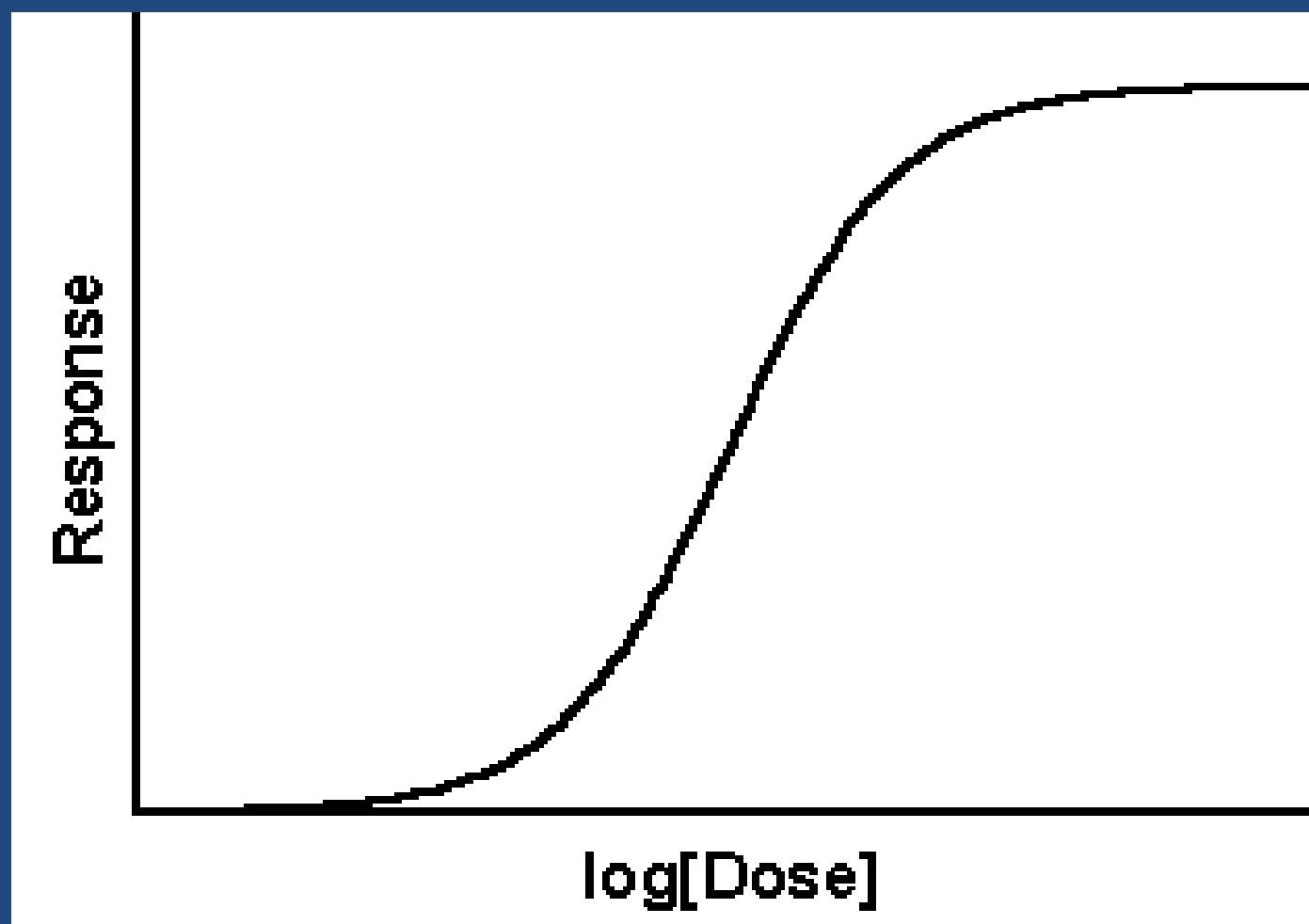


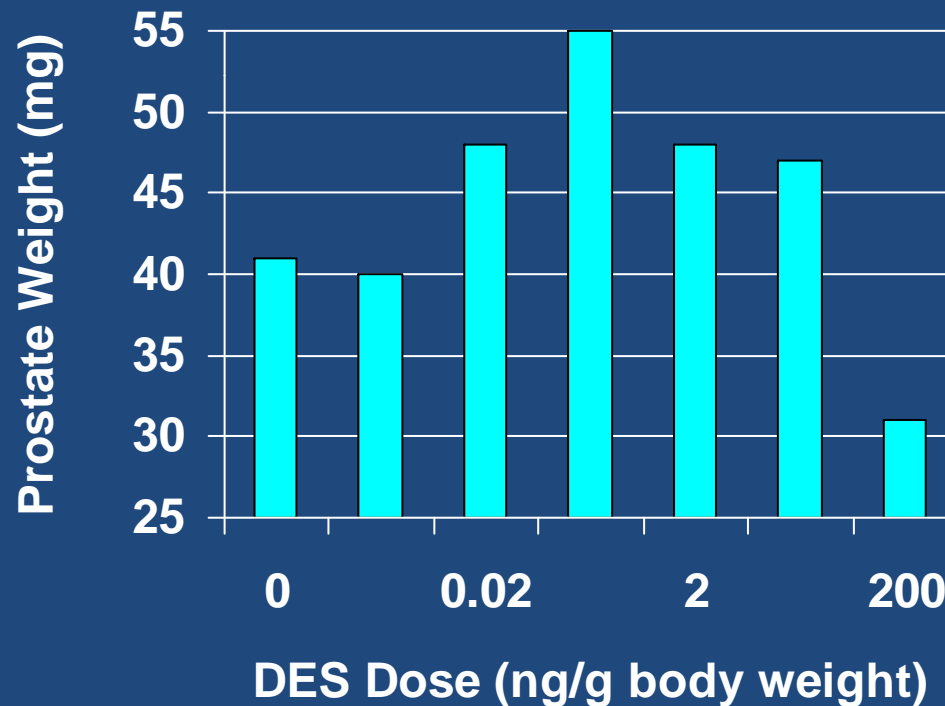
Figure 1. Typical nonlinear, “threshold”, dose-response relationship ( $R = Ad^3$ ).



# Low-dose effects

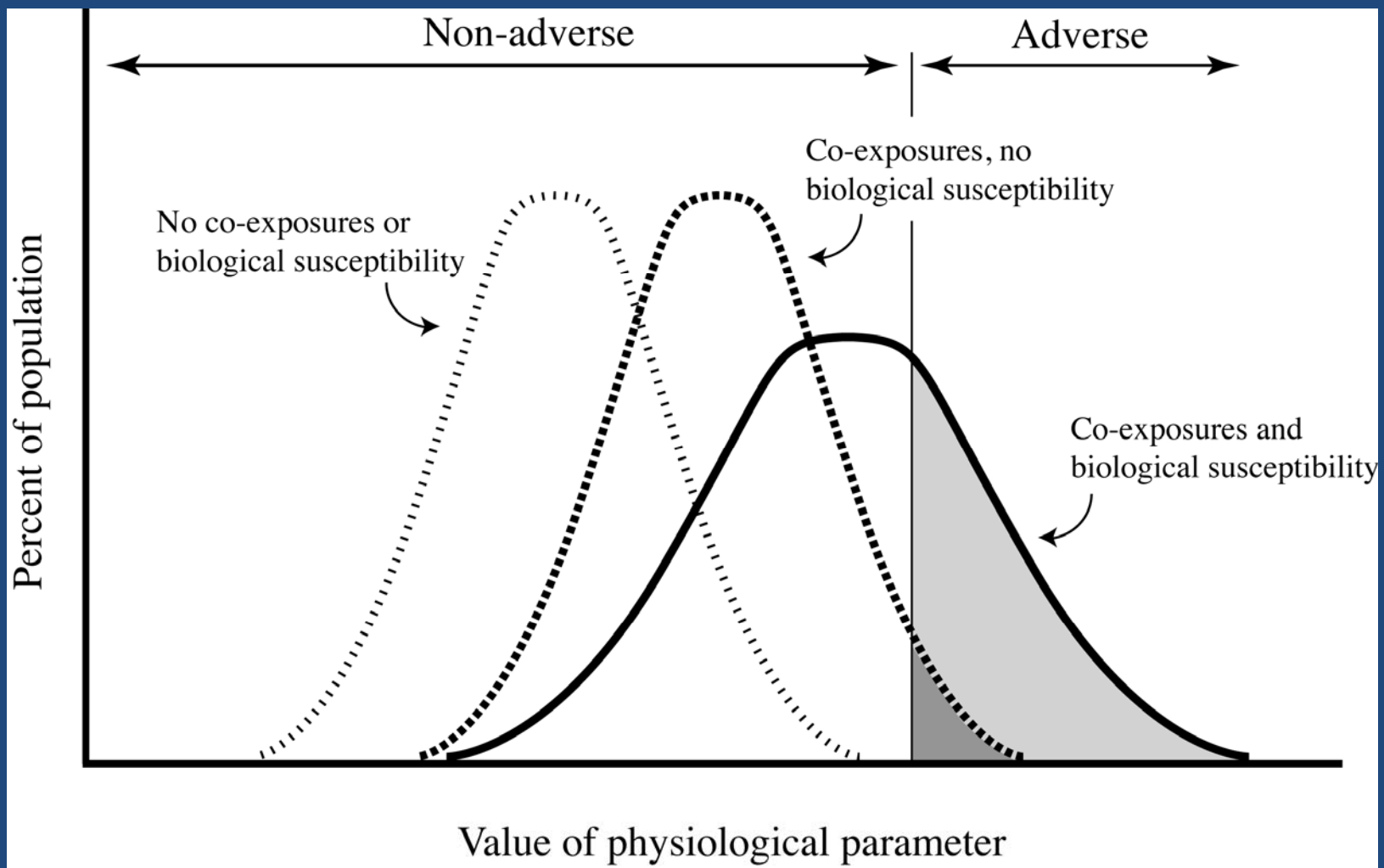
## “Inverted U” Dose-Response: DES and Prostate Size in Mice

vom Saal et al, Proc Natl Acad Sci, 94:2056-2061,1997



## Context: Susceptible individuals, communities, populations

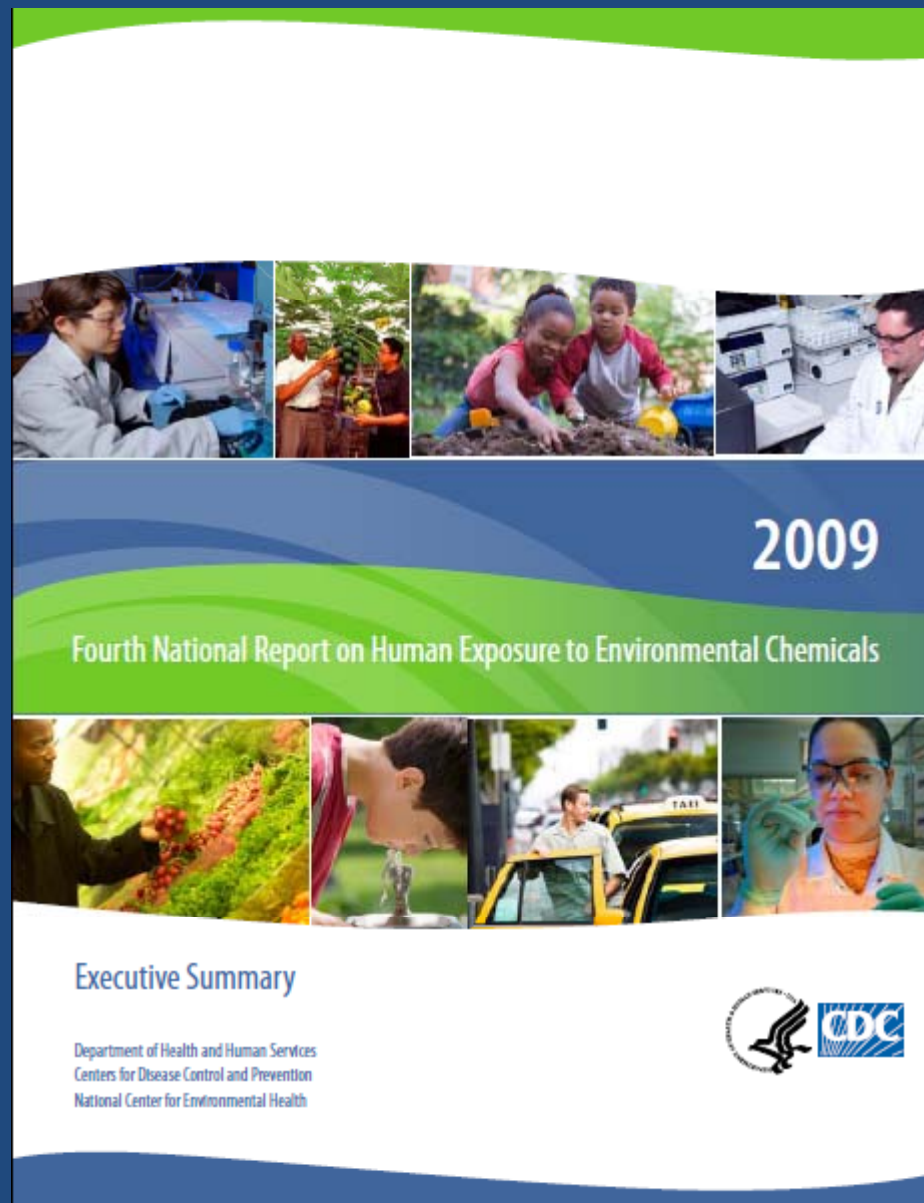
- Windows of vulnerability – e.g. fetus, child, elderly (timing)
- Biologic susceptibility—variability in metabolism, etc; associated illnesses
- Multiple exposures—additive, synergistic, subtractive; chemical and non-chemical



# Exposures are common and often ubiquitous

CDC:

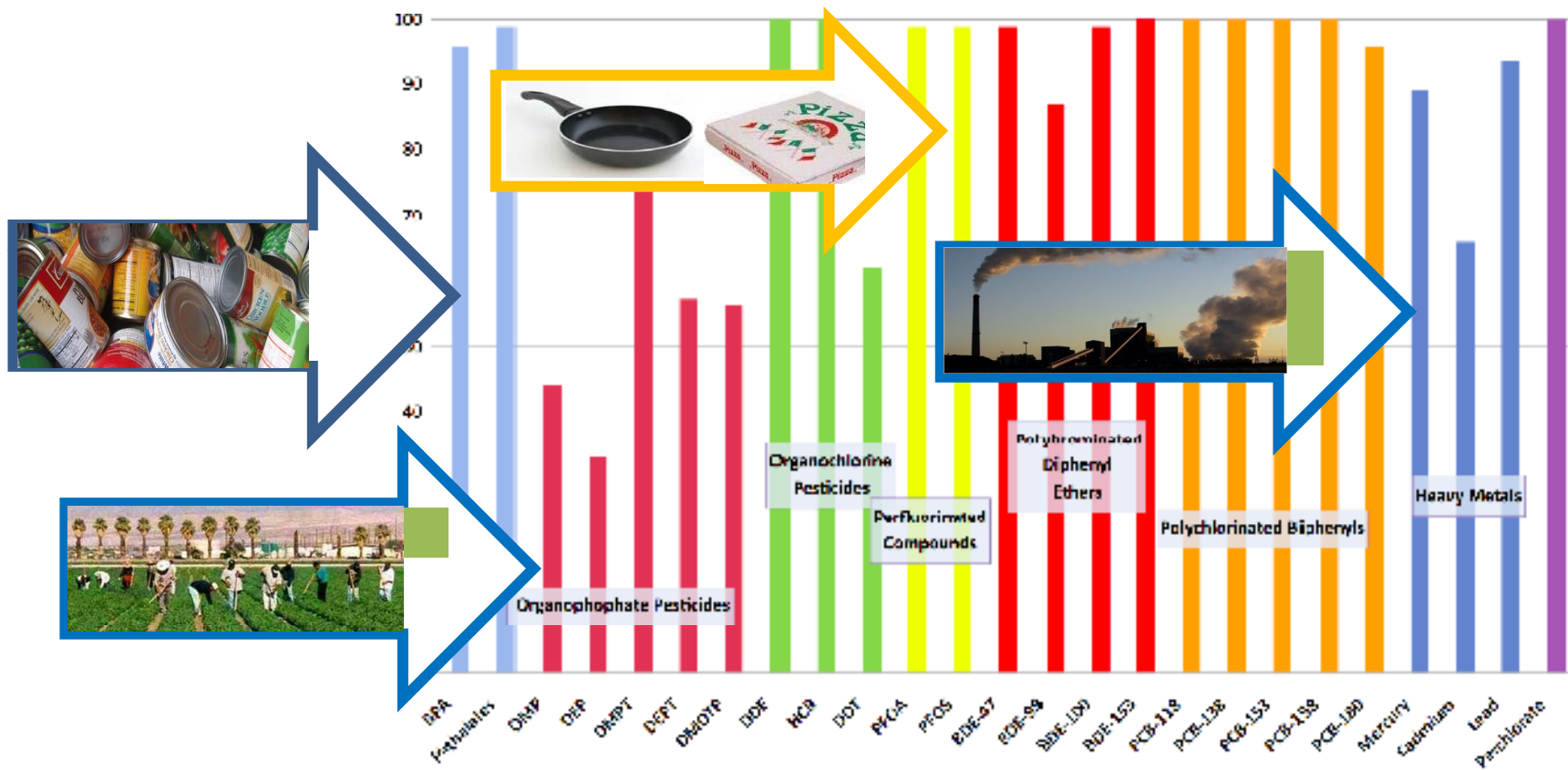
Reports on levels  
of 212 chemicals  
in a representative  
sample of the US  
population



<http://www.cdc.gov/exposurereport/>

# Widespread Exposure to Chemicals with Reproductive & Developmental Toxicity

Percentage of U.S. Pregnant Women with Detectable Level of Analyte

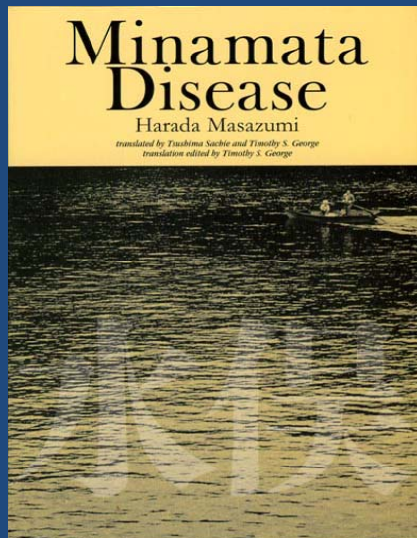


Based on analysis of representative sample of U.S. population by NHANES 2003-2004. Note, not all women were tested for all chemicals

Source: Woodruff TJ, Zota AR, Schwartz JM 2011. Environmental Chemicals in Pregnant Women in the US: NHANES 2003-2004. Environ Health Perspect :- doi:10.1289/ehp.1002727



# Lessons learned



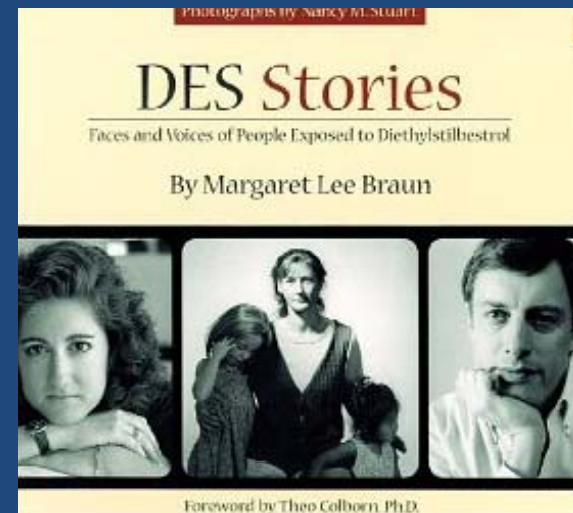
The placenta does not protect the fetus from damaging chemicals

*Methylmercury*



The fetus can be uniquely sensitive to chemical exposures

*Thalidomide*



Health impacts of fetal exposure to exogenous chemicals can be delayed

*Diethylstilboestrol (DES)*

# Cancer

- Genetic mutations; impaired DNA repair; activation of cancer-causing/promoting genes (oncogenes); inactivation of tumor suppressor genes
- Non-genetic contributions to cancer development, persistence, promotion—e.g. tumor-promoting inflammation, immune suppression

The Panel was particularly concerned to find **that the true burden of environmentally induced cancer has been grossly underestimated.** With nearly 80,000 chemicals on the market in the United States, many of which are used by millions of Americans in their daily lives and are un- or understudied and largely unregulated, exposure to potential environmental carcinogens is widespread.

The Toxic Substances Control Act of 1976 (TSCA) may be the most egregious example of ineffective regulation of environmental contaminants.



# Reproductive and developmental impacts

- Infertility (male, female); reduced fertility
  - some solvents (dry cleaning, degreasers, glues/adhesives, fuels);
  - some pesticides;
  - metals;
  - perfluorinated chemicals (non-stick; stain resistant)
- Fetal death; miscarriage—e.g.; solvents, lead
- Decreased birth weight; e.g. air pollution, some pesticides, perfluorinated compounds (inconsistent evidence)

# Reproductive and developmental impacts

- Birth defects—e.g. some pesticides, various solvents
- Childhood cancer—leukemia and maternal pesticide exposures, paternal exposure to carcinogens (inconsistent evidence); solvents (Woburn leukemia cluster)

# Reproductive and developmental impacts

- “Functional” abnormalities; e.g., neurodevelopment; reproductive, immune systems
- Neurodevelopment: lead, mercury, arsenic; PCBs; some solvents, pesticides, PBDEs
- Increased susceptibility to adult disease

# Endocrine disruptors

- Multiple mechanisms—mimics, antagonists, alter metabolism, synthesis, receptor levels/activity, etc.
- Estrogenic
- Androgenic/anti-androgenic
- Thyroid hormone disruptors
- Other

# Thyroid disrupting compounds

- PCBs
- PBDEs (flame retardants)
- Perfluorinated compounds (PFOS, etc)
- Perchlorate , nitrate, thiocyanate (inhibit iodine uptake; dietary iodine inadequate in 1/3 of women of reproductive age in the US [CDC])
- Triclosan
- Etc.

Exposures to many of these are ubiquitous; **Why should we think there is a “safe” threshold for any one?**



# Anti-androgens: e.g. several phthalates, pesticides, others

- Phthalates:
  - Large animal testing database
  - Developmental sensitivity
  - Decreased steroidogenesis (testosterone)
  - Decreased fertility/atrophic testes;
  - Undescended testes; other malformations in males.
  - Widespread exposures in humans (NHANES)

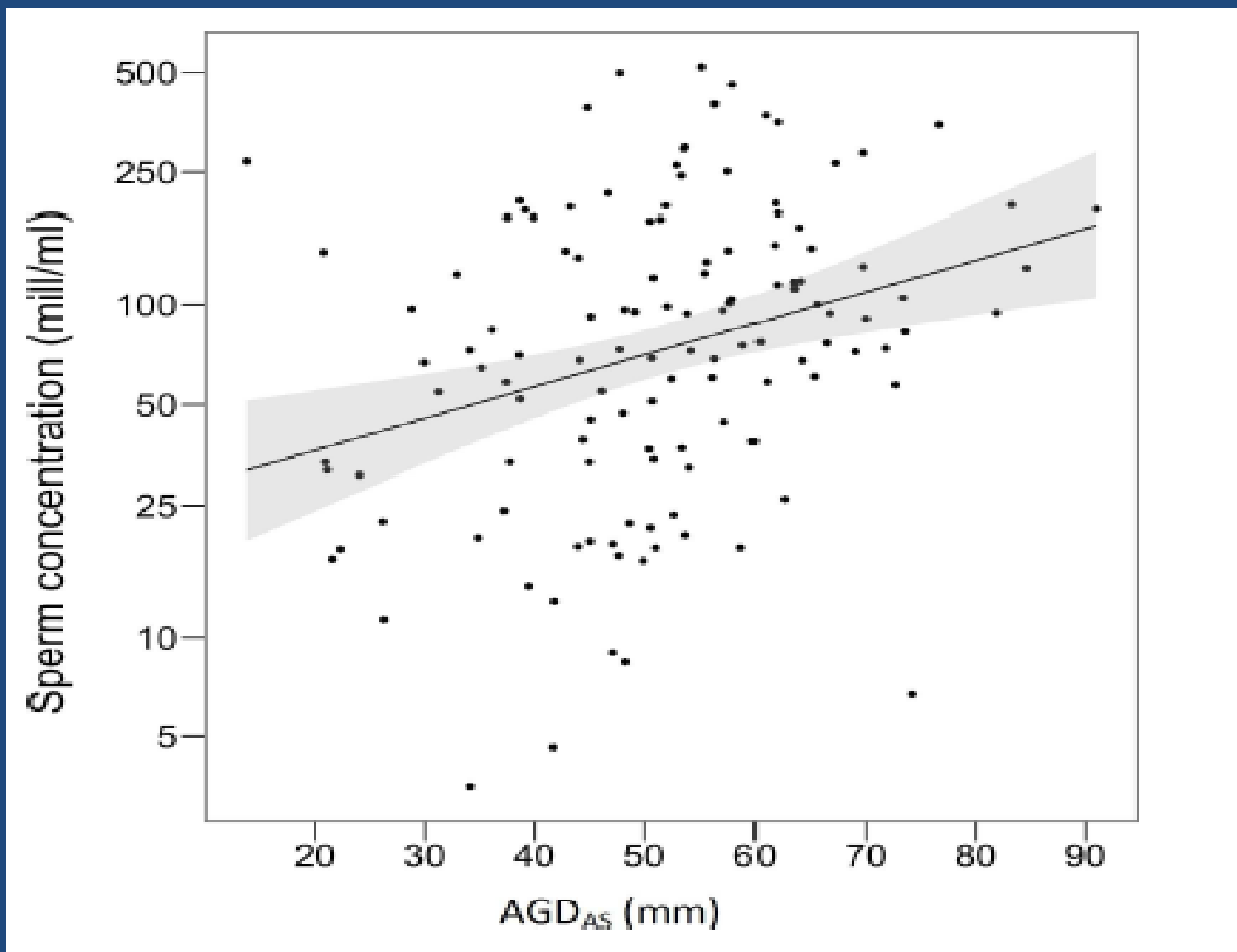
Prenatal maternal urinary phthalate metabolites (N = 85)  
Phthalate monoester metabolite level by **anogenital index category**

monoester	Long Mean; ng/ml	intermediate	short
MBP	13.1	22.2	38.7
MBzP	10.6	15.1	25.8
MEP	124	592	1076
MiBP	2.3	3.3	7.7

Degree of testicular descent and penile volume correlated with AGD

Swan, EHP, 2005

NHANES 2: MBP 50%'ile: 30 ug/L (general population)



Mendiola, EHP, 2011

N=126; 18-22 y.o.

## Pesticides – neurodevelopmental effects (animal studies)

- Unique role of neurotransmitters during brain development
- Organophosphates, pyrethroids, DDT – mice, single low dose on day 10 of life – permanent changes in neuroreceptor levels; hyperactivity as adults; reduced learning

# Organophosphates—human studies

- New York City—urban
- Salinas Valley—agricultural
- Ecuador

## Summary of effects of prenatal chlorpyrifos exposure—New York

- Highest prenatal chlorpyrifos exposure was associated with:
  - 3.5 to 6-point decrease in 36-month development scores (Bayley MDI and PDI)
  - significantly increased risk for diagnosis of ADHD and Pervasive Developmental Disorder
- Effects persist at age 7 (WISC-IV—impaired working memory, full-scale IQ with higher prenatal exposures)

## CHAMACOS birth cohort; agricultural workers; Salinas Valley

- Prenatal organophosphate exposures (as measured by metabolites in maternal urine) associated with:
  - Decreased gestation time and poorer neonatal reflexes
  - Decreased Bayley MDI at 24 mos.
  - Attention problems at age 5

(Eskenazi, EHP, 2007; Marks EHP, 2010)

# Pesticides: Parkinson's disease

- Human studies –
  - 24/31 studies show ↑ risks for PD.  
(OR 1.6-7); positive dose-response where examined (Brown 2006)
- Animal studies -
  - Combinations of maneb and paraquat; prenatal exposure “primes” the brain, increasing adult susceptibility (Cory-Slechta 2005)

This combination recently shown to be associated with increased risk in humans as well. (Costello, 2009)



Case-control; 368 cases; 341 controls

Maneb, paraquat exposures estimated from pesticide use data and GIS land maps; length of residence; controlled for age, smoking, sex, occupational exposures

Age at time  
of dx

Exposure  
within 500  
m of home

Age Group and Exposure	Cases		Controls		Odds Ratio <sup>a</sup>	95% Confidence Interval
	No.	%	No.	%		
<i>1974–1999 Time Window</i>						
≤60 years						
Missing data	2	3	4	5		
No exposure	18	23	34	39	1	Reference
Paraquat or maneb only	38	48	42	48	1.77	0.84, 3.75
Both paraquat and maneb	21	27	7	8	5.07	1.75, 14.71
>60 years						
Missing data	11	4	9	4		
No exposure	97	34	92	36	1	Reference
Paraquat or maneb only	114	39	111	44	0.90	0.60, 1.34
Both paraquat and maneb	67	23	42	17	1.36	0.83, 2.23

Costello, Am J Epid; 2009

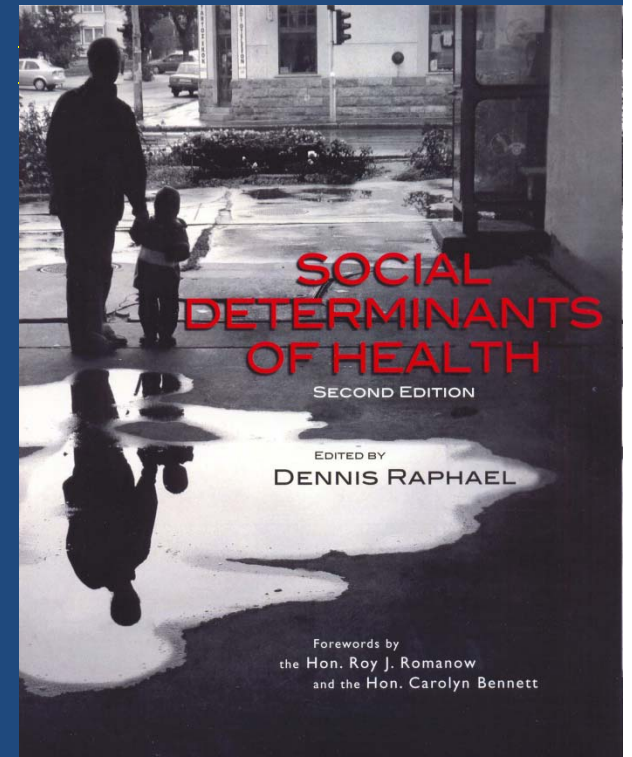
# The challenges inherent in putting it all together

- Aggregate chemical exposures
  - Similar or differing mechanisms of toxicity
  - Dose and timing of exposure
- Cumulative risk of chemical and non-chemical stressors



# Socioeconomic, Psychosocial Stressors

- Lower socioeconomic status → ↑ risk of impaired neurodevelopment, cardiovascular disease, diabetes, obesity, metabolic syndrome, Alzheimer's disease, many kinds of cancer, asthma.
- Due to: Combinations of increased exposures to hazards, increased susceptibility, decreased capacity to cope and recover.
- Elevated levels of inflammatory cytokines, glucocorticoids, sympathetic activity



# Asthma

- Many air pollutants trigger asthma attacks and increase their severity
- Ambient ozone, traffic-related pollution in children increases the incidence of asthma (McConnell, 2002; Clark, 2010)
- Lower SES consistently associated with greater asthma morbidity

In people with asthma, high traffic density increases the risk of frequent asthma symptoms in all people, but more in people who are poor (adjusted for age, sex, race/ethnicity)

Traffic density (VMT per square mile)	Relative risk (95% CI)*			Population attributable risk percentage (95% CI)		
	Below FPL	Above FPL	Total population	Below FPL	Above FPL	Total population
0–20,000	1.00	1.00	1.00			
20,001–200,000	1.28 (0.40–3.12)	1.30 (0.94–1.76)	1.40 (1.04–1.86)	6.3 (–16.7–33.6)	4.7 (–1.0–11.2)	5.2 (–1.6–13.1)
>200,000	<b>2.80</b> (1.04–4.91)	<b>1.38</b> (0.93–1.96)	1.72 (1.23–2.32)	<b>37.4</b> (1.3–56.5)	<b>6.2</b> (–1.2–14.2)	16.5 (6.5–26.5)

Meng, et al, Ann Epid, 2008

# Why should people who are poor have more problems with asthma?

- Greater exposure to asthma triggers—single and cumulative
- Reduced access to health care
- Reduced compliance with medical interventions
- Psychosocial factors

# SES, psychological stress, asthma

n = 76

13 yo +/- 2.8

1/2 with asthma

All symptom-free  
when measured

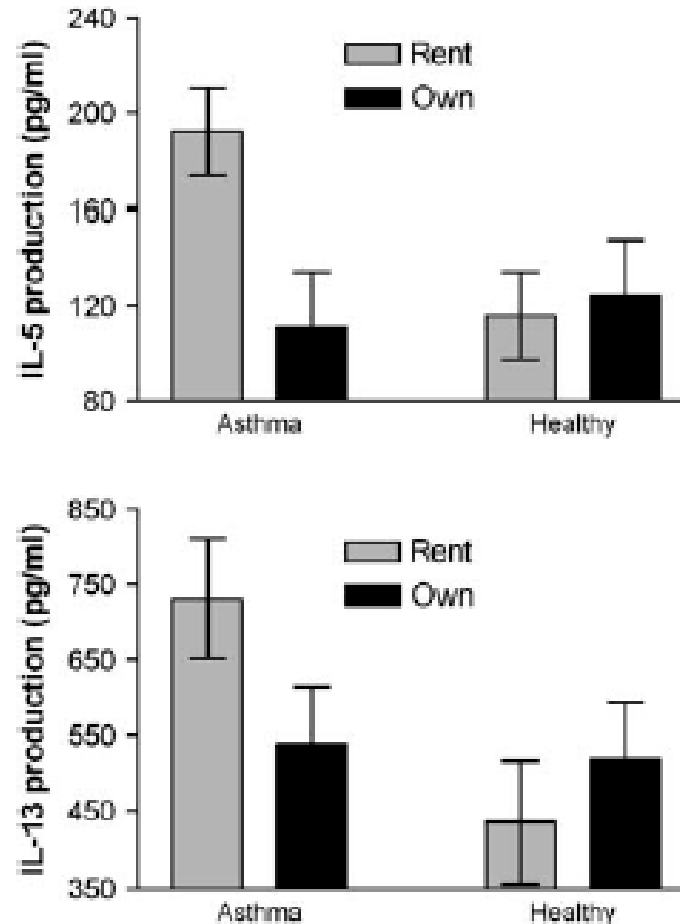
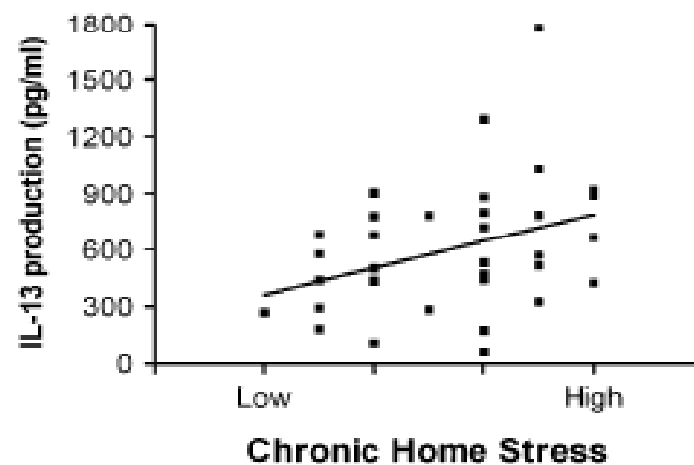
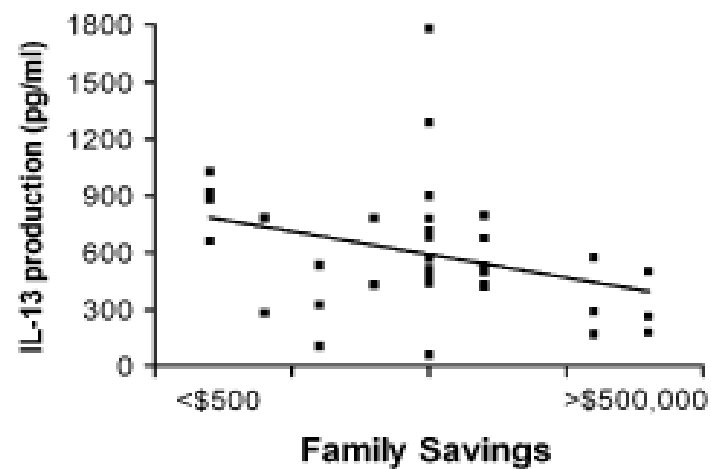


FIG 1. Differences in production of IL-5 and IL-13 for families who rent their homes versus families who own their own home by medical group status.



**FIG 2.** *Top panel*, Association of family savings with production of IL-13 among children with asthma. *Bottom panel*, Association of chronic home stress with production of IL-13 among children with asthma.



# Lead: developmental hazard

- Lead – impaired IQ, learning, attention; hyperactivity, impulsiveness, aggression; failure to complete school, trouble with the law
- In children, exposures and effects are enhanced with iron deficient diet and lower socioeconomic status

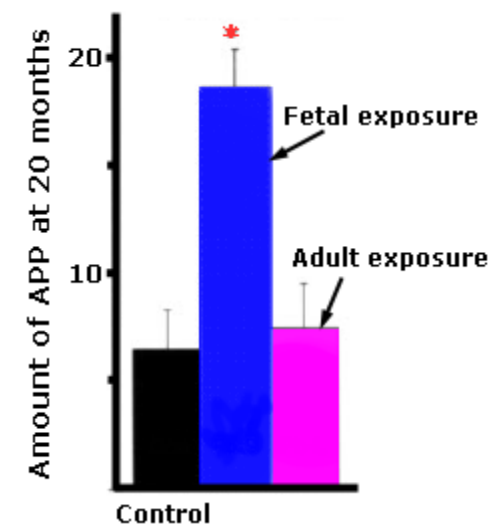
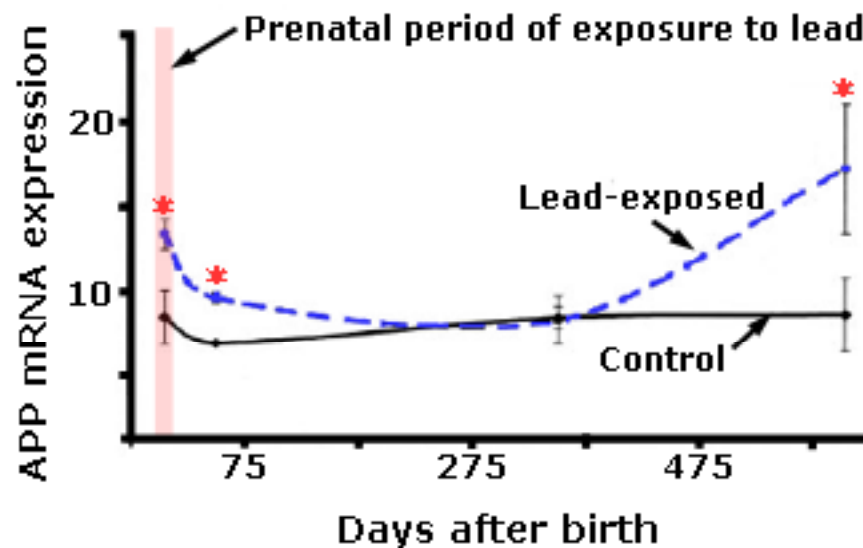
# Lead: impacts in older people

Cumulative community exposure (bone lead)

- ↑cognitive impairment Shih 2006
- Up to 15 years more cognitive aging comparing highest to lowest quartiles Weisskopf 2007
- Larger effect with increased stress and in less cohesive neighborhoods that generate hypervigilance, alarm, perceived threat

# Fetal programming

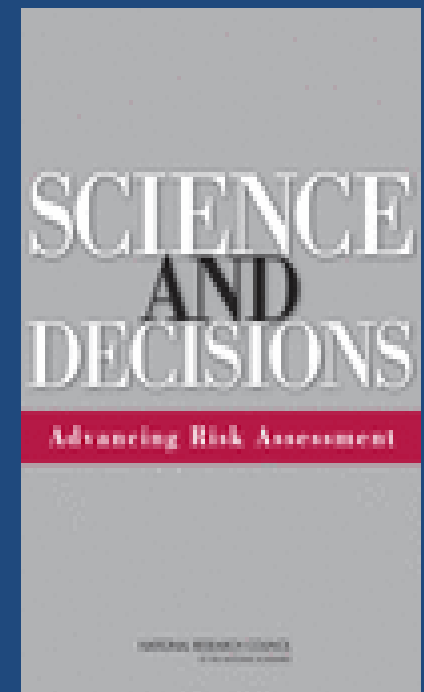
APP gene: amyloid precursor protein



Basha *et al.* 2005

# Science and Decisions: Advancing Risk Assessment—2009

The framework for risk assessment of chemicals should be modified to account for **uncertainty and variability** in responses to exposures attributable to **age, ethnic group, and socioeconomic status**, as well as other attributes that affect individuals and make them a part of a vulnerable group.



# Areas of reform: NAS

- 1) Test more chemicals for toxicity by developing and using rapid testing methods that can reliably predict which chemicals are likely to be toxic and which are not. (“Tox 21”)
- 2) Identify and incorporate variability in human exposure and vulnerability into health assessments, so that all people are better protected.
- 3) In assessing the risk of chemicals, incorporate information about the potential impacts of exposure to multiple chemicals. In addition, consider other factors, such as exposure to biological and radiological agents and social conditions.

## Areas of reform: NAS

- 4) For chemicals with toxic effects, presume that all exposures - even low ones - are associated with some level of risk, unless there are sufficient data to reject this assumption.
- This recommendation is based on:
  - Uncertainties about shape of dose-response curve
  - Co-exposures
  - Co-exposures plus susceptibility

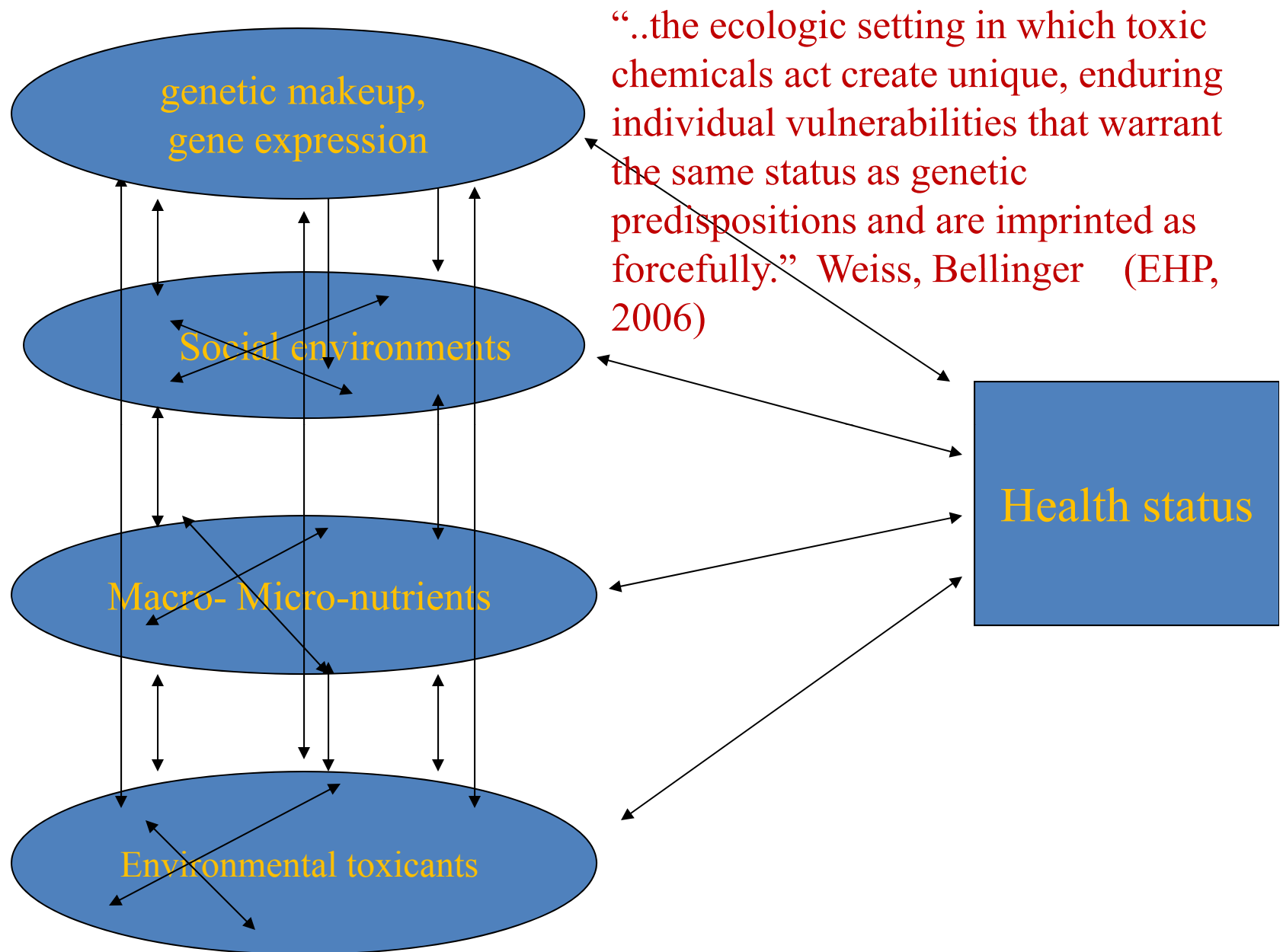
## Areas of reform: NAS

- 5) When information is missing or unreliable, use scientifically-based default assumptions that will protect health to improve the timeliness of the chemical assessment and decision-making process, and set clear scientifically-based criteria for when to depart from these assumptions.

# Science and Decisions

- Although the recommended framework has at its core the risk-assessment paradigm, the committee recommends identification of options to reduce identified hazards or exposures **at the earliest stages of decision-making** and using risk assessment to evaluate the merits of the various options





Modified from: Hubbs-Tait et al. Psychological science in the public interest

# Resources

- Critical Windows of Development ([www.endocrinedisruption.com](http://www.endocrinedisruption.com)): Online tool from The Endocrine Disruption Exchange (TEDX)
- TOXNET (<http://toxnet.nlm.nih.gov/>): Databases on toxicology, hazardous chemicals, environmental health, and toxic releases
- Collaborative on Health and Environment (CHE) database (<http://database.healthandenvironment.org/>)