Chemical Exposures: the Ignored Environmental Risk Factor(s) for Neurodegenerative Diseases and Neurodevelopmental Disorders

D. A. Cory-Slechta
Department of Environmental Medicine
University of Rochester Medical Center

Toxic Substances Control Act: 86,405 chemicals, 41,587 are currently active

Some Classes of Chemicals

- Disinfection byproducts
- Personal Care and Consumer Product Chemicals and Metabolites
- Flame Retardant Metabolites
- Fungicides and Metabolites
- Herbicides and Metabolites
- Sulfonyl Urea Herbicides
- Insect Repellent and Metabolites
- Carbamate Pesticides and Metabolites
- Organochlorine Pesticide Metabolites
- Organophosphorus Insecticides
- Pyrethroids and Metabolites
- Metals and Metalloids
- Perchlorate and Other Anions
- Perfluoroalkyl and Polyfluoroalkyl Substances
- Phthalate and Phthalate Alternative Metabolites
- Phytoestrogens and Metabolites
- Polycyclic Aromatic Hydrocarbon Metabolites
- Heterocyclic Amines
- Volatile Organic Compounds and Metabolites
- Polybrominated Diphenyl Esters
- Polychlorinated Dibenzo-p-Dioxins
- Polychlorinated Dibenzofurans
- Dioxin-like PCBs

Why Are Environmental Chemical Exposures Ignored?

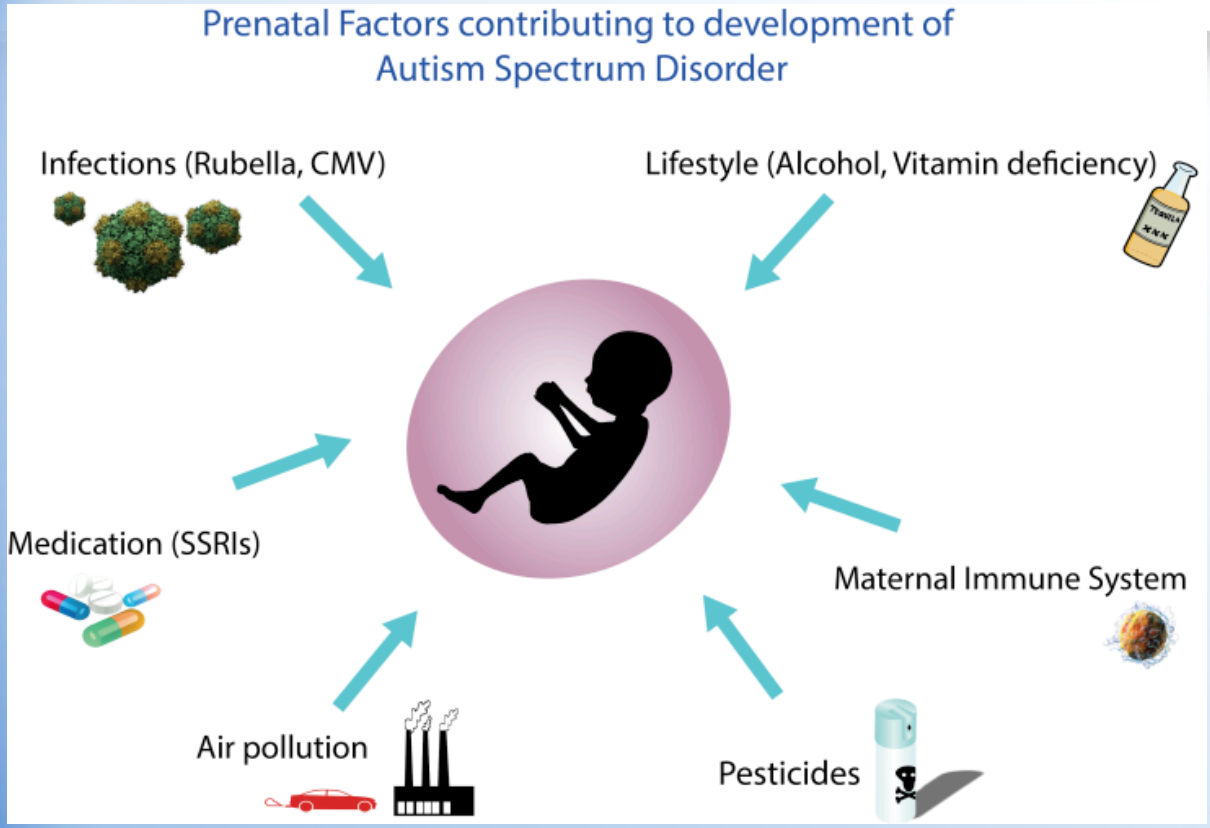
- *They can't be important as genes…*
- Exposures are very low, so nothing to be concerned about
- Effect sizes are small
- EPA is protecting us
- So many chemicals, where would you start?

The Over-Promise of Genetics

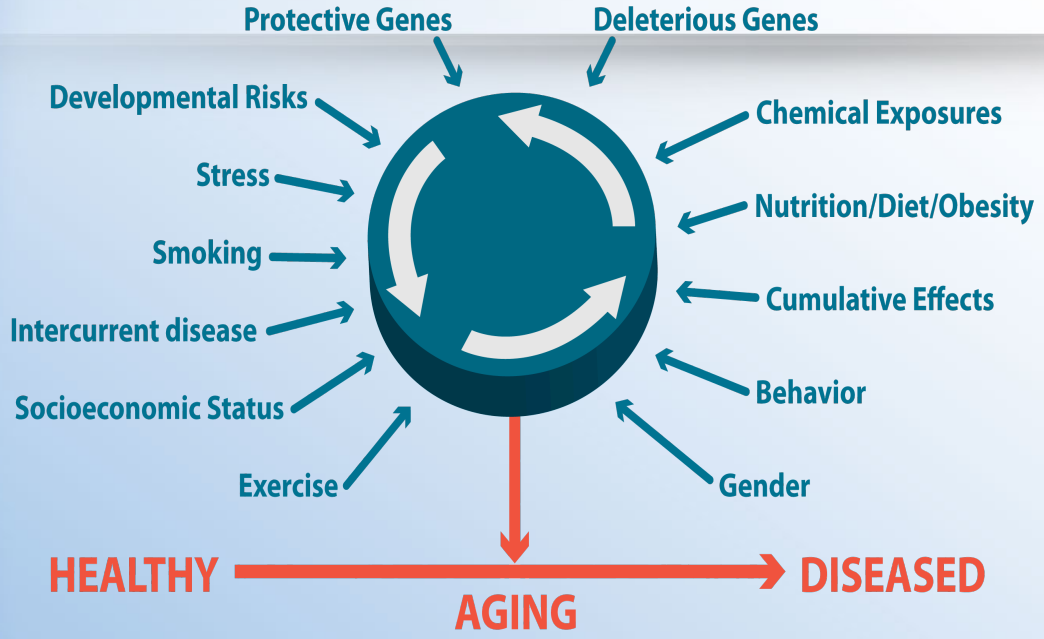
- “In the 1990s, prominent biologists and journalists predicted that by 2020 each of us would carry a genome card, which would allow physicians to access our entire genome sequence and routinely use this information to diagnose and treat common and debilitating conditions. This is not yet the case. Why not? Common and debilitating diseases are rarely caused by single-gene mutations, and this was recognized before these genome card predictions had been made. ***Debilitating conditions, including common psychiatric disorders, are typically caused either by rare mutations or by complex interactions of many genes, each having a small effect, and epigenetic, environmental, and microbial factors.*** In such cases, having a complete genome sequence may have limited utility in diagnosis and treatment. Genome sequencing technologies have transformed biological research in many ways, but had a much smaller effect than expected on treatments of common diseases.”

A. Berkowitz, Journal of Neurogenetics, 34:189-197, 2020

Most Human Diseases and Disorders Arise From Interactions of Multiple Risk Factors Across Time: Before Birth



Human Diseases and Disorders Arise From Interactions of Multiple Risk Factors Across Time: After Birth



While many environmental risk factors are increasingly recognized in neurodevelopmental disorders and neurodegenerative disease, environmental chemical exposures are typically not appreciated

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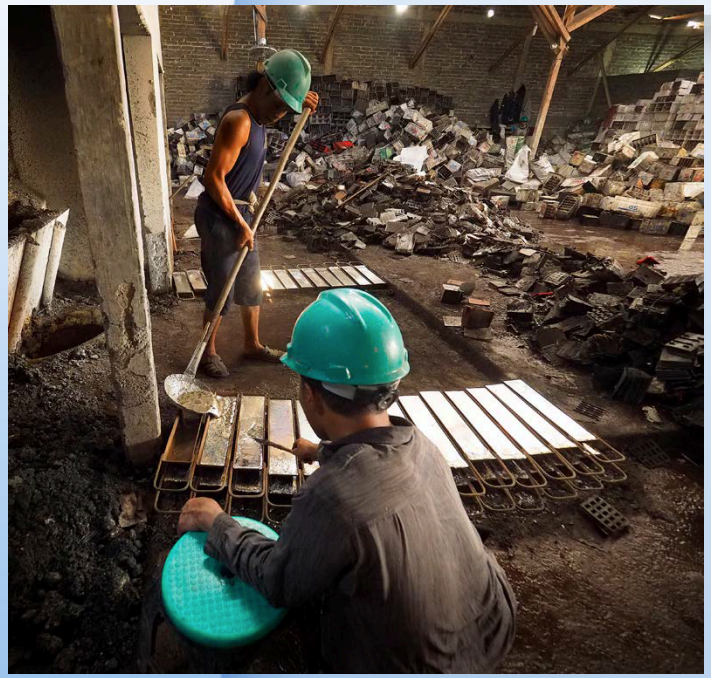
Exposure to Lead: the Poster Child

- **2000 BC Dioscerides "Lead makes the mind give way."**
- **1854 - Tetraethyl lead discovered by German chemist**
- ***1887 - US medical authorities diagnose childhood lead poisoning***
- **1921 - Midgley discovers that tetraethyl lead curbs engine knock**
- **1922 - Public Health Service warns of dangers of lead production, leaded fuel**
- **1923 - Leaded gasoline goes on sale in selected markets**
- **1936 - 90 percent of gasoline sold in US contains Ethyl**
- ***1971- Lead-Based Paint Poisoning Prevention Act passed***

In the 1950s, a few clinicians in children's hospitals and health departments in several eastern cities became concerned with the cases of childhood lead poisoning that they saw and treated. Their interest resulted in expanded case finding and in research based on case summaries of the long-term neurological sequelae of exposure to lead.

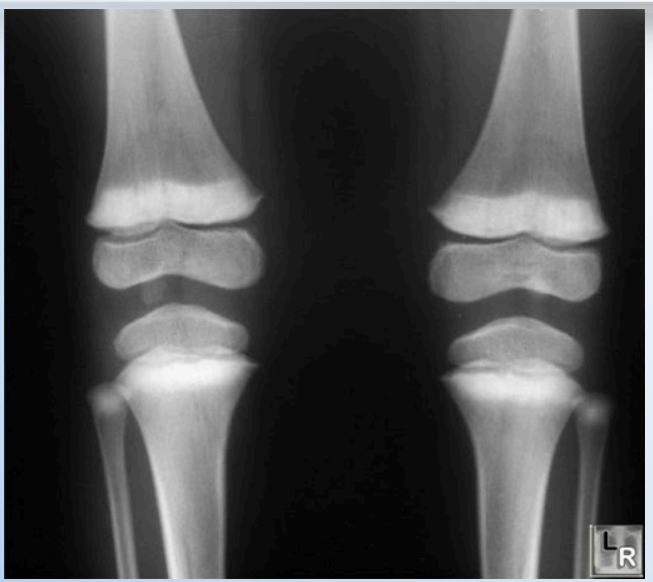
And it Continues….



Nigeria gold rush sees 200 children killed in outbreak of lead poisoning

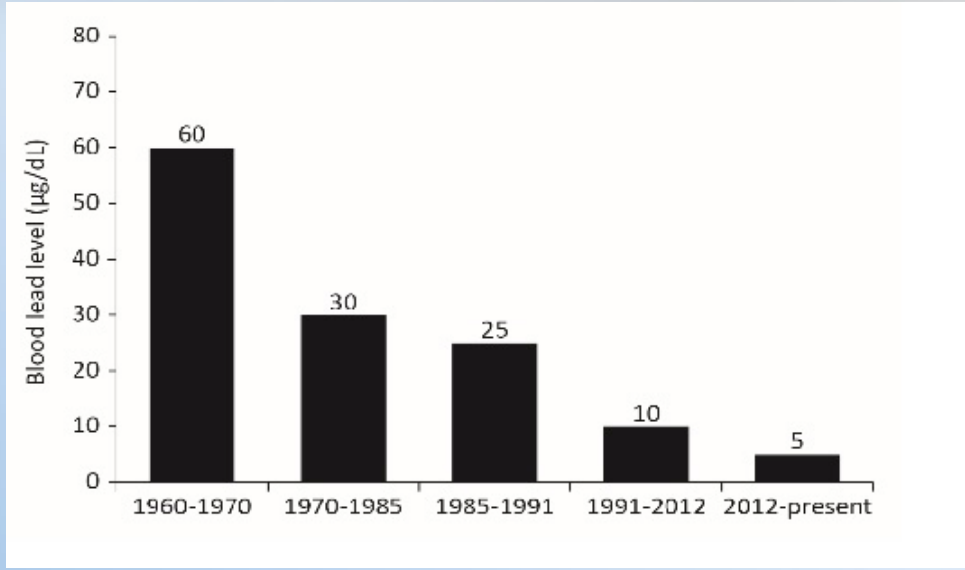
Xan Rice and Guardian East Africa correspondent | 23rd September 2010

Brain is the Target Organ, While Bone Accumulates Pb



Bone Pb has a half-life of decades; during conditions such as pregnancy and breastfeeding, when calcium requirements are very high (e.g., pregnancy and lactation), Pb moves out of bone and back into the blood stream, thus setting up a fetal exposure route

The Decline in Levels of Blood Pb Considered Safe by CDC



2012 – CDC states that no safe level of lead exposure in children can be identified; 5 ug/dl is listed as the reference level for intervention

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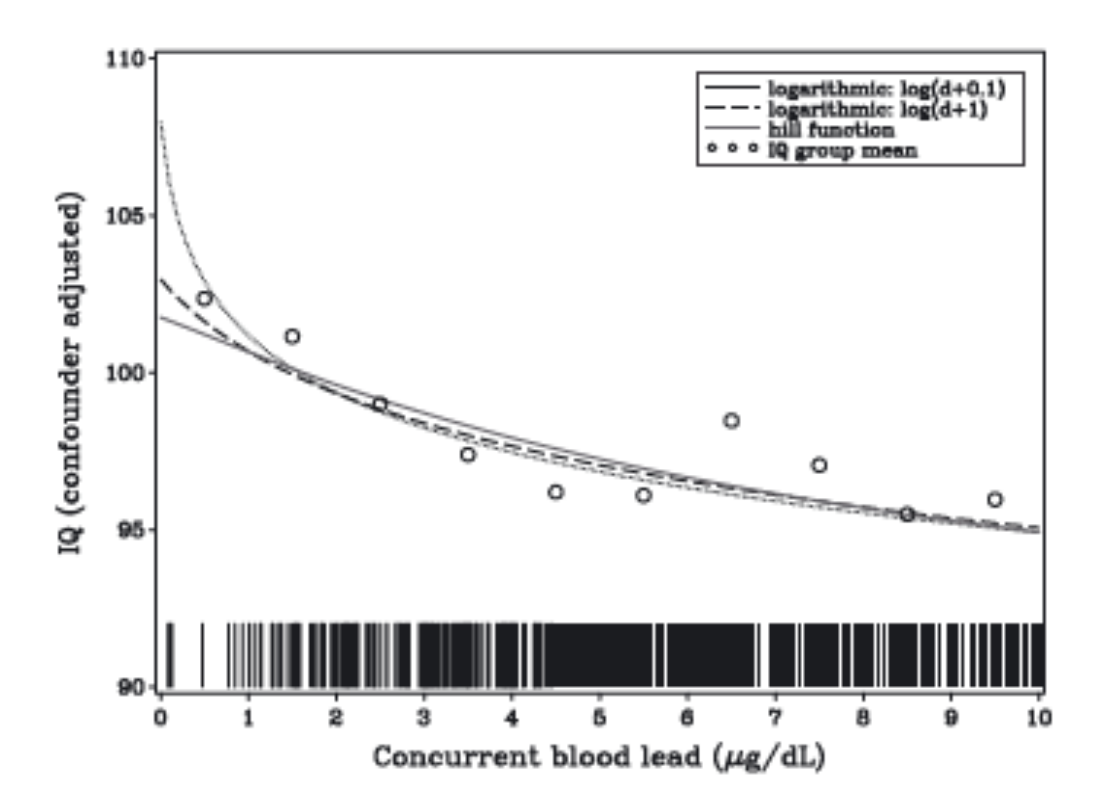
Low Level Lead Exposure and IQ Loss



Budtz-Jorgensen et al., 2012

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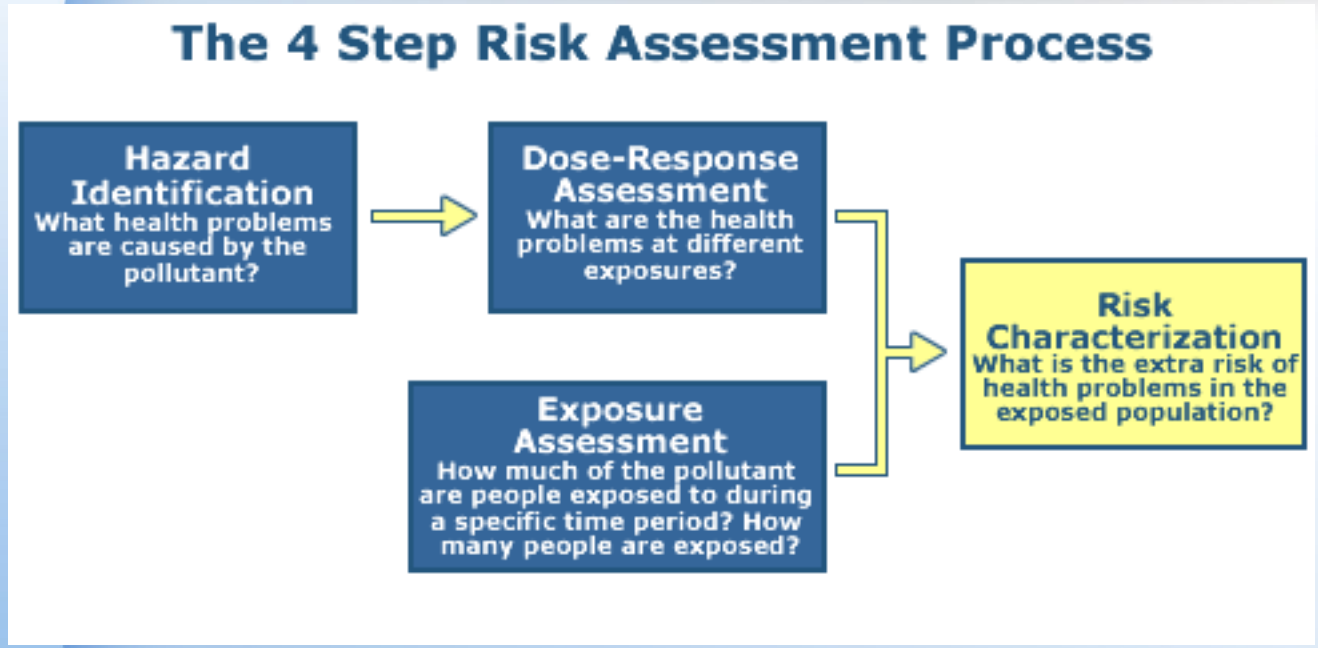
The EPA Risk Assessment Paradigm



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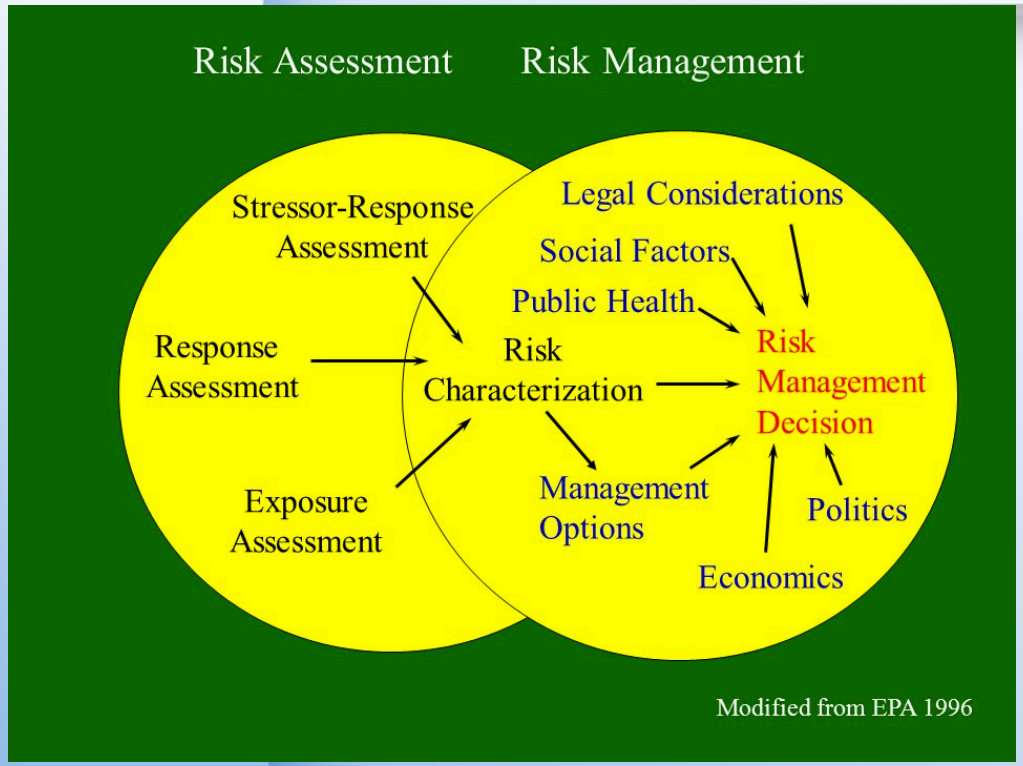
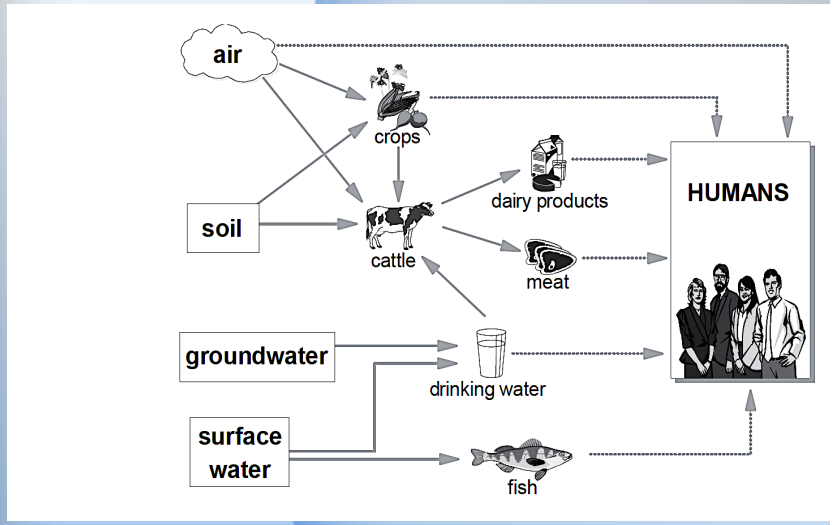
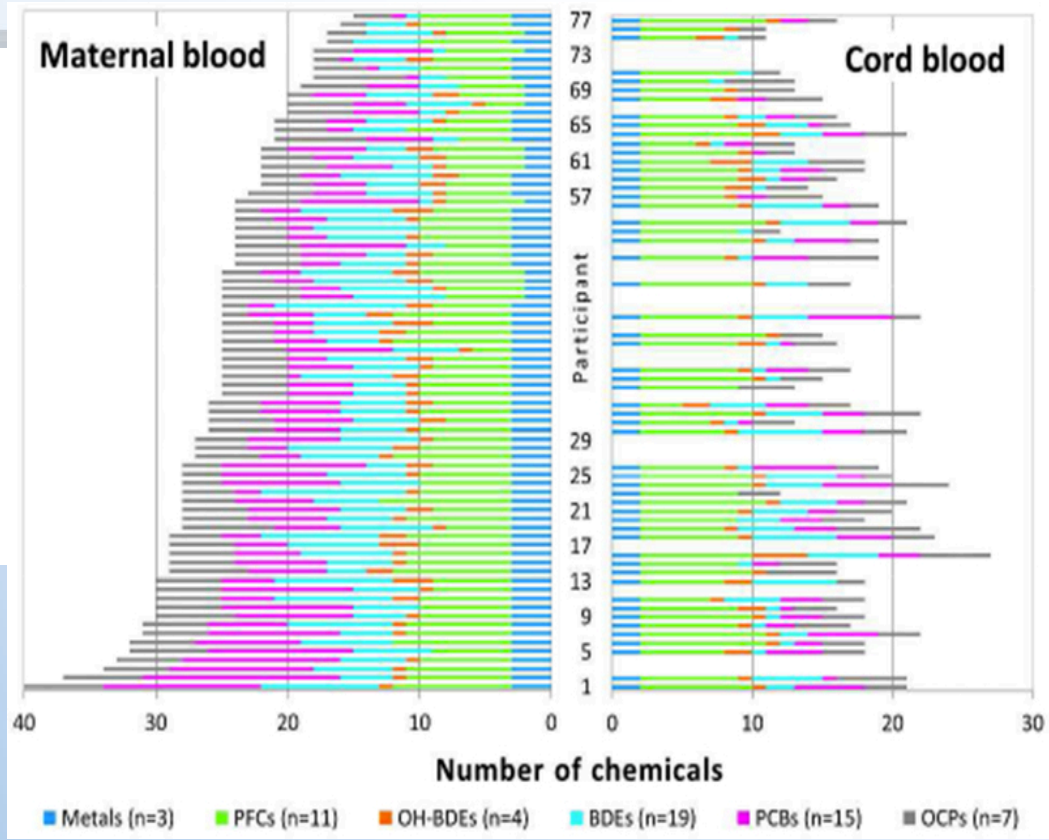


- Risk Management is risk characterization *modified with respect to economic and political considerations*
- Risk assessment is performed one chemical at a time

But Humans are Exposed to Multiple Chemicals





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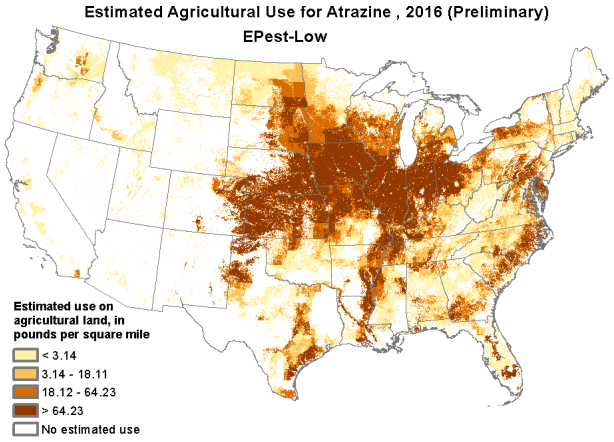
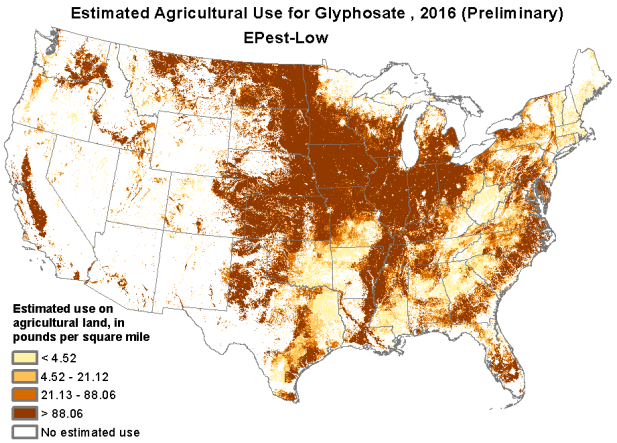
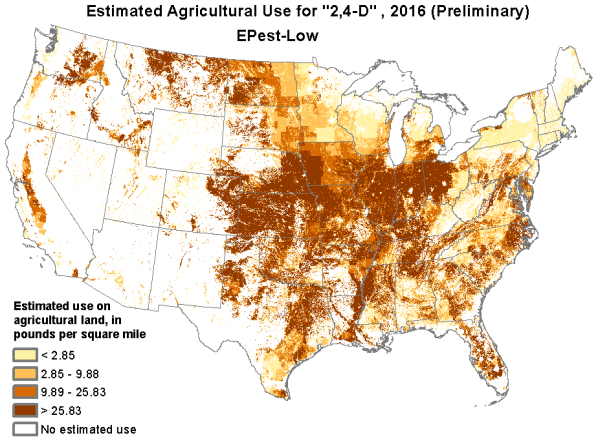
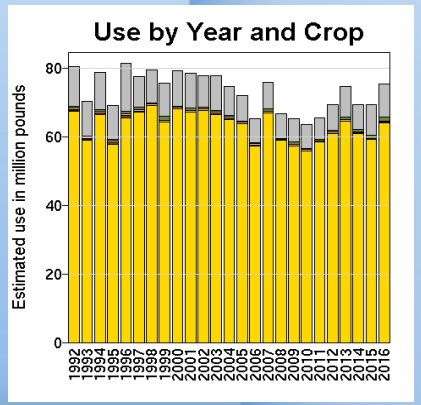
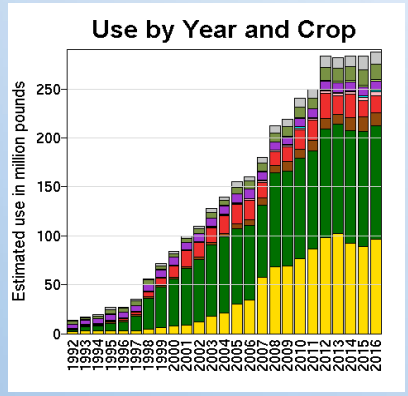
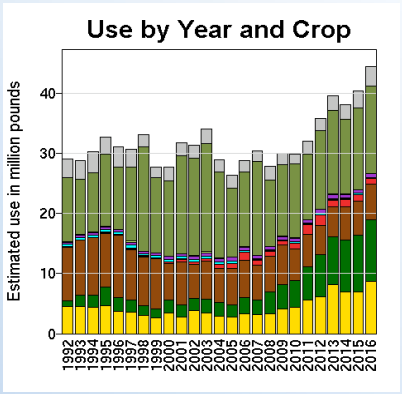






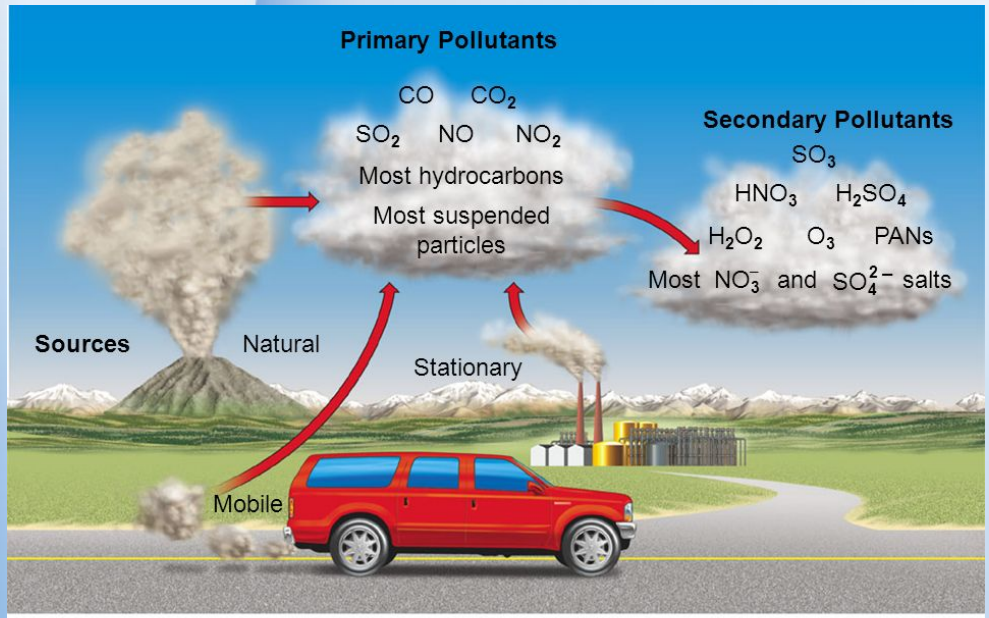




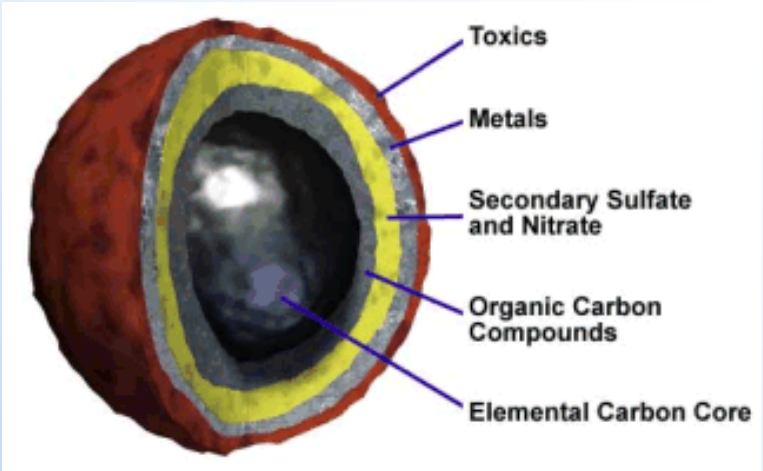


Air Pollution: A Mixture of Particles, Gases, and Adsorbed Elements/Metals and Organics

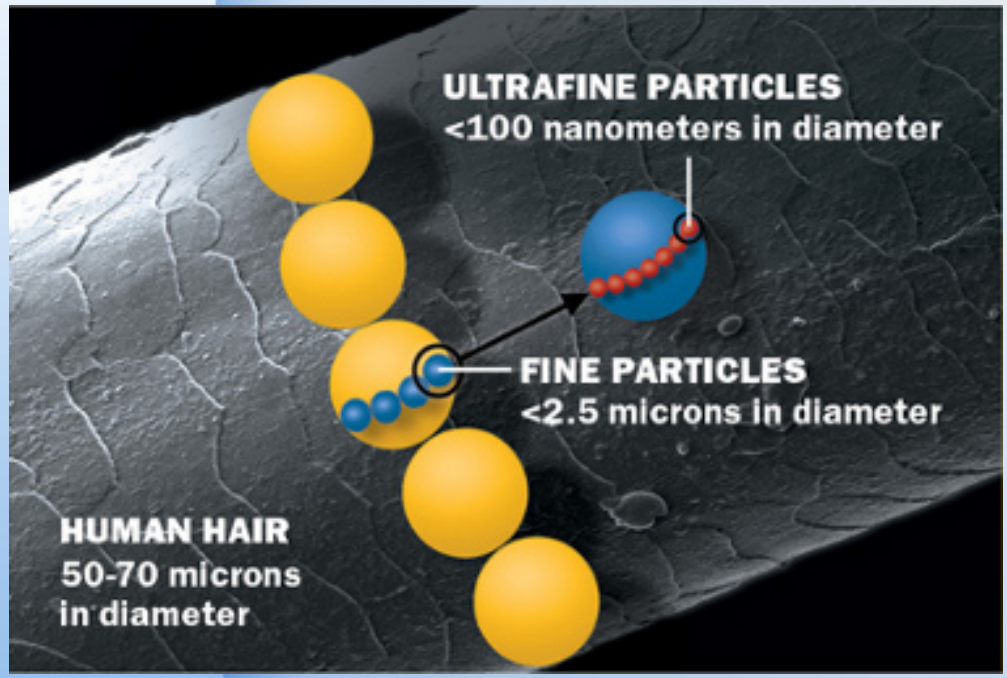
Primary source is traffic-generated



Primary vs. Secondary



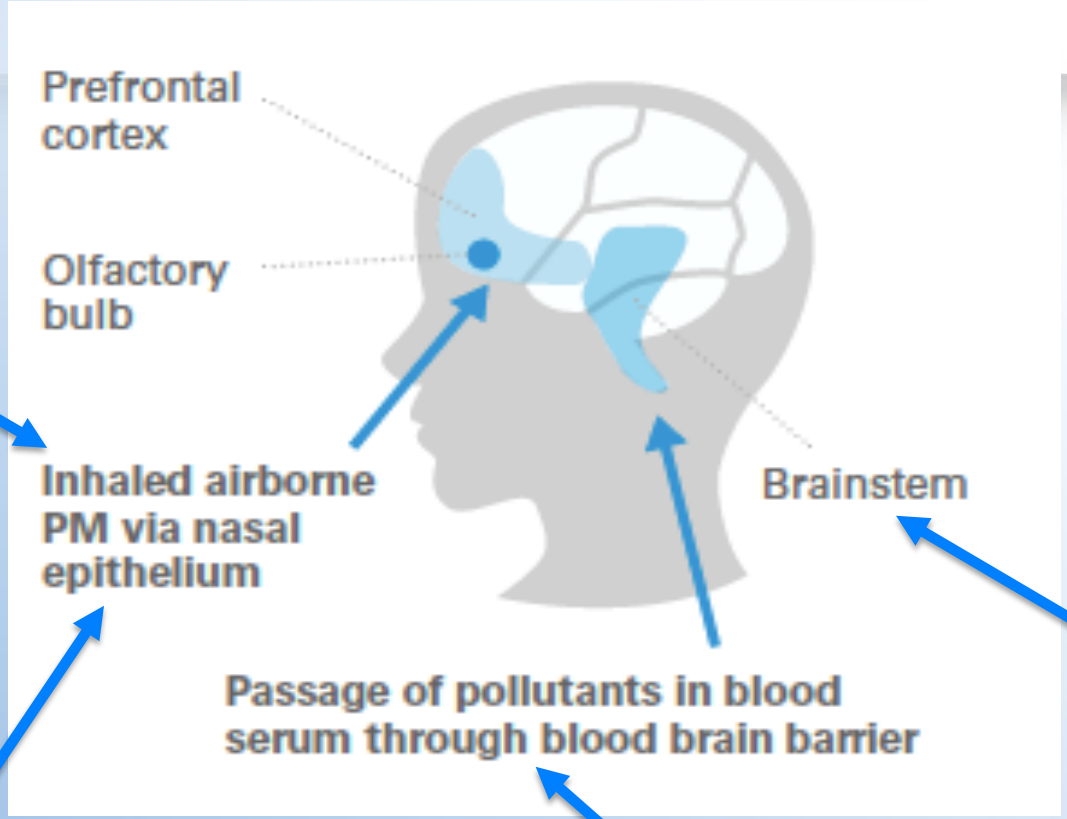
Ultrafine Particles (UFPs): Air Pollution's Most Reactive Component



U.S. EPA regulates fine ($PM_{2.5}$, ≤ 2.5 um) and coarse (PM_{10}, ≤ 10 um) particles, but not UFPs

Routes of Particle Entry into Brain After Birth

Contaminants on UFPs are taken up into brain, *bypassing the blood brain barrier and thus not reflected in serum markers*

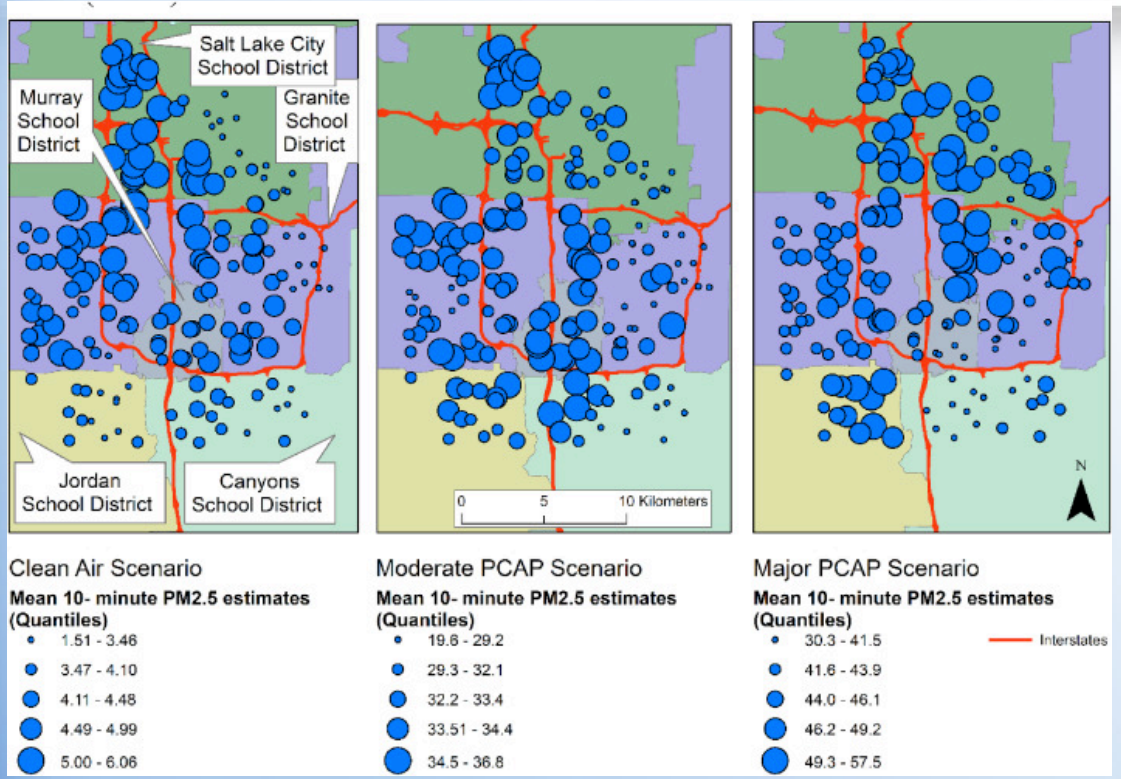


Including via vagal nerve

Via olfactory and trigeminal nerves

Particle solubility releases contaminants

And Such Exposures are Inversely Related to Race and Socioeconomic Status



Mullen et al., 2020

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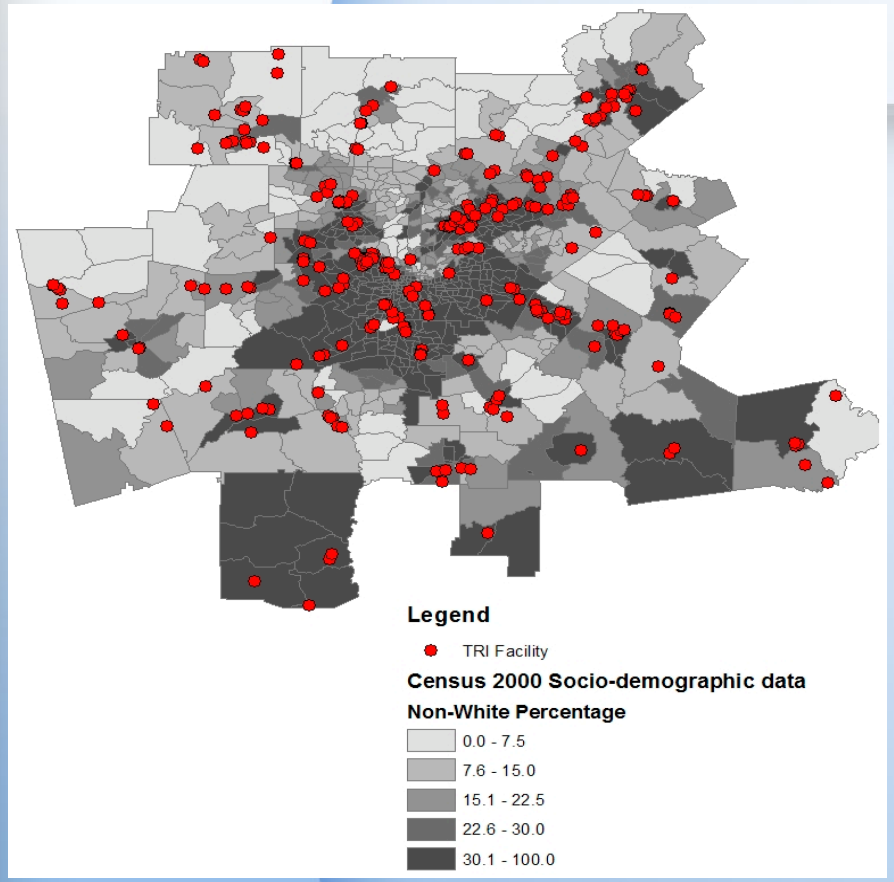
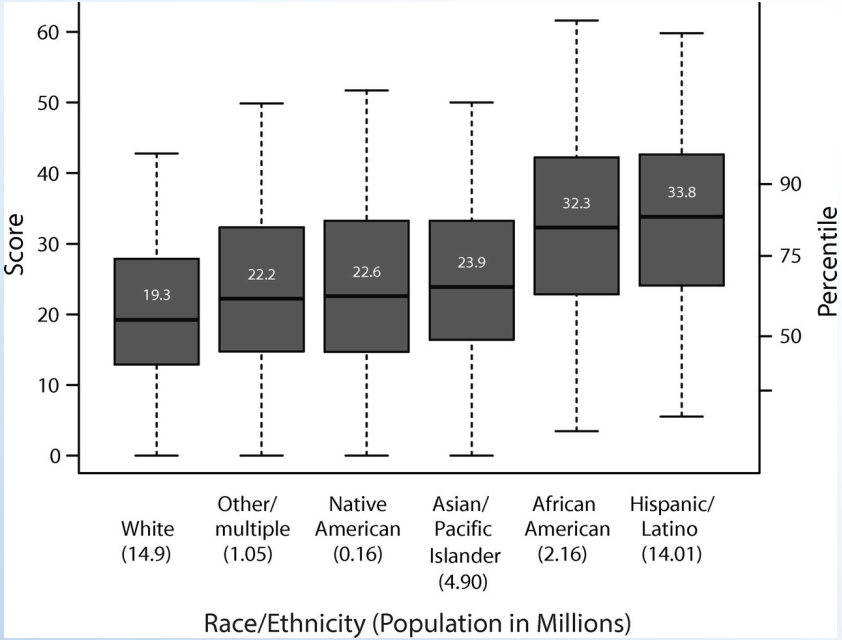


Johnson et al., 2016

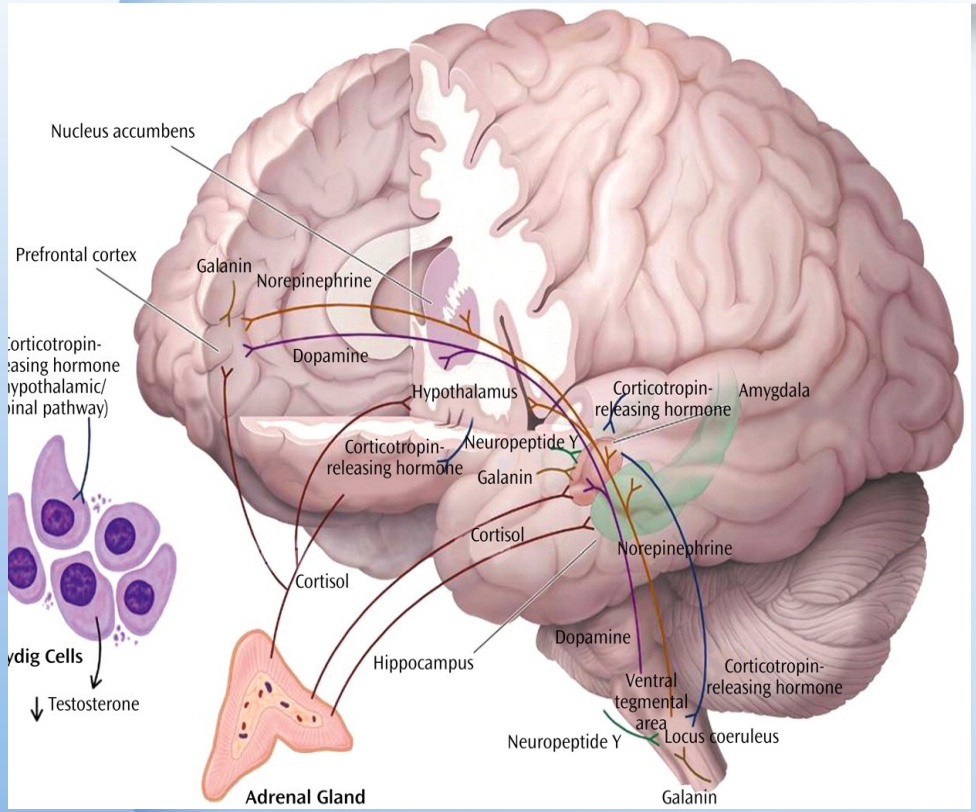


Cushing et al., 2015

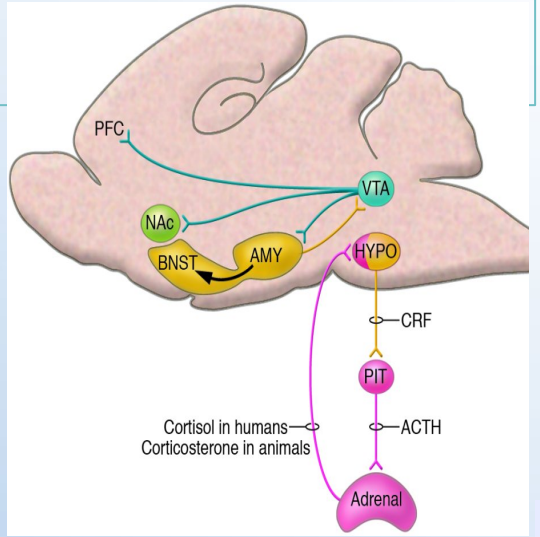
Consideration of Multiplicity of Exposures is Particularly Important as it Establishes a Framework for Interaction Effects

- Lead exposure occurs in the context of:
  - stress of poverty, violence, neighborhood crime
  - poor education
  - resource deprivation
  - inadequate prenatal care

Both Pb and Prenatal Stress Affect the Same Biological Targets: HPA Axis and CNS Mesocorticolimbic System



- HPA axis and brain mesocorticolimbic systems interact to mediate behavioral functions, including cognition and aspects of attention deficit disorder
- ***Many CNS effects of Pb can be enhanced by prenatal stress***

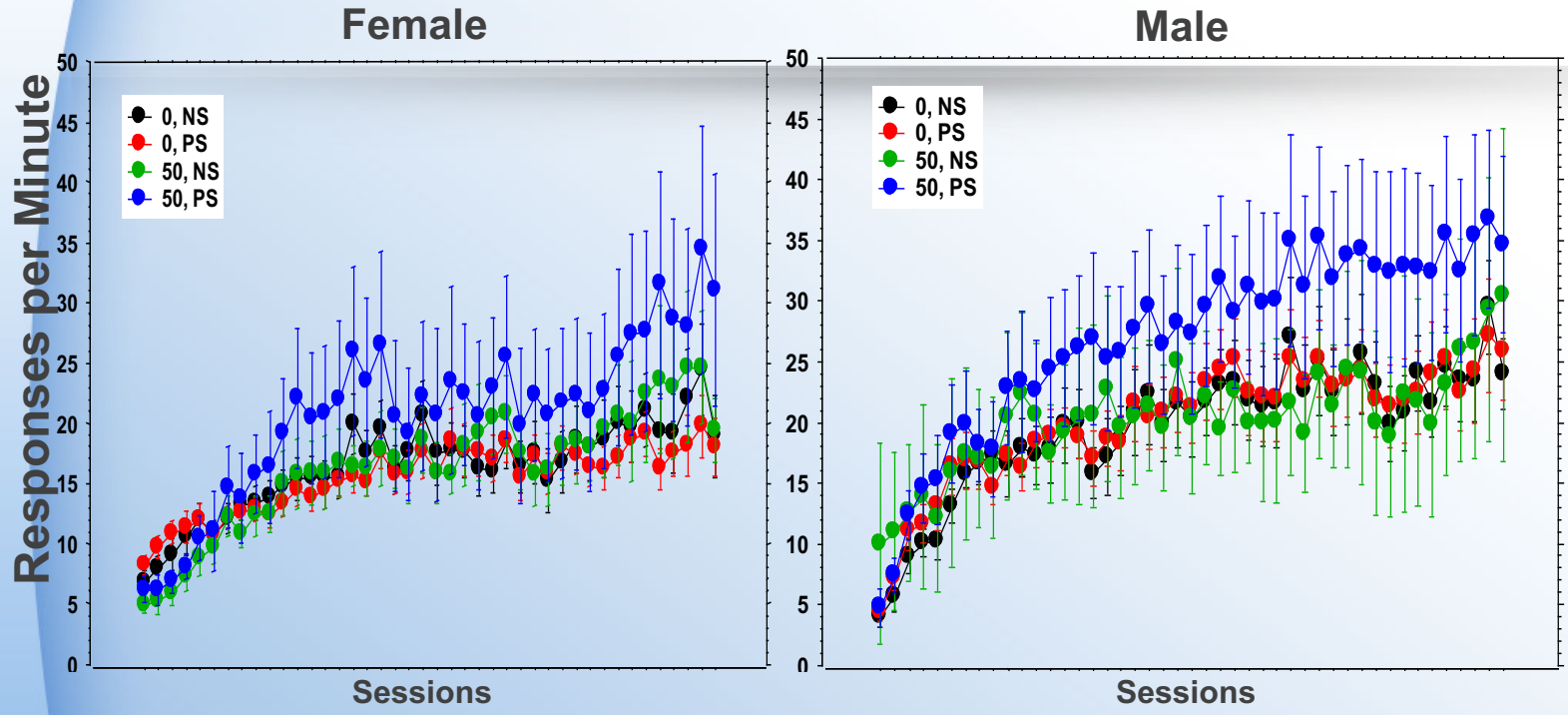


Animal Models Do Not Tend to Be Realistic Simulations of Human Environmental Conditions

← Chemical Exposure

Study of Chemical Exposures as Risk Factors in Isolation May Therefore Underestimate Toxicity

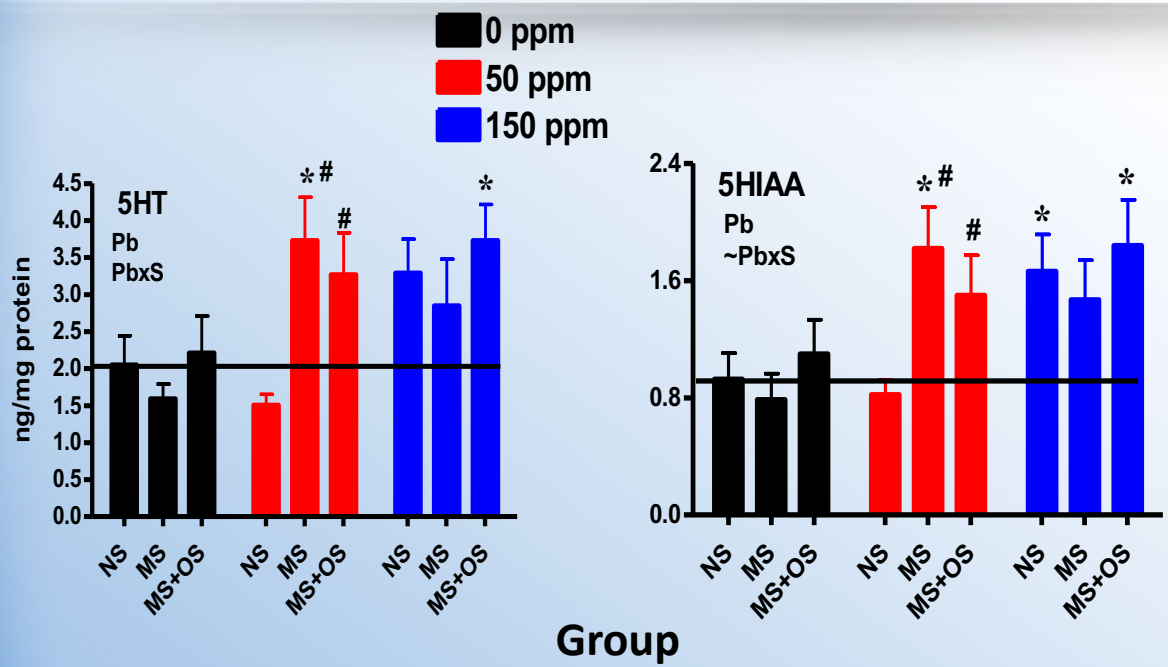
Lifetime Pb and Stress in Mouse Models



Lifetime Pb and prenatal stress synergistically increase FI response rates in males, with similar, but non-significant trends in females

Cory-Slechta et al., 2012

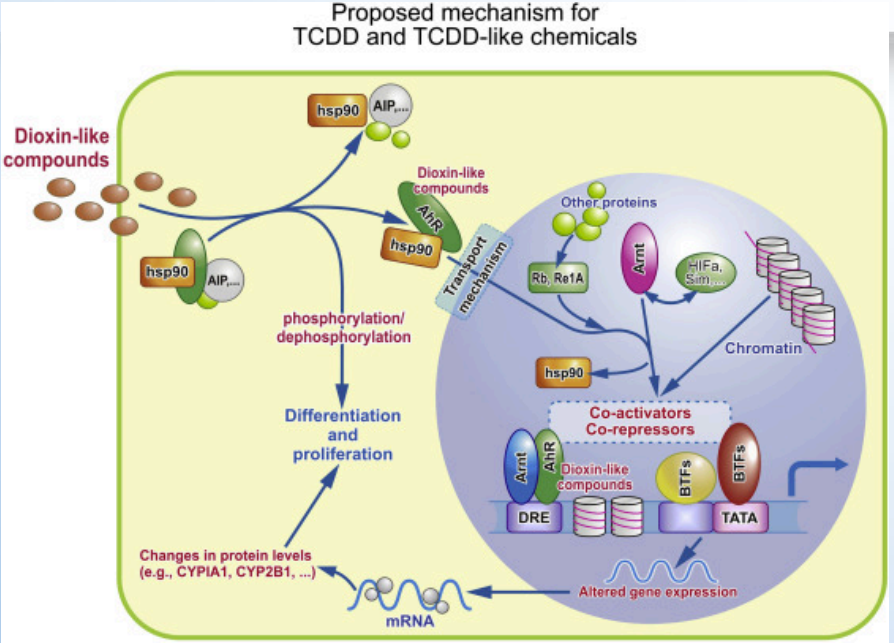
Enhanced Effects of Pb and Stress on Brain Neurotransmitters: Frontal Cortex Serotonin in Females



NS=No stress; MS=maternal stress;
MS+OS= maternal and offspring stress

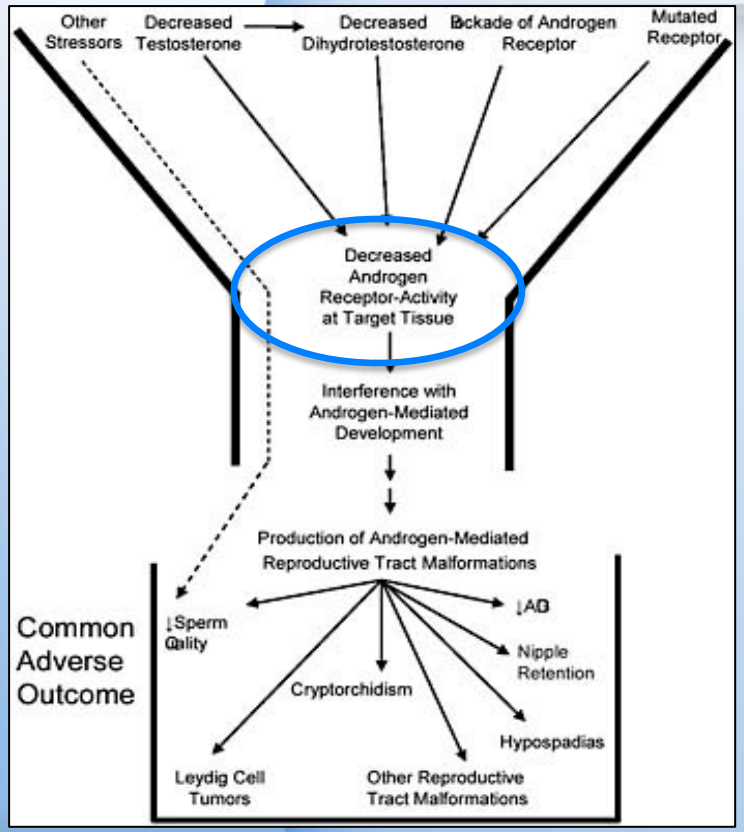
Virgolini et al.. 2008

And Chemicals Can Interact with Each Other

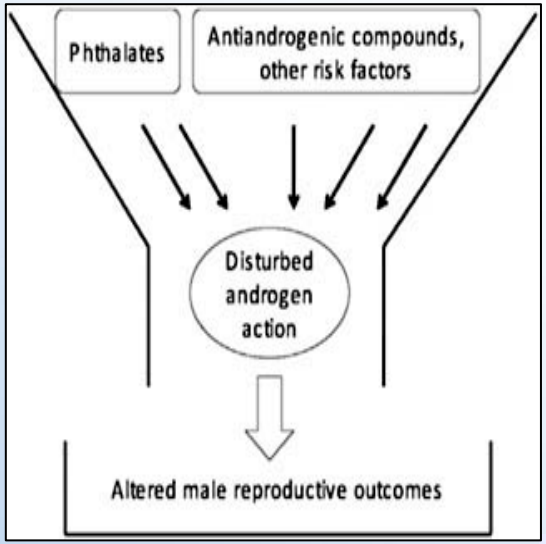


For example: Chemicals that share the same mechanism of action;
However, this is a small fraction of the possible interactions

More Likely Scenarios: Interactions of Chemicals That Act on the Same System



Any chemical that can produce androgen insufficiency or block androgen receptor signaling in the developing male fetus would induce risk for male reproductive tract malformations



Resulting in Dose-Additive Effects

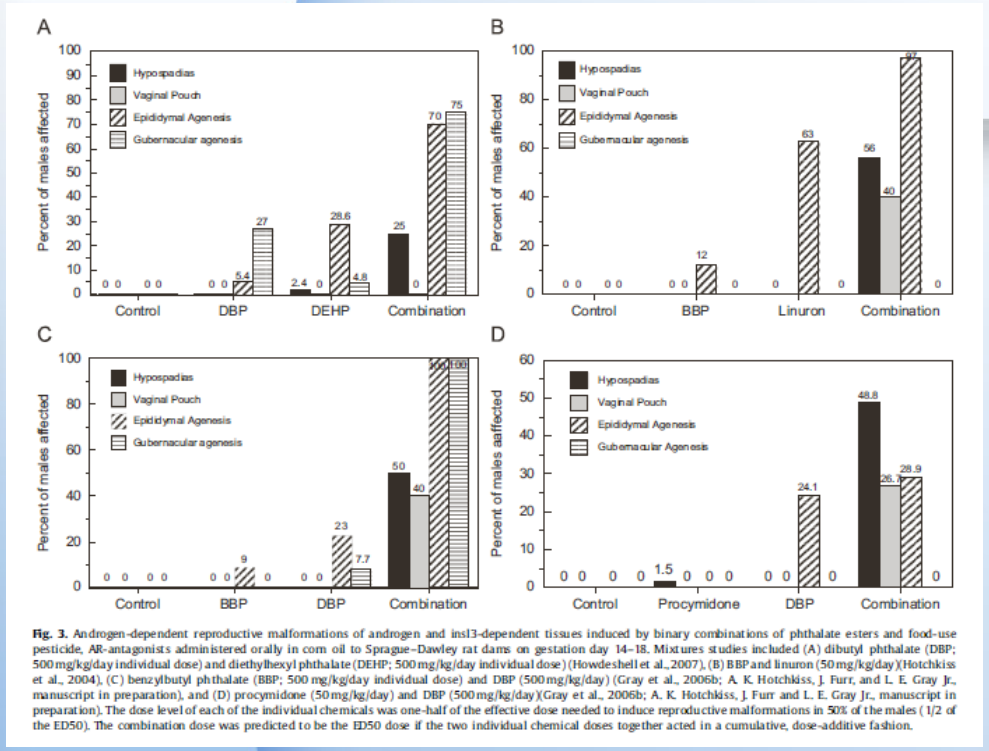
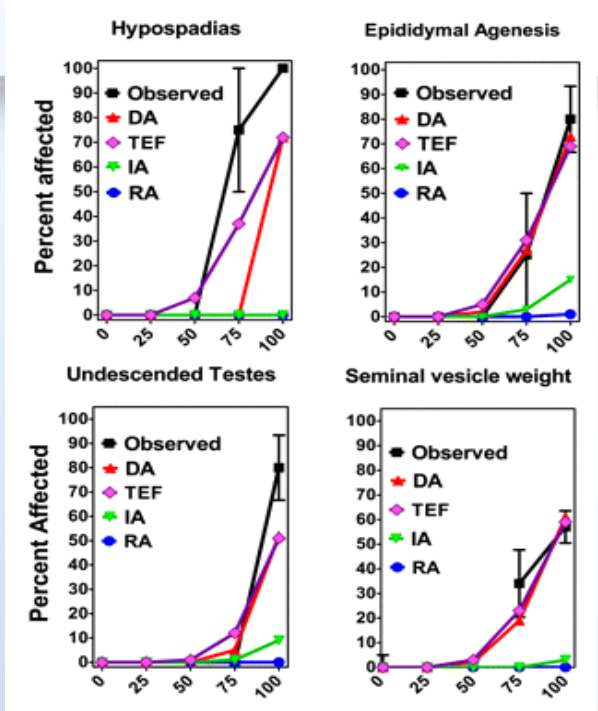


Fig. 3. Androgen-dependent reproductive malformations of androgen and ins13-dependent tissues induced by binary combinations of phthalate esters and food-use pesticide, AR-antagonists administered orally in corn oil to Sprague–Dawley rat dams on gestation day 14–18. Mixtures studies included (A) dibutyl phthalate (DBP; 500 mg/kg/day individual dose) and diethylhexyl phthalate (DEHP; 500 mg/kg/day individual dose) (Howdeshell et al., 2007), (B) BBP and linuron (50 mg/kg/day)(Hotchkiss et al., 2004), (C) benzylbutyl phthalate (BBP; 500 mg/kg/day individual dose) and DBP (500 mg/kg/day) (Gray et al., 2006b; A. K. Hotchkiss, J. Furr, and L. E. Gray Jr., manuscript in preparation), and (D) procymidone (50 mg/kg/day) and DBP (500 mg/kg/day)(Gray et al., 2006b; A. K. Hotchkiss, J. Furr and L. E. Gray Jr., manuscript in preparation). The dose level of each of the individual chemicals was one-half of the effective dose needed to induce reproductive malformations in 50% of the males (1/2 of the ED50). The combination dose was predicted to be the ED50 dose if the two individual chemical doses together acted in a cumulative, dose-additive fashion.

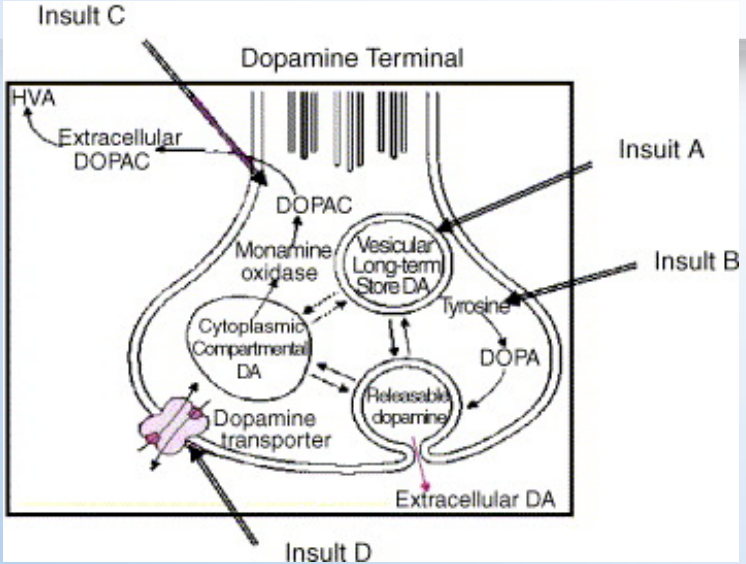
Howdeshell et al., 2009



Rider et al., 2009

Mixtures of phthalate esters with one another and with other anti-androgenic compounds exhibit cumulative, largely dose-additive effects on male reproductive tract development when administered during sexual differentiation.

Multiple Hit Hypotheses



Schematic depicting the multiple-hit hypothesis as applied to a dopamine terminal. Four concurrent insults are depicted that occur at different target sites of the dopamine terminal: insult A affecting the vesicular transporter; insult B affecting the metabolism of tyrosine to DOPA; insult C breakdown of DOPAC and insult D affecting the DA transporter. The brain may readily be able to compensate for the effects of an individual chemical itself acting on a particular target system of the brain. However, when multiple target or functional sites within that particular system are attacked by different mechanisms, the system may no longer be able to homeostatically re-regulate itself, thereby leading to sustained or cumulative damage.

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- They can't be important as genes…
- Not high enough exposures so nothing to be concerned about
- Effect sizes are small
- EPA is protecting us
- *So many chemicals, where would you start?*

An Algorithm for Cumulative Risk Assessment

- Start with a disease or disorder
- Find chemicals which are known individually to influence the chosen disease or disorder
- Those would have different mechanisms that assumedly converge, perhaps downstream, within the same physiological system
- Economic costs of addressing risk from these chemicals could also be calculated for cost-benefit analysis