

Toxic Threats of Environmental Chemicals and Brain Development

Mark Miller MD, MPH
 Director Pediatric Environmental Health Specialty Unit
 University of California San Francisco*

Assistant Clinical Professor Pediatrics UCSF
 Office of Environmental Health Hazard Assessment, Cal EPA
 (Comments do not represent state of California)

*Funded by US EPA and Agency for Toxic Substances Disease Registry through AEOC



I am going to tell you about an overwhelming amount of material you have never heard of

I am not going to tell you about anything you don't already know

Unique Susceptibilities of Children

- Exploratory behavior
- Crawling
- Hand to mouth activity
- Restricted diet
- Teens – work, hobbies, high risk behaviors



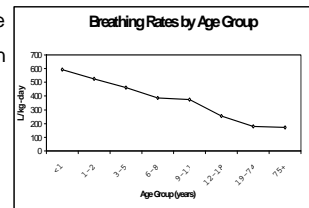
Children differ physiologically:



- Still growing and developing
- Absorption, metabolism, & elimination different
- Blood-brain barrier still forming in young infants

Increased Exposure from Inhalation and Dermal Absorption

- Increased metabolic rate
- Higher minute ventilation
 - Newborn 400 ml/min/kg
 - Adult 150 ml/min/kg
- Roughly double the surface area to body wt.
 - Increased absorption from dermal route



Miller M et al., Intl J Tox 2002

Barker's Hypothesis "fetal origin of adult disease"

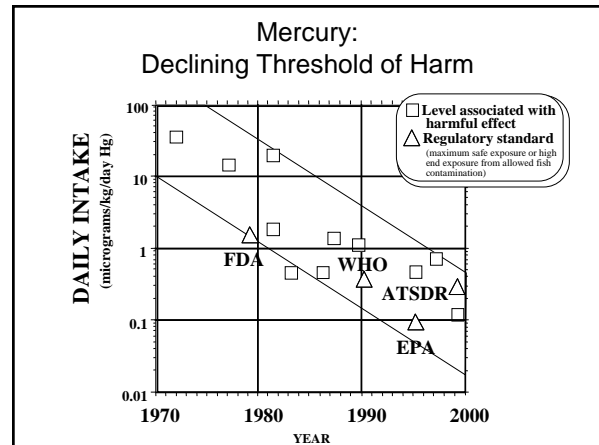
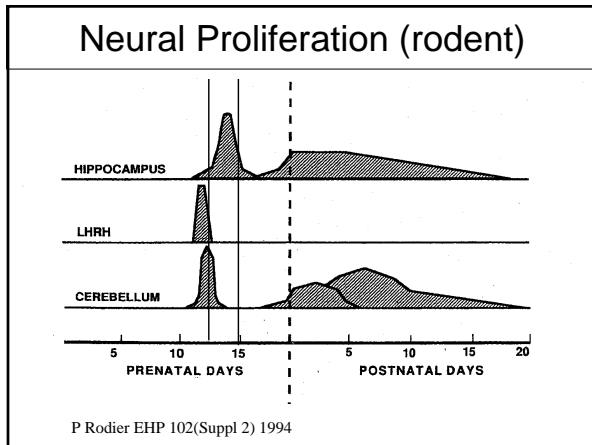
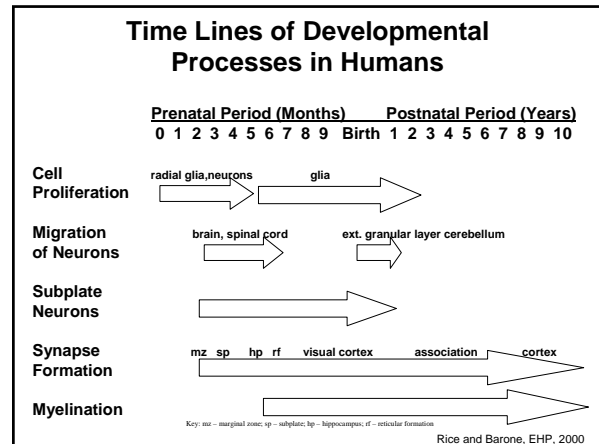
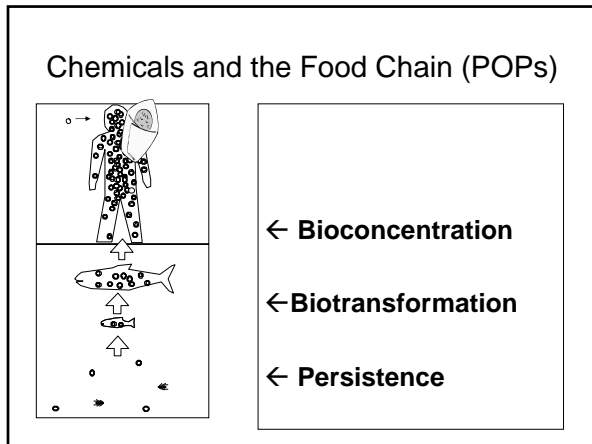
- Steep rise in post war cardiovascular (CV) mortality followed by fall
 - Not explained by lifestyle
- CV disease parallel areas of high infant mortality (LBW) and poverty
 - Why not areas of affluence associated with lifestyle risks (high fat intake?)
- Early life plasticity –
 - Adaptation results in "reprogramming"



• Undernutrition *in utero* and *in infancy* resulted in changes in organ structure, function, and metabolism that were permanent

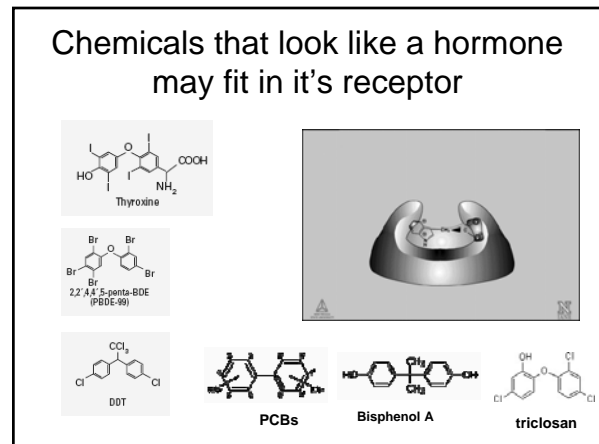
- adult lipid profiles linked to high cholesterol and hypertension
- impaired glucose regulation (insulin resistance)
- Metabolic syndrome





Specific processes disrupted by neurodevelopmental toxicants

proliferation	radiation, ethanol, <u>mercury</u> , cholinesterase inhibitors
migration	radiation, <u>mercury</u> , ethanol
differentiation	ethanol, nicotine, <u>mercury</u> , lead
synaptogenesis	radiation, ethanol, lead, triethyl tin, parathion, PCBs
gliogenesis & myelination	dec. thyroid, ethanol, lead
apoptosis	ethanol, lead, <u>mercury</u>
signaling	ethanol, cholinesterase inhibitors, <u>mercury</u> , lead, PCBs



Hormones act at very low levels. Chemicals disrupting that signal need be present in tiny amounts

- Thyroid hormones are present in micrograms/liter (ppb) to picograms/liter (ppq) amounts
- Bisphenol A is detected in 92% of Americans tested with geometric mean of 2.6 micrograms/liter (ppb)

Even Sub-clinical Thyroid Hormone Levels Appear Harmful

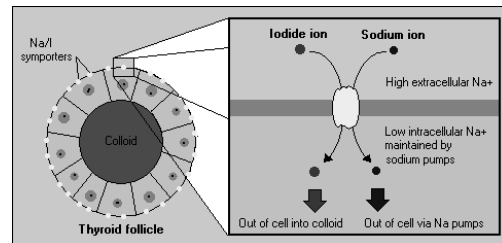
- Being in the lowest 10% of maternal T₄ at 12 weeks gestation resulted in a decrease of 8 IQ points at 2 years
 - Additional study confirms finding in infants (NBAS)
 - These are not mothers identified as having an illness

Pop, et al., Clin Endocrin 2003
Pop, et al., Pediatrics 2006

New technology determines; perchlorate in water widespread



The ability of the thyroid gland to transport and concentrate iodide from blood is absolutely necessary for the synthesis of thyroid hormones.



Perchlorate causes decreased T₄ in smokers

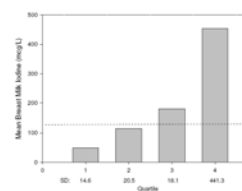


Environmental Chemical + Diet + Habit

- NHANES 2001-2002 (n=2,299)
- Woman + Smoker + perchlorate + low iodine = mean decrease in T₄ 1.36 mcg/dl
- Impact in smokers more than 2X as great

•Steinmaus, et al., EHP 2007

Breast milk in Boston



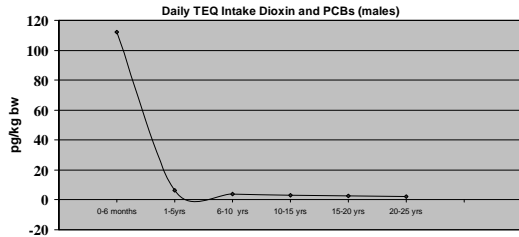
•Hashed line Adequate Intake 110-130 mcg/d IOM

- Estimated that as many as 47% may be providing insufficient iodine
- Median perchlorate 9.1 mcg/L
 - Exceeds RfD
 - highest > 400 mcg/l

Pearce et al., J Clin Endocrin Metab 2007

Fat Soluble Chemicals

Highest Intake in Breastfeeding infants



Source: Patandin et al, Environmental Health Perspectives, 107:1, 1999.

Breastfeeding Still Best

After prenatal exposure at 11 years:

- Decrease in full scale and verbal IQ
- Decrease in word and reading comprehension
- Decrease in memory and attention
- Twice as likely to be 2 or more years behind in reading ability



Exposure from Breastfeeding:

Regardless of exposure level – do best if breastfed

Jacobsons

Specific processes disrupted by neurodevelopmental toxicants

proliferation	radiation, ethanol, mercury, cholinesterase inhibitors, thyroid
migration	radiation, mercury, ethanol, thyroid
differentiation	ethanol, nicotine, mercury, lead, thyroid
synaptogenesis	radiation, ethanol, lead, triethyl tin, parathion, PCBs, thyroid
gliogenesis & myelination	ethanol, lead, thyroid
apoptosis	ethanol, lead, mercury
signaling	ethanol, cholinesterase inhibitors, mercury, lead, PCBs, thyroid (via laminin)

The PBDEs -- Flame Retardants



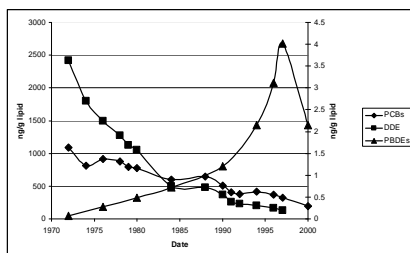
Use

- High-impact plastic
- Foam cushions (furniture)
- Textile coatings (drapes, furniture)
- 74.9 million pounds per year used in the Americas**

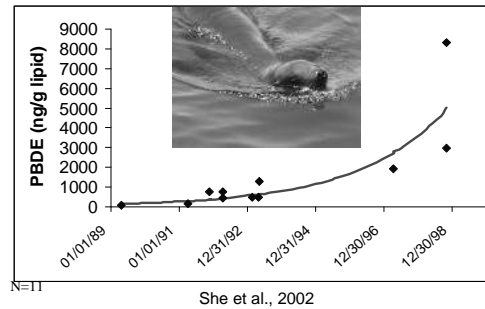
• Toxicity concerns include

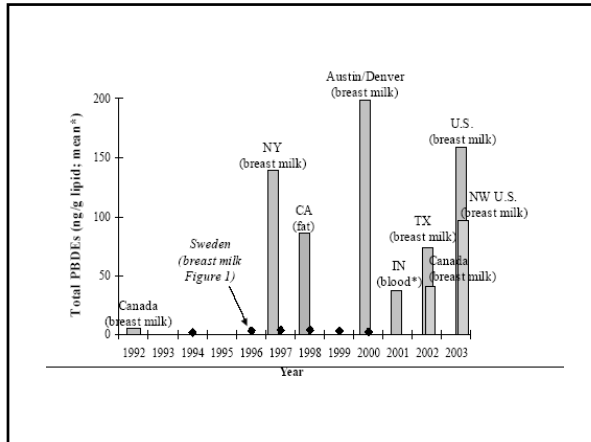
- highly bioaccumulative
- endocrine disruption
- altered behavior and learning (animal studies)

Organohalogenes in Breastmilk (Sweden)



PBDEs in blubber of California seals has increased markedly





Similar Findings in Rodents

PCB

- Change in activity level
- Effects on learning and memory
- Thyroid hormone production / transport
- Alter Ca⁺ homeostasis and neurotransmitters

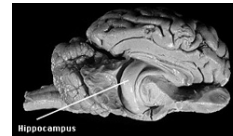
PBDE

- Change in activity level
- Effects on learning and memory
- Thyroid hormone production / transport
- Alter Ca⁺ homeostasis and neurotransmitters

When exposed to PCB and PBDE together neurodevelopmental effects noted at 1/10 the dose and worsen with age

(Eriksson et al., SOT, 2003)

The **hippocampus** is a part of the forebrain. It belongs to the limbic system and plays major roles in short term memory and spatial navigation, mood and behavior.



hippocampus size is influenced by maternal nurturing behavior such as licking after birth.

Well-licked rats have more developed hippocampi, more synapses, and produced less of the stress hormone cortisol.

(U Pennsylvania School of Veterinary Medicine)

Morris Water Maze

- Test of memory and spatial learning
- LG babies do better
 - Non-LG babies raised by LG mom's do better
- Babies with prenatal maternal stress but same post-natal environment do worse

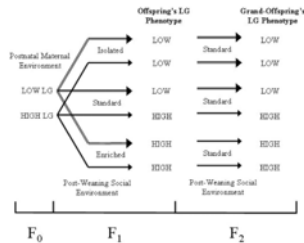
It is a combination of genetics and pre / postnatal environment that determines function into adulthood

Parenting influences the sort of adult a child becomes

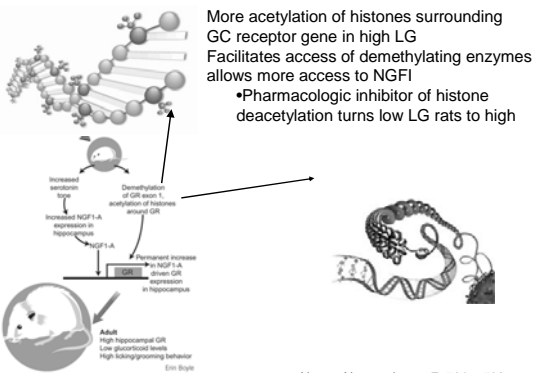
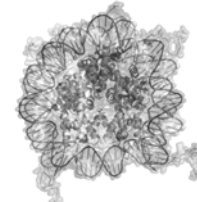
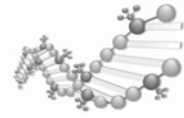
- Associated with oxytocin receptor (OTR) binding in brain regions critical for maternal care (medial pre-optic area of hypothalamus)
 - Higher in LG
 - OTR antagonist on postnatal day 3 abolishes difference
- Postweaning isolation reduces LG offspring exploration, OTR binding, and LG behavior
- Postweaning enrichment enhances these in low LG offspring

Weaver et al., Nature Neuroscience 2004

Phenotypes maintained in next generation without manipulation of housing, etc.



Champagne and Meany, Behavioral Neuroscience 2007

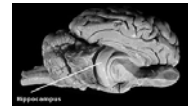


Nature Neuroscience 7, 791 – 792 (2004) Sapolsky R

Does this relate to humans?

- Study of adults looked at:

- Birth wt.
 - Parent Bonding Inventory
 - MRI of hippocampus
- Women with low birth wt. and low PBI had smaller hippocampus

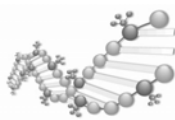


Postnatal environment modulates the neurodevelopmental consequences of prenatal risk

Buss, J Neuroscience, 2007

Early Life Lead Exposure and Alzheimer's Disease?

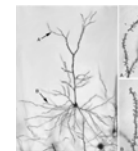
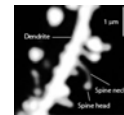
- Plaque and neurofibrillary tangles
- B amyloid and APP make up plaques
- Expression of genes related to these upregulated by lead exposure in early childhood (10mcg/dl)
- Methylation patterns altered
- Monkeys exposed to lead in early life develop plaque and NFTs in old age



Wu et al., J Neuroscience 08

Synaptic plasticity

- Dendritic spine 1000s per dendrite
- Input from neurons
- Rapidly changing in response to environment
- Neuro-chemical foundation of learning, memory, motivation
- Estradiol rapidly increases CA1 pyramidal cell dendritic spine synaptic density
 - Suggested that deficiencies related to neuro-degenerative disorders and age-related cognitive deficits
 - Sexually dimorphic



pyramidal cell / parietal cortex rat
Grazyna Gorny

BPA – environmental estrogen

- BPA “completely abolishes” estrogen-activated hippocampal spine synapse formation at levels less than EPA ref dose (in female primates)
 - Similarly, in males interferes with testosterone synaptic response (rats)
 - Alters sexually dimorphic behaviors (exploration and anxiety)
 - Associated with increased anxiety, disorders of mood and cognition

Rubin, Endocrinology 06

CDC finds BPA in 92% of Americans children > adults



Over 50% of canned goods on US market shelves are lined with BPA resin. It is not possible to identify the BPA lining via visual inspection.

- BPA acts as a weak estrogen in animals and probably does so in humans as well.
- It has chemical properties similar to estradiol and can impact biological systems in very low dose.
- In animals, prenatal exposures lead to changes in behavior including hyperactivity, increased aggression, impaired learning

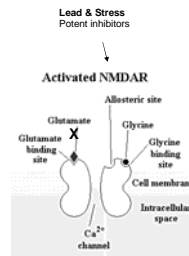


Low socioeconomic status (surrogate for increased stress?)

- Associated with increased risk for:
 - Decrease in IQ
 - Learning disorders
 - Emotional and behavioral problems
 - Deficits in language, memory, and attention
- Higher risk for lead exposure
 - Those living in pre-1946 housing, typical of inner city/low income, 4X greater risk of elevated blood lead levels

Melman et al., Environ Health Persp 1998

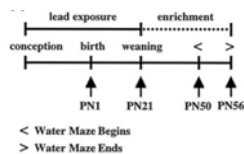
Spatial Learning and LTP in hippocampus dependant on activation of NMDA glutamate receptors



- Some of the same mechanisms are in play whether the insult is stress or an environmental chemical (lead).

Environmental enrichment enhances LTP and improves spacial learning

Social environment, exploration, play, spacial learning



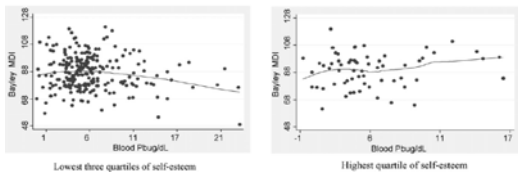
Guilarte T, Ann Neurology, 2003

Environmental enrichment affective in ameliorating neuro-cognitive effects

- Lead – association with cognitive deficit <10mcg/dl only in “lower class”, “upper class” only with >10mcg/dl at birth
- PCBs - prenatal exposure only had negative effect in “less optimal” parenting and home characteristics
- ETS – greatest cognitive effect in those with “unmet basic needs in the areas of food, housing, and clothing”

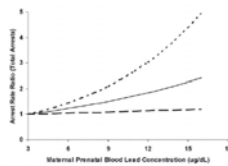
Weiss and Bellinger, 2006

Maternal self-esteem appears to attenuate negative lead effect



Surkan et al, Neurotoxicology 2008

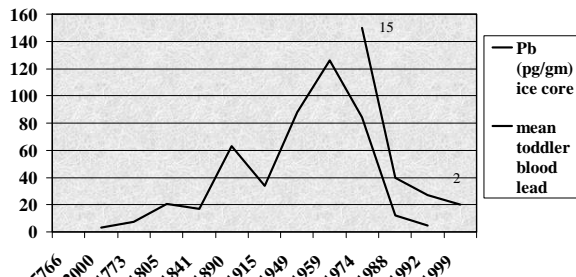
Prenatal blood lead associated with future arrests and criminal activity



- Lead associated with learning, memory, attention deficits and impulsivity, aggression and abnormal infant-maternal interaction.
 - Reduces MAO A activity (violent and criminal behavior)

Wright et al., 08 Plos

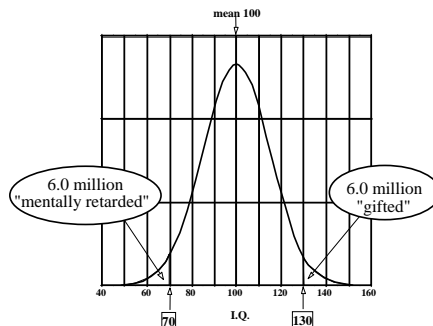
Greenland Snow and Ice Lead



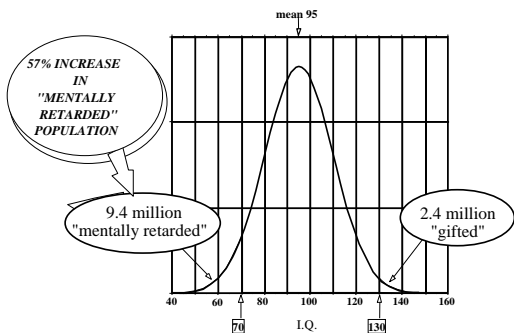
Derived from Candelone Et Al. 1995 J of Geophysical Research Vol.100 No. D8 and CDC, NHANES 2 and 3

The Significance of Small Effects: The Population Perspective

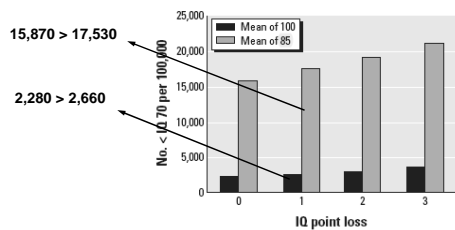
Effects of A Small Shift in IQ Distribution



5 Point Decrease in Mean IQ



Neurotoxic chemicals: impact much greater in disadvantaged communities



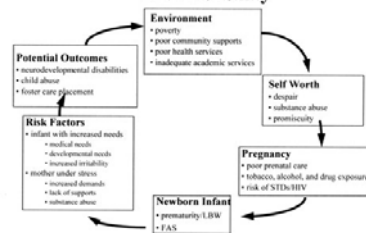
Weiss and Bellinger, 2006 EHP

Economic impacts (conservative estimate)

- Lead = \$43 billion/year
 - Neurobehavioral disorders = \$9 billion
- TOTAL=\$52 billion/year

Landrigan et al., Environmental Health Perspectives 2002

Cycle of Disadvantage and Disability



Courtesy Leslie Rubin MD, ISDD

Summary

- Kids are exposed to chemicals that alter brain development
 - There are sensitive people and sensitive time periods
 - Brain is particularly vulnerable due to the many complicated structures that develop and the long period over which development occurs
 - Early exposures may result in lifetime deficits as well as disorders not identified until years later, even old age.

- In at least some cases, the way in which chemicals cause disruption of brain development/function are by the same mechanisms that also at work when a child fails to thrive as a result of social/psychological causes.
 - the same type of interventions that work to ameliorate the deficits related to social/psychological causes may be effective for chemically originated causes.

- Widespread exposures to low doses of chemicals may cause relatively small impacts on individuals but the impact on the population may be great.
 - Otherwise disadvantaged communities bear the brunt of environmental contamination
 - They are predisposed to be the most severely impacted and at the same time have the least services

Early experience is not necessarily destiny

- Our children's potential for health needs to be thought of in the context of the entire environment and the web of life
 - "I do not know of a society that takes loving care of it's people and not the environment nor of one that takes care of the environment but not it's people" *Paul Hawkins*