

Environmental threats to child development

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Network

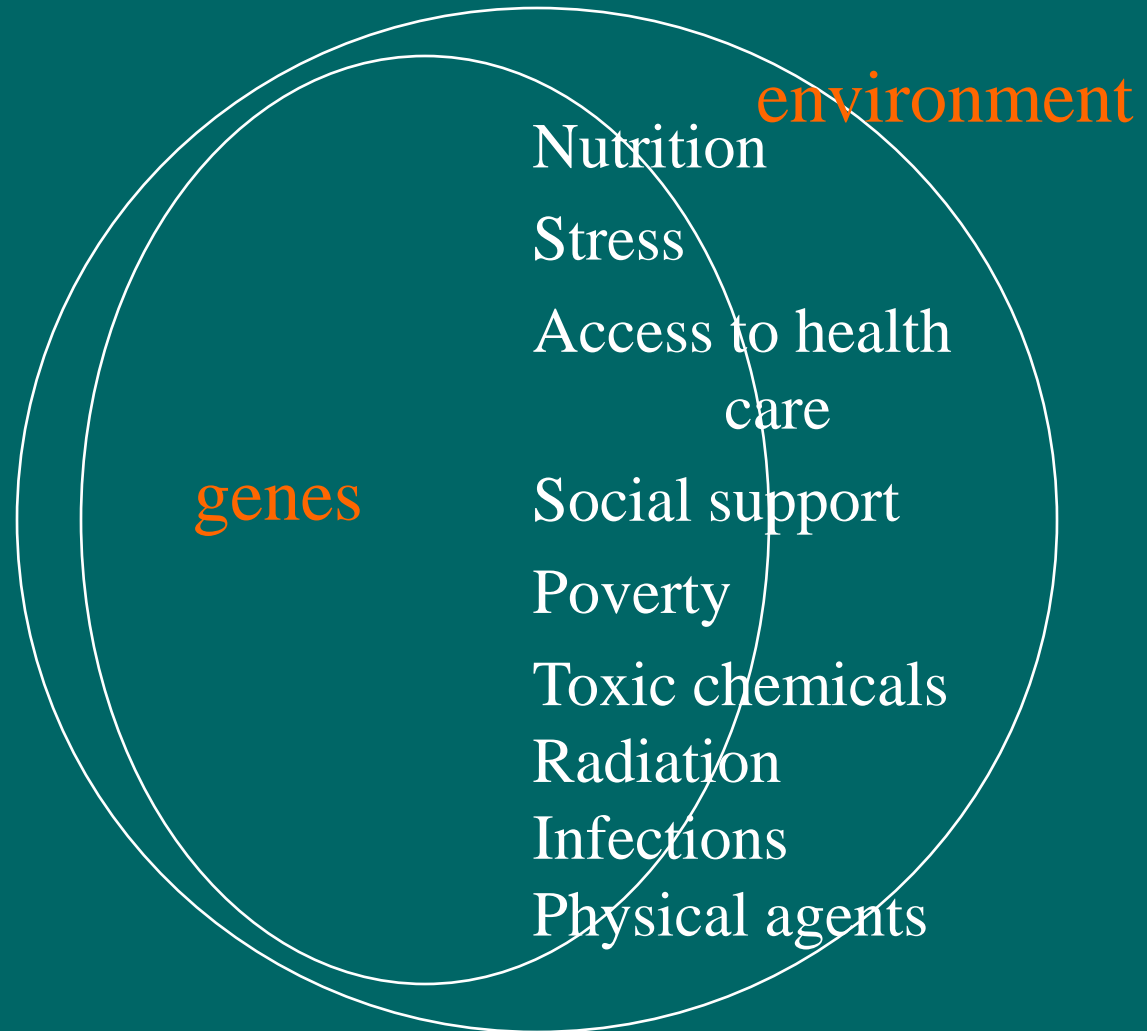
www.sehn.org

LDA, Michigan; Oct. 2008

Outline

- Contributors to developmental disorders
- Challenges to understanding
- Environmental contributors: examples
- An integrated model

HEALTH



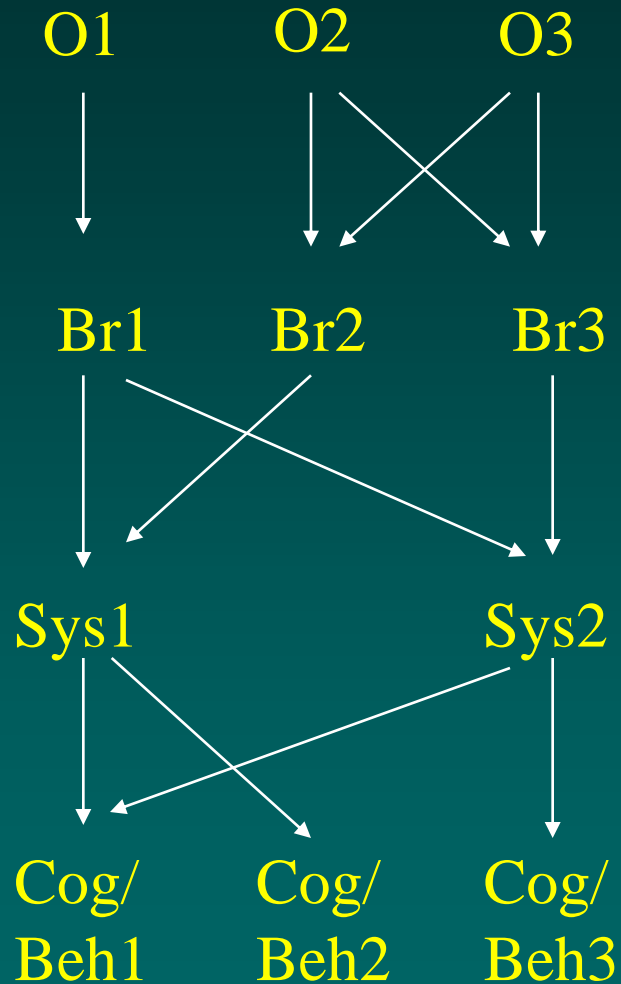
Causes of developmental disabilities

- More than one factor in most cases
- Prenatal
 - Genetic (not single gene disorder in most cases), nutritional/metabolic, chemical agents, hypothyroidism, central nervous system birth defects
- Peri-natal—injury, low oxygen, infections, toxic exposures
- Post-natal—infections, trauma, tumors, low oxygen, other environmental factors

Challenges to understanding

- No good biologic markers—most diagnoses are based on functional status
- Experimental animal models are limited
- Delays in diagnosis > difficult to reconstruct earlier events
- Limited toxicity data for many chemicals

CAUSAL MODELING: Complex Neural Systems Model



BIOLOGICAL ORIGINS:
Genetic, Toxic, Infectious,
Immunological, Diet, etc.

ABNORMAL BRAIN CONDITIONS:
Abnormal Cells, Cell Organization,
Or Cell Chemistry

**MALFUNCTIONING
BRAIN / PROCESSING
SYSTEMS**

**MIXTURES OF
COGNITIVE AND
BEHAVIORAL SIGNS**

(Adapted from Morton & Frith, 1995)

Cellular Events in Neurodevelopment

Each of these events is subject to disruption by environmental agents

- Division
- Migration
- Differentiation
- Formation of synapses
- Pruning of synapses
- Apoptosis
- Myelination

Active
throughout
childhood &
adolescence



Chemical agents and neurodevelopmental impacts

Determinants of chemical toxicity

- The dose makes the poison. Yes, but.....
- Dose is more than amount
- Amount, duration, pattern, and TIMING
- Periods of vulnerability
- Importance of life stage

Time Lines of Developmental Processes in Humans

Prenatal Period (Months) Postnatal Period (Years)
 0 1 2 3 4 5 6 7 8 9 Birth 1 2 3 4 5 6 7 8 9 10

Cell Proliferation



Migration of Neurons



Subplate Neurons



Synapse Formation



Myelination (see text)



Key: mz – marginal zone; sp – subplate; hp – hippocampus; rf – reticular formation

Neurodevelopmental Toxicants:

What Do We Know?

- Extensive data on effects of lead, mercury, polychlorinated biphenyls (PCBs), alcohol, nicotine.
- Less extensive but some data on neurotoxic pesticides, solvents other than alcohol.
- Still fewer data on other compounds

Problem: Most data obtained for a few chemicals. No data available for majority.

Brazelton Neonatal Behavioral Assessment Scale (BNBAS)

- 17 reflexes and a range of behaviors including muscle tone, activity level, attention and orientation, and arousal.
- Transitory and not predictive of later neurological function

Bayley Scales of Infant Development

- Mental Development Index (MDI); Psychomotor Development Index (PDI)
- Focuses on the rate at which the infant attains age-appropriate developmental skills (attention, memory, learning, motor skills)
- Predictive validity for school-age cognitive function is poor for children who perform within the normal range; **abnormalities are predictive of later performance**
- Apical; sensitive; not specific for brain regions

Fagan visual recognition memory test

- Assesses recognition memory and visual discrimination
- Specific for those functions
- Moderately predictive of intellectual function in childhood

Several tests of IQ

- McCarthy Scales of Children's Abilities
- Wechsler Pre-school and Primary Intelligence
- Stanford-Binet
- Kaufman Assessment Battery for Children

Lead, alcohol, nicotine

- Alcohol – hyperactivity, cognitive deficits
- Nicotine – IQ deficit, learning and attention deficits; includes environmental tobacco smoke (LBW, intrauterine growth retardation)
- Lead – impaired IQ, learning, attention; hyperactivity, impulsiveness, aggression; failure to complete school, trouble with the law

A close-up, warm-toned photograph of a newborn baby's face, showing the eye, nose, and mouth. The baby is looking slightly to the right.

BodyBurden

The Pollution in Newborns

A benchmark investigation of industrial chemicals, pollutants, and pesticides in human umbilical cord blood

www.ewg.org

Environmental Working Group;
2004

10 specimens of
cord blood

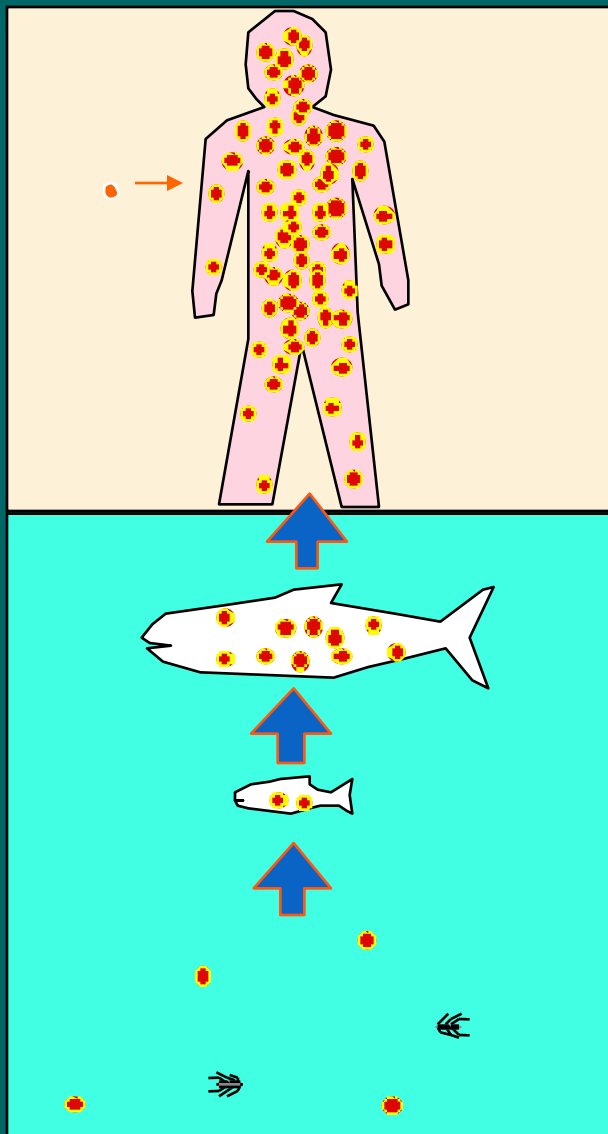
Body burden: the pollution in newborns

- Tested for 413 chemicals
- 287 chemicals detected; 200 average
- 180 cause cancer in humans or animals,
- 217 are toxic to the brain and nervous system, and 208 cause birth defects or abnormal development in animal tests.
- The dangers of pre- or post-natal exposure to this complex mixture of carcinogens, developmental toxins and neurotoxins have never been studied.

Chemicals and pollutants detected in human umbilical cord blood

- Mercury (Hg)
- Polyaromatic hydrocarbons (PAHs) – 9/18
- Polybrominated dibenzodioxins and furans (PBDD/F) – 7/12
- Perfluorinated chemicals (PFCs) – 9/12
- Polychlorinated dibenzodioxins and furans (PBCD/F) – 11/17
- Organochlorine pesticides (OCs) – 21/28
- Polybrominated diphenyl ethers (PBDEs) – 32/46
- Polychlorinated Naphthalenes (PCNs) – 50/70
- Polychlorinated biphenyls (PCBs) – 147/209

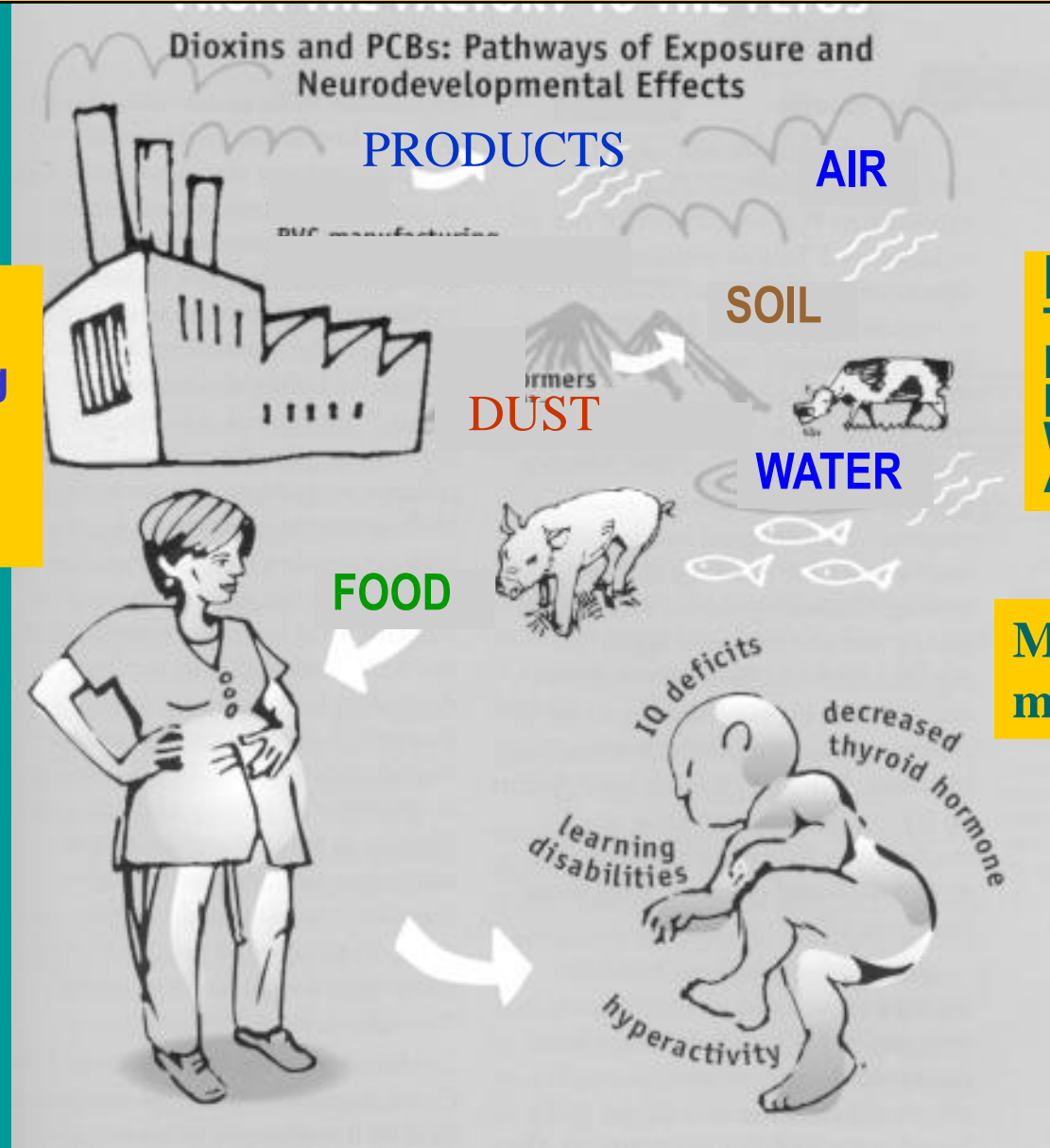
PBTs



- **Persistent**
- **Bioaccumulative**
- **Toxic**

From Factory to Fetus

Dioxins, PCBs, BFRs, mercury : Pathways of Exposure and Neurodevelopment



Dioxins:
Chemical mfg
PVC Manufacturing
Medical/Municipal incinerators
Metal smelters
Paper bleaching

**Brominated
Flame
Retardants**

PCBs:
Transformers
Landfills
Hazardous Waste Sites
Air deposition

**Mercury;
methylmercury**

Methylmercury

Effects of Higher Dose Prenatal Exposure

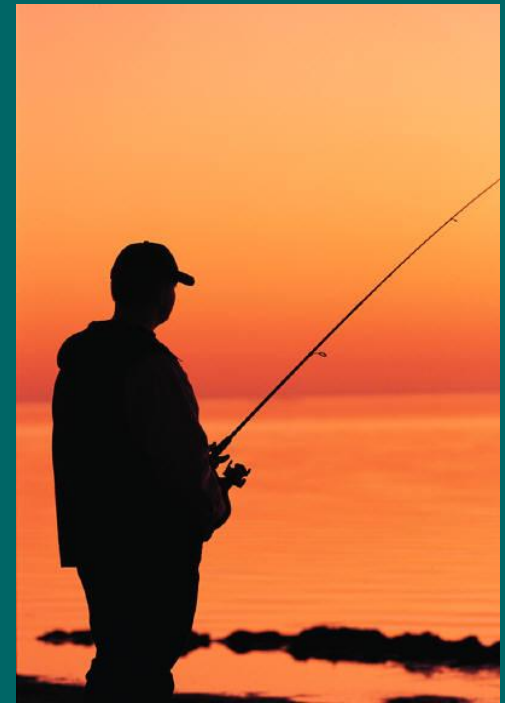
- Severe cognitive impairment; mental retardation
- Seizures
- Cerebral palsy
- Disturbances of vision, hearing, sensation
- Abnormal gait
- Abnormal speech
- Disturbances of swallowing and sucking

Methylmercury—low dose effects, prenatal exposure

- Impairments (at age 7-9) of:
 - motor skills
 - attention
 - visual spatial skills
 - language
 - memory

Mercury Risks

- EPA concludes that up to 620,000 babies born every year in the US with methylmercury exposures above EPA's reference dose
- Most exposure is via consumption of contaminated fish



Polychlorinated biphenyls (PCBs)

- Industrial chemicals no longer manufactured
- PBT
- Source: fish from contaminated waters; other fatty foods including processed foods

PCBs—high dose developmental effects

- Hyperpigmented skin
- Nail, tooth, gum abnormalities
- Mental retardation
- Hyperactivity

PCBs—low dose; pervasive developmental effects

Infant

- **Decreased**
 - Birth weight
 - Head circumference
 - Performance on Brazelton Neonatal Behavioral Assessment (BNBA)

PCBs: Pervasive Developmental Effects

Early Childhood

- Memory, attention, verbal ability, information processing
- Psychomotor development
- Sustained activity, high level play
- Hyperactivity

Preteen

- Word and reading comprehension
- Full scale and verbal IQ
- Memory and attention

PCB interactions with other factors

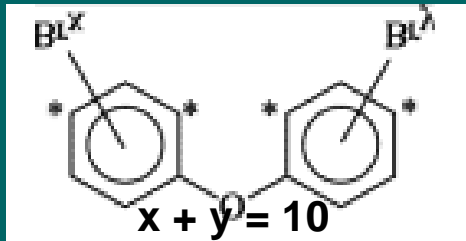
- **Non-breast fed children much more susceptible to PCB effects**
- **Children with small splenium (in corpus callosum) also much more susceptible (a susceptible subgroup)**

Brominated flame retardants

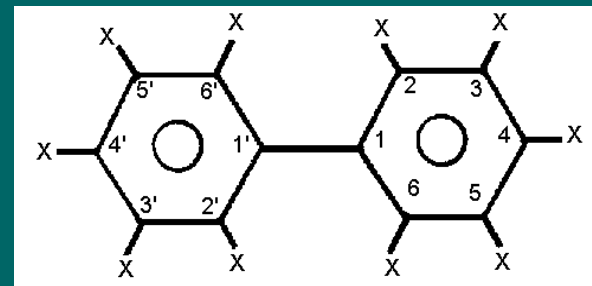
- Organic chemicals containing the element bromine.
- Added to products to inhibit ignition or spread of flames.
- Over 75 different brominated flame retardants.

Some of the most commonly used BFRs resemble PCBs

Over 150 million pounds annually

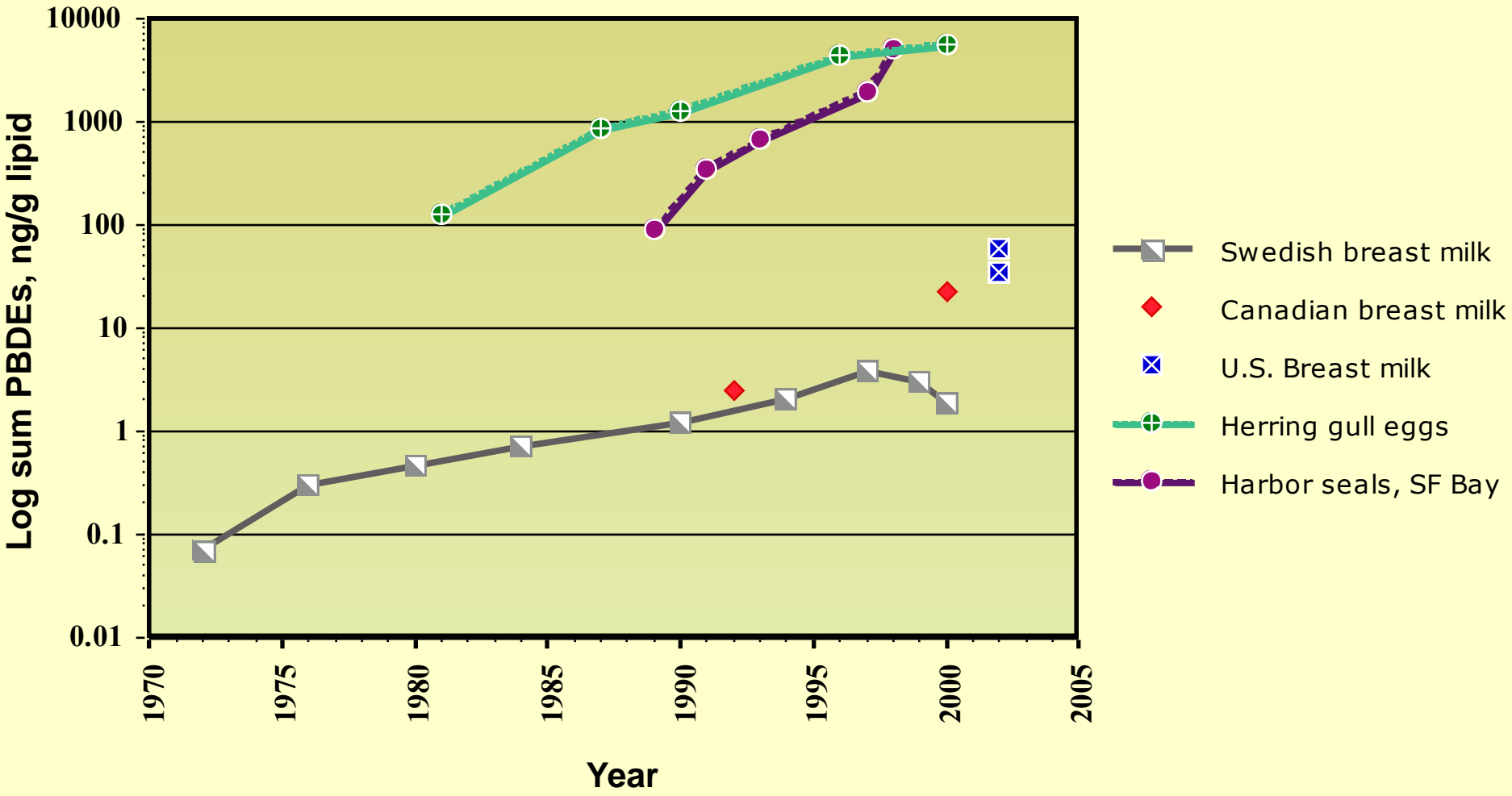


PBDEs



PCBs

Human and Wildlife Levels of PBDEs



Source: Hites, 2004; Lunder 2003

Neurodevelopmental studies

- Animal tests: Exposure to some PBDEs during critical windows of brain development results in decreased memory and learning that worsens with age.

(Eriksson, 2001; Viberg, 2003)

- No human neurodevelopmental data
- High-end human exposure levels approach those that cause impacts in animal studies.
- May also act through thyroid hormone disruption

Non-persistent, non-
bioaccumulative toxic
compounds (examples)

Solvents

- Alcohol—hyperactivity, cognitive deficits
- Toluene—impacts similar to alcohol
- Other solvents encountered in workplace:
 - Hair stylists, painters, photo lab, graphic design, etc.; at least 8 weeks of pregnancy
 - Children tested at 3-9 yrs old: **lower IQ, language, memory, attention; hyperactive**
 - (N=32 plus matched controls)
(Laslo-Baker, Arch Pediatr Adolesc Med. 2004)

Assessing impacts of pesticides on the developing brain

- Cell culture preparations
- Animal testing—prenatal; neonatal period
(in rodents corresponds to third trimester
in humans)
- Human studies: epidemiologic
 - Importance of accurate exposure assessment
 - Controlling for other variables; confounders
 - Various tests for neonatal and childhood cognitive and motor function

Organophosphate pesticides

- A family of chemicals
- Exposures often estimated by measuring urinary metabolites
- Urinary metabolites are generally not specific for a single family member except for chlorpyrifos, malathion

Organophosphate pesticides

- Rodent studies: neonatal exposures > hyperactivity; changes in neurochemistry (Slotkin et al. 2006)
- Neurodevelopmental impacts are NOT exclusively due to cholinesterase inhibition
- Impacts on brain chemistry and architecture differ among OPs.

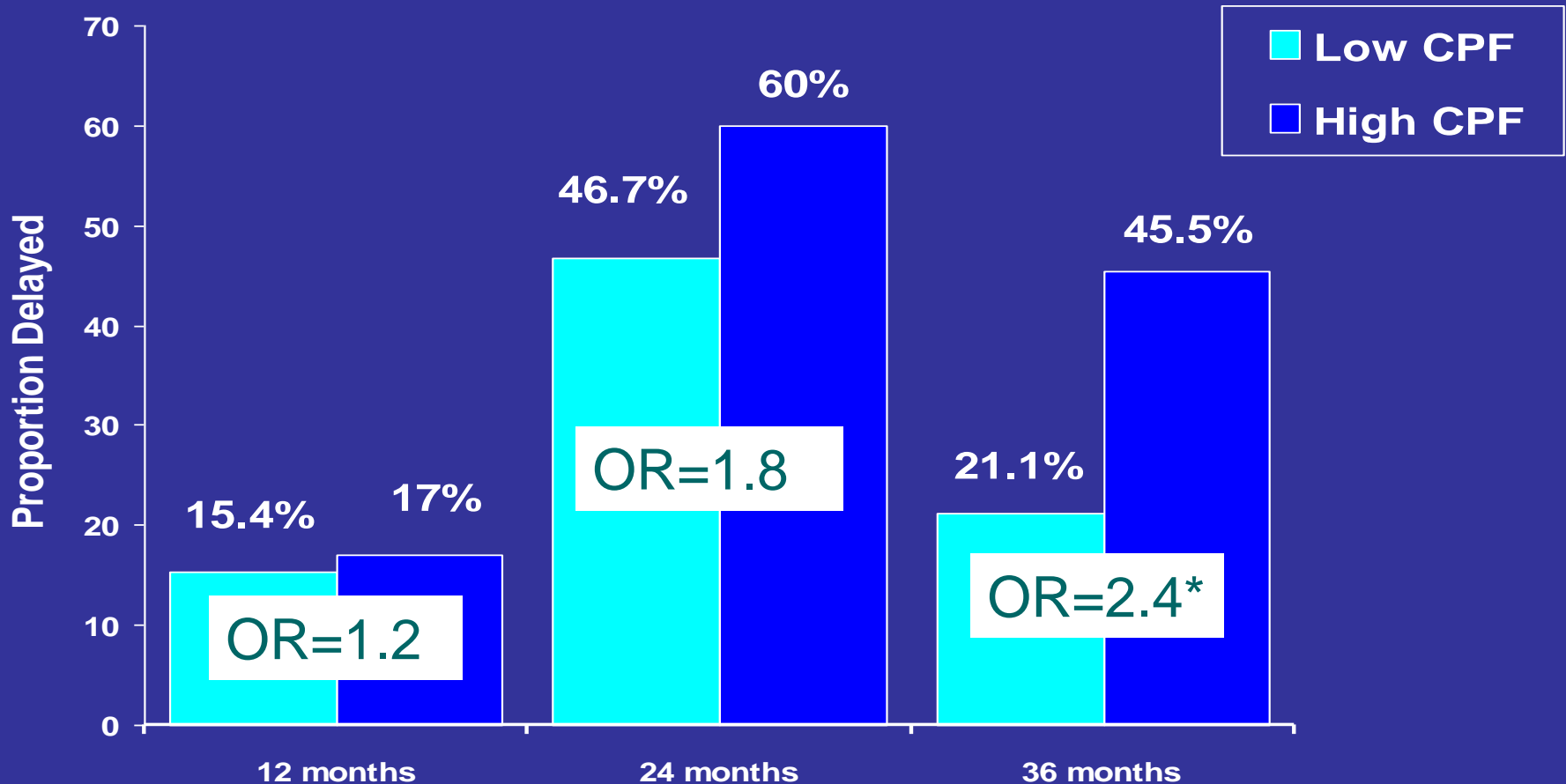
Organophosphates—human studies

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

Summary of effects of prenatal chlorpyrifos exposure—New York

- Prenatal chlorpyrifos exposure was associated with a 3.5 to 6-point adjusted mean decrement in 36-month development scores (Bayley MDI and PDI)
- This decrement resulted in a 2-fold inc. risk of developmental delay (< 80) on the Bayley MDI, and a 5-fold risk of delay on the PDI
- Prenatal pesticide exposure was associated with significantly increased risk for diagnosis of ADHD and Pervasive Developmental Disorder

Cognitive Delay (< 85) at 12, 24 & 36 months on the Bayley, by level of chlorpyrifos exposure (N=228)

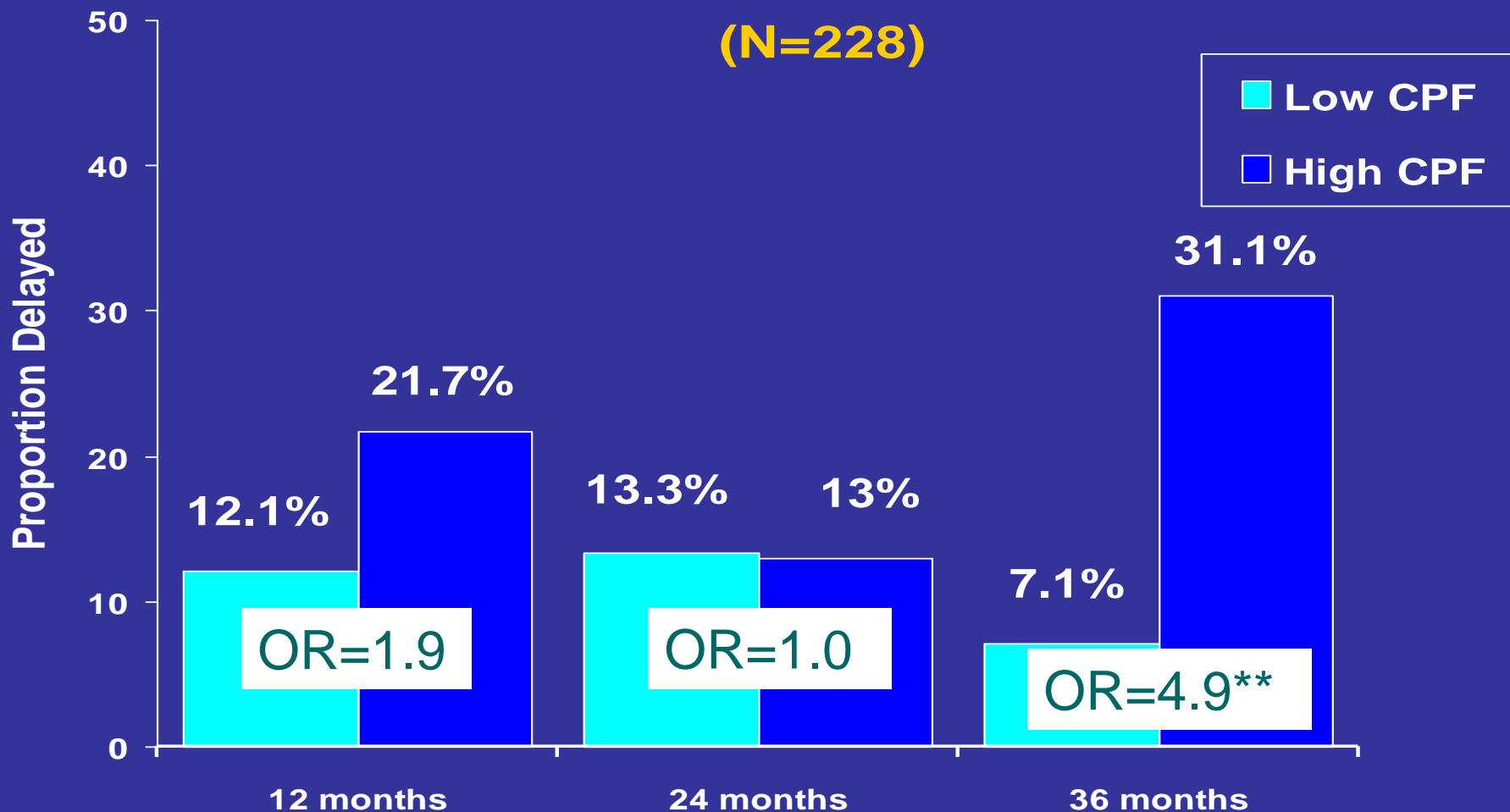


Logistic regression adjusted for race/ethnicity, sex, gestational age, ETS, maternal IQ, maternal education, HOME Inventory

*p<.01

Motor Delay (< 85) at 12, 24 & 36 months on the Bayley, by level of chlorpyrifos exposure

(N=228)



Logistic regression adjusted for race/ethnicity, sex, gestational age, ETS, maternal IQ, maternal education, HOME Inventory

**p<.001

CHAMACOS birth cohort; agricultural workers; Salinas Valley

- Prenatal organophosphate exposures (as measured by DAP metabolites) associated with:
 - Decreased gestation time and poorer neonatal reflexes
 - Decreased Bayley MDI at 24 mos.

Eskenazi, et al. EHP, 2007

Pesticides and autism spectrum disorder (ASD)

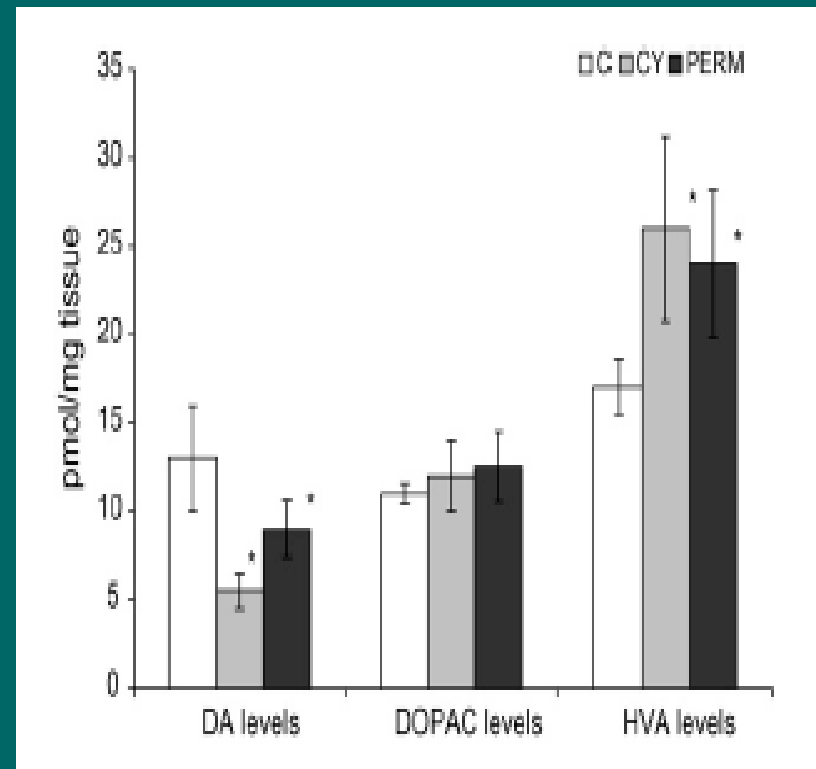
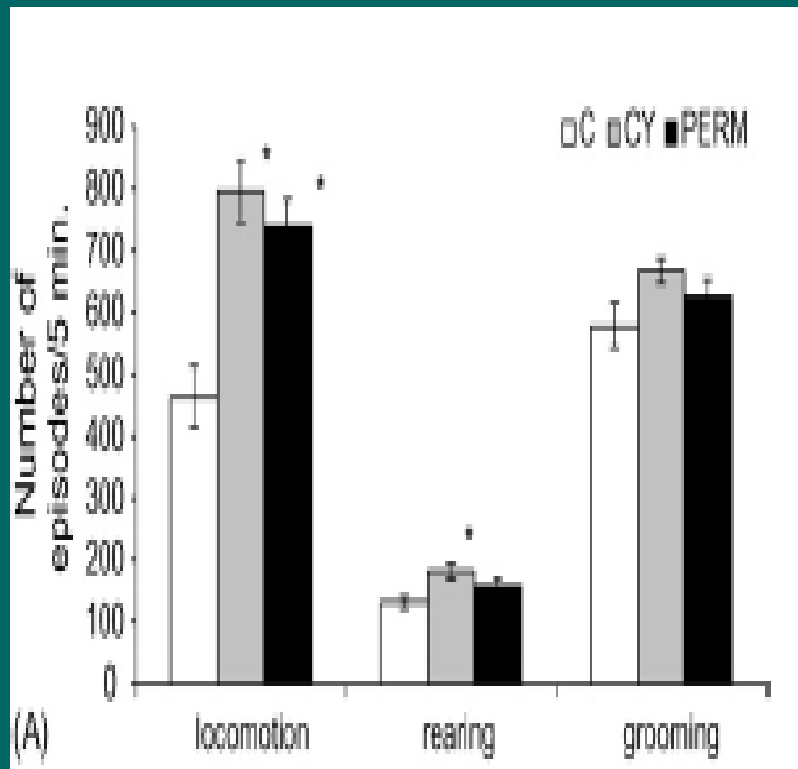
- Hypothesis: residential proximity to agricultural pesticide applications during pregnancy could be associated with ASD in offspring.
- Retrospective, case-control study
- Cases identified CA Dept of Developmental Services
- Pesticide use from CA Dept Pesticide Regulation

(Roberts, et al; EHP; 2007)

Pesticides and autism spectrum disorder (ASD)

- Risk for ASD was associated with residential proximity to organochlorine pesticide applications occurring around the period of CNS embryogenesis (endosulfan, dicofol)
- This association increased with dose and was attenuated with increasing distance of residence from the field site.
- Limits: misclassification of exposure; confounders or effect modifiers

Effect of neonatal cypermethrin and permethrin (1/10 LD50; postnatal day 6-15) on adult behavior— Wistar rats



Nasuti, et al. Toxicology; 2007

Pesticide summary

- Prenatal exposure to OP pesticides can increase risk of cognitive, motor delays; increase risk of ADHD, PDD
- Prenatal exposure to organochlorines may be associated with increased risk of autism spectrum disorder (needs further study and confirmation)
- Animal studies: neonatal pyrethroids/pyrethrins alter behavior and neurotransmitter levels in adulthood; may also increase risk of adult disease; human data lacking

Nutrition

Nutrition and brain development

- All nutrients are important for normal brain growth and development; some more than others
 - Protein, iron, zinc, iodine, selenium, folate, vitamin A, choline, polyunsaturated fatty acids (both omega 3 and omega 6 fatty acids)

Dietary supplements and ADHD

- Most, but not all studies show improvement in ADHD symptoms with omega 3 fatty acid supplements
- Some support for zinc supplements as well (zinc deficiency relatively common)
- Iron supplements helpful in children who are iron deficient.

Sinn, Nutr Rev, 2008

Iron and brain development

- Iron deficiency: 10% US toddlers, ↑ poverty, obesity; more common in developing countries
- Iron deficiency > impaired IQ, auditory discrimination, memory
- Excessive iron > impaired neurodevelopment (Lozoff, 2008)

Interactions

Nutrition and lead absorption: interactions

- Lead absorption increased with:
 - Iron-deficient diet
 - Calcium-deficient diet
 - High fat diet
- Iron deficiency up-regulates iron transporters of Fe into the brain

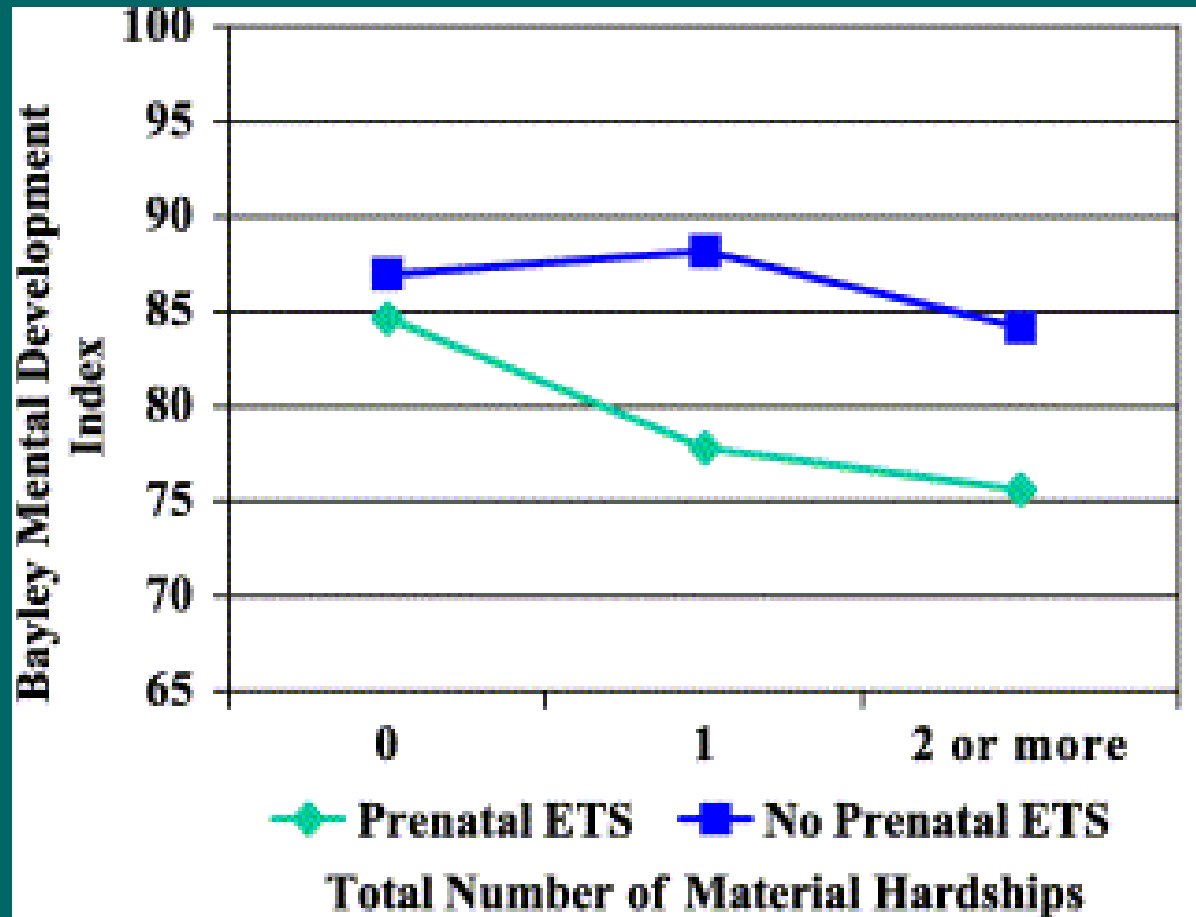
Intervention studies

- Most interventions require addressing lead reduction, iron repletion, improved social circumstances **collectively** in order to have much beneficial effect.

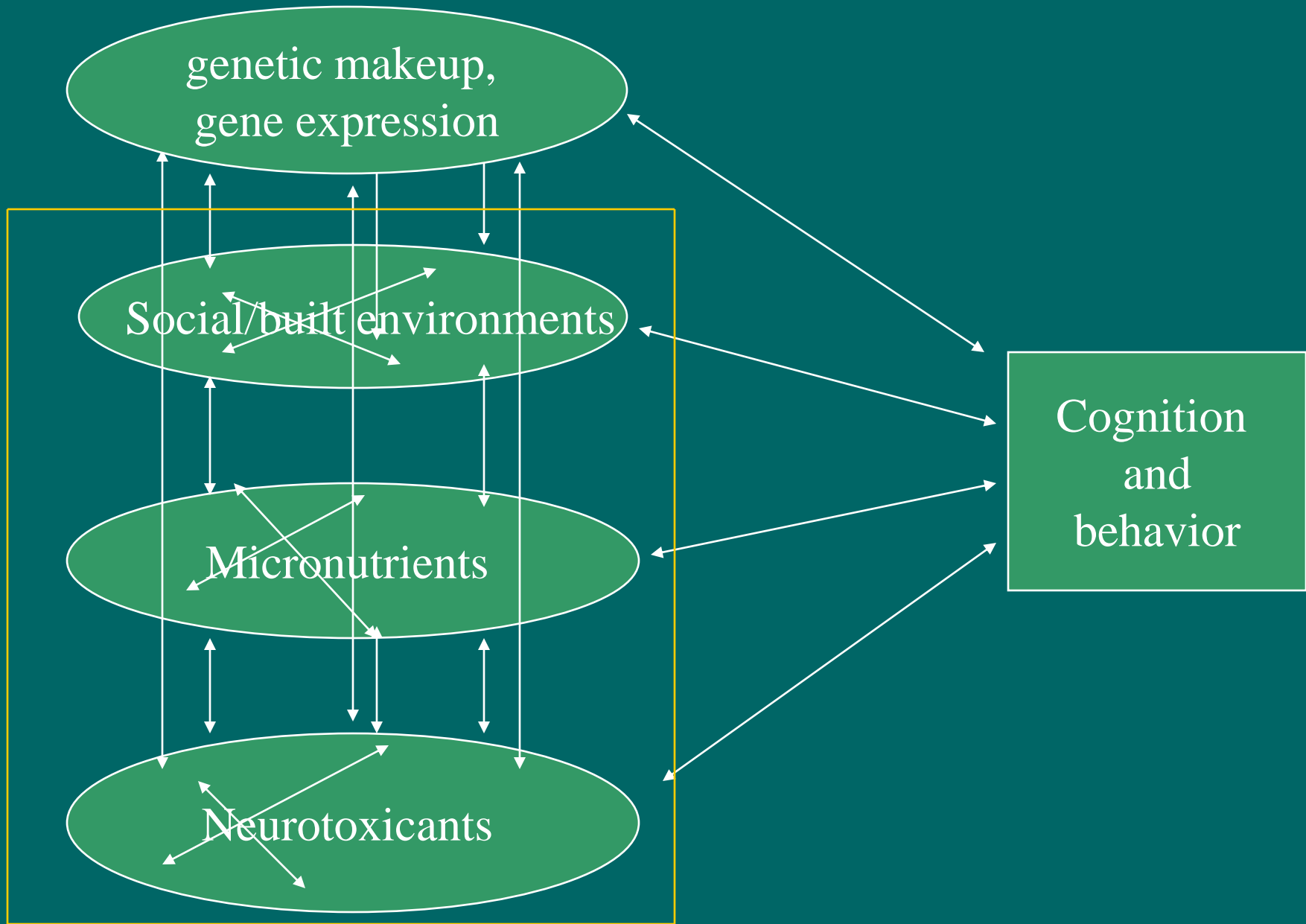
(e.g., Ruff, EHP, 1996)

- BUT, even then, brain vulnerability outweighs plasticity; i.e., “catch-up” with remediation not as effective as primary prevention

2 yr old MDI; prenatal ETS, material hardships



^aAdjusted for race/ethnicity, gender, gestational age at delivery, age at testing, marital status, maternal age, and level of PAH exposure.



Brain development and function—summary

- Critical sequence—spatial and temporal dimensions
- Vulnerable to disruption
- Influenced by multiple, interacting environmental factors
- Size, timing, duration influence impact
- Long-term susceptibility
- Early life exposures may have long term consequences
- Need integrated model for understanding AND responding

Policy implications

- Need to think of collective conditions as well as individual risk factors
- Need for pre-market testing of chemicals
 - Pesticides: neurodevelopmental testing
 - Other industrial chemicals—regulatory reform
 - Consider safer alternatives
- More attention to nutrition during pregnancy, infancy, childhood; promote breast feeding
- Educational needs: health professionals, teachers, policy makers
- Interdisciplinary coordination to protect prospective parents and developing children.

Resources

- Collaborative on Health and the Environment
www.healthandenvironment.org
- Greater Boston Physicians for Social Responsibility www.igc.org/psr
- Environmental Health News
www.environmentalhealthnews.org
- Science and Environmental Health Network
www.sehn.org