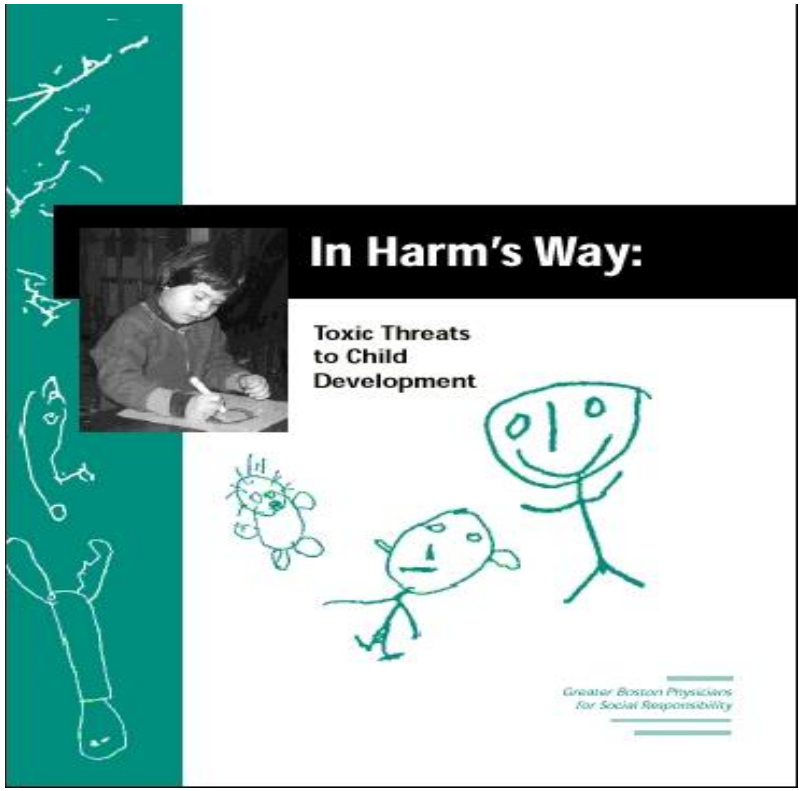
Training Program for Health Professionals



Greater Boston Physicians for Social Responsibility

www.igc.org/psr/

September 2002

PROGRAM OUTLINE

Section I. Neurodevelopmental Disabilities

Section II. Links Between Chemicals and Disabilities

Section III. Magnitude of the Chemical Threat

Section I. Outline: Neurodevelopmental Disabilities

1. Clinical/Public Health Dimensions
2. The Research/Evidence Problem
3. Conceptual Framework
4. Clinical Traits ⟺ Syndromes
5. Underlying Cellular Biology

Prevalence of Learning and Behavioral Disabilities

Total: 17%, 12 million children

- **Learning disabilities: 5-10%**
- **ADHD: 3-5%**
- **Autism: 0.05%**

Reported Trends: Real? Better reporting? Changing criteria?

Learning disabilities

- **191%** ⬆ ***Children in special education: 1977-1994***

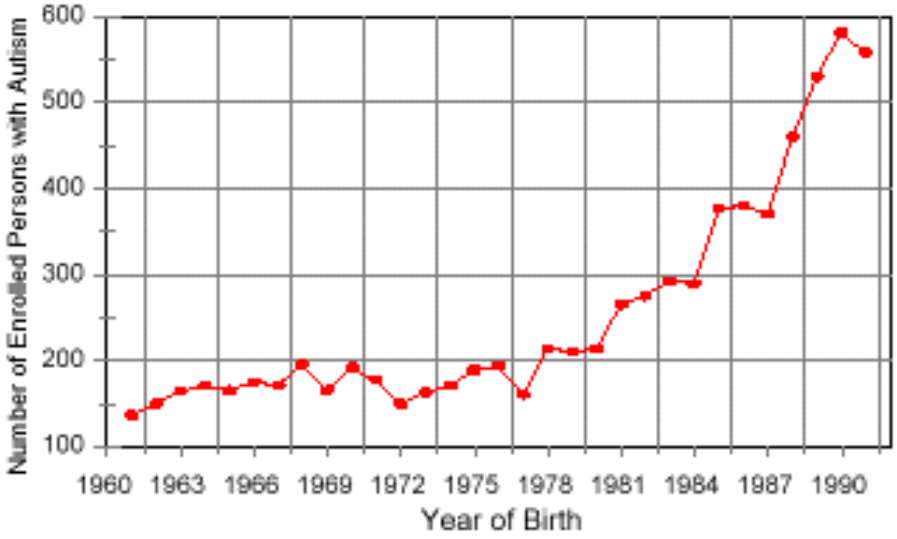
ADHD

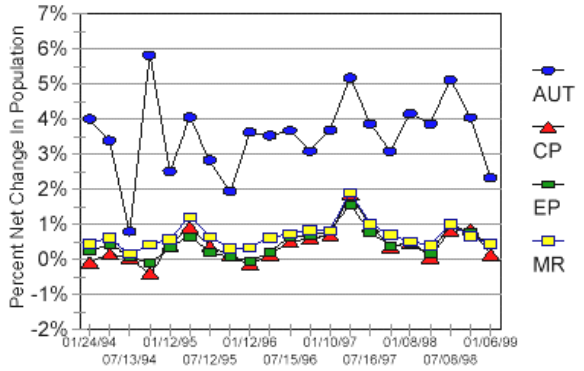
- **1** ➡ **20%** ***Reported prevalence***
- **>800%** ⬆ ***Ritalin use since 1971***

Trends, Prevalence, and Clusters

Autism

- 100% ↑ *Autism over 30 years*
- 210% ↑ *Autism in California DSS System: 1987-1998*
- 400% ↑ Above nation: *Prevalence in Brick Township, NJ*





Problem of Staggering Proportions

Whether new, newly recognized, or a combination of both,

developmental disabilities are a problem of staggering proportions.

Associated Effects on Individuals, Families, and Communities

- Financial stress
- Emotional stress
- Suicide
- Substance abuse
- Employment problems
- Academic difficulties

Economic Implications

- **$81.5 – 167 billion/yr**
  - **Estimated U.S. costs of neuro-developmental deficits, hypo-thyroidism, related childhood disorders**
- **$9.2 billion/yr**
  - **Est. costs of neurobehavioral disorders attributable to environmental pollutants**
- **Over $8,000/yr**
  - **Special education costs for a child with autism;**

  $80-100,000/yr
  - **costs of residential treatment**

ADHD doubles health care costs for children – comparable to costs for children with asthma.

Difficulties in Epidemiological Research

- **What makes evidence convincing?**
- **The current state of evidence – what do we know/not know?**

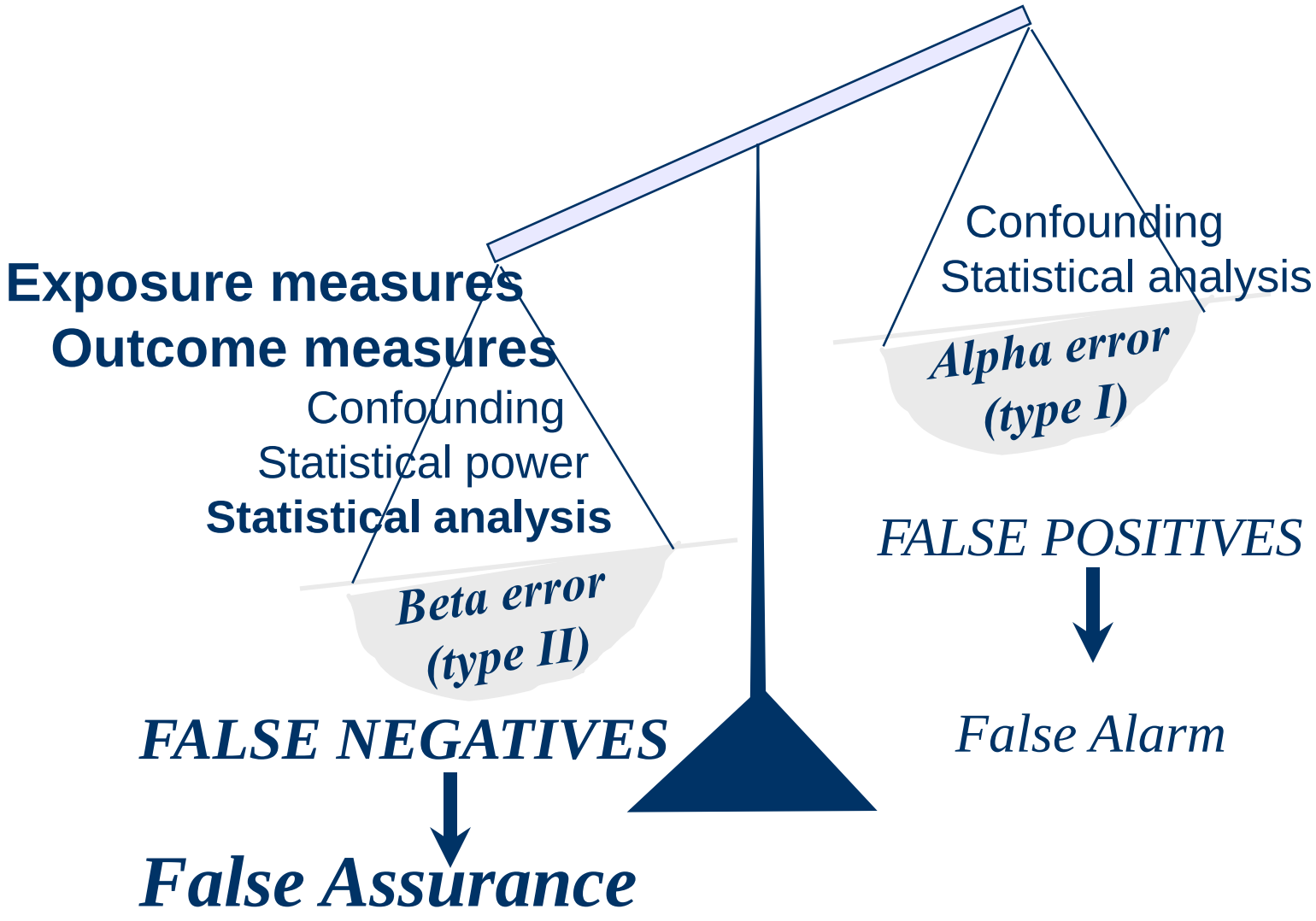
Difficulties in DNT Epidemiological Research

- Latency: Long periods between when exposures occur and effects surface
- Windows of vulnerability
- Gene-environment interactions
- Susceptible sub-populations
- Multiple exposures
- Epidemiological shortcomings

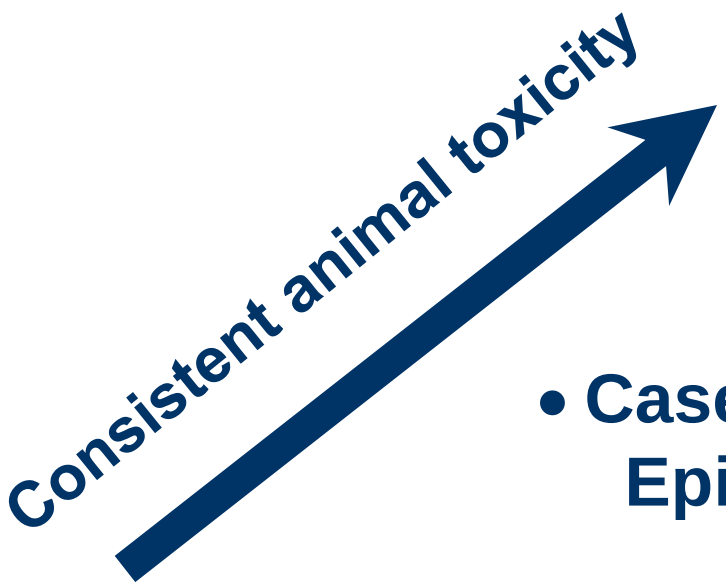
Epidemiology Shortcomings

- Confounders
- Exposure misclassification
- Recall bias
- Difficult outcome classification

Under-Recognition of Toxic Threats



What Makes Evidence Convincing?



MORE CONVINCING

- **Controlled Clinical Trials**
- **Case-Control and Cohort Epidemiologic Studies**
- **Cross-Sectional Epidemiologic Studies**

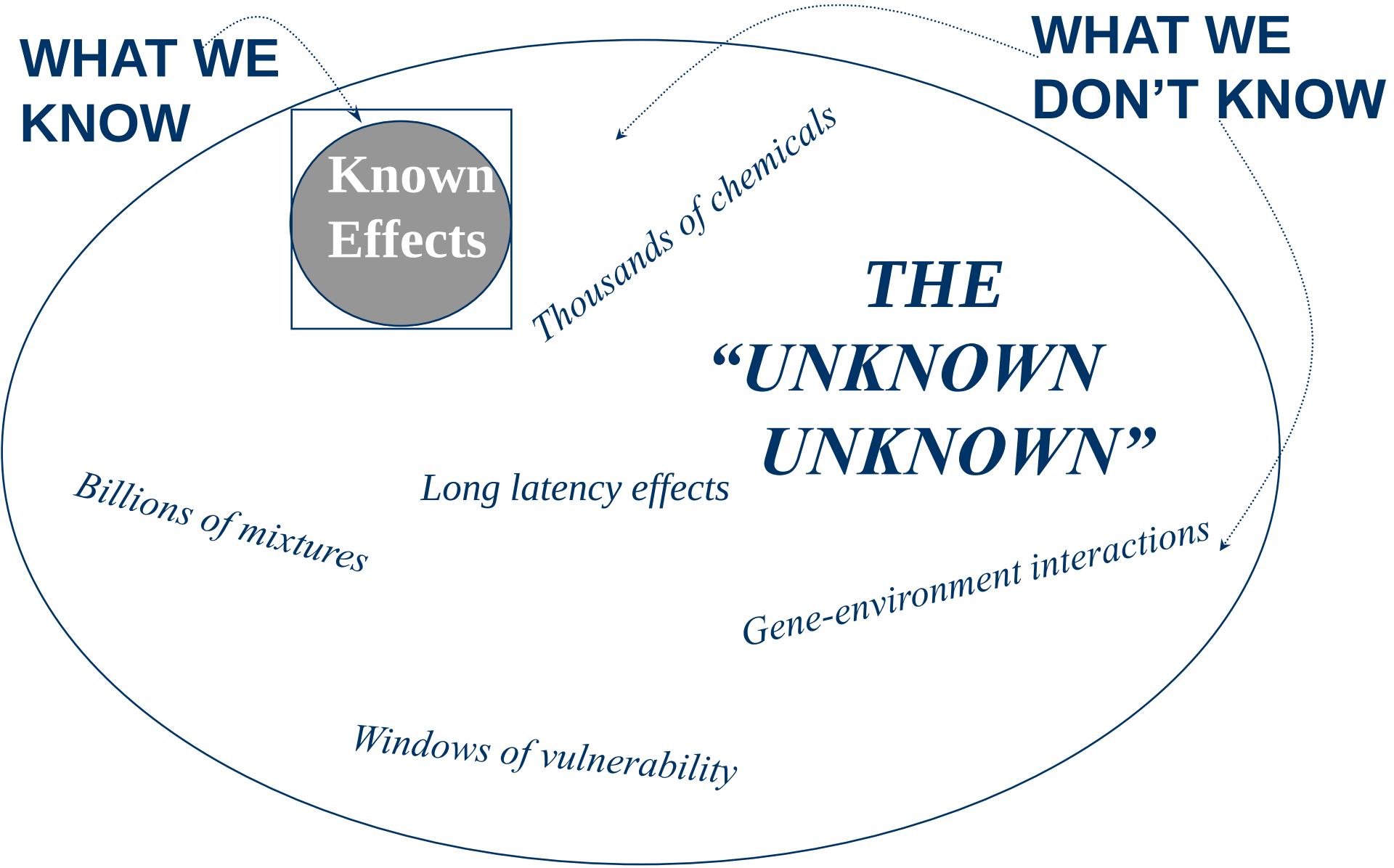
LESS CONVINCING

What Makes Evidence Convincing?

Building Blocks for a Strong Epidemiology Study

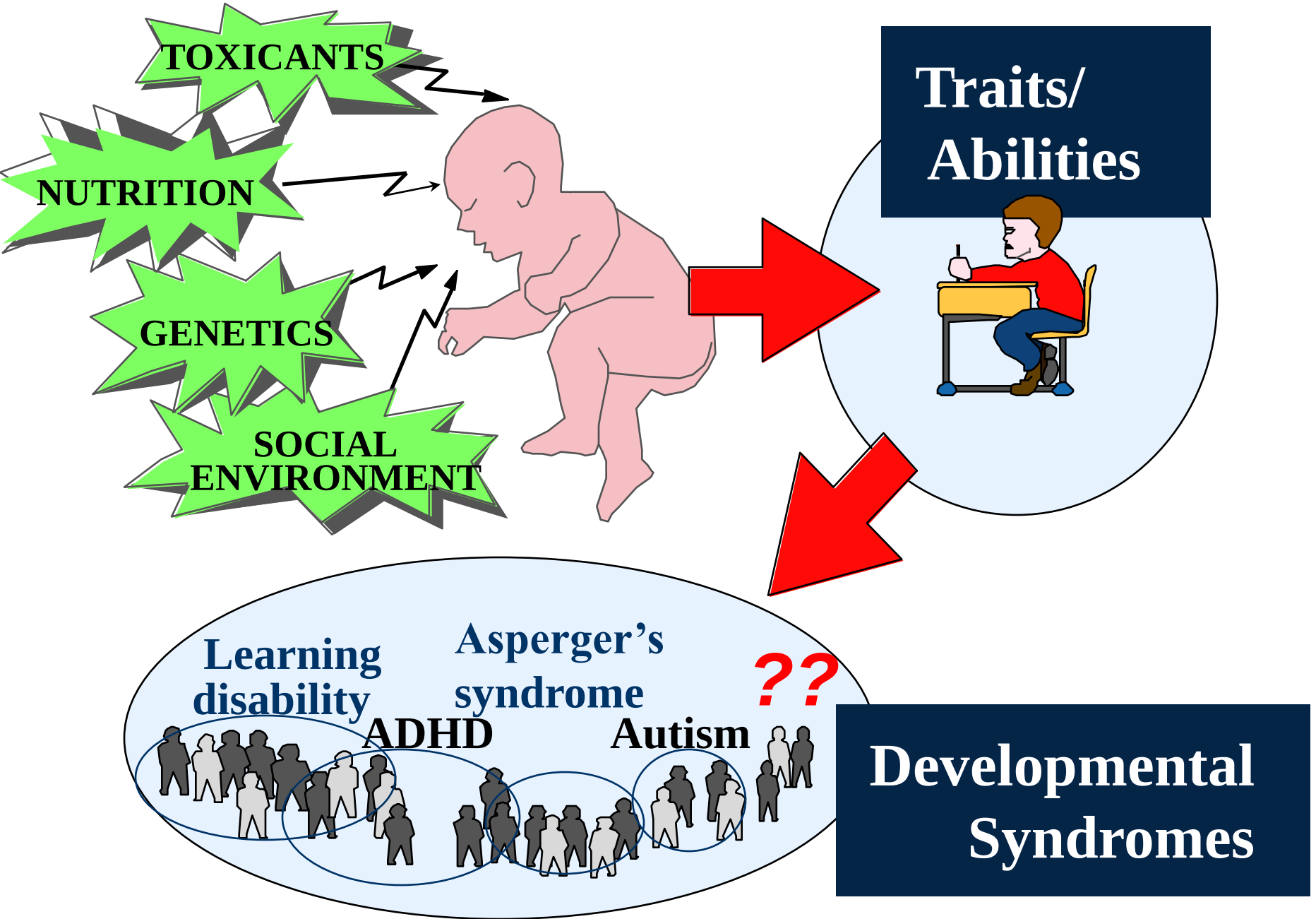
- Short latency
- Specific outcomes
- Adequate sample size
- Control of confounding
- Precise exposure measures
- Well-defined outcome measures

Under-recognition of Toxic Threats:
Epistemological Bias

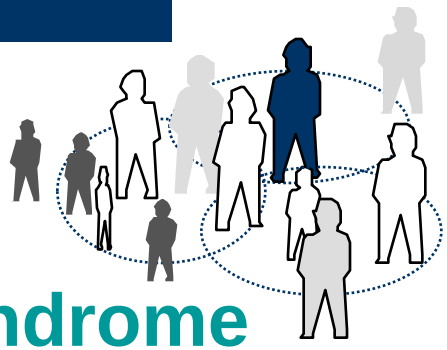


LEARNING, BEHAVIOR, AND DEVELOPMENT:
A SPECTRUM OF ACADEMIC DISCIPLINES

Framework for Understanding



Traits/Abilities vs. Clinical Syndromes



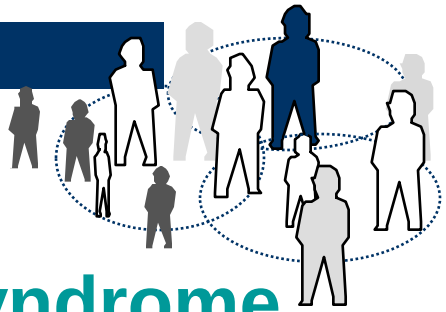
Trait/Ability

- Attention ability
- Impulsivity
- Executive function
- Memory
- Social adjustment
- Reading and verbal skills

Clinical Syndrome

- ADHD
- Learning disabilities
- Asperger's syndrome
- Autism

Traits/Abilities vs. Clinical Syndromes



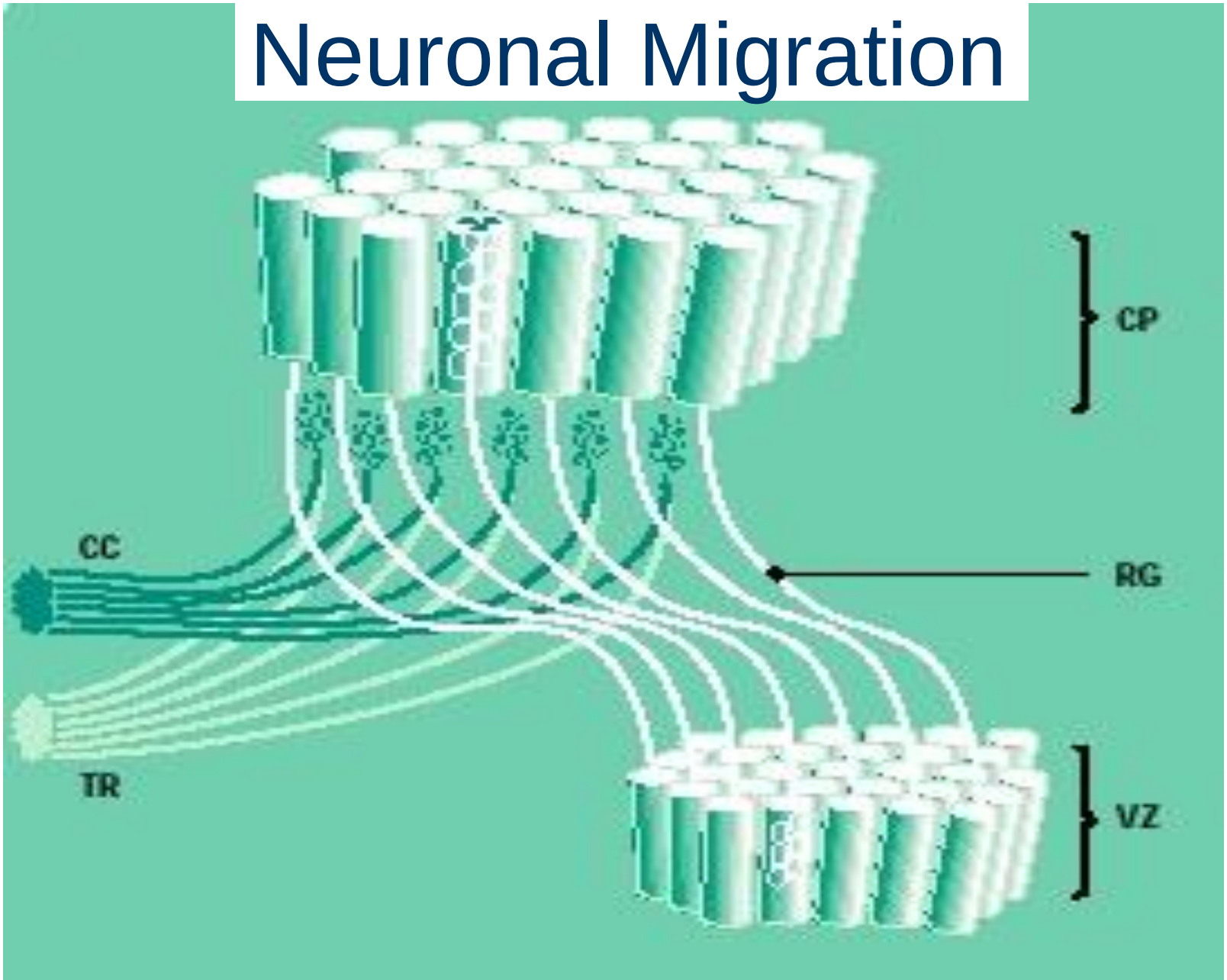
Trait/Ability

- Quantitative, dimensional
- Objective tests
- Animal models
- Apply to “normal” populations
- Definable criteria
- Useful research tools

Clinical Syndrome

- Qualitative, categorical
- Clinical judgment (subjective)
- No animal models
- Different from “normal”
- Variable diagnostic criteria
- Provide management strategies

Neuronal Migration



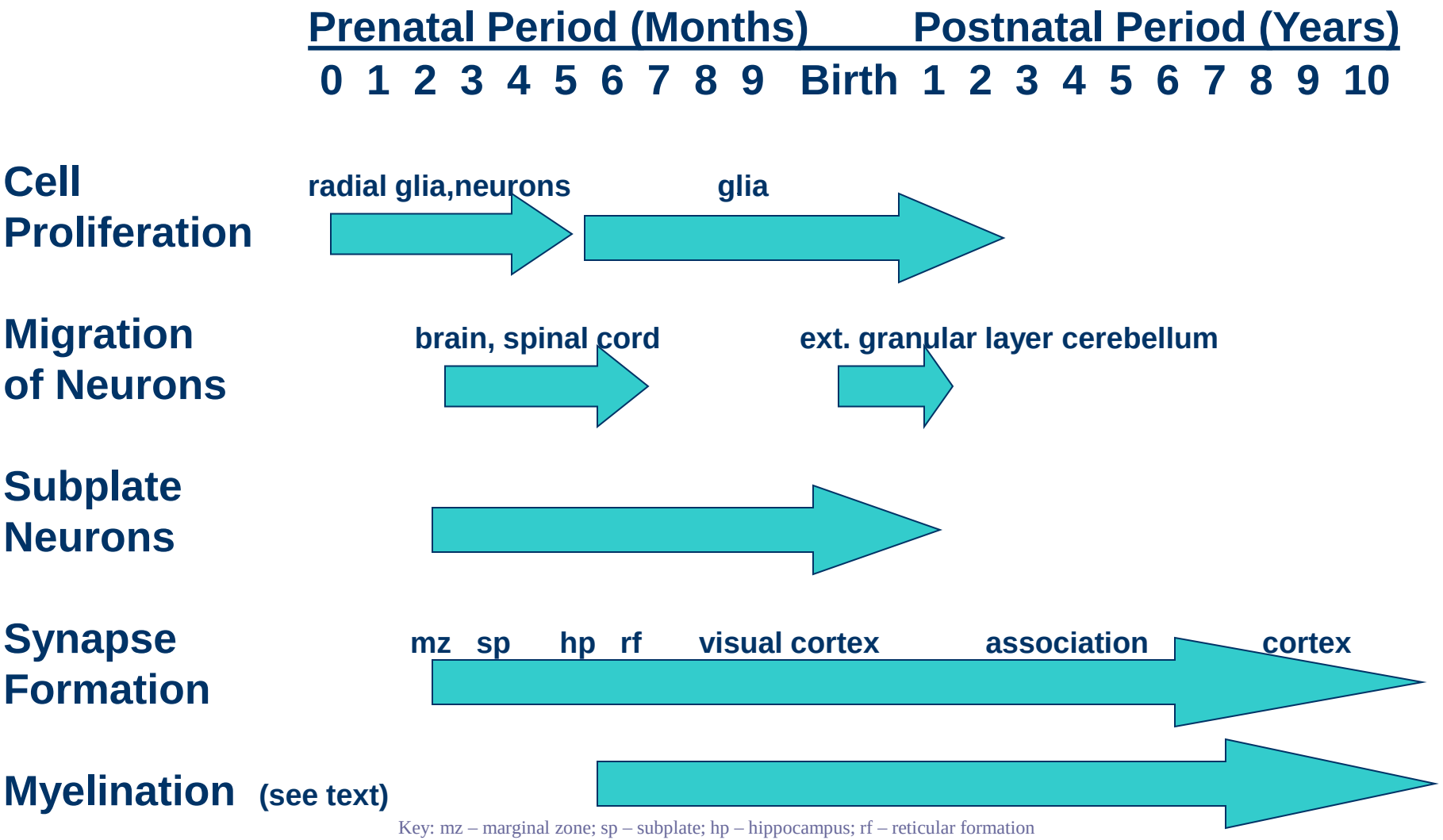
Cellular Events in Neurodevelopment

Events:

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

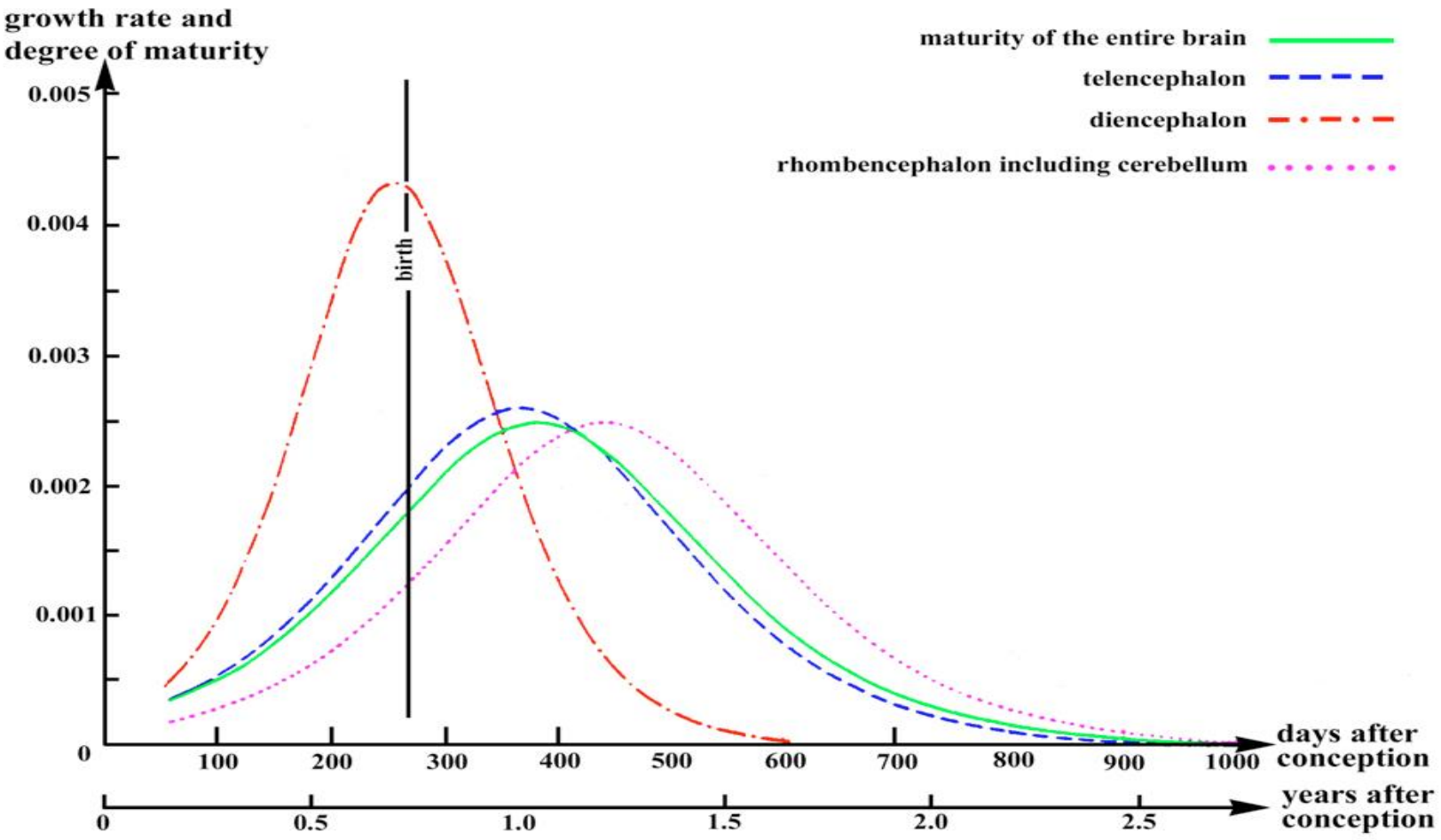
Active throughout childhood & adolescence

Time Lines of Developmental Processes in Humans



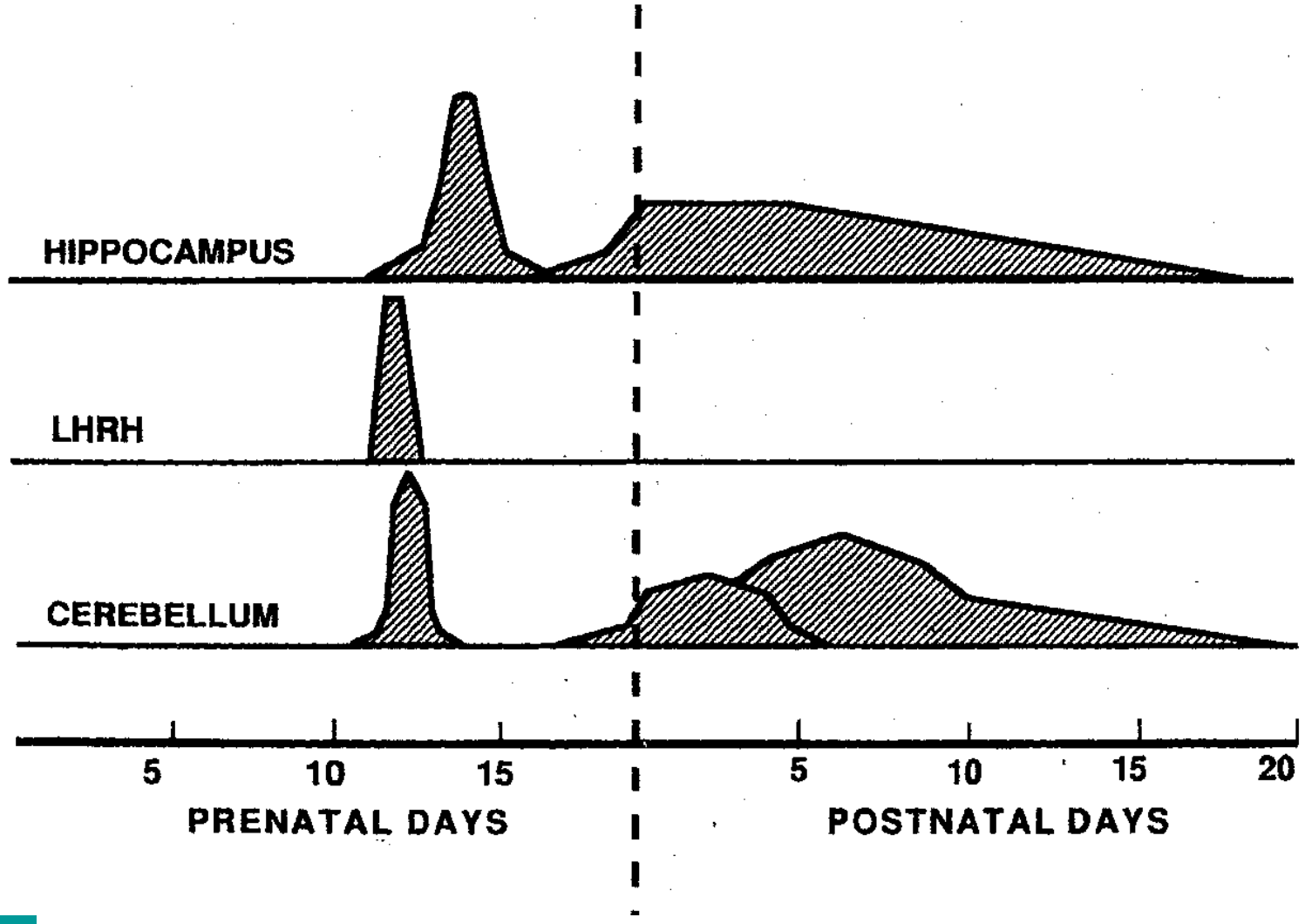
Key: mz – marginal zone; sp – subplate; hp – hippocampus; rf – reticular formation

Human Brain Growth Rate



Herschkowitz *et al.*, 1997; *Neuropediatrics*, 28:296-306.

Neural Proliferation (rodent)

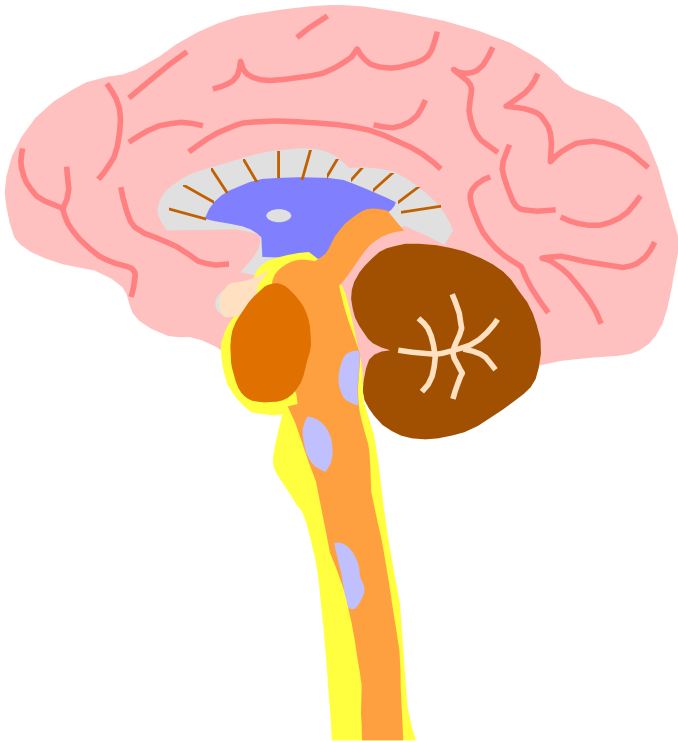


P Rodier EHP 102(Suppl 2) 1994

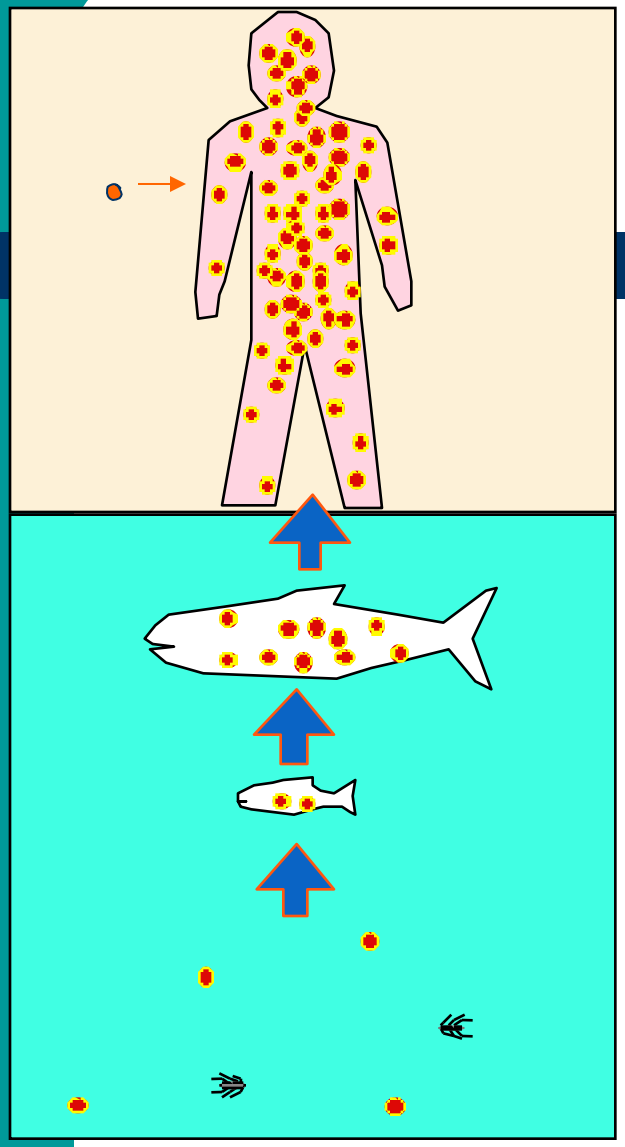
Cellular Events in Neurodevelopment

Summary:

- Critical sequence
- Vulnerable to disruption
- Size, timing, duration influence impact
- Downstream effects
- Susceptible throughout adolescence



Basic Toxicology: Exposure-related Concepts



- **Persistence**
- **Bioconcentration**
- **Transient exposures**

Section II Outline
Links: Chemicals and Disabilities

- **Basic Toxicology**
- **Lead**
- **Mercury**
- **PCBs**
- **Pesticides**

Toxicity-related Concepts: specific processes disrupted by neurodevelopmental toxicants

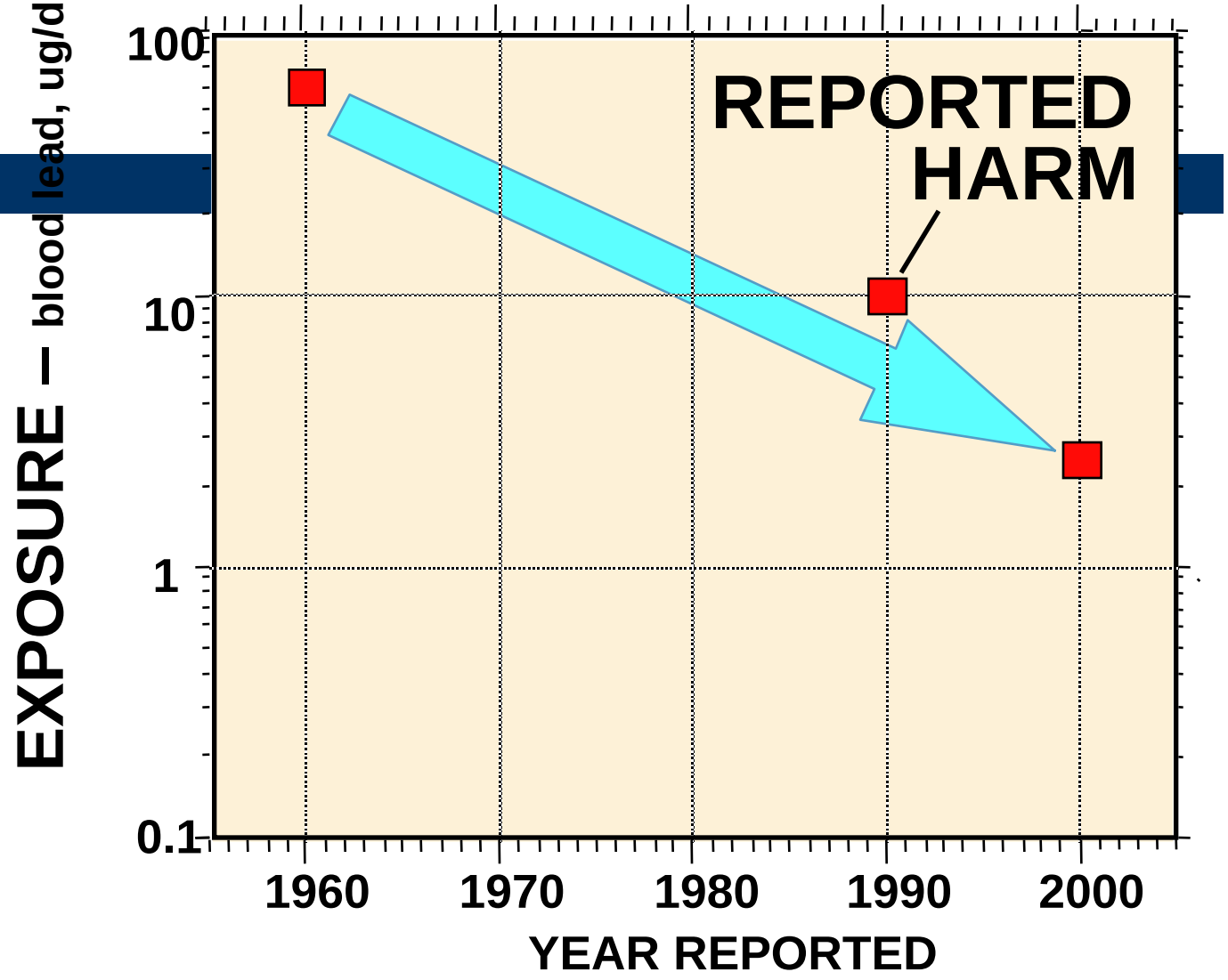
proliferation	radiation, ethanol, mercury, cholinesterase inhibitors
migration	radiation, mercury, ethanol
differentiation	ethanol, nicotine, mercury, lead
synaptogenesis	radiation, ethanol, lead, triethyl tin, parathion, PCBs
gliogenesis & myelinization	dec. thyroid, ethanol, lead
apoptosis	ethanol, lead, mercury
signaling	ethanol, cholinesterase inhibitors, mercury, lead, PCBs

Neurodevelopmental Toxicants: *The State of Knowledge*

- **Only 12 chemicals tested for neurodevelopmental toxicity according to current EPA guidelines.**
- **Extensive data on effects of lead, mercury, polychlorinated biphenyls (PCBs), alcohol, nicotine.**
- **Less extensive but substantial data on neurotoxic pesticides, solvents other than alcohol.**
- **Still fewer data on other compounds including manganese, fluoride.**

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

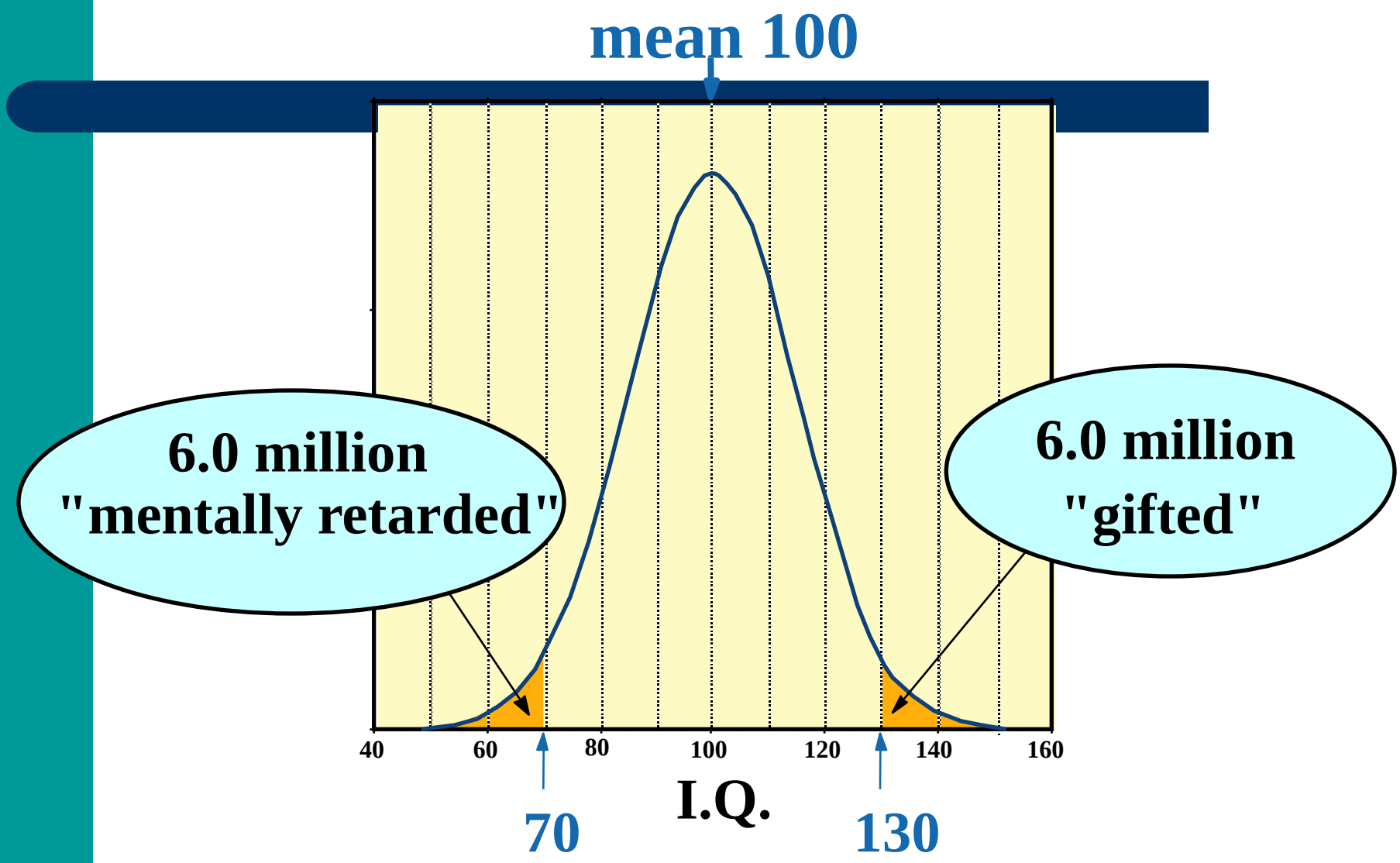
DECLINING THRESHOLD OF HARM - LEAD



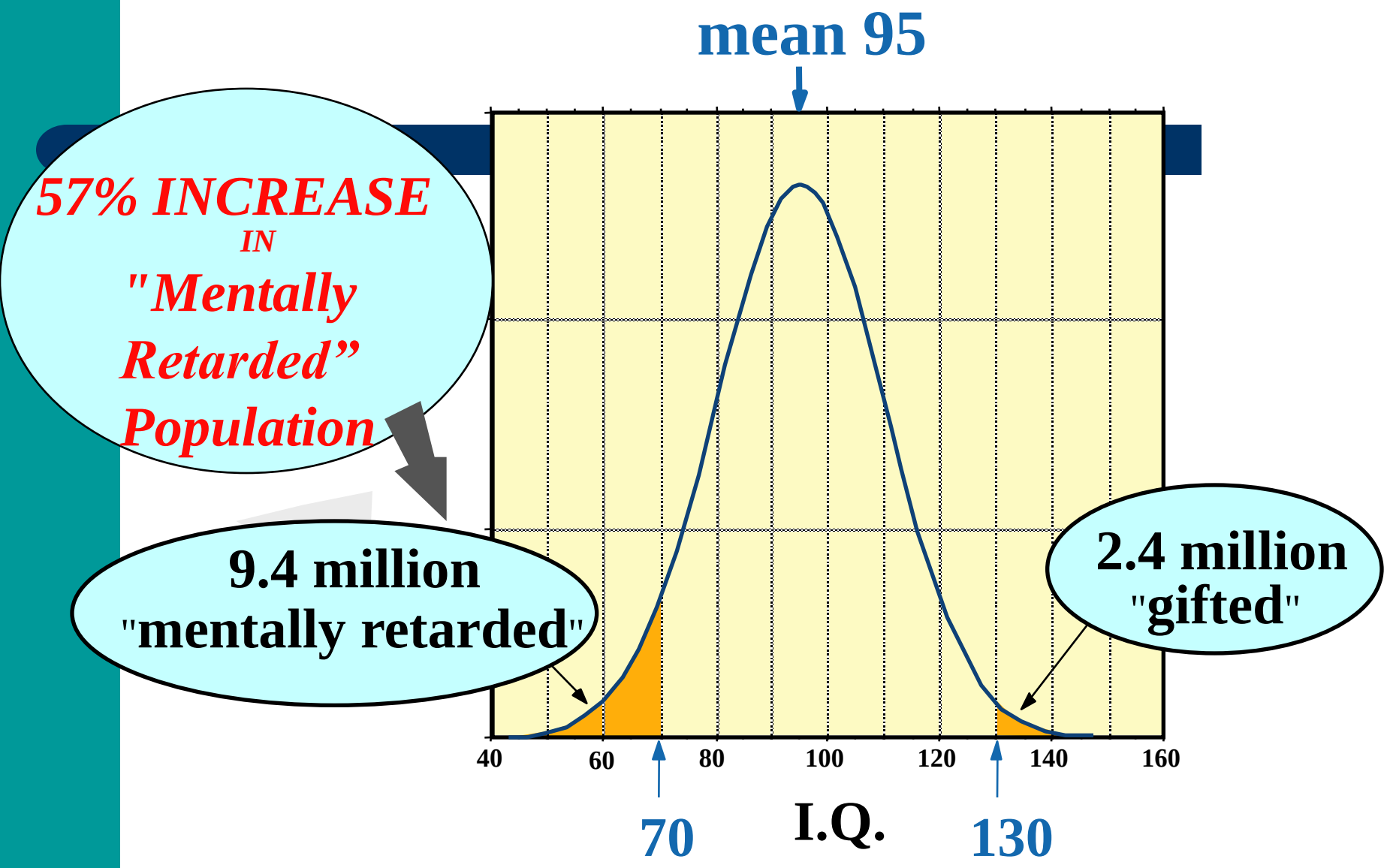
Note: Exposures expressed in micrograms/deciliter (blood le

The Significance of Small Effects:

EFFECTS OF A SMALL SHIFT IN IQ DISTRIBUTION IN A POPULATION OF 260 MILLION



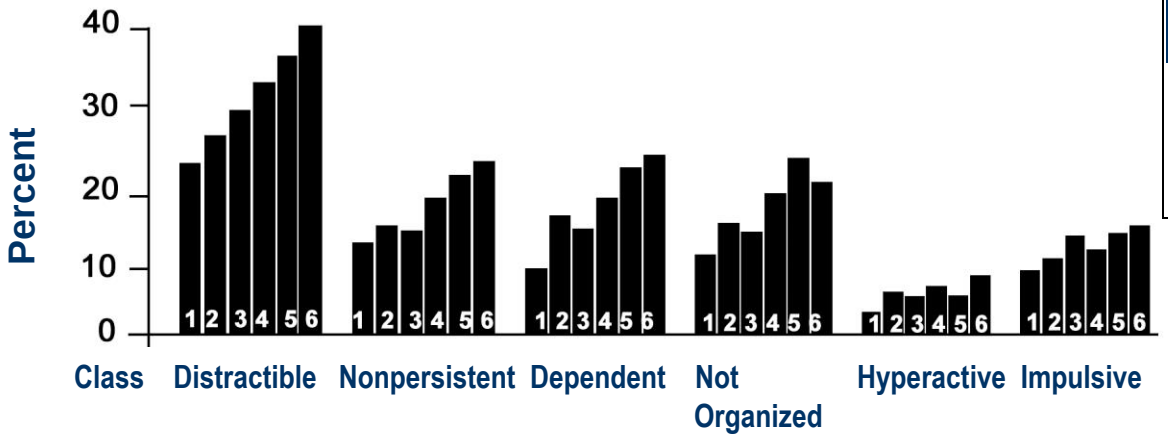
5 Point Decrease in Mean IQ



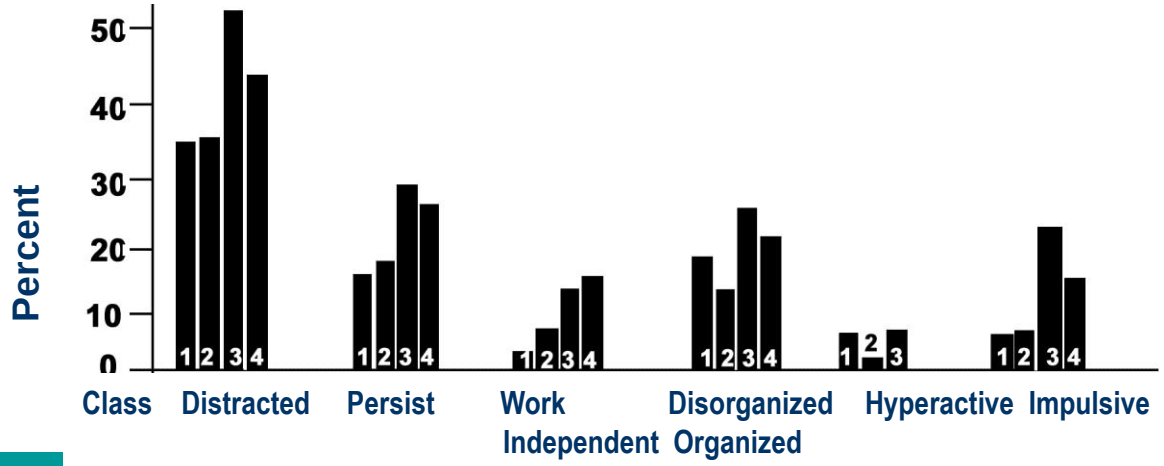
Effects of Lead on Cognitive and Behavioral Traits

Association of Teacher Ratings With Student Lead Burden

Lead

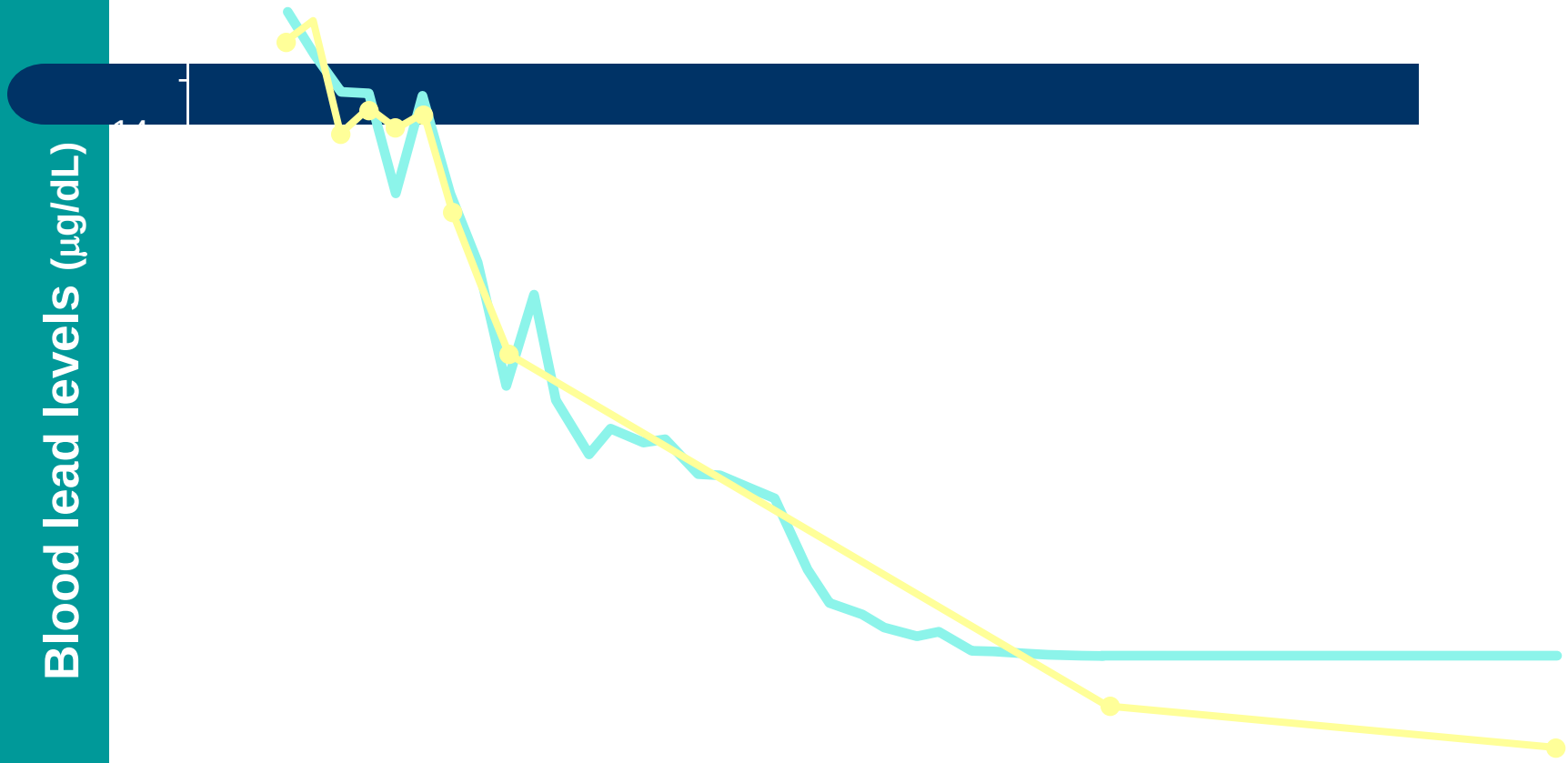


Class	Dentine Lead (ppm)
1	<5.1
[redacted]	
4	11.9-17.1
5	17.2-27.0
6	>27

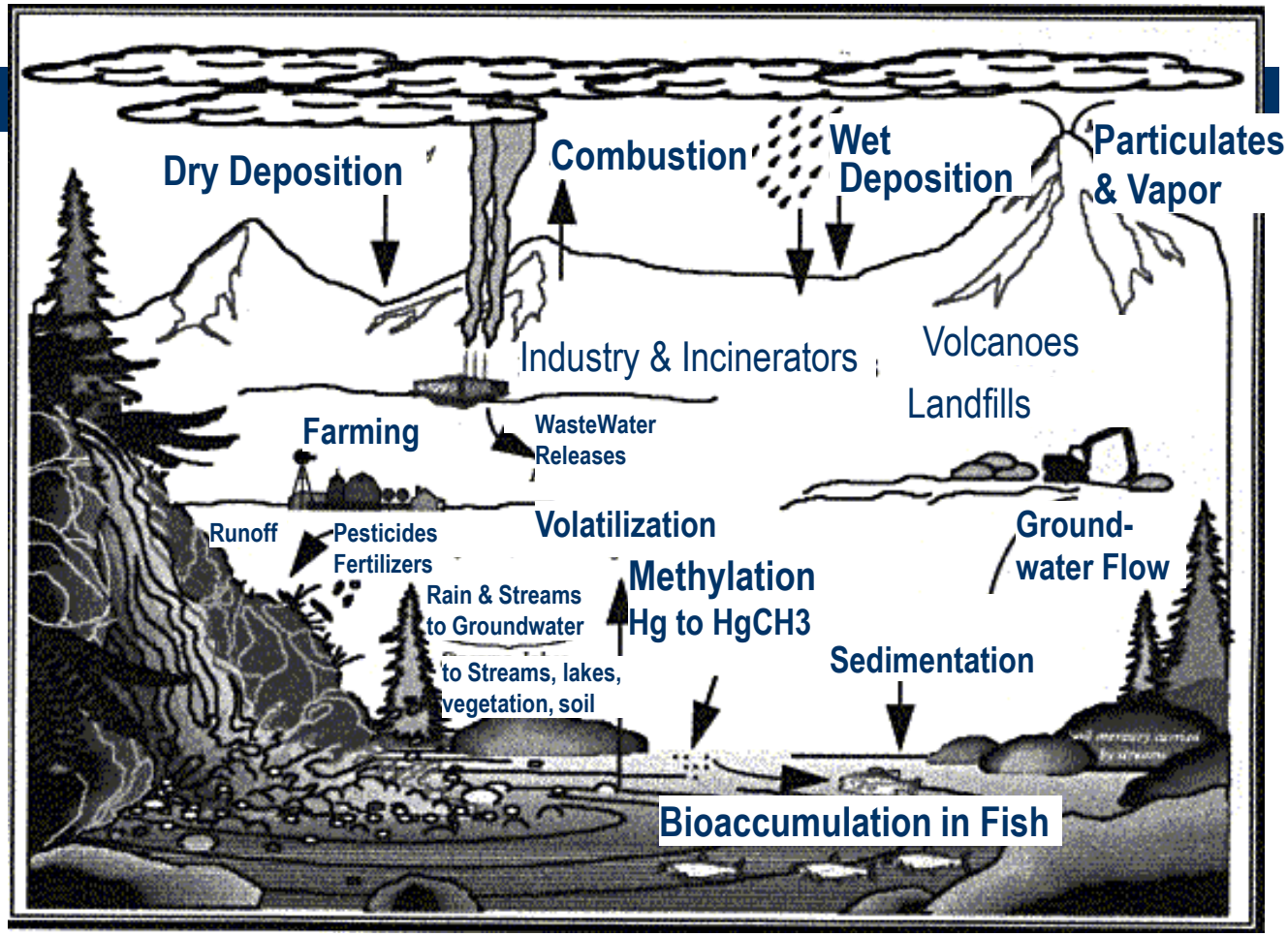


Class	Blood Lead, (micrograms/dl)
1	7-10
2	11-12
3	13-16
4	17-32

Blood lead levels i



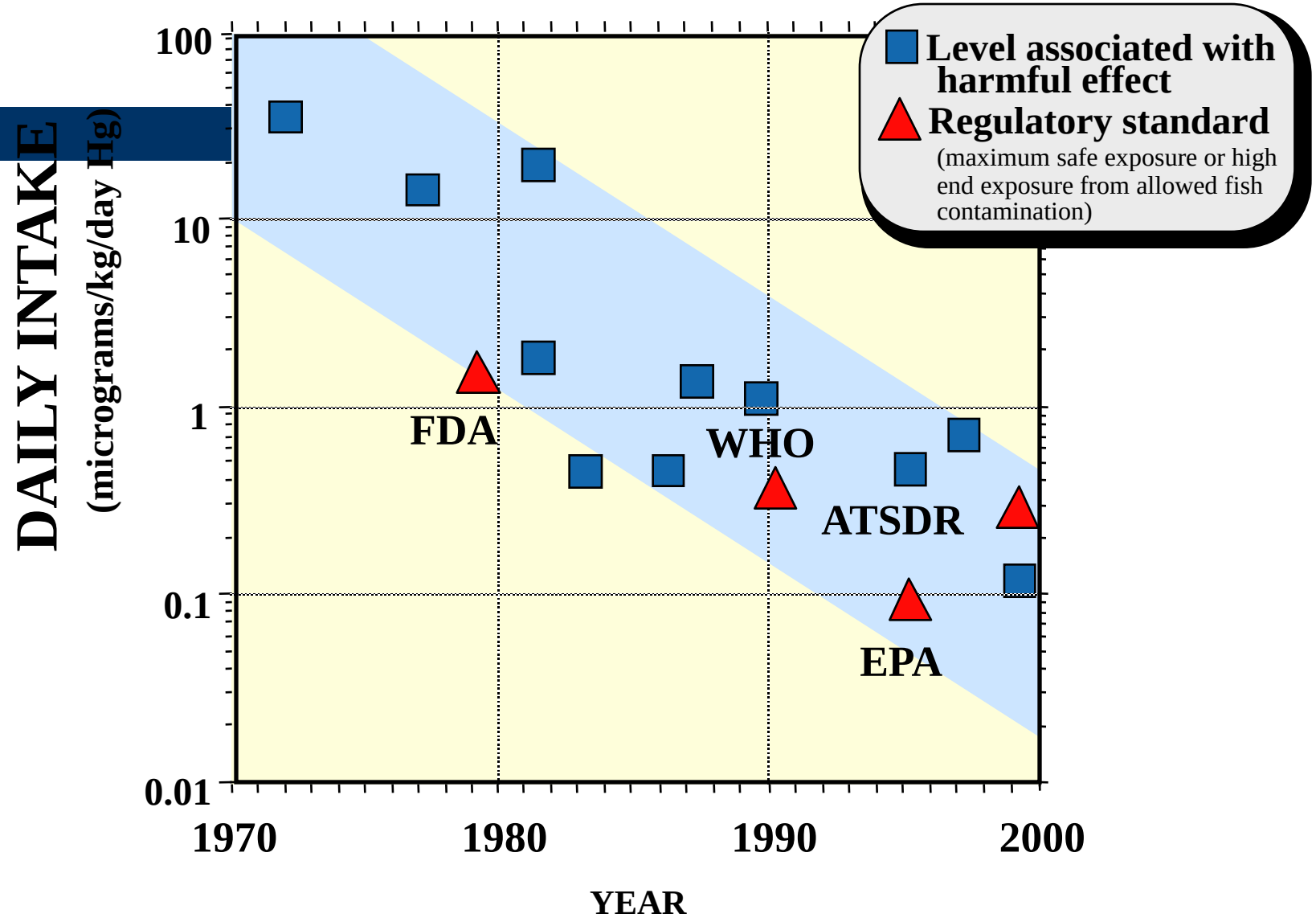
An Overview of Mercury



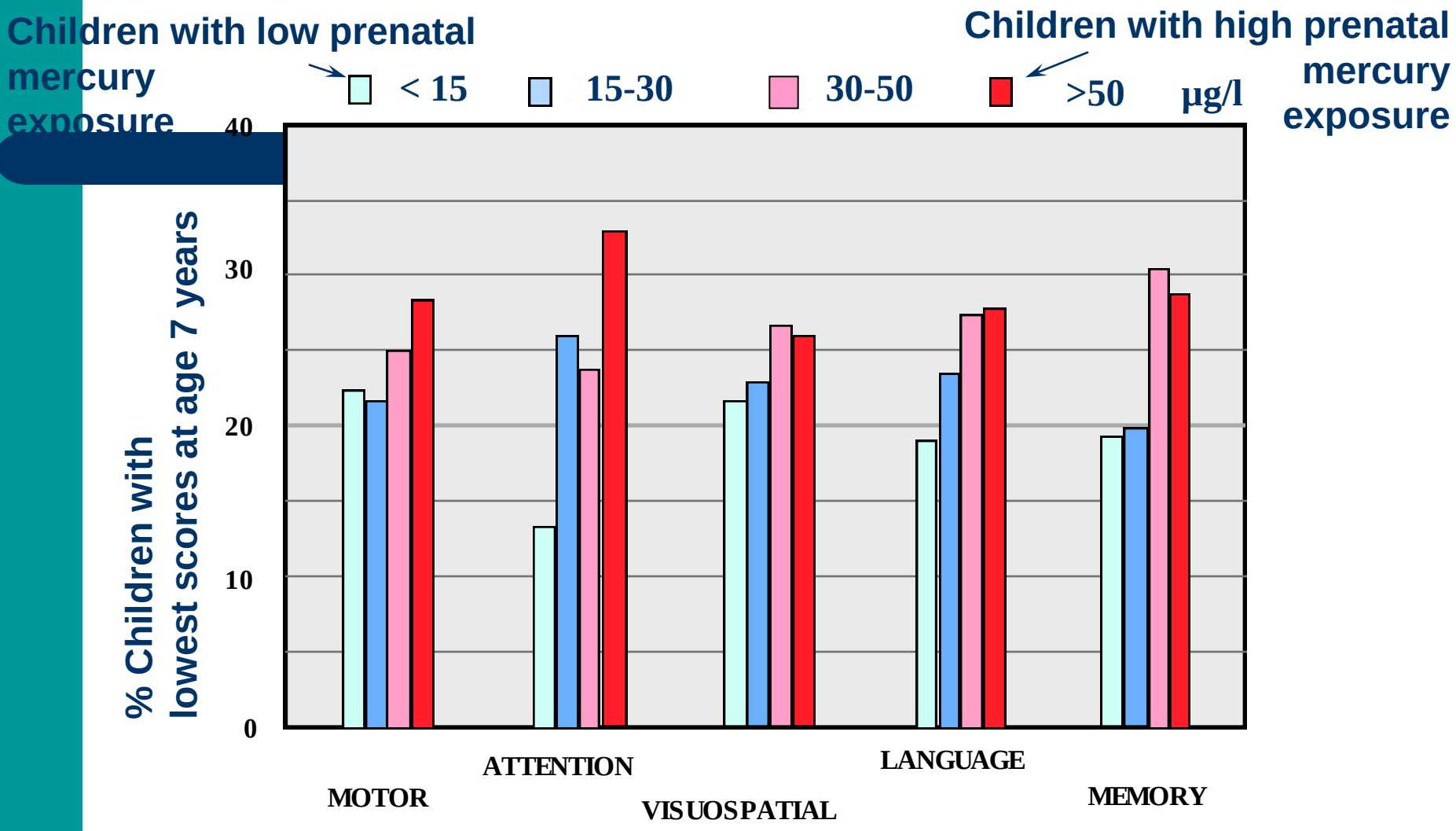
Mercury
Effects of Higher Dose Prenatal Exposure

- Mental retardation
- Seizures
- Cerebral palsy
- Disturbances of vision, hearing, sensation
- Abnormal gait
- Abnormal speech
- Disturbances of swallowing and sucking
- Abnormal reflexes

Mercury:
Declining Threshold of Harm



Mercury
Effects of Low Dose Prenatal Exposure



Source: Grandjean, et. al., "Cognitive Deficit in 7-year-Old Children with Prenatal Exposure to Methylmercury", Neurotoxicology and Teratology, Vol. 19, No. 6, 1997

Figure shows prenatal mercury exposure levels of Faroese children with scores in the lowest quartile after adjustment for cofounders. For each of the five major cognitive functions, one neuropsychological test with a high psychometric validity was selected.

Mercury Exposures

Advised Exposure Limit

- **EPA Reference Dose (“safe” upper limit) – 0.1 microgram/kilogram/day**
- **Equivalent consumption limit**
  - Women: 1.5 oz. swordfish or 7 oz. tuna/week
  - Child: 1 oz. tuna per 20 lb. body weight/week

Mercury Exposures

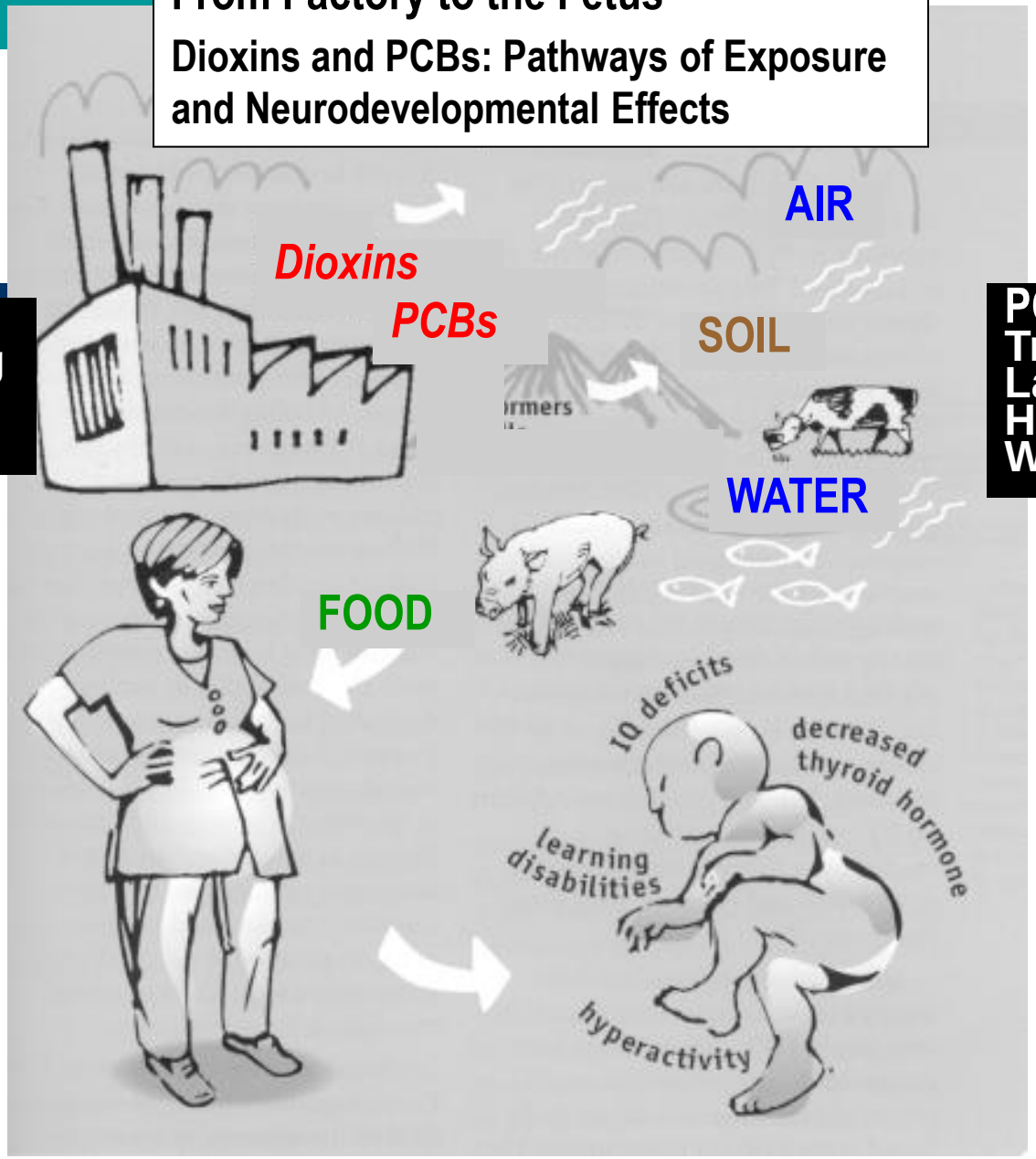
Current exposures

- **>10% of women of reproductive age exceed Reference Dose (RfD)**
- **50% of women who eat fish exceed RfD on any given day**
- **Higher risk: Subsistence fishers, immigrants, Native Americans**

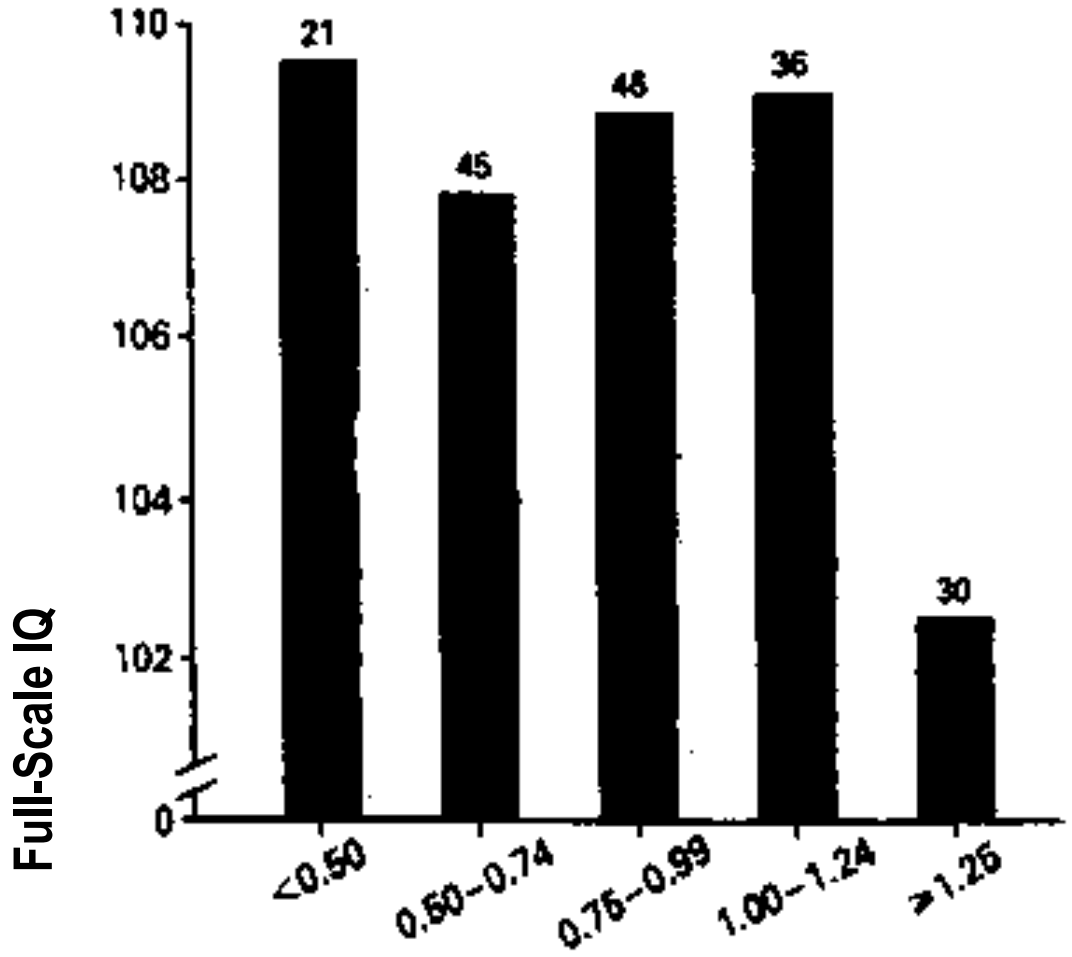
From Factory to the Fetus

Dioxins and PCBs: Pathways of Exposure and Neurodevelopmental Effects

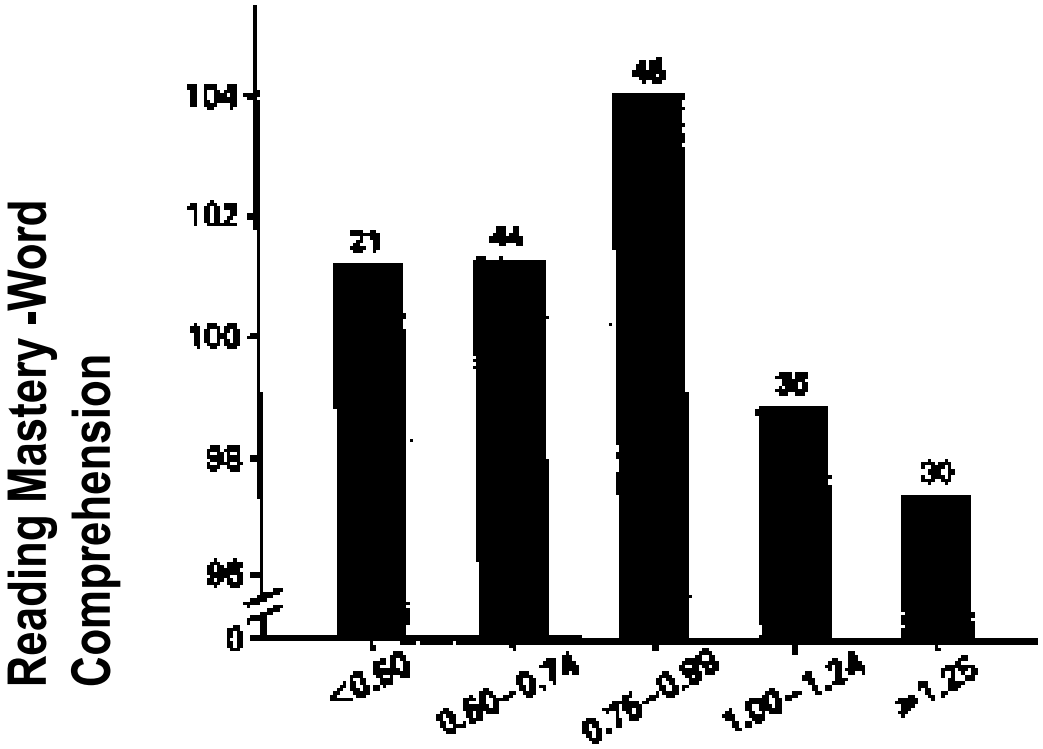
Dioxins:
PVC Manufacturing
Medical/Municipal
Incinerators



PCBs:
Transformers
Landfills
Hazardous Waste Sites



Prenatal Exposure to Polychlorinated Biphenyls (PCBs) ug/g of fat



Prenatal Exposure to Polychlorinated Biphenyls (PCBs) ug/g of fat

PCBs: PERVASIVE DEVELOPMENTAL EFFECTS

Infant

- Birth weight
- Head circumference
- Gestational age
- Performance on Brazelton Neonatal Behavioral Assessment (BNBA) - motor immaturity, poor lability, startle

PCBs: PERVASIVE DEVELOPMENTAL EFFECTS

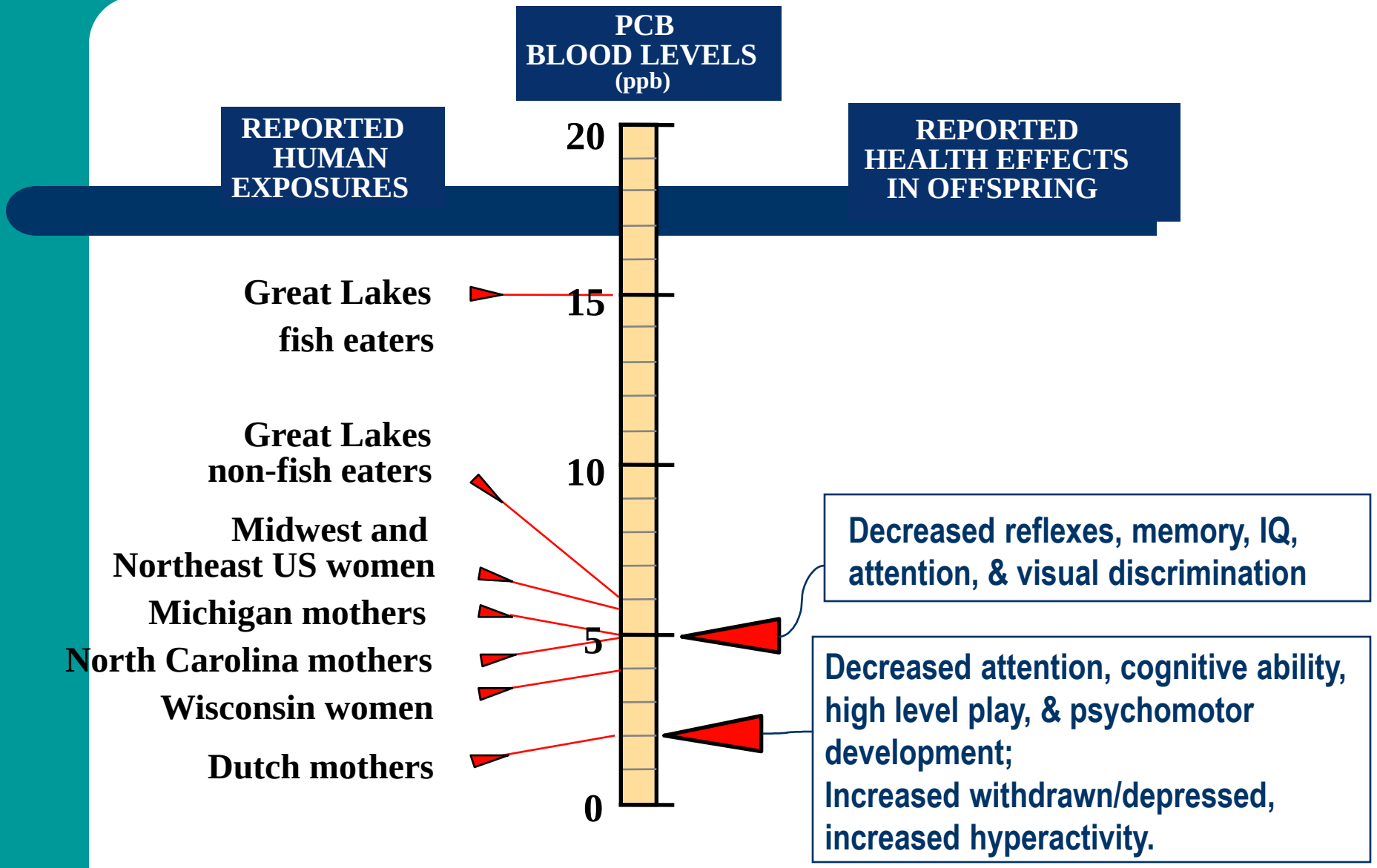
Early Childhood

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

Preteen

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

PCBs: Inadequate Margin of Safety



PCB Effects on Thyroid Hormone

- **Altered thyroid hormone**

  Mothers: ↓ Thyroid Hormone, ↑ Thyroid Stimulating Hormone (TSH)

  Infants: ↓ Thyroid Hormone, ↑ TSH

  Seals and Rats: Thyroid Hormone

- **Developmental Implications**

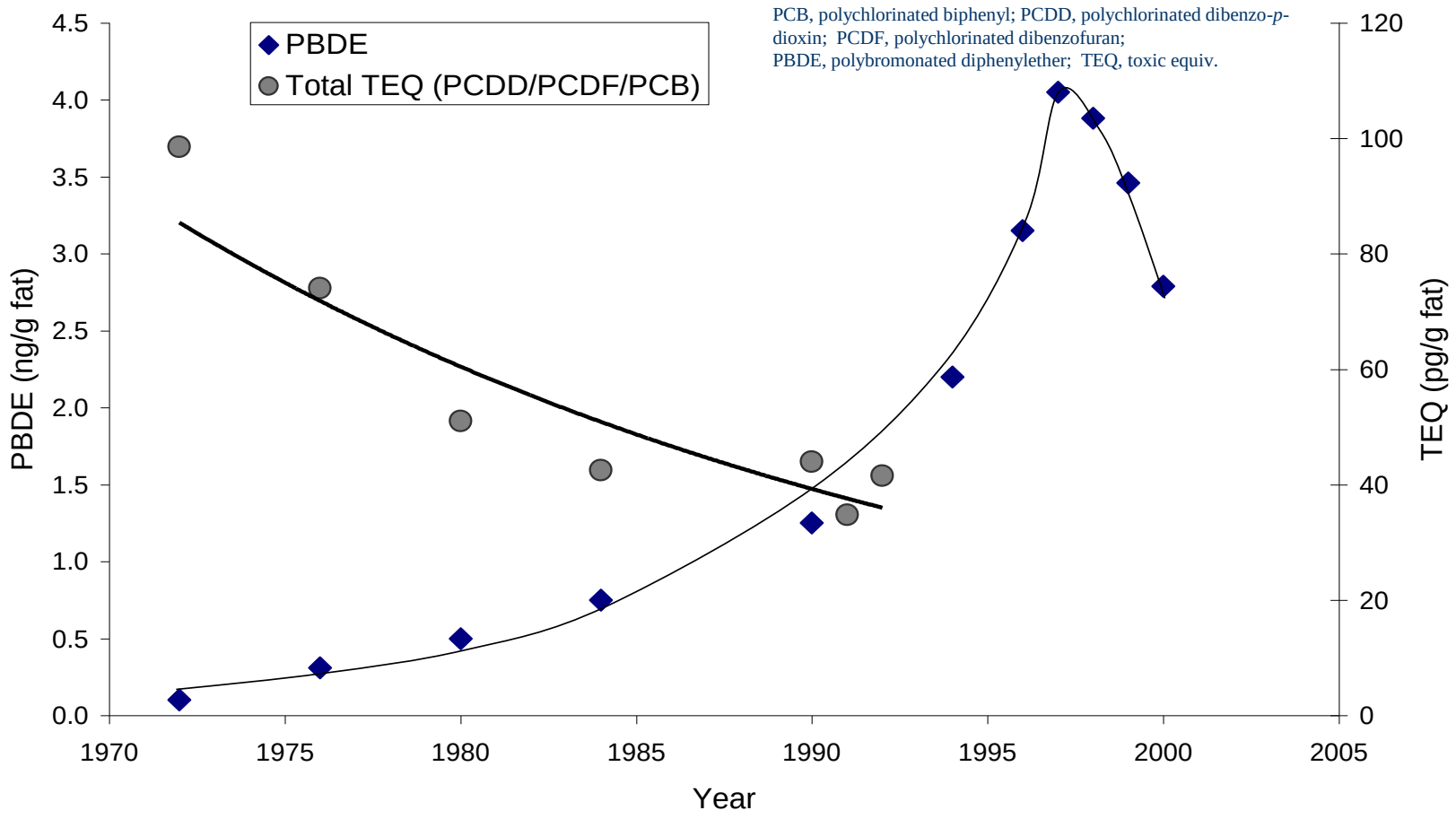
  Elevated maternal TSH during pregnancy, with or without reductions of thyroid hormone, associated with reduced IQ at age 7-9 yrs.

PCB Neurodevelopmental Effects: Possible Mechanisms

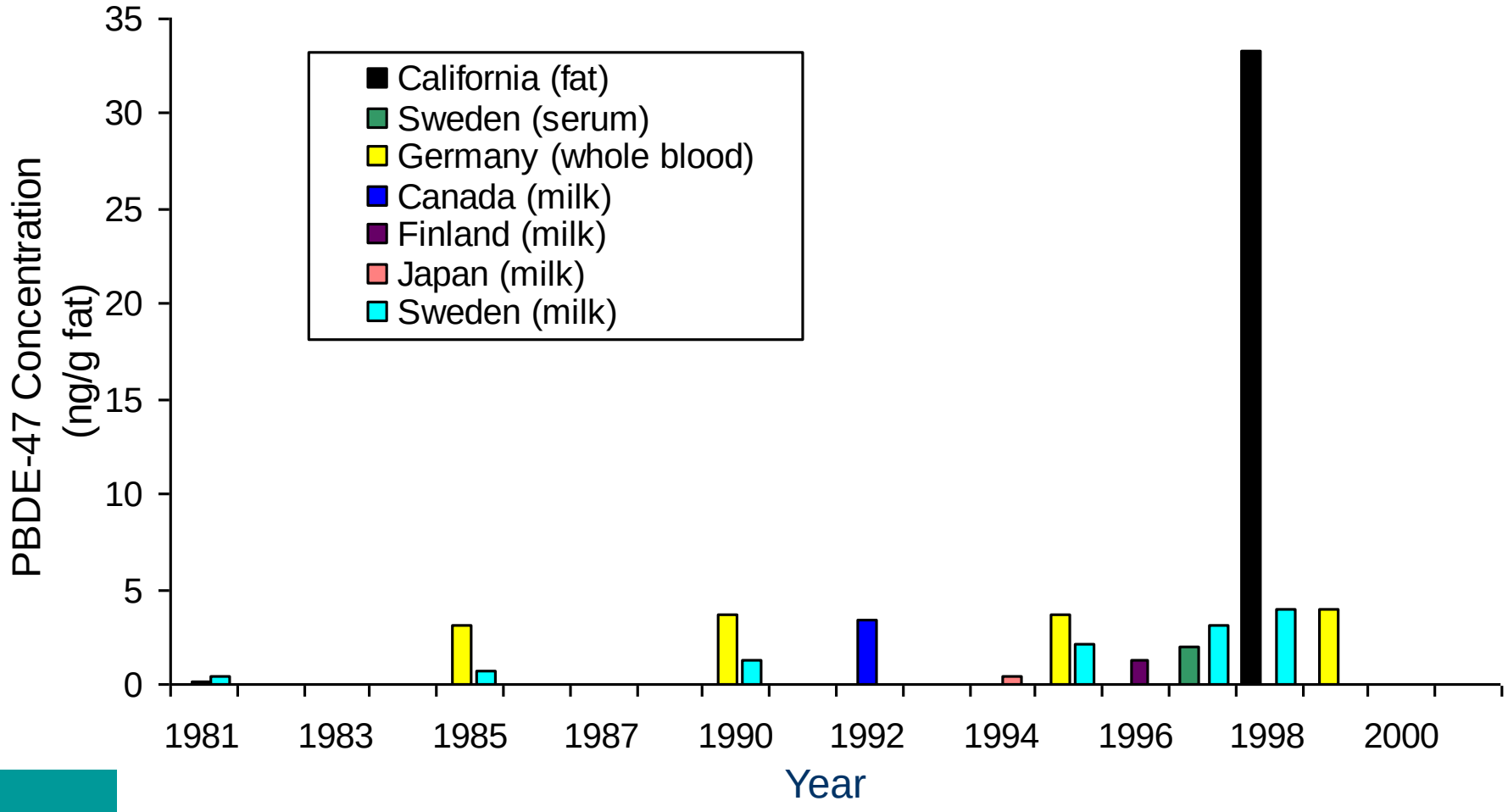
- **Altered neurotransmitter levels**
- **Ah receptor mediated effects (dioxin-like PCBs)**

  Disruption of production of growth factors and hormones including enzyme induction, modulation of growth factors, hormones
- **Interference with thyroid hormone**
  - metabolism through enzyme induction
  - interference with thyroid-hormone-mediated gene transcription
  - displacement of thyroxin from carrier protein

Organohalogen Compounds in Breast Milk in Sweden



PBDE Levels in Humans



PBDE, polybrominated diphenylethers. (She et al., 2001)

Pesticides

- Physical, chemical or biological agent intended to kill an undesirable plant/animal pest
- Major classes: insecticides, fungicides, herbicides
- Most pesticides are synthetic agents new to humans and the environment
  - Developed since 1940's
  - 891 pesticidal "active ingredients" licensed by US EPA*
  - 523 used on food or feed
- Inherent toxicity
  - 140 pesticides currently considered neurotoxic by EPA

* 1999 estimates

Acute, High Dose Toxicity

US Poison Control (2000)

- 11,000 unintentional organophosphate (OP) exposures; 3000 treated in health care facility
- includes 4000 children < 6 yr

World Health Organization

- 3 million acute, severe poisonings/yr
- 220,000 deaths/yr

Acute Toxicity: Tip of the Iceberg?

Limits of acute poisoning data

- Incomplete coverage of U.S. population
- Unreported incidents
- Long term impacts of acute/high level exposures

Limits of pesticide toxicity data

- Few studies of impact of chronic/low-dose exposures
- Few developmental/neurodevelopment studies

State of evidence: Analagous, perhaps, to what was known about lead toxicity in early 1900s?

Background Pesticide Exposures Widespread

- Reported use: 98% of families, 80% during pregnancy
- In Humans - detectable chlorpyrifos metabolites in 92% of children's, 82% of adults' urine samples
- In Food - detectable residues of at least one pesticide on 72% fruits/vegetables
- In Homes – 3 to 9 pesticide residues in typical home with 70% infant exposure from dust
- In Air - indoor air levels 10-100X higher than outdoor air
- In Water - >90% stream samples, 50% of wells

Rural Exposures: Agricultural Health Study

Exposures to farmers and families of farmer pesticide applicators:

- **27% of applicators store pesticides in their home**
- **94% of clothing worn for pesticide work is washed in the same machine as other laundry**
- **40% of wives of applicators also mixed or applied pesticides**
- **Over 50% of children aged 11 or more do farm chores**

Prenatal Exposures: The Urban Environment

Meconium assays in 20 newborns (Whyatt 2001):

- diethylphosphate (DEP); diethylthio-phosphate (DETP)
- Metabolites of chlorpyrifos, diazinon, parathion, organophosphate (OP) insecticides

Detections:

- DEP in 19/20 (95%) of samples (range 0.8-3.2 ug/g)
- DETP in 20/20 (range 2.0-5.6 ug/g)

In animal toxicity tests, chlorpyrifos, diazinon linked to adverse neurodevelopmental effects.

Minnesota Children's Pesticide Exposure Study

Urinary metabolites in 90 urban and non-urban Minnesota children, 3-13 yrs old (Adgate 2001):

Metabolite	*Parent Pesticides*
– 3,5,6-trichloro-2-pyrifinol (TCPy)	chlorpyrifos & related cmpds
– 1-naphthol (NAP)	carbaryl or napthalene
– malathion dicarboxylic acid (MDA)	malathion

Detections in first-morning-void samples

- TCPy 93%
- 1-NAP 45%
- MDA 37%

Insecticide Sites of Action

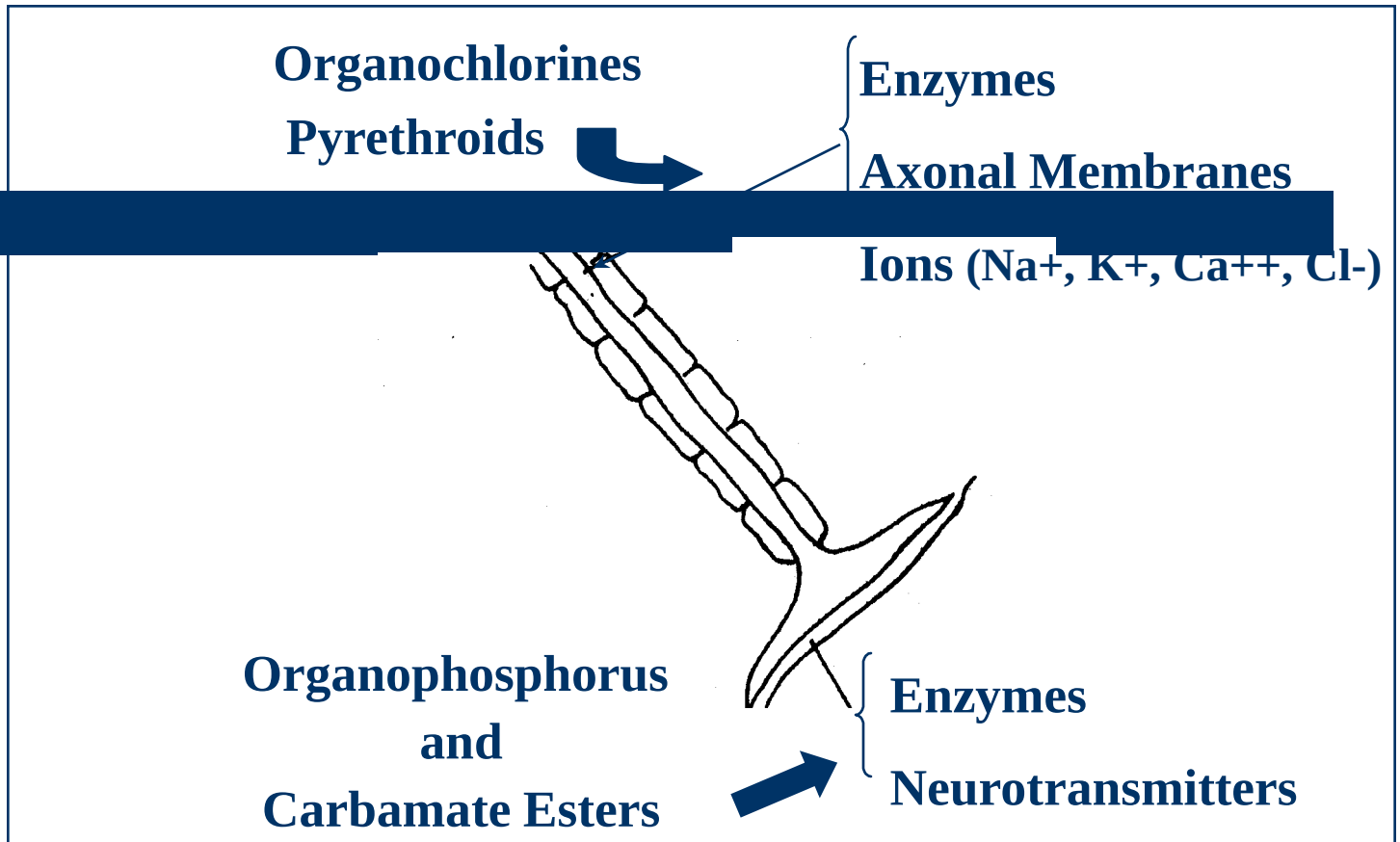


Figure 22-4. Potential sites of action of classes of insecticides on the axon and the terminal portions of the nerve.

Casarett and Doull's Toxicology: The Basic Science of Poisons, 5th Edition, Ed: Klaassen, CD. McGraw-Hill, New York, 1996. P. 649

Example of Pesticide Mechanism:

Organophosphate (OP)

Blocks function of cholinesterase

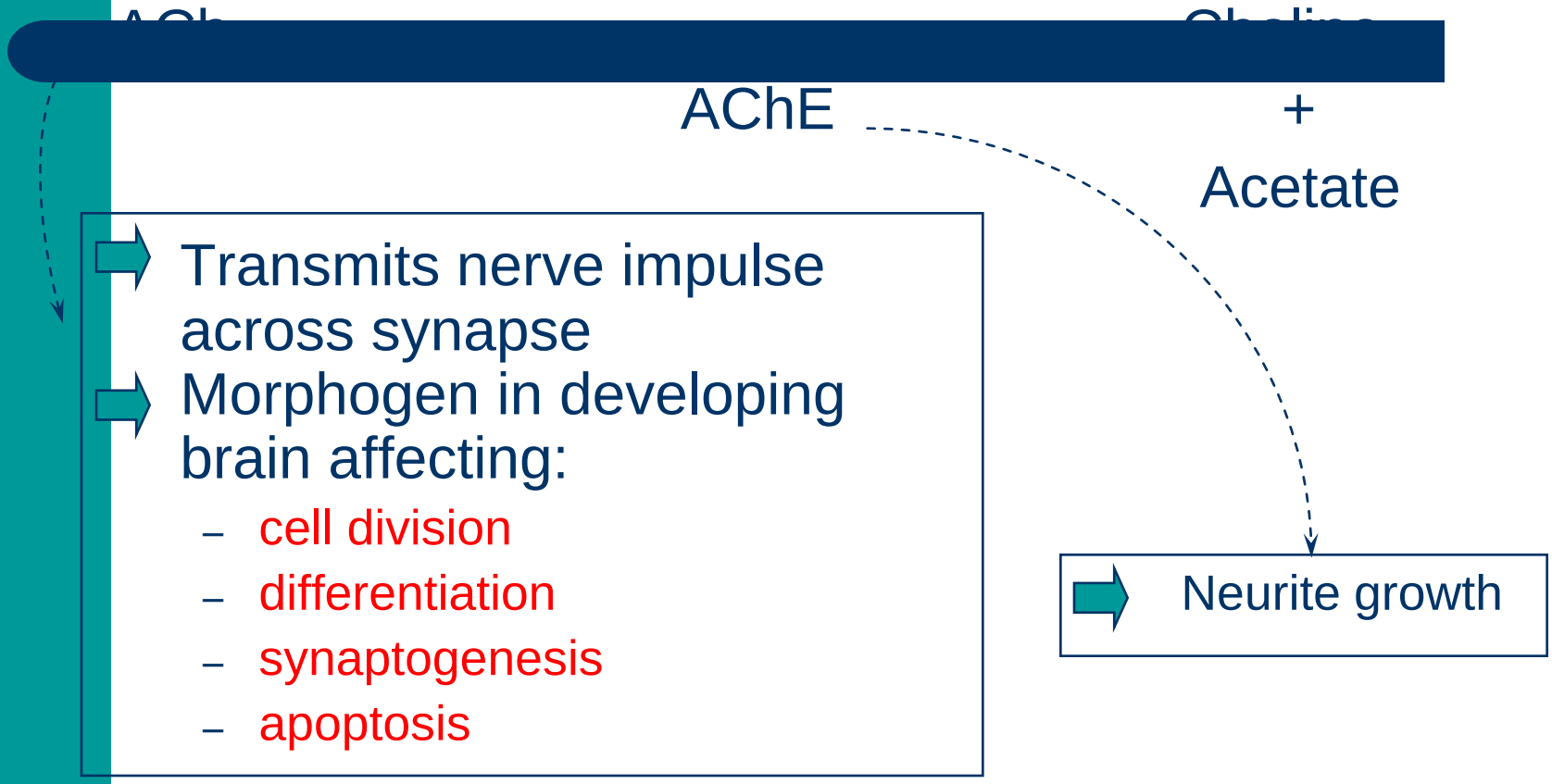
Increases levels of acetylcholine,
an important neurotransmitter

Effecting:

*Nerve impulse transmission

*Brain growth and development

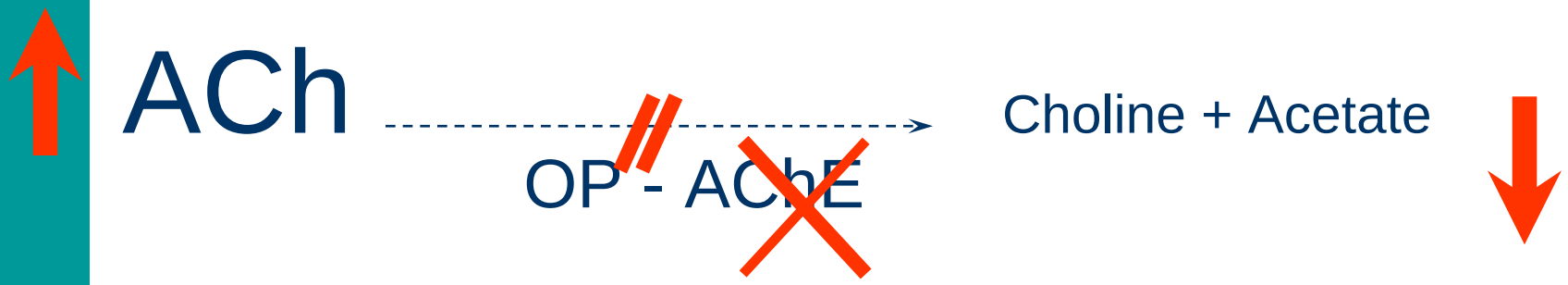
Normal Functions of Acetylcholine & Acetylcholinesterase



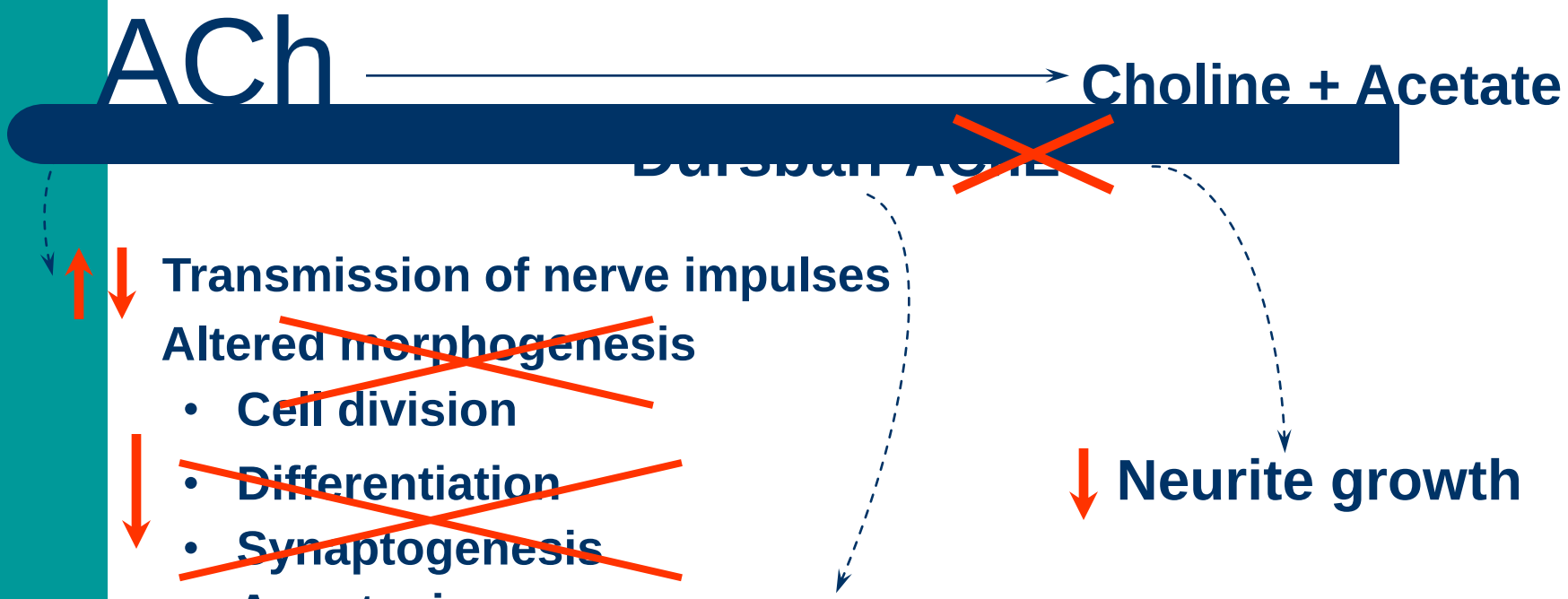
Organophosphate Pesticides (OP) Mechanisms of Toxicity

1. Normal:

2. With OP pesticide:



Disruption of ACh & AChE Function by Dursban



Noncholinergic Dursban effects:

- ↓ DNA synthesis, interfering with cell signaling cascades (cholinergic and noncholinergic cells)

Organophosphate Pesticide (OP) Effects in Laboratory Animals

OP	Cellular effect	Behavior
DEP	↓ muscarinic cholinergic receptors in brain	hyperactivity at 4 mos. of age
Dursban	↓ muscarinic cholinergic receptors in brain	altered reflexes righting cliff avoidance
	↓ brain weight	auditory startle ↓
Diazinon		↓ delayed reflexes contact placing ↓ coordination ↓ endurance

All low dose (<7 mg/kg/day)

Early developmental exposure

New Risk Assessments Raise Concerns

- Concerns raised by EPA risk assessments of individual OPs, resulting in:
  - Dursban – over the counter sales banned
  - Diazinon – banned indoors, phase out 4 yrs
- EPA assessment of cumulative OP risks:
  - Only cumulative impact on cholinesterase inhibition considered
  - No developmental neurotoxicity testing available for most of the 35 registered OPs

Section III Outline:
Magnitude of the Chemical Threat

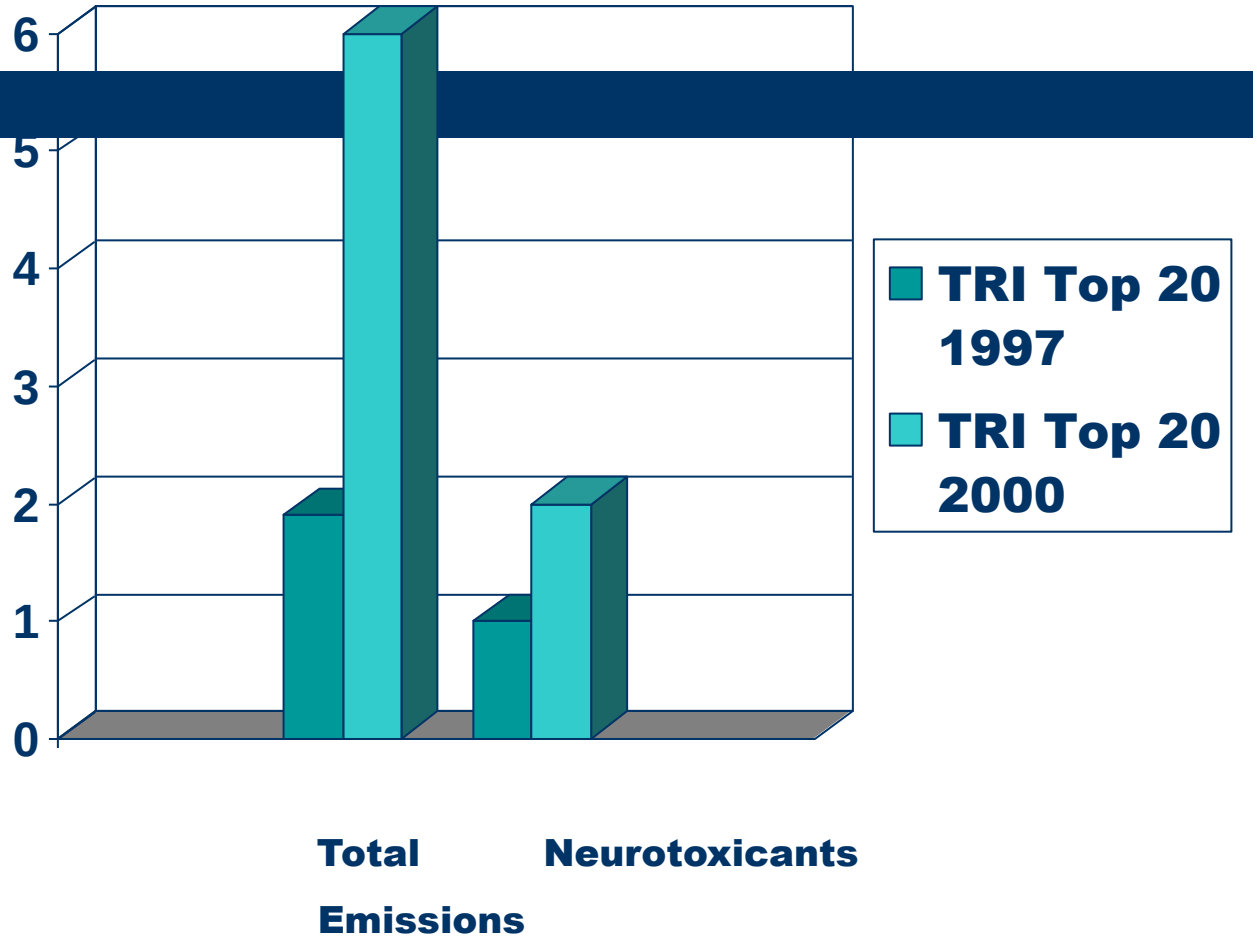
- **Production and Releases**
- **(Lack of) Regulatory Oversight**
- **Conclusions**

The Chemical Environment

- 80,000 chemicals in the Federal inventory
- 2,000 to 3,000 new chemicals introduced each year

Toxics Release Inventory Top 20 Chemicals

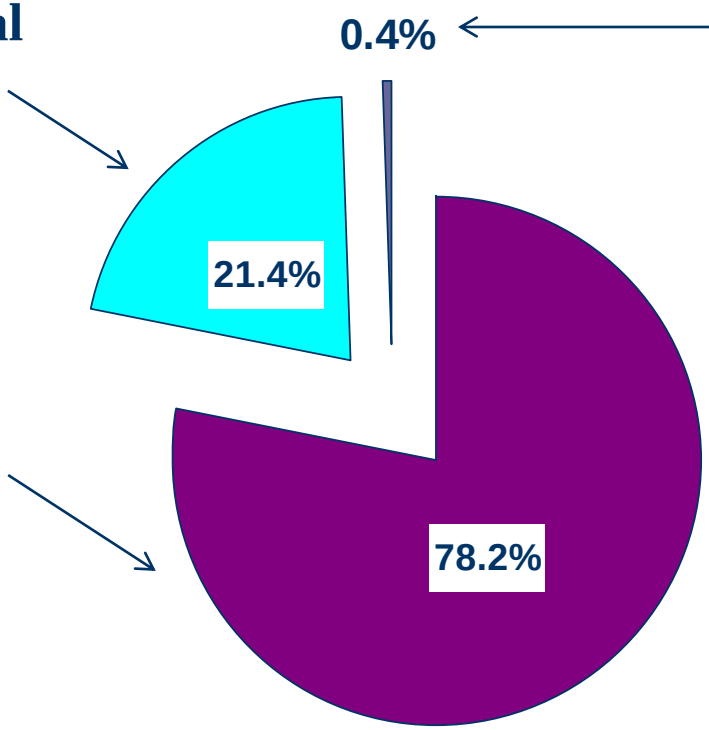
Over 2 Billion lbs of Neurotoxic Emissions in 2000



TRI – Toxics Release Inventory

Developmental Testing of 2,863 Chemicals Produced > 1 million lbs/year

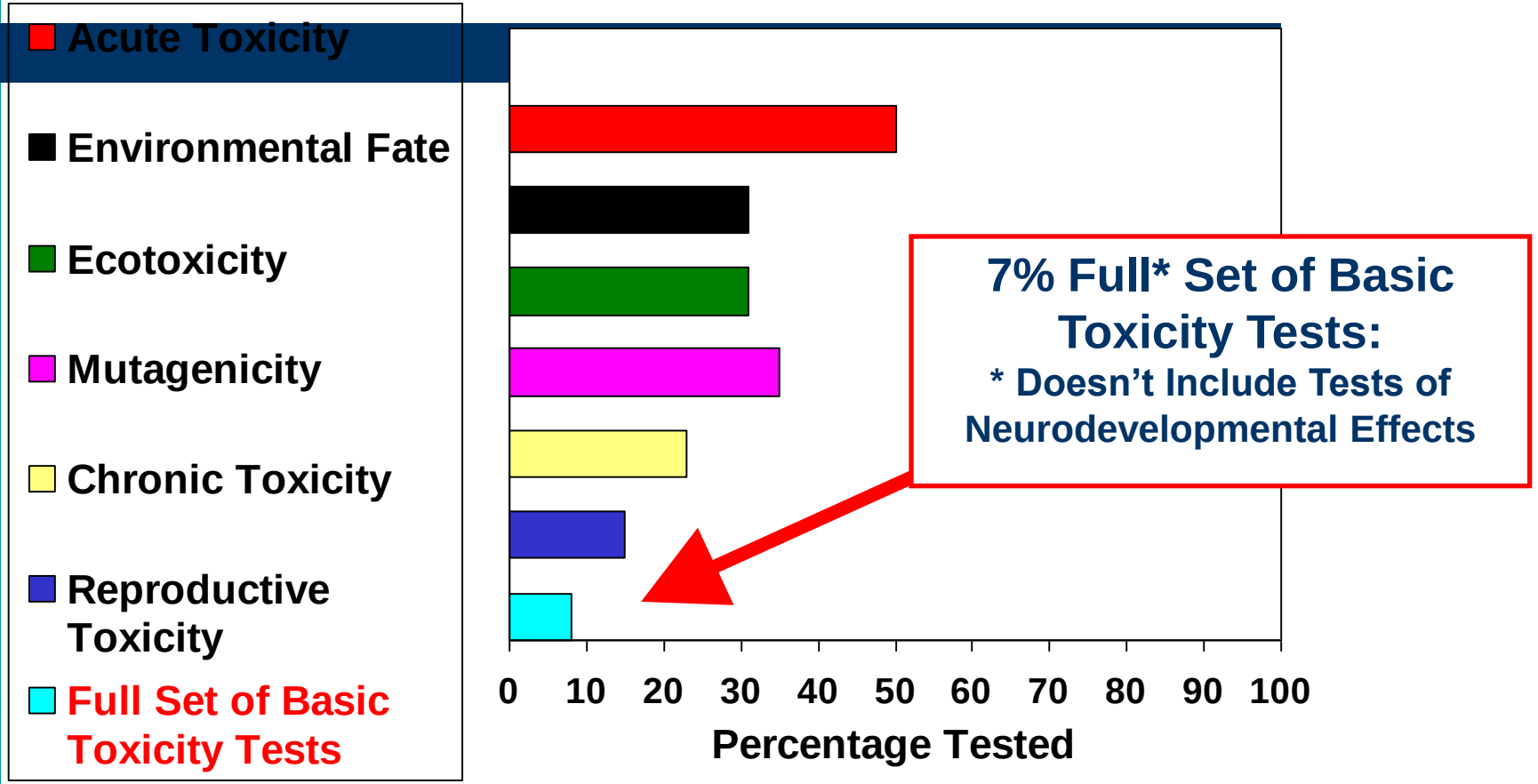
Some Data On Developmental Toxicity



12 Tested for Neurodevelopmental Toxicity According to EPA Guidelines

No Data On Developmental Toxicity

Hazard Data - Chemicals Produced > 1 Million Pounds/Year



Failure to Evaluate Impacts on Children in Chemical Regulation

- Developmental neurotoxicity testing (DNT) not required
- DNT testing not in proposed voluntary testing schemes
- Even for chemicals with some toxicity data, database has important deficiencies.

Failure to Evaluate Impacts on Children

- Deficiencies in animal studies:
  - Underestimate human DNT by 100-10,000 fold (Hg, Pb, PCBs)
  - Single genetic strains
  - Test single chemical exposures (real exposures are to mixtures)
  - To test 10% commercial chemicals in combinations of three requires 85 billion tests.
- Prospective epidemiological studies rarely available

Emerging Themes

- With increasing scientific understanding, as neurodevelopmental effects emerge, estimates of toxic thresholds tend to fall.
- Animal testing for neurodevelopmental toxicity has underpredicted human vulnerability by a factor of 100-10,000 (HG, lead, PCBs).
- Subtle effects in individuals may carry profound impacts when expressed over a population.
- Adverse effects of some developmental neurotoxicants are synergistic or additive.

Guiding Principles

1. Disabilities are widespread. Chemical exposures are important preventable contributors to these conditions.

2. Apparent toxicity at high doses should be a red flag for possible harm from low-dose “background” exposures.

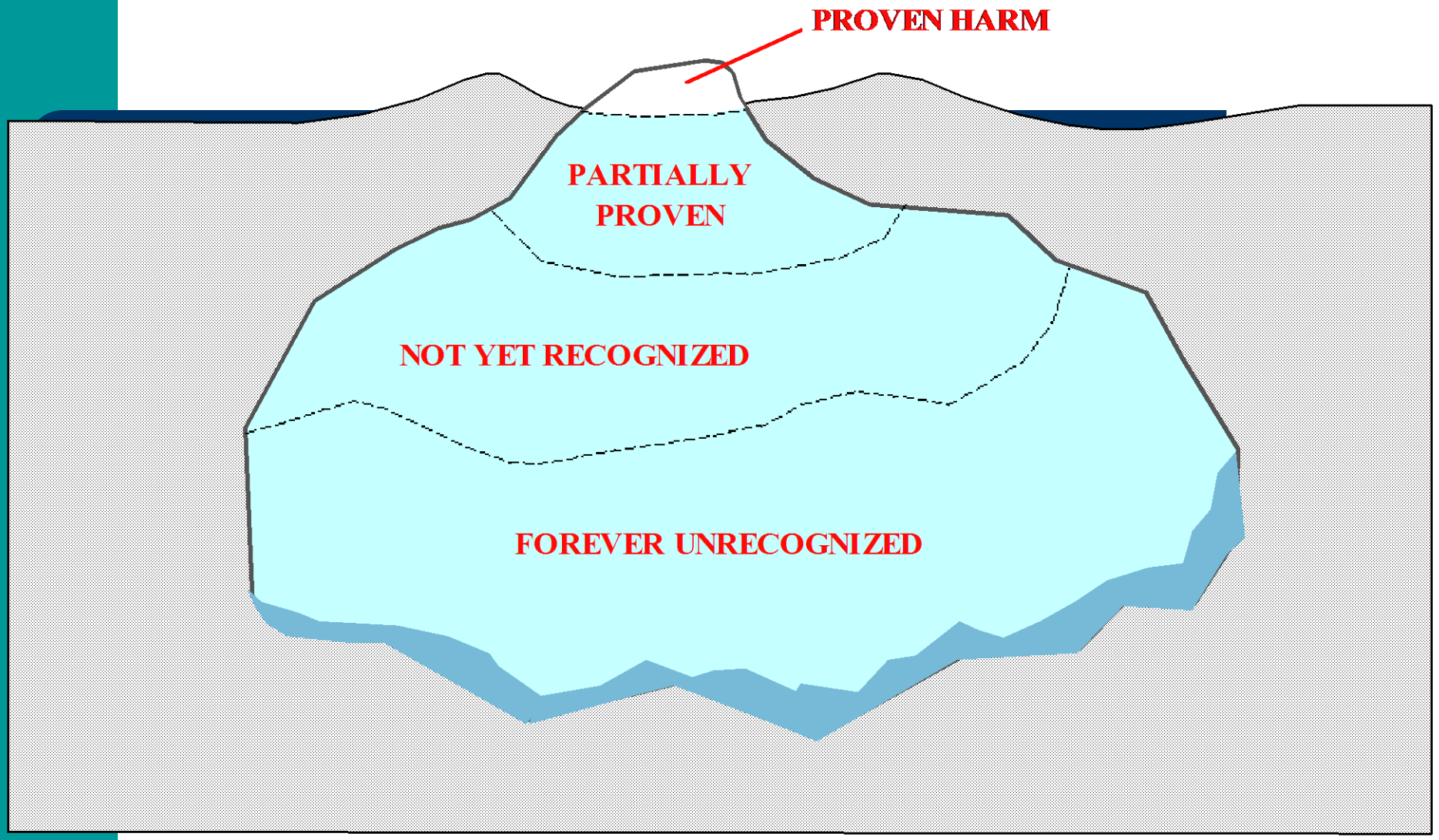
Guiding Principles

3. Due to the slow rate at which "proof" of harm materializes, generations are at risk and may be harmed before adequate regulatory response occurs.

Guiding Principles

4. Protecting children from toxic threats will require a more flexible regulatory system capable of preventing as well as responding to widespread exposures and harm.

THE TOXIC ICEBERG



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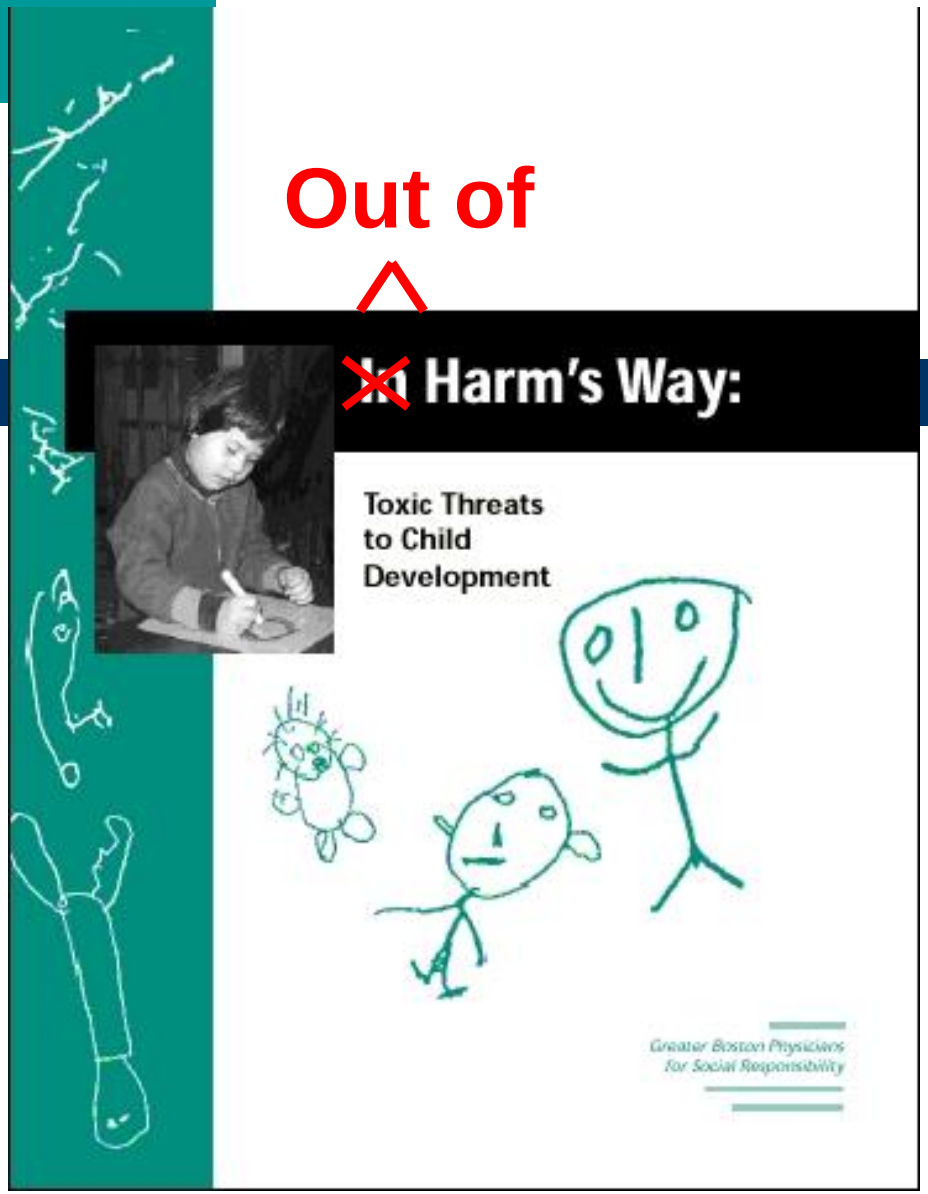
In Harm's Way:
Toxic Threats
to Child
Development
Greater Boston Physicians
for Social Responsibility

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For more information on this presentation and related training materials contact: GBPSR, 11 Garden St., Cambridge, MA 02138.