NEURODEVELOPMENTAL EFFECTS OF PRENATAL EXPOSURE TO ENVIRONMENTAL TOXINS:

Scope of the Issue and Survey of Recent Literature

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A global pandemic of neurodevelopmental toxicity

- **"Subclinical decrements in brain function are even more common than these neuro-developmental disorders (Autism & ADHD)"**

- **"Strong evidence exists that industrial chemicals widely disseminated in the environment are important contributors to what we have called the *global, silent pandemic of neurodevelopmental toxicity*"**

Source: Grandjean and Landrigan (Lancet Neurology, 2014)

Overview

- **Introduction**
  - Neurodevelopmental Disorders and Trends
  - Vulnerability of Developing and Young Brain
  - Epigenetic role in acquiring a disorder
  - Toxic Environmental Agents
  - Literature Survey Selection Criteria
- **Findings from Literature Survey**
- **Concluding Remarks**
- **Discussion**

Neurodevelopmental Disorders

Attention Deficit Hyperactivity Disorder (ADHD)

- 3 types: hyperactive, inattentive, combined (most common)
- difficulty sustaining attention, impulsivity, hyperactivity, impaired executive function (i.e. planning, working memory, ability to "shift gears")

Autistic Spectrum Disorder (ASD)

- Social reciprocity and relationships, perceiving others' emotions, verbal and nonverbal communication and abstract language
- Inflexible behavior (upset by change)
- Issues in other areas, e.g., obsessive compulsivity, anxiety, sensory processing, digestive and immune system, sleep

Subclinical decrements of brain function

- Behaviors resemble ASD or ADHD, but do not meet criteria for a diagnosis
- may include: Lower memory, lower IQ (even a few points), lower motor or visual perceptual skill ability, sensory processing issues, mood dysregulation, learning disability

Prevalence of Neurodevelopmental Disorders over Time

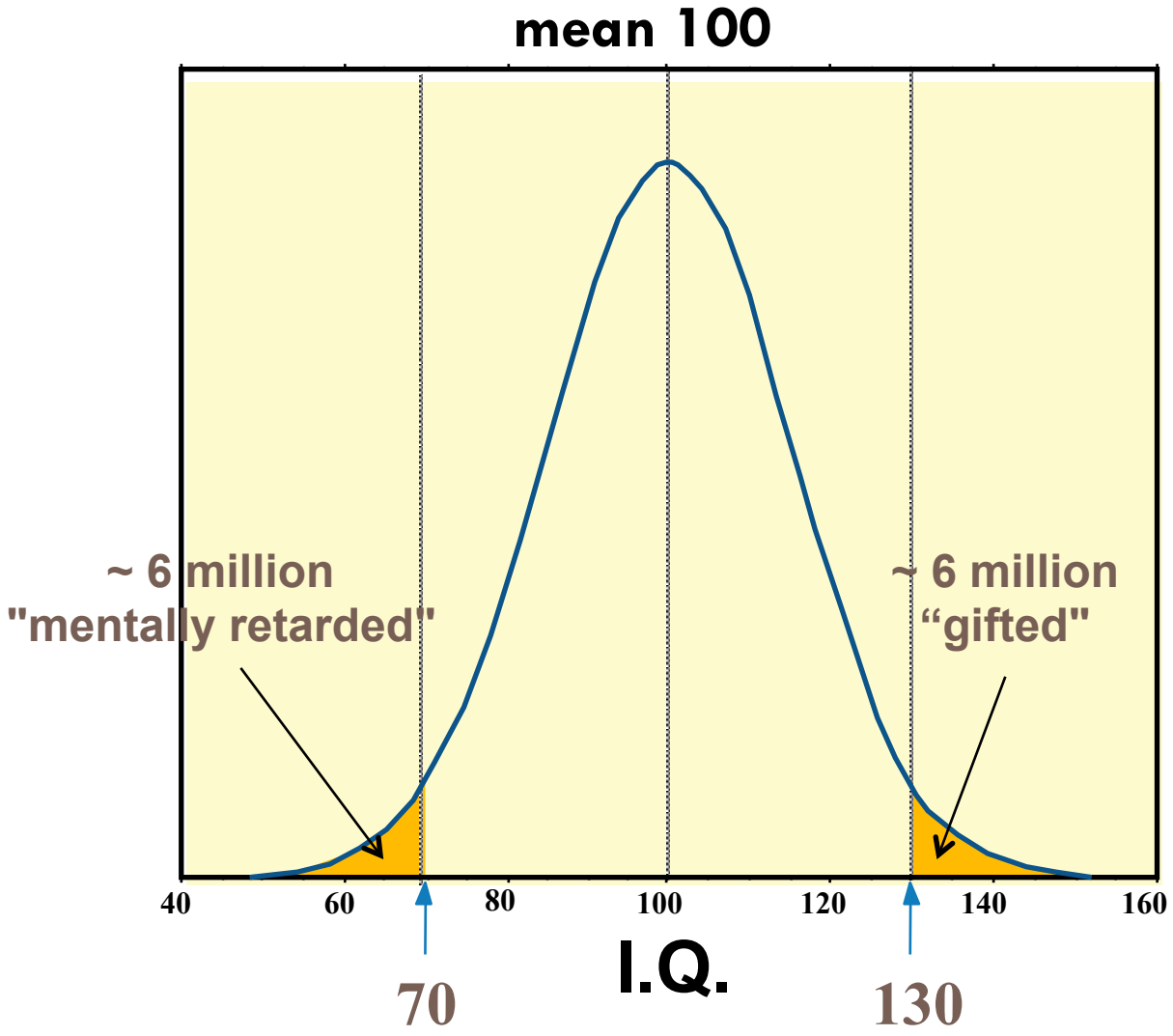
- **ASD**: Current 1 in 68 (2010)
  vs. 1 in 152 (2002)

- **ADHD diagnoses**: Current 11.0% in 2011 (9.5% in 2007, 7.8% in 2003)

- **Learning disability**: In 2010, nearly 10 % of children age 12-17 yrs were affected

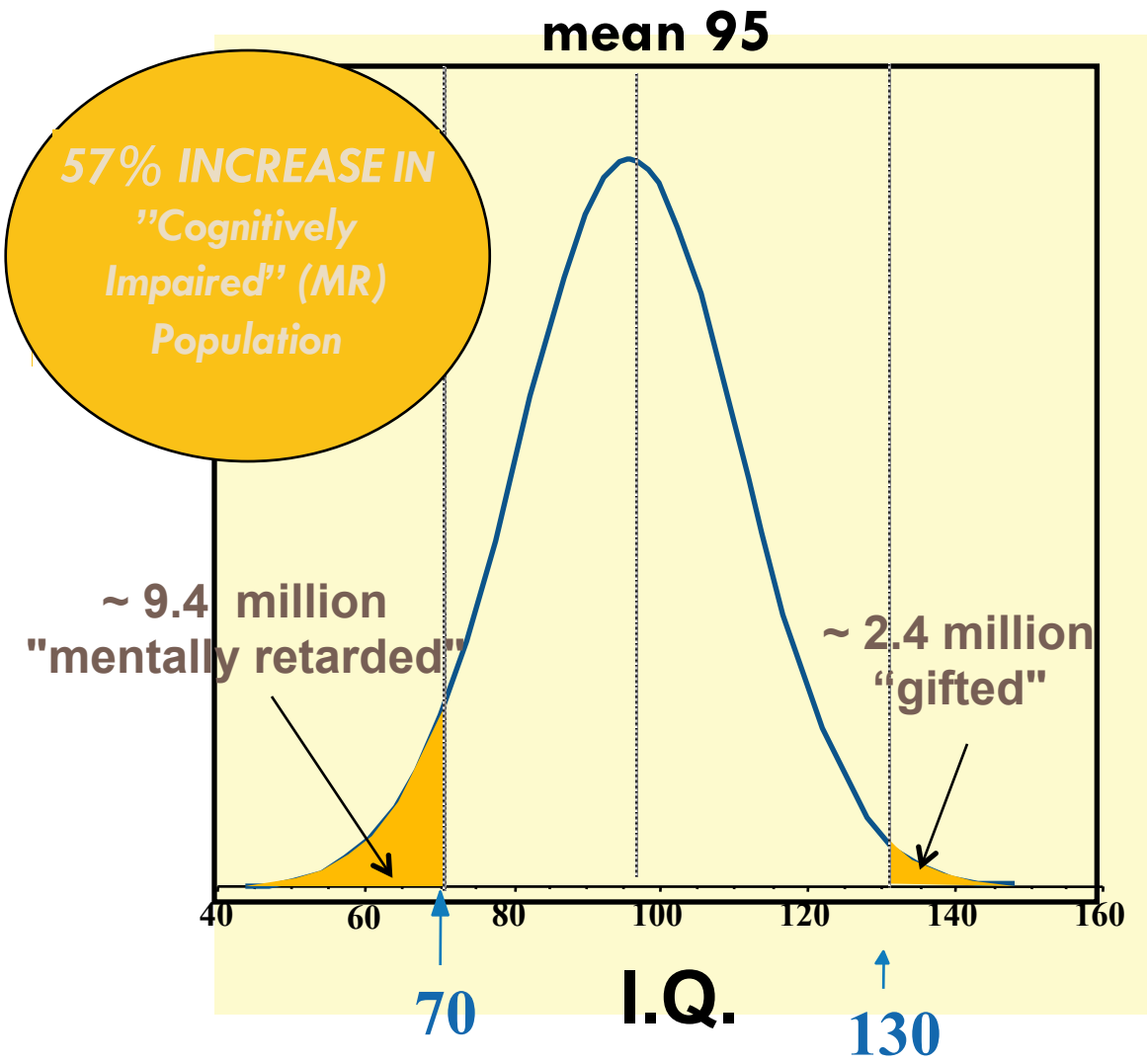
Source: CDC

The Significance of Small Effects: IQ Points



Example: population of 260 million

The Significance of Small Effects:
5 point decrease in Mean IQ



FIVE point IQ decline means high costs to society:

Less innovative genius,
More special ed needs

Example: population of 260 million

Toxic Environmental Agents

- **Over 80,000 synthetic chemicals used in the US**
  - Most untested with little regulatory oversight in assuring safety
  - Roughly 1,000 of these chemicals are "High Production Volume" (HPV)

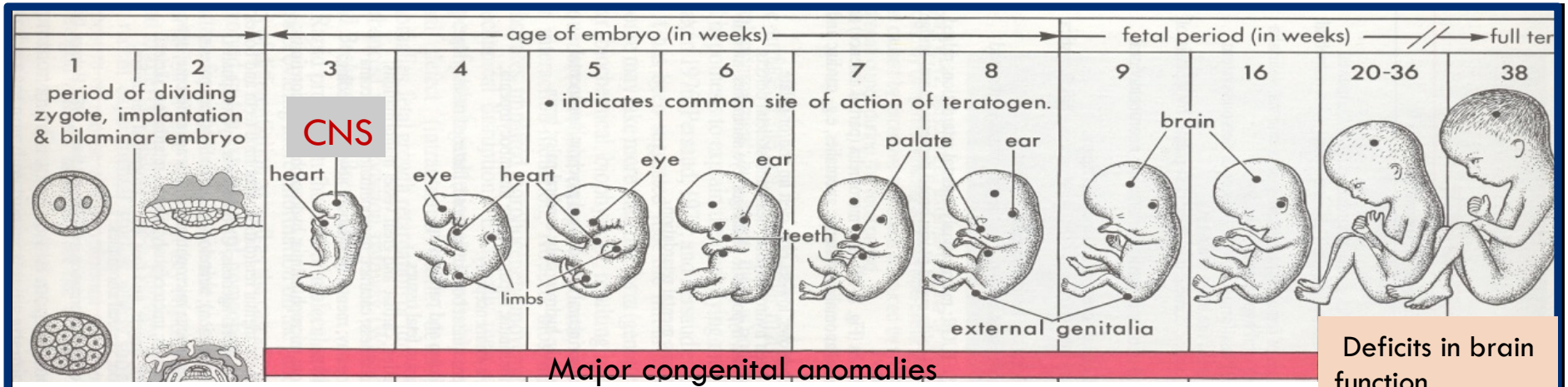
- **Over 200 chemicals reported to be neurotoxic to human adults (NTP)**
  - About half of these are HPV
  - Additional 1,000 chemicals have been reported to be neurotoxic to animals in lab studies

Vulnerability of the Developing and Young Brain

- "The Central Nervous System (brain and spinal cord) is the most vulnerable of all the body systems to developmental injury." (Rodier, 2004)

- Environmental chemicals can cause permanent brain injury at low levels of exposure that would have little or no adverse effect in an adult. **The placenta does not block passage of these toxicants.** (Grandjean and Landrigan, 2014)

CNS and Brain Formation



- *Neural cell proliferation* and complex *differentiation*
- Migration of neural cells into different regions of the brain
- Formation of connector cables called *axons* and *dendrites*
- Formation of *synapses* (electrochemical messages between cells)
- Normal cell death or *pruning* of excess neurons & synapses
- *Myelination*, fatty insulator sheaths formed on neurons & synapses

What causes Neurodevelopmental Disorders?

Multiple factors interact in complex ways during fetal development.

Internal factors

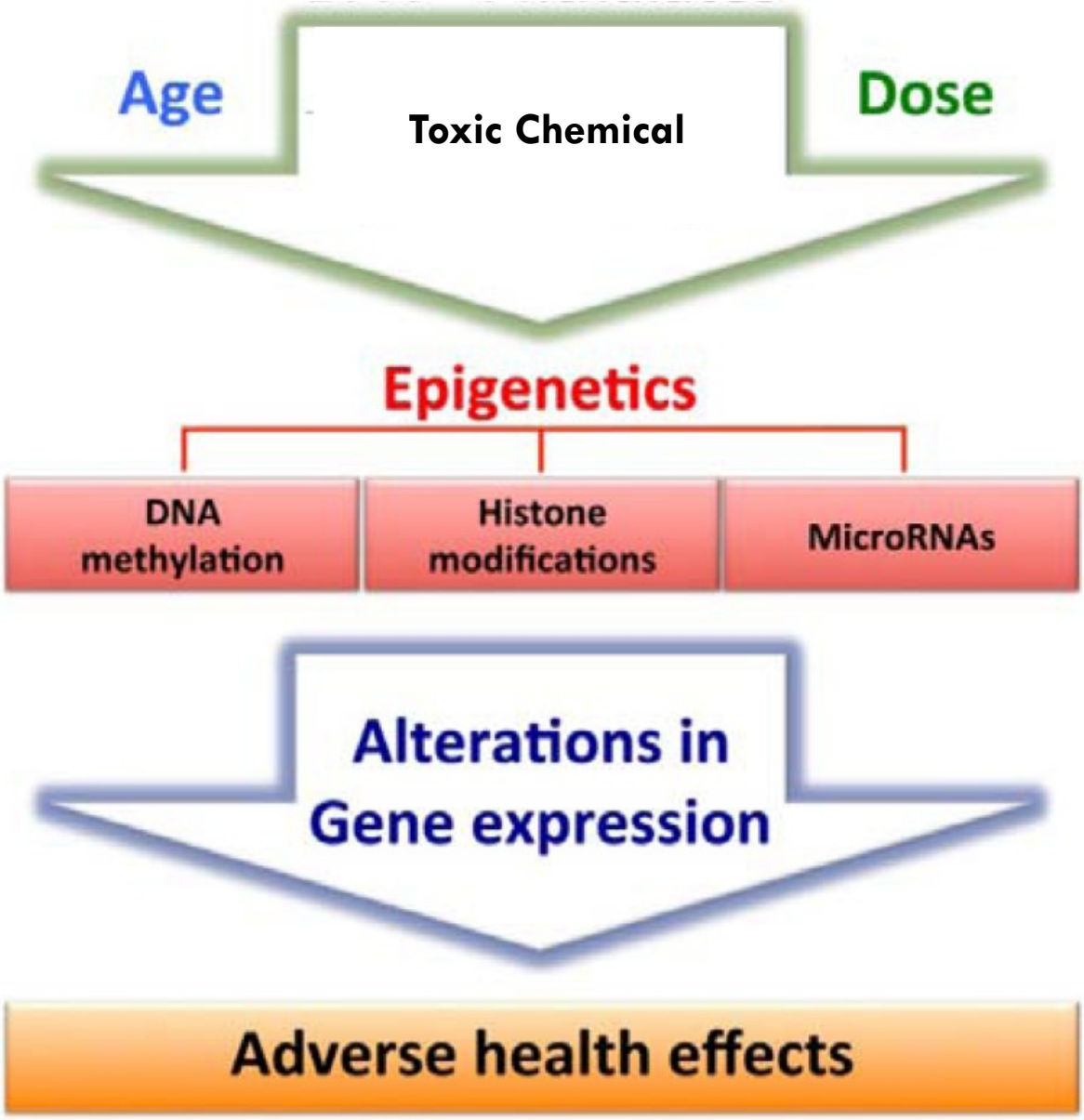
Heredity:

Genetic traits &susceptibility

External factors

- **Exposure to toxins (triggering epigenetic mechanisms)**
- **Nutrition**
- **Social environment**

Epigenetic Mechanisms of Toxic Chemicals



Source: Singh and Li (2012)

American College of Obstetricians (ACOG) and the American Society for Reproductive Medicine (ASRM) *Joint Committee Opinion Exposure to Toxic Environmental Agents (2013)*

*"Patient exposure to **toxic environmental chemicals** and other stressors is **ubiquitous**, and preconception and prenatal exposure can have a **profound and lasting effect**."*

*"…calling for **timely action to identify and reduce exposure** while addressing the consequences of such exposure."*

Economic Implications

Special education 13.3% (1 in 8) of Oregon children received special education services in 2013-14 (ODOE)

Costs an additional $9,370/yr per student (NEA)

~ $800 million/yr on Special Ed and early intervention (ODOE, 2005)

Medical costs are typically higher for children with ASD or ADHD

Emotional costs to impaired individuals and their families are incalculable

Neurotoxic Environmental Agents Covered

- **Lead (Pb)**
- **Methylmercury (CH_3Hg)**
- **Polychlorinated biphenyls (PCBs)**

- **Brominated flame retardants (PBDEs)**
- **Pesticides (Organophosphate Insecticides)**
- **Other Endocrine Disruptors (phthalates, BPA)**
- **Perflourinated chemicals (e.g., in Teflon, Scotchguard)**

- **Air Toxics, including:**
  - Motor vehicle exhaust (inc. Diesel Particulate Matter, DPM)
  - Polycyclic aromatic hydrocarbons (PAHs)

Criteria for Literature Presented

- Prenatal Human Exposures
- Longitudinal Study with Prospective Cohorts
  - Exception: Air and Soil pollution studies
- Biomonitoring Conducted
- Validated neurodevelopmental Tests/Instruments, Imaging, or spatiotemporal modeling techniques
- Statistically significant findings ($p<0.05$)
- Biological plausibility of exposure & neurodevelopmental effect
- Peer-reviewed studies
- Preferably corroborated

Lead (Pb)
Methyl Mercury (CH_3Hg)
and
PCB Studies


Aviation fuel (avgas) used by piston-engine aircraft is leaded

Effects of Lead on Cognitive and Behavioral Traits (well-established, from previous studies)

ADHD

- ↑ hyperactivity
- ↑ impulsivity
- ↑ distractibility
- ↑ diff. w instructions
- ↑ conduct problems
- ↓ executive function
- ↓ attention/vigilance
- ↓ social skills

LD

- ↓ reading, math
- ↓ spelling
- ↓ pattern recognition
- ↓ word recognition

OTHER

- ↓ fine motor
- ↓ visual motor
- ↑ aggressive
- ↑ antisocial
- ↑ off-task

Neurodevelopmental Effects of Prenatal Lead (Pb) Exposure

REFERENCE	SUBJECTS			EXPOSURE PATHWAY	OUTCOMES AT FOLLOW-UP (F/U)
	Location	N	F/U		
Boucher et al. (2014, EHP)	Canadian Arctic	94	6 mo & 11 mo	Ingestion of game animals (hunted w/ lead shot)	**Traits associated with ADHD**
Boucher et al. (2012, EHP)	Inuit population	279	11.3 yrs old (mean)	Ingestion of game animals (hunted w/ lead shot)	**Traits associated with aggression and ADHD, correlating with child blood, but not cord blood ***
Jedrychowski et al. (2009, Early Hum Dev)	Krakow, Poland	457	3 yrs old	Living in older urban housing	**Lower cognitive function in boys ****
McDermott et al. (2014, Dev Med & Child Neuro) (Retrospective study)	South Carolina	10,051 pregnant Medicaid recips	Until 9 yrs old	Contaminated soil during 6th month of pregnancy	**Increased incidence of severe intellectual disability (p = 0.025) for lead & arsenic combined**

F/U:= follow up

* this one study also looked at post-natal exposure for comparison

** low cord blood lead levels: med value = 1.21 µg/dL; only 1% had levels above 3 µg/dL

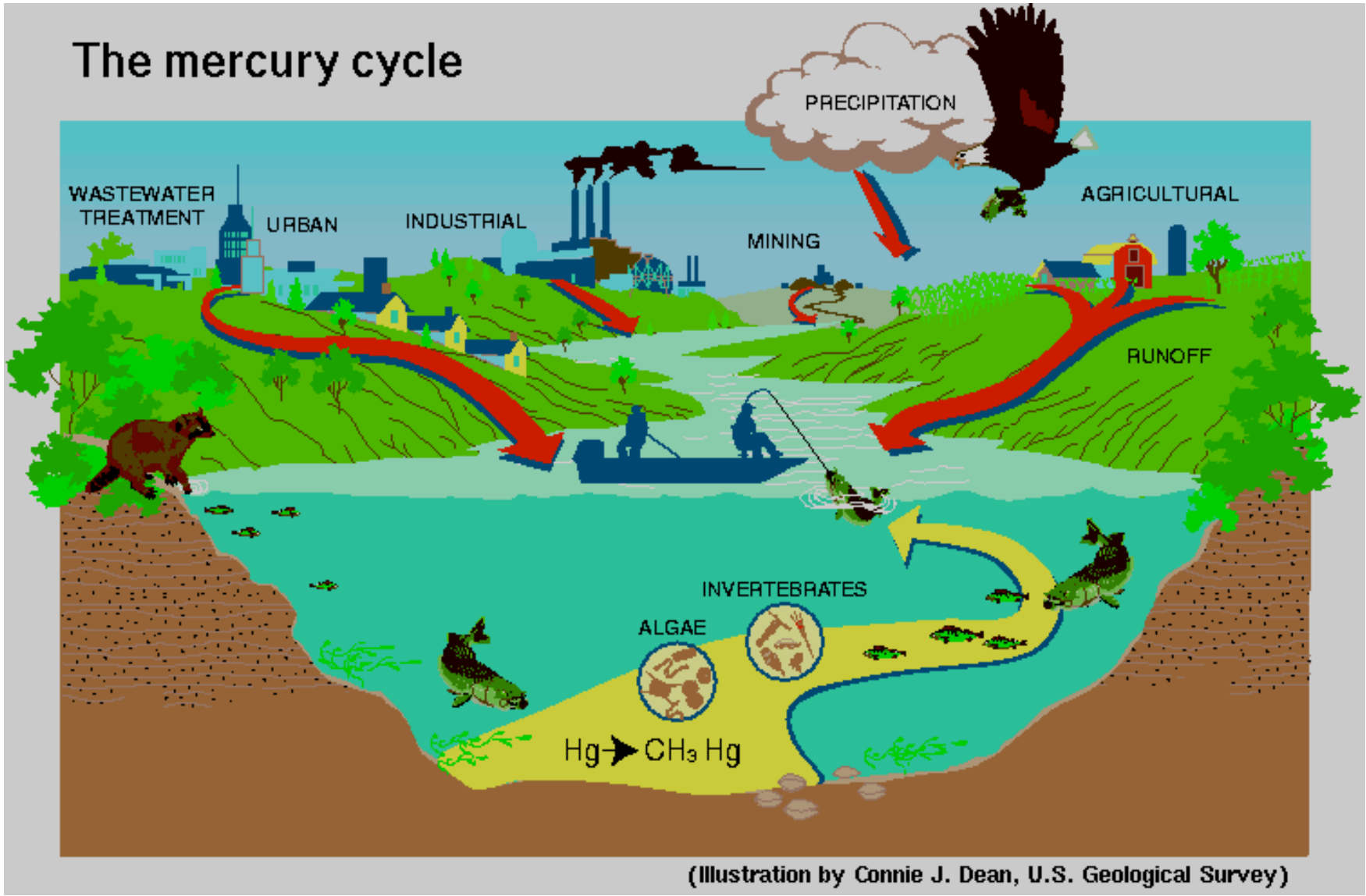
Methylmercury

The coal-fired Gavin Power Plant in Cheshire, Ohio

Faroes Islands in N. Atlantic,
midway between Iceland & Denmark

Seychelles Islands in Indian Ocean,
off east-central coast of Africa

The Mercury Cycle



Neurodevelopmental Effects of Prenatal Methylmercury Exposure

REFERENCE	SUBJECTS			EXPOSURE PATHWAY	OUTCOMES AT FOLLOW-UP (F/U)
	Location	N	F/U		
Boucher et al. (2014)	Canadian Arctic	94	6 mo 11 mo	Seafood ingestion	**Traits associated with ADHD**
Boucher et al. (2012)	Inuit population	279	11.3 yrs old (mean)	Seafood ingestion	**Traits associated with ADHD**
Ng et al. (2013)	Taiwan	168	2 yrs old	Seafood ingestion	**Decline in all areas of development *in genetically predisposed individuals***
Orenstein et al. (2014)	New Bedford Harbor area, MA	393	8 yrs old	Contaminated harbor (Superfund site)	**Decreased visual and verbal memory and impaired learning associated with Hg in maternal hair**
McDermott et al. (2014)	South Carolina	10,051 pregnant Medicaid recips	≤ 9 yrs old	Contaminated soil during pregnancy	**Increased incidence of mild intellectual disability** (p = .007)*
Blanchard et al. (2011)	Bexar Co. TX & Santa Clara Co. CA		3-5 yrs old	Inhalation of ambient air near coal plants	**Higher Autism rates** among children living in areas having higher concentration of ambient air mercury per square mile (levels > 3 SD above mean level of Hg distribution) **
Windham et al. (2006)	SF Bay area	284 children w/ASD; 657 controls	<9 yrs old	Inhalation of ambient air in urban setting	**Association between autism and estimated metal concentrations** in air (p<0.05) **

* Retrospective; Spatial/Temporal Model ** Spatiotemporal Modeling using US EPA ambient air monitoring data


Elevated PCB levels detected in resident fish near the Bonneville Dam

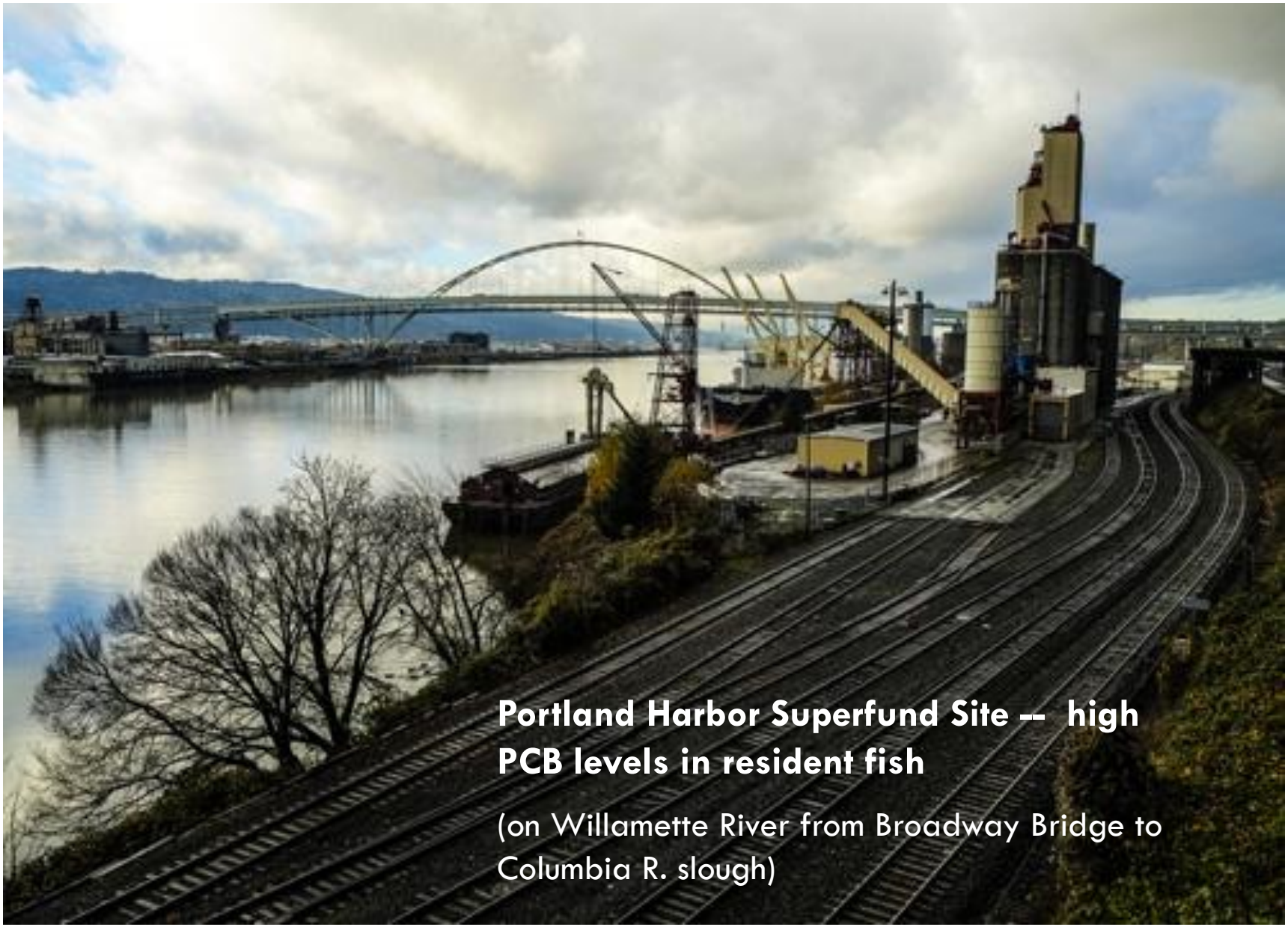


Image courtesy of Mother Nature Network

Neurodevelopmental Effects of Prenatal Exposure to PCBs

REFERENCE	SUBJECTS			EXPOSURE PATHWAY	OUTCOMES AT FOLLOW-UP
	Location	N	F/U		
Boucher et al. (2009) (review of 9 studies)	US, Canada, and Europe	Varies, from135 to 900	Varies by study	Ingestion of seafood and unknown sources	**Traits assoc. with ADHD, and decreased cognition—** visual recognition memory and verbal ability
Sagiv et al. (2012)	New Bedford Harbor area, MA	578 + 584	8 yrs old	Living on contaminated harbor (Superfund site)	**Traits assoc. with ADHD,** but only in boys
Boucher et al. (2014)	Canadian Arctic (Inuit population)	94	6 mo. & 11 mo.	Seafood consumption	**Decreased cognition** (visual recognition memory) in infants
Boucher et al. (2012)	Canadian Arctic (Inuit population)	279	mean age 11.3 yrs	Seafood consumption	**No associations** with ADHD traits
Orenstein et al. (2014)	New Bedford Harbor area, MA	393	8 yrs old	Living on contaminated harbor (Superfund site)	**No associations** with decreased cognitive function (Authors state exposure levels quite low)

Polybrominated Chemicals(PBDEs)

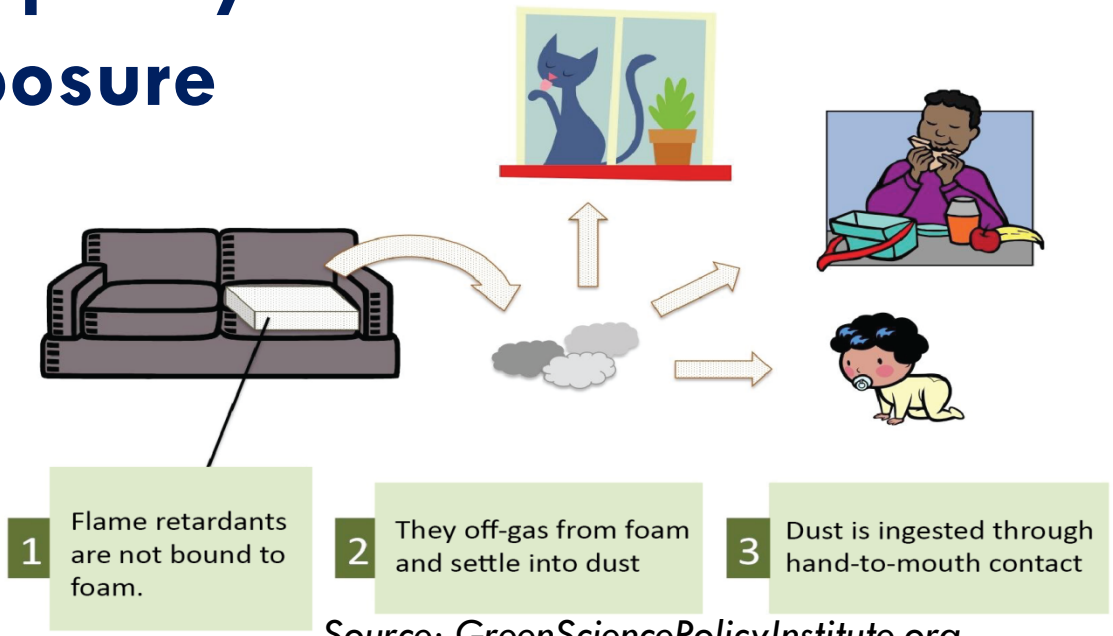
Phthalates

Bisphenol-A (BPA)

Pesticides

Fluorochemicals (PFOA/S)

Polybrominated Diphenyl Ether (PBDE) Exposure



Source: GreenSciencePolicyInstitute.org

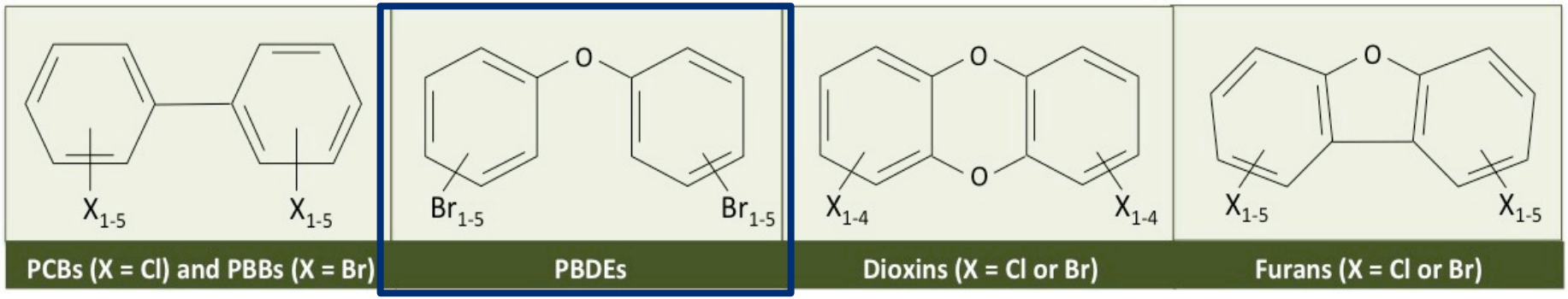
- **California's Technical Bulletin 117 (TB117)***
  - Furniture foam withstand open flame for 12 seconds
  - Penta-BDE used from 1975-2004 (98% of use in N America)
  - ≥3 pieces of stuffed furniture in the home associated w/~27% increase in women's blood PBDE levels (Castorina et al., 2011)

- **Baby Products:** Car seats, changing table pads, sleep positioners, mattresses, nursing pillows, and other products (Stapleton et al., 2011)

as of Jan 1, 2014,TB117-2013** is in effect and flame retardants are not needed, but can still be used*

Biological Pathways of Neurotoxicity associated with PBDE Exposure

- **Structurally similar to PCBs & PBBs, Dioxins and Furans**

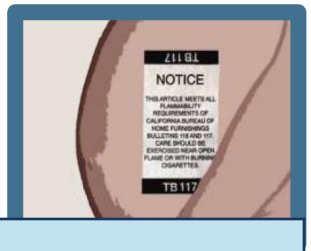


Source: GreenSciencePolicyInstitute.org

- **Animal studies**
  - certain PBDEs can mimic thyroid hormones
  - PBDEs can disrupt the equilibrium of the thyroid hormone system → impair neurological functioning (Darnerud et al. 2001)

- **Human Studies:** 10-fold increase in PBDE chemicals in pregnant women → decrease TSH (~11-19 %; Chevrier et al., 2010)

Neurotoxicity of Prenatal PBDE Exposure



Source & Congener	Standard Assessment	Assessment Age (N)	Outcome (p<0.05)
Herbstman et al. (2010) **BDE-47 ,-99 ,-100,-153**	BSID-II	**1-3 yrs (~110/BDE)**	2 yrs: ↓ MDI
	WPPSI-R	**4 & 6 yrs (~100 /yr)**	4 yrs: ↓ Full –scale IQ, Verbal IQ & Performance IQ 6 yrs: ↓ Full IQ, ↓ Performance IQ *
Eskanazi et al. (2013) **ΣPBDE (47,99, 100, &153)**	CBCL, K-CPT, & WPPSI-III	**5 yrs (~240)**	↑ ADHD traits (on K-CPT)
	CADS, BASC-II, & WISC-IV	**7 yrs (~260)**	↑ ADHD traits (by CADS) ↓ Verbal Comprehension IQ
Chen et al. (2014) **BDE-47 & ΣPBDE**	BSID-II	**1-3 yrs (>220/yr)**	No significant associations
	BASC-2	**2-5 yrs old (>165/ yr)**	2&3 years: Externalizing Behavior 3&5 years: hyperactivity 3 years: Behavioral Symptoms
	WPPSI-III	**5 yrs old (190)**	↓ Full Scale IQ

*when language & interview/assessment location included in multivariate linear regression model

BASC-2:= Behavior Assessment System for Children,2nd Edition**; BSID-II**:=Bayley Scales of Infant Development-II; **CADS**:= Conners' ADHD/DSM-IV Scales; **CBCL**:=Child Behavior Checklist; **K-CPT**:=Conner's Kiddie Continuous Performance Test; **WISC**:= Wechsler Preschool and Primary Scale of Intelligence; **WPPSI**:= Wechsler Preschool and Primary Scale of Intelligence (R= Revised; III= 3rd Ed.)

Figure adapted from Castorina et al. (2011)

Phthalate Exposure

Ingestion

- Direct: Infant formula and cow's milk, groundwater & drinking water (e.g., DEHP), medications & nutritional supplements (DBP & DEP)
- Indirect: Toys * & Plastic Containers

Dermal Absorption

- Clothing (e.g., waterproof clothing or faux leather gloves w/ DEHP)
- Cosmetics & personal care products (e.g., lotions)
- Denture material (soft lining plasticizers)

Inhalation

- Personal care products (e.g., fragrance)
- Indoor air and house dust
- Baked modeling clay

Intraveneous

- medical devices (e.g., made with PVC softened with DEHP)

**As of 2008- DEHP, DBP, BBP banned in US; DINP, DIDP, DnOP provisionally banned (Section 108 of the Consumer Product Safety Improvement Act of 2008 & 2011 Amendments)*

Biological Pathways of Neurotoxicity associated with Prenatal Phthalate Exposure

In laboratory rat studies, phthalate exposures modify:

- **Thyroid function or reduce Thyroid hormone levels**
  - Thyroid function plays key role in fetal & postnatal brain development
- **Testosterone production in male rats**
  - Testosterone plays key role in male brain development
- **Fatty acid transfer across placenta (possibly)**
  - Reduces the lipid content of fetal brain
- **Aromatase activity directly (possibly)**
  - Estradiol is synthesized from cholesterol, catalyzed by aromatase
  - In males & females, estradiol is necessary for brain development

Neurotoxicity of Prenatal Phthalate Exposure

Source & No. metabolites	Standard Assessment	Assessment Age (N)	Outcome (p<0.05)
Kim et al. (2011) 3 metabolites	BSID-III for MDI and PDI	**6 Mnths** (460)	**Boys**: prenatal phthalate→ ↓ MDI and PDI p>0.05 for girls
Tellez-Rojo et al. (2013) 9 metabolites	BSID-III for MDI and PDI	**2-3 yrs** (135)	**Girls**: 5 phthalate metabolites → ↓ MDI
Whyatt et al. (2012) 4 metabolites	BSID-III for MDI and PDI	**3 yrs** (319)	**Boys & Girls**: MnBP & MiBP → ↓ PDI **Girls**: MnBP → ↓ MDI
Kobrosly et al. (2014) 7 metabolites	CBCL	**6-10 yrs** (153)	**Boys**: inattentiveness, rule-breaking, aggression, conduct problems, or oppositional behavior Null association for girls
Lien et al. (2014) 7 metabolites	CBCL	**8-9 yrs** (122)	**Boys & girls**: all DEHP metabolites → delinquent & aggresssive behavior, internalizing &/or externalizing problems
Factor-Litvak et al. (2014) 6 metabolites	Weschler, 4th Ed (WISC IV)	**7 yrs** (328)	**Boys & girls**: MnBP & MiBP → ↓ full scale IQ (**Boys** associations stronger)

BSID-III:= Bayley Scales of Infant Development-III; **CBCL** := Child Behavior Checklist;
MDI:= Mental Development Index; **PDI** := Psychomotor Development Index;
N:= number of mother-child pairs

Bisphenol A (BPA) Exposure

93% of all urine samples collected by the CDC in the 2003-04 National Health and Nutrition Examination Survey (NHANES III) found detectable levels of BPA in people ≥ 6 yrs old

Adapted from FDA.gov

Dietary Ingestion (primary route)

- Canned food & food storage containers, polycarbonate tableware, water bottles
  - temperature, rather than age, of container may influence leaching
- Breast milk

Dermal Absorption (limited extent)

- paper currencies and cash register receipts

Biological Pathways of Neurotoxicity associated with Prenatal BPA Exposure

In laboratory mice and rat studies, BPA:

- **Acts as a thyroid hormone (TH) antagonist**
  - TH deficits in-utero → "permanent alterations of cerebral cortical architecture consistent with those observed in brains of patients with autism" (Miodovnik et al., 2011)

- **Binds to estrogen receptor → estrogen signaling pathways**
  - Estrogen & Testosterone regulate & interact w/ neurotransmitters
  - Effects the structure and function of brain

- **Alters brain structure → changes in behavior**
  - ↑ aggression, memory impairment & hyperactivity in male mice
  - Disrupts cognition, social behaviors & brain function

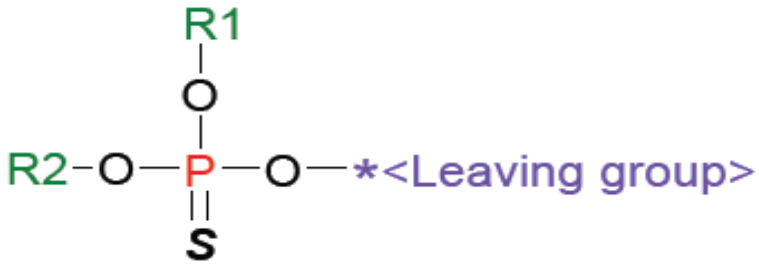
Neurotoxicity of Prenatal BPA (p-PBA) Exposure

Source	Standard Assessment	Assessment Age (N)	Outcome (p<0.05)
Braun et al. (2009)	BASC-2	**2 yrs old** (249)	**Girls**: ↑ Aggression (16 wk p-BPA stronger association than 26-week)
Braun et al. (2011)	BASC-2 BRIEF-P	**3 yrs old** (244)	**Girls**: mean p-BPA → hyperactivity, anxiety & depression (BASC-2) & emotional control & inhibit scales of BRIEF-P
Perera et al. (2012)	CBCL	**3-5 yrs** old (198)	**Boys**:↑ emotionally reactive & aggression **Girls**: ↑ anxiety/depression & aggression
Harley et al. (2013)	BASC-2 &CADS	**7 yrs** (~290)	**Boys**: internalizing problems, anxiety, & depression (BASC-2)
	CPT	**9 yrs** (~266)	No significant association (Boys or Girls) w/CPT scores

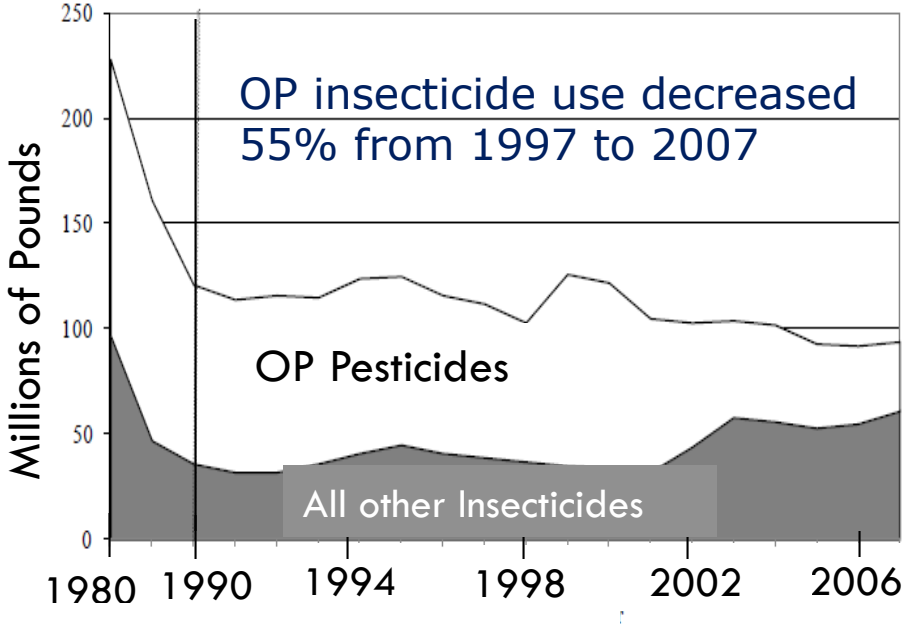
N:= number of mother-child pairs

BASC-2:= Behavior Assessment System for Children 2; B**RIEF-P** := Behavior Rating Inventory of Executive Function- Preschool; **CADS:**= Conners' ADHD/DSM-IV Scales; **CBCL:**= Child Behavior Checklist *;* **CPT:**= Connors' Continuous Performance Test for ADHD;

Organophosphate (OP) Insecticides

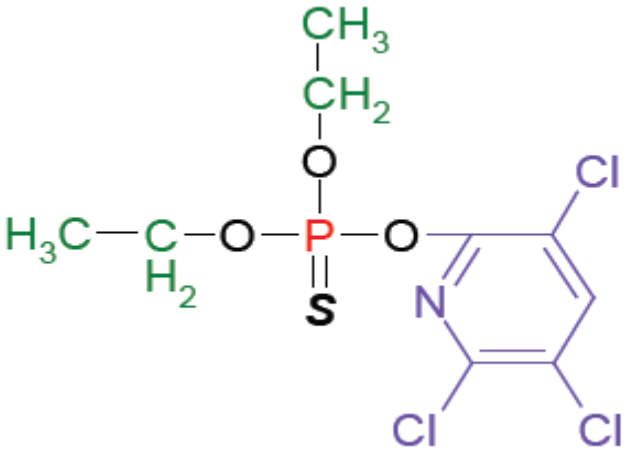


- **In 2007, roughly 33 million pounds of OP insecticide applied (~ 36% of all insecticides, Grube et al., 2011)**
- **In the US, over 30 OP pesticides registered in 2010**



Graph adapted from EPA (2011)

Chlorpyrifos (CPF)



- **Major OP insecticide**
- **In use since 1965 for agricultural & pest control**
  - EPA phased out residential use in 2001, but still heavily used in agricultural

2007 Rank	Active OP Ingredient	Millions of Pounds
1	Chlorpyrifos	8-11
2	Malathion	5-9
3	Acephate	4-6
4	Naled	1-2
5	Dicrotophos	1-2

Source: EPA (2011)

OP Insecticide Exposure & Metabolism

- **Diet is primary route of exposure**
- **Secondary routes: soil track-in & indirect ingestion (hand-to-mouth activity) by children**

- **Rapid metabolism of OPs**
  - **excreted in urine w/in 3-6 days of exposure**
- **Majority of OP pesticides breaks down into 6 DAP metabolites**
  - cannot be traced back to original parent compound

OP Insecticide Toxicity

- Inhibits cholinesterase enzymes in nervous system
- Increases level of glial cell markers in rodents
- Vulnerable subpopulations
  - fetus and children with lower levels of detoxifying enzymes (paraoxonase or CPF-oxonase) (Holland et al., 2006)
  - certain genetic polymorphisms can affect CPF metabolism (Berkowitz et al., 2004)

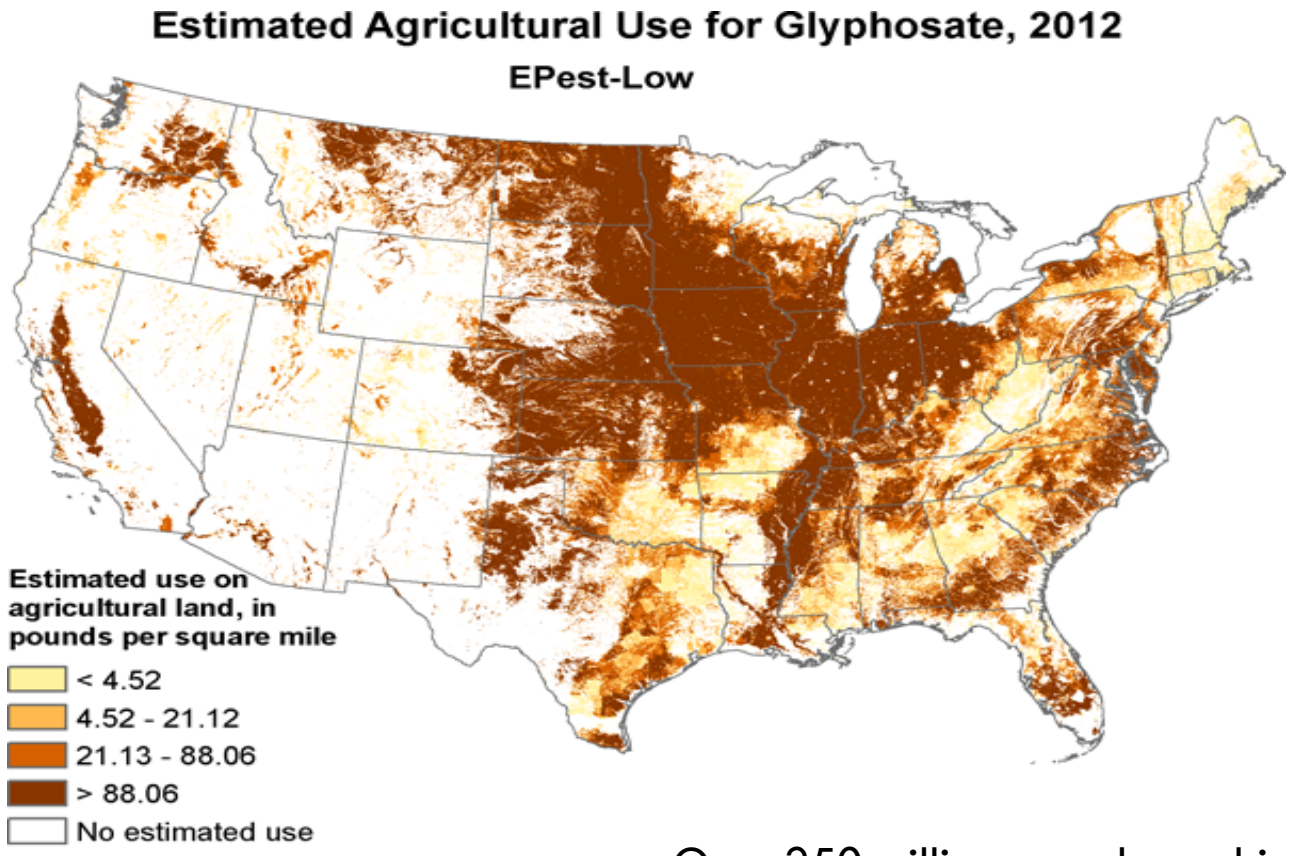
Neurotoxicity of Prenatal OP Exposure

Source & Pesticide	Assessment	Assessment Age (N)	Outcome (p<0.05)
Eskanazi et al. (2007) OPs*	BSID-II	6&12^{mths} (395)	No significant associations
	BSID-II& CBCL	24^{mths} (372)	↑OP → ↓MDI & increased risk of PDD traits
CPF & Malathion			*CPF & Malathion NOT associated w/any outcome*
Marks et al. (2010) OPs*	NEPSY-II & CBCL	3.5 yrs (~320)	↑OP → ↑ADHD traits **in boys** (CBCL)
	CBCL, K-CPT, & Hillside	5 yrs (~320)	↑OP → ↑ADHD traits (CBCL)
Bouchard et al. (2011) OPs*	WISC-IV	7 yrs (329)	↑ OP → ↓Full Scale IQ (& all four subscales of WISC-IV)
Lovasi et al. (2011) CPF	BSID-II	3 yrs (265)	↑CPF → ↓ MDI
Rauh et al. (2011) CPF	CBCL & WISC-IV	7 yrs (265)	↑CPF → ↓Full Scale IQ & Working Memory Index
Rauh et al. (2012) CPF	MRI brain scans	6-11 yrs (40)	↑CPF → Enlargements of brain regions, correlating with decreased IQ

•OPs measured by 6 DAP metabolites CPF:= chlorpyrifos **N:**= number of mother-child pairs

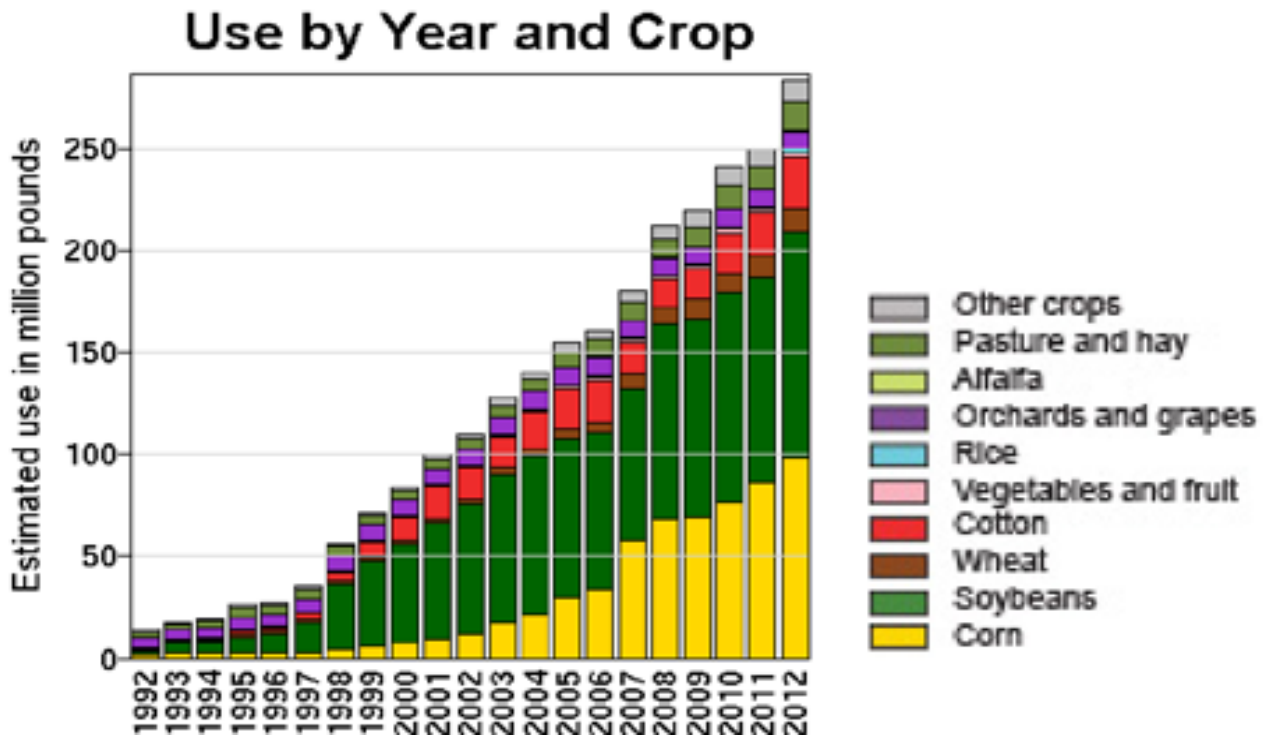
BSID-II := Bayley Scale of Infant Intelligence-Revised; CBCL:= Child Behavior Checklist; Hillside:= Hillside Behavior Rating Scale for ADHD scale; K-CPT:= Conners' Kiddie Continuous Performance Test; MDI := Mental Development Index Score; MRI:= magnetic resonance imaging; NEPSY-II:= Visual attention subtest; PDD := Pervasive Developmental Disorder; WISC-IV:= Wechsler Intelligence Scale for Children, 4th Ed.

Glyphosate



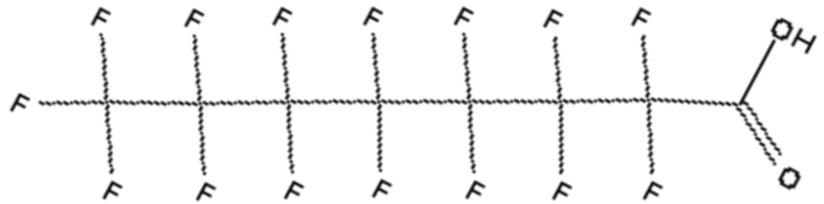
Over 250 million pounds used in 2012
Source: USGS, 2012

Gylphosate use by Year and Crop

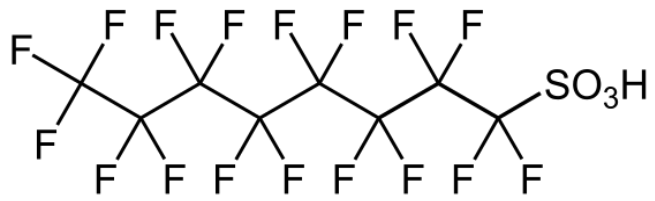


Perflourooctanoic acid (PFOA) & Perfluorooctane Sulfonate (PFOS) Exposure

PFOA



PFOS



Ingestion (primary route of exposure)

- **Direct:** Fish, Drinking Water, Breast Milk
- **Indirect:** Food packaging (e.g., microwave popcorn), non-stick cookware (e.g., Teflon), Dust

Dermal Contact

- Personal care products (e.g., makeup, lotions, dental floss)
- Clothing (e.g.., waterproof material)
- Furniture (e.g., upholstery)

2010/15 PFOA Stewardship Program: 8 major companies, inc. BASF, 3M/Dyneon & Dupont , will phase out PFOA emissions & product content by 2015

Neurodevelopmental Toxicity associated with Prenatal PFOA/S Exposure is *very limited*

Reference & Chemical	Standard Assessment	Assessment Age (N)	Outcome (p<0.05)
Fei & Olsen (2011) PFOA/S	SDQ & DCDQ	7 yrs (787 & 537)	**No adverse association** w PFOA/S levels and hyperactivity (SDQ) and motor difficulties (DCDQ)
Stein et al. (2013) PFOA	CCPT-II WASI WIAT-II NEPSY-II	6-12 yrs (320)	**No adverse association** b/w PFOA & IQ, cognitive development, attention & impulsivity & other neuro-psychological effects. Those w/greatest PFOA exposure level were "most dissimilar to ADHD profile".
Ode et al. (2014)* PFOA/S	ADHD (using DSM criteria)	n/a** (206)	**No adverse association** b/w fetal exposure to PFOA/S and ADHD
Hoyer et al. (2015) PFOA/S	SDQ & DCDQ	5-9 yrs (1,106)	**PFOA associated with ↑ hyperactivity score (SDQ)** No adverse association b/w PFOA/S levels and motor difficulties (DCDQ)

*matched case-control study; ** year of delivery from 1978-2000; **N**:= number of mother-child pairs

SDQ := Strengths and Difficulties Questionnaire (ADHD) ; **DCDQ**:= Developmental Coordination Disorder Questionnaire (motor coordination); **CCPT-II**:= Connor's Continuous Performance Test-II (computer administrated to test for sustained attention and impulsivity); **NEPSY-II**:= neuropsychologically-based instrument designed to test specific brain behavior and ID markers or atypical cognitive development; **WASI** := Weschler Abbreviated Scale of Intelligence (full- , verbal -, and Performance- IQ); **WIAT-II**:= Weschler Inidividual Acheivement Test-II

Precautionary Principle

"When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."

Wingspread Conference, 1998

Air Pollution Studies

Smog is under control. Air Toxics are not.

What's in the air?

Criteria Pollutants (monitored):

Ozone (O_3)

Nitrogen oxides (NO_x)

Carbon monoxide (CO)

Particulate matter

(PM 2.5 and 10)

Sulfur oxides (SO_x)

Lead (also an air toxic)

Air Toxics:

Volatile Organic Compounds

Polycylic Aromatic Hydrocarbons (PAHS)

Metals

Dioxins and many others

Greenhouse gases:

Carbon dioxide (CO_2)

Methane (CH_4)

Nitrous Oxide (N_2O)

Sources of Air Pollution

Mobile Sources

Industrial Sources

Regional Sources

VOC, NOx, PM

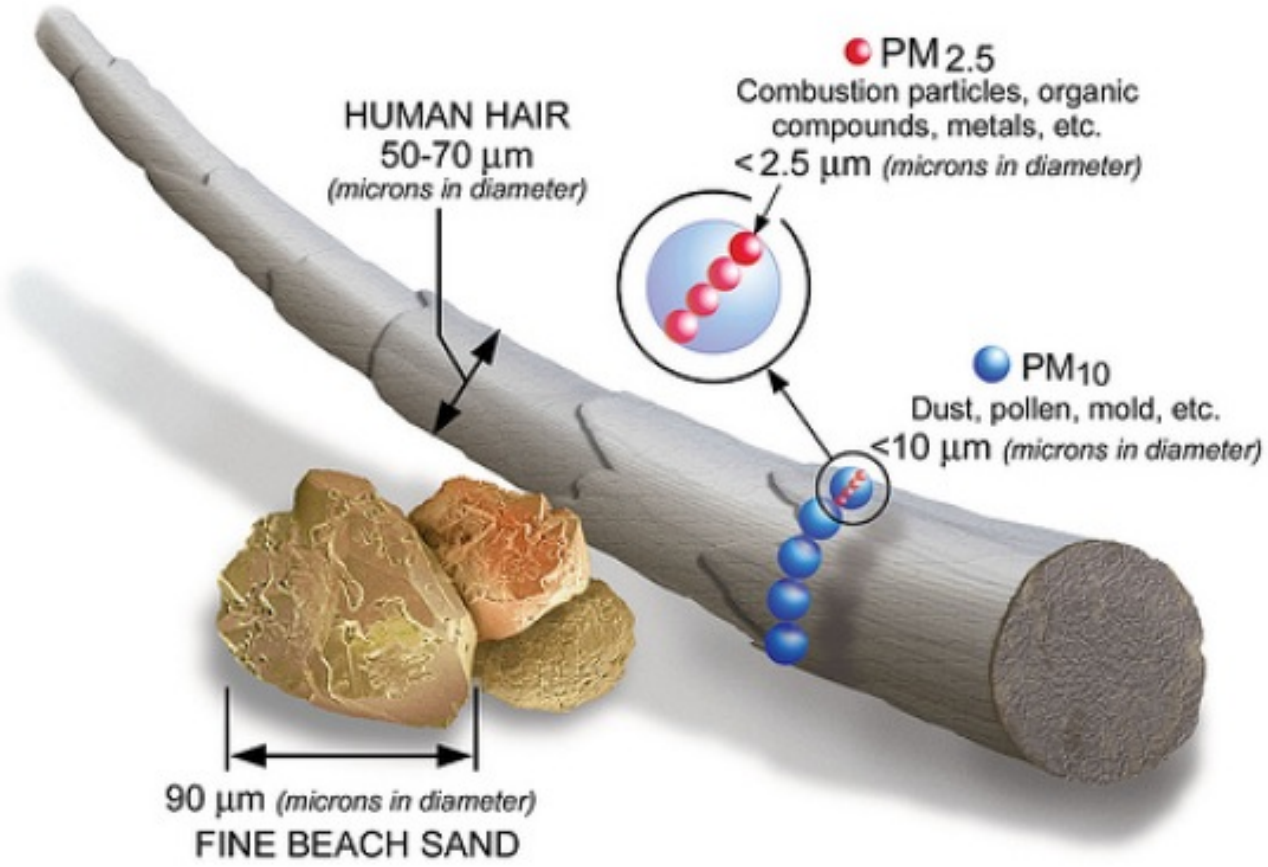
Chemistry & Meteorology

Health and Ecosystem Effects

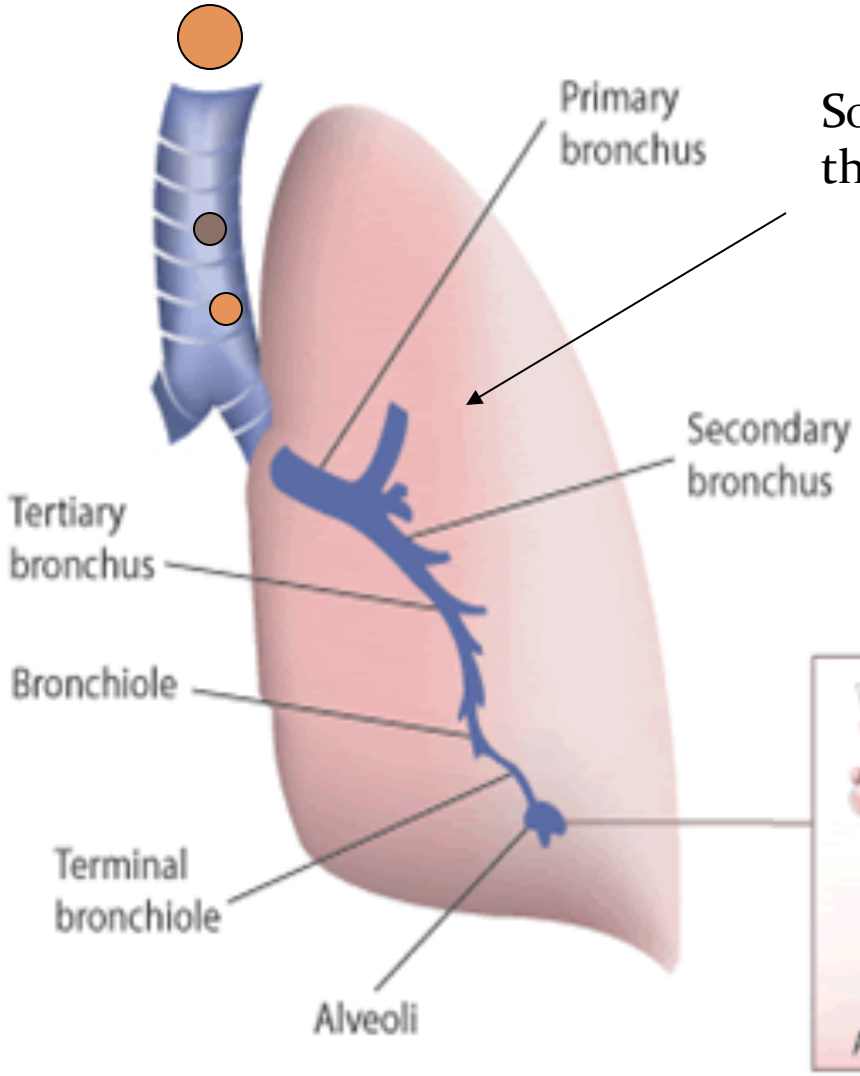
Biogenic Sources

Criteria Pollutants: Particulate Matter

Considered the most lethal form of air pollution.



Entering the System



Some pollutants penetrate through the lungs

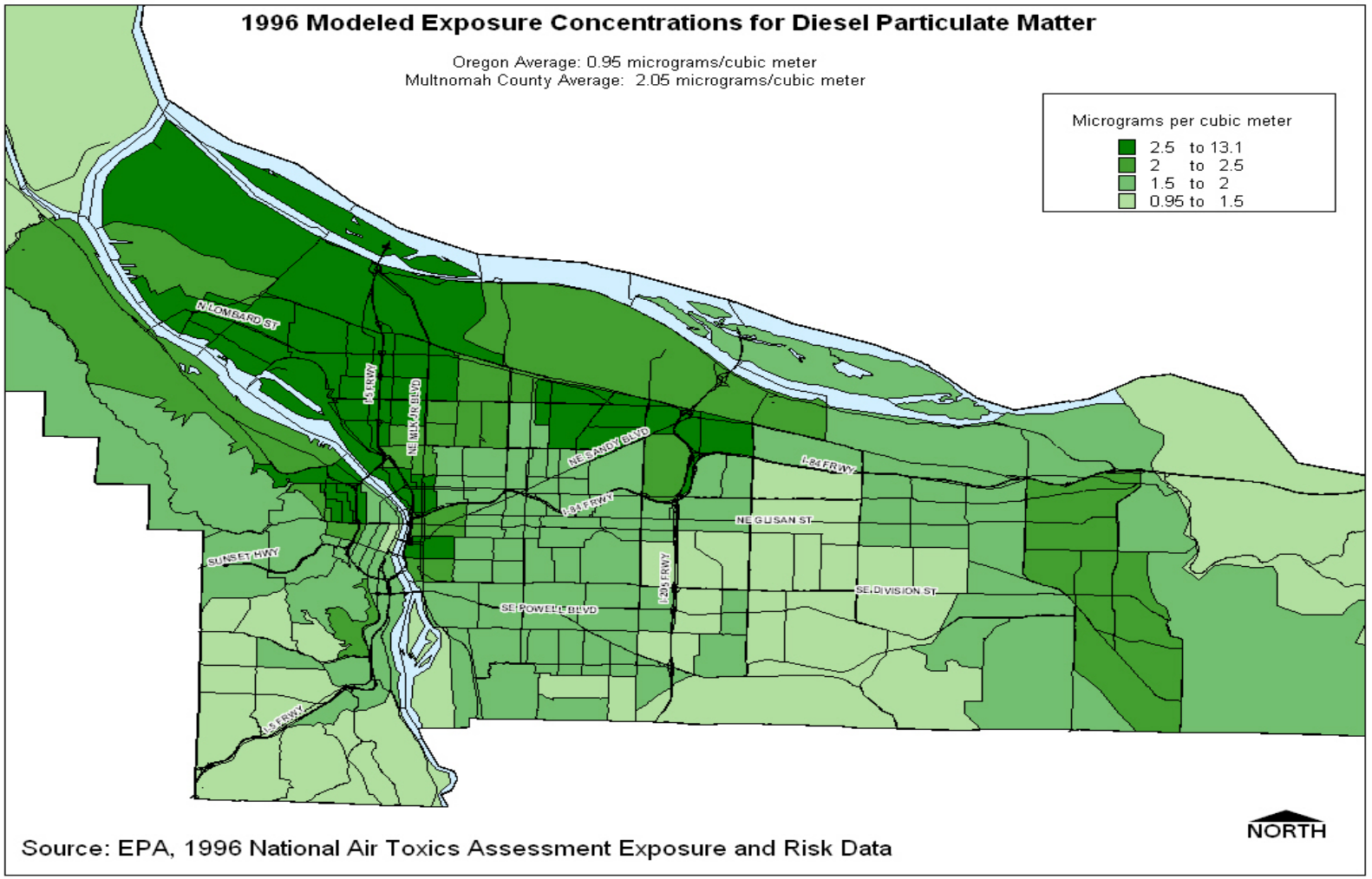
Pollutants trapped in nasal mucous tend to leave the body.

Toxicants attached to particulate pollution more easily enter the body.

Polycyclic Aromatic Hydrocarbons (PAHs)

- Large family of organic chemicals
  - examples: benzo(a)pyrene, dioxins, naphthalene
- Many very carcinogenic, estrogen receptors, and/or genotoxic
- Often enter the body on or in particulate

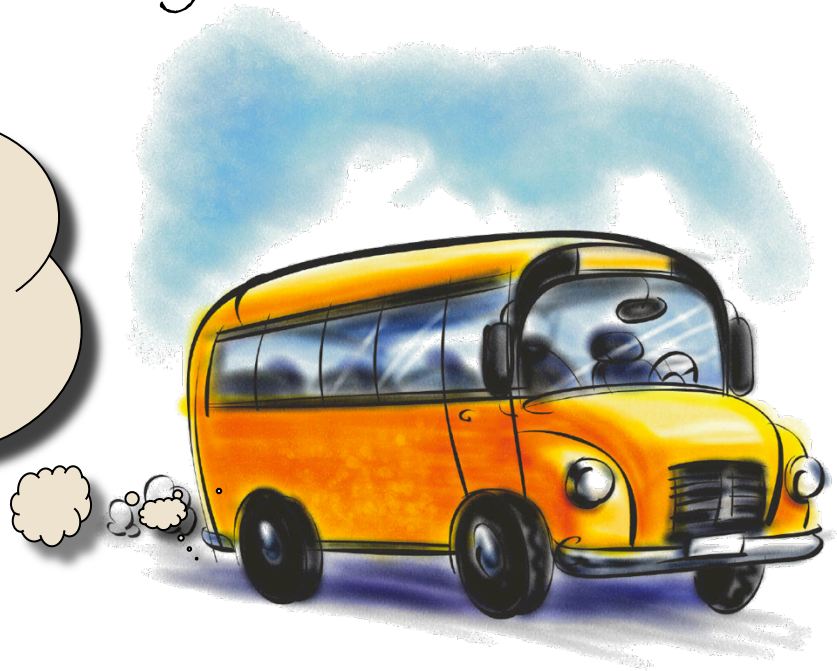
Exposure to diesel particulate



Diesel: A Toxic Soup of Its Own

"…A child riding a school bus is being exposed to as much as 46 times the cancer risk considered "significant" by EPA and under federal law."

Acetaldehyde ● ethyl benzene ● phenol ● arsenic formaldehyde ● phosphorus ● benzene ● hexane PAHs ● biphenyl ● lead ● selenium ● 1,3-butadiene manganese ● styrene ● cadmium ● methanol ● toluene chromium ● naphthalene ● xylene ● cresol ● nickel



Proposed Mechanisms of Neurodevelopmental Effects of Air Toxins

- Inflammatory agents in brain cells
  - produce reactive oxygen species (ROS) that disrupt normal brain structure, architecture and function
- Inflammatory cytokines and mitochondrial damage
- Enzymes which scavenge ROS (protects cells) are more effective in girls
- Epigenetic agents of change during development
  - Disrupting normal gene function and timing of brain neuron connections
- Immune dysregulation

Source: Costa et al. (2014)

Columbia Center for Children's Environmental Health (CCEHS) Studies

- Gold Standard: Perera et al. at Columbia University in New York
  - linking an environmental factor with a biomarker measurement and a specific measurable neurodevelopmental outcome
  - Latest publication in 10 year series: Early Life Exposure to Polycyclic Aromatic Hydrocarbons and ADHD behavior problems (2014) in PLoS One

- Peterson et al (2015): Prenatal PAH exposure to ↓ white matter (on left) by MRI, ↓ cognition, ↑ ADHD traits

Neurodevelopmental Effects of Prenatal PAHs (90% Diesel Exhaust) Exposure

Reference	Location	N	Assessment		Outcomes (p<0.05)
			Method	Age	
Cord Blood PAH-DNA Adducts					
Perera et al. (2014)	NYC	740	CBCL, Connors	7-9 yrs	Inattentive, ADHD
Tang et al. (2014)	China	110 (2002) 107 (2005	HC pre & post Coal Power Plant closure	7-10yrs	↓ PAH adducts, ↑ HC
Jedrychowski et al. (2014)	Poland	170	Full-scale WISC, verbal IQ	7 yrs	↓verbal IQ
Spatiotemporal Models					
Lin et al. (2014)	Taiwan	533	BSID	6,12,18 months	↓ gross motor development
Kim et al. (2014)	S Korea	520	BSID	6,12,24 months	↓ psychomotor & cognitive development
Newman et al. (2013)	Cincinnati	576	BAS	7 yrs	↑ Hyperactivity
Volk et al. (2013)	Calif.	279	ASD Diagnostic Instruments	2-5 yrs	↑risk of ASD
Siddique et al. (2011)	New Delhi	969	DSM-IV		↑ADHD (boys only)

HC := Head Circumference; BSID:= Bayley Scale of Infant Development; BAS := Behavioral Assessment System

Air Pollution Effects in Recent Novel Studies

Reference	Location	N	Assessment		Outcome (p<0.05)
			Method	Age (yrs)	
Raz et al. (2015)	USA	100,000 245 ASD	Retrospective Interview	10-15	↑ Risk ASD with PM2.5 all three trimesters but mostly third trimester (ST modeling). Corroborates previous publications.
Calderon-Garciduenas et al. (2011)	Mexico City	20	MRI, WISC, serum inflammatory marker	7	↓ Brain volume in Parietal & Temporal cortical matter, with ↑ white matter hyperintensities,; ↓ Vocabulary and Digit spans; ↑ inflammatory marker
Amoly et al. (2014)	Barcelona	2011	CBCL	5-8	Complex ST modeling: Living AND playing near Green (parks) and Blue (ocean) spaces, >300 meters from major pollution sources , children have ↓ ADHD symptoms. Children living closer have ↑ risk of ADHD symptoms

ST := spatiotemporal

Concluding Remarks

What To Do? Policy

In Oregon

- Diesel bills (Greenlick, Dembrow) in the OR legislature
- Columbia Riverkeepers & US Army CORPs landmark agreement to slash toxic oil/PCB pollution in the Columbia and Snake rivers

Nationally

- Research to identify non-toxic alternatives (e.g., green chemistry)
- Collaboration b/w government and industry to implement responsible disposal and collection practices
  - e.g., Safer Sofa Foam Exchange (currently in SF Bay Area; http://greensciencepolicy.org/safer-sofa/)

Globally

- Minamata convention (Oct. 2013): 130 nations agreed to both compulsory and voluntary measures to limit mercury release

What Can Be Done? Toxic Reform

- Implement new, federal regulation to test and update *all* chemicals in use today
- Restructure the 1976 Toxic Substances Control Act (TSCA) to effectively achieve these goals
- Adopt safer production and uses of all chemicals
- Encourage the training of medical students, physicians, and other health professionals about the human health effects of toxic chemical exposures with the help of the AMA

American Medical Association Resolution (2008)

Reminders:

- Pick up Hand-out:
- Recommendations to limit personal exposures to the environmental toxins we've discussed today, though bear in mind, a lot of this is beyond the control of individuals and requires action for policy changes.

- If you want our references, give us your email contact info

Acknowledgements

- Susan Katz, MD and Agnes Lobscheid, PhD

- Colleagues at Oregon Physicians for Social Responsibility

- Thank you for attending our session!

Dedicated to Dwight Meredith and family, in memory of Debbie Meredith

Discussion