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National Institute of Environmental Health Sciences

Epigenetics: Exposures, Genes & Generations

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30 October 2013

HEALTH & ENVIRONMENTAL FUNDERS NETWORK

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

The National Institute of Environmental Health Sciences

- One of the National Institutes of Health, but located in Research Triangle Park, NC
- Wide variety of programs supporting our mission of environmental health:

-- Intramural laboratories

-- Extramural funding programs

-- Disease Prevention

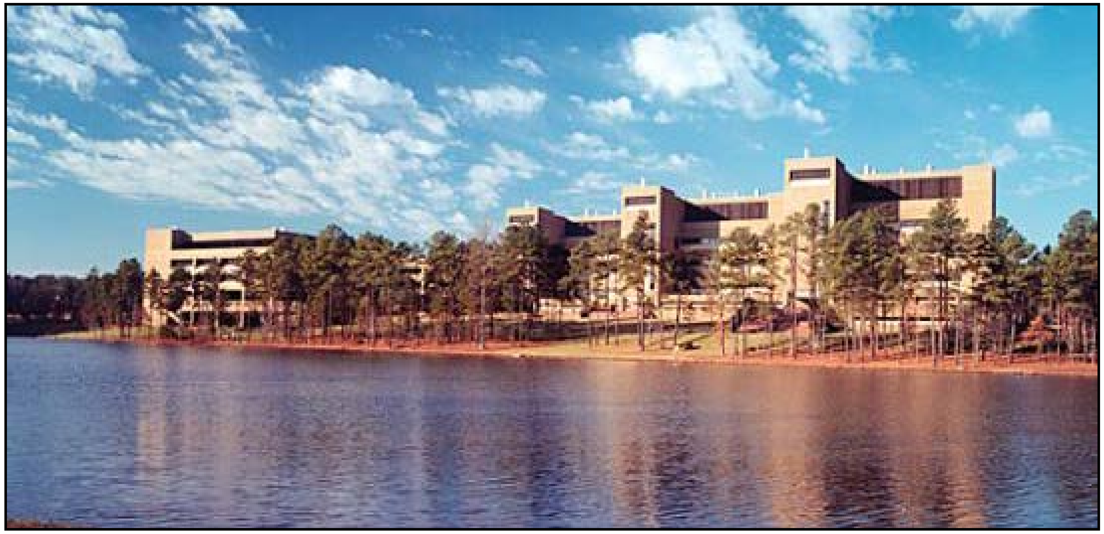
-- Clinical research program

-- National Toxicology Program

-- Public Health Focus

A New Vision and Mission for NIEHS and NTP

- Our ***vision*** is to provide global leadership for innovative research the improves public health by preventing disease and disability
- Our ***mission*** is to discover how the environment affects people in order to promote healthier lives.



Strategic Themes

- Studying ***basic mechanisms*** and ***windows of susceptibility***
- Linking ***individual and population exposure*** to risk
- Creating better ***predictive models*** and 21st Century tools
- Enhancing ***communication*** and ***diversity*** in all aspects of research
- ***Training*** a multidisciplinary group of scientists
- Improving ***coordination*** between gov't agencies and other groups

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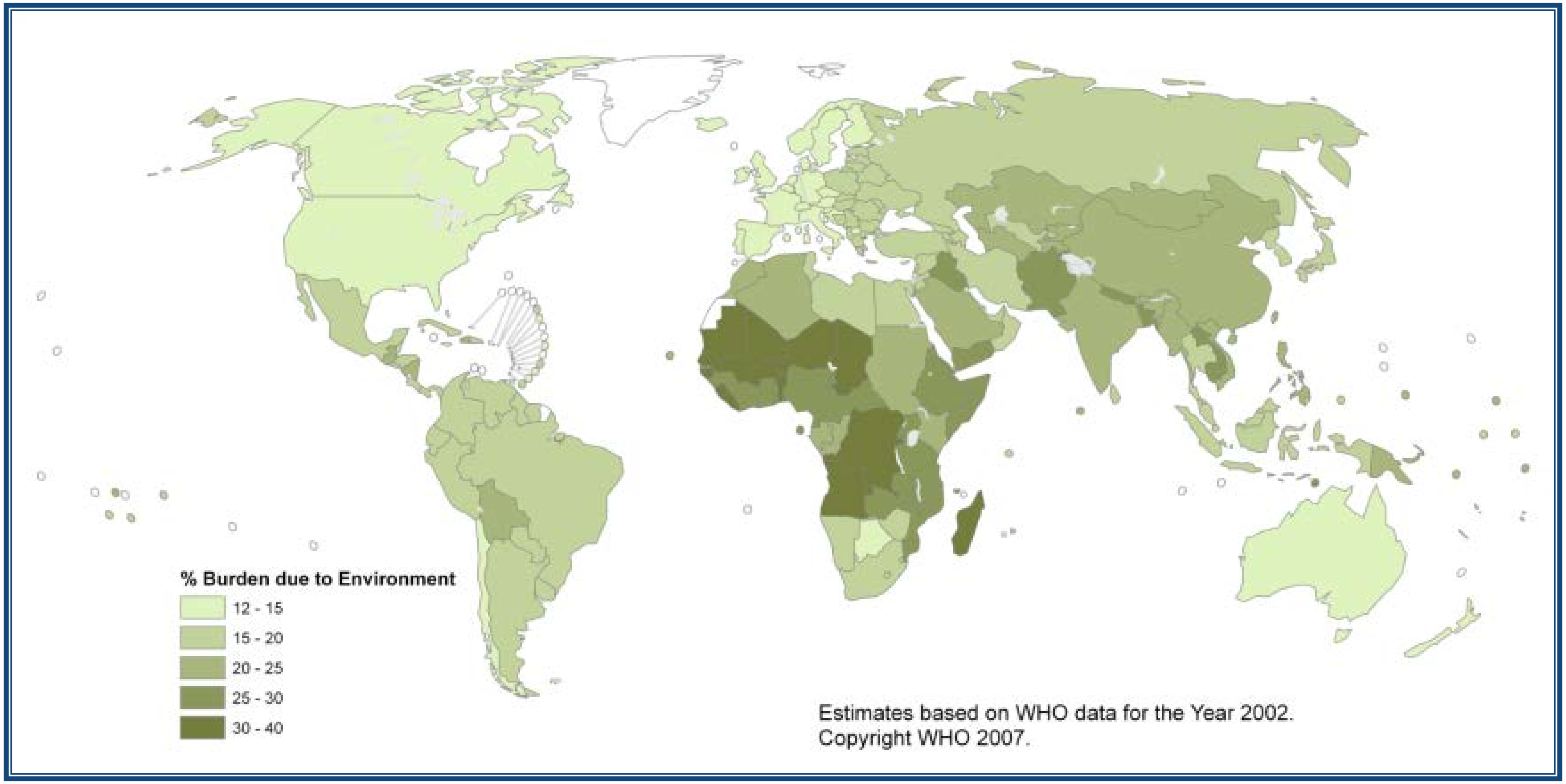
Toxicology for the 21st Century Goals….

- Identify patterns of compound-induced biological response in order to:
  - *characterize toxicity/disease pathways*
  - *facilitate cross-species extrapolation*
  - *model low-dose extrapolation*
- Prioritize compounds for more extensive toxicological evaluation
- Develop predictive models for biological response in humans

Environmental burden of disease: moving beyond infectious agents and high exposures



http://www.who.int/quantifying_ehimpacts/en/

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Why Environmental Health Matters

- 13 million deaths could be ***prevented*** per year by improving our environment
- Environmental factors influence 85 out of the 102 non-communicable diseases in WHO report
- Environmental factors account for at least 2/3 of cancer cases in the United States
- You can't change your genes, but you ***CAN*** change your environment

WHO Global Health Report (2010); Horton, R., Lancet (2013)

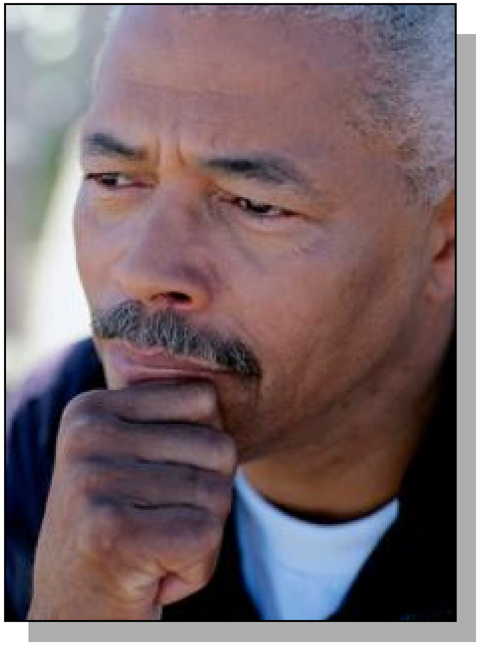
"ENVIRONMENT" Includes:

- Industrial chemicals
- Agricultural chemicals
- Physical agents (heat, radiation)
- By-products of combustion and industrial processes (dioxin)
- Infectious agents
- Microbiome (gut flora)
- Foods and nutrients
- Prescription drugs
- Lifestyle choices and substance abuse
- Social and economic factors

Ubiquitous Human Exposure

- Chemicals are *widely dispersed in our environment*
- Chemicals are often dispersed at biologically effective levels, exposure to humans is common
- Exposures do not occur singly
- One exposure can alter the body's response to other exposures
- Combinations must be studied
- The "Exposome" is the totality of exposures for a person

New ways of thinking about environmental health sciences…



OLD… chemicals act by overwhelming the body's defenses by brute force at very high doses

NEW… chemicals can act like hormones and drugs to disrupt the control of development and function at very low doses to which the average person is exposed

NEW… susceptibility to disease persists long after exposure **(epigenetics)** and may lead to transgenerational effects

…and about disease causation

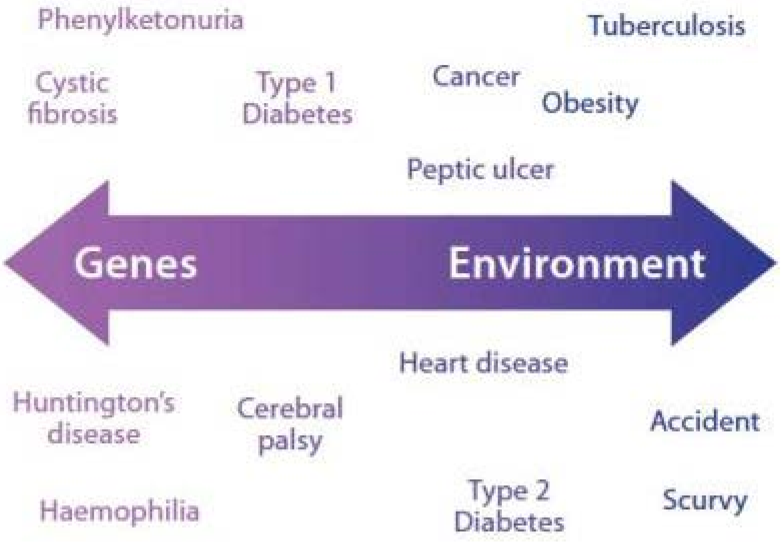
- Complex diseases
  have complex causes.

- Cancer and birth defects
  are not the only endpoints.

- The environment is a contributor to: obesity, diabetes, cardiopulmonary disease, autoimmune disease, reproductive dysfunction, neurodevelopmental disorders, schizophrenia, addiction, Alzheimer's Disease, and depression, and cancer and birth defects .

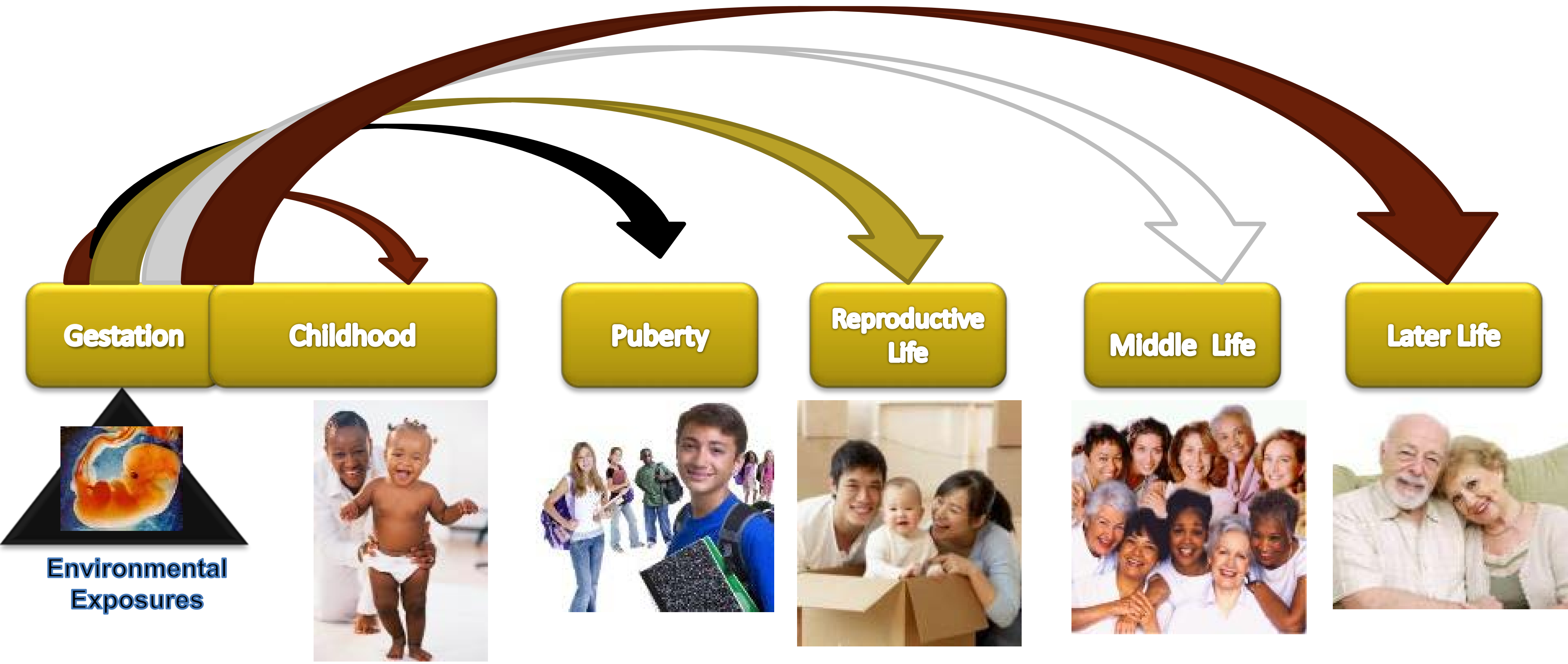
Research Challenges in Environmental Health

- Investigating the timing of exposure and windows of susceptibility
- Measuring individual biological responses and accounting for genetic susceptibility
- Tying mechanisms such as altered gene expression, epigenetic modifications, to adverse health outcomes

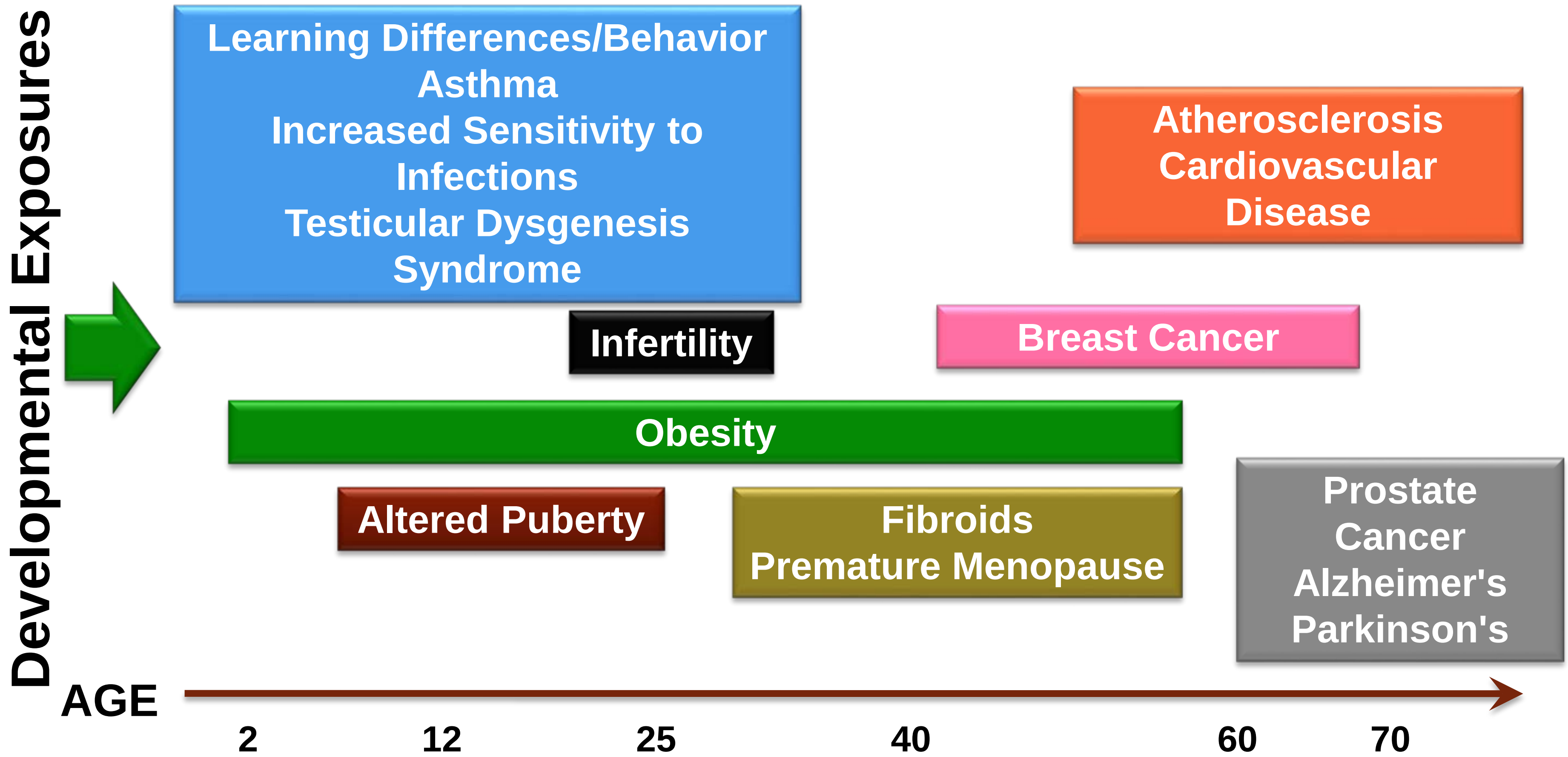


Developmental Origins of Disease:

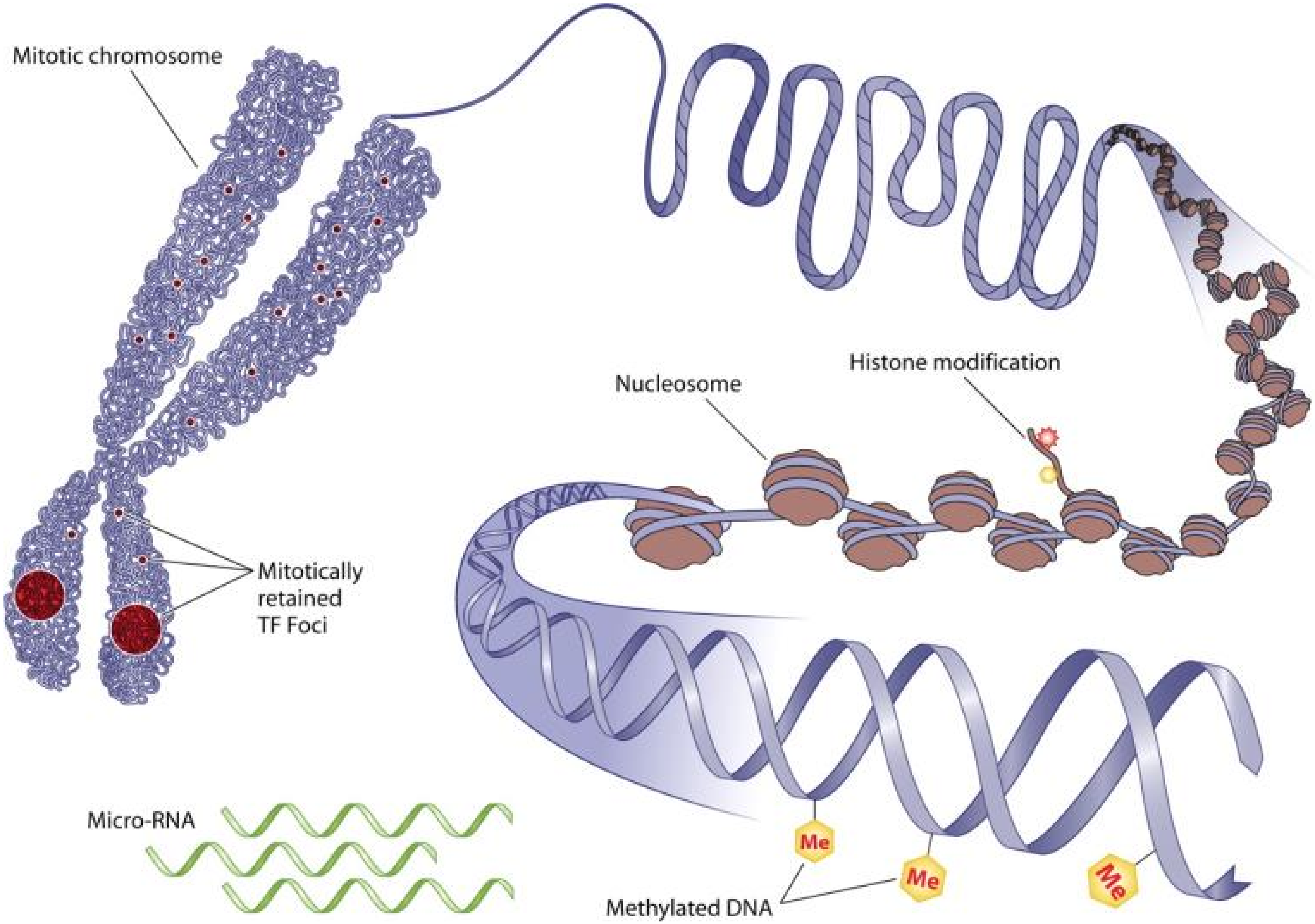
Developmental Exposures Lead to Disease Throughout Life



Examples of Developmental Origins of Health and Disease (DOHAD)



Mechanisms of inheritable epigenetics



Zaidi S K et al. Mol. Cell. Biol. 2010;30:4758-4766

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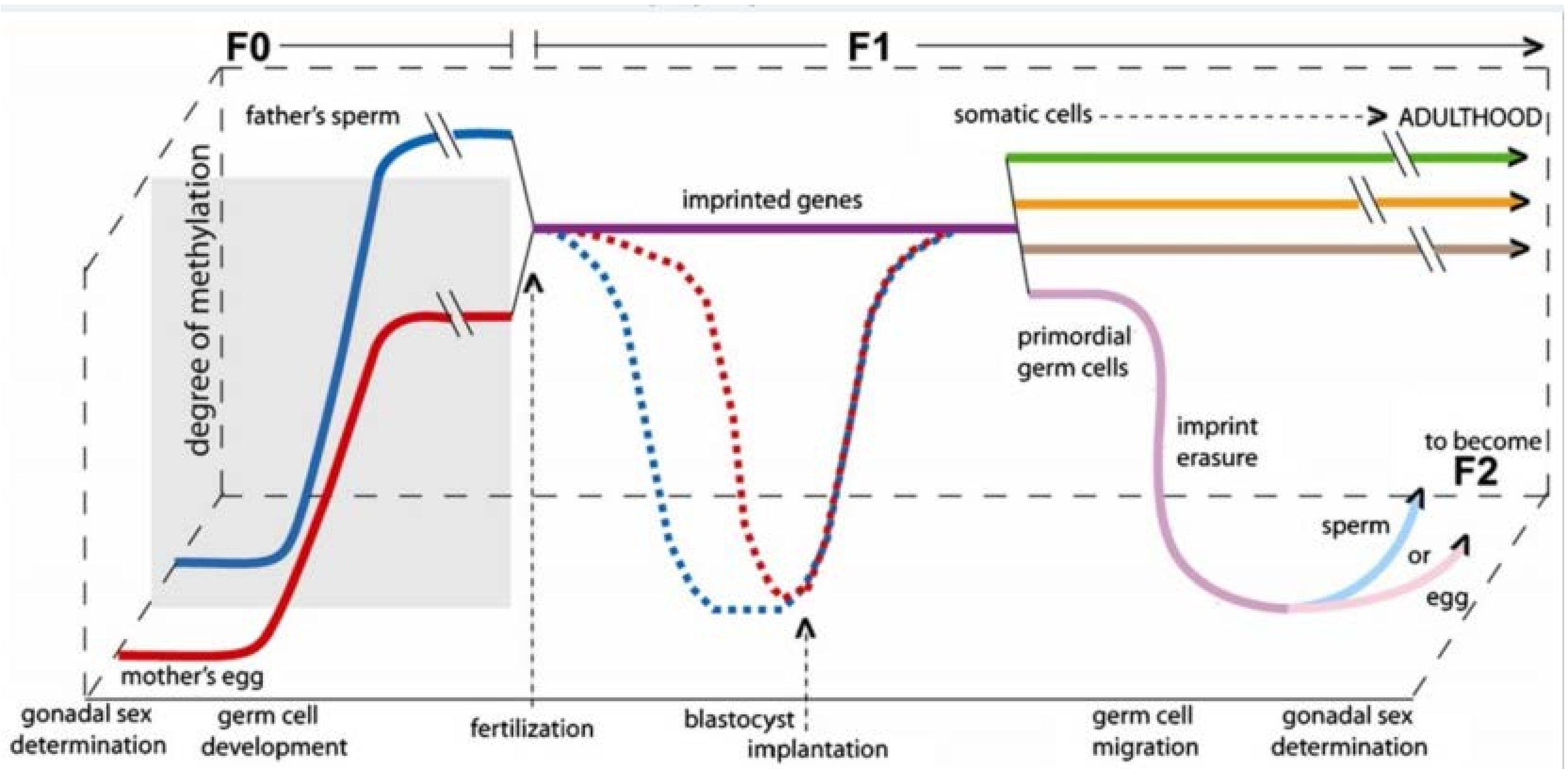
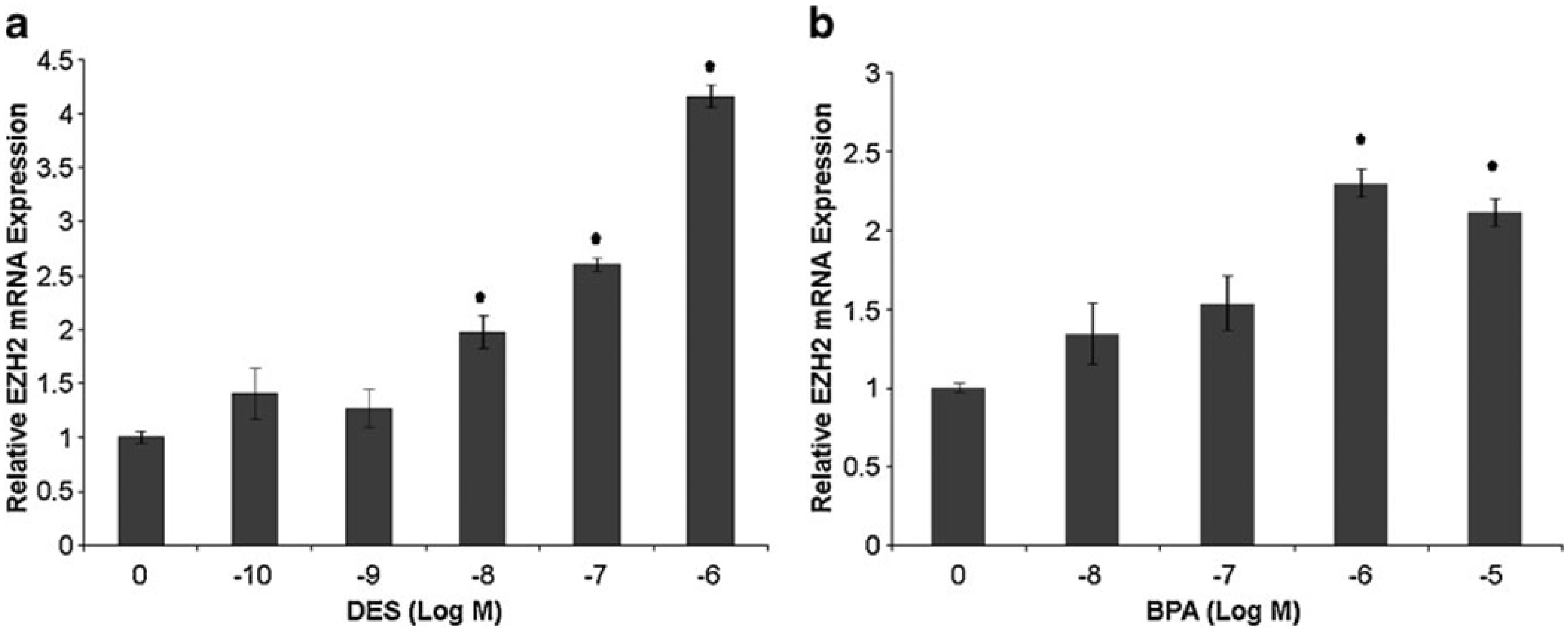
Timing of DNA methylation and de-methylation



Perera and Herbstman, 2011

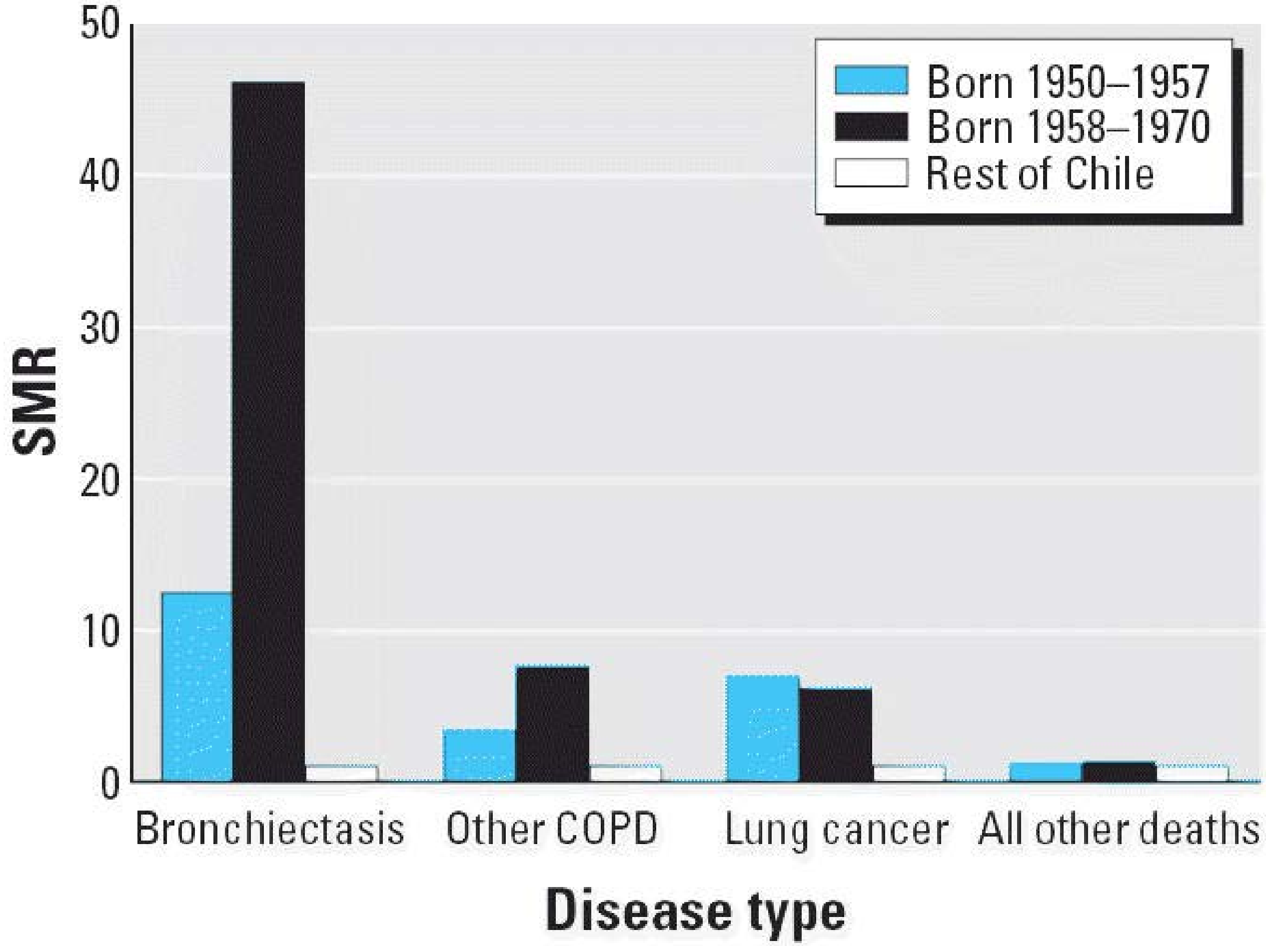
Cancer- DES and BPA

- Both Diethylstilbestrol (DES) and Bisphenol A (BPA) have been shown to cause epigenetic changes associated with cancer after *in utero* exposures

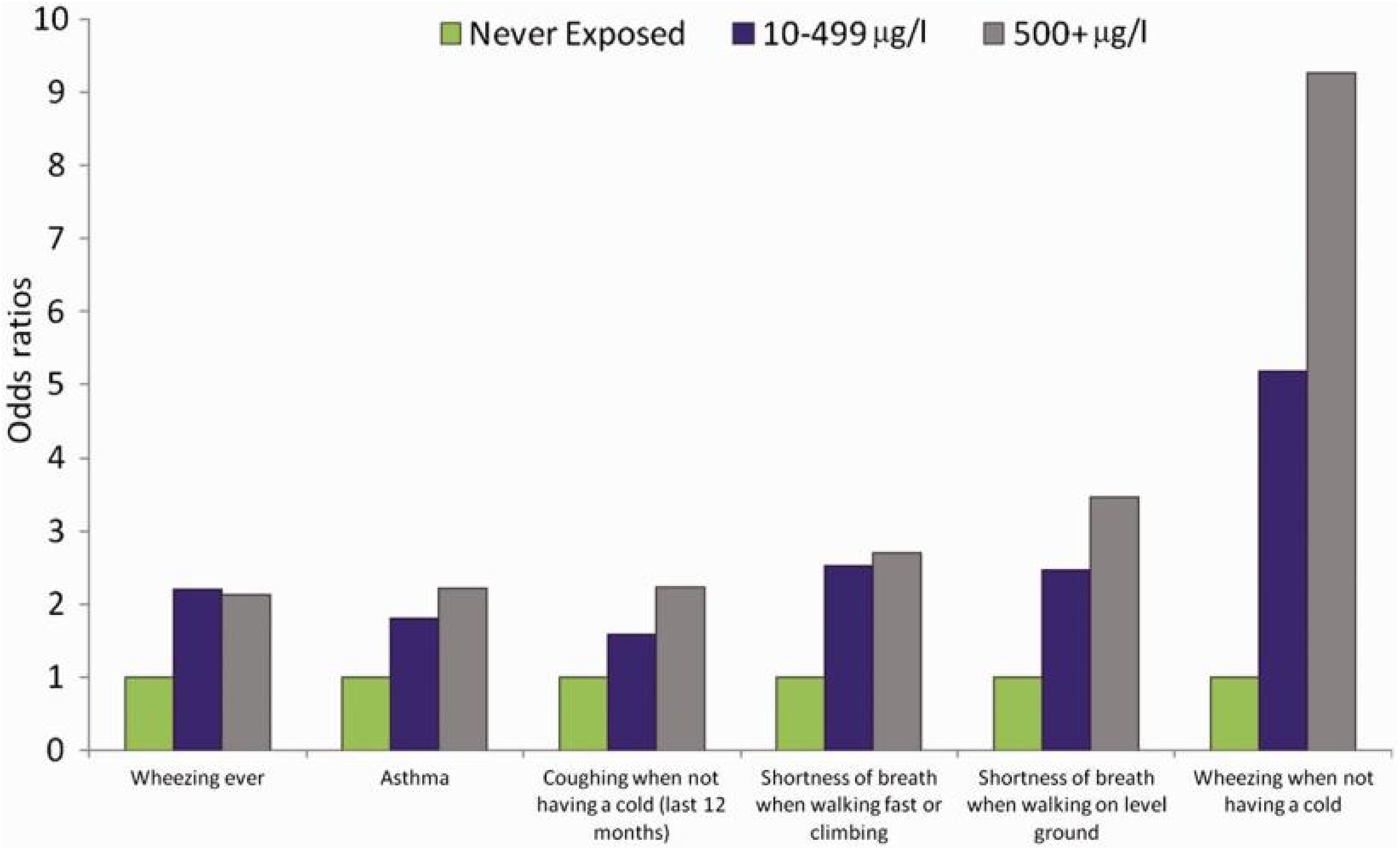


Doherty LF, et al. Horm Canc. 2010;1:146-155

In utero exposure to arsenic increases risk of COPD and lung cancer (Smith et al., 2006)

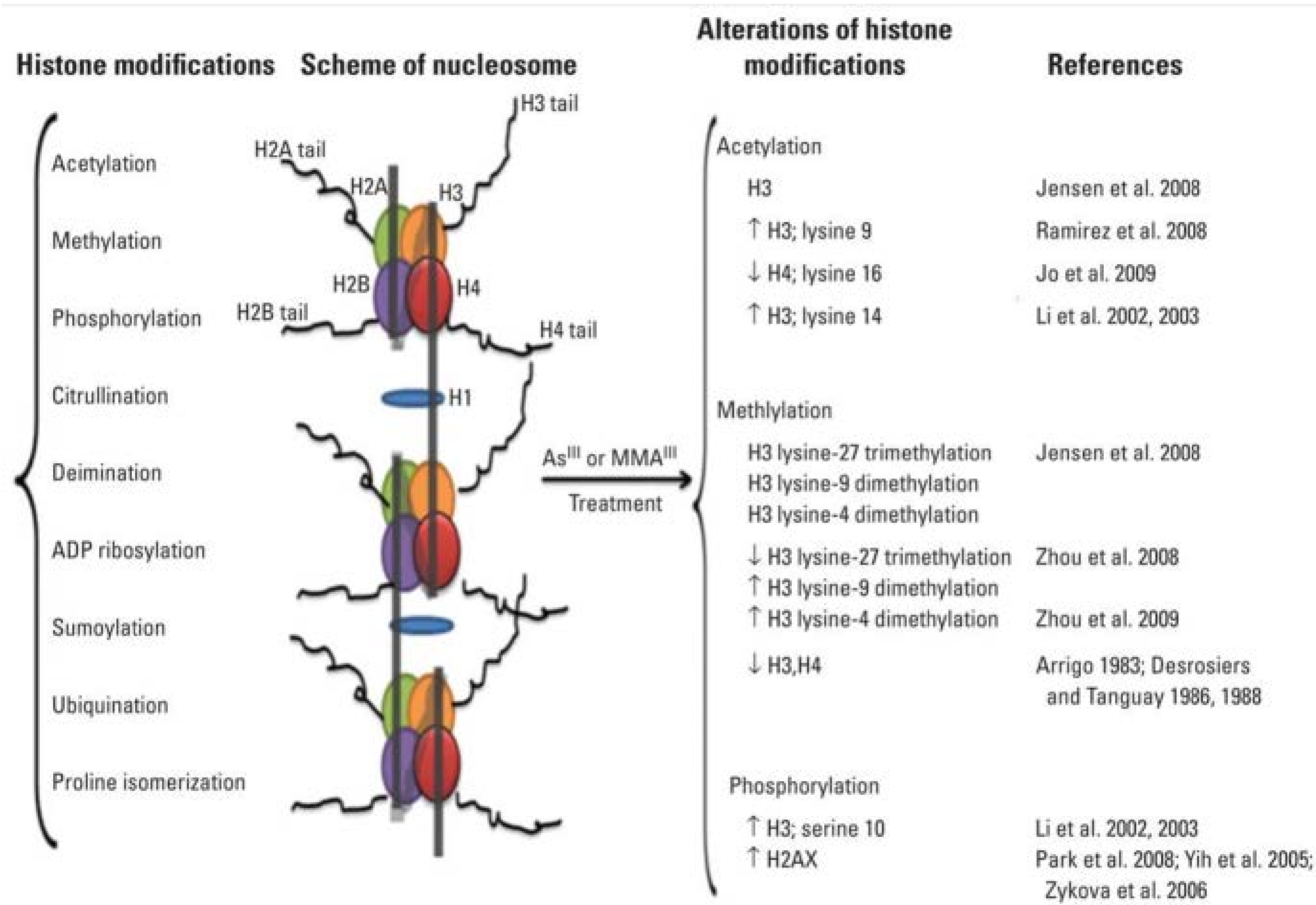


Odds ratios for respiratory symptoms which exceeded 2.0 in the highest arsenic exposure



Smith A H et al. Int. J. Epidemiol. 2013;42:1077-1086

Epigenetic modifications linked to arsenic



X Ren, et al. Environ Health Perspect. 2011 Jan;119(1):11-9.

Persistence of Effects

- Health effects of exposure can be observed ***long after*** the actual exposure has stopped
- This is especially true when exposures occur during growth and development, processes that are very sensitive to endocrine regulation
- Animal researchers discovered that endocrine disruptors can produce latent effects by subtly altering the structure of DNA molecules (epigenetics)
- The NIEHS is conducting human studies on the latent effects of EDC exposure, including studies of children with behavioral, mental and physical abnormalities who were exposed to phthalates, PAHs or flame retardants before birth

Asthma

- Most cases of asthma are now thought to originate in early life

•ETS
•Traffic-related pollutants
•Viral infection
•Bacterial exposures
•Dust mites
•Nutritional factors
•PAHs

•Airborne environmental irritants (ETS, DEPs)
•Viral infection (lower respiratory)
•Dust mite allergens
•Nutritional deficiencies (vitamin D)

Asthma - PAHs

- *In utero* exposure to polycyclic aromatic hydrocarbons (PAHs) has been associated with altered methylation patterns and with childhood asthma

Characteristics*	PAH<2.41 (N = 30)	PAH≥2.41 (N = 26)	Subjects (N = 56)	Odds Ratios (95% CI's)
Ethnicity (%AA)	15 (50%)	15 (58%)	30 (54%)	1.4 (0.5, 3.9)
Gender (% Males)	12 (40%)	12 (46%)	24 (43%)	1.3 (0.4, 3.7)
ACSL3 5'CGI Status (% Methylated)	7 (23%)	21 (81%)	28 (50%)	13.8 (3.8, 50.2)[b]

ACSL3 5'CGI Methylation Status	Methylated	Unmethylated	All	Odds Ratios (95% CI's)
Asthma (% Yes with asthma)[a]	11/28 (39%)	4/28 (14%)	15/56 (27%)	3.9 (1.1, 14.3)
Median PAH exposure with in each group[b] (Min, Max)	3.39 ng/m^3 (1.11, 34.48)	1.7 ng/m^3 (0.49, 3.33)	2.26 ng/m^3 (0.49, 34.48)	

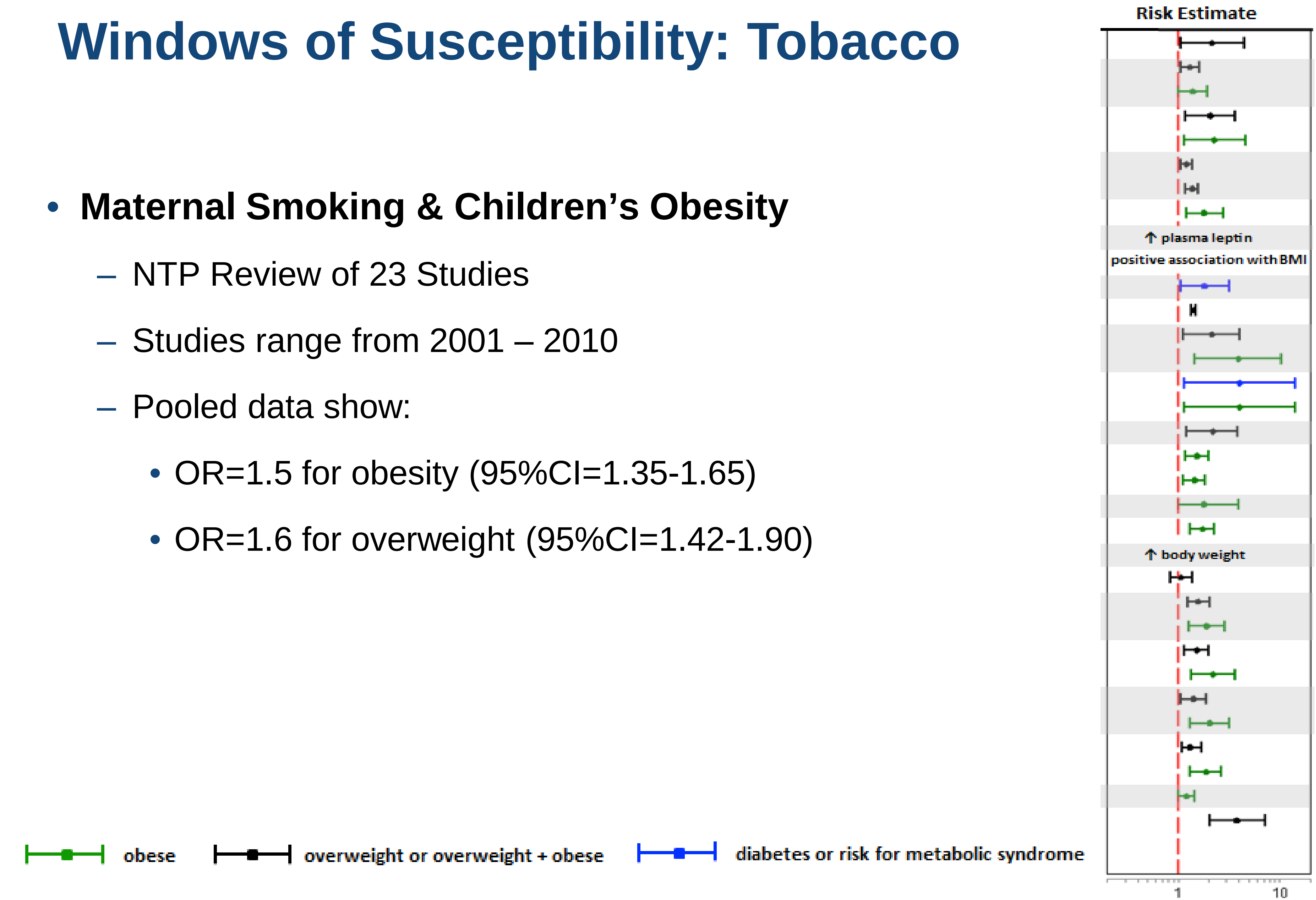
Perera F, et al. PLoS ONE 2009; 4(2): e4488.

Children's Research on Air Pollution and the Immune System

- Living within 75m of a major roadway associated with increased risk of asthma
- Genetic variations in immune response to air pollutants may increase susceptibility
- Children in a high-pollution environment showed impaired function of regulatory T cells compared to children in low-pollution setting
- Ambient air pollution may worsen asthma via an immune mechanism
- The pollution may mediate epigenetic changes in regulatory T cells (Nadeau, Journal of Allergy and Clinical Immunology, 2010)

Windows of Susceptibility: Tobacco

- **Maternal Smoking & Children's Obesity**
  - NTP Review of 23 Studies
  - Studies range from 2001 – 2010
  - Pooled data show:
    - OR=1.5 for obesity (95%CI=1.35-1.65)
    - OR=1.6 for overweight (95%CI=1.42-1.90)



Chemical Obesogens

- Exposure to tobacco smoke *in utero* has been associated with obesity, hypertension, and gestational diabetes mellitus

Table 4. aORs[a] for obesity, hypertension, T2DM, and GDM by *in utero* exposure to tobacco smoke among women, stratified by adult smoking.[b]

	Nonsmokers (n = 51,852)		Smokers (n = 22,171)		
Outcomes	Cases	aOR (95% CI)	Cases	aOR (95% CI)	p-Interaction[c]
Before pregnancy					
Obesity	4,565	1.75 (1.64, 1.87)	2,387	1.29 (1.18, 1.40)	< 0.01
Hypertension	105	1.48 (0.98, 2.23)	31	2.56 (1.23, 5.33)	0.24
T2DM	91	1.02 (0.64, 1.62)	41	1.38 (0.74, 2.56)	0.38
GDM	385	1.25 (1.00, 1.55)	162	1.48 (1.08, 2.02)	0.33

[a]Adjusted for woman's age and education. All models except for obesity were also adjusted for prepregnancy BMI (kg/m^2). [b]All models except for GDM were stratified by adult smoking before pregnancy; GDM model was stratified by adult smoking during pregnancy (n = 55,402 for nonsmokers and n = 18,250 for smokers). [c]Interaction term between *in utero* tobacco smoke (yes/no) and adult smoking (yes/no).

Cupul-Uicab LA, et al. Environ Health Perspect. 2012;120(3):355-360.

Bisphenol A and Obesity in Children

Table 2. Association of Urinary Bisphenol A Concentration and Odds and Prevalence of Obesity in Strata Defined by Sample Characteristics[a]

	All		Urinary Bisphenol A Concentration Quartile[b]						
			1 (n = 685)	2 (n = 700)		3 (n = 737)		4 (n = 716)	
	Unweighted No., Obese/Total	Obese in Stratum, % (SE)[c]	Prevalence (95% CI), %	OR (95% CI)	Prevalence (95% CI), %	OR (95% CI)	Prevalence (95% CI), %	OR (95% CI)	Prevalence (95% CI), %
Entire sample	590/2816	17.8 (1.3)	10.0 (7.6-12.5)	2.22 (1.53-3.23)[d]	19.9 (15.0-24.7)	2.09 (1.48-2.95)[d]	18.9 (14.8-23.0)	2.53 (1.72-3.74)[d]	22.1 (17.0-27.2)
Sex									
Female	265/1366	16.5 (1.5)	10.8 (6.7-14.8)	1.86 (1.10-3.17)[e]	18.4 (12.4 to 24.3)	1.65 (0.93-2.92)	16.6 (11.6-21.6)	2.00 (1.15-3.49)[e]	19.5 (13.5-25.5)
Male	305/1450	19.0 (1.8)	9.4 (6.5-12.4)	2.63 (1.56-4.43)[d]	21.6 (15.2-27.9)	2.56 (1.66-3.96)[d]	21.1 (15.2-27.0)	3.14 (1.79-5.48)[d]	24.7 (17.2-32.1)
Age group, y									
<12	227/1055	18.0 (1.6)	12.2 (6.8-17.5)	1.72 (1.05-2.81)[e]	19.2 (11.7-26.6)	1.91 (1.14-3.21)[e]	20.9 (15.1-26.6)	2.34 (1.31-4.18)[e]	24.3 (18.1-30.5)
≥12	363/1761	17.6 (1.5)	9.6 (6.1-13.1)	2.59 (1.49-4.48)[f]	21.6 (15.7-27.5)	2.14 (1.25-3.64)[f]	18.6 (13.3-23.8)	2.57 (1.55-4.23)[f]	21.5 (15.3-27.6)
Race/ethnicity									
Hispanic	227/1004	23.2 (1.9)	22.4 (17.2-27.6)	1.24 (0.80-1.92)	26.5 (20.2-32.7)	0.94 (0.58-1.49)	21.3 (14.9-27.7)	1.02 (0.65-1.59)	22.8 (16.0-29.7)
Non-Hispanic white	124/787	15.5 (1.7)	4.7 (1.8-7.6)	4.32 (2.08-8.99)[d]	17.5 (10.6-24.4)	4.21 (2.01-8.77)[d]	17.1 (11.7-22.4)	6.03 (2.88-12.62)[d]	22.8 (15.8-29.8)
Non-Hispanic black	216/893	24.5 (1.9)	20.8 (13.8-27.9)	0.99 (0.58-1.66)	20.7 (15.2-26.2)	1.38 (0.78-2.47)	26.8 (19.2-34.3)	1.34 (0.75-2.38)	26.1 (18.3-33.8)
Other	23/132	10.3 (2.9)	7.1 (−2.4 to 16.7)	2.84 (0.64-12.4)	17.7 (3.8-31.7)	2.11 (0.30-14.8)	13.9 (0.5-27.3)	1.22 (0.25-5.86)	8.6 (2.5-14.6)

Tresande et al. *JAMA.* 2012;308(11):1113-1121.

Prenatal Pesticide Exposure Lowers Child IQ

Prenatal Exposure to Organophosphate Pesticides and IQ in 7-Year Old Children

Maryse F. Bouchard, Jonathan Chevrier, Kim G. Harley, Katherine Kogut, Michelle Vedar, Norma Calderon, Celina Trujillo, Caroline Johnson, Asa Bradman, Dana Boyd Barr, Brenda Eskenazi

ehp
ENVIRONMENTAL HEALTH PERSPECTIVES
ehponline.org
Online 21 April 2011

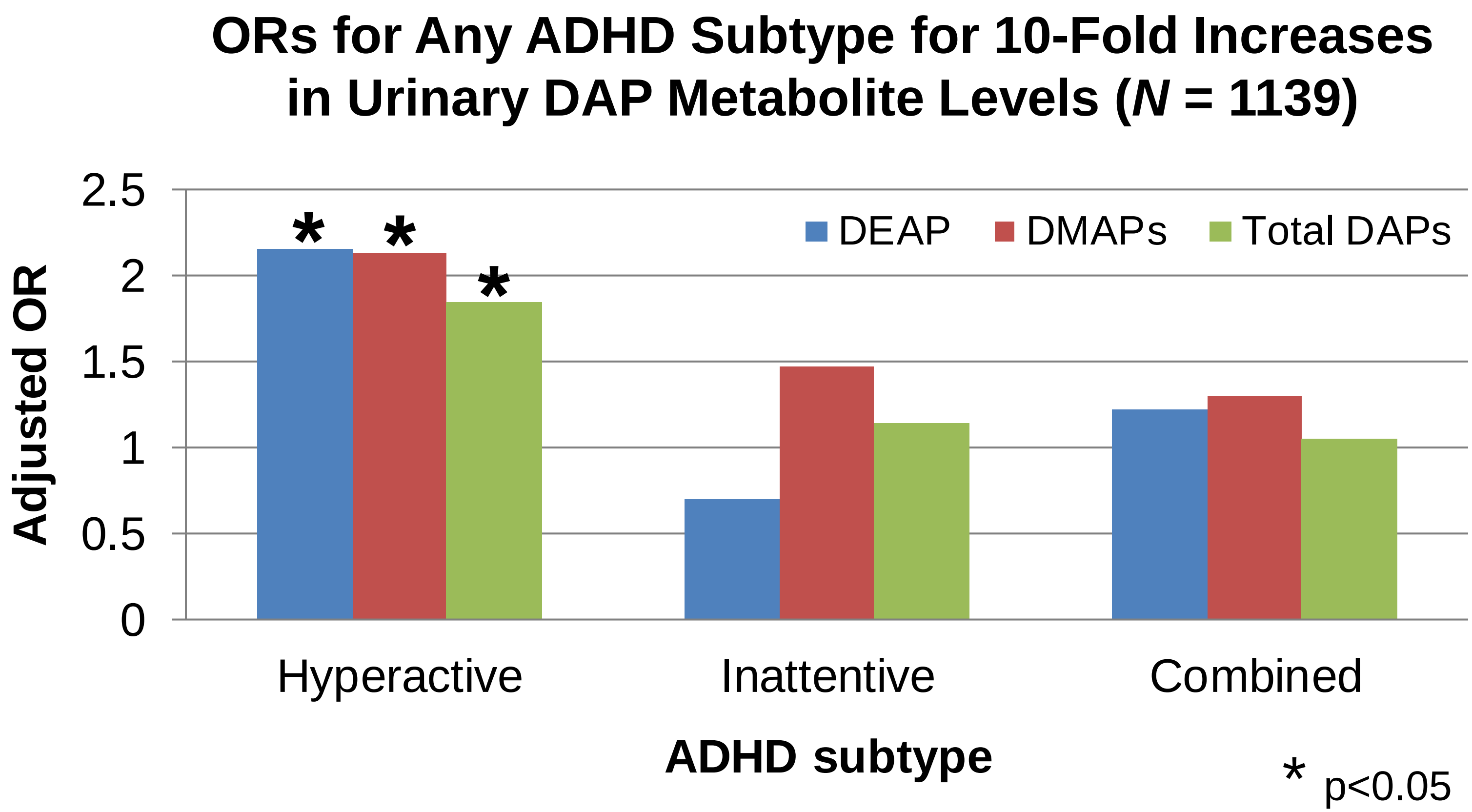
7-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide

Virginia Rauh, Srikesh Arunajadai, Megan Horton, Frederica Perera, Lori Hoepner, Dana B. Barr, Robin Whyatt

Prenatal Exposure to Organophosphates, Paraoxonase 1, and Cognitive Development in Childhood

Stephanie M. Engel, James Wetmur, Jia Chen, Chenbo Zhu, Dana Boyd Barr, Richard L. Canfield, and Mary S. Wolff

Pesticide Exposure Linked to Risk of ADHD



Adjusted for gender, age, race/ethnicity, PIR, fasting duration, and logarithmically transformed urinary creatinine concentration.

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Chemicals with **Substantial** Evidence of Developmental Neurotoxicity (n≈100)

2-Ethoxyethyl Acetate	Diazepam	Naltrexone
Acibenzolar-*S*-methyl	Cytosine Arabinoside	Nicotine
Acrylamide	DEET	Methoxyethanol, 2-
Aldicarb	Deltamethrin	Methylazoxymethanol
Allethrin	Diazinon	Methylmercury
Aluminum (cl or lactate)	Dieldrin	Ozone
Amino-nicotinamide(6-)	Diethylstilbestrol	Paraquat
Aminopterin	Diphenylhydantoin	Parathion (ethyl)
Amphetamine(*d*-)	Epidermal Growth Factor	PBDEs
Arsenic	Ethanol	PCBs (generic)
Aspartame	Ethylene thiourea	Penicillamine
Azacytidine(5-)	Flourouracil(5-)	Permethrin
Benomyl	Fluazinam	Phenylacetate
Benzene	Fluoride	Phenylalanine (d,l)
Bioallethrin	Griseofulvin	Phthalate, di-(2-ethylhexyl)
Bis(tri-n-butyltin)oxide	Haloperiodol	Propylthiouracil
Bisphenol A	Halothane	Retinoids/vit.A/isotretinoin
Bromodeoxyuridine(5-)	Heptachlor	Salicylate
Butylated Hydroxy Anisol	Hexachlorobenzene	Tebuconazole
Butylated hydroxytoluene	Hexachlorophene	Tellurium (salts)
Cadmium	Hydroxyurea	Terbutaline
Caffeine	Imminodiproprionitrile (IDPN)	Thalidomide
Carbamazepine	Ketamine	THC
Carbaryl	Lead	Toluene
Carbon monoxide	Lindane	Triamcinolone
Chlordecone	LSD	Tributyltin chloride
Chlordiazepoxide	Maneb	Trichlorfon
Chlorine dioxide	Medroxyprogesterone	Trichloroethylene
Chlorpromazine	Mepivacaine	Triethyllead
Chlorpyrifos	Methadone	Triethyltin
Cocaine	Methanol	Trimethyltin
Colcemid	Methimazole	Trypan blue
Colchicine	Methylparathion	Urethane
Cypermethrin	Monosodium Glutamate	Valproate
Dexamethasone	MPTP	Vincristine
Diamorphine hydrochloride	Naloxone	

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Thank you!

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NIEHS Strategic Plan Website
http://www.niehs.nih.gov/strategicplan