

Green Chemistry as a Tool for Prevention

How Children's Environmental Health Informs the Design of Safer Substances



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Biomonitoring of Chemicals & Pollutants

2009

Fourth National Report on Human Exposure to Environmental Chemicals

CDC measured 212 substances in the 2003-04 NHANES cohort

Acrylamide
Acrylamide hemoglobin adducts *
Cycteamide hemoglobin adducts *
Cotinine
N,N-Diethyl-meta-toluamide (DEET)
Environmental Phenols
Benzophenone-3 (2-Hydroxy-4-methoxybenzophenone) *
Bisphenol A (2,2-bis[4-(4-hydroxyphenyl) propane] *)
4-tert-Octylphenol (4-[1,1,3,3-tetra-methylbutyl] phenol) *
Triclosan (2,4,4'-Trichloro-2-hydroxyphenyl ether) *
Perchlorate *
Pesticides
Fungicides
Pentachlorophenol
ortho-Rhanyphenol
Herbicides
Azochlor mercaptate
Alachlor mercaptate
Atrazine mercaptate
2,4-Dichlorophenoxyacetic acid
Metolachlor mercaptate
2,4,5-Trichlorophenoxyacetic acid
Carbamate Insecticides
Carbofuranphenol
2-Isopropoxyphenol
Organochlorine Pesticides
Aldrin
Dieldrin
Endrin
o,p'-Dichlorodiphenyltrichloroethane
p,p'-Dichlorodiphenyldichloroethane (DDE)
p,p'-Dichlorodiphenyltrichloroethane (DDT)
Heptachlor epoxide
Hexachlorobenzene
beta-Hexachlorocyclohexane
gamma-Hexachlorocyclohexane (Lindane)
Styrene
trans-Nonachlor
Oxychlorane
2,4,5-Trichlorophenol
2,4,6-Trichlorophenol
Organophosphorus Insecticides: Dialkyl Phosphate Metabolites
Diethylthiophosphate (DEETP)
Diethylphosphate (DEP)
Diethylthiophosphate (DETP)
Dimethylthiophosphate (DMTDP)
Dimethylphosphate (DMP)
Dimethylthiophosphate (DMTP)
Organophosphorus Insecticides: Specific Metabolites
3-Chloro-7-hydroxy-4-methyl-2H-chromen-2-one/ol
2-(Diethylamino)-6-methylpyrimidin-4-ol-one
2-Isopropyl-4-methyl-6-hydroxypyrimidine
Metolachlor dicarboxylic acid
para-Nitrophenol
3,5,6-Trichloro-2-pyridinol
Pyrethroid Pesticides
2,2-(2-Chlorovinyl)-2,2-dimethylcyclopropane carboxylic acid
cis-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid
trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid
4-Fluoro-3-phenoxybenzoic acid
3-Phenoxybenzoic acid

Metals
Antimony
Arsenic, Total *
Arsenic (V) acid *
Arsenobetaine *
Arsenocholine *
Arsenous (III) acid *
Dimethylarsinic acid *
Monomethylarsonic acid *
Trimethylarsine oxide *
Barium
Beryllium
Cadmium
Cesium
Cobalt
Lead
Mercury
Molybdenum
Platinum
Thallium
Tungsten
Uranium
Perfluorocarboxylics
Perfluorobutane sulfonic acid (PFBS) *
Perfluorodecanoic acid (PFDA) *
Perfluorododecanoic acid (PFDDA) *
Perfluorooctanoic acid (PFPOA) *
Perfluorooctanesulfonic acid (PFOS) *
2-(Ethyl-perfluorooctane sulfonamido) acetic acid (Et-PFO-2-(N-perfluorooctane sulfonamido) acetic acid (Me-P-Perfluorooctanoic acid (PFOA) *
Perfluoroundecanoic acid (PFUA) *
Phthalates
Mono-benzyl phthalate (MBzP)
Mono-n-butyl phthalate (MBzP)
Mono-2-carboxypropyl phthalate (MCPP)
Mono-cyclohexyl phthalate (MC6P)
Mono-ethyl phthalate (MEP)
Mono-(2-ethyl-5-carboxypropyl) phthalate (MECPP) *
Mono-(2-ethyl-5-oxohexyl) phthalate (MECHP)
Mono-2-ethylhexyl phthalate (MEHP)
Mono-isobutyl phthalate (MBIP)
Mono-isooctyl phthalate (MBIP)
Mono-methyl phthalate (MMP)
Mono-n-octyl phthalate (MCP)
Phytoestrogens
Daidzein
Enterodiol
Enterolactone
Equol
Genistein
O-Demethylangolensin
Brominated Fire Retardants
2,2,4-Tribromodiphenyl ether (BDE 17) *
2,4,4'-Tribromodiphenyl ether (BDE 28) *
2,2',4,4'-Tetrabromodiphenyl ether (BDE 47) *
2,3',4,4'-Tetrabromodiphenyl ether (BDE 66) *
2,2',3,4,4'-Pentabromodiphenyl ether (BDE 85) *
2,2',4,4',5-Pentabromodiphenyl ether (BDE 99) *
2,2',4,4',5,5'-Hexabromodiphenyl ether (BDE 100) *
2,2',4,4',5,5'-Hexabromodiphenyl ether (BDE 153) *
2,2',3,4,4',5'-Hexabromodiphenyl ether (BDE 154) *
2,2',3,4,4',5,5'-Heptabromodiphenyl ether (BDE 183) *
2,2',4,4',5,5'-Hexabromodiphenyl ether (BB 153) *

Non-Dioxin-Like Polychlorinated Biphenyls
2,4,4'-Trichlorobiphenyl (PCB 28)
2,2',3,5'-Tetrachlorobiphenyl (PCB 44) *
2,2',4,5'-Tetrachlorobiphenyl (PCB 49) *
2,2',5,5'-Tetrachlorobiphenyl (PCB 52) *
2,3',4,4'-Tetrachlorobiphenyl (PCB 66)
2,4,4',5'-Tetrachlorobiphenyl (PCB 74)
2,2',3,4,5'-Pentachlorobiphenyl (PCB 87)
2,2',4,4',5'-Pentachlorobiphenyl (PCB 99)
2,2',4,5,5'-Pentachlorobiphenyl (PCB 103)
2,3,3',4',6'-Pentachlorobiphenyl (PCB 110)
2,2',3,3',4,4'-Hexachlorobiphenyl (PCB 128)
2,2',3,4,4',5' and 2,3,3',4,4',6'-Hexachlorobiphenyl (PCB 138 & 158)
2,2',3,4',5,5'-Hexachlorobiphenyl (PCB 146)
2,2',3,4',5,6'-Hexachlorobiphenyl (PCB 149)
2,2',3,5,5',6'-Hexachlorobiphenyl (PCB 151)
2,2',4,4',5,5'-Hexachlorobiphenyl (PCB 153)
2,2',3,3',4,4',5'-Heptachlorobiphenyl (PCB 170)
2,2',3,3',4,4',5,5'-Heptachlorobiphenyl (PCB 172)
2,2',3,3',4,4',5,6'-Heptachlorobiphenyl (PCB 173)
2,2',3,3',5,5',6'-Heptachlorobiphenyl (PCB 178)
2,2',3,4,4',5,5'-Heptachlorobiphenyl (PCB 180)
2,2',3,4,4',5,6'-Heptachlorobiphenyl (PCB 183)
2,2',3,4',4',5,5'-Heptachlorobiphenyl (PCB 187)
2,2',3,3',4,4',5,5'-Octachlorobiphenyl (PCB 194)
2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 195)
2,2',3,3',4,4',5,5',6'-Octachlorobiphenyl (PCB 196 & 203)
2,2',3,3',4,5,5',6'-Octachlorobiphenyl (PCB 199)
2,2',3,3',4,4',5,5',6'-Nonachlorobiphenyl (PCB 206)
2,2',3,3',4,4',5,5',6,6'-Decachlorobiphenyl (PCB 209) *
Dioxin-Like Chemicals
Polychlorinated Dibenzo-p-dioxins
1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin (HpCDD)
1,2,3,7,8-Hexachlorodibenzo-p-dioxin (HxCDD)
1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin (HxCDD)
1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (HxCDD)
1,2,3,4,6,7,8,9-Octachlorodibenzo-p-dioxin (OCDD)
1,2,3,7,8-Pentachlorodibenzo-p-dioxin (PeCDD)
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)
Polychlorinated Dibenzofurans
1,2,3,4,6,7,8-Heptachlorodibenzofuran (HpCDF)
1,2,3,4,7,8,9-Heptachlorodibenzofuran (HpCDF)
1,2,3,4,7,8-Hexachlorodibenzofuran (HxCDF)
1,2,3,6,7,8-Hexachlorodibenzofuran (HxCDF)
1,2,3,7,8,9-Hexachlorodibenzofuran (HxCDF)
2,3,4,6,7,8-Hexachlorodibenzofuran (HxCDF)
1,2,3,4,6,7,8,9-Octachlorodibenzofuran (OCDF)
1,2,3,7,8-Pentachlorodibenzofuran (PeCDF)
2,3,4,7,8-Pentachlorodibenzofuran (PeCDF)
2,3,7,8-Tetrachlorodibenzofuran (TCDF)
Coplanar Polychlorinated Biphenyls
3,4,4',5-Tetrachlorobiphenyl (PCB 81)
3,3',4,4',5-Pentachlorobiphenyl (PCB 126)
3,3',4,4',5,5'-Hexachlorobiphenyl (PCB 169)
Mono-ortho-substituted Polychlorinated Biphenyls
2,3,3',4,4'-Pentachlorobiphenyl (PCB 105)
2,3',4,4',5-Pentachlorobiphenyl (PCB 118)
2,3,3',4,4',5-Hexachlorobiphenyl (PCB 156)
2,3,3',4,4',5,5'-Hexachlorobiphenyl (PCB 157)
2,3',4,4',5,5'-Hexachlorobiphenyl (PCB 167)
2,3,3',4,4',5,5'-Heptachlorobiphenyl (PCB 189)

Polycyclic Aromatic Hydrocarbons (PAHs)
2-Hydroxyfluorene
3-Hydroxyfluorene
9-Hydroxyfluorene
1-Hydroxynaphthalene (1-Naphthol)
2-Hydroxynaphthalene (2-Naphthol)
1-Hydroxyphenanthrene
2-Hydroxyphenanthrene
3-Hydroxyphenanthrene
4-Hydroxyphenanthrene
1-Hydroxypyrene
Disinfection By-Products (Trihalomethanes)
Bromodichloromethane *
Dibromochloromethane (Chlorodibromomethane) *
Tribromomethane (Bromoform) *
Trichloromethane (Chloroform) *
Volatile Organic Compounds (VOCs)
Benzene
Chlorobenzene (Monochlorobenzene) *
1,2-Dibromo-3-chloropropane (DBCP) *
Dibromomethane *
1,2-Dichlorobenzene (ortho-Dichlorobenzene) *
1,3-Dichlorobenzene (meta-Dichlorobenzene) *
1,4-Dichlorobenzene (para-Dichlorobenzene) *
1,1-Dichloroethane *
1,2-Dichloroethane (Ethylene dichloride) *
1,1-Dichloroethene (Vinylidene chloride) *
cis-1,2-Dichloroethane *
trans-1,2-Dichloroethane *
Dichloromethane (Methylene chloride) *
1,2-Dichloropropane *
2,5-Dimethylfuran (DMF) *
Ethylbenzene *
Hexachloroethane *
Methyl tert-butyl ether (MTBE) *
Nitrobenzene *
Styrene *
1,1,2,2-Tetrachloroethane *
Tetrachloroethene (Perchloroethylene) *
Tetrachloromethane (Carbon tetrachloride) *
Toluene *
1,1,1-Trichloroethane (Methyl chloroform) *
1,1,2-Trichloroethane *
Trichloroethene (Trichloroethylene, TCE) *
meta- and para-Xylene *
ortho-Xylene *

Biomonitoring of Chemicals & Pollutants: Umbilical Cord Blood and Breast Milk

BodyBurden
The Pollution in Newborns

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

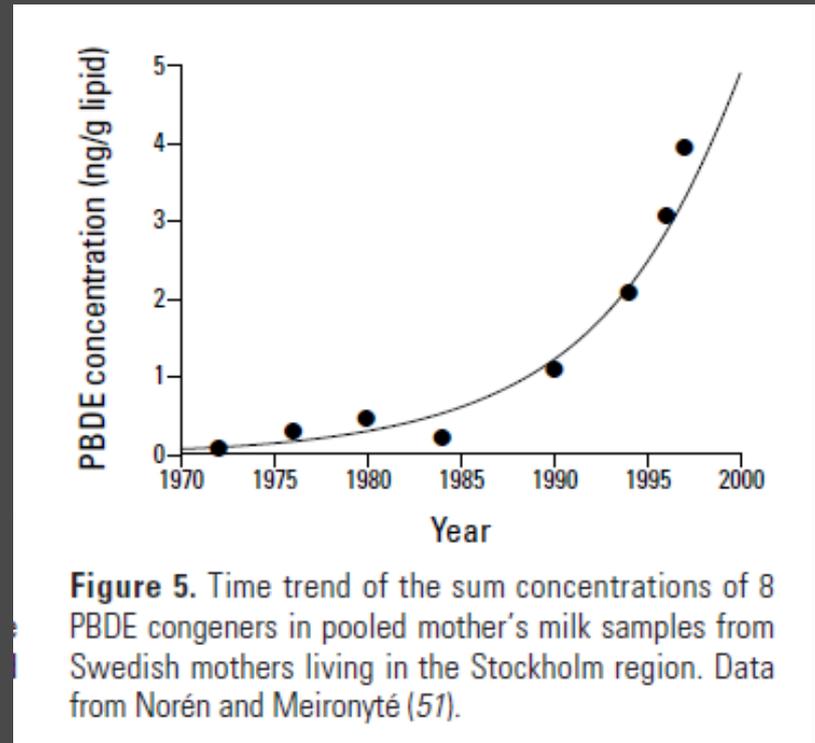
- Mercury
- PCBs
- Flame retardants
- Solvents
- Stain repellants
- Dioxins and furans
- Organochlorine pesticides...

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ENVIRONMENTAL WORKING GROUP

JULY 14, 2005

PBDE Levels in Breast Milk, Sweden



What Does it Mean to Protect Children's Health?

Vulnerability of Infants and Children

Hazard

- Rapidly developing organ systems *in utero* through puberty¹
- Altering gene expression produces later disease¹
- Developmental effects can span generations¹

Exposure

- Lower metabolic enzyme function²
- Immature brain, blood/brain barrier³
- Children eat, drink and breathe more per pound than adults^{4,5}
- Increased absorption (skin, GI) decreased elimination (liver, kidney)⁵
- Increased exposure through hand-to-mouth behavior and breast milk

1. Grandjean, et al. 2007. *Basic & Clinical Pharmacology & Toxicology*, 102, 73-75

2. Spyker JM, Avery DL. *J Toxicol and Environ Health* 1977:989-1002.

3. Rodier PM. *Environmental Health Perspectives* 1995; **103 Suppl 6**:73-6.

4. Plunkett L. in Guzelian PS, Henry CJ, Olin SS, eds. *Similarities and Differences between Children and Adults*. Washington, DC: ILSI Press, 1992:79-94.

5. National Research Council. *Pesticides in the Diets of Infants and Children*. Washington, DC: National Academy Press, 1993.





Editorial

Role of exposure to environmental chemicals in the developmental basis of disease and dysfunction

Jerrold J. Heindel*

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There is a major paradigm shift taking place in science that while simple is profound. It states that the root of many diseases, including reproductive diseases and dysfunctions, will not be found by examination of disease onset or etiology hours, days, weeks, or even years prior to disease onset. The new paradigm suggests that susceptibility to disease is set *in utero* or neonatally as a result of the influences of nutrition and exposures to environmental stressors/toxicants. *In utero* nutrition and/or *in utero* or neonatal exposures to environmental toxicants alters susceptibility to disease later in life as a result of their ability to affect the programming of tissue function that occurs during development. This concept, that is still a hypothesis undergo-

Review

The Developmental Origins of Adult Disease

Journal of the American College of Nutrition, Vol. 23, No. 6, 588S–595S (2004)

Published by the American College of Nutrition

Developmental Origins

The recent discovery that people who develop coronary heart disease grew differently to other people during fetal life and childhood has led to a new ‘developmental’ model for the disease [1]. To explore the developmental origins of chronic

MiniReview

Late Insights into Early Origins of Disease

Philippe Grandjean

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Journal compilation © 2008 Nordic Pharmacological Society. *Basic & Clinical Pharmacology & Toxicology*, 102, 94–99

The recognition of developmental origins of diseases and functional deficits constitutes a paradigm shift in toxicology and public health [1]. This new insight supersedes the past belief that development was generally a homogeneous and invariant sequence of developmental stages and instead stresses plasticity, continuity and multicausality [2]. It will likely have tremendous impact on prevention and pollution abatement in the future, and this conference is testimony

Critical Windows of Development

Step 1. Click the black triangles to read about normal human prenatal development.

Step 2. Choose a chemical to see where and when exposure to low doses affects lab animals.

Then click the colored triangles for study details.

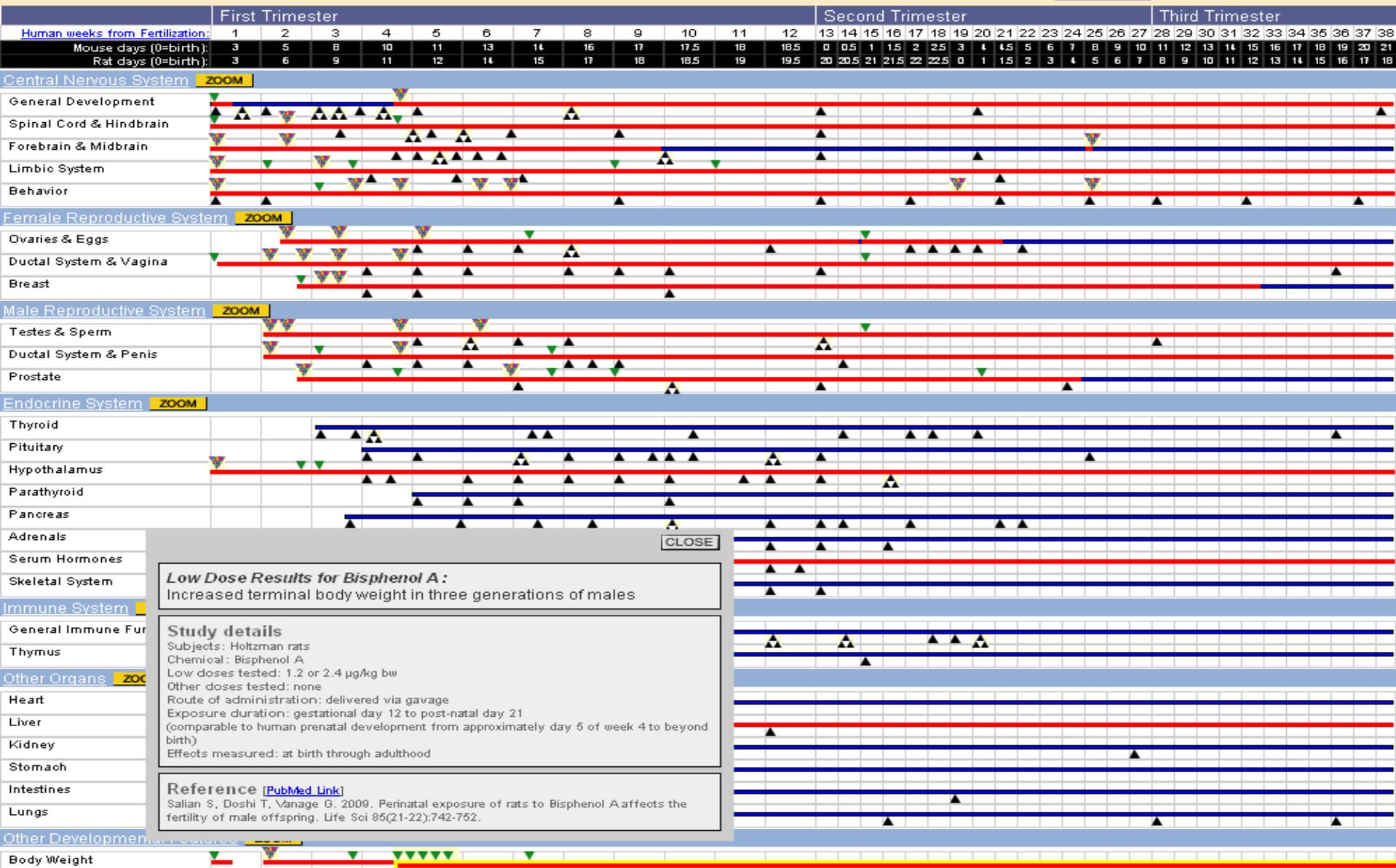
[Back to TEDX Website](#)
[Link to Medical Dictionary](#)

KEY (What the Bars & Triangles Mean)

Low-Dose Chemical Research ([Dose Information](#))

- On/Off All Chemicals
- On/Off **Bisphenol A**
- On/Off **Dioxin**
- On/Off **Phthalates**
- On/Off **Chlorpyrifos**
- On/Off Human Development

[More chemicals...](#)



Low Dose Results for Bisphenol A:
Increased terminal body weight in three generations of males

Study details
Subjects: Holtzman rats
Chemical: Bisphenol A
Low doses tested: 1.2 or 2.4 µg/kg bw
Other doses tested: none
Route of administration: delivered via gavage
Exposure duration: gestational day 12 to post-natal day 21
(comparable to human prenatal development from approximately day 5 of week 4 to beyond birth)
Effects measured: at birth through adulthood

Reference [\[PubMed Link\]](#)
Salian S, Doshi T, Vanage G. 2009. Perinatal exposure of rats to Bisphenol A affects the fertility of male offspring. Life Sci 85(21-22):742-752.

Low Dose BPA and Obesity?

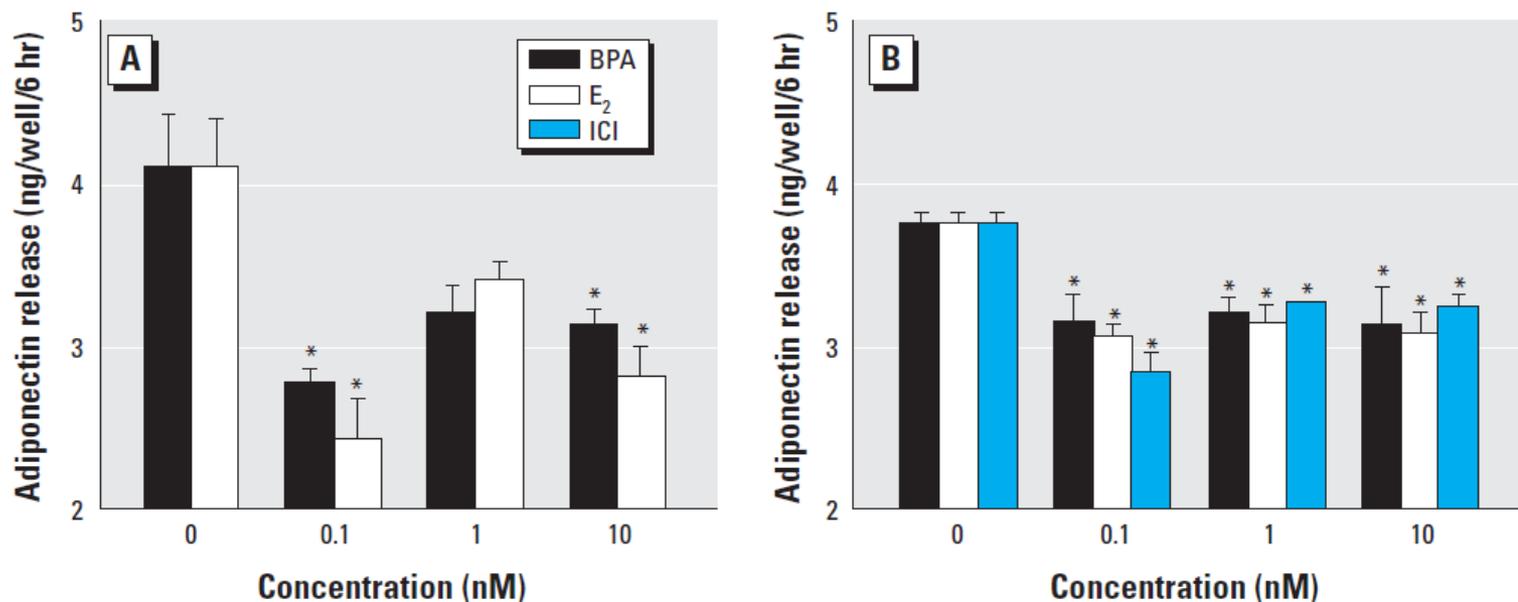


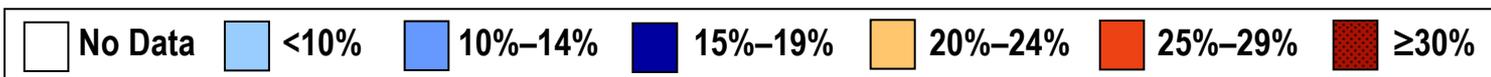
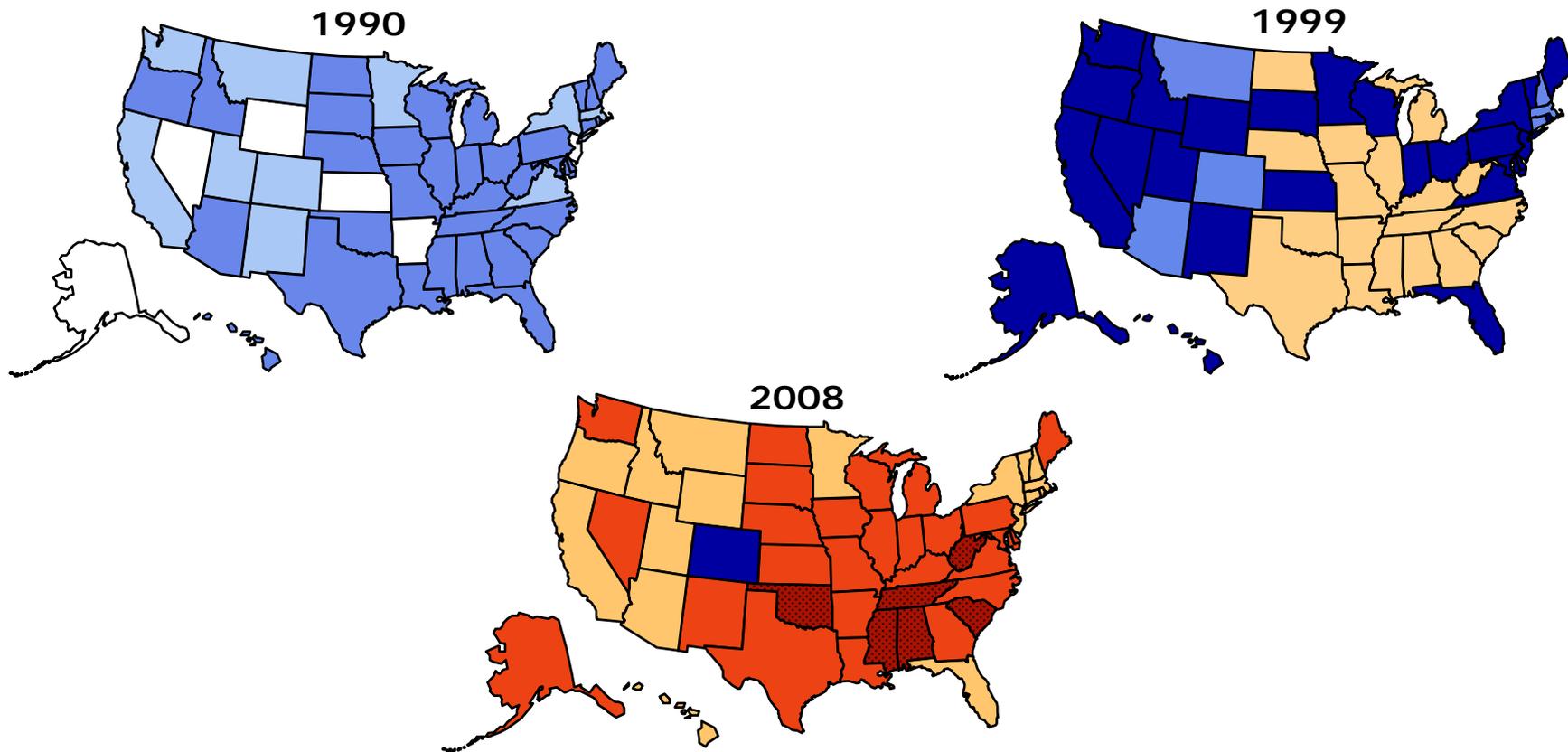
Figure 3. BPA and E₂ suppress adiponectin release from mature abdominal SC adipocytes from a non-obese woman (A) and an obese woman (B). (A) Effect of treatment with increasing doses of BPA or E₂. (B) Effect of treatment with increasing doses of BPA, E₂, and ICI. Each value is the mean \pm SE of four determinations.

* $p < 0.05$ compared with control.

Obesity Trends* Among U.S. Adults

BRFSS, 1990, 1999, 2008

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



The Obesity Epidemic – a Public Health Priority

34% of the US population is clinically obese (BMI > 30)

- Double worldwide average (Flegal et al. *JAMA* 2010;303:235-241)

Obesity accounts for 8% of healthcare costs in Western Countries

- \$147 billion annually in US (2009) Finkelstein, et al. *Health Affairs* 2009, no. 5: w822–w831
- \$7.7 billion/year in CA (2004) Finkelstein, et al. *Obesity Research* 2004;12(1):18–24

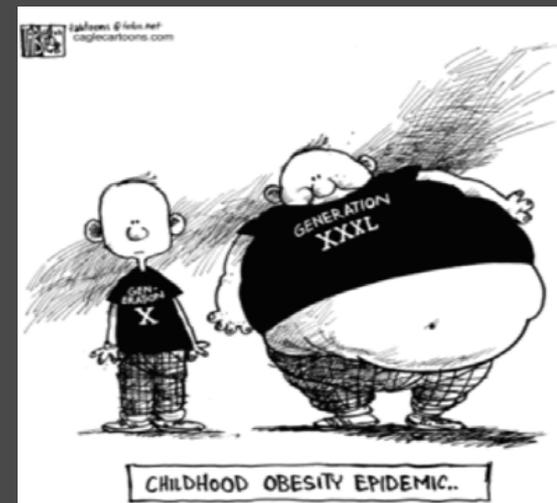
Obesity is associated with “metabolic syndrome” (includes type 2 diabetes and cardiovascular disease)

- Central (abdominal) obesity
- High cholesterol
- Hypertension
- Insulin resistance
- Prothrombotic and pro-inflammatory states

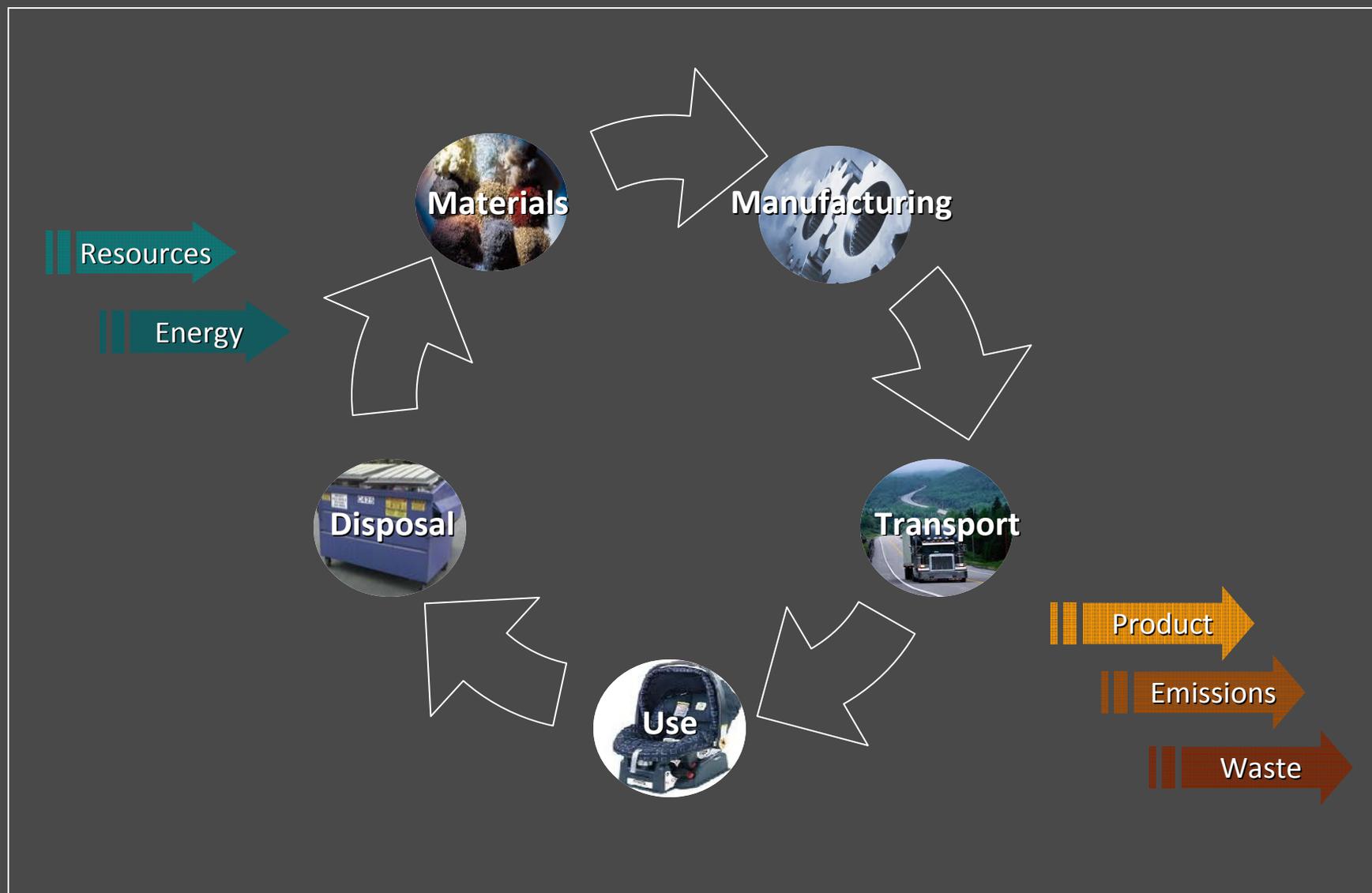
Some endocrine disrupting compounds may act as *obesogens*

- Stimulate adipogenesis and fat storage
- Disturb adipose tissue promoting increased fat
- Alter appetite control
- Disrupt energy balance and metabolism

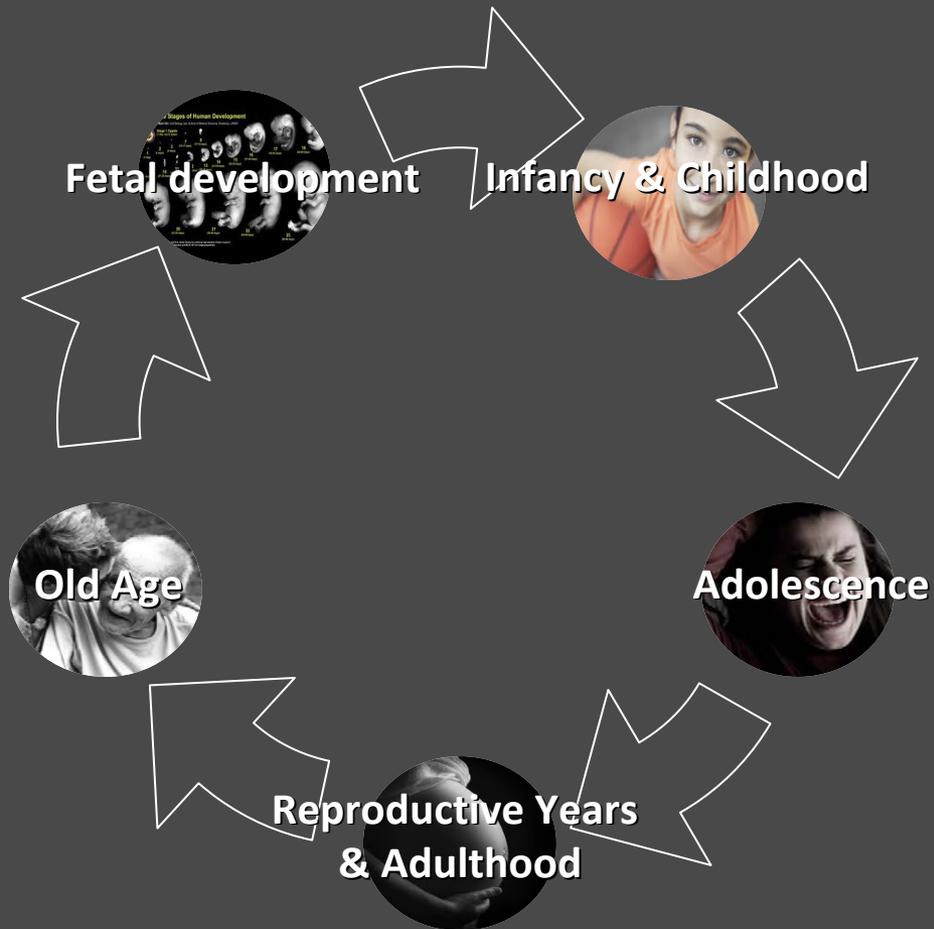
(Grun *Molecular Endocrinology* 23: 1127–1134, 2009)



Green Chemistry Addresses Hazard Across the Product Lifecycle



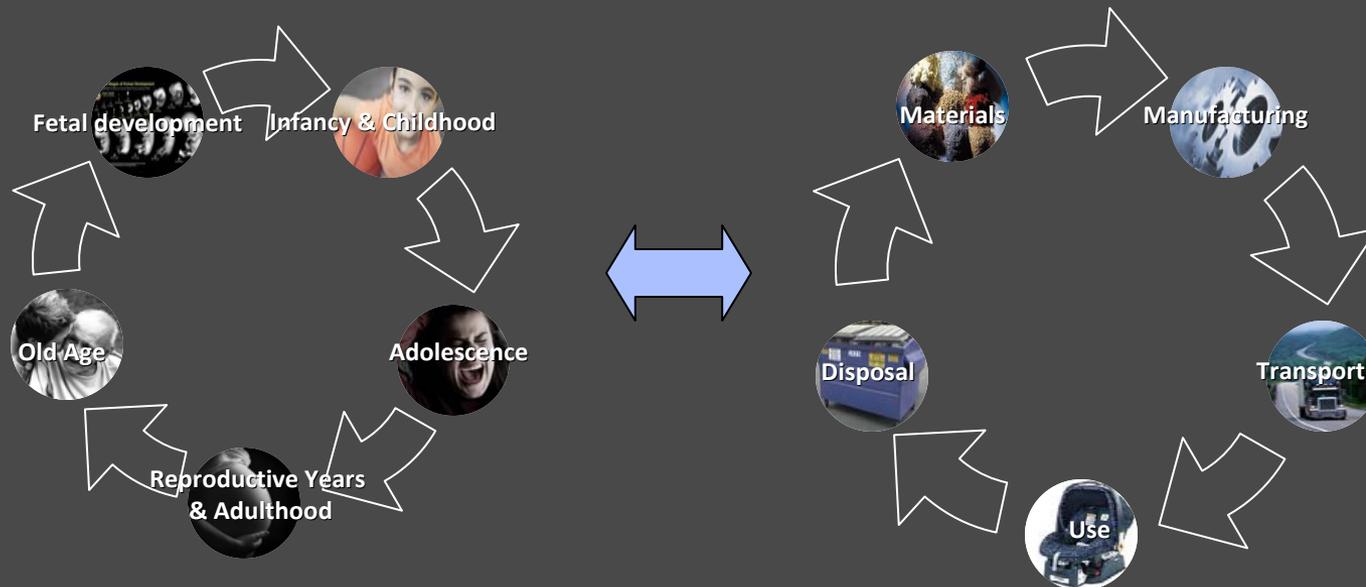
Public Health Addresses Hazard Across the Human Lifecycle



How Can We Reduce Hazards Associated with All Aspects of the Product Lifecycle across All stages of the Human Life Span?

Design inherently safer substances:

- Connect the dots between molecular mechanisms of disease and chemical design
- Identify substances with potential for trans-generational effects (e.g., epigenetic effects, environmental persistence, bioaccumulation)
- Use children's health outcomes to prioritize substances for substitution





The Presidential Green Chemistry Challenge Awards Program: Summary of 2010 Award Entries and Recipients

FRX Polymers Inc.

Green Chemistry to Replace Bromine-Based Flame Retardants

Flame-retardant materials are a legal requirement globally for many plastics in electrical, building, construction, fiber, and textile applications. Flame-retardant plastics and additives comprise a worldwide materials market of over \$15 billion with annual growth rates of 5–6 percent. Over 60 percent of all current plastic formulations include a class of flame-retardant additives known as brominated hydrocarbons. This popular class of flame retardants is, however, being shown to have severe, undesirable effects including persistence in the environment, bioaccumulation, and toxicity in rodent studies. In addition, the burning or thermal disposal of these additives can result in highly toxic dioxins and furans. These problems combine to place great pressure on companies to eliminate brominated agents as flame retardants.

FRX Polymers has developed green chemistry that allows diphenyl methyl phosphonate to polymerize effectively with an aromatic diol into either an oligomer or polymer with a phosphorus content of greater than 10 percent. This unique polymer has the highest limiting oxygen index measured for a thermoplastic material. FRX Polymers has also developed a low-cost, green synthesis for the diphenyl methyl phosphonate monomer. Yields from both the monomer and polymer processes are essentially quantitative. The phenol coproduct of polymerization is reused, so that little or no waste (less than 5 percent) is generated from the production of FRX polymers and copolymers. Eliminating bromine in favor of phosphorus in flame-retardant additives is expected to allow greater recovery and recyclability of plastics after use.