



Exposure to Neurotoxic Chemicals & Neurodevelopmental Disease

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and the Environment

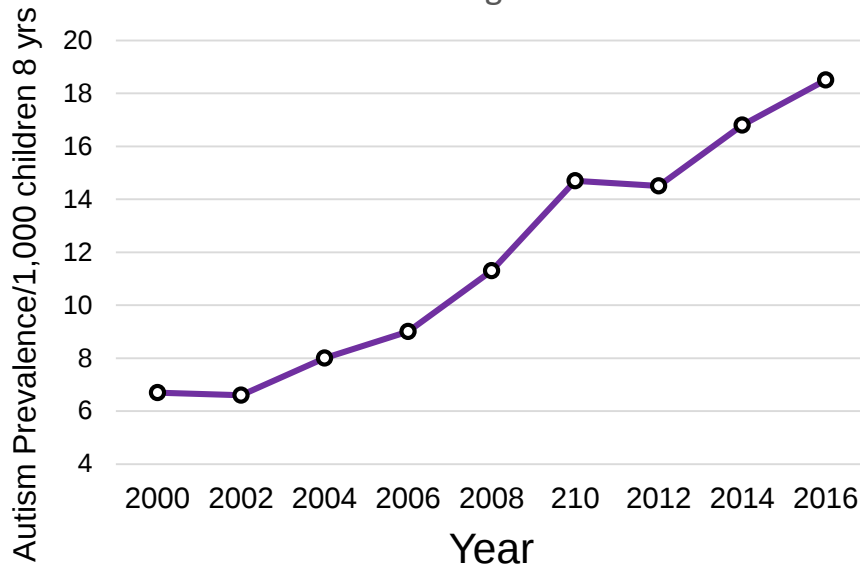


Outline

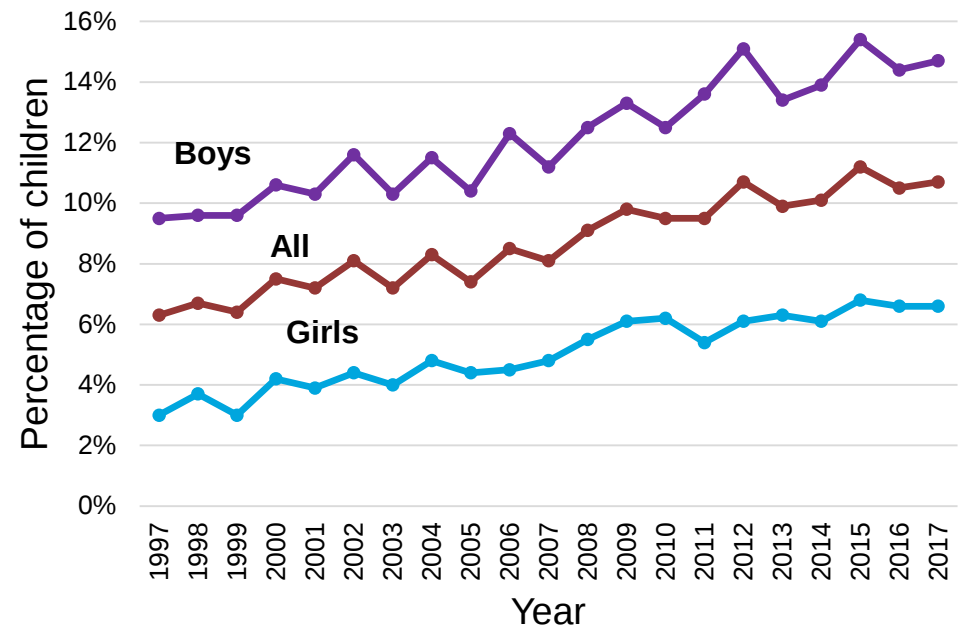
- Overview neurodevelopmental outcomes and chemical exposures
- Why chemical exposures matter for neurodevelopmental outcomes & opportunities for prevention
- Where are there other opportunities for new studies & prevention?

Increasing Prevalence of Neurodevelopmental Disorders

Childhood Autism Prevalence in the US
Autism and Developmental Disabilities
Monitoring Network

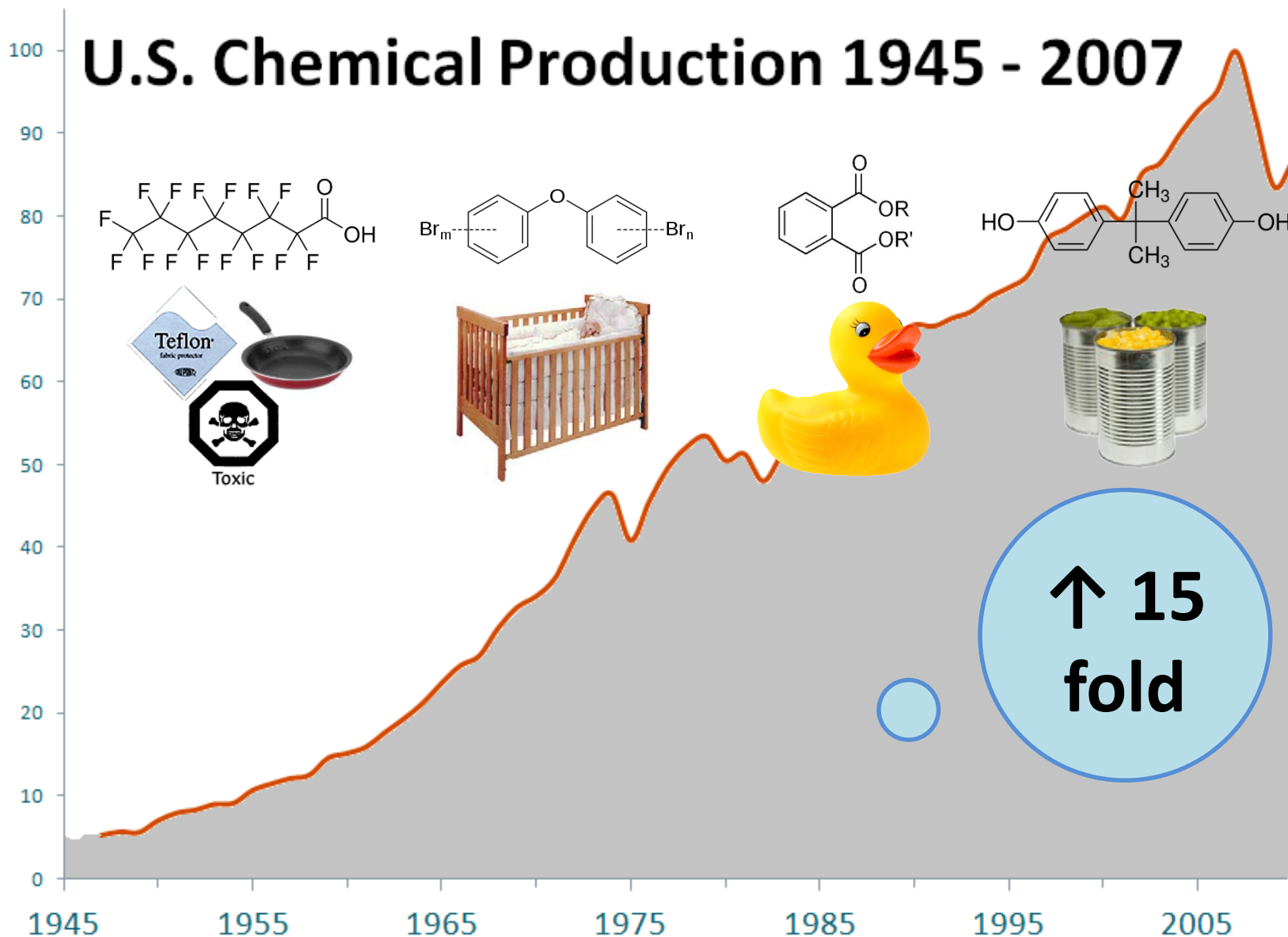


Percentage of Children 5-17 years
reported to have ADHD, 1997-2017



U.S. Chemical Production 1945 - 2007

Production compared to the year 2007



Exposures start in utero to Toxic Chemicals

Industrial Chemicals in Virtually Every U.S. Pregnant Woman

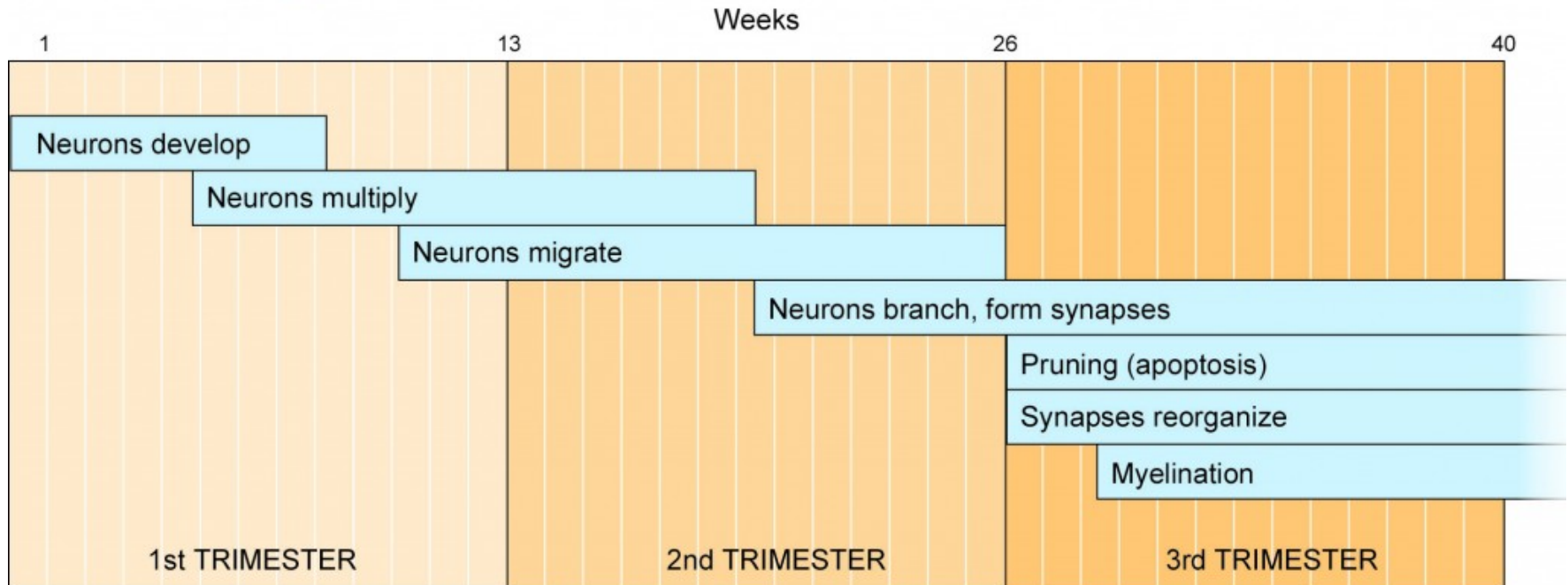
43

industrial chemicals found
in pregnant women

Perchlorate	PCB-170
1-Hydroxypyrene	PCB-153
3-Hydroxyphenanthrene	PCB-146
2-Hydroxyphenanthrene	PCB-118
1-Hydroxyphenanthrene	PCB-110
1-Naphthol	PCB-105
2-Naphthol	PCB-101
2-Hydroxyfluorene	PCB-99
3-Hydroxyfluorene	PCB-74
9-Hydroxyfluorene	PCB-66
Mono-(3-carboxypropyl) phthalate (MCP)	PCB-52
Mono-(2-ethyl-5-carboxypentyl) phthalate (MECP)	PCB-49
Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)	PCB-44
Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)	PCB-28
Mono-ethyl phthalate (MEP)	PBDE-153
Mono-n-butyl phthalate (MnBP)	PBDE-100
Mono-isobutyl phthalate (MiBP)	PBDE-47
Mono-benzyl phthalate (MBzP)	Perfluorononanoic acid (PFNA)
Benzophenone-3	Perfluorooctane sulfonic acid (PFOS)
Hexachlorobenzene	Perfluorooctanoic acid (PFOA)
p,p' - Dichlorodiphenyldichloroethene (DDE)	PCB-138 and -158
1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin (HpCDD)	



Critical periods of fetal brain development occur during in utero



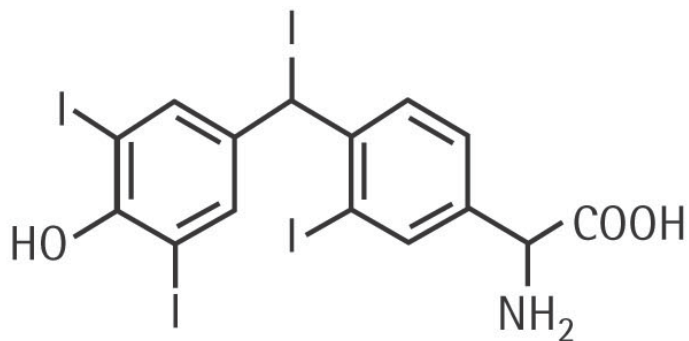
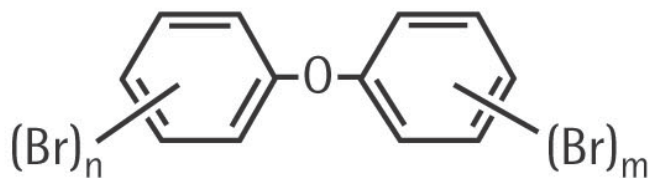
Comparing the Environment to Other Risk Factors - IQ

Table 2. Estimated FSIQ point losses associated with different risk factors in a population of 25.5 million children.

Risk factor	Total no. of FSIQ points lost	
Medical conditions		34 million
Congenital heart disease	104,805	
Preterm birth	34,031,025	
Type 1 diabetes	185,640	
Acute lymphocytic leukemia	135,788	
Brain tumors	37,288	
Duchenne muscular dystrophy	68,850	
Neurodevelopmental disorders		38 million
ASDs	7,109,899	
Pediatric bipolar disorder	8,164,080	
ADHD	16,799,400	
Postnatal traumatic brain injury	5,827,300	
Socioeconomic, nutritional, psychosocial factors		15 million
Nonorganic failure to thrive	5,355,000	
Iron deficiency	9,409,500	
Environmental chemical exposures		40 million
Methylmercury	284,580	
Organophosphate pesticides	16,899,488	
Lead	22,947,450	

Polybrominated Diphenyl Ethers (PBDEs)

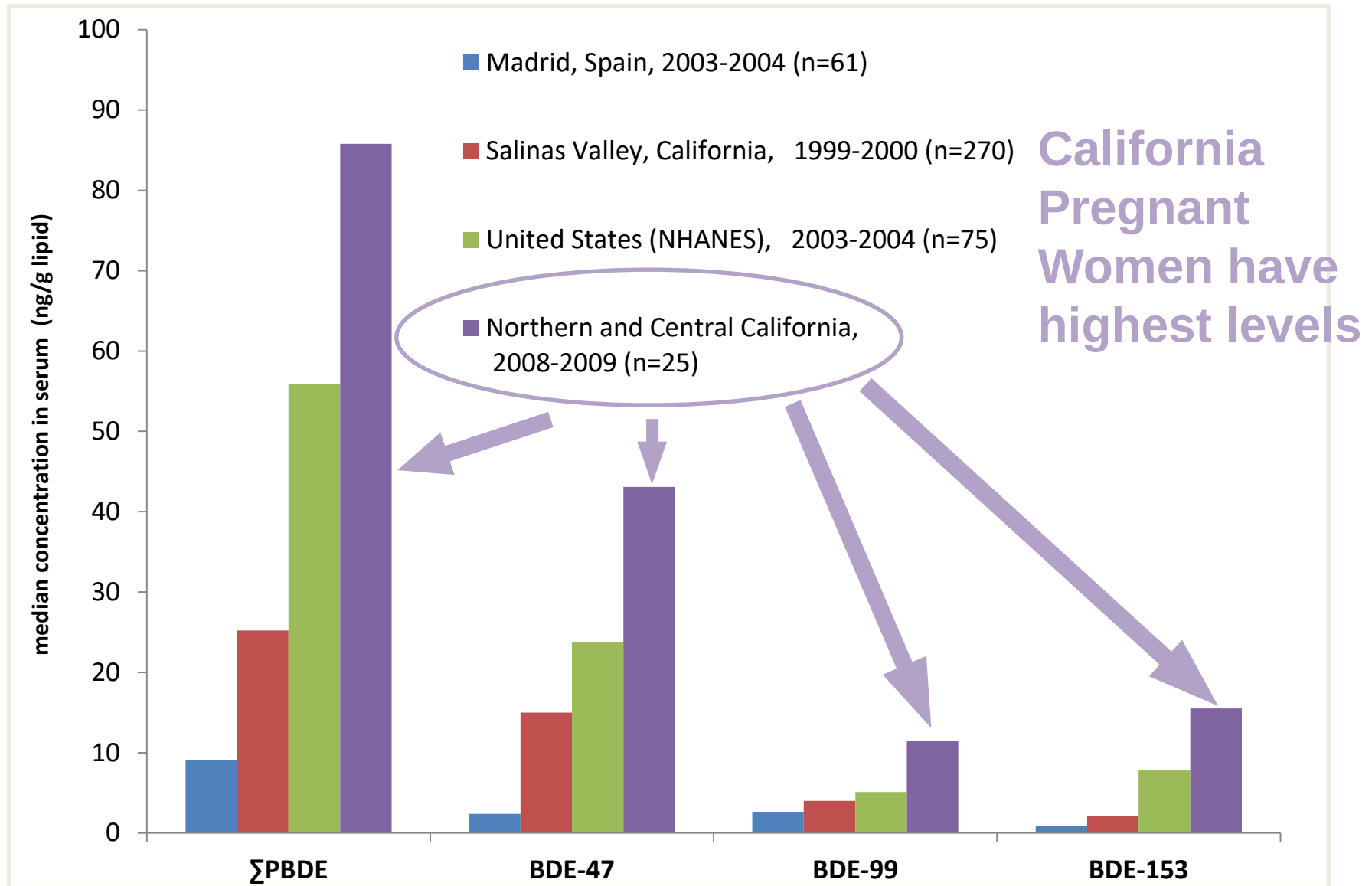
Flame chemicals

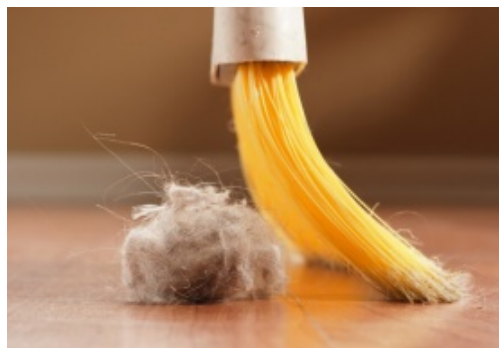


Thyroid hormone



Exposure shows - flame retardants in pregnant women worldwide – up to 100%

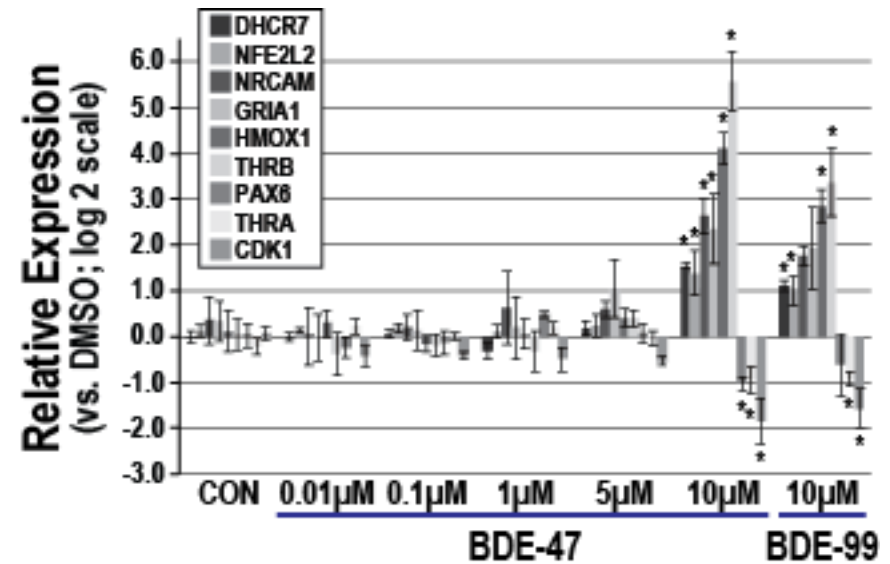
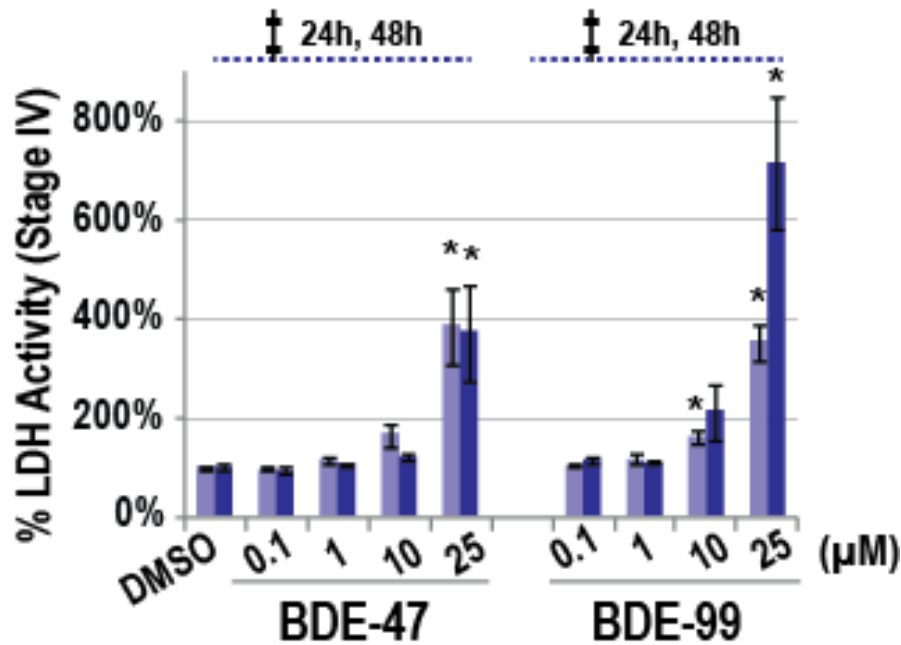




PBDEs

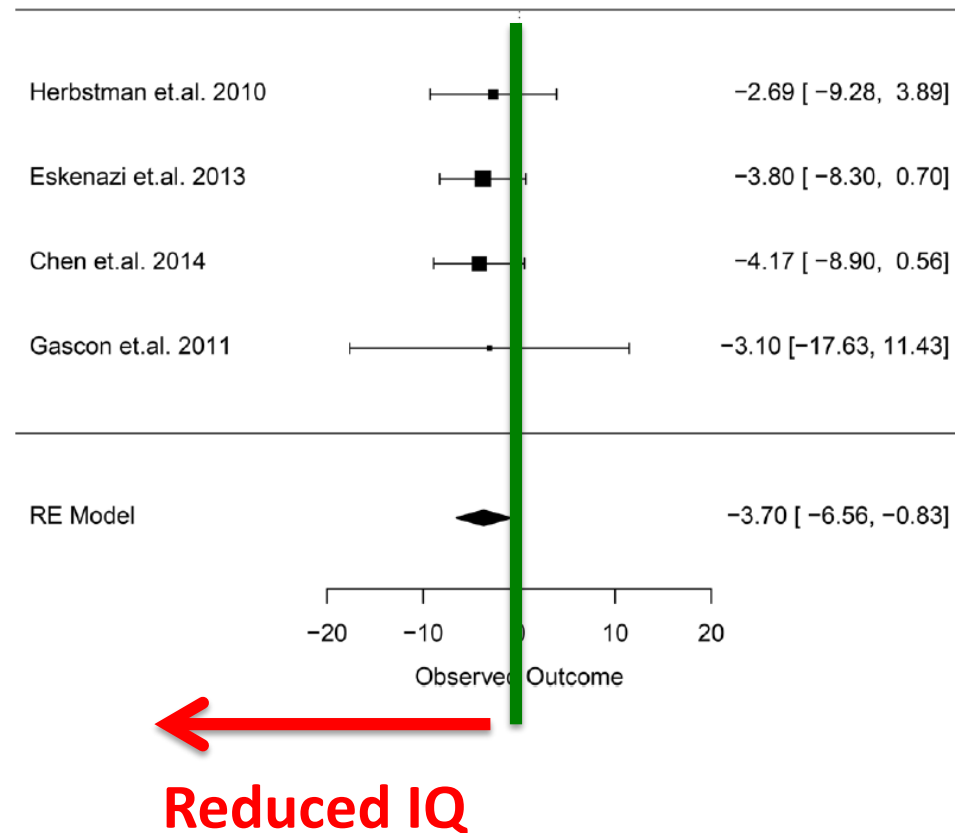
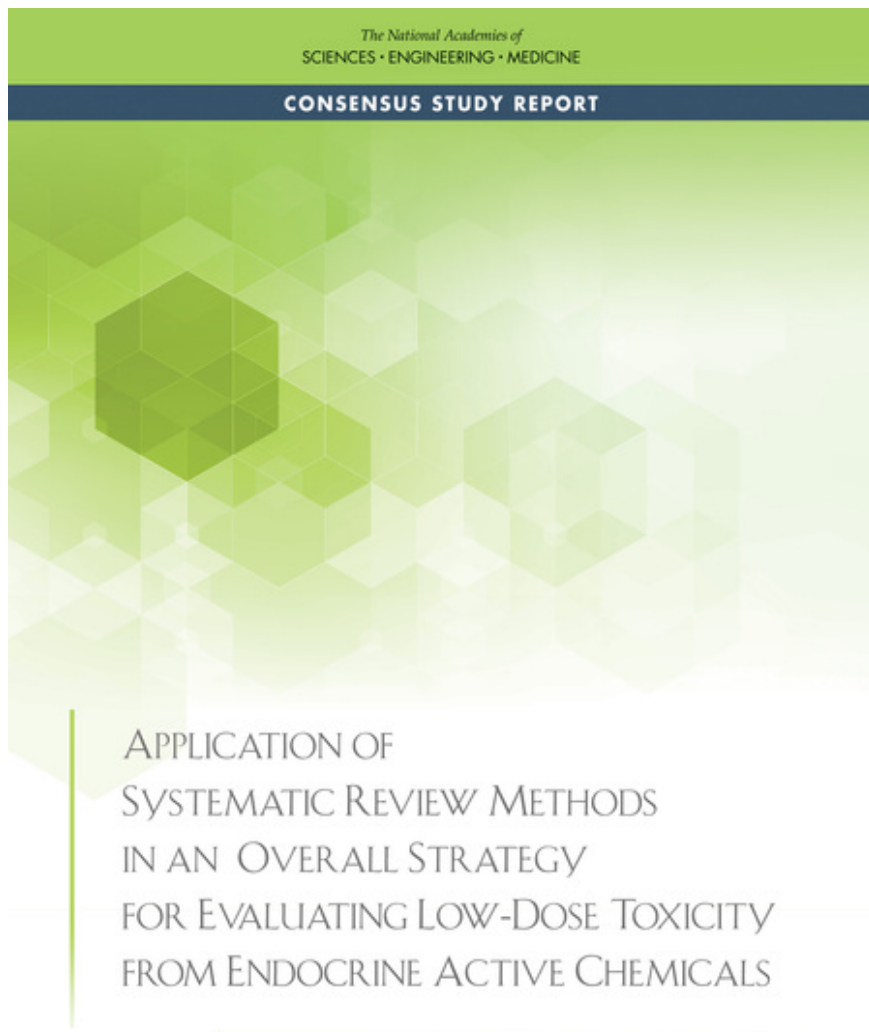
- **In humans**, thyroid hormone disruption identified as possible mechanistic link
- **In vitro**, disruption of developing fetal human brain cells
- **In animals**, affects learning, memory, and attention

PBDE's induce developmental toxicity in Human Embryonic Stem Cell Model of Neurogenesis



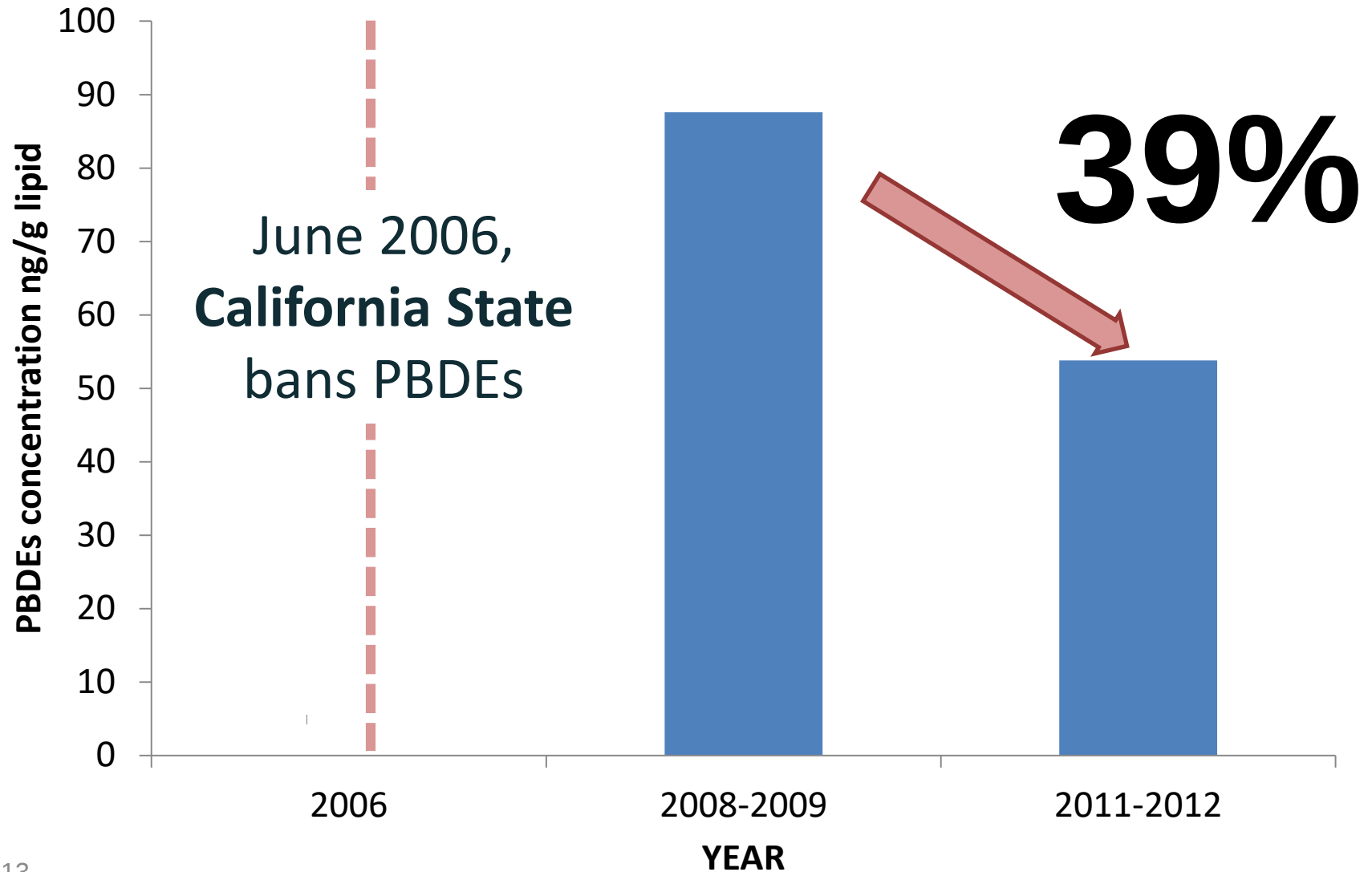
- PBDEs affect cytotoxicity and function of hESC-derived neural progenitor cells (NPCs)
- BDE-47 causes concentration-dependent global changes in gene expression in NPCs
- Genes/pathways altered included: thyroid hormone signaling, CNS development, oxidative stress, cell cycle targets at doses as low as 10 µM

PBDES 'presumed' hazard to human intelligence



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CA Ban on PBDEs Lowered Levels in Pregnant women

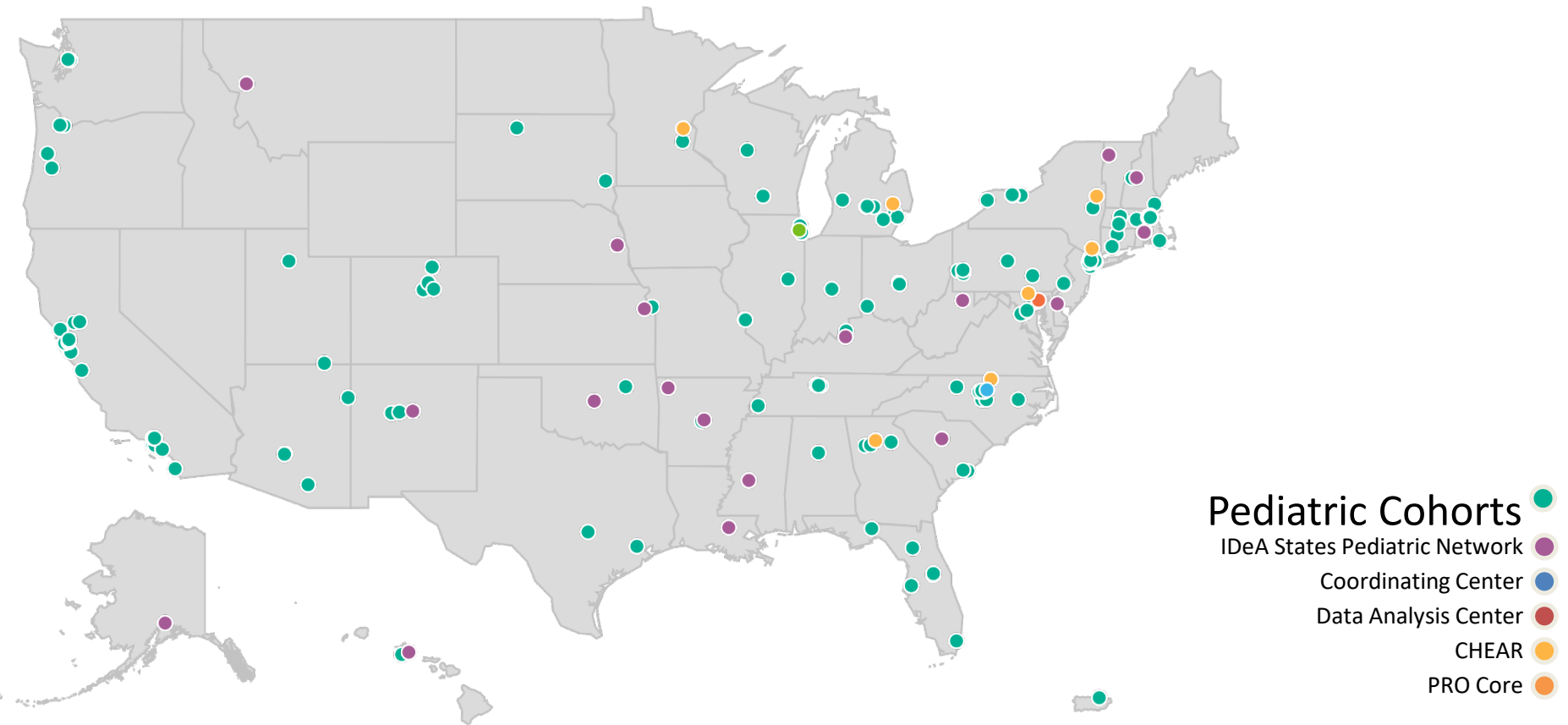


Out of the Frying Pan Into the Fire



NIH - Environmental influences on **C**hild **H**ealth **O**utcomes (ECHO) Program

Opportunity to understand and address Neurodevelopmental outcomes



Linked longitudinal child cohorts of ~ 50,000 children across the US

Improve child health by understanding risk factors and interventions

– Pregnancy outcomes, Obesity, **Neurodevelopment** and Respiratory

Prioritized candidate chemicals for biomonitoring in child health cohort based on:

Selected Chemical Panels

Alternate flame retardants & Organophosphorus flame retardants

flame retardants, and applied to consumer products as plasticizers, stabilizers, lubricants,

Alternative plasticizers

developed as substitutes for phthalates

Aromatic amines

used in dyes and pigments (e.g hair dyes, mascara, tattoo ink, toners, paints), polyurethane production, polymeric resins, corrosion inhibitors, rubber vulcanization accelerators, and pharmaceuticals

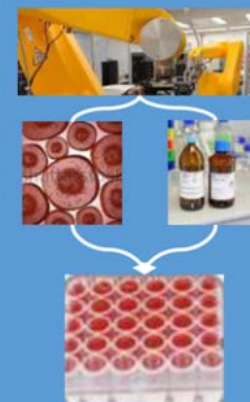
Environmental phenols

consumer and household products and serve as plasticizers, detergents, and preservatives

Pesticides

- Present in consumer products
- Biomonitoring ($\geq 10\%$ in biospecimen) or environmental media ($\geq 20\%$ detection frequency in air, house dust, food, drinking water)
- Potential toxicity includes Neurotoxicity
 - Use USEPA ToxCast assays
 - Opportunity to identify other potential neurotoxicants
 - 9,000 compounds;
 - ~1500 different endpoints

Step 1. Set up



Step 2. Data collection



Step 3. Data QC and analysis



Opportunity: ~100 Novel Chemicals to be measured in ECHO prenatally

Alternative Flame Retardants

Melamine MEL
Cyanuric Acid CYA
Ammelide AMD
Ammeline AMN

Pesticides

Azoxystrobin Azoxystrobin
Cyprodinil Cyprodinil
Metalaxyl Metalaxyl
Propiconazole Propiconazole
Pyrimethanil Pyrimethanil
Tebuconazole Tebuconazole
Nitenpyram NIT
Thiamethoxam THX
Imidacloprid IMI
Acetamiprid ACE
Thiacloprid THI
Clothianidin CLO
Dinotefuran DIN
Flonicamid FLO
Sulfoxalor SUL
Imidaclothiz IMZ
6-Chloronicotinic acid 6-CN
N-desmethyl thiamethoxam N-DMT
Thiacloprid-amide TA
N-desmethyl-acetamiprid N-DMA
Metribuzin Metribuzin
Tetraconazole Tetraconazole
Atrazine Atrazine
Aromatic amines
2-Methylaniline MTA

Alternative Plasticizers

mono-ethyl phthalate mEP
mono-butyl phthalate mBP
mono-benzyl phthalate mBzP
mono-(2-ethylhexyl) phthalate mEHP
mono-(2-ethyl-5-hydroxyhexyl) phthalate mEHHP
mono-(2-ethyl-5-oxohexyl) phthalate mEOHP
mono-carboxy-iso-octyl phthalate mCIOP
mono-carboxy-iso-nonyl phthalate mCINP
Mono-ethyl terephthalate (4-Ethoxycarbonyl) benzoic acid) mETP
mono-tert-butyl terephthalate mTBTP
Mono-benzyl- terephthalate mBzTP
Mono-2(ethylhexyl) terephthalate mEHTP

Organophosphorus-based flame retardants

2,2-Bis(chloromethyl) propane-1,3-diyltetrakis(2-chloroethyl) bisphosphate V6
2-Ethylhexyl diphenyl phosphate EHDPP
Bis(2-ethylhexyl) phosphate BEHP
Tris(2-butoxyethyl) phosphate TBOEP
Tris(2-ethylhexyl) phosphate TEHP
tri-n-butyl phosphate TNBP
Tri-iso-butyl phosphate TIBP
trimethylphenyl phosphate TMPP
Triethyl phosphate TEP
Triphenyl phosphate TPHP
tripropyl phosphate TPP
Tris(2-chloroethyl) phosphate TCEP

Organophosphorus-based flame retardants

cresyl diphenyl phosphate CDPP
Trimethyl phosphate TMP
Dibutyl phosphate DNBP
Diisobutyl phosphate DIBP
Bis(butoxyethyl) phosphate BBOEP
Diphenyl phosphate DPHP
Bis(2-methylphenyl) phosphate BMPP

Environmental phenols

Bisphenol A diglycidyl ether BADGE
Bisphenol AF BPAF
Bisphenol B BPP
3,3',5,5'-Tetrabromobisphenol A TBBP-A
2,2',6,6'-Tetrachlorobisphenol A TraTBA
4-n-Nonylphenol 4-NP
Bisphenol A (2,3-dihydroxypropyl) glycidyl ether BADGE-H2O
Bisphenol A bis(2,3-dihydroxypropyl) glycidyl ether BADGE-2H2O
Bisphenol A (3-chloro-2-hydroxypropyl) glycidyl ether BADGE-HCl
Bisphenol A bis(3-chloro-2-hydroxypropyl) glycidyl ether BADGE-2HCl
3,3',5-Trichlorobisphenol A TrCBA
4,4'-di-hydroxy diphenylmethane BPF
bis(4-hydroxyphenyl)propane BPA
4,4'-sulfonyldiphenol BPS
4,4'-cyclo-hexylidenebisphenol BPZ
4,4'-(1-phenylethylidene)bisphenol BPAP

Environmental phenols

4,4'-(1,4-phenylenediisopropylidene)bisphenol BPP
Benzophenone-1 BP-1
Benzophenone-2 BP-2
Benzophenone-3 BP-3
Benzophenone-6 BP-6
Benzophenone-8 BP-8
4-hydroxybenzophenone 4-OH-BP
methyl paraben MeP
ethyl paraben EtP
n-propyl paraben PrP
n-butyl paraben BuP
benzyl parabe BzP
heptaparaben HeP
hydroxy-methyl paraben OH-MeP
hydroxy-ethyl paraben OH-EtP
4-Hydroxybenzoate 4HB
Triclocarban TCC
Triclosan TCS
2,4,5-trichlorophenols 2,4,5-TCp
2,3,4,5-tetrachlorophenols 2,3,4,5-TeCPs
2,3,4,6-tetrachlorophenols 2,3,4,6-TeCPs
2,3,5,6-tetrachlorophenols 2,3,5,6-TeCPs
pentachlorophenol PCP
4-n-octylphenol 4-OP
Others
8-hydroxy-2'-deoxyguanosine 8-OHdG
Cotinine Cotinine

Example summary: organophosphorus-based flame retardants

Name	Exposure/Environmental Media				Health Effects/Toxicity										Biomarkers				
					In Vivo/In Vitro					HTP Assay		QSAR Model							
	Dermal Contact	Biofluids/hair/nails	Air, Indoor Dust	Food, Water	Endocrine	Developmental	Reproductive	Neurotoxicity	Carcinogenicity	Neurotoxicity	Endocrine	Obesity	Developmental	Carcinogenicity	Reproductive	Plasma / Serum	Hair/fingernails	Urine	Breast Milk
Organophosphorus-based Flame Retardants																			
2,2-Bis(chloromethyl) propane-1,3-Diyltetrakis(2-chloroethyl) bisphosphate (V6)		[142]	[29, 404, 405],			[415]		[416].									[142]	[142]	
2-Ethylhexyl diphenyl phosphate (EHDPP)		[407-409]	[408, 410-413]	[27, 414]													[409]	[407]	
Bis(2-ethylhexyl) phosphate (BEHP)		[417].	[140, 143]	[418]														[417].	
Di-quandine hydrogen phosphate																			
Triethyl phosphate (TEP)			[419-421]	[28]		[415, 422]	[423]												
Tris (2,3-dibromopropyl) phosphate (TBP)*		[424]	[413]				[424, 425]											[424]	
Tris(2,3-dichloropropyl) phosphate (TDCnPP)		[426]	[419, 427]	[428]	[429]	[430]		[431]									[426]		
Tris(2-butoxyethyl) phosphate (TBOEP)		[407, 432-434]	[24, 155, 315, 407, 411, 419, 435, 436]	[27, 28]	[437, 438]	[315, 439, 440]	[441]	[442-444]									[409]	[407, 432-434, 445]	[433, 445]
Tris(2-chloro-iso -propyl) phosphate (TCIPP)		[108, 445]	[88, 89, 155, 315, 404, 407, 410, 412]	[28]		[315, 406]	[406]											[108]	[445]
Tris(2-ethylhexyl) phosphate (TEHP)		[433]	[420, 425, 446]	[27]		[447, 448]	[449]										[409]	[433]	[433]
Tris(tribromoneopentyl)phosphate (TTBNPP)				[450, 451]															

Conclusions

- Environmental chemical exposures are ubiquitous
- Environmental chemicals can contribute to neurodevelopmental disorders
- New tools and cohorts provide opportunity to understand & prevent environmental contributors to neurodevelopmental disorders



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