Characterizing novel industrial chemical exposures during critical periods of development

Opportunities within the Environmental influences on Child Health Outcomes (ECHO) Program

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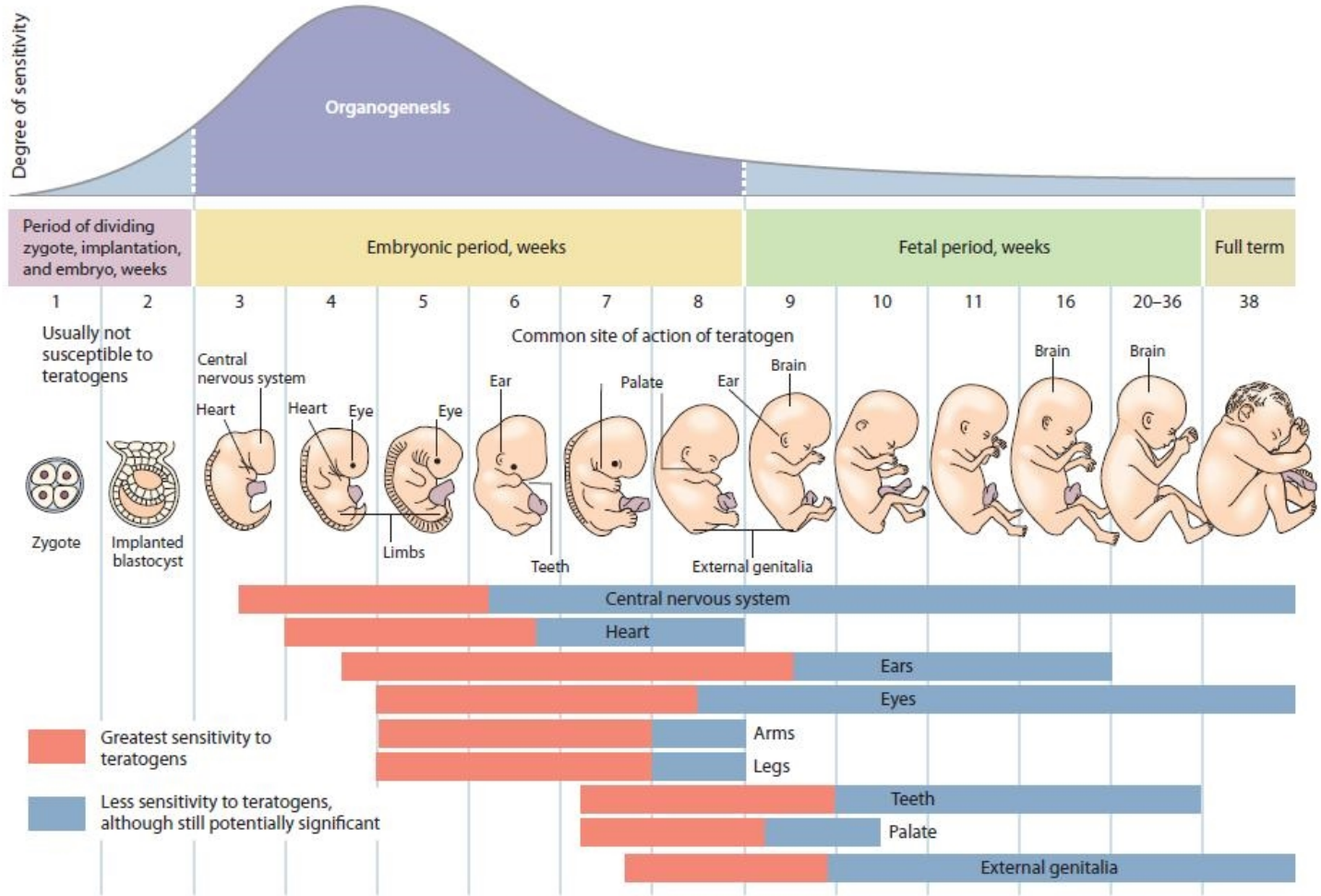
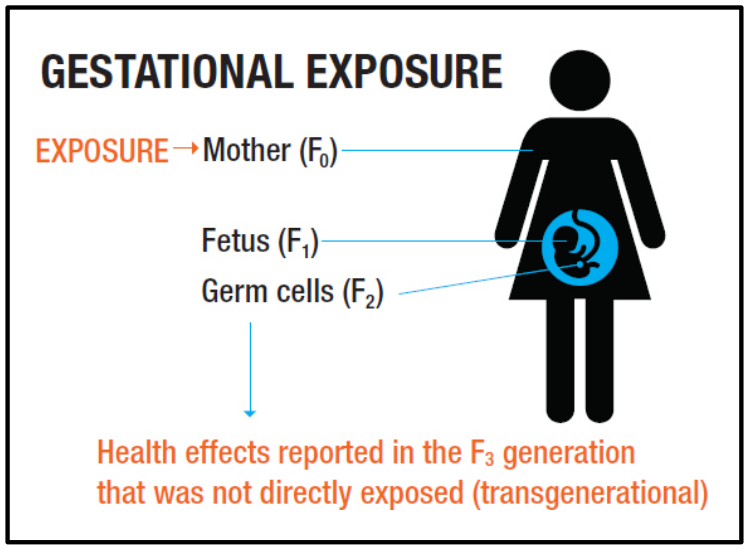
CHE Partnership Webinar

Critical periods of development

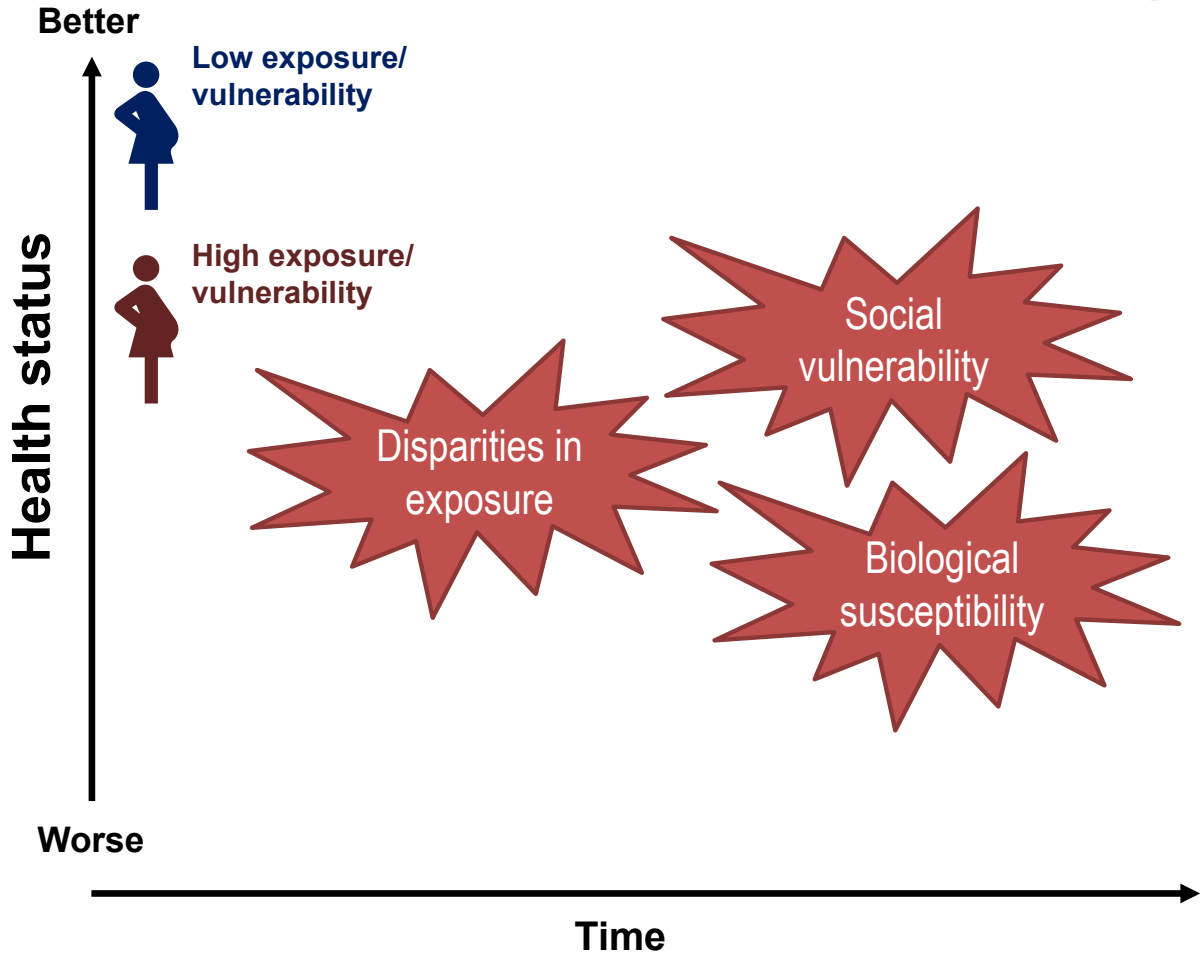


Santrock, 2009; pg. 74

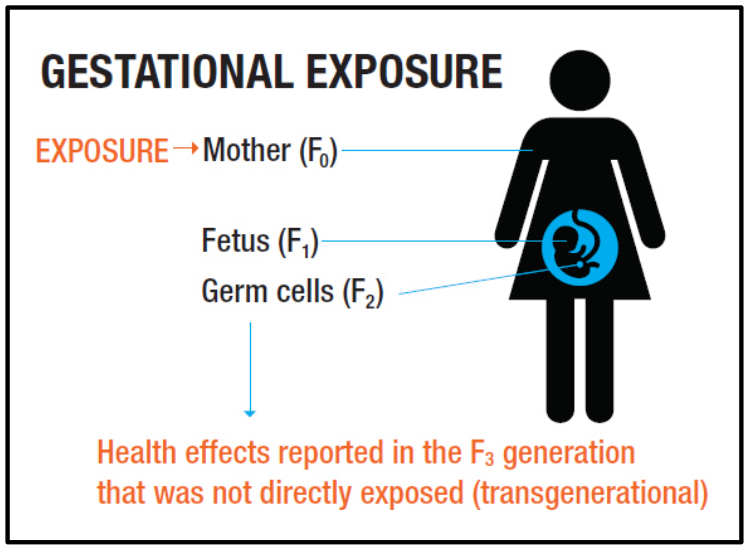
Transgenerational propagation of health disparities



Source: NAP 2018. Gulf War and Health: Volume 11, Figure 3-3



Transgenerational propagation of health disparities



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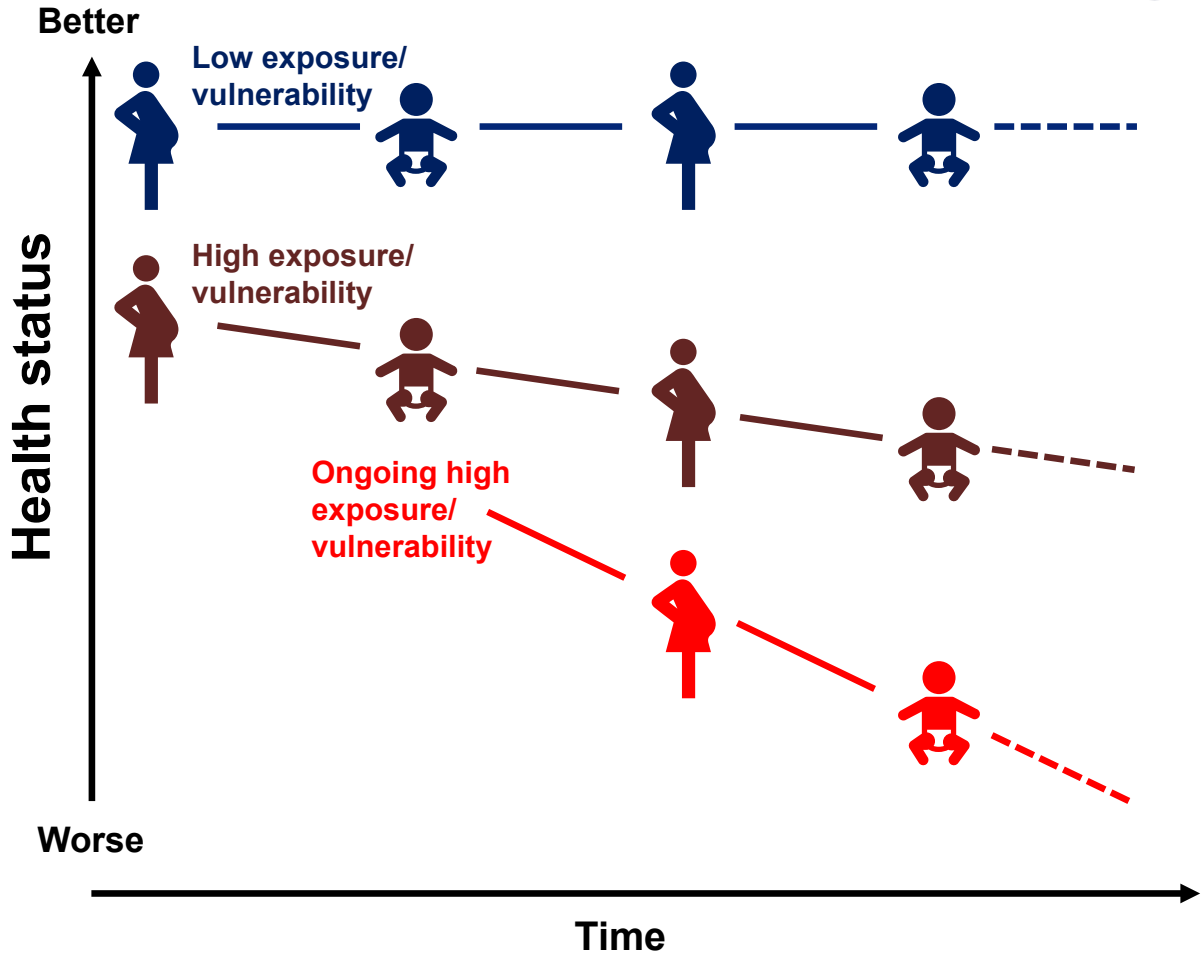
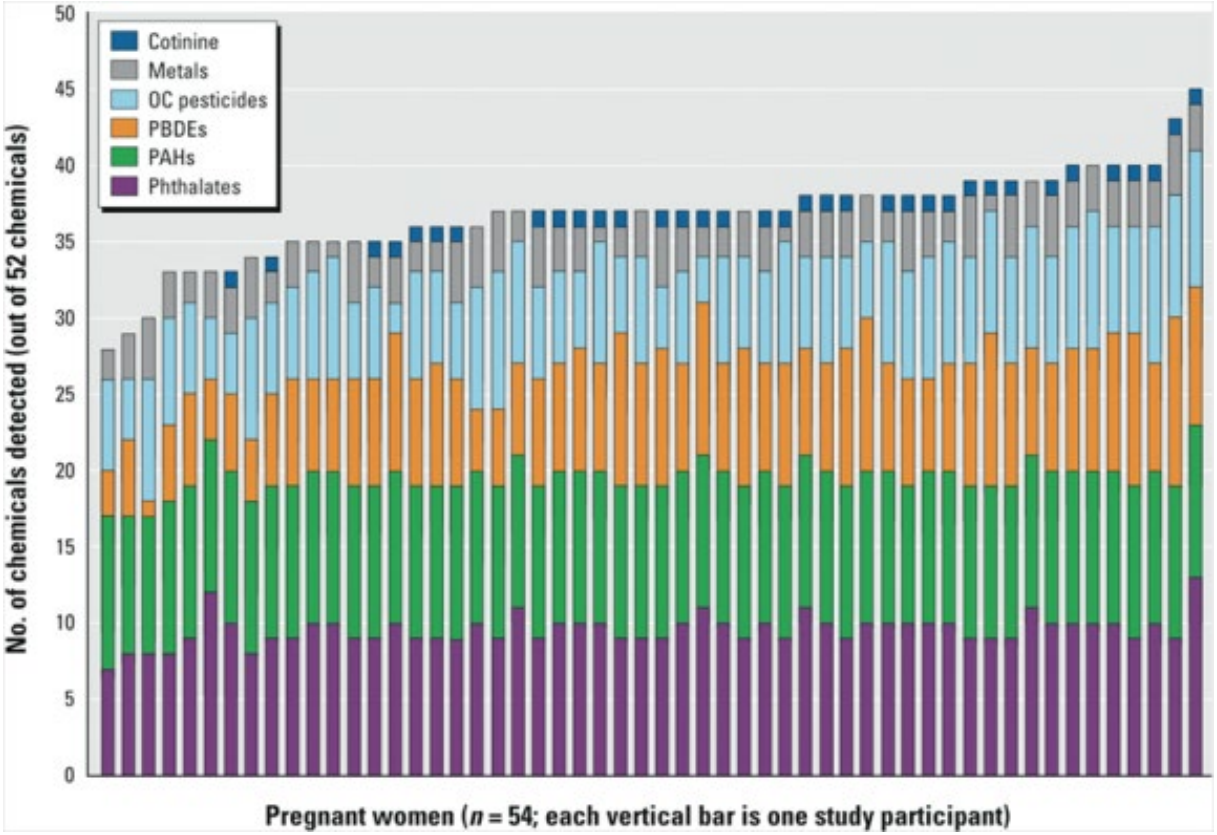
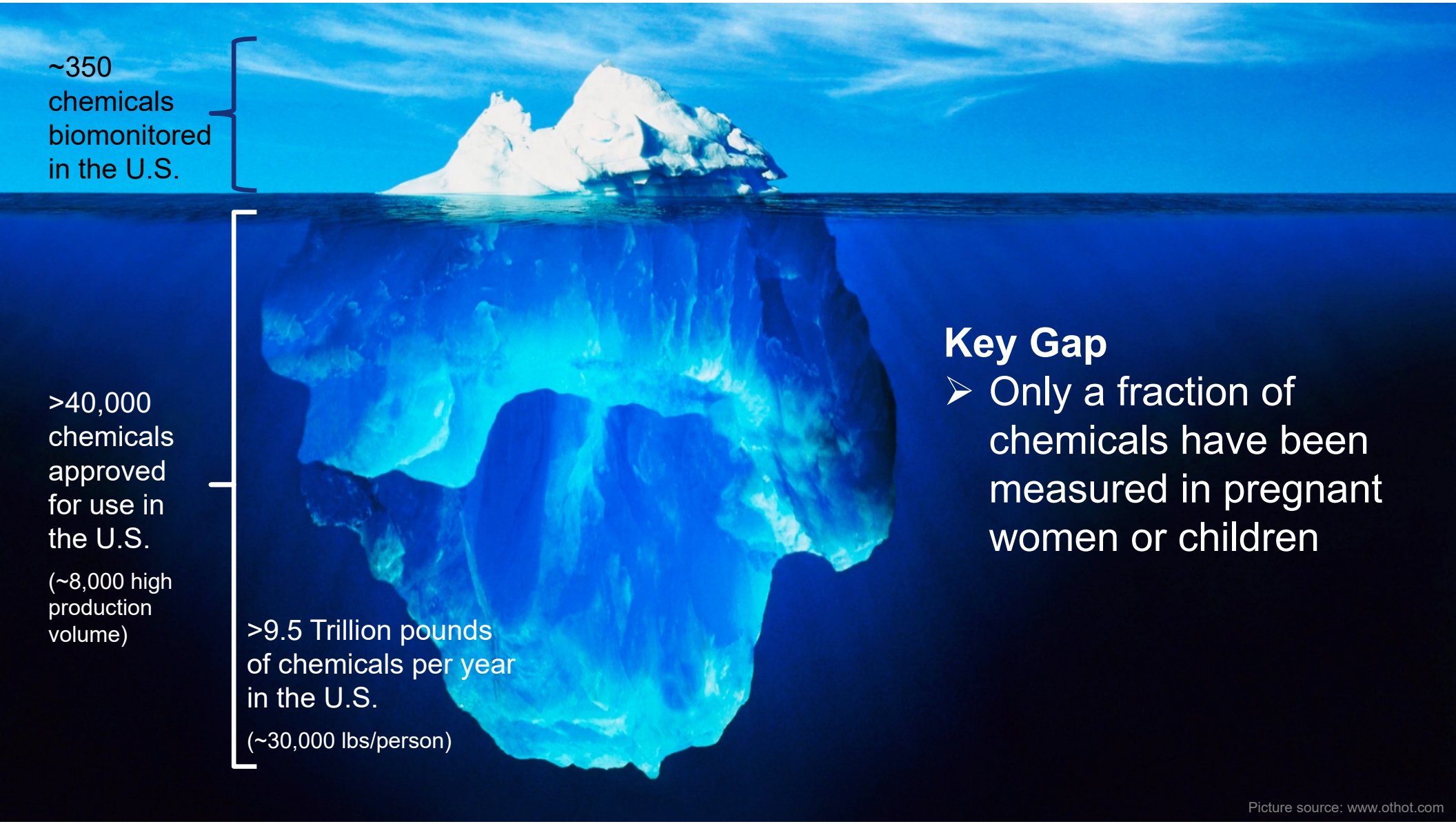


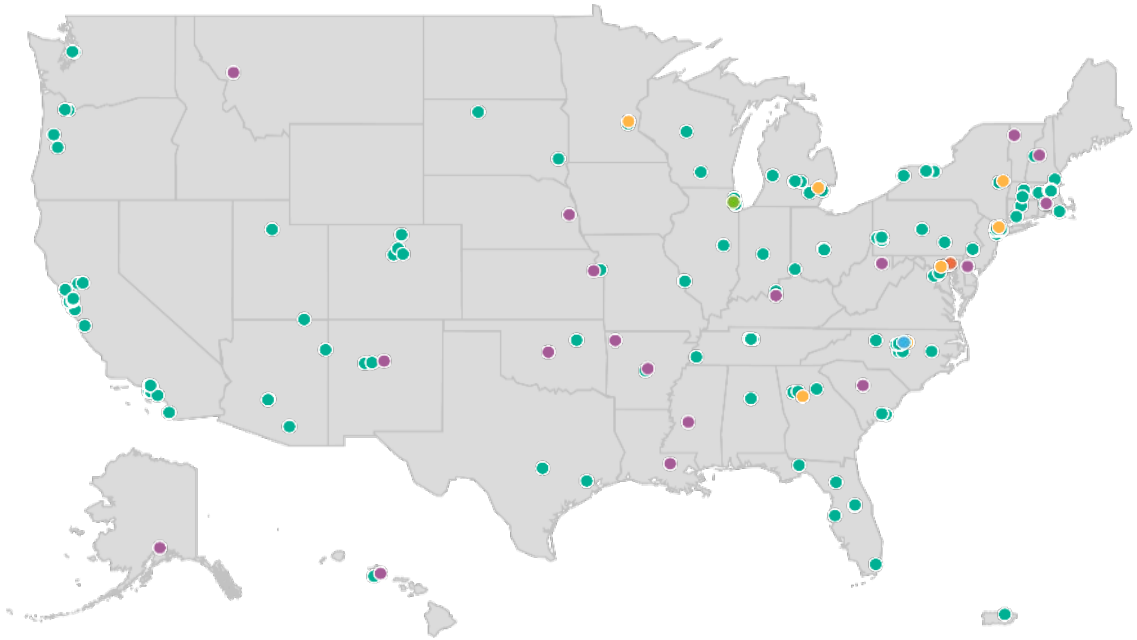
Chemicals are found in virtually all U.S. pregnant women



Woodruff et al. *EHP* 2011


~350 chemicals biomonitored in the U.S.
>40,000 chemicals approved for use in the U.S.
(~8,000 high production volume)
>9.5 Trillion pounds of chemicals per year in the U.S.
(~30,000 lbs/person)
Key Gap
➢ Only a fraction of chemicals have been measured in pregnant women or children
Picture source: www.othot.com

Environmental influences on Child Health Outcomes (ECHO) Program



>55,000 children from 71 longitudinal cohorts across the US

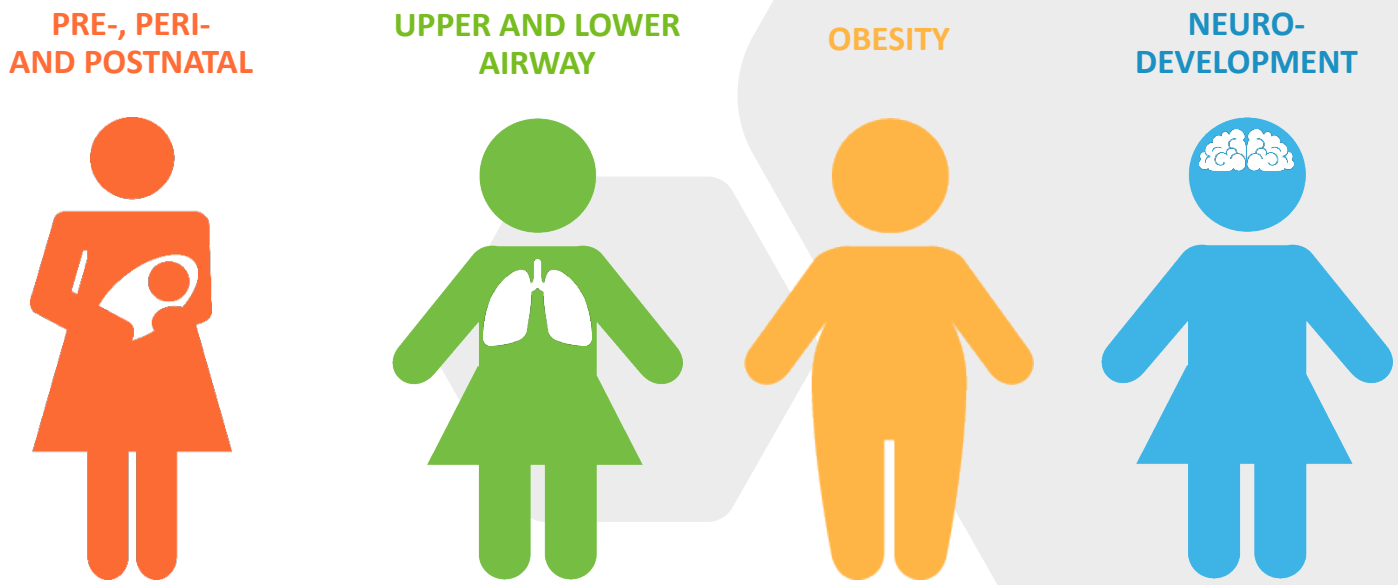
Children's race/ethnicity

- 45% Non-Hispanic White
- 25% Hispanic
- 13% Non-Hispanic Black
- 11% Non-Hispanic Other Race
- 6% Unknown/not reported/other

ECHO
Environmental influences on Child Health Outcomes
A program supported by the NIH

OBJECTIVE

Identify novel chemicals of importance to children's health



Identifying and prioritizing candidate chemicals

Review

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP5133.

Identifying and Prioritizing Chemicals with Uncertain Burden of Exposure: Opportunities for Biomonitoring and Health-Related Research

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Background: The National Institutes of Health's Environmental influences on Child Health Outcomes (ECHO) initiative aims to understand the impact of environmental factors on childhood disease. Over 40,000 chemicals are approved for commercial use. The challenge is to prioritize chemicals for biomonitoring that may present health risk concerns.

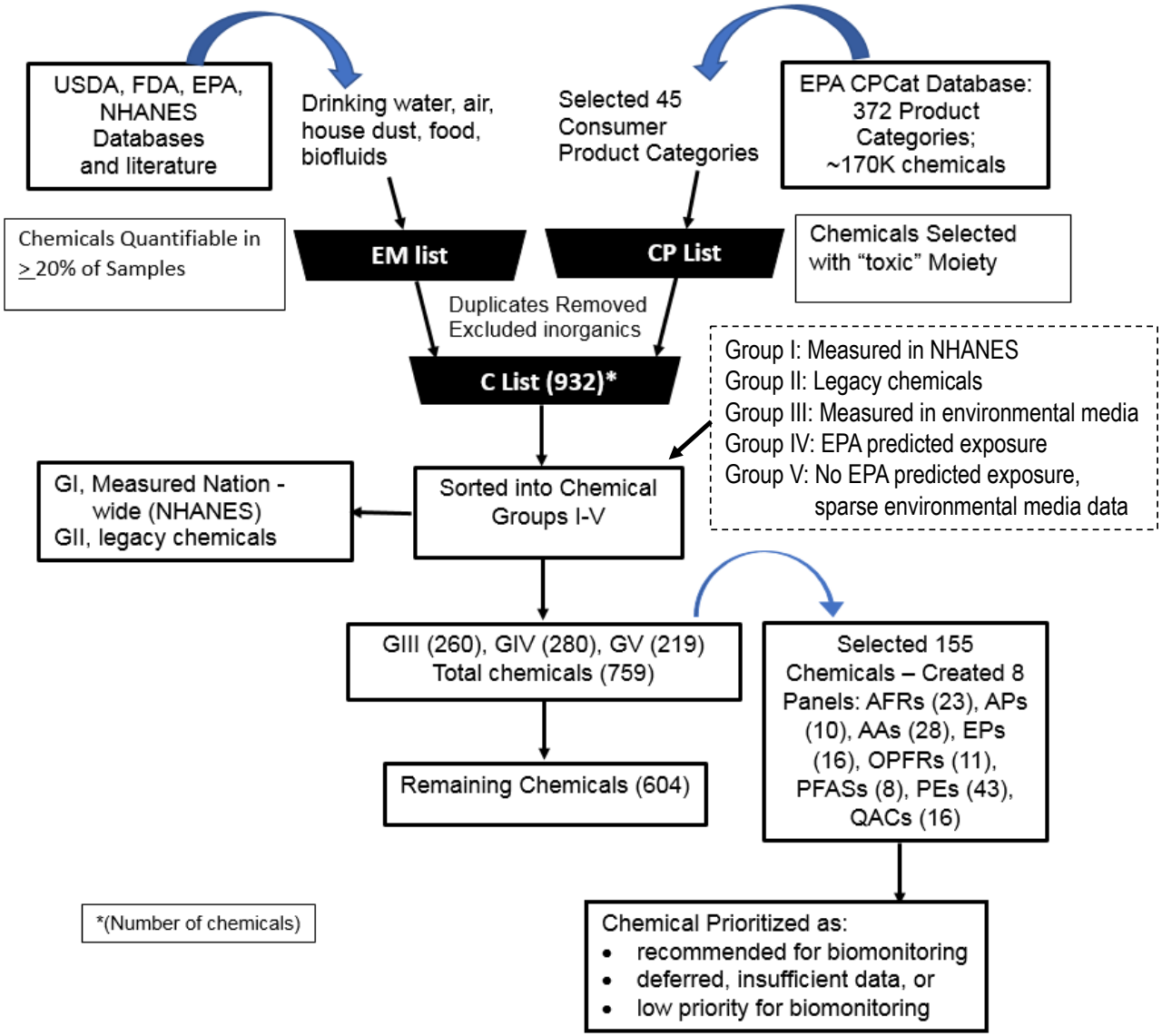
Objectives: Our aim was to prioritize chemicals that may elicit child health effects of interest to ECHO but that have not been biomonitored nationwide and to identify gaps needing additional research.

Methods: We searched databases and the literature for chemicals in environmental media and in consumer products that were potentially toxic. We selected chemicals that were not measured in the National Health and Nutrition Examination Survey. From over 700 chemicals, we chose 155 chemicals and created eight chemical panels. For each chemical, we compiled biomonitoring and toxicity data, U.S. Environmental Protection Agency exposure predictions, and annual production usage. We also applied predictive modeling to estimate toxicity. Using these data, we recommended

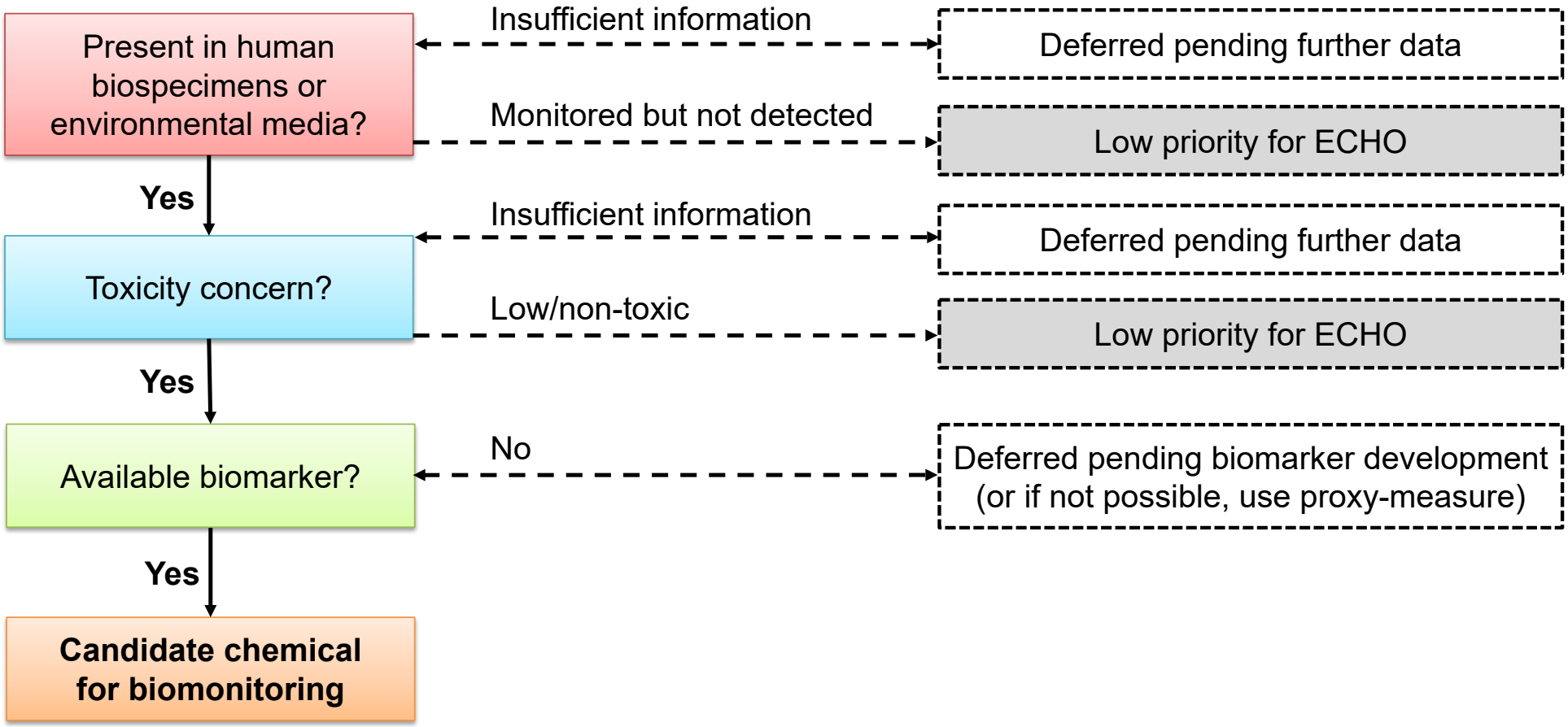
Pellizzari et al. *EHP* 2019

Conducted a rigorous review of extant data to prioritize 155 chemicals in 8 classes

Chemical Classes
Alternate flame retardants
Alternative plasticizers
Aromatic amines
Environmental phenols
Organophosphorus flame retardants
Perfluoroalkyl substances
Pesticides
Quaternary ammonium compounds



Criteria for recommending chemical biomonitoring in ECHO



Example: organophosphorus-based flame retardants

Present in human biospecimens or environmental media?

Name	Exposure/Environmental Media: Dermal Contact	Biofluids/hair/nails	Air, Indoor Dust	Food, Water
2,2-Bis(chloromethyl) propane-1,3-Diyltetrakis(2-chloroethyl) bisphosphate (V6)		[142]	[29, 404, 405],	
2-Ethylhexyl diphenyl phosphate (EHDPP)		[407-409]	[408, 410-413]	[27, 414]
Bis(2-ethylhexyl) phosphate (BEHP)		[417].	[140, 143]	[418]
Diquanidine hydrogen phosphate				
Triethyl phosphate (TEP)			[419-421]	[28]
Tris (2,3-dibromopropyl) phosphate (TBP)*		[424]	[413]	
Tris(2,3-dichloropropyl) phosphate (TDCnPP)		[426]	[419, 427]	[428]
Tris(2-butoxyethyl) phosphate (TBOEP)		[407, 432-434]	[24, 155, 315, 407, 411, 419, 435, 436]	[27, 28]
Tris(2-chloro-*iso* -propyl) phosphate (TCIPP)		[108, 445]	[88, 89, 155, 315, 404, 407, 410, 412]	[28]
Tris(2-ethylhexyl) phosphate (TEHP)		[433]	[420, 425, 446]	[27]
Tris(tribromoneopentyl)phosphate (TTBNPP)				[450, 451]

	Quantified in media/ biofluids; qual. id in biofluids
	Qualitative id in media or dermal contact
	No or sparse data

Example: organophosphorus-based flame retardants

Toxicity concern?

Name	Health Effects/Toxicity: In Vivo/In Vitro: Endocrine	Developmental	Reproductive	Neurotoxicity	Carcinogenicity	HTP Assay: Neurotoxicity	Endocrine	Obesity	QSAR Model: Developmental	Carcinogenicity	Reproductive
Organophosphorus-based Flame Retardants											
2,2-Bis(chloromethyl) propane-1,3-Diyltetrakis(2-chloroethyl) bisphosphate (V6)		[415]		[416].							
2-Ethylhexyl diphenyl phosphate (EHDPP)											
Bis(2-ethylhexyl) phosphate (BEHP)											
Diquanidine hydrogen phosphate											
Triethyl phosphate (TEP)		[415, 422]	[423]								
Tris (2,3-dibromopropyl) phosphate (TBP)*			[424, 425]								
Tris(2,3-dichloropropyl) phosphate (TDCnPP)	[429]	[430]		[431]							
Tris(2-butoxyethyl) phosphate (TBOEP)	[437, 438]	[315, 439, 440]	[441]	[442-444]							
Tris(2-chloro-*iso*-propyl) phosphate (TCIPP)		[315, 406]	[406]								
Tris(2-ethylhexyl) phosphate (TEHP)		[447, 448]	[449]								
Tris(tribromoneopentyl)phosphate (TTBNPP)											

In Vivo /In Vitro Studies
Human study, risk Assess.
In vivo animal studies
In vitro experiments
No or sparse data

QSAR Models
Toxicant-High reliability
Toxicant-Medium reliability
Toxicant-Low
Not likely a toxicant
No prediction

Example: organophosphorus-based flame retardants

Available biomarker?

Name	Biomarkers			
	Plasma/Serum	Hair/fingernails	Urine	Breast Milk
Organophosphorus-based Flame Retardants				
2,2-Bis(chloromethyl) propane-1,3-Diyltetrakis(2-chloroethyl) bisphosphate (V6)		[142]	[142]	
2-Ethylhexyl diphenyl phosphate (EHDPP)		[409]	[407]	
Bis(2-ethylhexyl) phosphate (BEHP)			[417].	
Diquanidine hydrogen phosphate				
Triethyl phosphate (TEP)				
Tris (2,3-dibromopropyl) phosphate (TBP)*			[424]	
Tris(2,3-dichloropropyl) phosphate (TDCnPP)		[426]		
Tris(2-butoxyethyl) phosphate (TBOEP)		[409]	[407, 432-434, 445]	[433, 445]
Tris(2-chloro-*iso*-propyl) phosphate (TCIPP)			[108]	[445]
Tris(2-ethylhexyl) phosphate (TEHP)		[409]	[433]	[433]
Tris(tribromoneopentyl)phosphate (TTBNPP)				

	Parent or metabolite
	No or sparse data

Recommended biomonitoring of novel chemicals in ECHO

Panel name	# Chemicals	# Recommended for biomonitoring	# Deferred	# Low priority for biomonitoring
Alternate flame retardants	23	**4**	16	3
Alternative plasticizers	10	**2**	5	3
Aromatic amines	28	**3**	25	0
Environmental phenols	16	**6**	9	1
Organophosphorus flame retardants	11	**5**	5	1
Perfluoroalkyl substances	8	**4**	4	0
Pesticides	43	**12**	28	3
Quaternary ammonium compounds	16	**0**	16	0
Total:	155	**36**	108	11

Assessing novel chemical exposures in ECHO

Develop and demonstrate feasibility of a method for multiple chemical extraction and measurement

102 urinary biomarkers in multi-class assay

Alternative Flame Retardant
Melamine

Aromatic Amines
2-Methylaniline
2-Methoxyaniline
3,4-Diclhoroaniline
2,4-Diaminotoluene
4,4'-Diaminodiphenylmethane

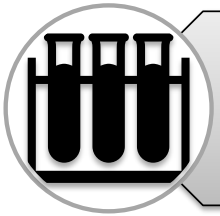
Organophosphorus-based flame retardants
2,2-Bis(chloromethyl) propane-1,3-diyltetrakis(2-chloroethyl) bisphosphate
2-Ethylhexyl diphenyl phosphate
Bis(2-ethylhexyl) phosphate
Tris(2-ethylhexyl) phosphate
Bis(2-butoxyethyl) phosphate
Tris(2-butoxyethyl) phosphate
Triethyl phosphate
Bis(2-methylphenyl) phosphate
Cresyl diphenyl phosphate
Dibutyl phosphate
Diphenyl phosphate
Di-isobutyl phosphate
Tri-iso-butyl phosphate
Tri-isopropyl phosphate
Trimethyl phosphate
Trimethylphenyl phosphate
Tri-n-butyl phosphate
Triphenyl phosphate
Tris(2-chloroethyl) phosphate

Environmental Phenols
Bisphenol A diglycidyl ether
Bisphenol AF
Bisphenol B
3,3',5,5'-Tetrabromobisphenol A
2,2',6,6'-Tetrachlorobispheol A
3,3',5-Trichlorobisphenol A
4-n-Nonylphenol
Bisphenol A (2,3-dihydroxypropyl) glycidyl ether
Bisphenol A bis(2,3-dihydroxypropyl) glycidyl ether
Bisphenol A (3-chloro-2-hydroxypropyl) glycidyl ether
Bisphenol A bis(3-chloro-2-hydroxypropyl) glycidyl ether
4-n-Octylphenol
4,4'-(1,4-Phenylenediisopropylidene)bisphenol
4,4'-(1-Phenylethylidene)bisphenol
4,4'-Cyclo-hexylidenebisphenol
4,4'-di-Hydroxydiphenylmethane
4,4'-Sulfonyldiphenol (Bisphenol S)
bis(4-Hydroxyphenyl)propane
2,4,5-Trichlorophenol
2,3,4,5-Tetrachlorophenol
2,3,4,6-Tetrachlorophenol
2,3,5,6-Tetrachlorophenol
Pentachlorophenol
4-Hydroxybenozoate
4-hydroxybenzophenone
Benzophenone-1
Benzophenone-2
Benzophenone-3
Benzophenone-6
Benzophenone-8
Benzyl paraben
Ethyl paraben
Heptaparaben
Hydroxy-ethyl paraben
Hydroxy-methyl paraben
Methyl paraben
n-Butyl paraben
n-Propyl paraben
Triclocarban
Triclosan

Pesticides
Azoxystrobin
Cyprodinil
Metalaxyl
Metribuzin
Propiconazole
Pyrimethanil
Tebuconazole
Tetraconazole
6-Cloronicotinic acid
Acetamiprid
Atrazine
Cynauric Acid
Ammelide
Ammeline
Clothianidin
Dinotefuran
Flonicamid
Imidacloprid
Imidaclotiz
N-desmethyl thiamethoxam
N-desmethyl-acetamiprid
Nitenpyram
Sulfoxaflor
Thiacloprid-amide
Thiamethoxam

Alternate Plasticizers
mono-Ethyl phthalate
mono-Butyl phthalate
mono-Benzyl phthalate
mono-(2-Ethylhexyl) phthalate
mono-(2-Ethyl-5-hydroxyhexyl) phthalate
mono-(2-Ethyl-5-oxohexyl) phthalate
mono-Carboxy-iso-octyl phthalate
mono-Carboxy-iso-nonyl phthalate
mono-Ethyl terephthalate
mono-Tert-butyl terephthalate
mono-Benzyl- terephthalate
mono-2(Ethyl hexyl) terephthalate

Assessing novel chemical exposures in ECHO

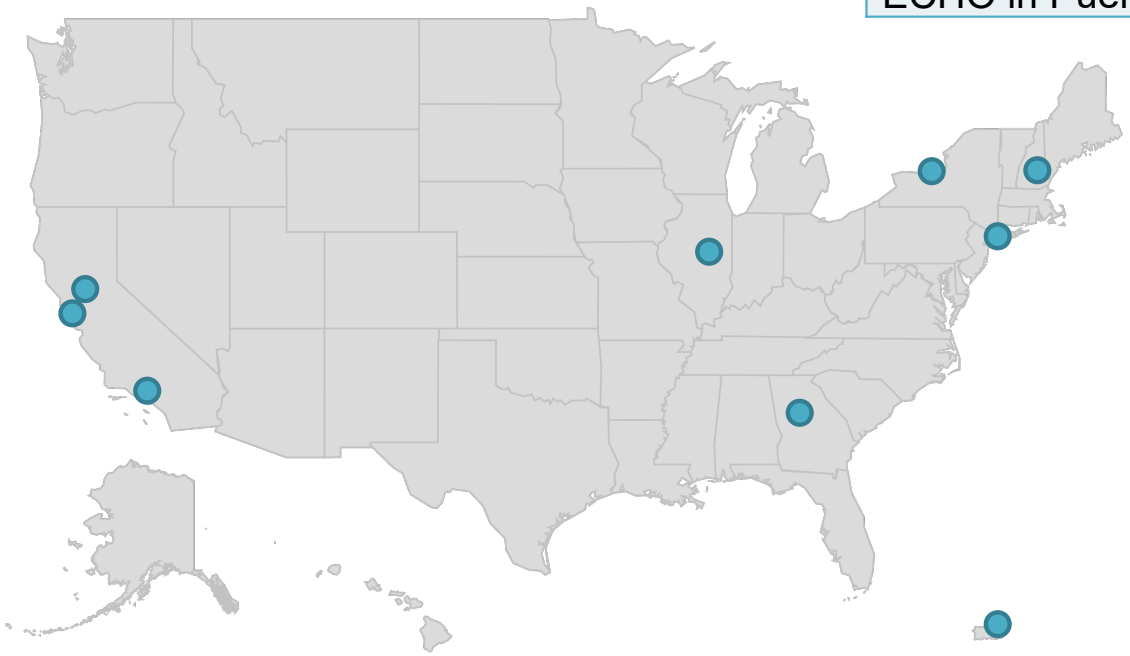


Develop and demonstrate feasibility of a method for multiple chemical extraction and measurement

Conduct a pilot study to measure novel chemicals in urine collected from pregnant women

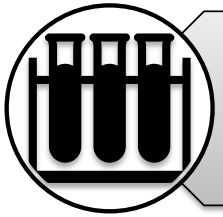
Pilot study measuring novel chemicals among 175 pregnant women from 9 ECHO cohorts

Cohort	Location	Enrollment
New Hampshire Birth Cohort Study	NH	2009-present
Fair Start	NY	2013-present
Rochester	NY	2016-present
Atlanta ECHO Cohort of Emory	GA	2014-present
Illinois Kids Development Study	IL	2013-present
MARBLES	CA	2006-present
Chemicals in our Bodies	CA	2014-present
MADRES	CA	2016-present
ECHO in Puerto Rico	PR	2011-present



Includes women from across the U.S. to capture geographic, temporal, and sociodemographic diversity

Assessing novel chemical exposures in ECHO

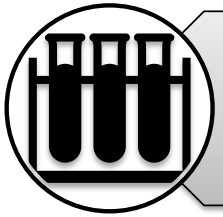


Develop and demonstrate feasibility of a method for multiple chemical extraction and measurement

Conduct a pilot study to measure novel chemicals in urine collected from pregnant women

Assess associations of prenatal novel chemical exposures with birth outcomes among >7500 children

Assessing novel chemical exposures in ECHO



Develop and demonstrate feasibility of a method for multiple chemical extraction and measurement

Conduct a pilot study to measure novel chemicals in urine collected from pregnant women

Assess associations of prenatal novel chemical exposures with birth outcomes among >7500 children

Perform future studies evaluating associations of novel chemicals with additional child health outcomes

Action and policy implications

- First study to assess exposures or health effects for majority of selected chemicals
- Chemical exposures can be reduced through a variety of programs, policies, and practices to protect children's health

EXPOSURE REDUCTION STRATEGIES

Zota et al. *J Epidemiol Community Health* 2017

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