A young girl with blonde hair styled in a braid is shown in profile, kissing the belly of a pregnant woman. The scene is intimate and tender, set against a bright, blurred background. The text is overlaid on the left side of the image.

Background and the epidemiological part of the project

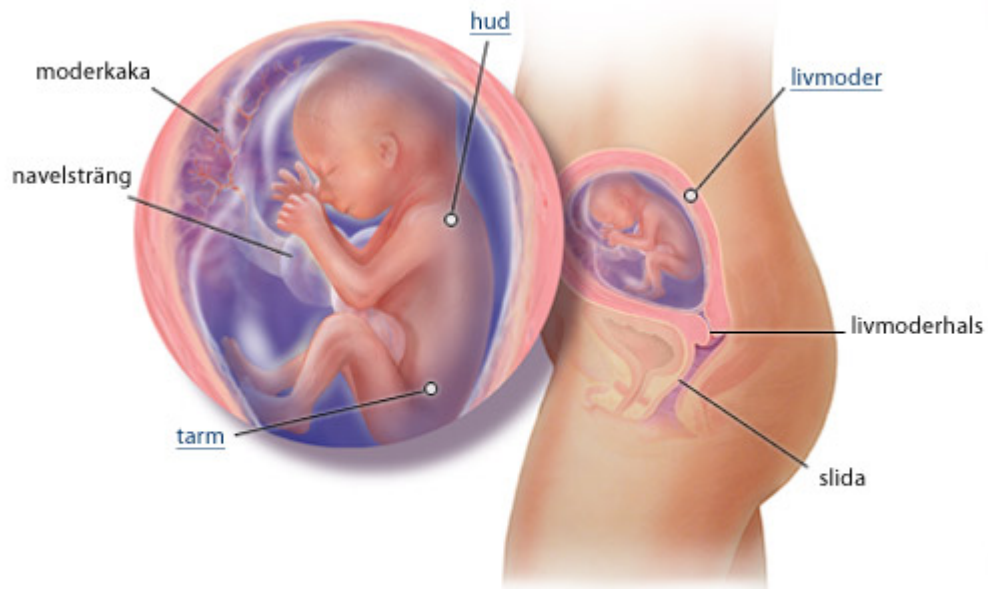
Carl-Gustaf Bornehag, PhD

Professor in Public Health Sciences

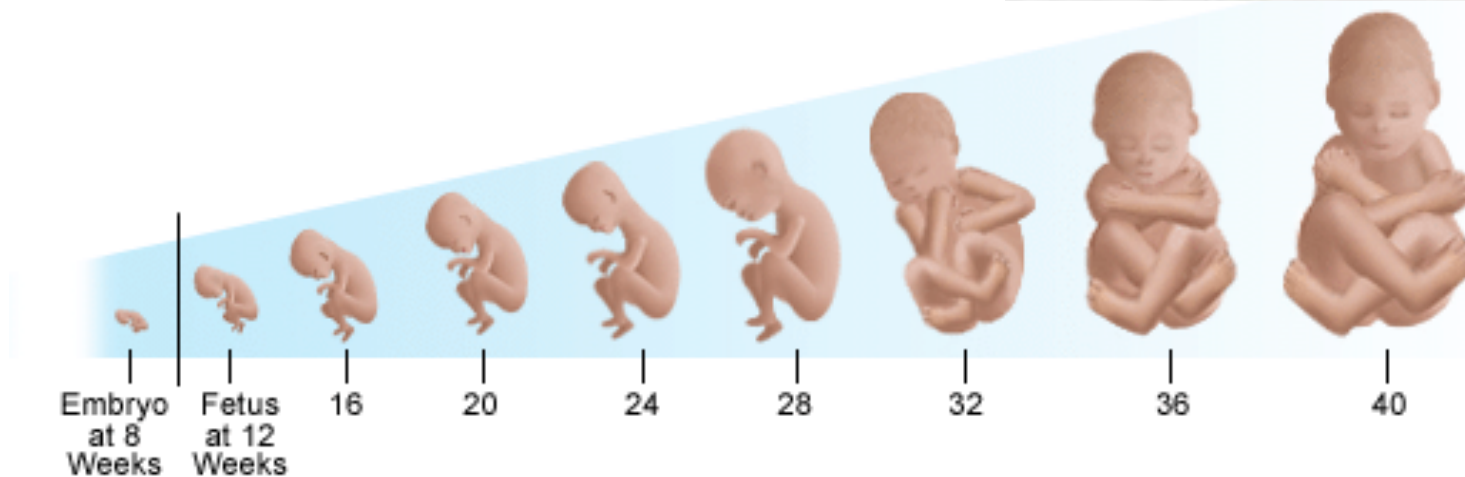
Karlstad University, Karlstad, Sweden

Icahn School of Medicine at Mount Sinai, New York, USA

Early life is important



Fetal Growth From 8 to 40 Weeks



The developmental basis of adult disease



A 70 year old man with cardiovascular disease

A 60 year old man with Parkinson's disease

A 50 year old women with breast cancer

A 40 year old man with type 2 diabetes

A 30 year man with infertility problem

A 20 year old man with overweight

A 10 year old boy with asthma

A 6 year old boy with ADHD

Malformed genitals

Low birthweight

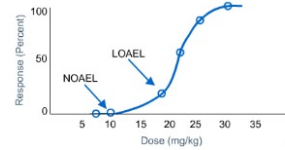
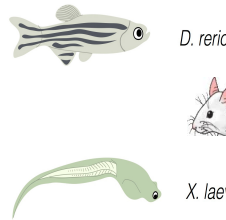
**Social, Psychological &
Environmental Determinants
for Health & Development**

Human Exposures vs. Regulatory Guideline Values



Human Exposure:
External estimates;
Biomonitoring

Experimental Evidence



**Reference
Dose
(RfD)**

$$\text{Regulatory Ratio} = \frac{\text{Human Exposure}}{\text{RfD}} * \text{Assessment Factor}$$

Risk assessment of chemicals is normally based on a single compound approach!

However, we are exposed to large number of chemicals in complicated mixtures!

Data from +2,300 pregnant women in SELMA



Research for a healthier future
Swedish Environmental Longitudinal, Mother and child, Asthma and allergy study

Matrix	Chemical Type	Compound (further description)	Abbreviation	LOD/ LOQ ^a	% ≥LOD	GM	
Urine	Phenols	2,4,4'-trichloro-2'-hydroxydiphenyl ether	Triclosan	0.100	92	1.27	
		bisphenol A	BPA	0.050	100	1.53	
	Plasticizers (Phthalate & non-phthalate)	Plasticizers (Phthalate & non-phthalate)	4,4-bisphenol F (BPA replacement analogue)	BPF	0.024	92	0.16
			bisphenol S (BPA replacement analogue)	BPS	0.009	98	0.07
			monoethyl phthalate	MEP	0.010	100	62.8
			monobutyl phthalate	MBP	0.100	100	67.5
			monobenzyl phthalate	MBzP	0.040	100	15.5
			mono(2-ethylhexyl) phthalate	MEHP	0.100	100	-
			mono(2-ethyl-5-hydroxyhexyl) phthalate	MEHHP	0.020	100	-
			mono(2-ethyl-5-oxohexyl) phthalate	MEOHP	0.030	100	-
			mono(2-ethyl-5-carboxypentyl) phthalate	MECPP	0.020	100	-
			di-(2-ethylhexyl) phthalate (parent compound)	DEHP ^b	-	-	63.8
			mono(hydroxy-iso-nonyl) phthalate	MHiNP	0.020	100	-
			mono(oxo-iso-nonyl) phthalate	MOiNP	0.010	100	-
			mono(carboxy-iso-octyl) phthalate	MCiOP	0.020	100	-
			diisononyl phthalate (parent compound)	DINP ^c	-	-	26.7
			monohydroxyisodecyl phthalate	MHiDP	0.031	100	1.25
			monocarboxyisononyl phthalate	MCiNP	0.031	100	0.68
			2-4-methyl-7-oxyooctyl-oxycarbonyl-cyclohexane carboxylic acid (phthalate replacement)	MOiNCH	0.023	99	0.31
			Other Short-Lived	Other Short-Lived	diphenylphosphate (organophosphate flame retardant)	DPHP ^d	0.042
	3,5,6-trichloro-2-pyridinol (organophosphate pesticide)	TCP			0.035	100	1.25
	3-phenoxybenzoic acid (pyrethroid pesticide)	PBA			0.017	99	0.16
	2-hydroxyphenanthrene (polycyclic aromatic hydrocarbon)	2OHPH			0.003	100	0.20
	Serum	Perfluoro-alkyl Substances (PFAS)	perfluorooctanoic acid	PFOA	0.020	100	1.55
			perfluorooctane sulfonate	PFOS	0.060	100	5.32
			perfluorononanoic acid	PFNA	0.010	100	0.53
perfluorodecanoic acid			PFDA	0.020	100	0.26	
perfluoroundecanoic acid			PFUnDA	0.020	99	0.22	
perfluorohexanesulfonic acid			PFHxS	0.030	100	1.31	
Plasma			Persistent Chlorinated	hexachlorobenzene	HCB	0.005	100
	trans-nonachlor	Nonachlor		0.005	78	0.01	
	dichlorodiphenyltrichloroethane alone	DDTa		0.015	99	-	
	dichlorodiphenyldichloroethylene	DDE		0.040	8	-	
	total dichlorodiphenyltrichloroethane	DDT ^e		-	-	0.19	
	polychlorinated biphenyl 74	PCB 74		0.005	73	-	
	polychlorinated biphenyl 99	PCB 99		0.005	81	-	
	polychlorinated biphenyl 118	PCB 118		0.005	99	-	
	polychlorinated biphenyl 138	PCB 138		0.005	100	-	
	polychlorinated biphenyl 153	PCB 153		0.005	100	-	
	polychlorinated biphenyl 156	PCB 156		0.005	90	-	
	polychlorinated biphenyl 170	PCB 170		0.005	100	-	
	polychlorinated biphenyl 180	PCB 180		0.005	100	-	
	polychlorinated biphenyl 183	PCB 183		0.005	76	-	
	polychlorinated biphenyl 187	PCB 187		0.005	98	-	
total polychlorinated biphenyls	PCB ^f	-	-	0.37			

Human epidemiology



Cell models



Risk
Assessment



Animal models

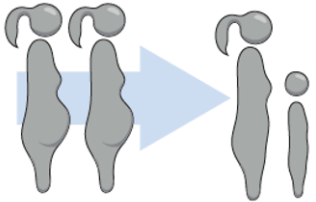


Similar Mixture Approach (SMACH)

1. Identification of bad actors (mixtures) for health effects in epidemiological data

Epidemiology
EDC levels in urine, blood and clinical data

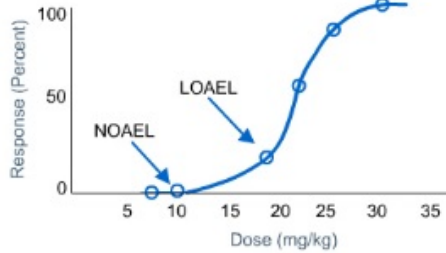
SELMA cohort



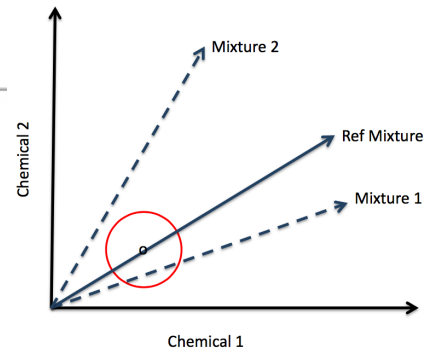
2. Composition of reference mixtures from population data for experimental evaluations



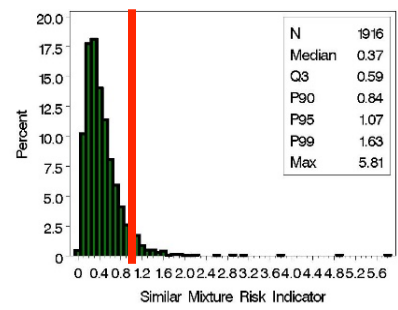
3. Experimental tests (in cells and animals) of reference mixtures for dose-response



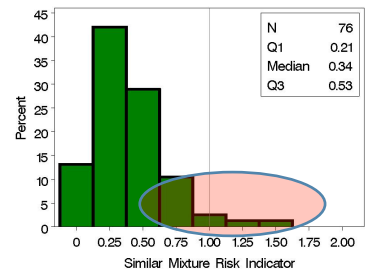
4a Test for sufficient similarity with the reference mixture (%)



4b For sufficient similar subgroups; test for extreme mixing proportions, SMRI > 1 (%)

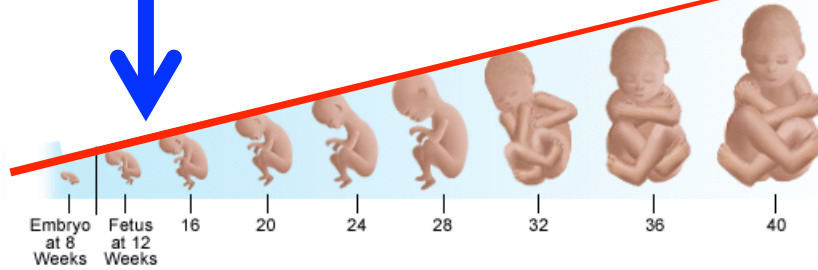


4c Demonstrate if health effects are associated with SMRI (adj risk, 95% CI)



Natural hormones

Estrogen
Testosterone
Thyroids. etc.



Neurodevelopment



15 EDCs (20 analytes)
(N=594)
Mixture approach (WQS)

Co-factors
creatinine, sex, smoking,
prematurity, mothers age, weight,
IQ, and education, diet, parity,
maternal education.

parentcircle

SIGNS OF LANGUAGE DELAY IN CHILDREN

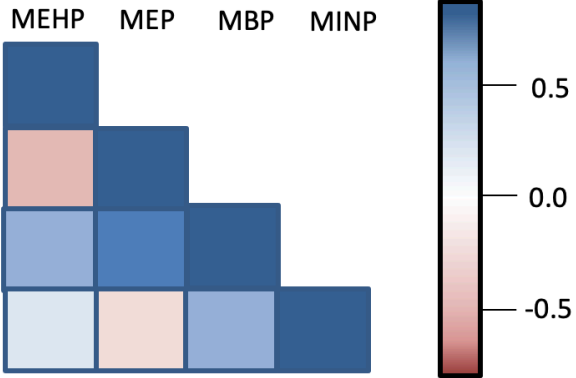
Birth to 3 months	Not smiling or playing with others
4 to 7 months	Not babbling
7 to 12 months	Making only a few sounds; not using gestures like waving or pointing
12 to 18 months	Saying only a few words
1½ to 2 years	Not putting two words together
2 years	Saying fewer than 50 words

Language delay in early life is a marker for **cognitive deficits** and neuropsychiatric diagnoses (**autism, ADHD**) later on

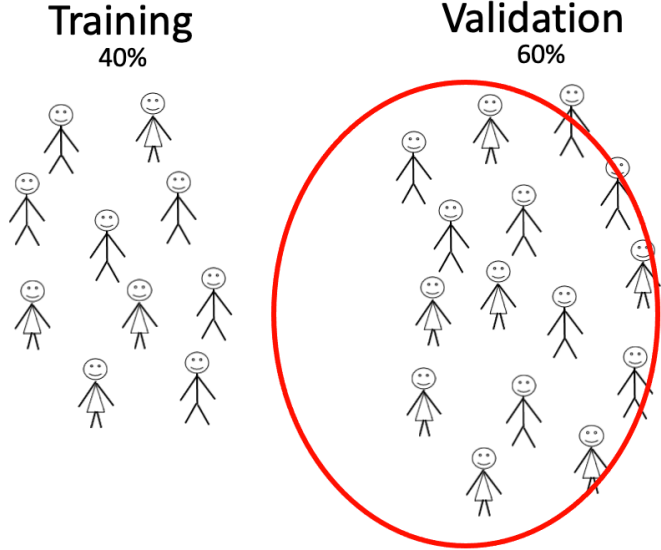
1st trimester urine/serum levels of 15 EDCs (20 analytes) in SELMA mothers

Compound	Metabolite	Median	95% percentile	GM (95% CI)
<i>Phthalate and metabolites in urine (ng/ml)</i>				
DEP	MEP	62.6	507.7	68.7 (65.3–72.3)
DBP	MBP	71.9	233.1	69.0 (66.5–71.5)
BBzP	MBzP	16.8	99.4	16.6 (15.8–17.4)
DEHP	MEHP	3.8	15.6	3.8 (3.6–3.9)
	MEHHP	16.6	66.6	16.3 (15.7–17.0)
	MEOHP	11.2	45.0	11.1 (10.7–11.6)
	MECPP	15.7	62.7	15.8 (15.2–16.4)
DiNP	MHiNP	5.9	54.6	6.2 (5.9–6.6)
	MOiNP	2.7	19.2	2.9 (2.8–3.0)
	MCiOP	8.7	74.9	9.8 (9.3–10.2)
BPA		1.5	6.2	1.5 (1.4–1.6)
Triclosan		0.8	351.4	1.3 (1.2–1.5)
<i>Perfluorinated compounds (PFAS) in serum (ng/ml)</i>				
PFOA		1.60	3.96	1.60 (1.56–1.64)
PFOS		5.35	12.29	5.30 (5.18–5.43)
PFNA		0.53	1.29	0.54 (0.53–0.55)
PFDA		0.25	0.59	0.26 (0.25–0.27)
PFUnDA		0.23	0.54	0.21 (0.21–0.22)
PFDoDA		0.03	0.08	0.03 (0.03–0.03)
PFHxS		1.23	3.71	1.32 (1.29–1.36)
PFHpA		0.02	0.09	0.02 (0.02–0.02)

Weighted Quantile Sum (WQS) Regression

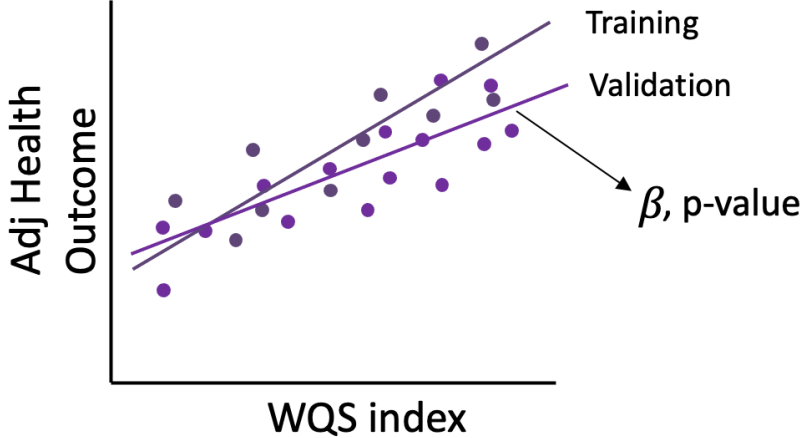
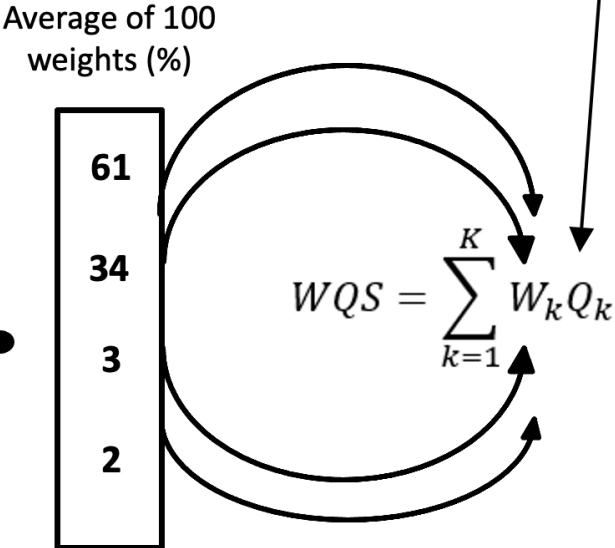


Subject ID	Concentration of MEHP (ng/ml)	Rank (Q) of MEHP
1	3.4	4
2	1.2	2
3	10.3	9



Weights (W, %)

	MEHP	MEP	MBP	MINP
MEHP	62	58	67	59
MEP	34	36	31	35
MBP	3	3	1	2
MINP	1	3	1	4



Mix N associated to Language delay

Identification of bad actors
among 15 EDCs

WQS regression

$\beta=1.4$ (0.4) $p<0.001$ (N=594)

Determination of mixing
proportions (%) of bad actors

Using geometric mean serum levels (mol/L) in
+2,300 SELMA mothers

Composition of a reference
mixture

Dosing 0.1X, **1X**, 10X, 100X, 1000X
where **1X** refers to SELMA

BPA

4

DEP

27

DBP

23

BBzP

11

DiNP

21

PFHxS

3

PFNA

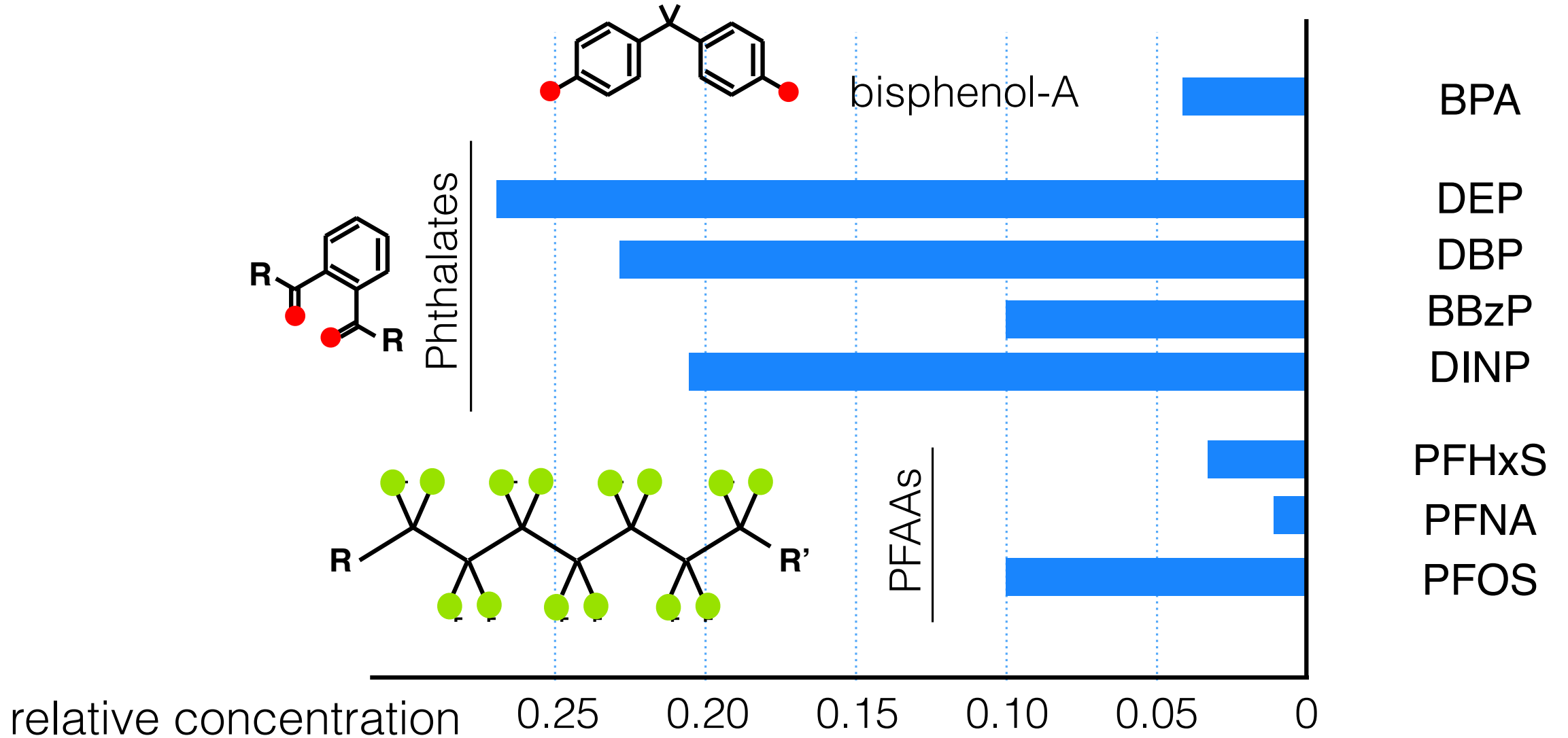
1

PFOS

10



Reference mixture Mix N



Conclusions

Exposure to a widespread chemical mixture of endocrine disruptors during pregnancy is associated with language delay in their children

