Human biomonitoring and mixture effects of food contact chemicals

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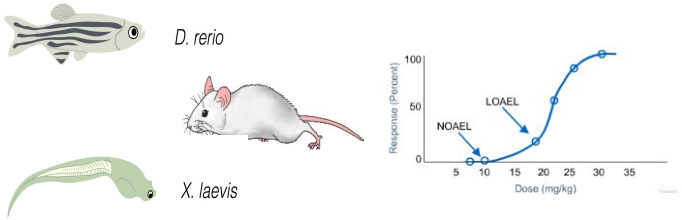
Outline

- Single compound and mixture exposures
- Weighted Quantile Sum (WQS) regression
- The SELMA study – aims, design and available data
- Prenatal mixture exposure and the importance for neurodevelopment and growth in children
- Conclusions

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!

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
		4,4-bisphenol F *(BPA replacement analogue)*	BPF	0.024	92	0.16
		bisphenol S *(BPA replacement analogue)*	BPS	0.009	98	0.07
	Plasticizers *(Phthalate & non-phthalate)*	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
		diphenylphosphate *(organophosphate flame retardant)*	DPHP[d]	0.042	100	1.33
	Other Short-Lived	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	0.04
		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

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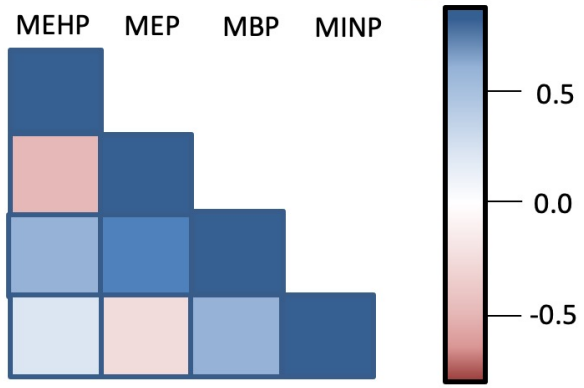
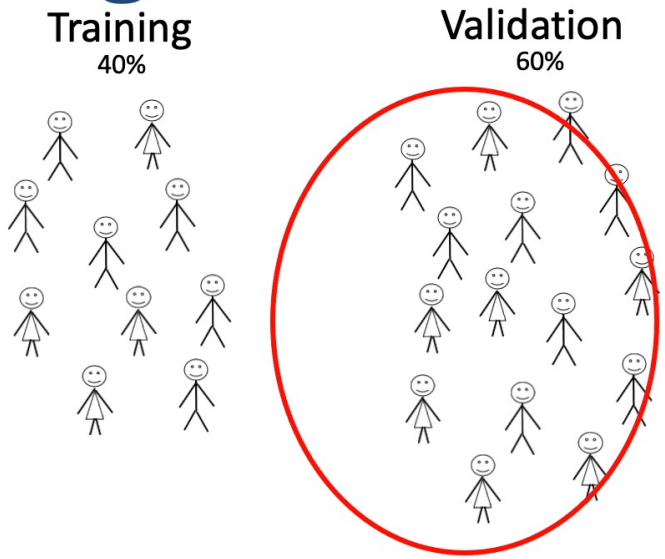
		polychlorinated biphenyl 170	PCB 170	0.005	100	–
		polychlorinated biphenyl 180	PCB 180	0.005	100	–
		polychlorinated biphenyl 183	PCB 183	0.005	76	–
		polychlorinated biphenyl 187	PCB 187	0.005	98	–
		total polychlorinated biphenyls	PCB[f]	–	–	0.37

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, %)

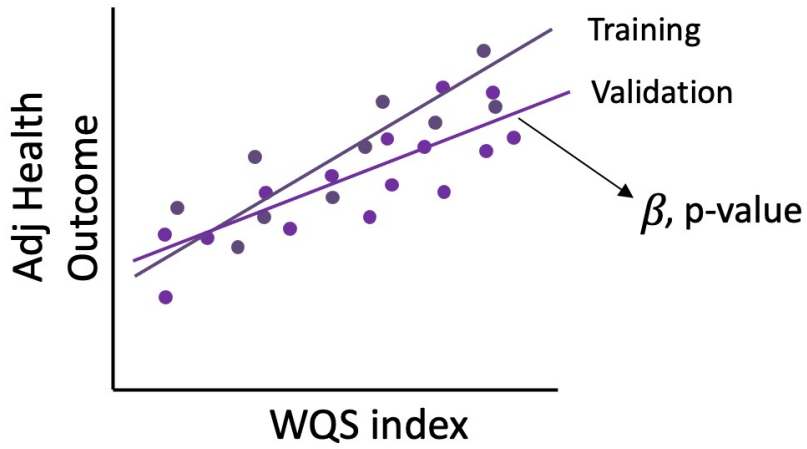
MEHP	62	58	67	59
MEP	34	36	31	35
MBP	3	3	1	2
MINP	1	3	1	4

100 times

Average of 100 weights (%)

61
34
3
2

$$WQS = \sum_{k=1}^{K} W_k Q_k$$

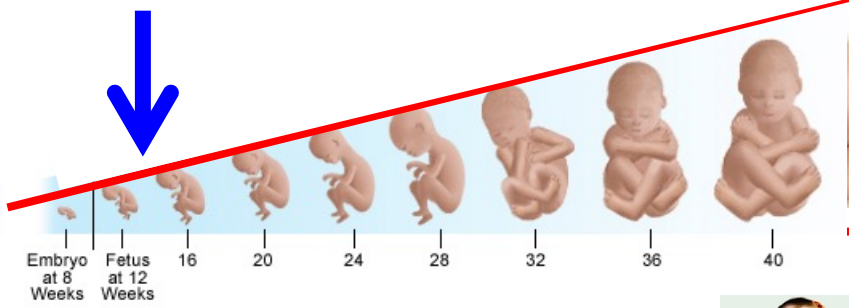


Research for a healthier future

Swedish Environmental Longitudinal, Mother and child, Asthma and allergy study

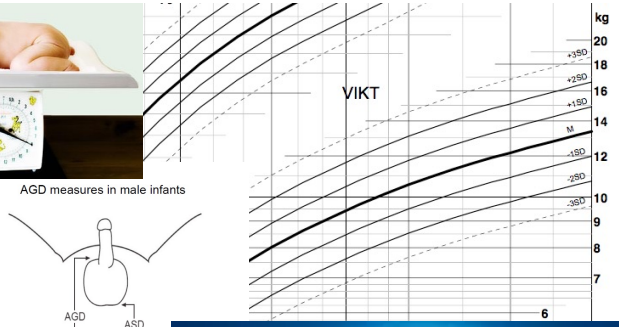
Natural hormones

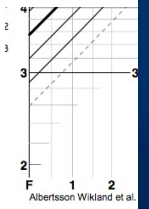
Estrogen
Testosterone
Thyroids. etc.



Health and development

AGD measures in male infants





26 EDCs (>40 analytes)
(N=+2,300)
Single Compounds & Mixtures

Pharmaceuticals (paracetamol)
Diet & Nutrition
Mothers Health
Stress
Etc.

Research for a healthier future

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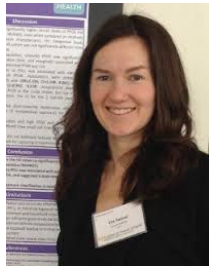
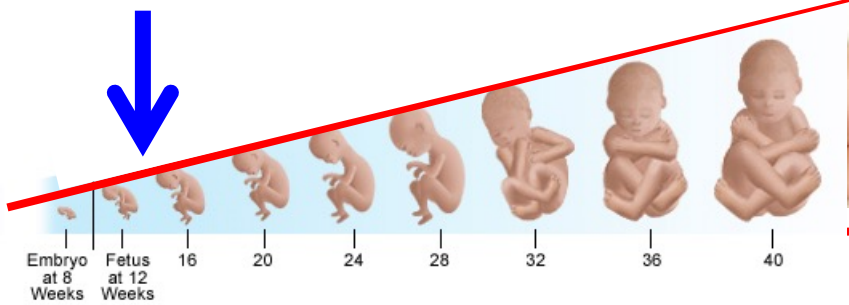
Estrogen
Testosterone
Thyroids. etc.



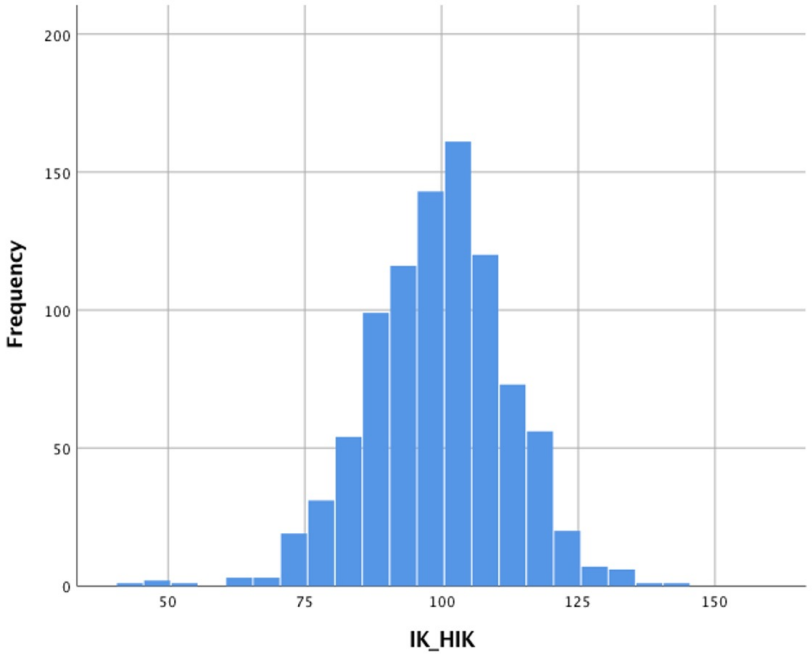
Eva Tanner
Mount Sinai, NY



26 EDCs (>40 analytes)
(N=917)
Mixture approach (WQS)

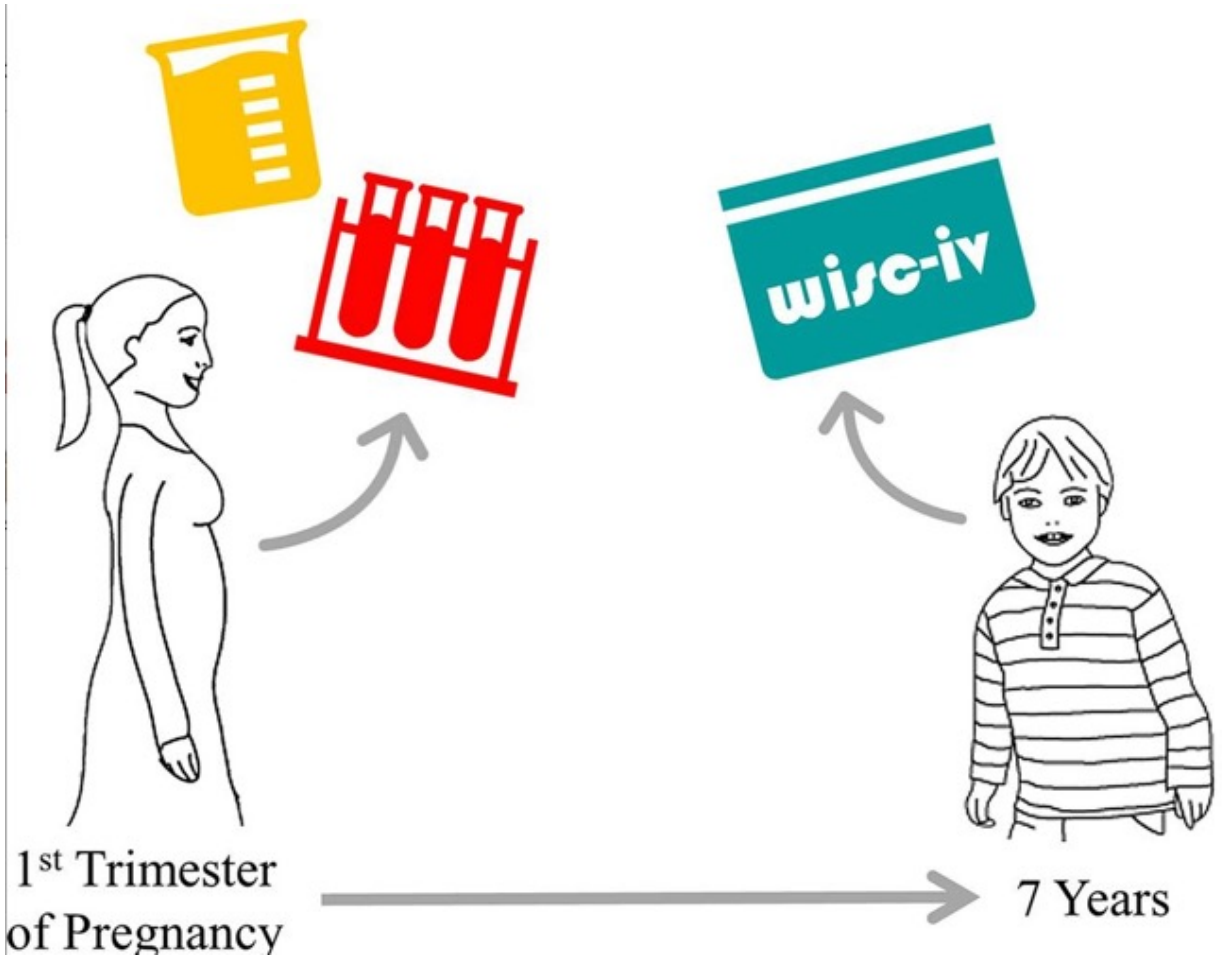
Co-factors
creatinine, sex, prematurity, mothers age, weight, IQ, and education, parity, and breastfeeding at 6 months of age

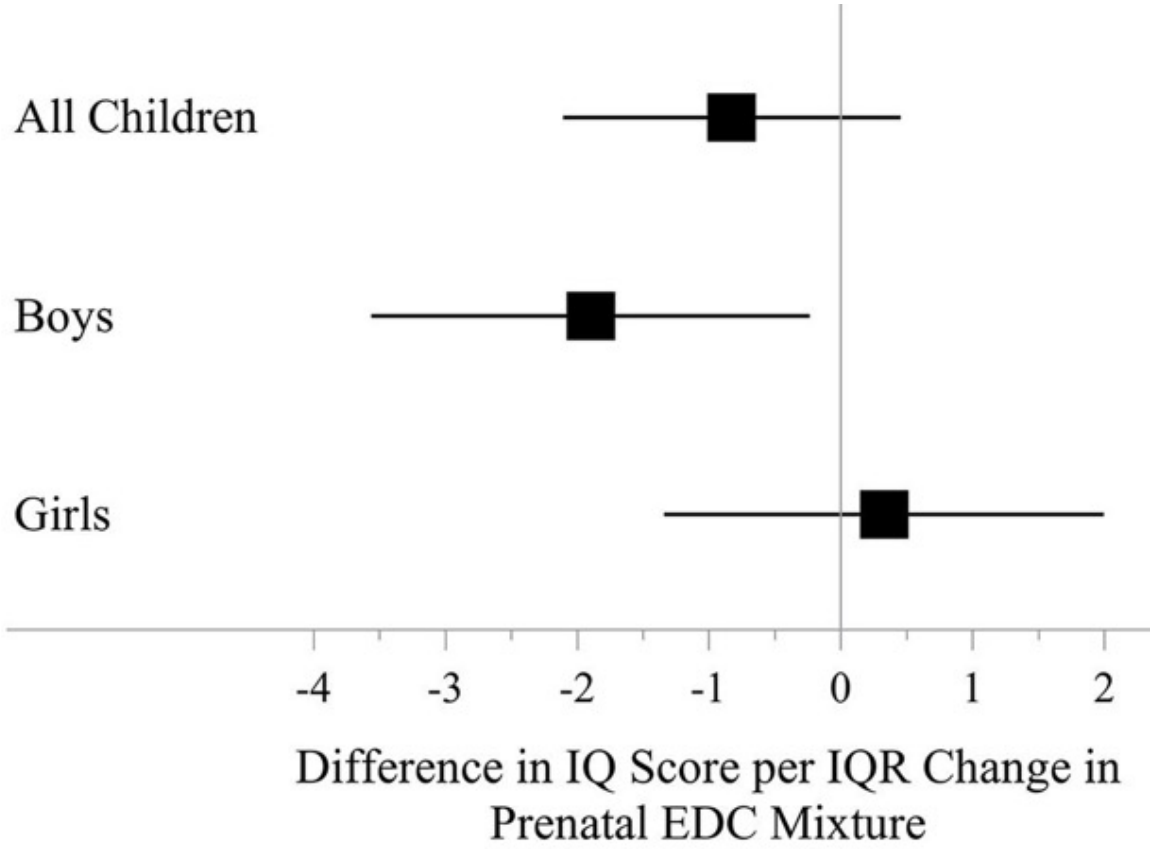
Cognitive function (IQ, WISC-IV) at 7y



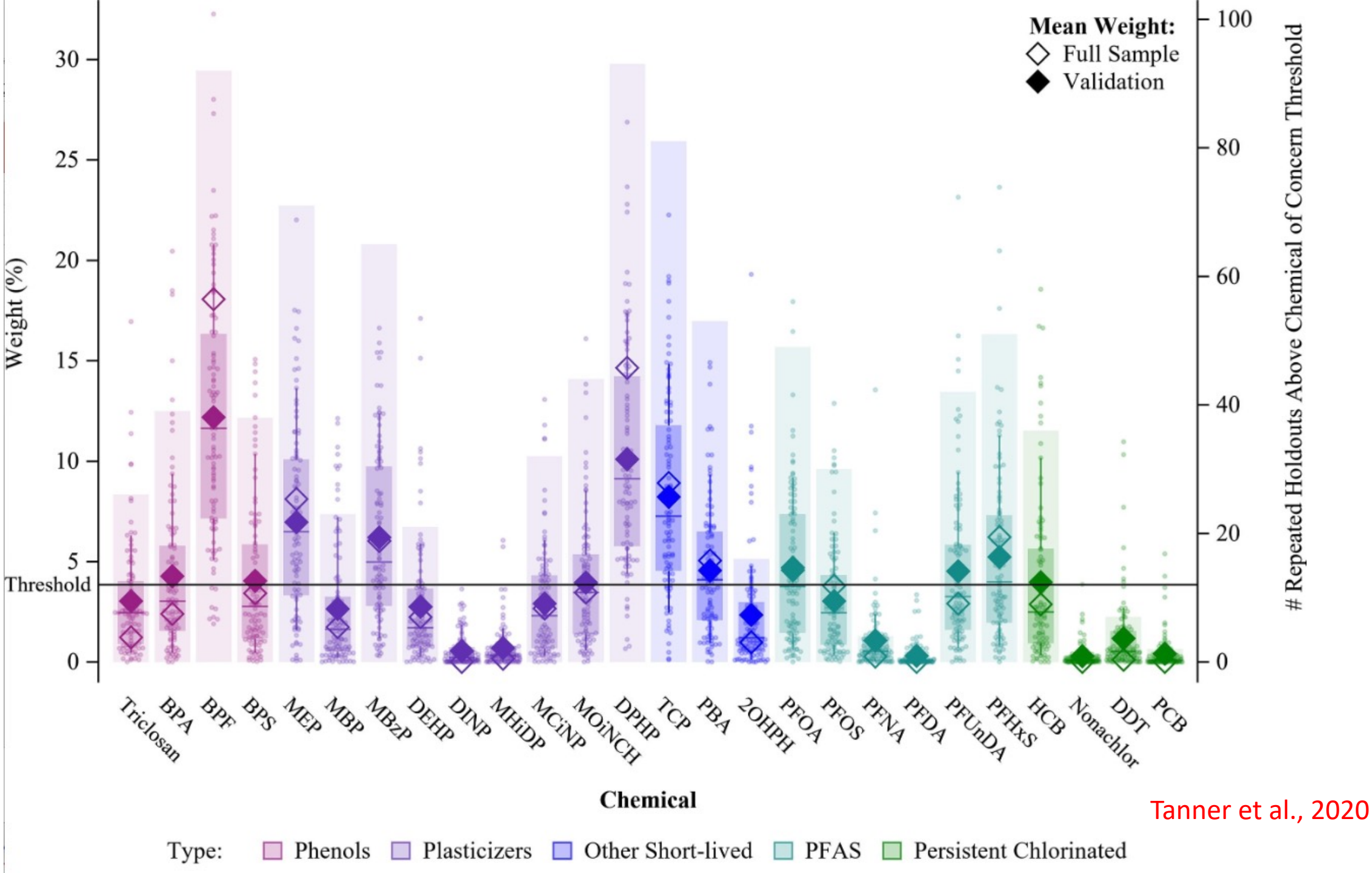
Tanner et al., 2020

Prenatal EDC mixture exposure and Childrens IQ at 7y (N=718) by WQS regression





Tanner et al., 2020



Tanner et al., 2020

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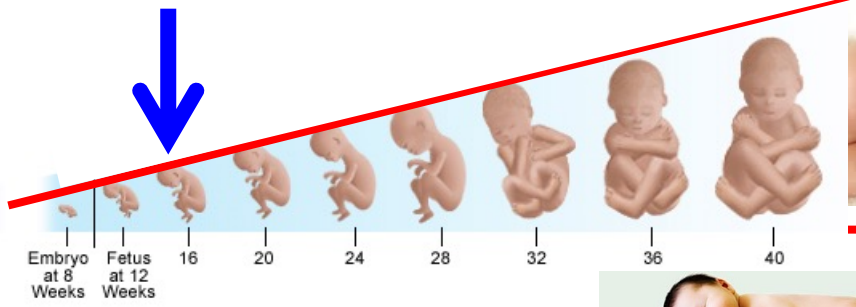
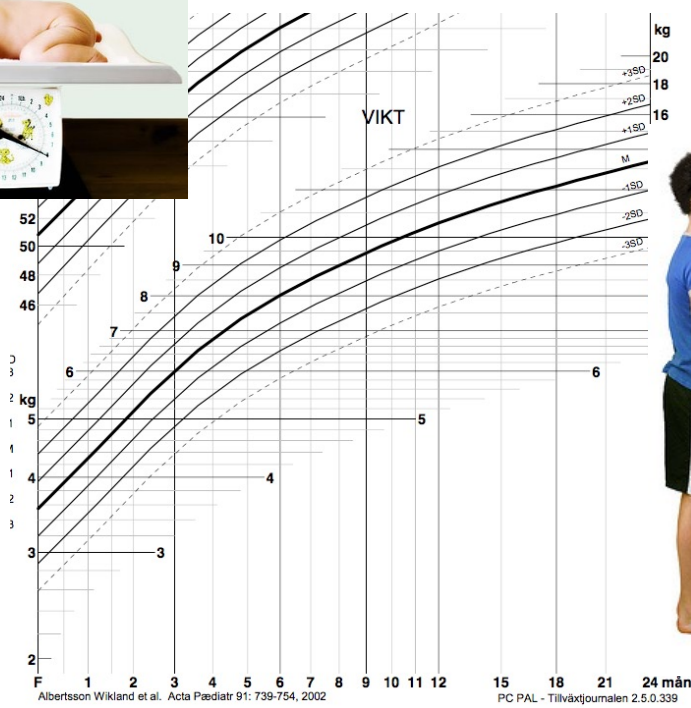
Natural hormones

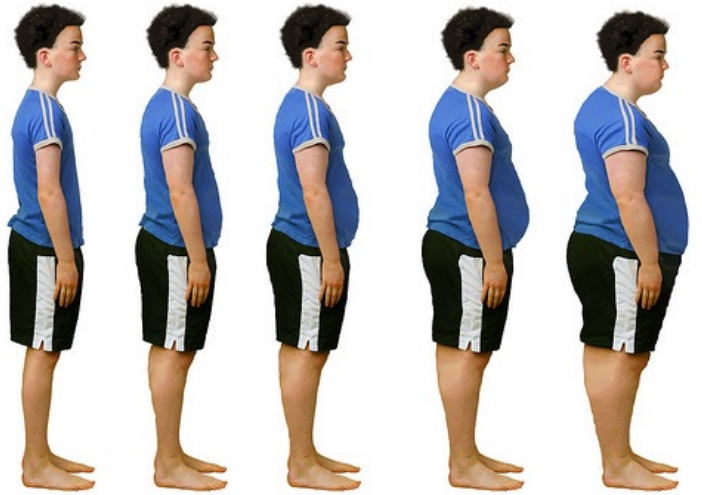
Estrogen
Testosterone
Thyroids. etc.



26 EDCs
Co-factors

Metabolism and Growth





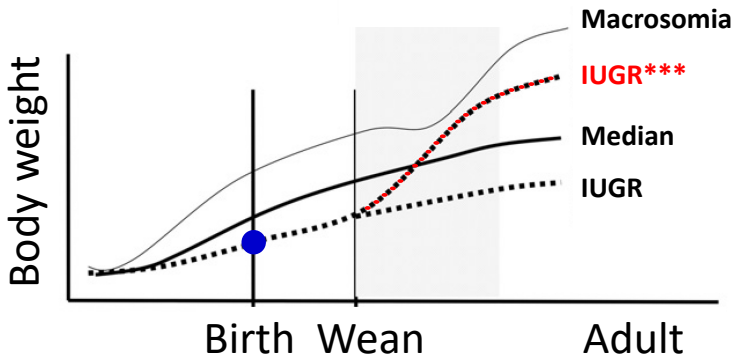
Credit: Combined Media @Flickr

Early life is important

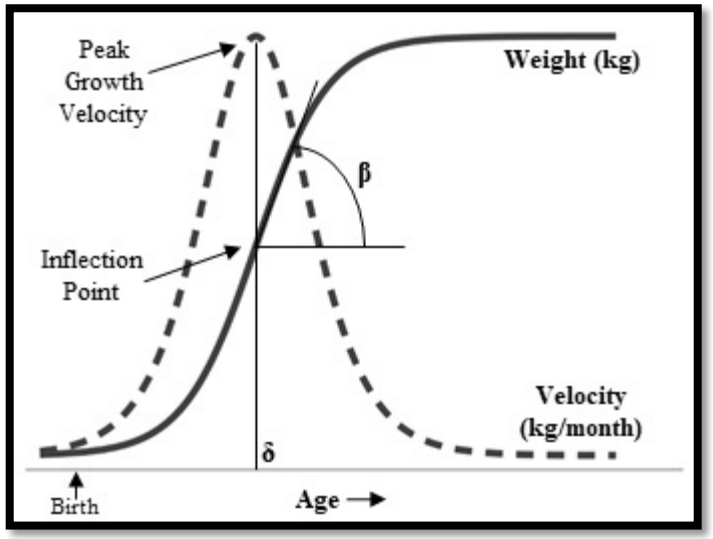
David Barker
(1938-2013)

Children's growth trajectory

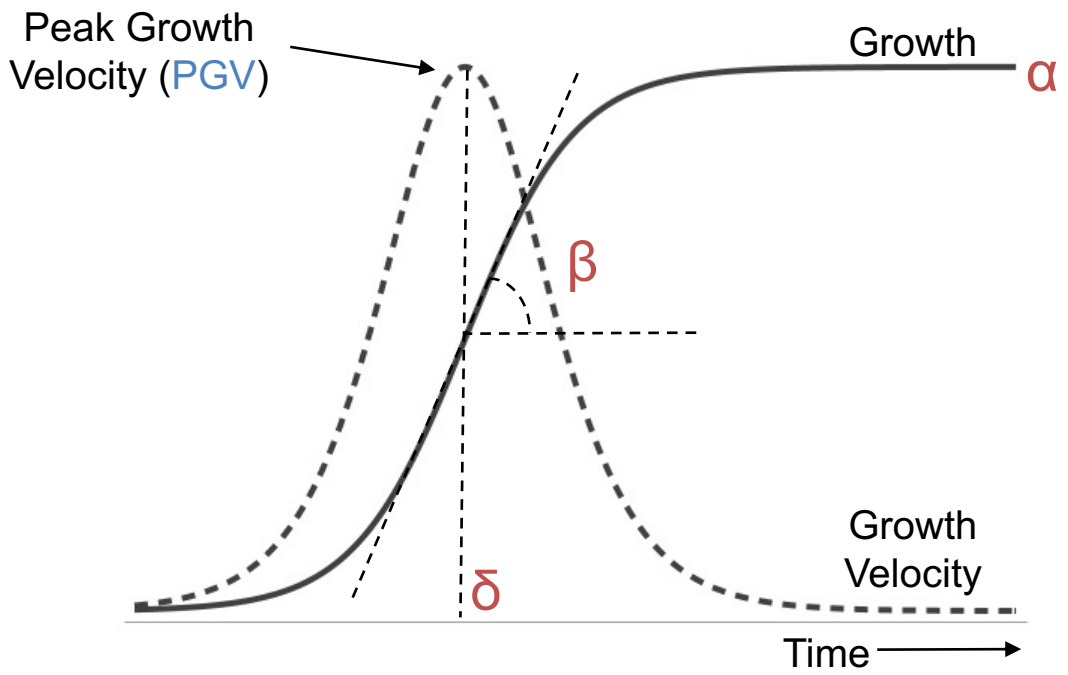
Low birth weight & Centile crossing



- The SELMA study has followed mother and children from early pregnancy until school-age
- Repeated weight measures has been collected (up to 15 times per child)
- Each child's weight trajectory was modeled using a double-logistic growth model
- The estimated growth parameters:
  - Birthweight z-scores
  - **β**= infant growth spurt rate (kg/months)
  - **δ** = age at peak growth velocity (months)



Adapted from Tanner et al., 2020



Adjusted associations between WQS index and children´s growth, overall and by sex, n=1,118

	Overall (n=1,118)	Boys‡ (n=584)	Girls‡ (n=534)	
	Beta (95%CI), p-value	**Beta (95%CI), p-value**	**Beta (95%CI), p-value**	**p-value$_{int}$**
Birthweight Z-scores	-0.11 (-0.16, -0.06), **<0.001**	-0.22 (-0.37, -0.07), **0.004**	-0.29 (-0.44, -0.14), <0.001	0.526
Infant growth spurt slope (kg/months) **(β)**	-0.01 (-0.03, -0.004), **0.007**	-0.08 (-0.11, -0.05), **<0.001**	-0.05 (-0.08, -0.01), 0.005	0.103
Infant age at PGV (months) **(δ)**	0.15 (0.07, 0.24), **<0.001**	-0.04 (-0.30, 0.22), 0.760	0.51 (0.26, 0.76), <0.001	**0.002**

Abbreviations: PGV = Peak growth velocity.

†Adjusted for maternal age, BMI, education, smoking, parity, child's sex and gestational age at birth. Stratified models were not adjusted for sex.

‡Results are derived from the model with interaction term WQS*sex and allowing for sex-specific weights. The p-value$_{int}$ is for the interaction term WQS*sex.

Svensson et al., 2021

Overall† and sex-specific weights‡ in the WQS linear regression analysis of prenatal EDC mixture exposure and children's gowth characteristics (N=1,118)

Components of the EDC mixture				Birthweight z-scores			Infant growth spurt rate			Age at infant PGV		
Matrix	**Chemical Class**	**Parent Compound (*if applicable*)**	**Analyte**	**Overall** Weights (%)	**Boys** Sex-specific weights (%)	**Girls** Sex-specific weights (%)	**Overall** Weights (%)	**Boys** Sex-specific weights (%)	**Girls** Sex-specific weights (%)	**Overall** Weights (%)	**Males** Sex-specific weights (%)	**Females** Sex-specific weights (%)
Urine	Phthalates	DEP	MEP	2.9	3.2	3.3	**4.3**	3.4	**6.6**	**7.5**	3.3	**10.9**
		DBP	MBP	**6.1**	1.1	**9.0**	0.1	3.4	0.1	1.0	1.6	0.4
		BBzP	MBzP	2.0	1.9	**7.0**	2.0	**3.8**	0.7	**4.7**	**4.0**	3.1
		DEHP	SumDEHP	2.0	0.8	3.5	3.1	1.6	1.9	1.0	2.2	
		DINP	SumDINP	<0.1	0.9	<0.1	3.5	3.0	**9.6**	1.3	0.9	0.8
		DiDP/DPHP	MHiDP	0.6	1.1	<0.1	0.1	1.6	0.8	<0.1	3.1	0.7
			MCiNP	**9.0**	**4.6**	**9.9**	0.2	**7.4**	**4.3**	1.6	**8.0**	**7.9**
	Plasticizer	DiNCH	MOiNCH	3.8	**10.7**	0.6	**7.5**	**4.1**	**9.5**	**10.9**	**5.3**	**7.8**
		TTP	DPP	0.9	2.6	0.4	**15.7**	**8.9**	**6.7**	**5.7**	3.3	2.0
	Antibacterial		Triclosan	**11.6**	**16.7**	**4.0**	**13.9**	**8.0**	**5.8**	**4.9**	3.2	**7.2**
	Bisphenols		BPA	0.8	1.9	0.9	1.2	3.3	1.7	**11.4**	**3.9**	**9.1**
			BPF	0.1	2.0	0.2	**5.5**	3.5	3.5	2.5	2.9	1.3
			BPS	**7.7**	**9.2**	2.4	0.5	**3.8**	0.6	2.9	3.3	2.1
	PAH		2OHPH	**10.4**	**7.8**	**7.4**	2.1	**4.1**	**4.8**	1.7	**8.1**	**6.5**
	Pesticide	Chlorpyrifos	TCP	0.6	**5.9**	<0.1	3.0	**5.4**	2.5	3.2	**5.1**	1.2
		Deltamethrin	3PBA	1.5	1.3	**7.4**	**4.1**	**4.1**	**10.2**	2.9	**5.9**	**7.0**
Serum	PFAS		PFOA	**12.6**	**5.8**	**11.2**	**14.1**	3.0	**16.1**	**27.7**	**6.0**	**22.7**
			PFOS	2.1	1.1	**5.5**	0.3	2.6	0.7	<0.1	2.6	<0.1
			PFNA	2.1	1.0	**4.8**	1.5	2.4	2.8	1.1	2.8	**4.2**
			PFDA	**6.2**	**4.9**	**5.7**	**5.2**	1.5	**6.5**	0.1	**6.1**	0.3
			PFUnDA	0.6	1.3	0.6	0.9	3.2	0.5	<0.1	3.2	0.4
			PFHxS	1.0	1.7	1.0	<0.1	3.3	0.2	0.8	3.7	0.7
Plasma	Organo-chlorine pesticide		HCB	**11.2**	**8.2**	**6.9**	2.0	**4.2**	0.4	0.2	1.0	0.3
			Trans-Nonachlor	1.0	1.7	1.0	<0.1	2.4	0.4	0.3	3.7	0.7
		DDT	DDT/DDE	3.5	1.3	**7.2**	0.9	2.7	0.7	0.3	1.5	0.1
	PCB		SumPCB	<0.1	1.6	0.2	**8.4**	**5.4**	2.5	**6.4**	**5.4**	2.7

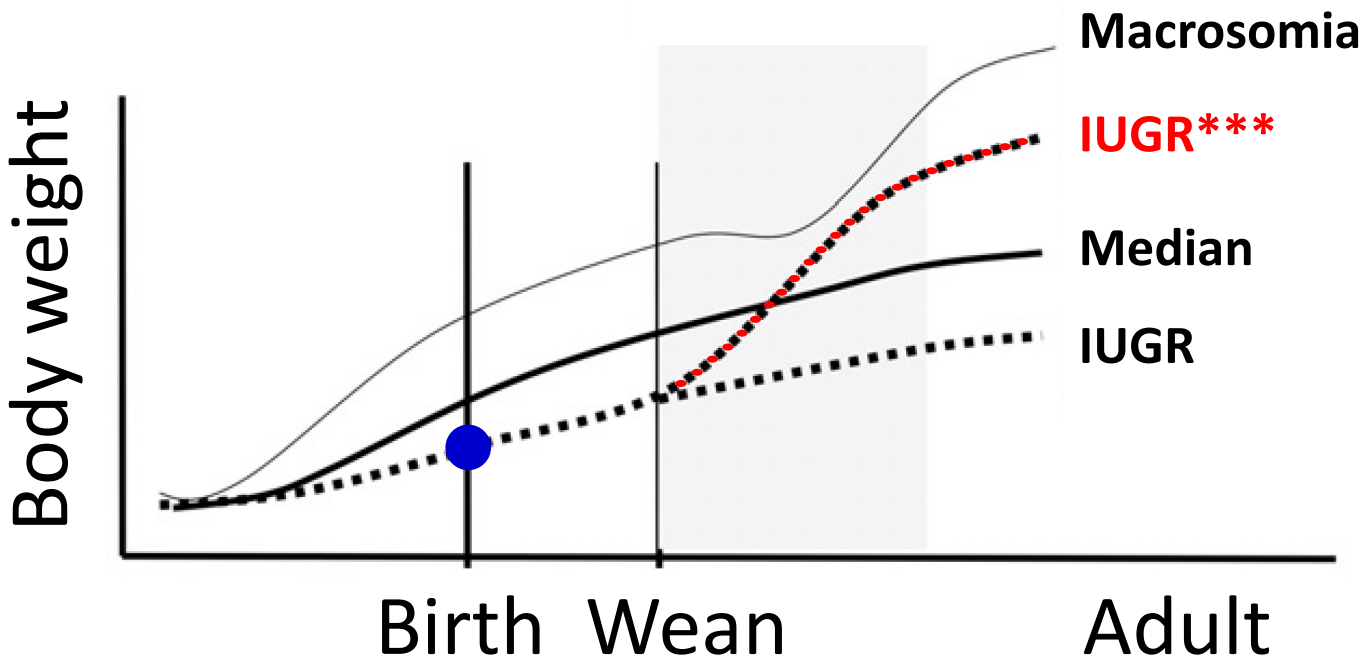
†Adjusted for maternal BMI, education, smoking, parity, child's sex and gestational age at birth. Stratified models were not adjusted for sex.

‡ Weights represent the percentage attributable to each component of WQS index, and the sex-specific weights is that percentage calculated within each group

Svensson et al., 2021

David Barker hypothesis

Low birth weight & Centile crossing



Take home message

- Humans are typically exposed to chemicals found in food packaging material (e.g., phenols, phthalates, PFAS, etc.)
- Human exposure is typically consisted of compolicated mixtures of single compounds, but risk assessment is based on a single comopound approach
- Advanced biostatistical models (e.g., WQS-regression) can handle complicated mixture exposures in epidemiology
- Epidemiological results are showing that prenatal exposure for mixtures of chemicals can be associated to health outcomes, e.g., neurodevelopment at 7y and weight trajectory from birth up to school age
- *Experimental studies have confirmed findings from epidemiolgical studies, e.g., prenatal exposure for a mixture of phthalates and a shorter anogenital distanse (AGD) in male humans and male mice (Bornehag et al., 2015; 2019)*