



EDC-MixRisk
safe chemicals for future generations

Novel Approaches for Chemical Mixture Risk Assessment

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Risk assessment strategies

		Single compound approach
Exposures		Single chemicals of interest
Evidence of risk	Epidemiological	Qualitative evaluation
	Experimental dose response (BMD, PODs, RfDs, etc.)	Guideline values (PODs/RfDs for humans; BE/HBM values)
		Hazard Quotient (HQ) Exposure/RfDs > 1

Published guideline values for urinary DBP, BBzP, DEHP and DINP

Diester	Metabolites in Mixture S0	Observed concentration in SELMA (N=2,313)		Published HBM or BE Values
		95 th percentile	99 th percentile	
DBP	MBP	239	590	2,700
BBzP	MBzP	102	257	3,800
DEHP	Sum of 4 metabolites	11	35	400
DINP	Mono-carboxyoctyl phthalate (MCOP)	77	261	1,500

Risk assessment strategies

		Single compound approach	Cumulative risk approach
Exposures		Single chemicals of interest	Groups of interest (assuming additivity) Co-exposures
Evidence of risk	Epidemiological	Qualitative evaluation	Qualitative evaluation
	Experimental dose response (BMD, PODs, RfDs, etc.)	Guideline values (PODs/RfDs for humans; BE/HBM values)	Guideline values (PODs/RfDs for humans)
Risk evaluation		Hazard Quotient (HQ)	Hazard Index (HI)
		Exposure/RfDs > 1	$\Sigma HQ > 1$

Risk assessment strategies

		Single compound approach	Cumulative risk approach	Whole mixture approach
Exposures		Single chemicals of interest	Groups of interest (assuming additivity) Co-exposures	Human relevance Co-exposures
Evidence of risk	Epidemiological	Qualitative evaluation	Qualitative evaluation	Selection of bad actors (WQS, etc.)
	Experimental dose response (BMD, PODs, RfDs, etc.)	Guideline values (PODs/RfDs for humans; BE/HBM values)	Guideline values (PODs/RfDs for humans)	BMD for reference mixture(s)
Risk evaluation		Hazard Quotient (HQ) Exposure/RfDs > 1	Hazard Index (HI) $\Sigma HQ > 1$	Test for sufficient similarity SMRI SMRI > 1



Research for a **healthier** future

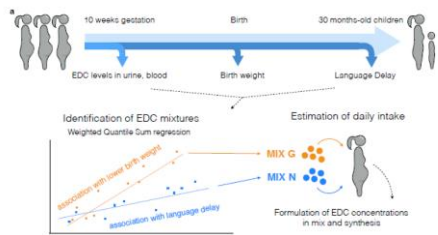
Swedish Environmental Longitudinal, Mother and child, Asthma and allergy study

**REAL LIFE CHEMICAL MIXTURES
BASED ON URINE/SERUM LEVELS
FROM +2,300 PREGNANT
WOMEN IN THE SELMA STUDY**

Whole mixture approach

four steps for risk assessment of chemicals
integrating human epidemiology and
experimental toxicology

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

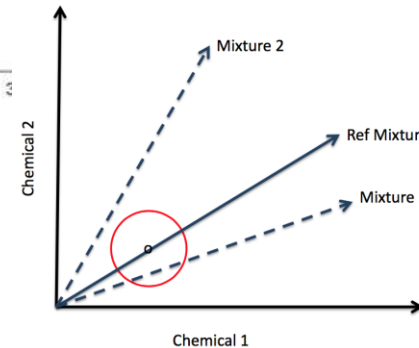
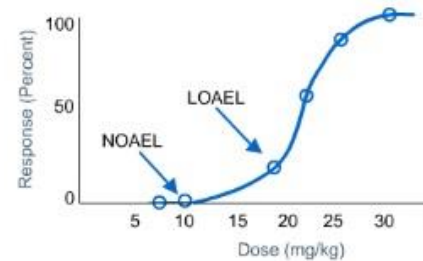


Mixture S
Mixture N
Mixture G

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



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

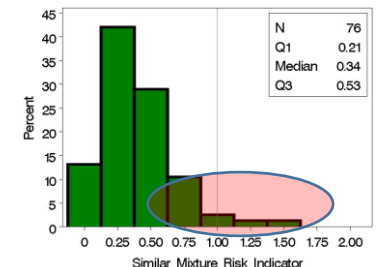
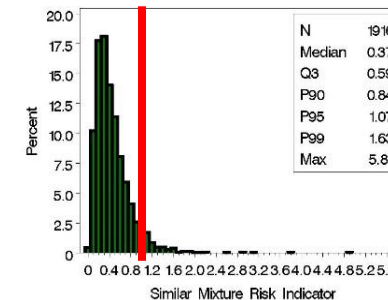


Sufficient Similarity Approach (SMACH)

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

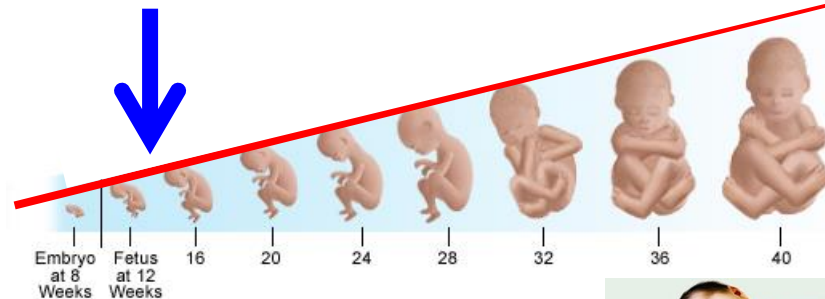
4b
For sufficient similar
subgroups; test for
extreme mixing
proportions,
SMRI>1 (%)

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



Natural hormones

Estrogen
Testosterone
Thyroids. etc.



20/54 EDCs
(N=+2,300)

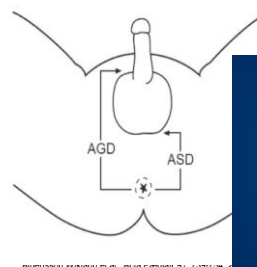
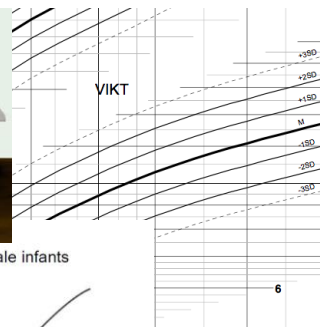
Mixtures

Metabolism and growth (G)
Sexual development (S)
Neurodevelopment (N)

Health and development



AGD measures in male infants

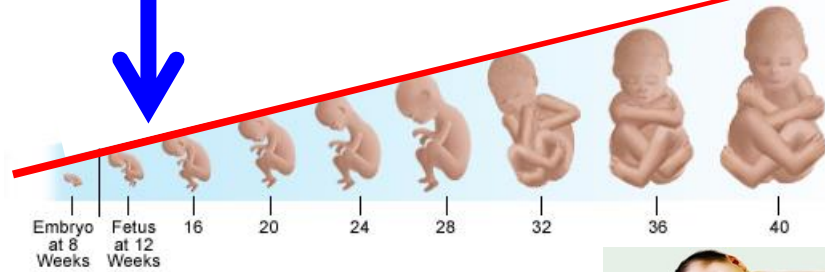


Analysis strategy in three steps for Mixture 0

1. Identification of bad actors for the three health domains
 - Weighted quantile sum (WQS) regression (Carrico, 2015)

Natural hormones

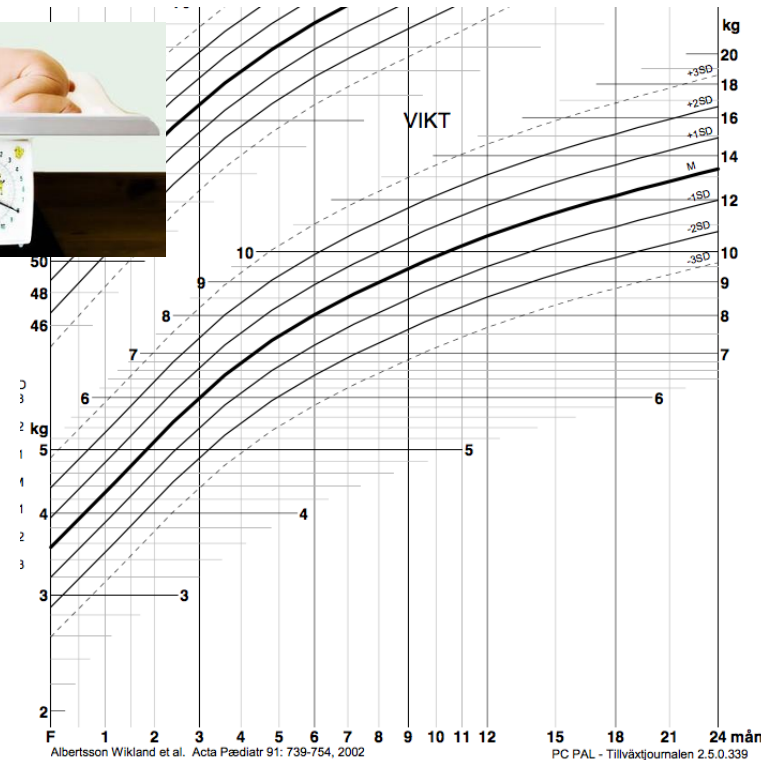
Estrogen
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20/54 EDCs
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Mixture G

Metabolism and growth

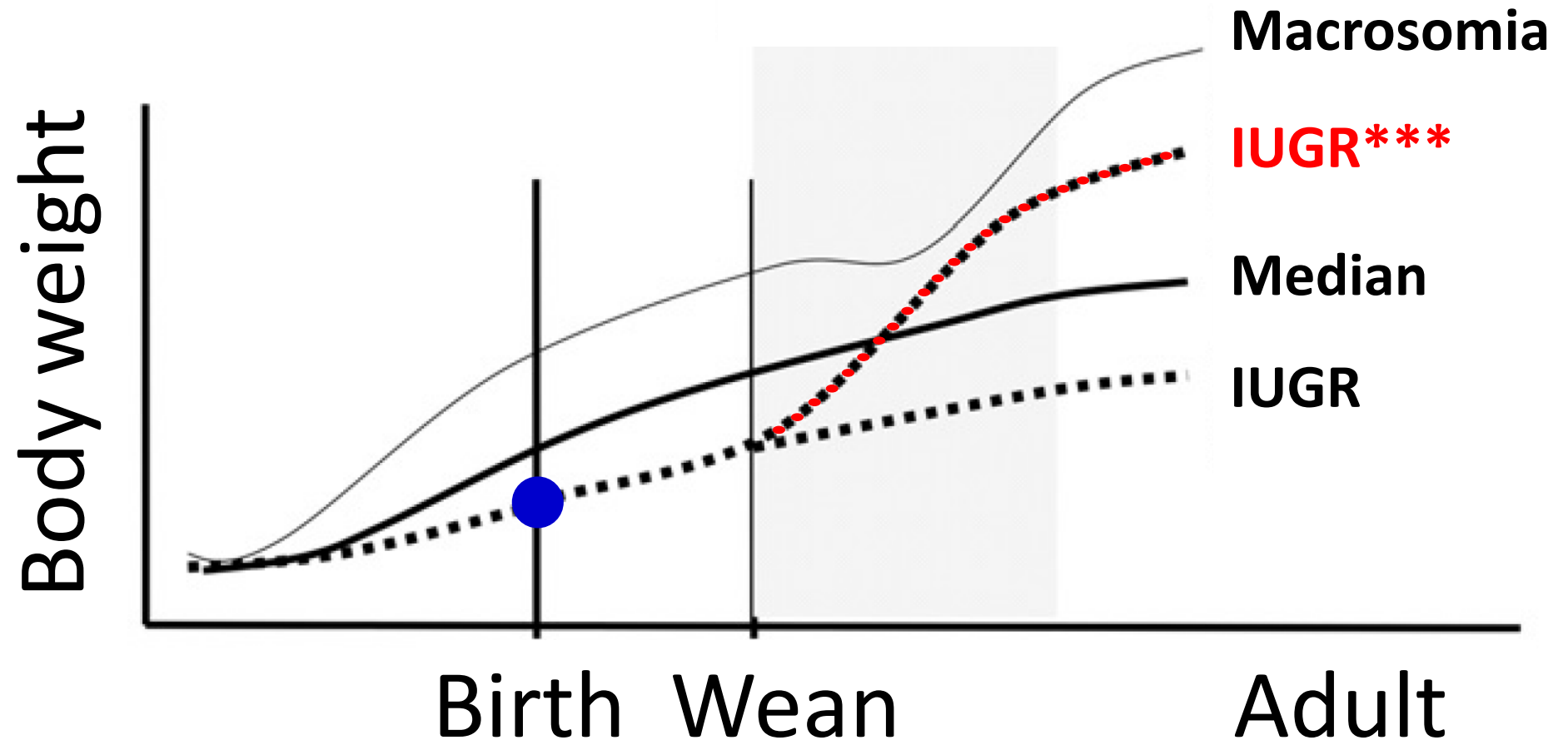




David Barker (1938-2013)

The fetal period is important for chronic diseases later on in life, e.g., hypertonia, diabetes, cardiovascular diseases...

Low birth weight & Centile crossing



Analysis strategy in three steps for Mixture 0

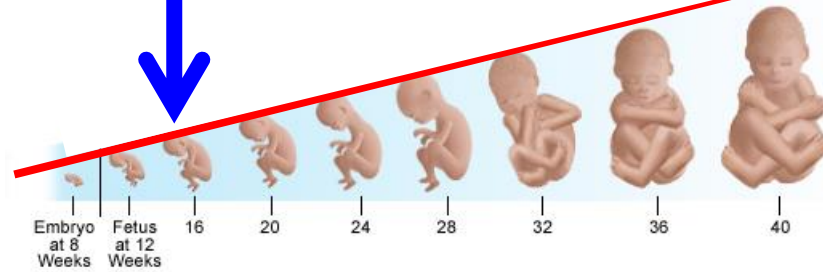
1. Identification of bad actors for the three health domains
 - Weighted quantile sum (WQS) regression (Carrico, 2015)
2. Estimation of serum levels of bad actors
 - Estimation of daily intake (DI) of urinary based bad actors (Koch et al., 2007)
 - Using toxicokinetic models (Fromme et al., 2007) estimating the plasma concentrations from DI
 - The PFASs were measured directly in serum levels

Analysis strategy in three steps for Mixture 0

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 - Using toxicokinetic models (Fromme et al., 2007) estimating the plasma concentrations from DI
 - The PFASs were measured directly in serum levels
3. Establishment of relevant mixtures, to be evaluated in experimental studies in cell and animal models
 - Estimation of mixing proportions of bad actors using serum levels in +2,300 pregnant women in SELMA
 - The mixing proportions were calculated in molar units across the chemicals

Natural hormones

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Thyroids. etc.



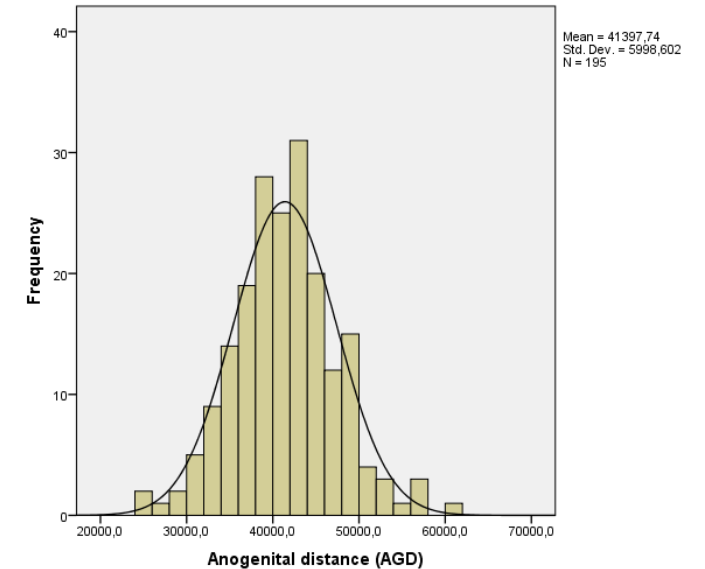
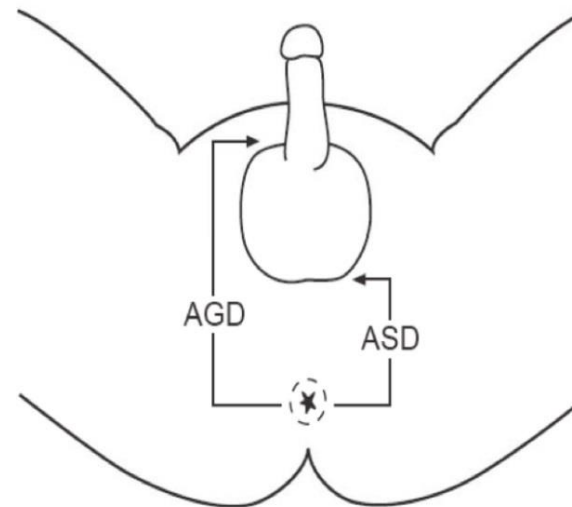
15 COMPOUNDS

Phthalates
Phenols
PFASs

Sexual development & fertility



AGD measures in male infants



Mixture S0

Identification of bad actors among 20 EDCs

Using Weighted Quantile Sum (WQS) regression

Determination of a typical mixture 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 where 1X refers to SELMA

DBP

2.3 E-08

33%

BBzP

1.1 E-08

16%

DEHP

1.5 E-08

21%

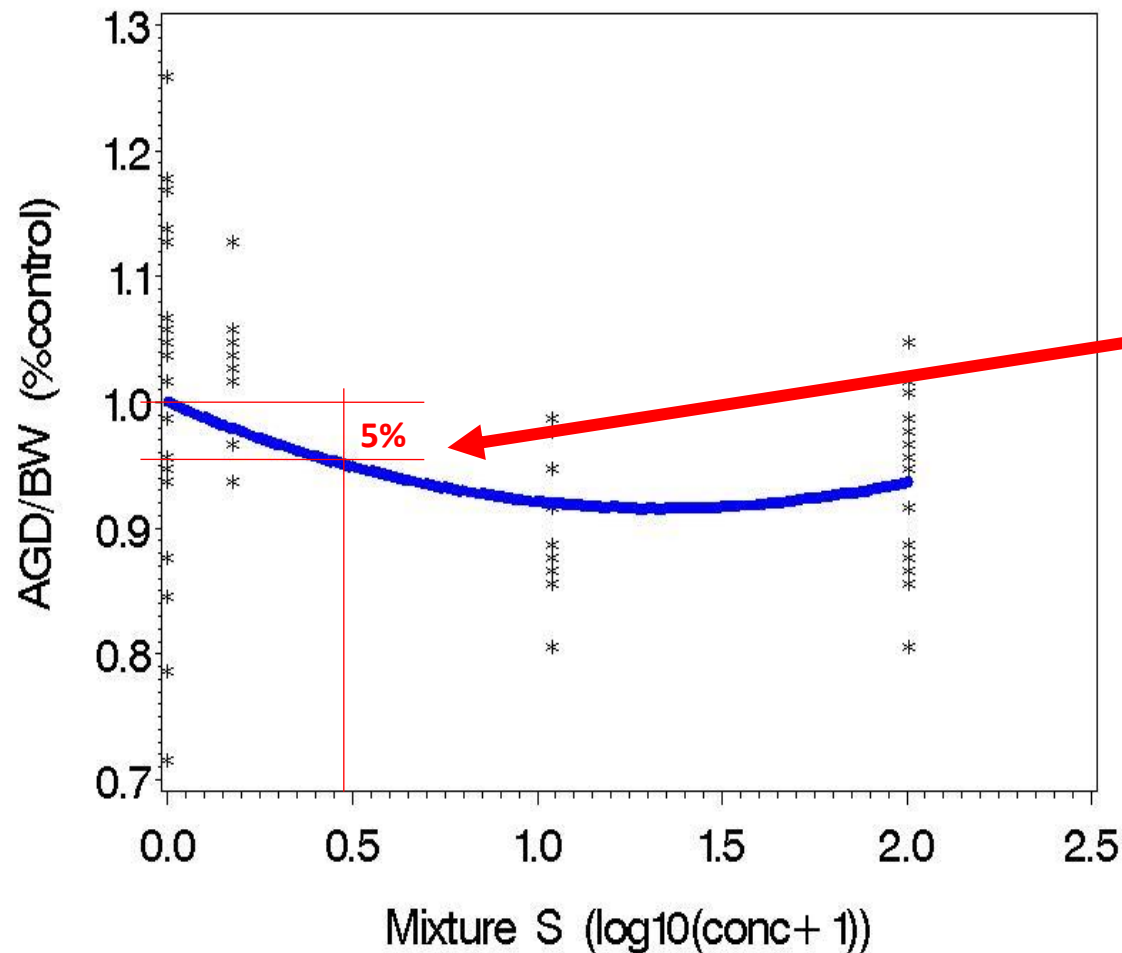
DiNP

2.1 E-08

30%



Test for dose-response relationship between Mixture S and AGD/BW in male mice



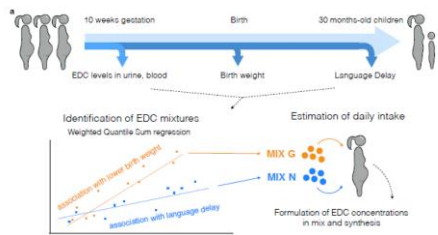
With a benchmark response (BMR) of a 5% decline in AGD/BW, the estimated benchmark dose (BMD) was 0.49 on the log scale

$10^{0.49} - 1 = 2.1X$ of "typical" SELMA exposure

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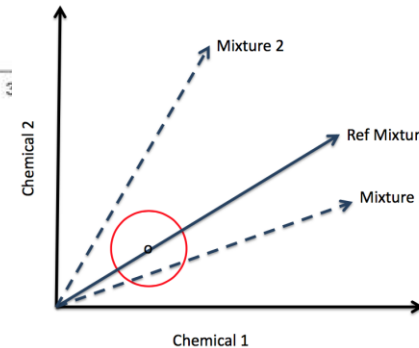
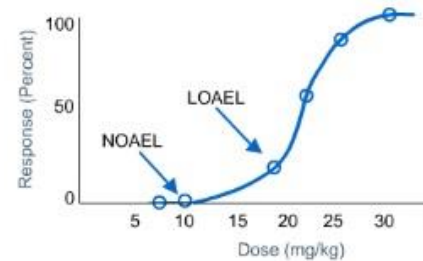


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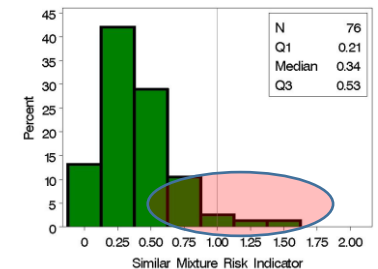
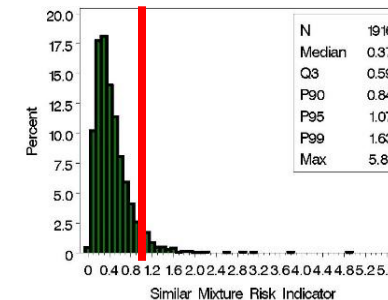


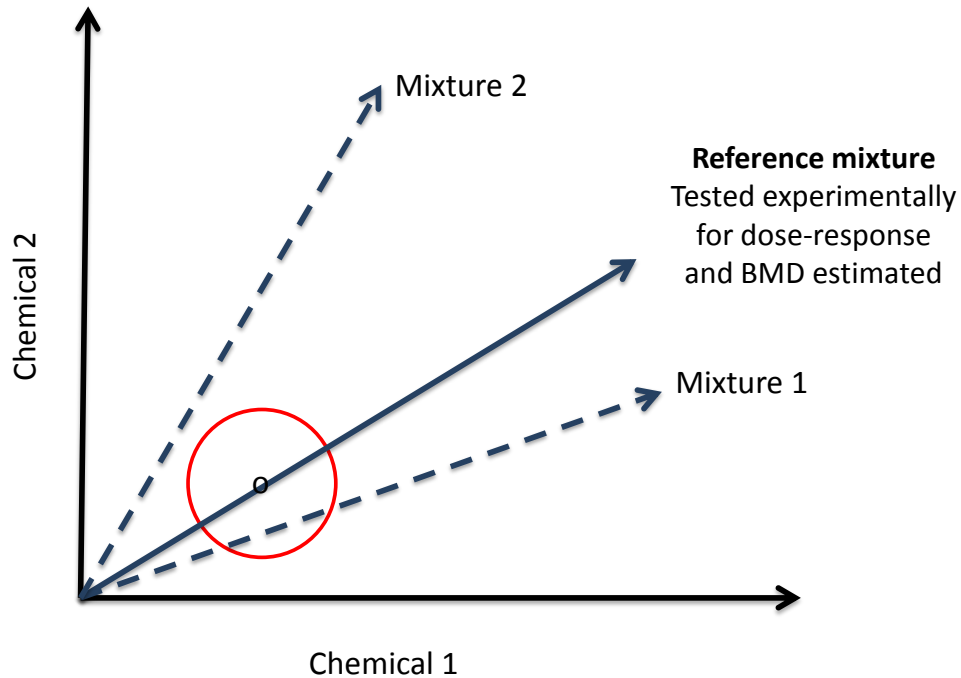
Table 5. Association between AGD in boys and log-transformed concentrations of phthalate metabolites in prenatal urine from an adjusted^a linear regression model.

Phthalate	Metabolite	AGDas		AGDap	
		β (95% CI)	<i>p</i> -Value	β (95% CI)	<i>p</i> -Value
DBP	MBP	−1.41 (−4.39, 1.57)	0.351	−2.06 (−5.29, 1.18)	0.211
DEP	MEP	0.63 (−1.29, 2.54)	0.518	−1.30 (−3.40, 0.81)	0.225
BBzP	MBzP	−1.66 (−3.56, 0.25)	0.088	−0.65 (−2.74, 1.44)	0.542
DEHP	MEHP	−1.28 (−3.74, 1.17)	0.304	−1.74 (−4.43, 0.95)	0.203
	oh-MEHP	−1.24 (−3.99, 1.51)	0.374	−1.50 (−4.50, 1.49)	0.324
	oxo-MEHP	−0.77 (−3.48, 1.94)	0.576	−1.25 (−4.19, 1.70)	0.406
	cx-MEPP	−0.89 (−3.69, 1.92)	0.534	−0.64 (−3.69, 2.40)	0.677
	ΣDEHP	−1.16 (−4.01, 1.68)	0.420	−1.39 (−4.49, 1.70)	0.375
	DiNP	−1.61 (−3.06, −0.16)	0.029	−1.23 (−2.83, 0.37)	0.131
	oxo-MMeOP	−1.82 (−3.47, −0.17)	0.031	−1.67 (−3.49, 0.15)	0.072
	cx-MMeHP	−1.51 (−3.26, 0.24)	0.091	−1.39 (−3.32, 0.53)	0.156
	ΣDiNP	−1.69 (−3.35, −0.02)	0.047	−1.46 (−3.29, 0.38)	0.119

^aAdjusted for age (months), gestational week of urine sampling, weight-for-age percentile, and creatinine.

4-5% (1.6-1.8 mm) reduction of AGDas in baby boys in SELMA

4a. Sufficient similarity

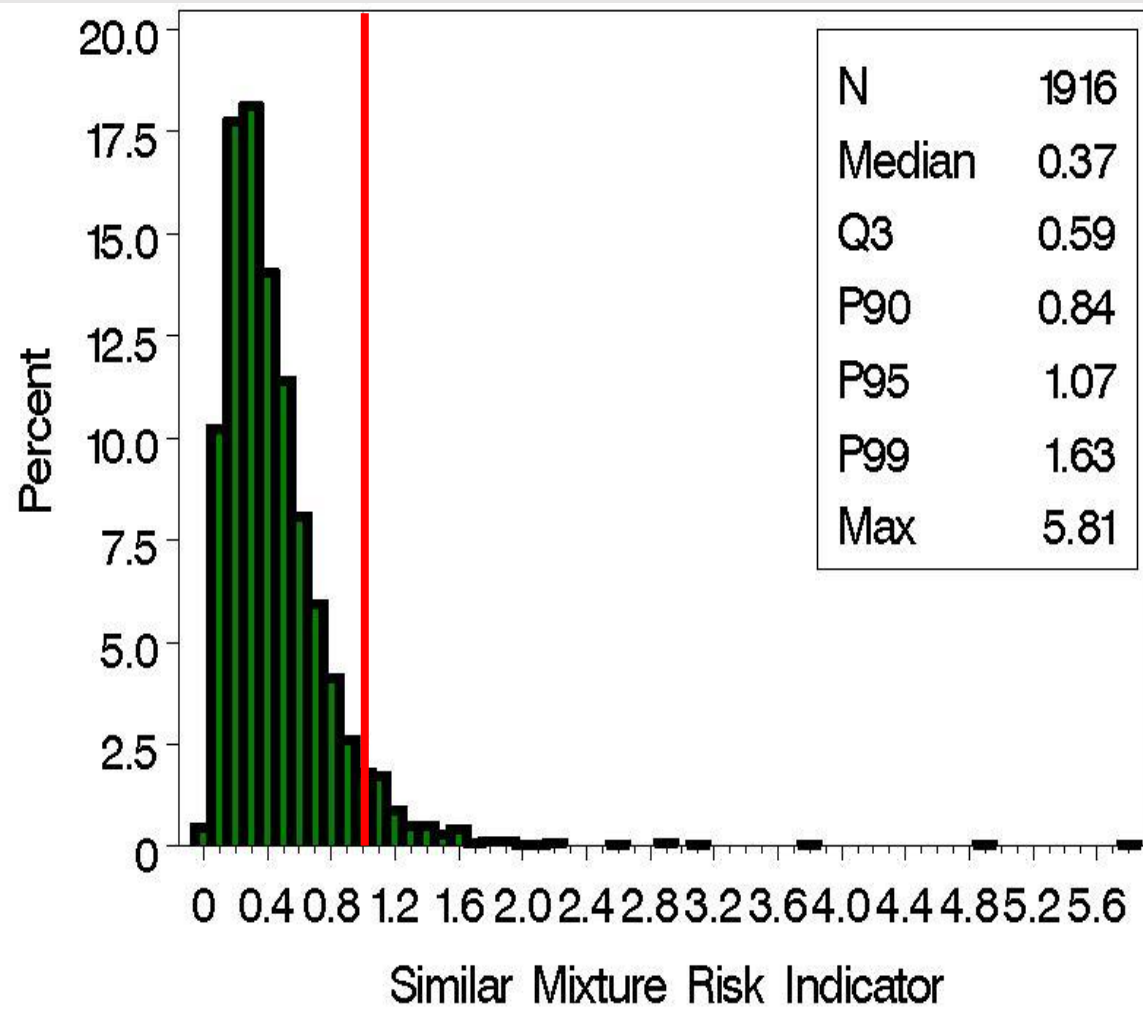


$$\hat{d}_i = \hat{T}_r \sqrt{\sum_{j=1}^4 (a_{ij} - a_{rj})^2}$$

BMD with BMR=0.95	0.49 (0.33)
ED (0.92)	1.05 (1.30)
Similarity Region Radius	1.05-0.49=0.56

**83% of the SELMA women
(N=1,916 out of 2,313) had
sufficiently similar mixing
proportions to Mixture S**

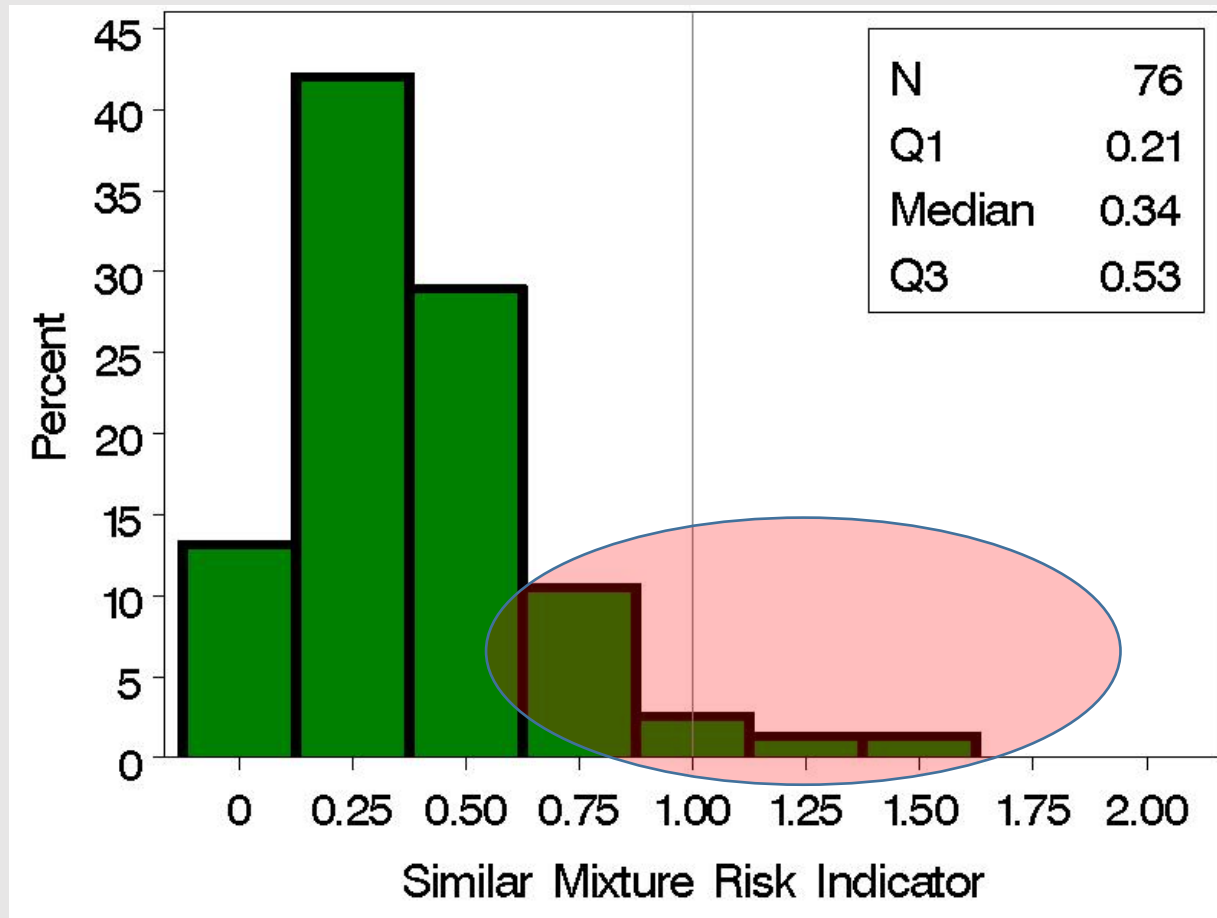
4b. Similar Mixture Risk Index (SMRI)



$$SMRI_i = \sum_{j=1}^4 \frac{E_j}{mRV_j}$$

For the set of sufficiently similar mixtures, roughly 7% of the SELMA women have concentrations extreme relative to the BMD (SMRI>1), corresponding to about 6% of the total population of 2,313 pregnant women

4c. Association between SMRI and AGD in baby boys



**Adjusted* AGDas was 5.9
mm shorter in the 4th vs. 1st
quartile of SMRI (p=0.045)**

*) Adjusted for gestational age at exposure, weight at evaluation, and creatinine

Conclusions

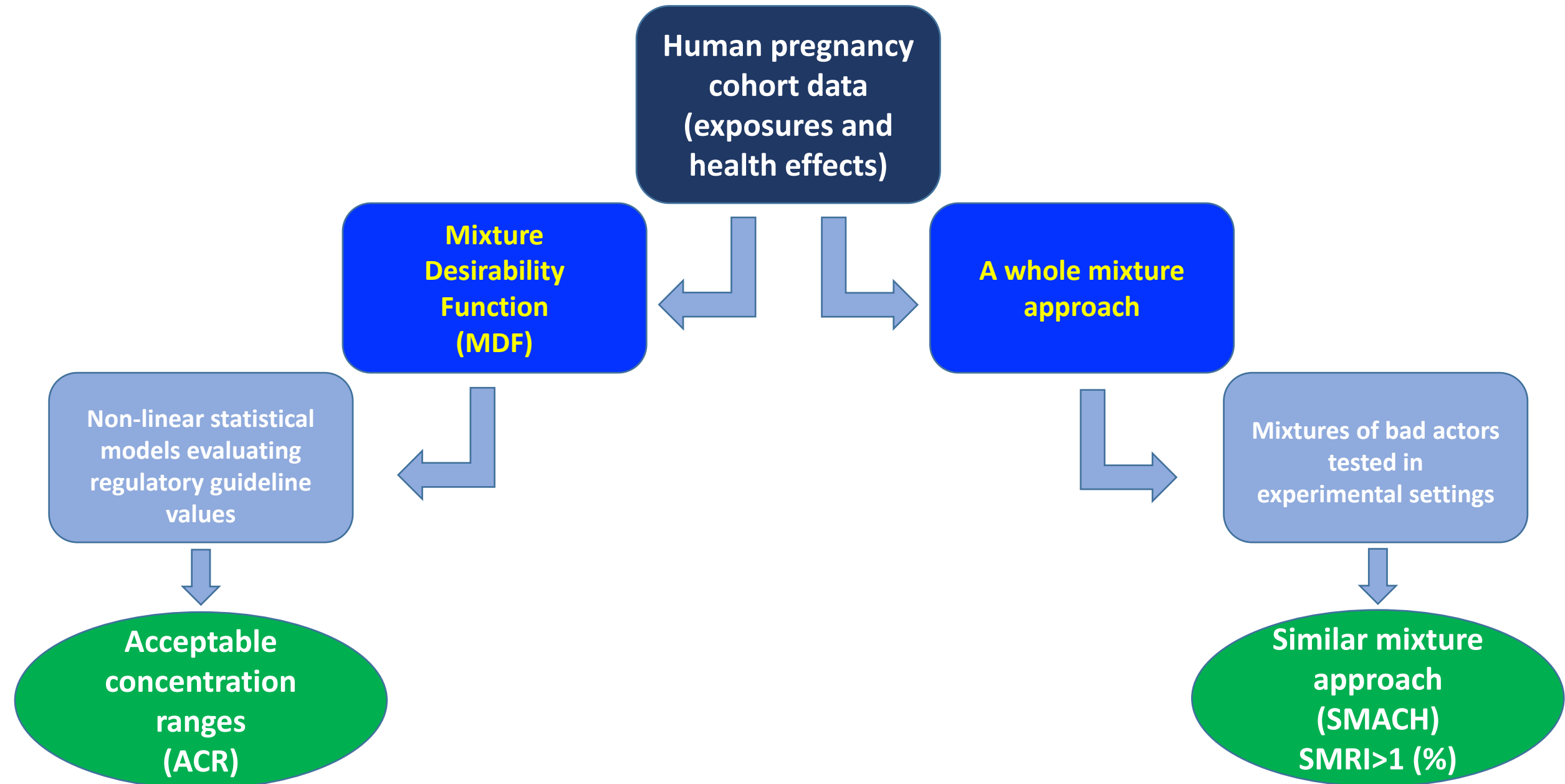
With a whole mixture approach, we could find a higher rate of pregnant women under risk (13%) when comparing with more traditionally models of additivity (HI) (3%), or a compound-by-compound strategy (1.6%), which is the most used risk assessment procedure

Bornehag, Kitraki, Panagiotidou, Stamatakis, Ruden, Shu, Lindh, Ruegg, Gennings

A novel approach to chemical mixture risk assessment - Linking data from population based epidemiology and experimental animal tests by the use of new statistical tools

Risk Analysis, in revision

New approaches for risk assessment of chemical mixtures



Incorporating regulatory guideline values in analysis of epidemiology data

Chris Gennings ^a  , Huan Shu ^b, Christina Rudén ^b, Mattias Öberg ^c, Christian Lindh ^d, Hannu Kiviranta ^e, Carl-Gustaf Bornehag ^{a, f}

Highlights

We introduce a new class of models that include the regulatory concept of “acceptable concentration range” (ACR)

These ACR models complement current risk assessment methods by estimating guideline values using human biomonitoring data

The results suggest that chemical-by-chemical approaches underestimate risk by a factor that range from 1 to 100 for different chemicals

On-going work

Analyses of all experimental data for Mixture 0

Analysis of Mixture 1 data

54 chemicals

Health outcomes at 7 years of age

Assess generalizability

Test for sufficient similarity in existing biomonitoring data (HB4EU)

Development of mixture assessment factors (MAFs) using ACR



Thank you!

