A Novel Empirical Strategy using Human Biomonitoring Data to Estimate Regulatory Guideline Values

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Biomonitoring Equivalents (BEs) & HBM values

Definition: The concentration or range of concentrations of a chemical or its metabolite **in a biological medium** (blood, urine, or other medium) that is consistent with an existing **health-based exposure guide-line**.

- derived by integrating available data on pharmacokinetics with existing chemical risk assessments.
- may be used with population biomonitoring data in a risk assessment context.

Krishnan et al 2010 Reg Tox and Pharm;
http://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/human-biomonitoring-commission-hbm-commission

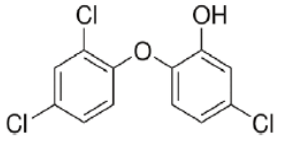
HBM Commission

"To achieve a harmonized assessment of humans internal exposure to pollutants, the HBM Commission determines **guidance values** (reference and HBM values) for selected substances according to defined criteria."

http://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/human-biomonitoring-commission-hbm-commission

HBM Commission: Triclosan

HBM-I: Precautionary
HBM-II: Health Hazard

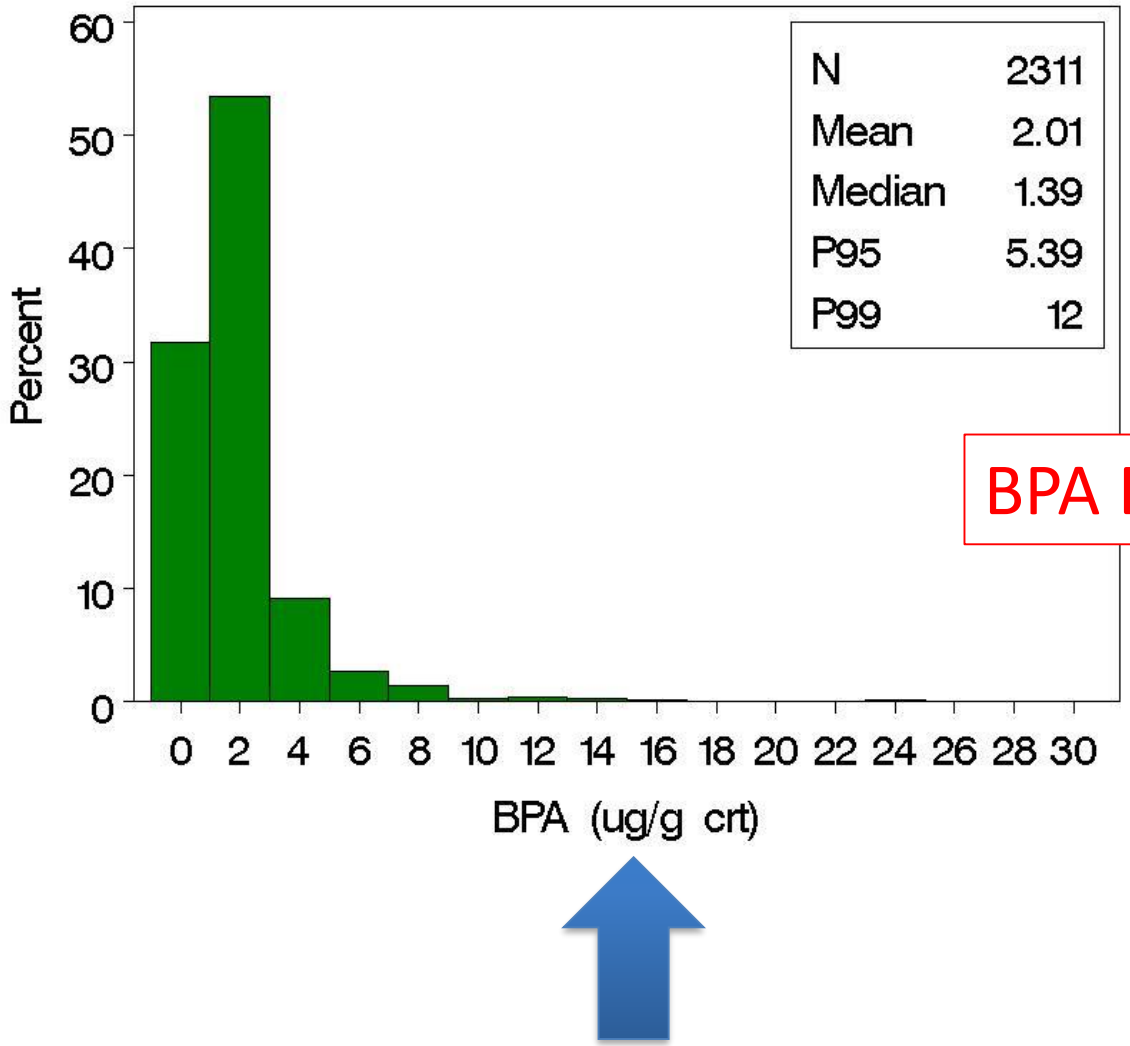
Derivation of HBM value for **TRICLOSAN** based on **BE – documentation**			
Substance	5-chloro-2-(2,4-dichlorophenoxy)phenol		
Parameter	**Value / Descriptor**	**Dimension**	**Comments**
HBM Guide value			
Guide value II (HBM-II, Health hazard value)	-	mg/l	not derived
Guide value I (HBM-I, Precautionary value)	children: 2 adults: 3	mg/l	(morning) urine, total triclosan (rounded value)
Year of issue	2015		
status	final		
General Information			
CAS No. substance	3380-34-5		
IUPAC name	5-chloro-2-(2,4-		

Tab. 1: NHANES 2009-2010 Triclosan concentrations in children and adults compared to HBM-I value. Margin of Safety is calculated as the ratio of the HBM-I value to the biomarker concentration.

Population	n	HBM-I	GM, mg/L	95th%ile. mg/L	MOS at GM	MOS at 95th %ile
Children, 6-11	415	2.16	0.0109	0.200	198	10.8
Adults, 20+	1914	3.24	0.0155	0.544	209	6.0

http://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/human-biomonitoring-commission-hbm-commission

Case Study: Prenatal Concentrations of BPA in SELMA pregnant women



BPA BE = 2.6 mg/g crt

Case Study: Schematic for derivation of BE values for BPA

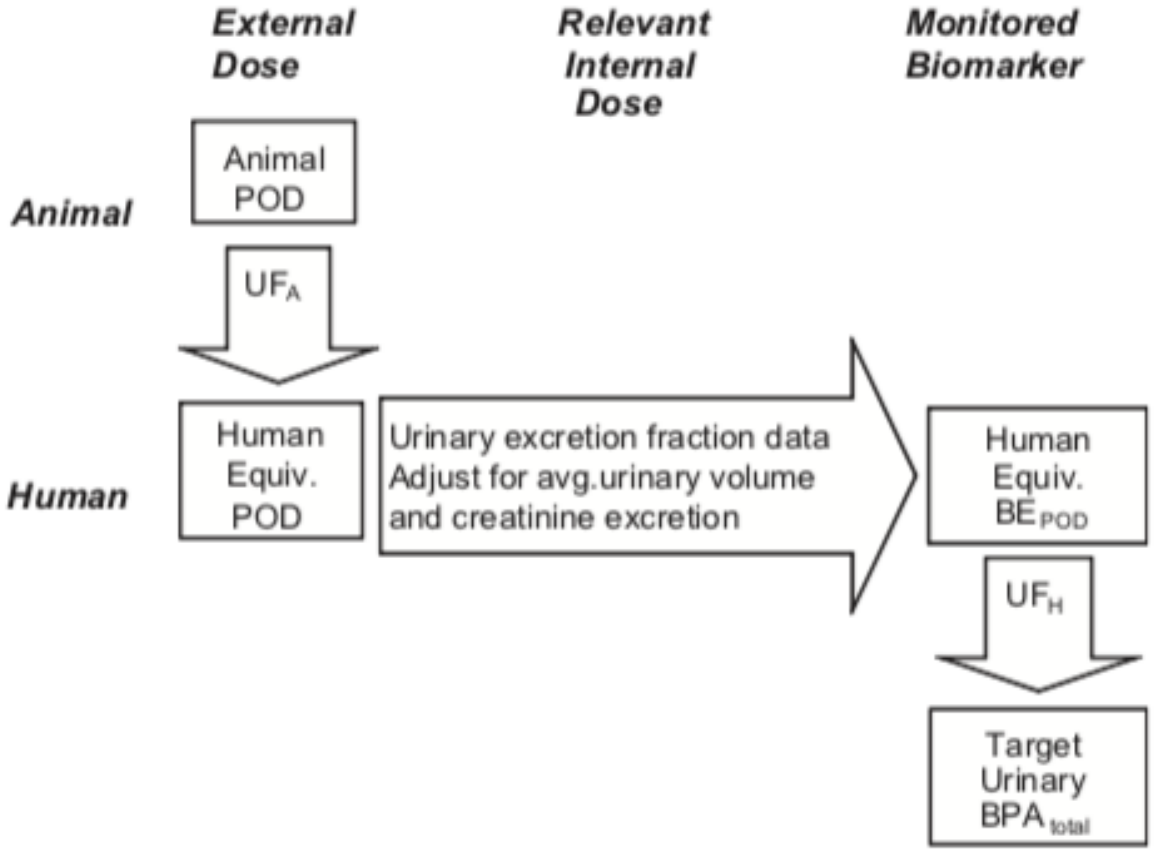


Fig. 1. General schematic for derivation of urinary BE values for BPA (Animal POD: 50 mg/kg/d (US EPA, 1993), 25 mg/kg/d (Health Canada, 2008) and 5 mg/kg/d (EFSA EU, 2006).

Krishnan et al 2010 Reg Tox and Pharm

Case Study: Health-based exposure guidance values for BPA

Table 1
Health-based exposure guidance values for BPA from various agencies.

Organization, criteria (year of evaluation)	Study description	Critical endpoint and dose	Uncertainty factors	Value
pTDI[a] (Health Canada, 2008)	90-day study in rats (NTP, 1982)	Reduced mean body weight NOEL: 500 ppm diet (25 mg/kg/day)	1000 – 10 for for subchronic to chronic extrapolation – 10 for interspecies differences – 10 for inter-individual differences	25 μg/kg-d
RfD[b], (IRIS US EPA, 1993)	Rat Chronic Oral Bioassay (NTP, 1982)	Reduced mean body weightLOAEL: 1000 ppm diet (50 mg/kg/day)	1000 – 10 for LOAEL-NOAEL extrapolation – 10 for interspecies differences – 10 for inter-individual differences	50 μg/kg-d
TDI[c], (EFSA-EU, 2006)	Three-generation study in the rat(Tyl et al., 2002)(supported by 2 generation study of Tyl et al., 2008)	Reductions in adult body weight and pup body and organ weightNOAEL of 5 mg/kg bw/day	100 – 10 for interspecies differences – 10 for inter-individual differences	50 μg/kg-d

Note: LOAEL – lowest observed adverse effect level, NOAEL – no observed adverse effect level, NOEL – no observed effect level.

[a] pTDI: provisional tolerable daily intake. This value represents an updated review of the toxicological literature on BPA, and the provisional designation reflects the recognition by Health Canada that additional toxicological research is ongoing to address issues raised by recent studies.

[b] RfD: reference dose, for chronic exposure.

[c] TDI: tolerable daily intake.

Krishnan et al 2010 Reg Tox and Pharm

Case Study: Kinetic information for BPA in humans

Table 2
Kinetic information for Bisphenol A in humans.

Species	Study description	Excretion rate	References
Human	Six healthy adult volunteers, orally exposed to 60–80 μg/kg d_{16}-BPA *free BPA was not found in urine	100% was excreted in urine within 96 h ($t_{1/2}$ = 5.4 h)	Völkel et al. (2002)
Human	6 healthy adult volunteers, Orally exposed to 0.35–0.45 μg/kg d_{16}-BPA *low levels of free BPA were found in urine of 2 of the subjects, accounting for 2% of administered dose	84%-97% was excreted in urine within 5 h ($t_{1/2}$ = 4 h)	Völkel et al. (2005)

Krishnan et al 2010 Reg Tox and Pharm

Case Study: Derivation steps

Table 5
Derivation of BE values consistent with exposure guidance values from Table 1. See also Fig. 1 for a schematic representing the process.

BE derivation steps	Exposure guidance value:	pTDI, Health Canada (2008)	RfD, US EPA (1993)	TDI, EFSA (2006)
1	POD, mg/kg-d:	25	50	5
2	Uncertainty factors (LOAEL to NOAEL, subchronic to chronic, and interspecies; see Table 1):	100	100	10
	Human-equivalent POD, mg/kg-d:	0.25	0.5	0.5
3	BPA concentration in urine per unit dose, mg/L per mg/kg-d:	39.6	39.6	39.6
	(mg/g creatinine per mg/kg-d):	(51.0)	(51.0)	(51.0)
	BE_{POD}, mg/L:	10	20	20
	(mg/g creatinine):	(13)	(26)	(26)
4	UF_H:	10	10	10
	BE, mg/L:	1	2	2
	(mg/g creatinine):	(1.3)	(2.6)	(2.6)

Note: BE – biomonitoring equivalent, BE_{POD} – biomonitoring equivalent point of departure, POD – point of departure, pTDI – provisional tolerable daily intake, RfD – reference dose, UF_H – inter-individual uncertainty factor, TDI – tolerable daily intake.

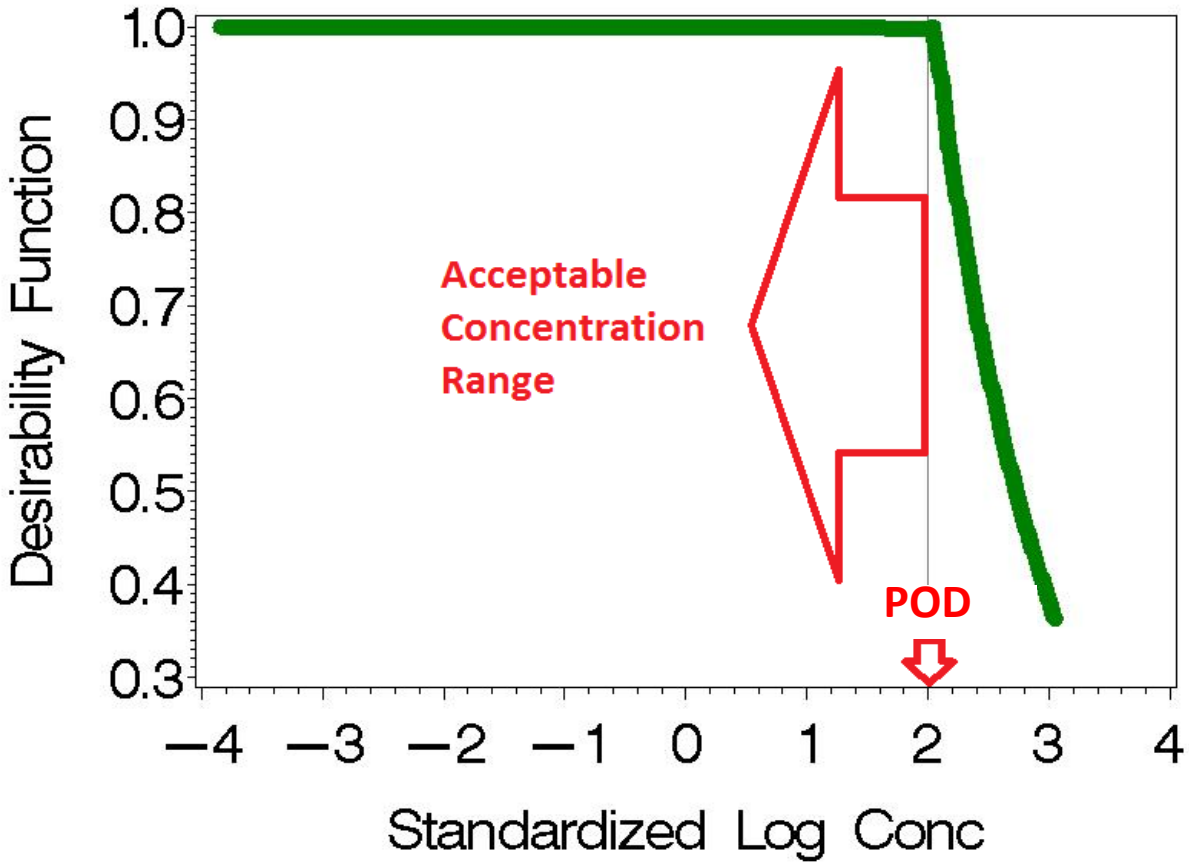
Krishnan et al 2010 Reg Tox and Pharm

Extension to Mixtures

Humans are exposed to many environmental chemicals, so why consider guidance values based on single chemical *in vivo* studies?

Can we estimate guidance values from observational human data which includes real world mixtures?

Motivation of ACR Models: HBM/BE values and Desirability Functions



Desirability Functions: Harrington 1965 Ind Qual Con

Desirability Functions embedded in a model: The ACR model (Gennings et al 2018 ENV INT)

Models include the risk assessment concept of "**acceptable concentration range**"

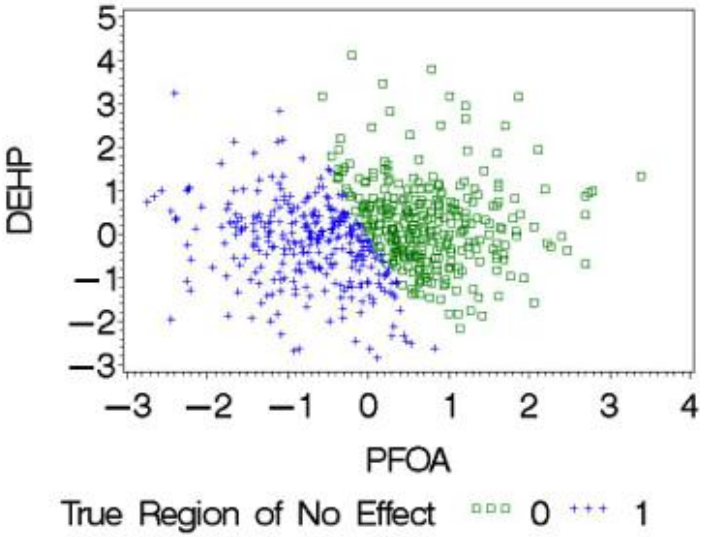
$$g(m) = b_0 + b_1 \exp\left[- g\left(x - d\right)\left\{ I\left(x > d\right)\right\}\right] + \sum_{c=1}^{C} q_c z_c$$

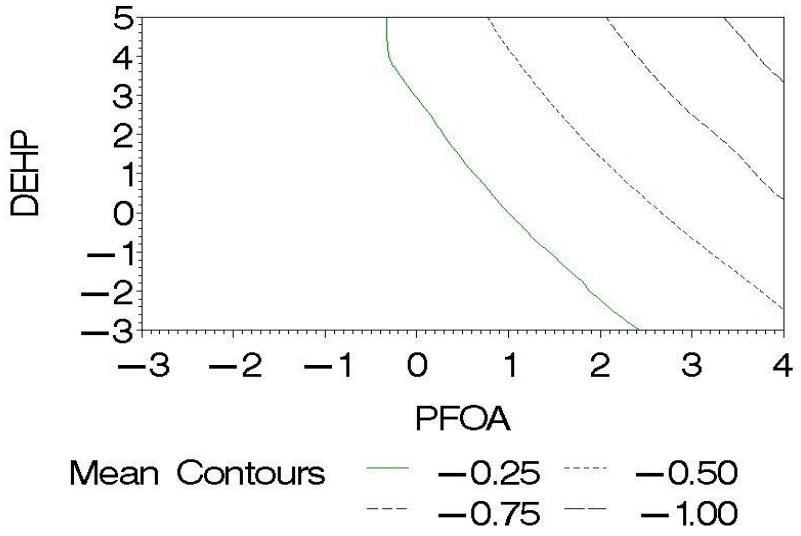
d_j

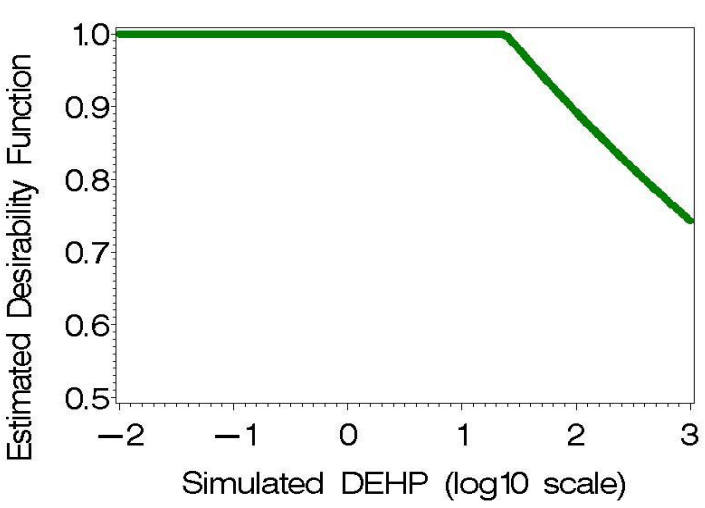
"join point parameter"

$$g(m) = b_0 + b_1\left(d_1 \times d_2 \times \ldots \times d_K\right)^{1/K} + \sum_{c=1}^{C} q_c z_c$$

Illustration with Simulated Data for PFOA and DEHP







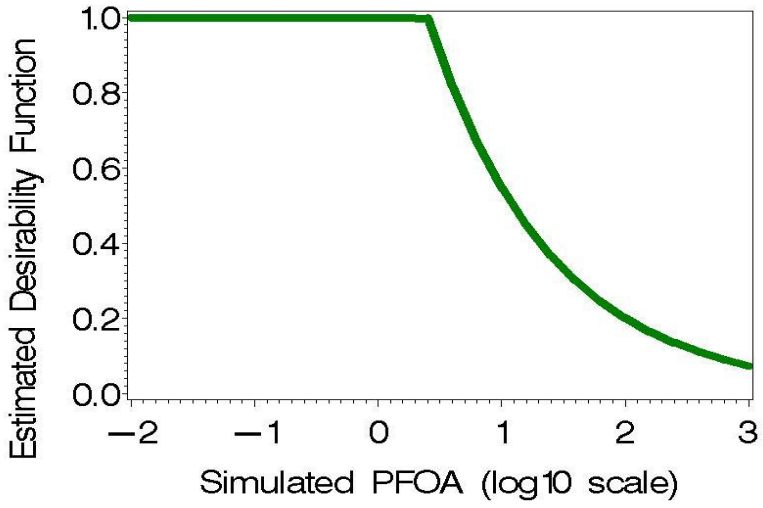
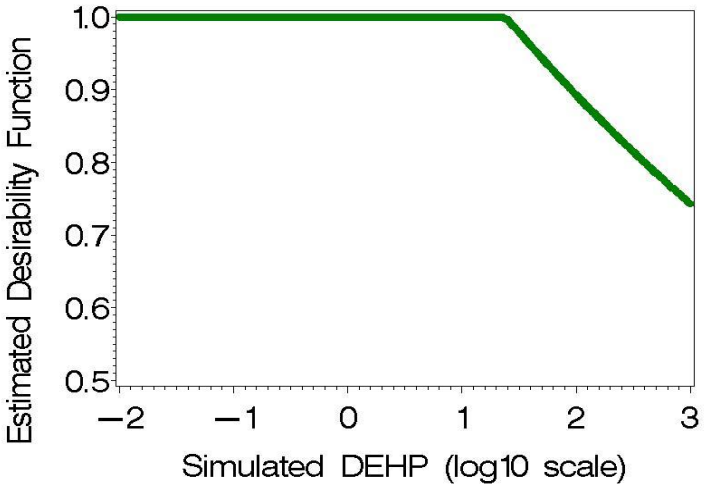
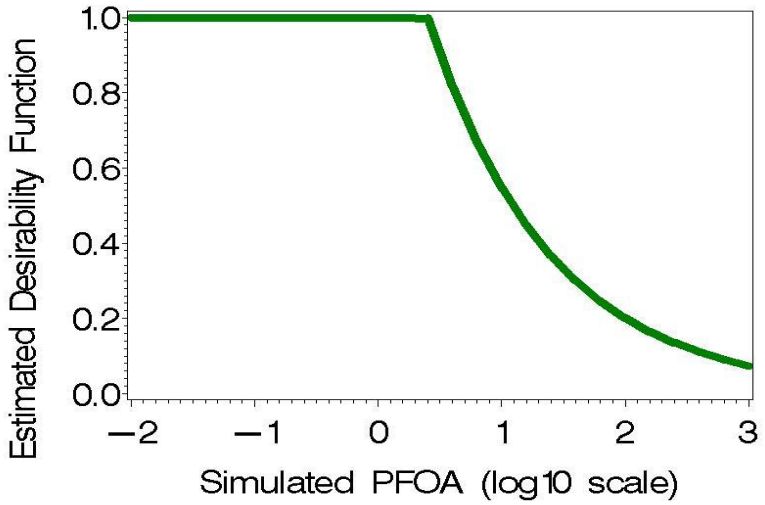
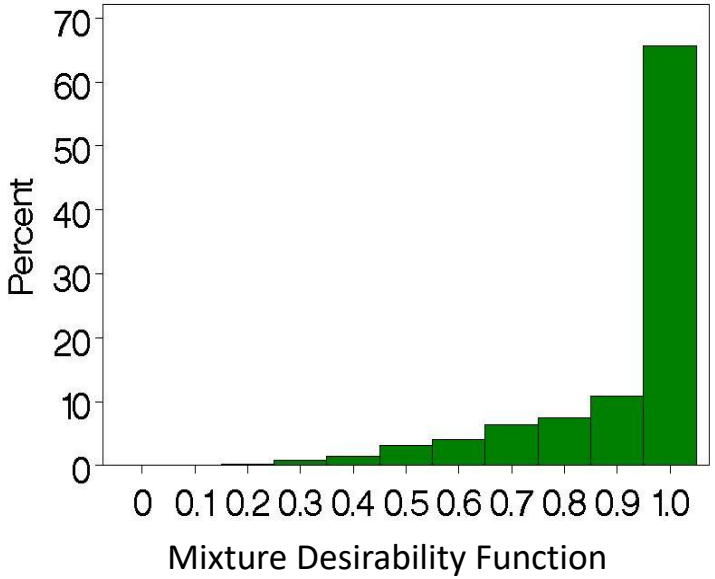
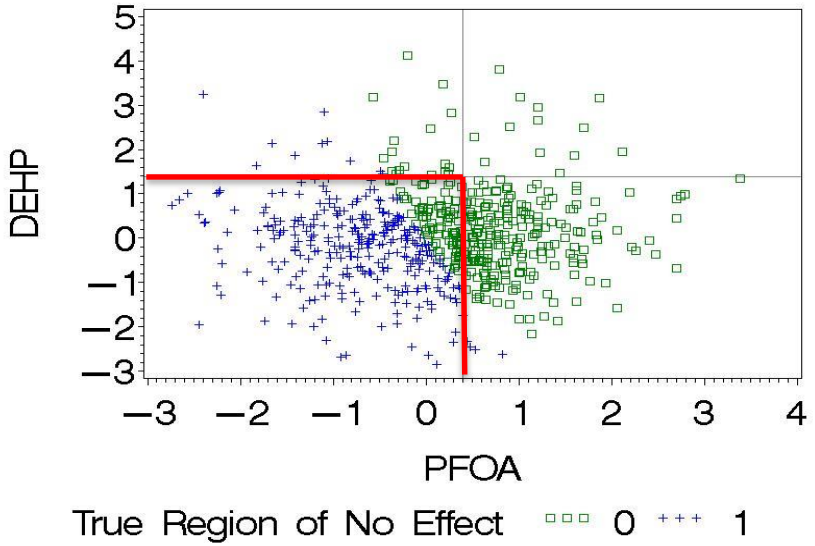


Illustration with Simulated Data for PFOA and DEHP









SELMA pregnancy cohort

Swedish pregnancy cohort

2,300+ prenatal samples (1st Tri)

Children's developmental health:
- Metabolism/growth
- Neurodevelopment
- Sexual development

Here we use
- Birthweight
- Language delay at 2.5 yrs

Research for a healthier future

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

1st trimester serum levels of persistent compounds (POPs) in 2,354 SELMA women

Published BE/HBM1 Values

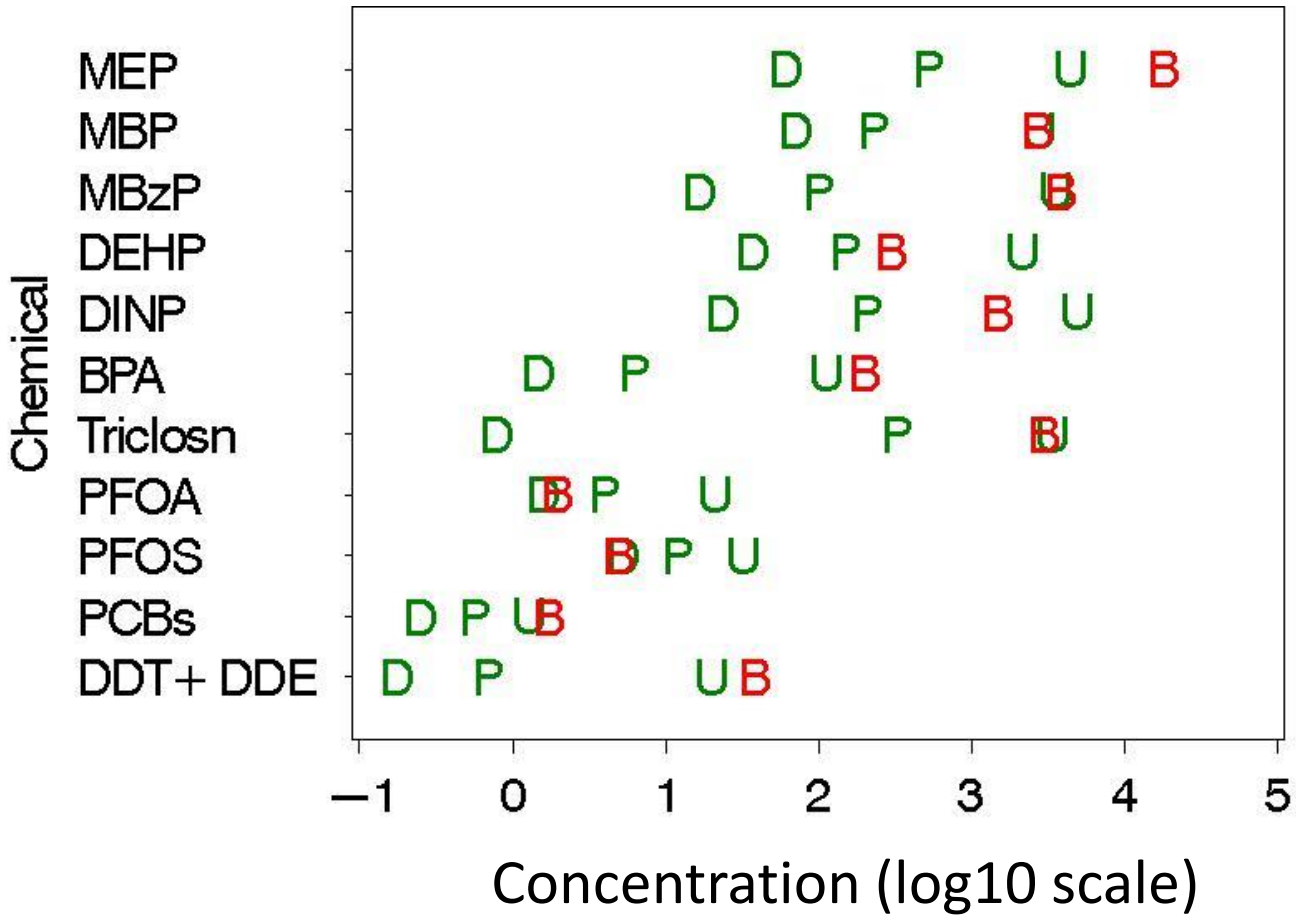
Compound (pg/mL)	>LOQ (%)	LOQ	Min	Median	95%	Max	Geometric Mean (95% CI)
PeCB	0,0	10	5,00	5,00	5,00	5,00	-
HCB	**99,9**	-	5,00	44,27	77,75	211,49	44.12(43.51-44.72)
alpha_HCH	0,3	20	10,00	10,00	10,00	115,89	10.04(10.00-10.07)
beta_HCH	39,1	15	7,50	7,50	37,52	3136,21	11.90(11.59-12.23)
gamma_HCH	0,0	20	10,00	10,00	10,00	24,62	10.003(9.996-10.011)
Oxychlordane	0,3	25	12,50	12,50	12,50	235,32	12.56(12.51-12.60)
Trans_nonachlor	**74,3**	5	2,50	7,81	21,95	219,44	7.10(6.89-7.31)
pp_DDT	8,6	15	7,50	7,50	22,20	1407,74	8.48(8.32-8.64)
pp_DDE	**99,4**	40	20,00	167,34	683,30	18482,18	183.38(177.71-189.24)
PCB_74	**70,1**	5	2,50	6,50	17,39	313,76	6.01(5.84-6.18)
PCB_99	**78,4**	5	2,50	7,66	18,50	64,53	7.00(6.82-7.18)
PCB_118	**98,0**	5	2,50	15,45	36,60	245,47	15.35(15.01-15.71)
PCB_153	**100,0**	-	9,98	106,30	243,60	542,28	103.58(101.35-105.85)
PCB_138	**100,0**	-	7,82	70,20	160,08	447,68	68.42(66.96-69.92)
PCB_156	**87,6**	5	2,50	11,25	27,81	69,26	10.29(10.01-10.59)
PCB_187	**96,3**	5	2,50	17,74	45,16	109,96	16.91(16.47-17.37)
PCB_183	**73,7**	5	2,50	7,43	18,99	54,54	6.64(6.46-6.82)
PCB_180	**100,0**	-	5,13	75,05	175,04	426,23	71.93(70.24-73.66)
PCB_170	**99,7**	-	2,50	39,09	91,49	216,92	37.60(36.70-38.52)
BDE_47	6,4	15	7,50	7,50	17,52	295,95	8.16(8.05-8.28)
BDE_99	1,4	15	7,50	7,50	7,50	102,19	7.63(7.58-7.68)
BDE_153	2,4	15	7,50	7,50	7,50	242,49	7.75(7.67-7.82)

1st trimester urinary levels of phthalates and phenols in 2,325 SELMA women

Published BE/HBM1 Values

Compound (ng/mL)	>LOQ (%)	LOQ	Min	Median	95%	Max	Geometric Mean (95% CI)
MEP	**100,0**	0,03	1,305	61,99	532,61	4419,35	68.75 (65.64-72)
MnBP	**100,0**	0,3	3,025	71,12	232,71	2718,94	69.13 (66.91-71.43)
MBzP	**100,0**	0,12	0,247	17,13	101,11	3544,51	16.88 (16.14-17.65)
MEHP	**99,6**	0,3	0,150	3,80	17,29	213,09	3.86 (3.72-4.01)
MEHHP	**100,0**	0,06	0,239	16,78	67,46	1012,98	16.62 (16.02-17.23)
MEOHP	**100,0**	0,09	0,045	15,93	65,08	757,17	11.26 (3.72-4.01)
MECPP	**100,0**	0,06	0,046	11,27	46,02	611,77	16.10 (15.55-16.67)
MHiNP	**100,0**	0,06	0,030	6,12	59,17	1726,48	6.42 (6.09-6.76)
MOiNP	**100,0**	0,03	0,049	2,78	20,25	635,49	2.97 (2.84-3.12)
MCiOP	**100,0**	0,06	0,329	9,04	78,28	1661,24	10.03 (9.61-10.48)
BPA	**99,4**	0,15	0,075	1,50	6,34	111,26	1.53 (1.48-1.59)
Triclosan	**74,2**	0,3	0,150	0,76	339,02	3356,79	1.23 (1.12-1.34)

SELMA 1st trimester Concentrations



LEGEND

D = Median

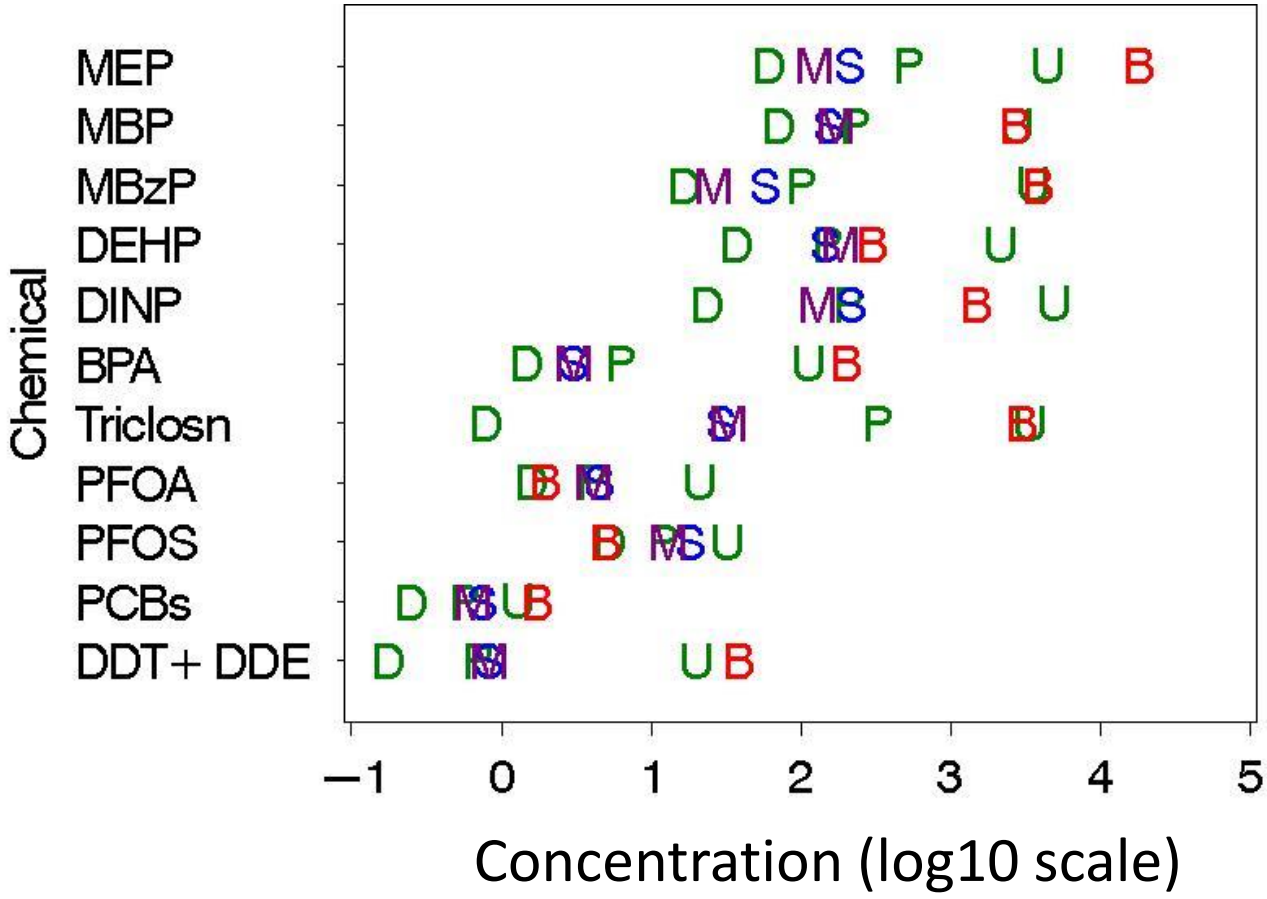
P = P95

U = Maximum

B = BE/HBM1

* PCBs = PCB138 + PCB153 + PCB180

SELMA Language Delay ACR Model



LEGEND

D = Median

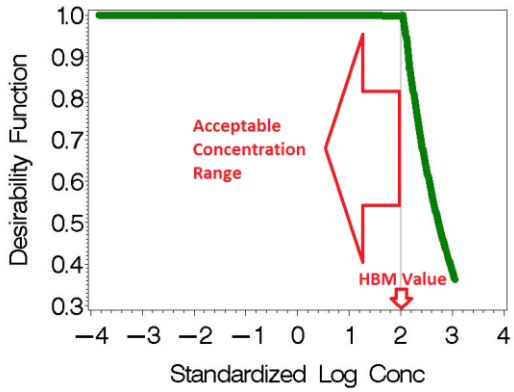
P = P95

U = Maximum

B = BE/HBM1

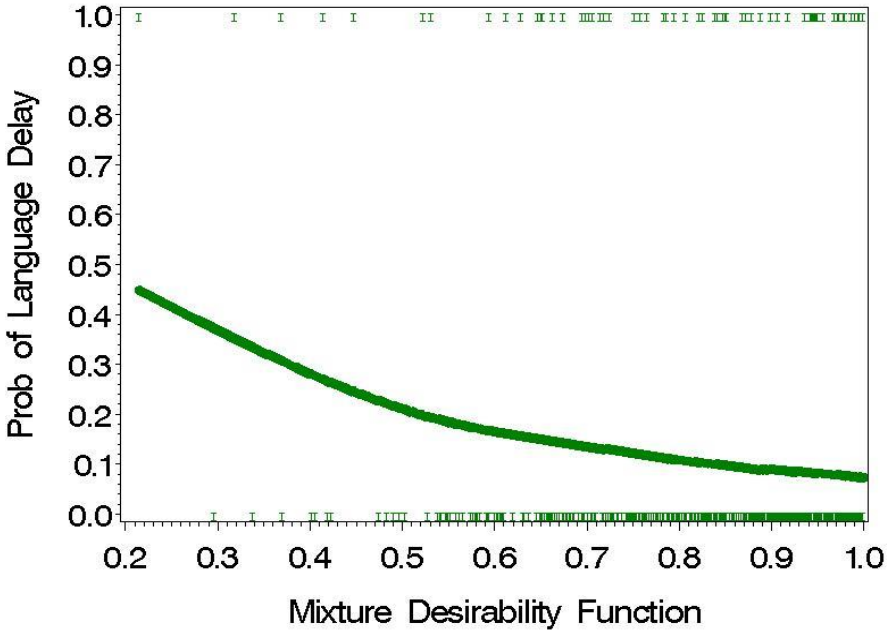
S = ACR Single Chem

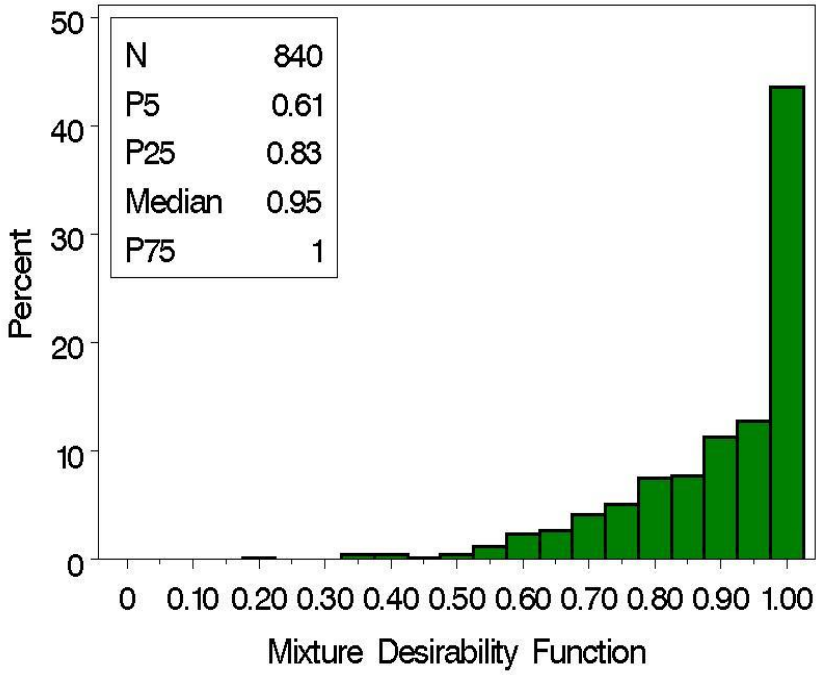
M = ACR Mixture



Mixture Guidance Values: SELMA Language Delay

LOESS plot of language delay and the estimated Mixture Desirability Function which is significantly associated with the **risk of language delay (p=0.008)** from SELMA data, adjusting for sex, creatinine, maternal education, maternal weight, maternal smoking status, and gestational age at birth (N=840)





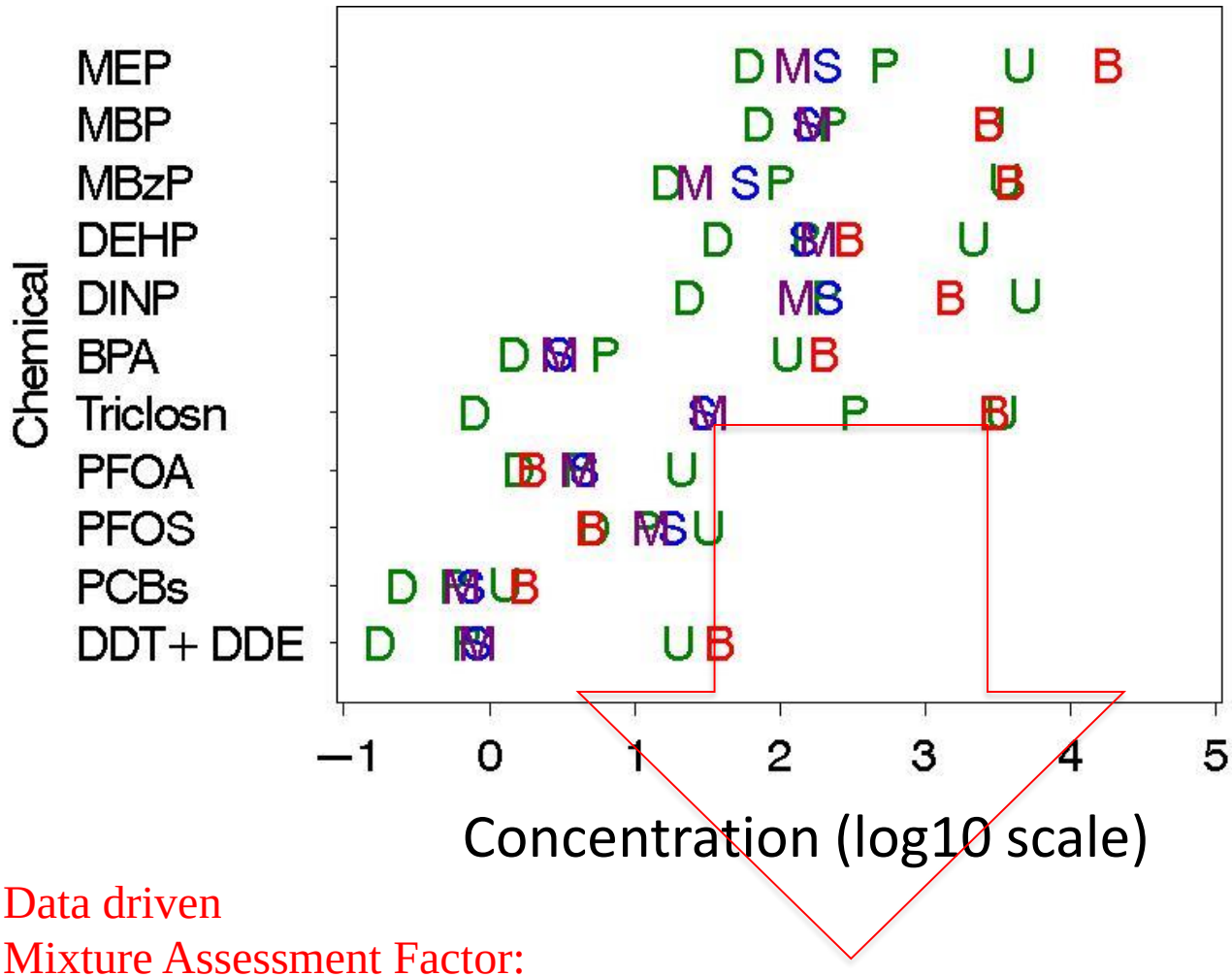
Assuming Established Guidance Values… in the analysis of LD

When the published HBM/BE values were fixed for the join point parameters in the ACR model, the constrained Mixture Desirability Function indicated:

- 75% (vs 45%)of the SELMA women had prenatal concentrations completely in the **acceptable range**; and
- the association with **language delay** was only borderline significant (p=0.068)

-- a **result not born out by** the ACR model with estimated join point values.

SELMA Language Delay ACR Model



LEGEND

D = Median

P = P95

U = Maximum

B = BE/HBM1

S = ACR Single Chem

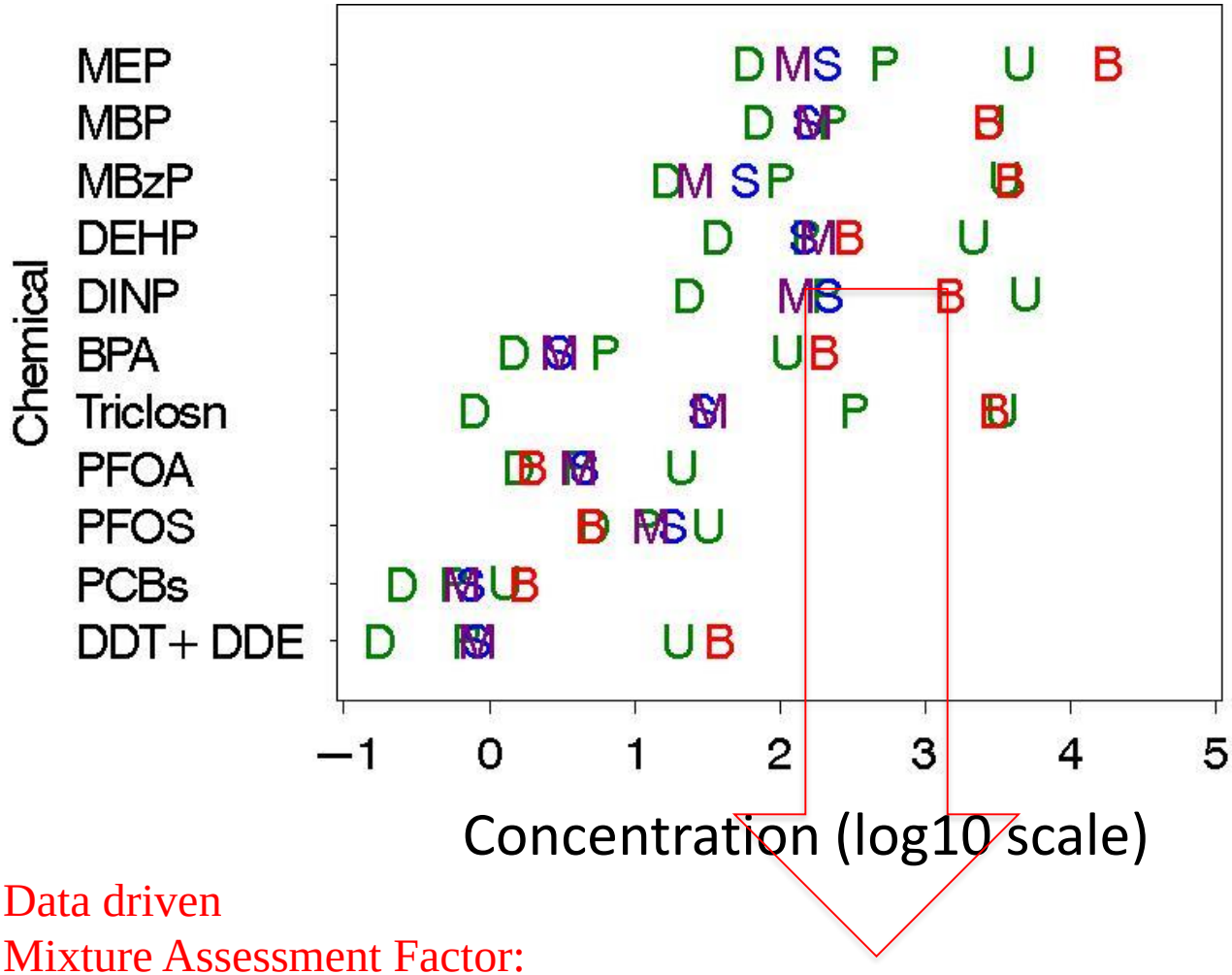
M = ACR Mixture

Data driven

Mixture Assessment Factor:

for Triclosan ~ 2 orders of magnitude = 100

SELMA Language Delay ACR Model



LEGEND

D = Median

P = P95

U = Maximum

B = BE/HBM1

S = ACR Single Chem

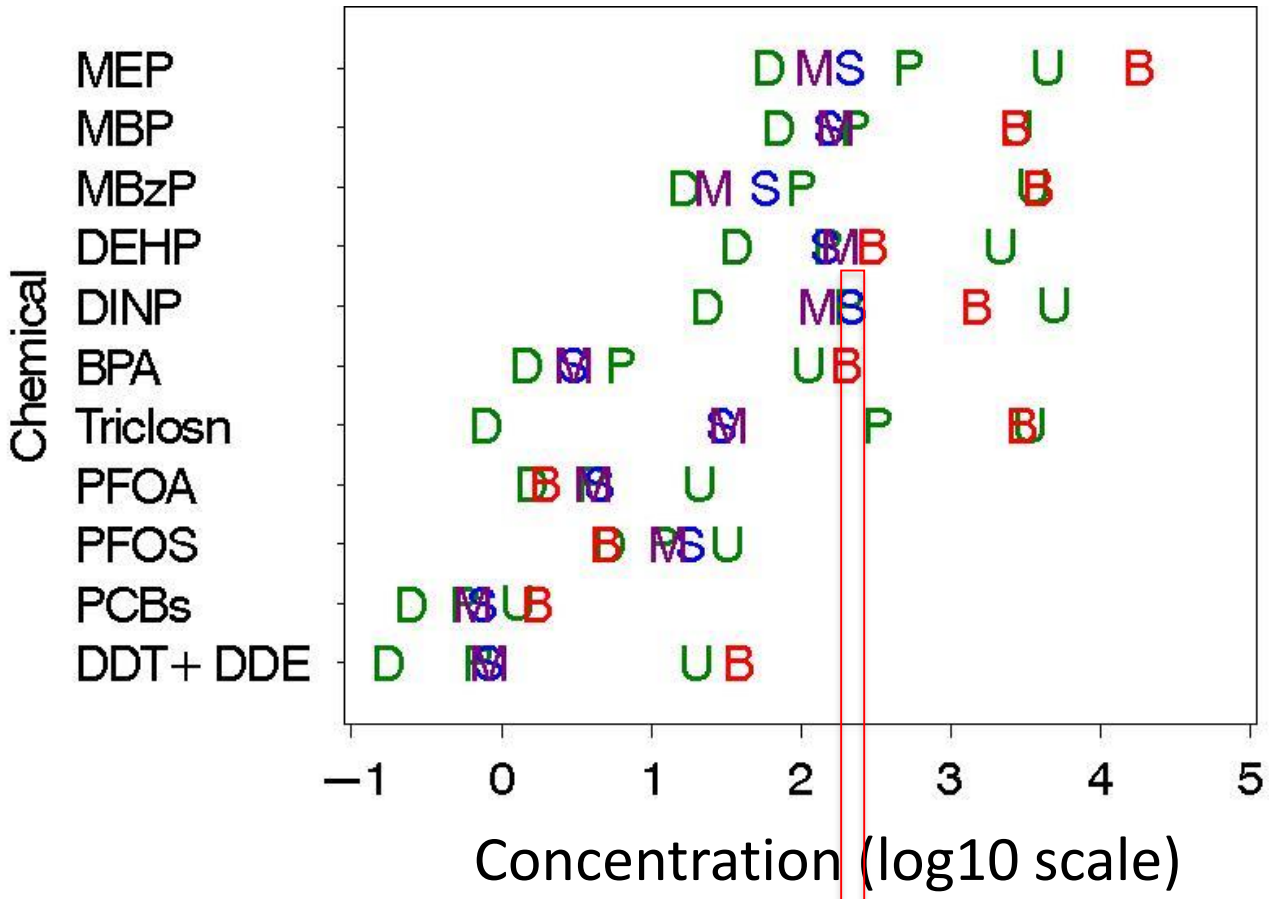
M = ACR Mixture

Data driven

Mixture Assessment Factor:

for DINP ~ 1 order of magnitude = 10

SELMA Language Delay ACR Model



LEGEND

D = Median

P = P95

U = Maximum

B = BE/HBM1

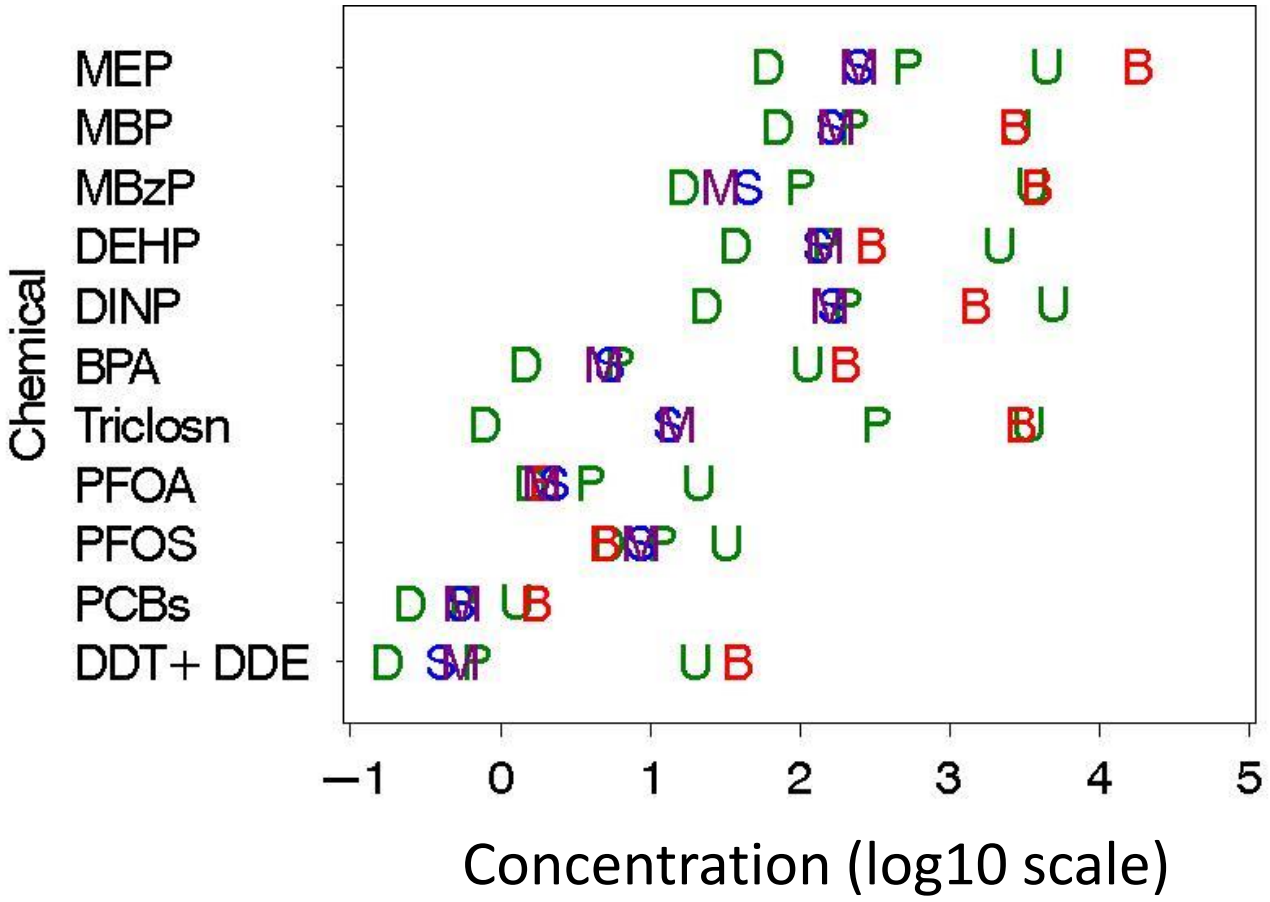
S = ACR Single Chem

M = ACR Mixture

Data driven
Mixture Assessment Factor:

for DEHP, MAF ~ 1

SELMA Birth Weight ACR Model



LEGEND

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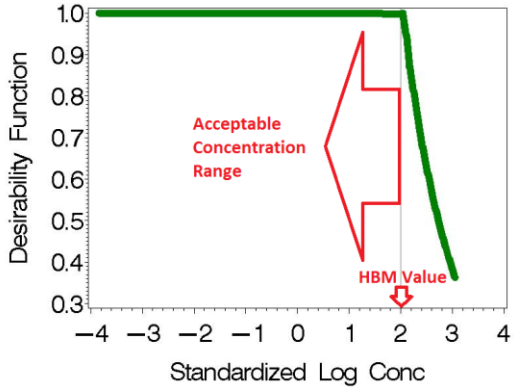
U = Maximum

B = BE/HBM1

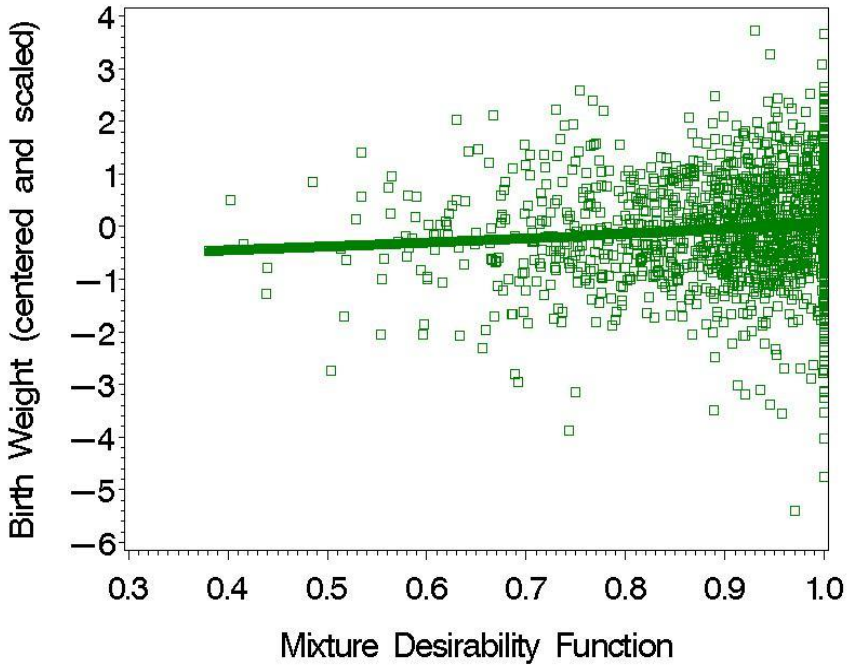
S = ACR Single Chem

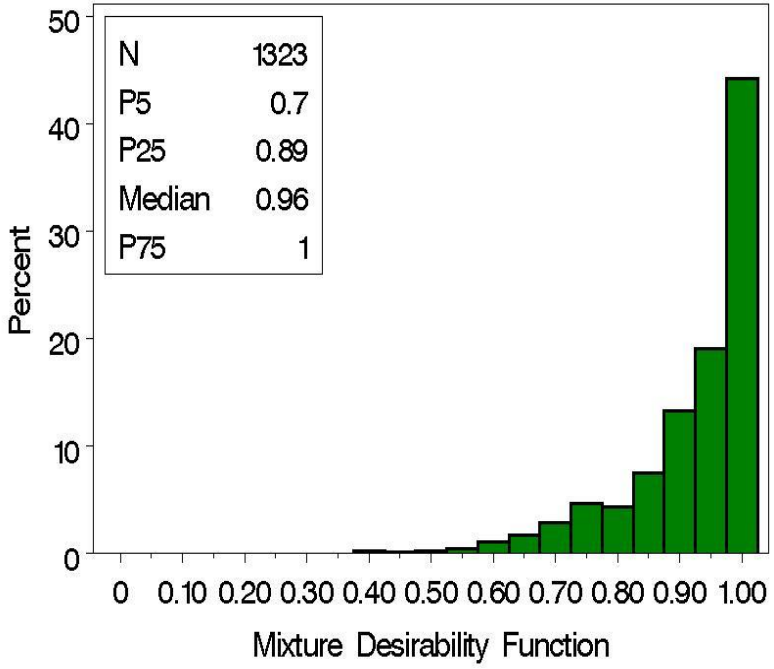
M = ACR Mixture



Mixture Guidance Values: SELMA Birth Weight

LOESS plot of **birth weight** and the estimated Mixture Desirability Function which is significantly **associated birth weight (p=0.001)** from SELMA data, adjusting for sex, creatinine, maternal education, maternal weight, maternal smoking status, gestational age at birth, parity, maternal age, and fish intake (N=1323)





Conclusions from the ACR Model

The ACR model parameterized to include **the risk assessment concept of acceptable range of concentrations** provides an indication that the **published guideline values are too high** to provide adequate protection for neurodevelopment and fetal growth from prenatal exposures to mixtures in the SELMA pregnancy cohort.

The ACR model may be useful in determining data-driven ‘mixture assessment factors’ (MAFs).

Extensions to the ACR model

Eva Tanner, PhD is working on characterizing and extensions to the ACR model

- Improved starting values to reduce time for parameter estimation;
- Simulation studies to study:
  - accuracy of estimating join points in single chemical analyses and in mixture analyses;
  - Does accuracy decrease as the number of components increases … a lot??
- Considerations of using an average instead of the geometric mean to combine the DFs for mixtures

Acknowledgements

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  - NIH (PRIME R01ES028811)
  - EDC-MixRisk; EU Horizon 2020 (#234880)

- **EDC-MixRisk consortium**: primarily,
  - Carl Gustaf Bornehag, Karlstad University (SELMA)
  - Huan Shu, Stockholm University (data management; risk assessment)
  - Christina Ruden, Stockholm University (risk assessment)
  - Christian Lindh, Lund University (chemical analyses; mixture construction)
  - Hannu Kiviranta, National Institute for Health and Welfare, Finland (chemical analyses)

- **SELMA** participants

Thank you!