The use of mixture assessment factors in mixture risk assessment

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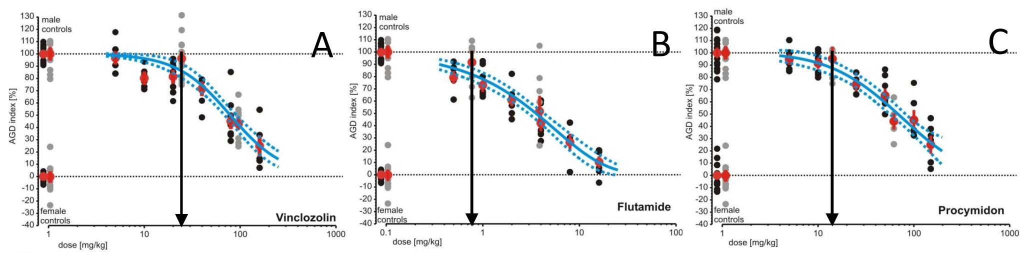
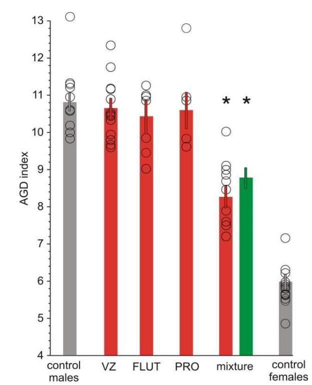
“Protection from mixture effects is achieved, as long as exposures stay below thresholds”

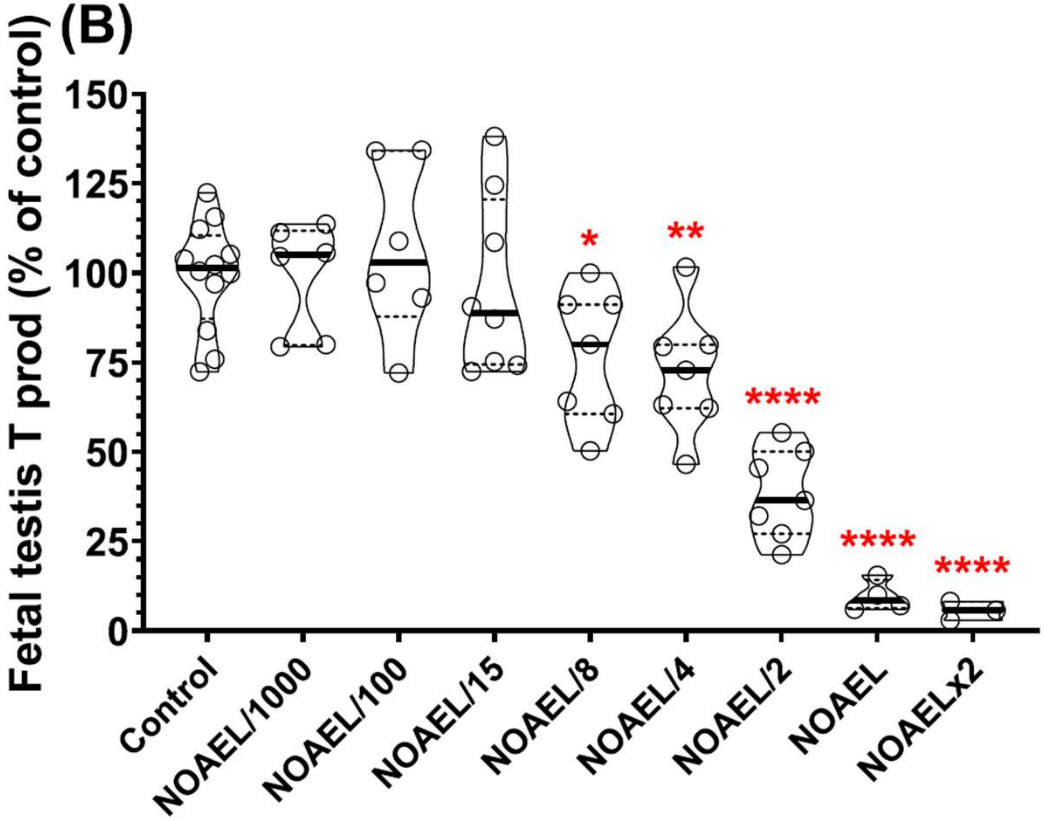
Anti-androgens in a rat developmental toxicity model





Hass U, Scholze M, Christiansen S, Dalgaard M, Vinggaard AM, Axelstad M, Metzdorff SB, Kortenkamp A: **Combined exposure to anti-androgens exacerbates disruption of sexual differentiation in the rat.** *Environ Health Perspect* 2007, **115(Suppl 1)**:122-128.

15 antiandrogens in a rat developmental model



Conley et al. 2021, Env Int 156, 106615

Mixture effects at low doses, **below** effect thresholds

Possible implications

Compliance with single chemical regulatory exposure limit values is **not necessarily protective**

Lower limit values needed for protection against mixture risks?

Mixture risk assessment case study

Scale of the problem

Mitigation

Mixture assessment factors as a solution?

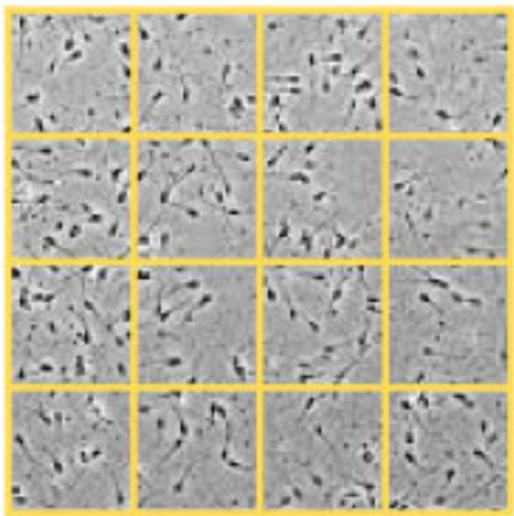
Application to risk assessment practice

Hazard Index

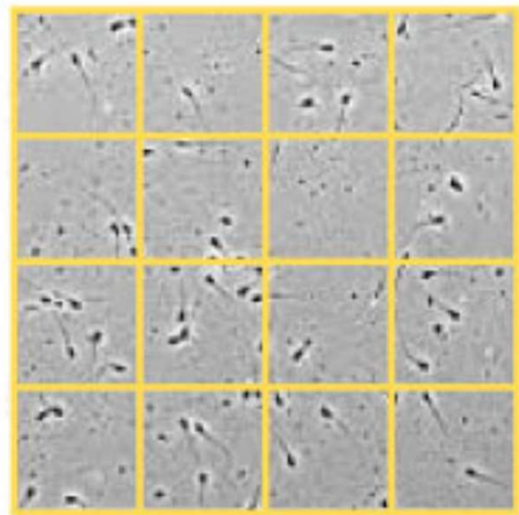
Sum of "risk quotients"

$$\frac{\text{Intake}_1}{\text{Reference dose}_1} + \frac{\text{Intake}_2}{\text{Reference dose}_2} < 1$$

Sperm concentration



101 mill/ml
(1973)



49 mill/ml
(2018)

Levine et al. 2022

29 chemicals

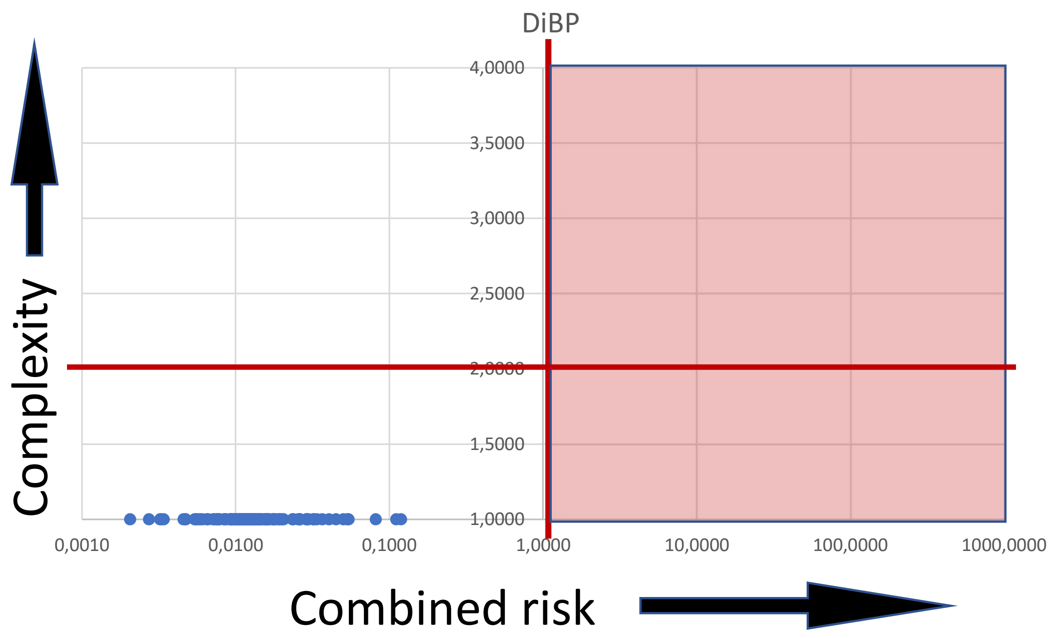
PCDD/F			**Phthalates**	DiBP
PBDE	BDE-209			DnBP
	BDE-183			DEHP
	BDE-154			DiNP
	BDE-153			BBzP
	BDE-100		**Bisphenols**	BPA
	BDE-99			BPS
	BDE-47			BPF
	BDE-28		**Painkillers**	Paracetamol
PCB	PCB 169			
	PCB 126			
	PCB 118			
Acrylamide				
n-Butyl paraben				
Pesticides	Chlorpyrifos			
	Vinclozolin			
	Procymidone			
	Prochloraz			
	Linuron			
	Fenitrothione			

Multiple chemicals monitored in the same sample

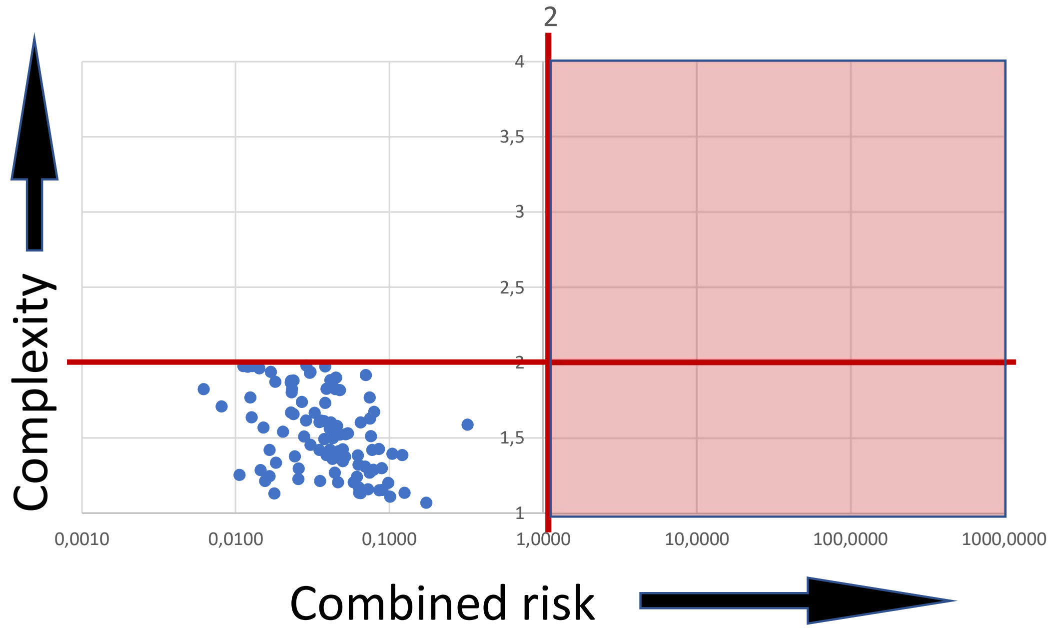
Phthalates	DiBP
	DnBP
	DEHP
	DiNP
	BBzP
Bisphenols	BPA
	BPS
	BPF
Painkillers	Paracetamol

Mixture risk assessment gets personal

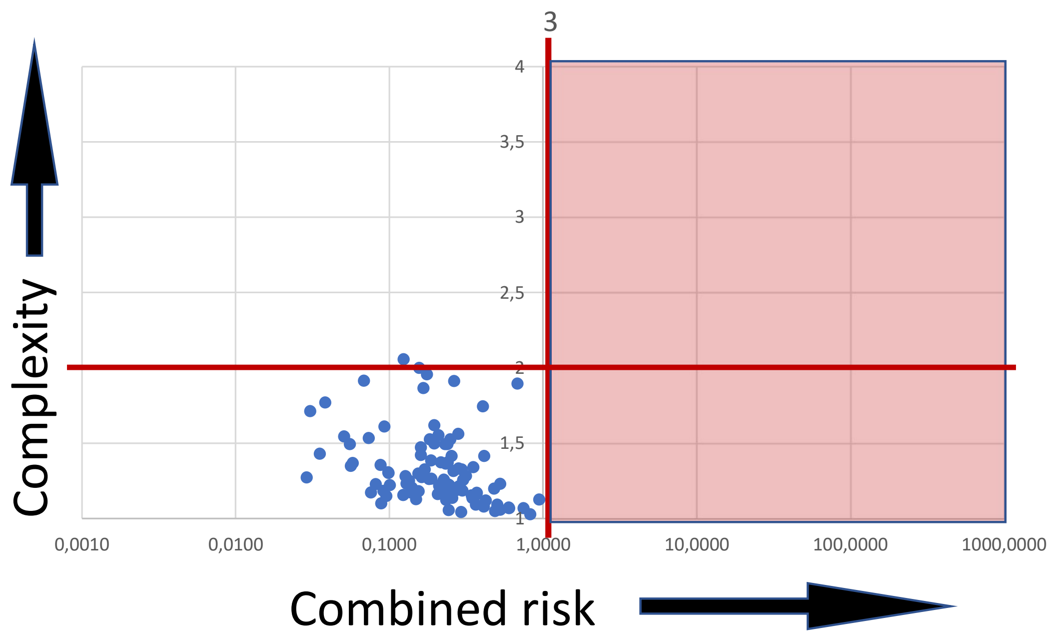
One phthalate



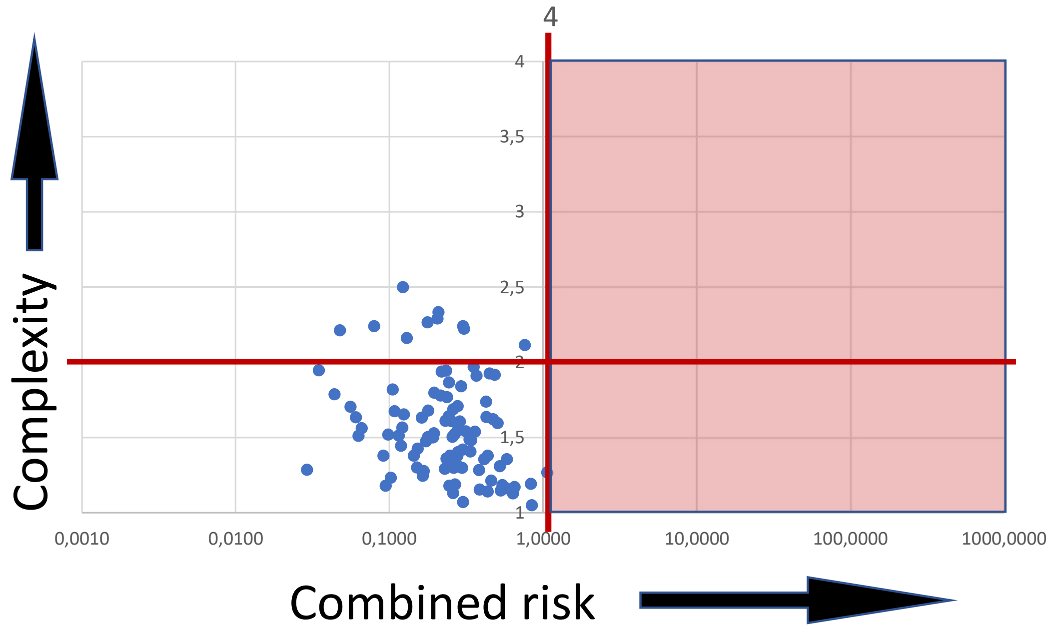
Two phthalates



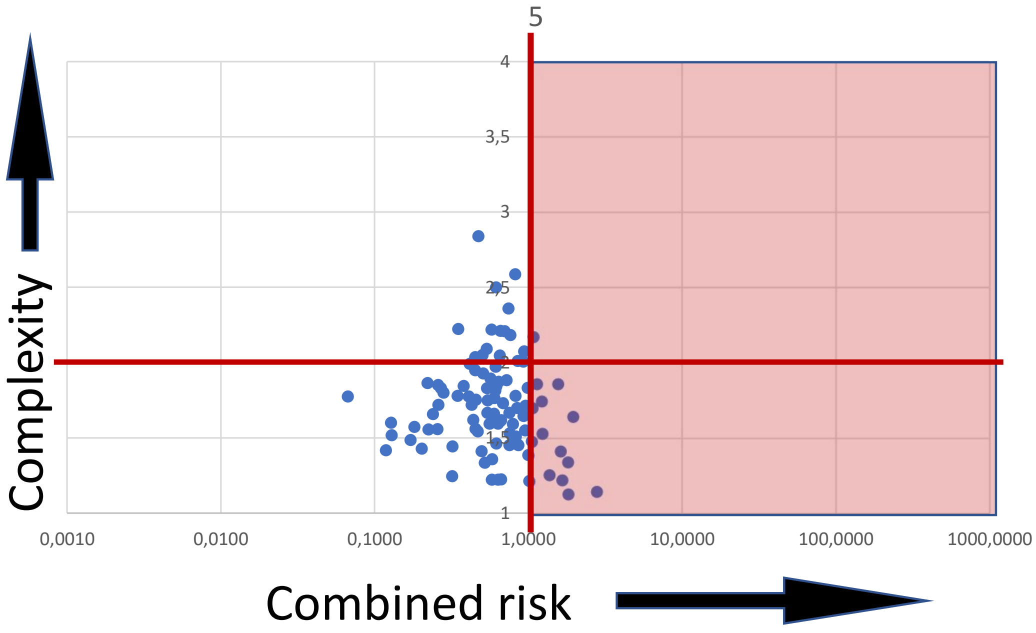
Three phthalates



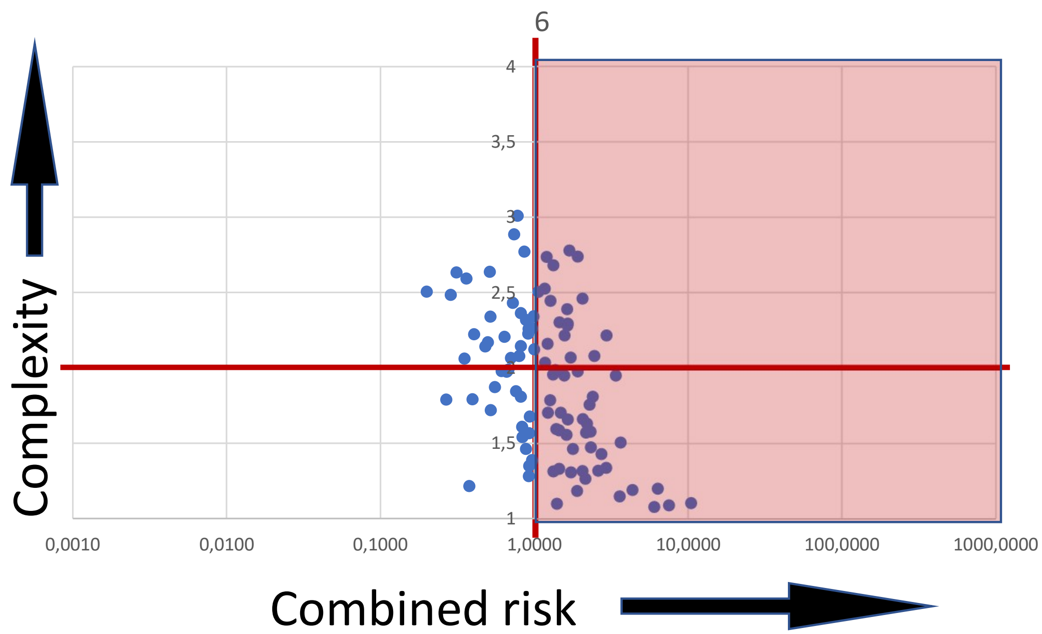
Four phthalates



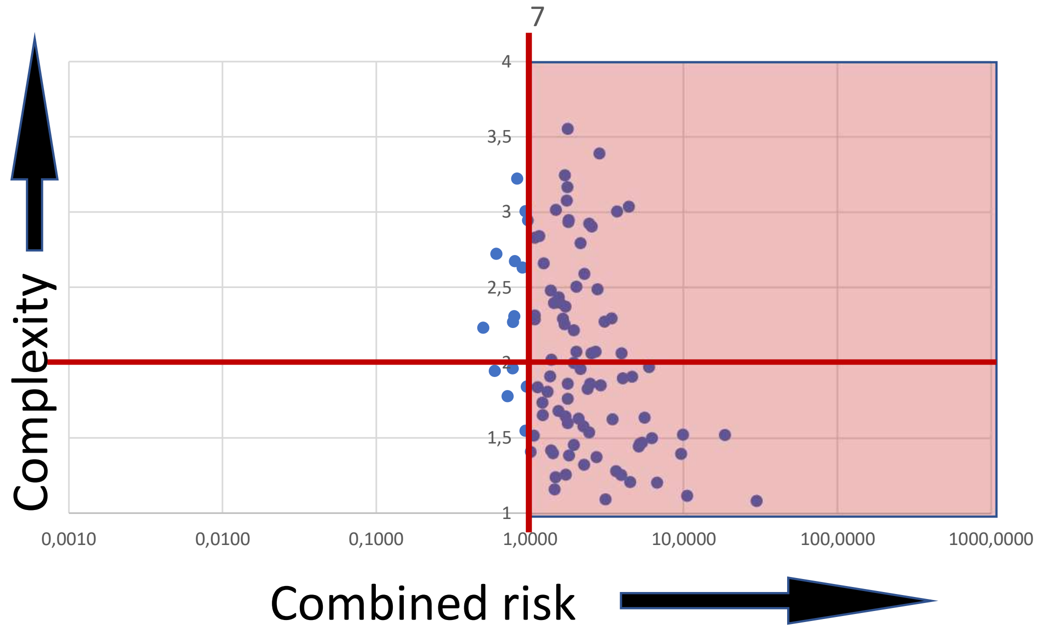
Five phthalates



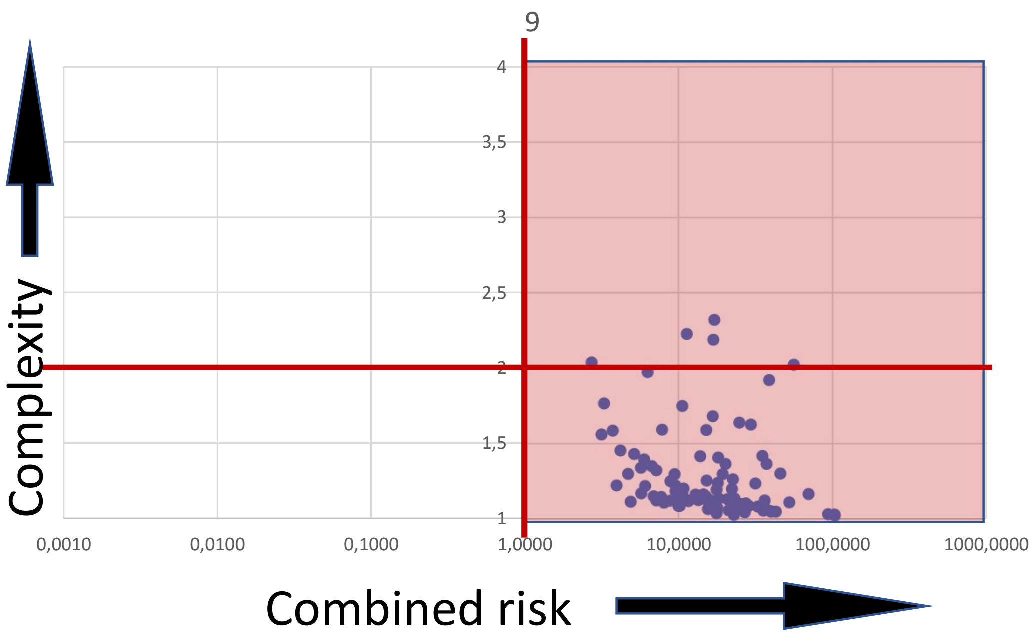
Five phthalates + bisphenol F



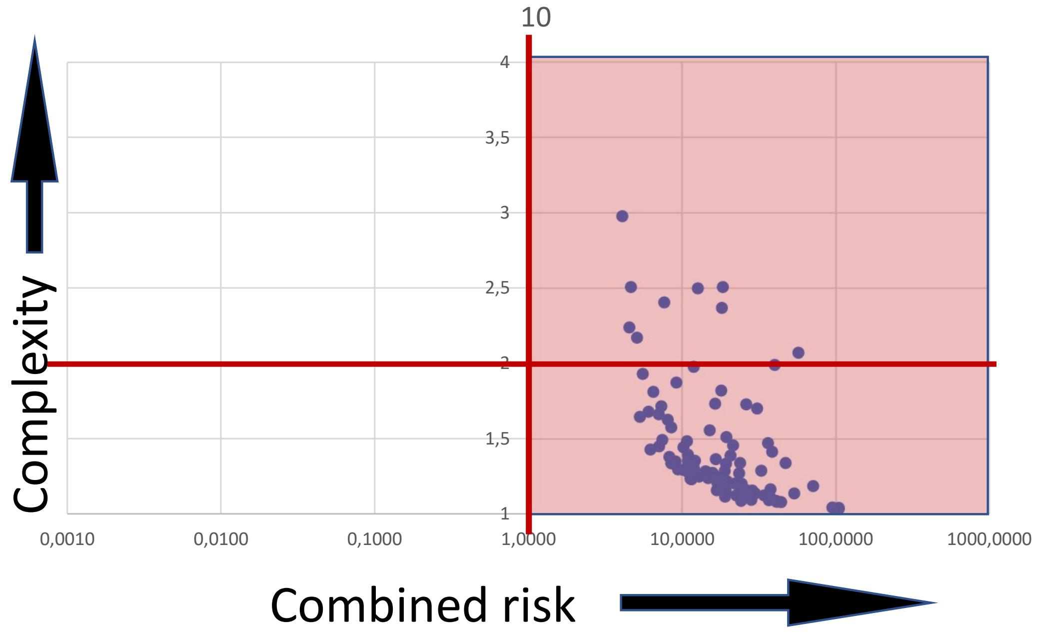
Five phthalates, bisphenol F, S



Phthalates, bisphenols F, S, A and paracetamol



Phthalates, bisphenols, paracetamol + 20 background chemicals

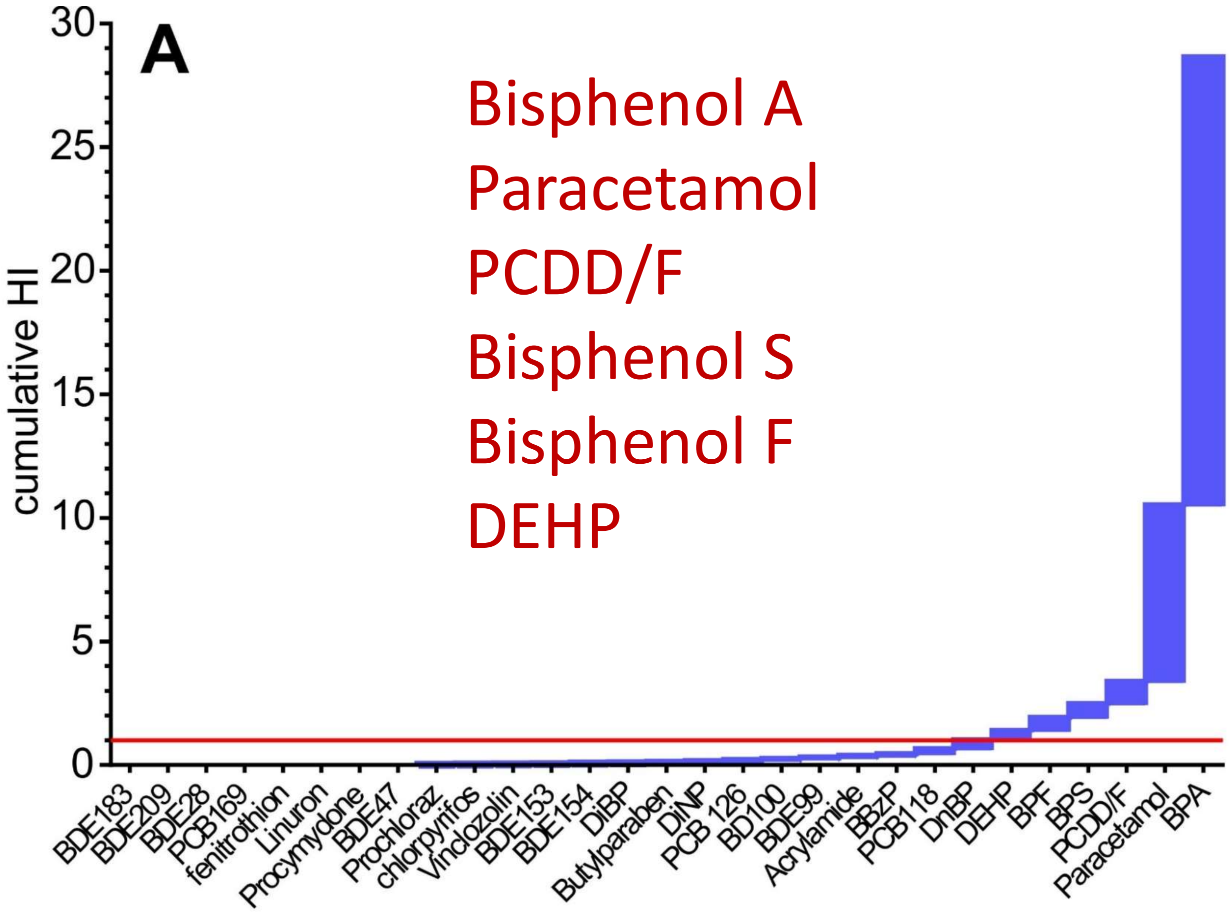


Exceedances of combined "acceptable" exposures

Range: 4 – 100-fold

Median: 18-fold

Drivers of mixture risks (semen quality)



Exceedance if all risk quotients ≤ 1

~ 5-fold

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Full length article

Combined exposures to bisphenols, polychlorinated dioxins, paracetamol, and phthalates as drivers of deteriorating semen quality

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Exposure limits for single chemicals **do not protect** against mixture risks

Assessment factors used to derive limit values do not deal with mixture risks

An additional factor is needed: **Mixture Assessment Factor (MAF)**

Proposed MAFs (Europe)

Area	Size	Reference
Environment	100	Janssen, 2004; van Vlaardingen, 2007
Environment	100	Tørsløv, 2013
Human health	100	Muilerman, 2011
Human health	10	Tørsløv, 2013, Petersen, 2014

No justifications given

Mode of application not defined

Two uses of MAFs

1. For downward correction of exposure limits

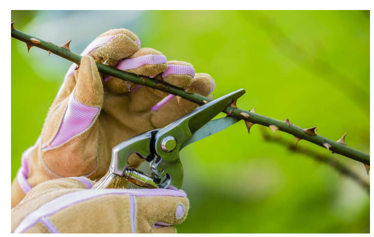
(regulatory values, reference doses, ADI, TDI)

Mixture Assessment Factor

2. For downward correction of index values in risk assessment

Risk quotient = 1

Risk quotient = 0.1; 0.01 etc



Mixture Allocation Factor

Theory- and data-driven sizing of a MAF

Data-driven sizing of a Mixture Assessment Factor

Mixture Assessment Factor

$$\sum_{i=1}^{n} \frac{EL_i}{AL_i} \times \frac{1}{MAF} \leq 1$$

KEMI (2015)

Procedure:

1. To separate single chemical compliance issues from true mixture problems, **set all RQ > 1 to 1**
2. Calculate **sum of adjusted RQ**
3. Use **sum** of adjusted RQ as **Mixture Assessment Factor**

Mixture Assessment Factor: Example

Lower bound, based on P50 or geometric mean, 2009 exposures					
Chemical	Exposure	Unit	Reference dose	Unit	Risk Quotient
Bisphenol A	0.048	µg/kg d	0.01	µg/kg d	1
Paracetamol	7	mg/kg d	1	mg/kg d	1
PCDD/F	0.25	pg/kg d	0.28	pg/kg d	0.9
Bisphenol F	0.006	µg/kg d	0.01	µg/kg d	0.6
DEHP	2.06	µg/kg d	10	µg/kg d	0.206
Bisphenol S	0.002	µg/kg d	0.01	µg/kg d	0.2
PCB 118	575	pg/kg/d	2900	pg/kg/d	0.198
DBP	0.88	µg/kg d	6.7	µg/kg d	0.131
BDE 99	0.18	ng/kg/d	2.88	ng/kg/d	0.063
BDE 100	0.15	ng/kg/d	2.88	ng/kg/d	0.052
Acrylamide	0.4	µg/kg d	8.3	µg/kg d	0.048
PCB 126	3.5	pg/kg/d	73	pg/kg/d	0.048
n-butylparaben	0.6	µg/kg d	30	µg/kg d	0.02
BDE 154	0.05	ng/kg/d	2.88	ng/kg/d	0.017
BBzP	0.15	µg/kg d	10	µg/kg d	0.015
BDE 153	0.04	ng/kg/d	2.88	ng/kg/d	0.014
DINP	0.77	µg/kg d	59	µg/kg d	0.013
DIBP	0.99	µg/kg d	100	µg/kg d	0.010
Vinclozolin	0.35	µg/kg d	50	µg/kg d	0.007
BDE 47	0.58	ng/kg/d	150	ng/kg/d	0.004
Procymidone	0.25	µg/kg d	100	µg/kg d	0.0025
Prochloraz	0.34	µg/kg d	160	µg/kg d	0.002
Linuron	0.069	µg/kg d	100	µg/kg d	0.00069
PCB 169	3.5	pg/kg/d	5330	pg/kg/d	0.00066
Fenitrothione	0.06	µg/kg d	200	µg/kg d	0.0003
BDE 28	0.02	ng/kg/d	150	ng/kg/d	0.000
BDE 209	0.61	ng/kg/d	1000000	ng/kg/d	0.000
BDE 183	0.02	ng/kg/d	1000000	ng/kg/d	0.000
Sum of RQ					**4.55**
MCR					**4.55**

n = 29

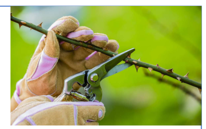
Mixture Assessment Factor: 4.55

Compliance with **4.55-fold lower Reference Doses** achieves HI ≤ 1

Lowering by a factor of 29 is not necessary

So unfair!

Data-driven sizing of a Mixture Allocation Factor



Mixture Allocation Factor

$$\sum_{i=1}^{n} \begin{cases} \frac{EL_i}{AL_i} > \frac{1}{MAF} = \frac{1}{MAF} \\ \frac{EL_i}{AL_i} \leq \frac{1}{MAF} = \frac{EL_i}{AL_i} \end{cases} \leq 1$$

KEMI (2021), Thomas Backhaus

Procedure:

1. To separate single chemical compliance issues from true mixture problems, **set all RQ > 1 to 1**
2. Through **iteration**, determine 1/MAF so that **sum of adjusted RQ = 1**

Mixture Allocation Factor: Example

	Risk Quotient	Risk Quotient adjusted	Risk Quotient with MAF
DiBP	0.007	0.007	0.007
DnBP	0.231	0.231	0.139
BBzP	0.017	0.017	0.017
DEHP	0.209	0.209	0.139
DiNP	0.006	0.006	0.006
BPF	3.140	1.000	0.139
BPS	0.332	0.332	0.139
BPA	7.363	1.000	0.139
Paracetamol	5.774	1.000	0.139
PCDD/F	0.893	0.893	0.139
		4.7	1.0
Mixture Allocation Factor	7.2		
inverse	0.139		

If **Risk Quotient adjusted** ≤ 1/MAF: **no change**

If **Risk Quotient adjusted** > 1/MAF: **change to 1/MAF**

Aim: Sum of Risk Quotients = 1

Small Risk Quotients are left untouched

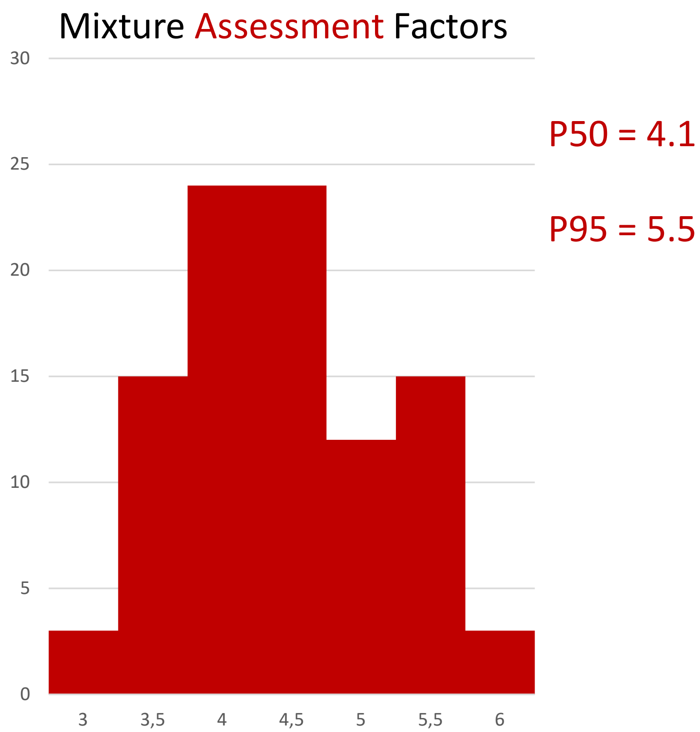
The price: MAF has to be larger (here: 7.2 versus 4.7)

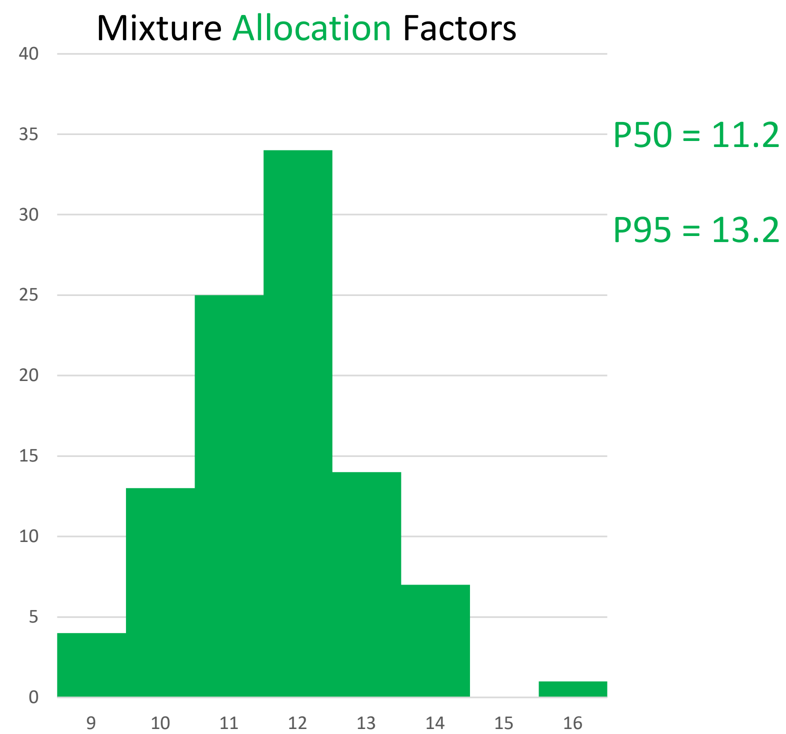
Individual-based Mixture Assessment Factors and Mixture Allocation Factors

> 20-fold variations in **Hazard Indices**

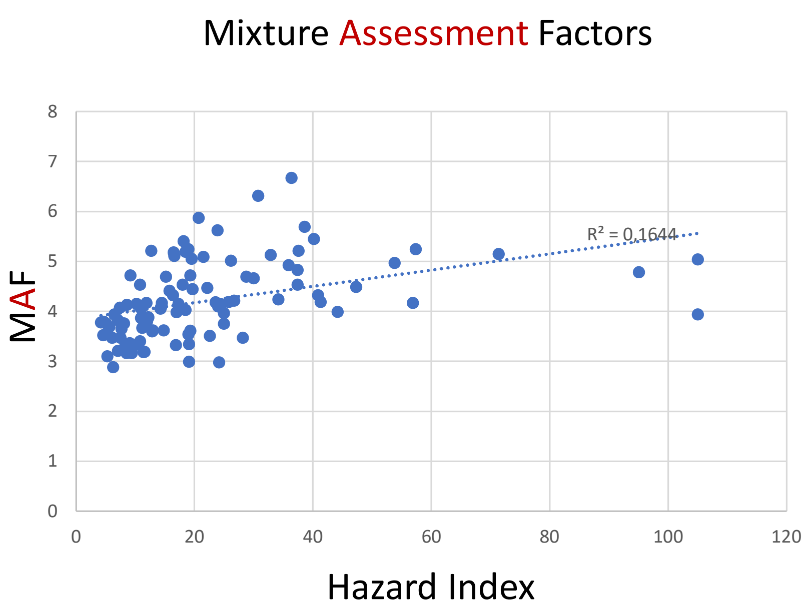
How do the Mixture Assessment Factors and Mixture Allocation Factors **vary for each subject**?

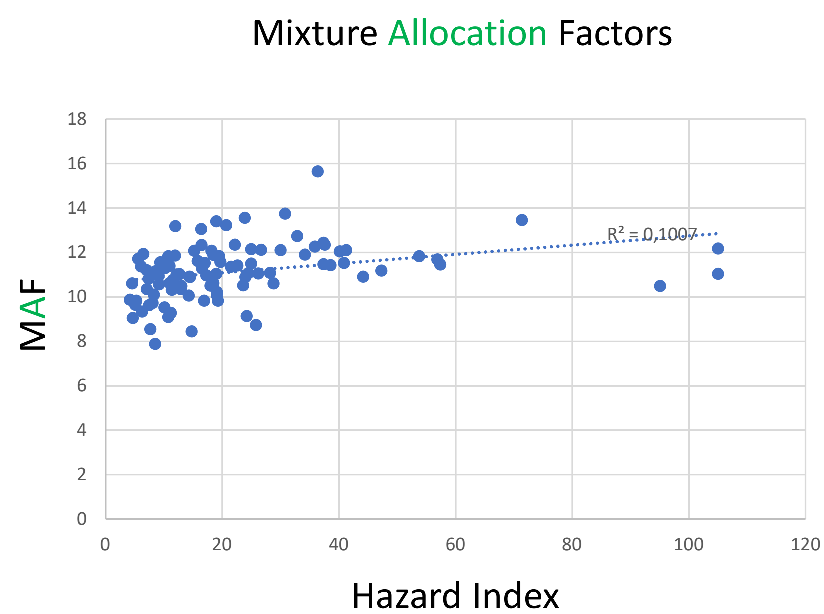
Individual-based factors: Frequency distributions





Do highly exposed individuals require larger MAFs?





This case study supports:

Mixture Assessment factor: 5.5

Mixture Allocation Factor: 13

However:

Minimum risk estimate

Not taken into account:

- Air pollution
- Perfluorinated chemicals
- Organophosphate pesticides

Risk estimates and **MAFs increase** the more substances we include in the assessment

Conclusions

- Use of a MAF in risk assessment and risk management is **scientifically justified**
- **Practicable**: Can be integrated in current risk management approaches
- **Urgent** for the protection against mixture risks
- More human health case studies needed to support data-driven sizing of a MAF

Clarity needed:

Which MAF are we talking about?

Thank you!