

SFT Paris, 24 Nov 2017

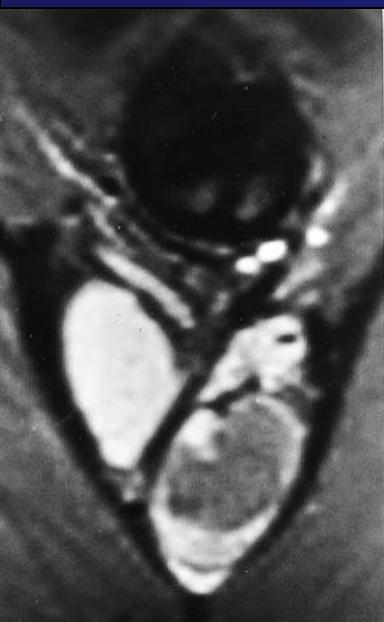
Antiandrogen cocktail effects

Andreas Kortenkamp

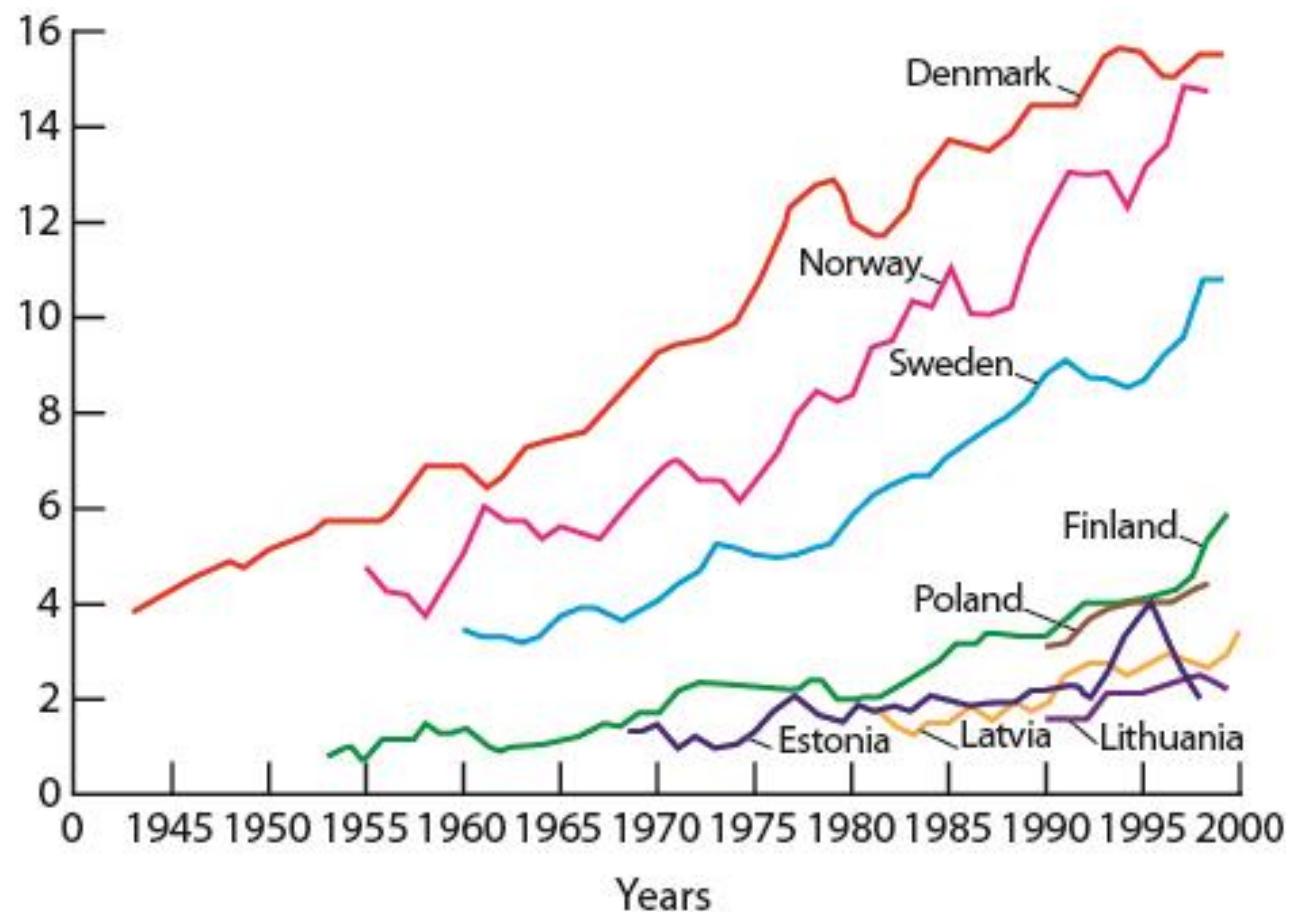
*Institute of Environment, Health and
Societies, Brunel University, London*



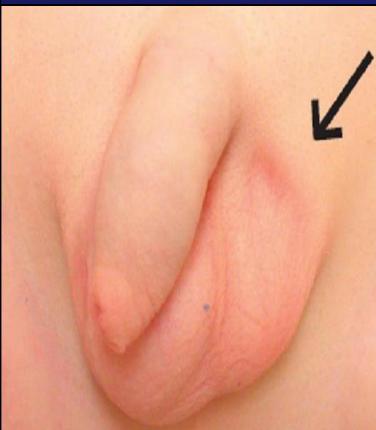
Testicular germ cell cancers



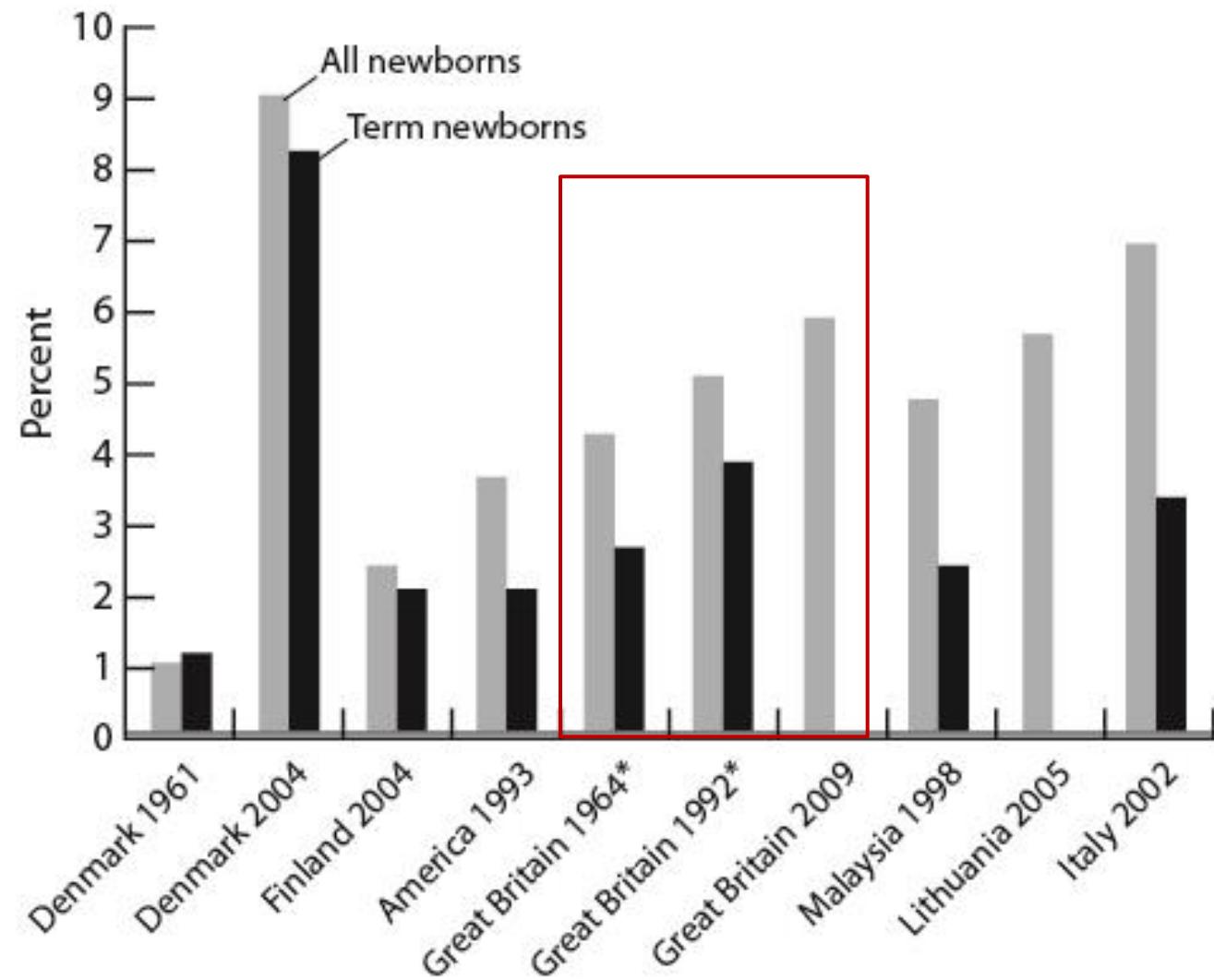
Cases per 100,000; age-standardised



Cryptorchidism



WHO, UNEP (2013)
State of the Science
of Endocrine
Disrupting
Chemicals 2012



A new approach to the problem

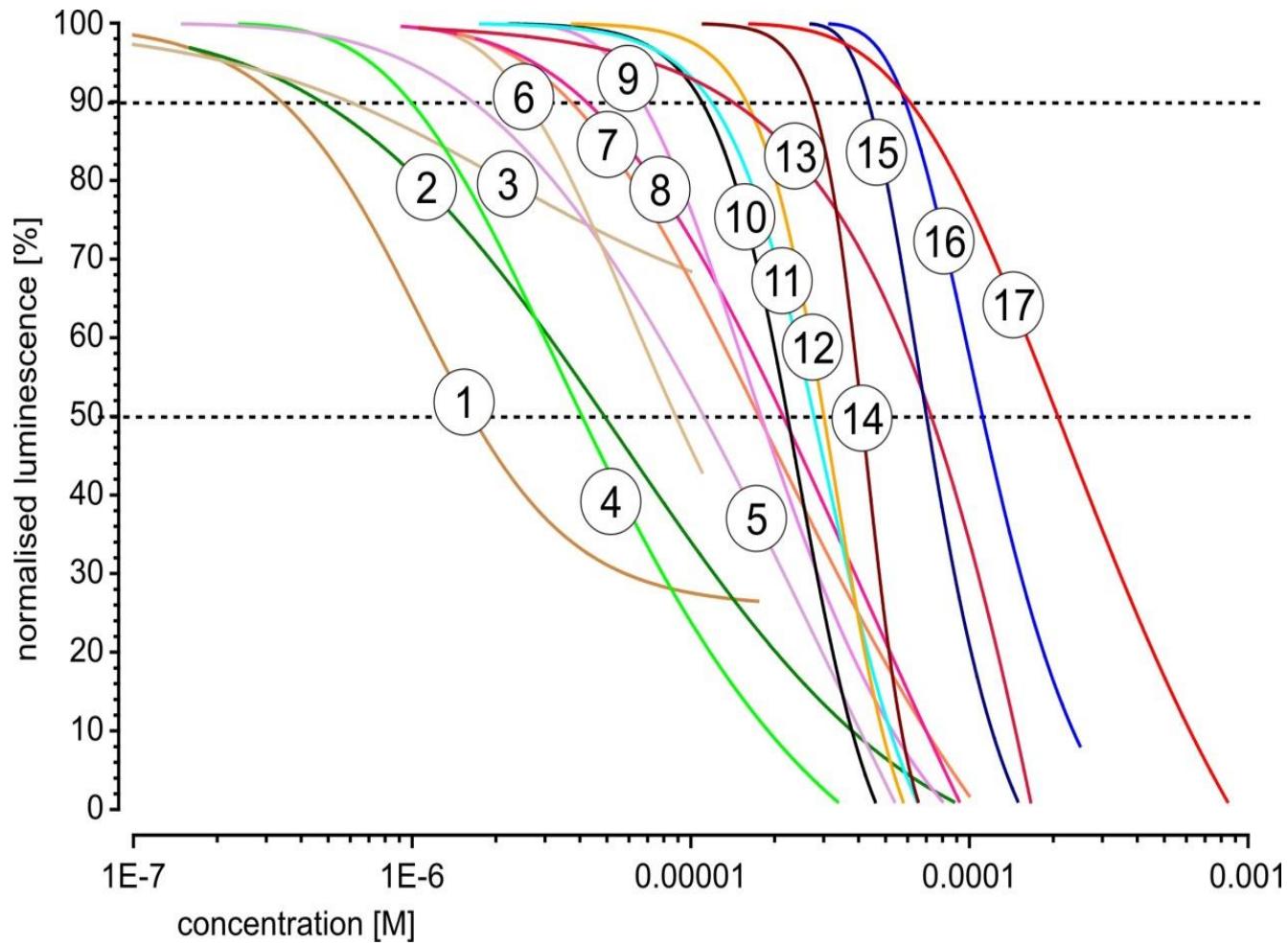
- Human exposure is to **large numbers** of chemicals, at **low levels**
- What can we learn from experimental mixture studies?
- **Two modalities:**
 - androgen receptor antagonism
 - testosterone synthesis suppression

AR antagonist chemicals

17 components

AR-Lux

BDE100
benzophenone 2
benzo(a)pyrene
bisphenol A
HHCB
PCB138
BHA
AHTN
benzophenone 3
PFOS
3-BC
4-MBC
BHT
n-butyl paraben
n-propyl paraben
ethyl paraben
methyl paraben

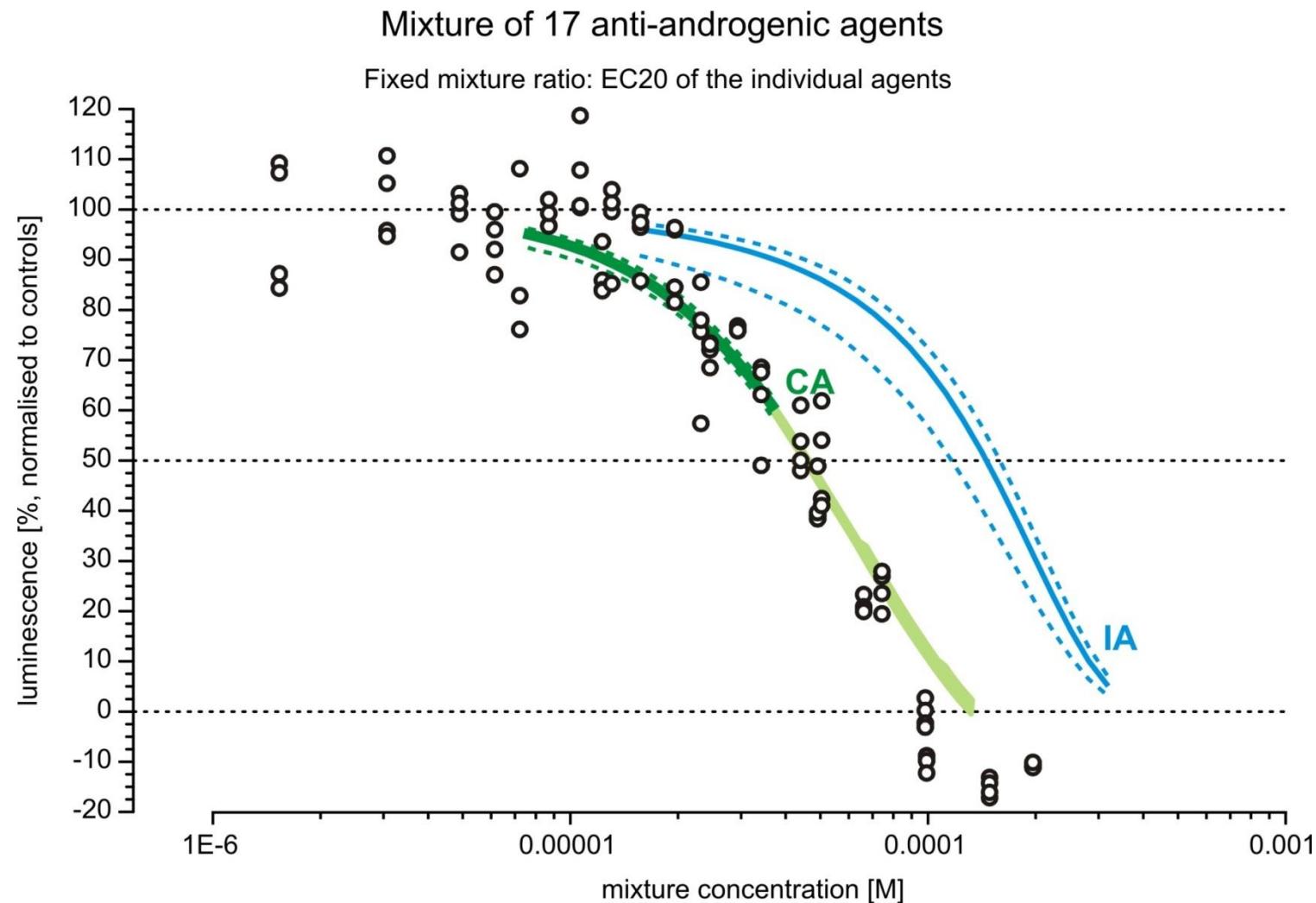


Predictability: anti-androgens

17
components

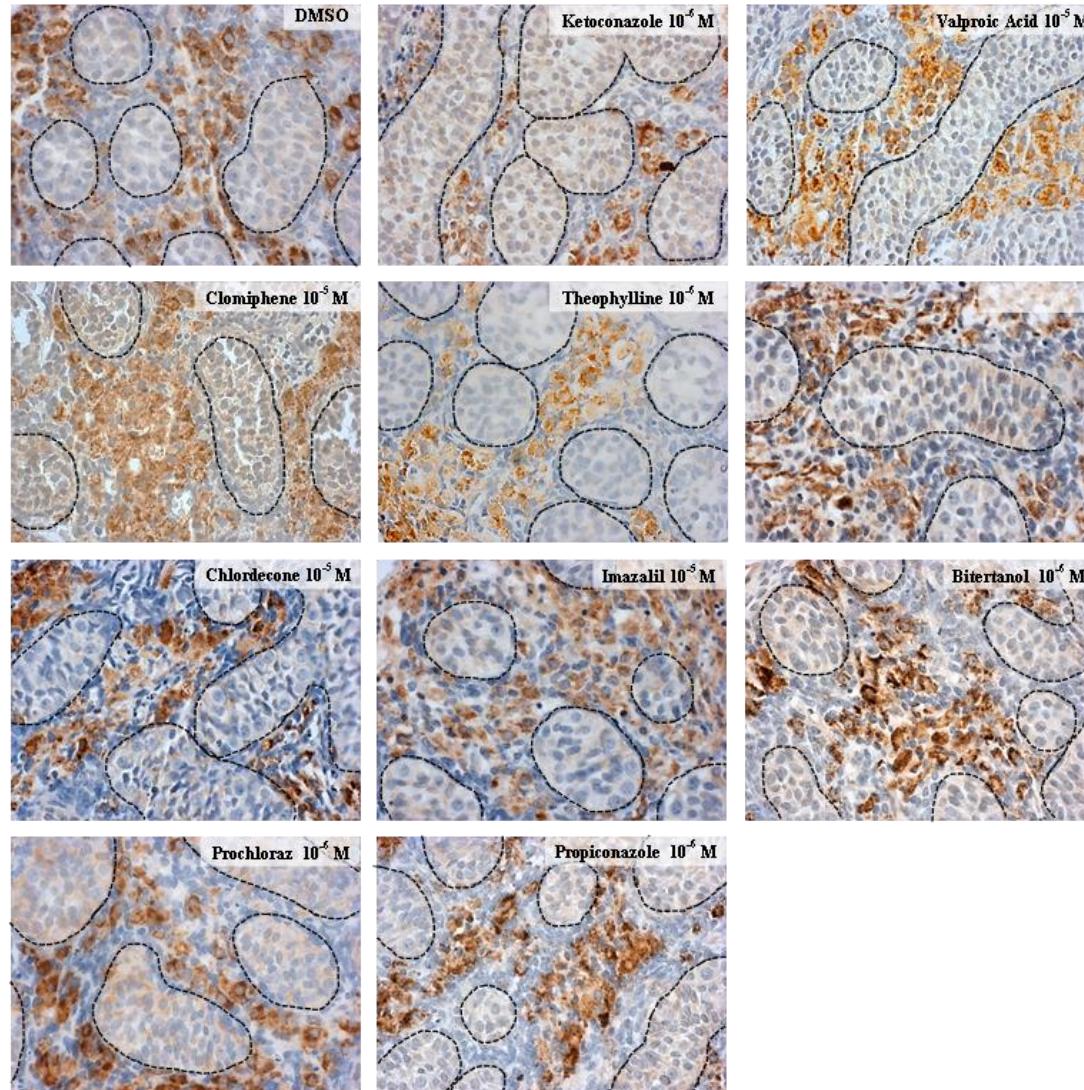
AR-Lux

Ermller et al. 2011
Tox. Appl.
Pharmacol. 257,
189-197



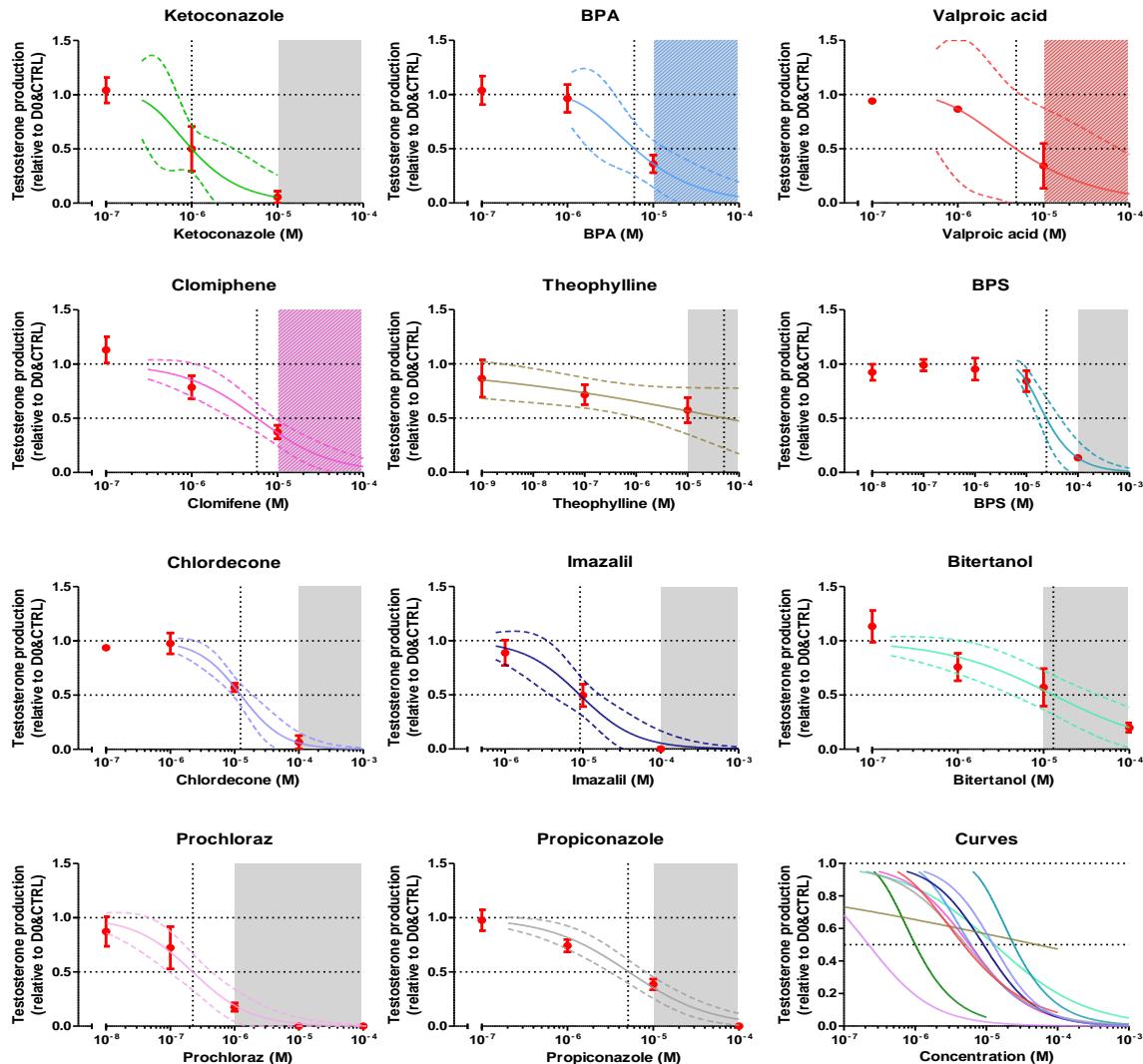
Human fetal testis explants

Gaudriault et al. (2017) Env Health Perspect
125 (8). doi: 10.1289/EHP1014



Human fetal testis explants: Testosterone levels

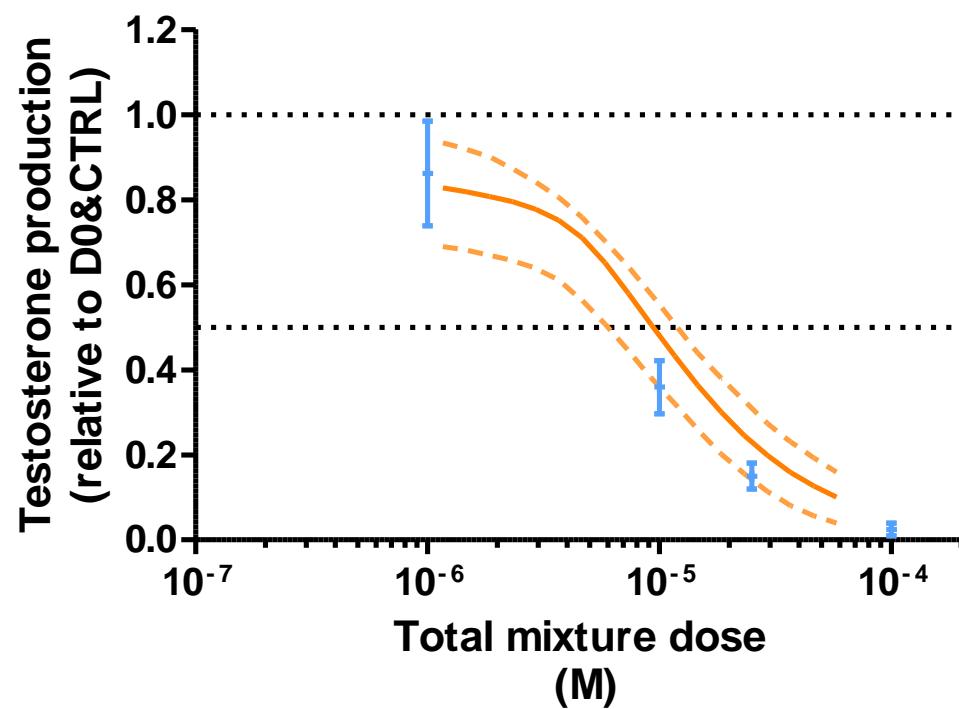
Gaudriault et al. (2017) Env Health Perspect
125 (8). doi: 10.1289/EHP1014



Cocktail effect: 8 components

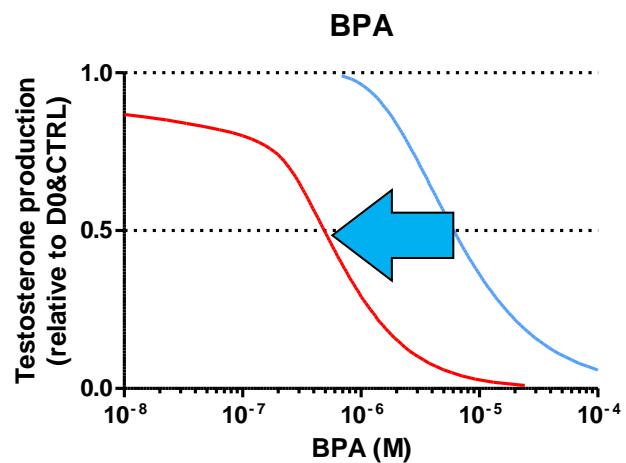
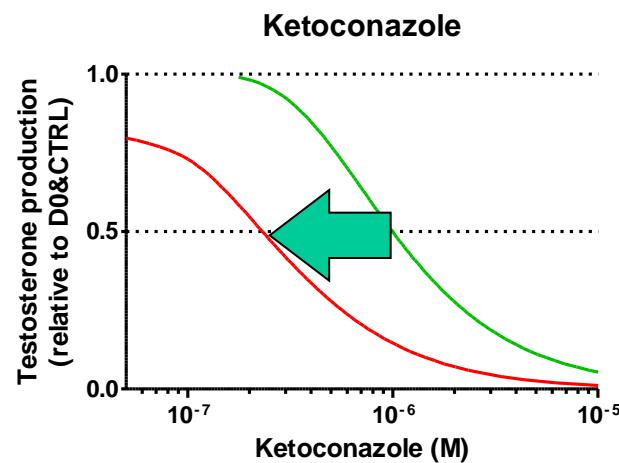
Gaudriault *et al.* 2017

Ketoconazole
BPA
Valproic acid
Clomiphene
Theophylline
BPS
Chlordecone
Imazalil

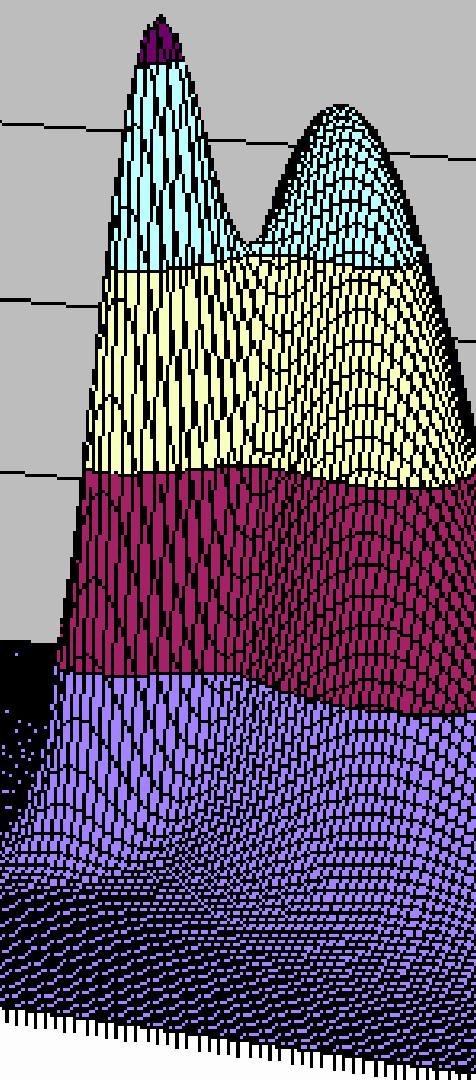


Perspective of a single chemical risk assessment

Presence of other chemicals shifts curve to the left



From “lab designer” mixtures towards reconstituted mixtures



- Data about human serum levels
- *In vitro* AR antagonist potency known
- Re-create mixtures *in vitro*

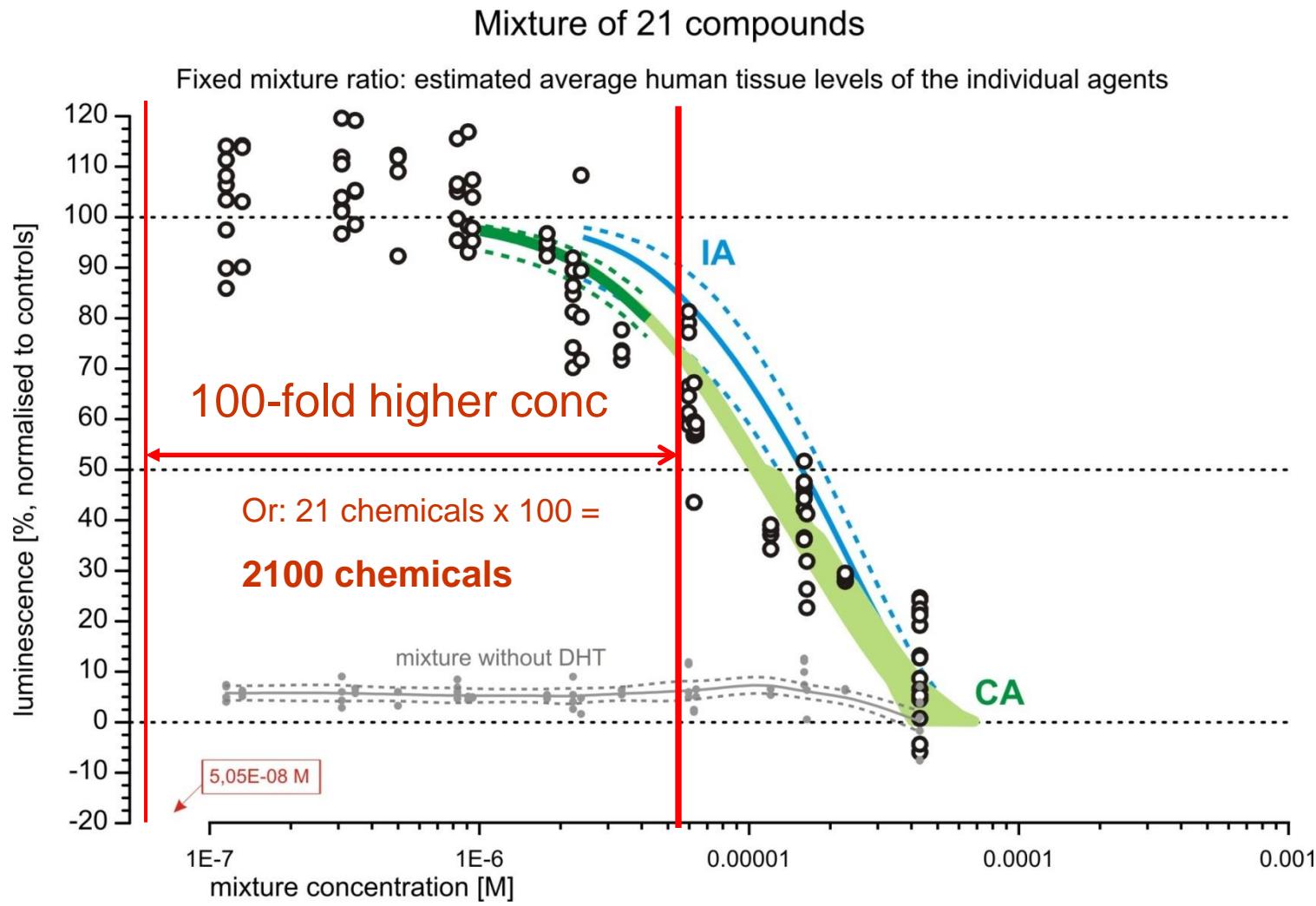
Selected chemicals: 21 AR antagonists

Exposure information (tissue levels) and their sources

Compound	Monitoring data	Statistical distribution	Adjustment for conjugationunc conjugated	Serum levels [M]	
				median	P95 ²⁾
Polychlorinated biphenyl 118	NHANES	empirical		8.6E-11	9.0E-10
Polychlorinated biphenyl 126				8.6E-11	9.0E-10
Polychlorinated biphenyl 138	NHANES	empirical		2.5E-10	1.4E-09
Polychlorinated biphenyl 153	NHANES	empirical		3.4E-10	2.2E-09
Polychlorinated biphenyl 180	NHANES	empirical		1.7E-11	1.5E-09
Benzophenone 2			10%	1.1E-11	7.0E-11
Benzophenone 3	Schlumpf et al	Gen. log-normal	10%	1.1E-11	7.0E-11
Galaxolide (HHCB)	Hutter et al	Gen. log-normal, bimodal	10%	1.6E-10	3.2E-10
Tonalide (AHTN)	Rimkus&Wolf 1996	gamma	10%	9.8E-12	2.5E-11
Butylated hydroxy anisole (BHA)			10%	5.6E-12	1.4E-11
Butylated hydroxy toluene (BHT)	Conacher	log-normal	10%	4.6E-11	1.1E-10
3-Benzylidene camphor			10%	9.2E-12	1.5E-11
4-Methylbenzylidene camphor (4MBC)	Schlumpf et al	Gen. Extreme value	10%	8.7E-12	1.4E-11
Benzo[a]pyrene	Neal et al. 2007	Gen. log-normal, bimodal		8.8E-10	2.8E-09
Polybrominated diphenyl ether 100 ¹⁾	NHANES	empirical		4.1E-11	3.9E-10
Bisphenol A	Schoenfelder et al	truncated normal	10%	1.8E-09	5.1E-09
Perfluorooctane sulfonate (PFOS)	NHANES	empirical		3.7E-08	9.2E-08
<i>n</i> -Butyl paraben	Frederiksen et al	Gen. log-normal	10%	9.8E-12	3.9E-10
<i>n</i> -Propyl paraben	Frederiksen et al	Gen. log-normal	10%	1.8E-10	1.3E-09
Ethyl paraben	Frederiksen et al	Gen. log-normal	10%	1.3E-10	1.0E-09
Methyl paraben	Frederiksen et al	Gen. log-normal	10%	1.0E-09	1.0E-08

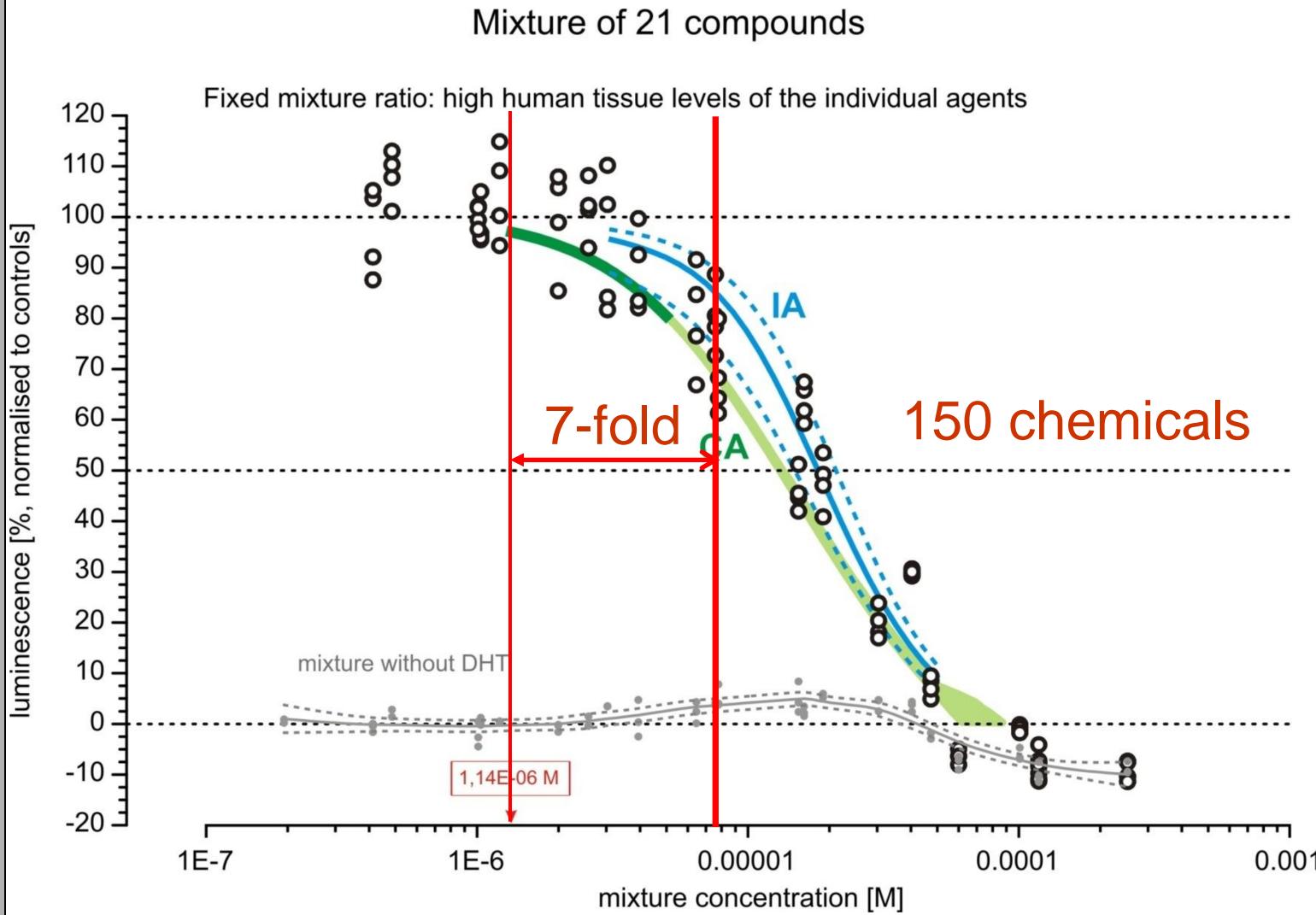
“Reconstituted”: 21 AR antagonists

Average tissue levels (serum)



“Reconstituted”: anti-androgens

High pollution



Limitations and omissions

- **Selection criterion:** availability of data on human internal exposure
- No pesticides included, **lack of data** on serum levels
- **Uncertainty** about full spectrum of active chemicals
- Limited to *in vitro* AR antagonists
- Influence of de-activation by conjugation?
- Androgen concentrations?



Pareto principle



Vilfredo Pareto (1906)

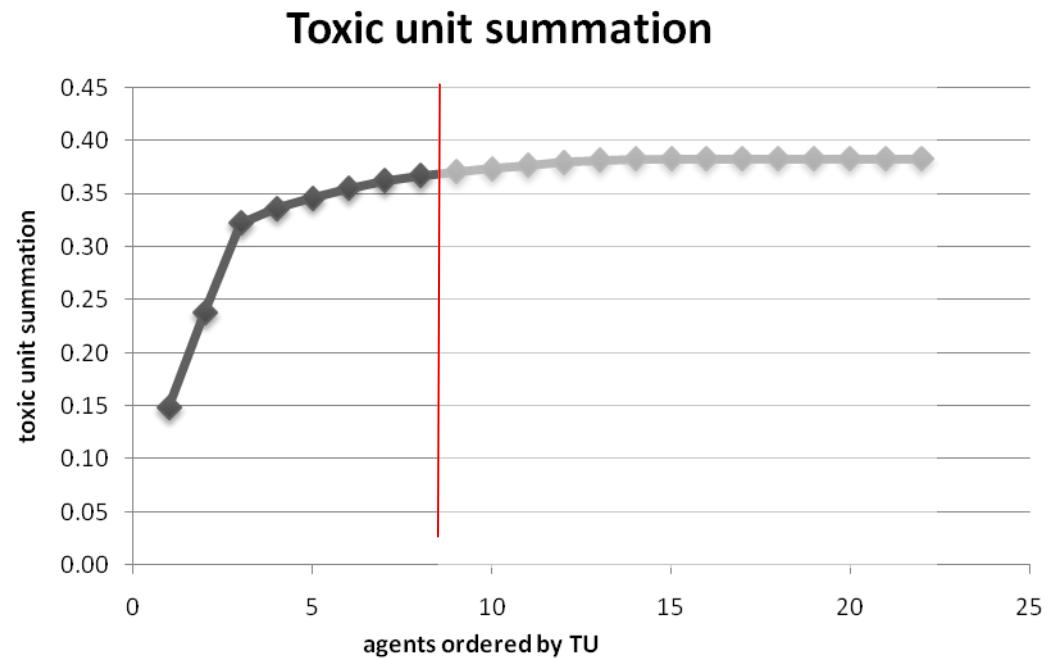
“80% of the land in Italy is owned by 20% of the people.”

A minority of the causes explains the majority of effects.

Applicable to environmentally relevant mixtures?

Not all chemicals contribute equally

TU	rank	compound
0.1486	1	Benzophenone-2
0.0897	2	Benzophenone-3
0.0838	3	BPA
0.0144	4	PFOS
0.0096	5	HHCB
0.0093	6	Benzo[a]pyrene
0.0071	7	3-BC
<u>0.0050</u>	<u>8</u>	<u>4-MBC</u>
0.0034	9	PCB 138
0.0031	10	PCB 126
0.0029	11	PCB 118
0.0029	12	PCB 180
0.0022	13	PCB 153
0.0007	14	AHTN
0.0001	15	BHT
0.0000	16	BDE100
0.0000	17	BHA
0.0000	18	Methyl paraben
0.0000	19	n-Butyl paraben
0.0000	20	Ethyl paraben
0.0000	21	n-Propyl paraben



~ 30% of chemicals: > 95% effect

A tentative estimate

- 40 – 400 chemicals at levels comparable to those measured for “known knowns”
- Only AR antagonism
- Excludes other *mechanisms*
- Excludes other *agents*, e.g. drugs or pesticides

An explanation gap?

- **Kortenkamp, A., Scholze, M. and Ermler, S. (2014)** Mind the gap: can we explain declining male reproductive health with known antiandrogens?, *Reproduction* 147 (4) : 515- 527

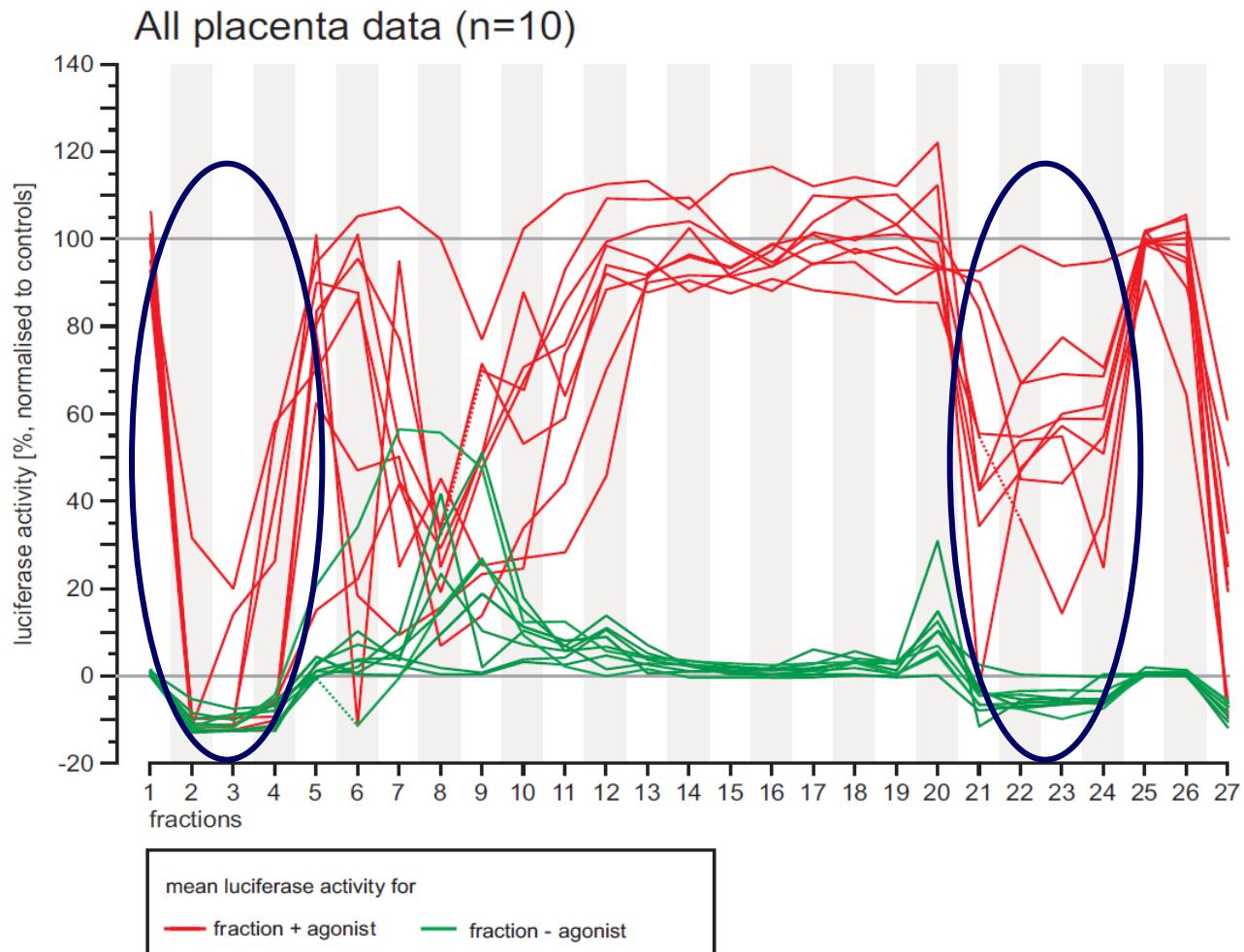
Human health studies: painkillers in pregnancy



- **Five studies**, 2 in Denmark, 1 in USA, 1 in The Netherlands, 1 in France
- Up to 4-fold higher chance of having a baby with **testis maldescent**
- Risk largest during **2nd trimester**
- Based on questionnaire results

Effect-directed analysis

Placenta
extracts,
profiled with
AR-reporter
gene assay



Acknowledgements

- European Commission
- EDEN project
- CONTAMED project
- Chemix (ANSES)



contamed

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Thank you

