Exposure to chemical mixtures:

A public concern

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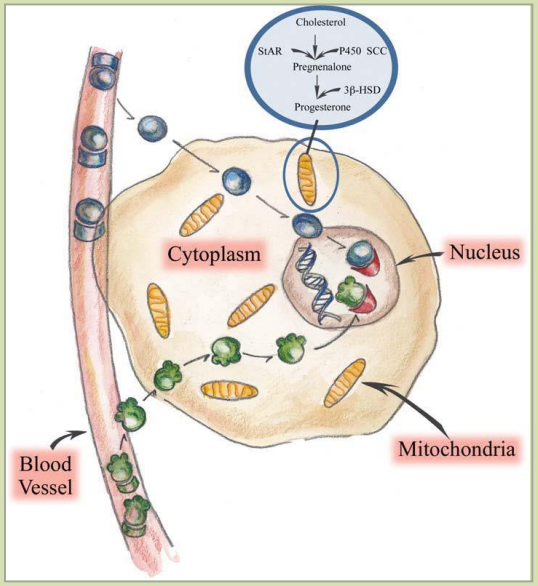
EFSA-RIVM Utrecht, 18th May 2016, The Netherlands

Pesticides

Deliberately made to be toxic to living organisms

- Cellular sites in target species similar to humans and other animals

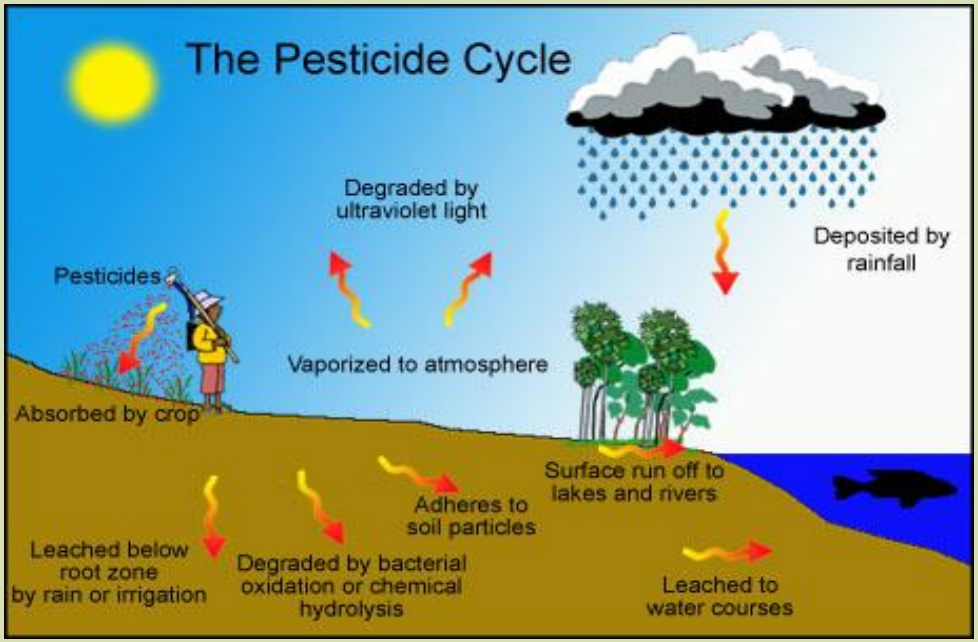


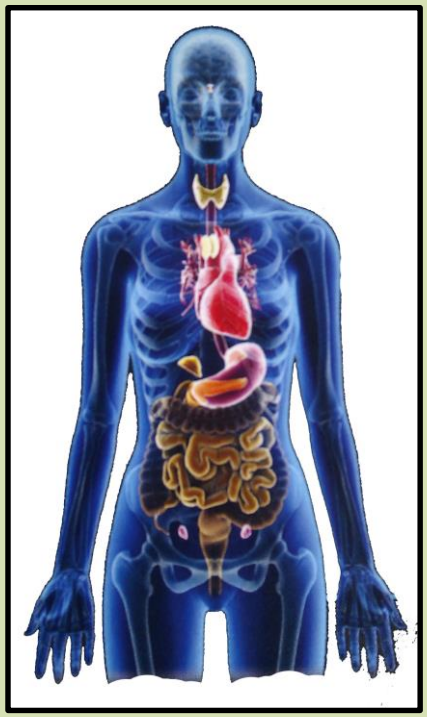
Pesticides are toxic to non-target species and humans

Low solubility ⟶ Contamination of ecosystems

Pesticides

Detected in: biota, soil, sediments, water systems, human tissues and blood, including newborns.





EU sales: 300,000,000 kg/year

Pesticide residues in food

Fruit or Vegetable	With residues	With multiple residues	Max residues/sample
Apples	67%	46%	**17**
Lettuce	58%	36%	**13**
Peaches	75%	53%	**15**
Strawberries	76%	63%	**15**
EU (Average)	47.2%		

European Food Safety Authority (2015)

ED-pesticides and humans

Endocrine-related cancers

endometri

prostate

breast

testicula

r

ovarian

thyroid

pancreas

brain tumours

Reproductive dysfunction

Reproductive organ

malformations

infertili

ty

foetal

sperm

quality

miscarria

ge

early growth

puberty

Neuro-developmental disorders

autism

behaviour

Learning deficit

impaired

cognition

Metabolic

obesity

diabetes

body weight

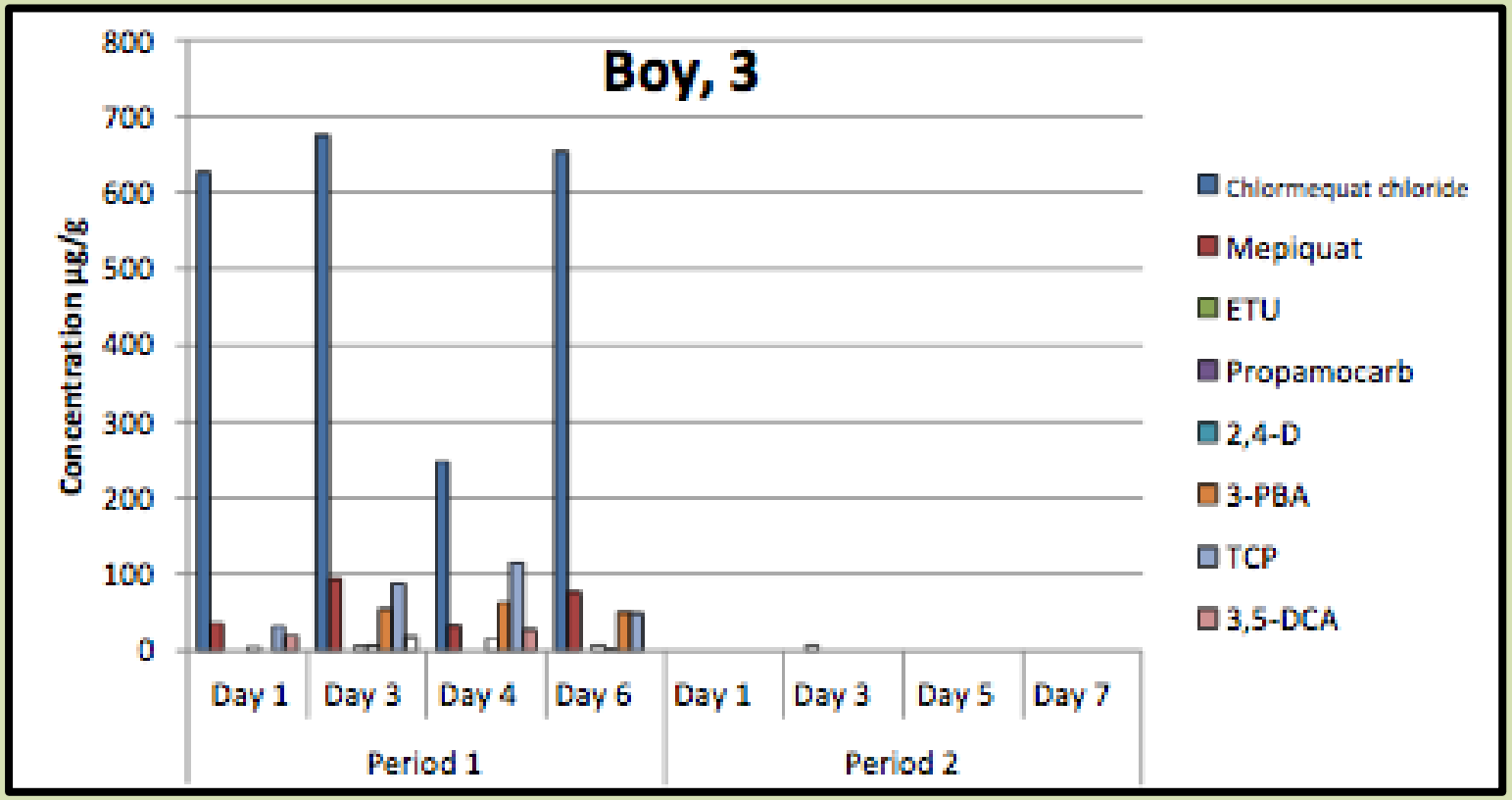
Neurodegenerative diseases

Parkinson

Alzheimer

Reality – exposure to pesticides

Correlation of pesticides in urine with high vegetable and fruit consumption (IVL, 2015).



Exposure to chemicals

Multiple routes of exposure, Multiple chemicals

Inhalation

Skin Contact

Ingestion

Air

Water

Food

+ hundreds of environmental pollutants

Daily Chemicals

Toxicity testing – Chemicals Safety

One species
Laboratory breed
(less responsive?)

Isolated environment
Dietary exposure to a single chemical

No observed adverse effect level (NOAEL)

Uncertainty factor (÷100)

Acceptable daily intake (ADI)
Acute Reference Dose (ARfD)
Maximum Residue Limit (MRL)

Highly unrealistic

Legal requirements - pesticides

PPPR (EC) 1107/2009, Article 4 (3b):

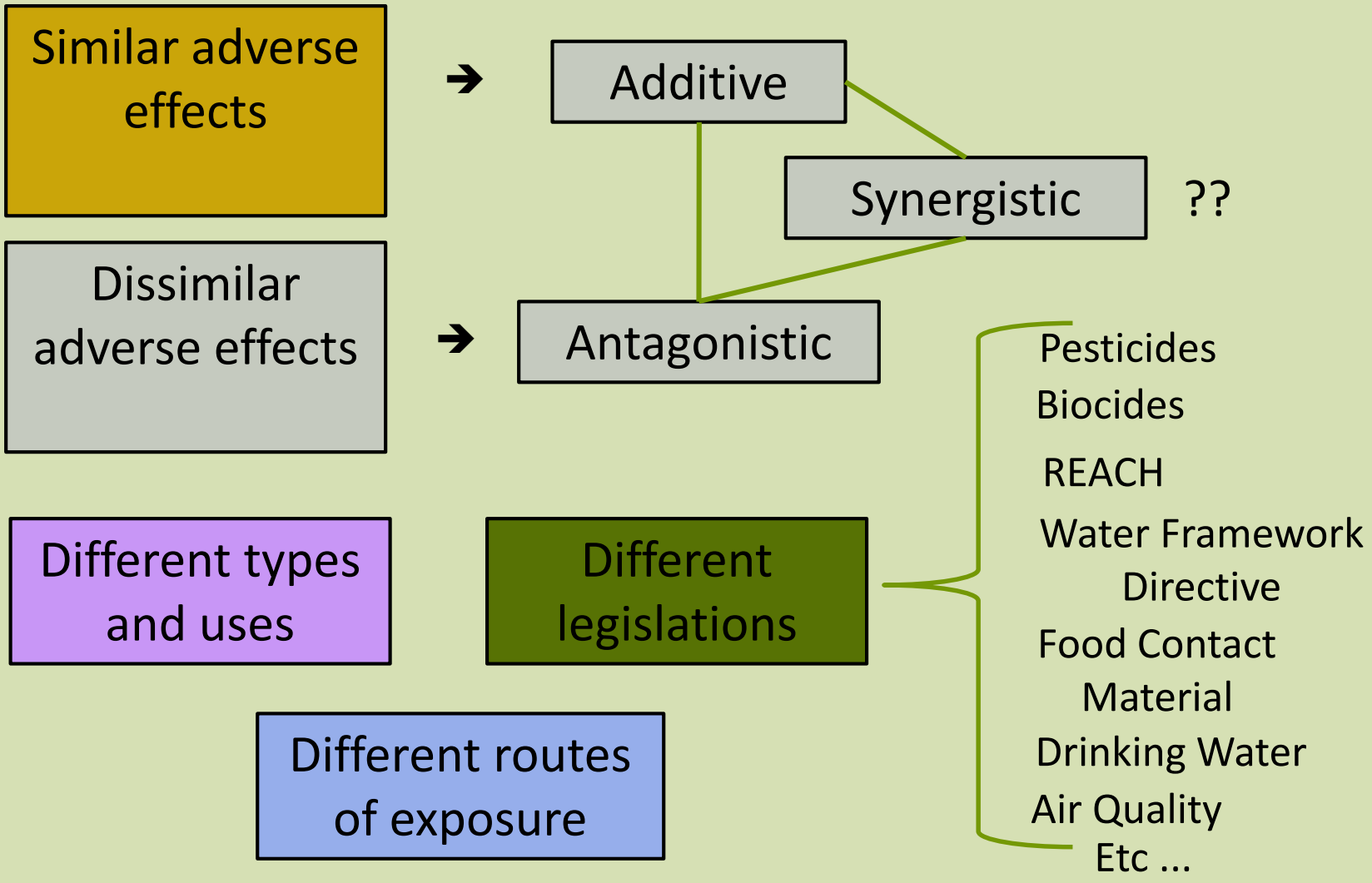
"*it shall have no immediate **or delayed harmful effect on human health**, including that of vulnerable groups, or animal health, directly or through drinking water (taking into account substances resulting from water treatment), food, feed or air, or consequences in the workplace or through other indirect effects, **taking into account known cumulative and synergistic effects** where the scientific methods accepted by the Authority to assess such effects are available; or on groundwater*"

MRL 396/2005, recital 6:

"*It is also important to carry out further work to develop a methodology to take into account cumulative and synergistic effects.* "

A true assessment of chemicals is urgent

Assessment of mixtures: A complex issue

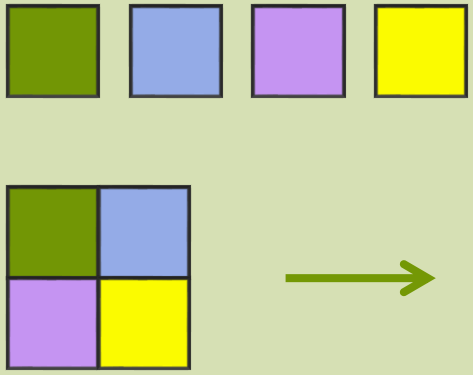


Mixture effects – Study 1: similar adverse effects

developmental toxicity study: gestation ➔ pups

Endocrine endpoints: ♂ anogenital distance (AGD); genital malformations, nipple retention

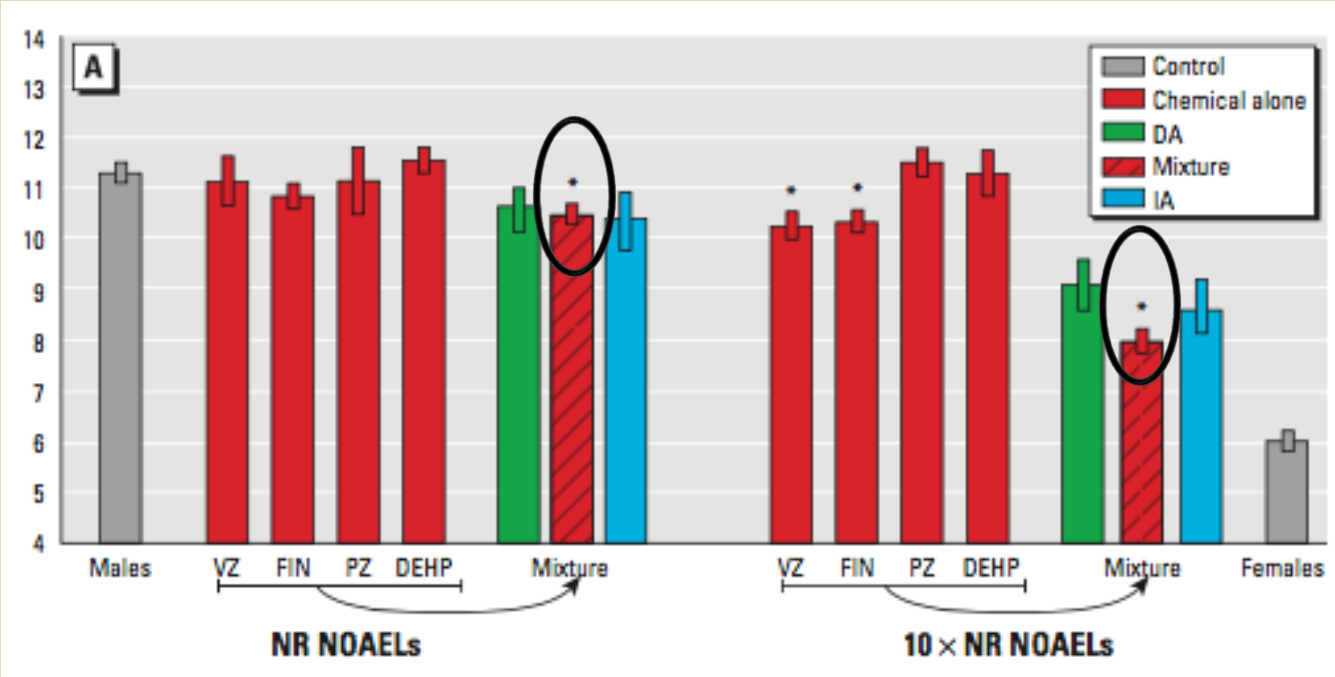
- Anti-androgens:
  - DEHP
  - Vinclozolin
  - Prochloraz
  - Finasteride



Christiansen S, Scholze M, Dalgaard M et al (2009). Synergistic Disruption of External Male Sex Organ Development by a Mixture of Four Antiandrogens. Environ Health Perspect, 117:1839–1846.

Mixture effects – Study 1: similar adverse effects

♂ AGD



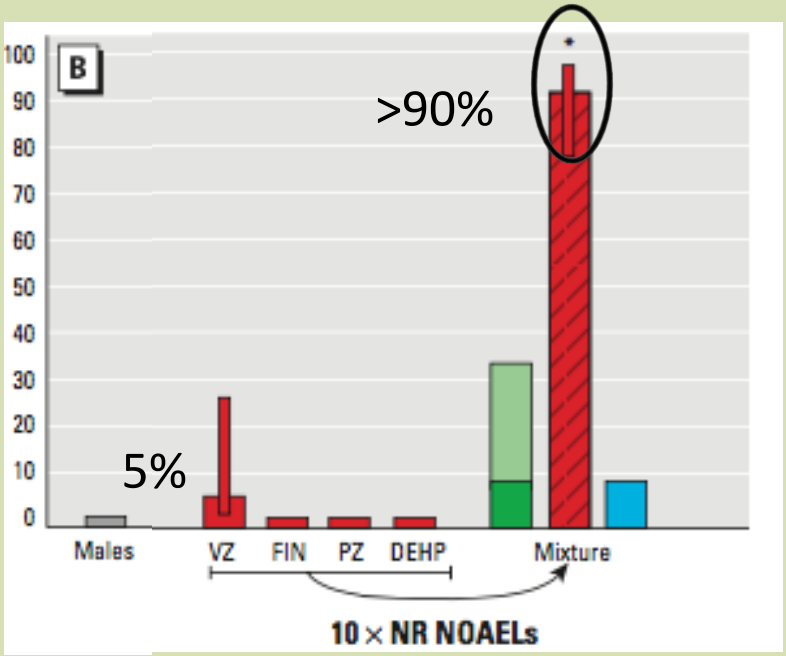
additive

synergistic

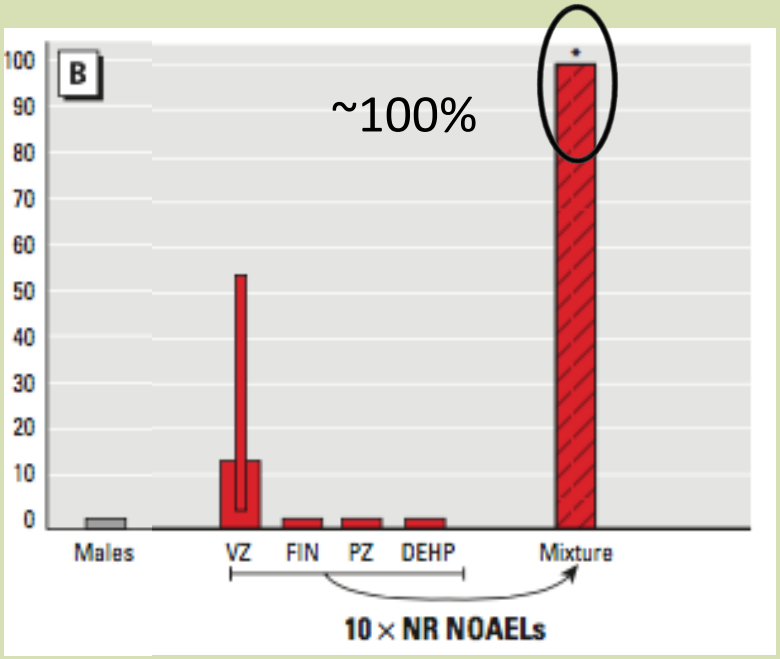
Christiansen S, Scholze M, Dalgaard M et al (2009). Synergistic Disruption of External Male Sex Organ Development by a Mixture of Four Antiandrogens. Environ Health Perspect, 117:1839–1846.

Mixture effects – Study 1: similar adverse effects

♂ Genital malformations % D16



♂ Genital malformations % D47



synergistic

Christiansen S, Scholze M, Dalgaard M et al (2009). Synergistic Disruption of External Male Sex Organ Development by a Mixture of Four Antiandrogens. Environ Health Perspect, 117:1839–1846.

Mixture effects – Study 2: Same uses ≠MoA

developmental toxicity study: gestation ➔ pups

Endocrine endpoints:
- ♀ gestation cycle, anogenital distance (AGD)
- ♂ genital malformations, nipple retention

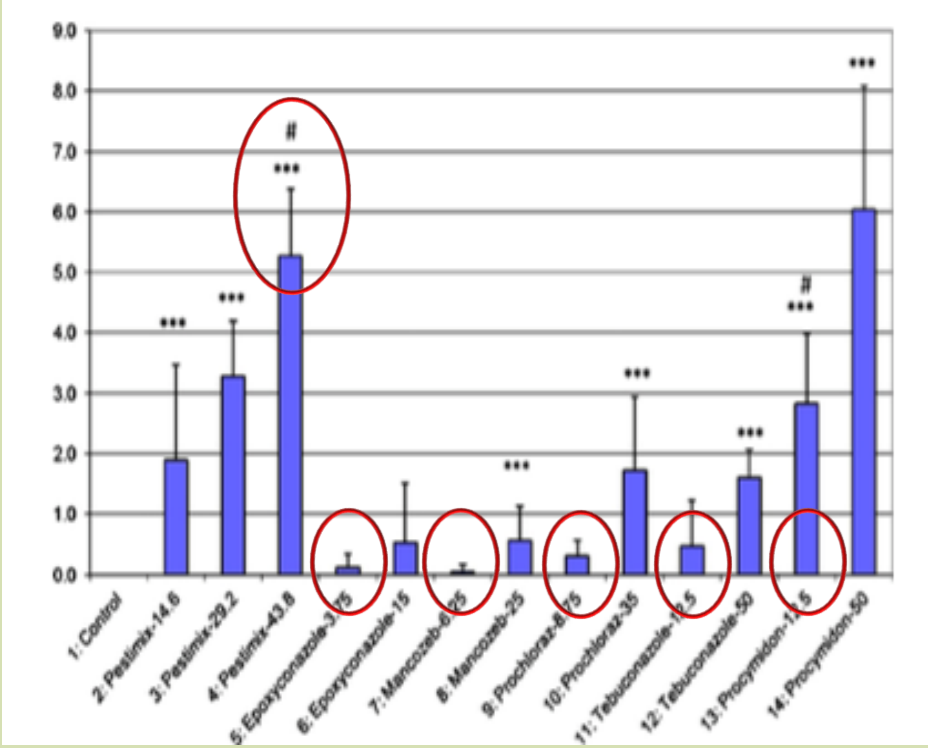
- Pesticides (≠MoA):
  - Epoxiconazol
  - Tebuconazol
  - Prochloraz
  - Mancozeb
  - Procymidone

< NOAEL or LOAEL

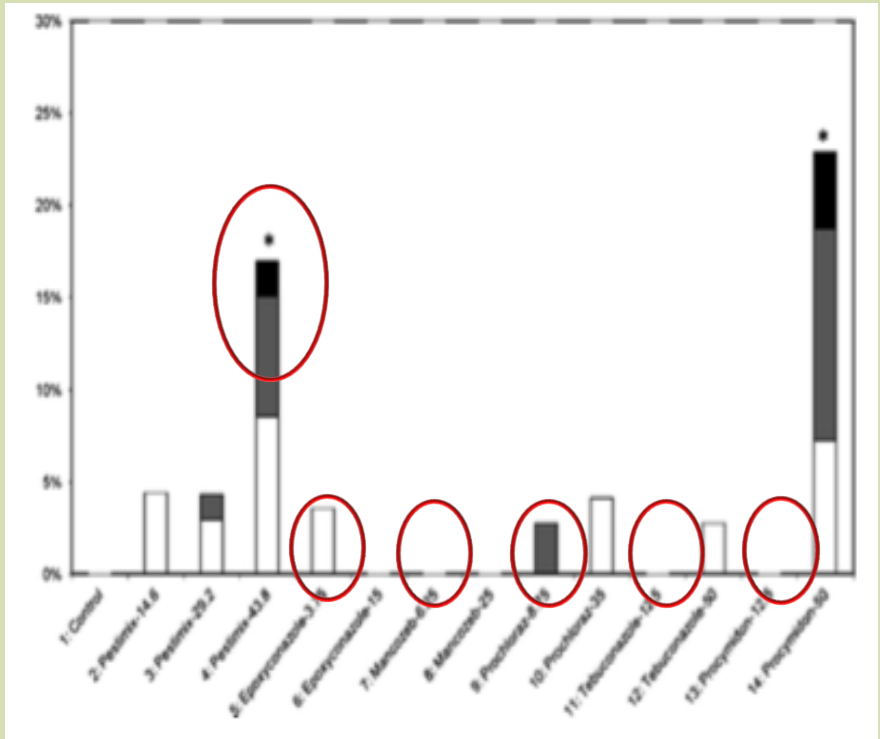
Hass U, Boberg J, Christiansen S, et al (2012). Adverse effects on sexual development in rat offspring after low dose exposure to a mixture of endocrine disrupting pesticides. Repro Toxicol, 34:261-274

Mixture effects – Study 2: Same uses ≠MoA

♂ Nipple retention



♂ Genital malformations



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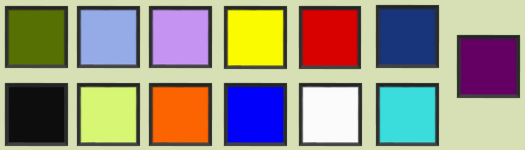
Mixture effects – Study 3: Realistic exposures

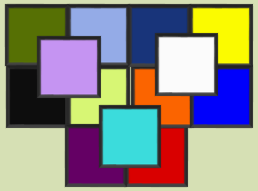
developmental toxicity study: gestation ➔ pups

Endocrine endpoints: ♂ nipple retention

- 13 chemicals:
  9 anti-androgenic
  4 estrogenic
  - Phthalates
  - BPA
  - Pesticides
  - UV-filters
  - Parabens
  - Paracetamol



<< NOAEL
150 & 450 human exposure



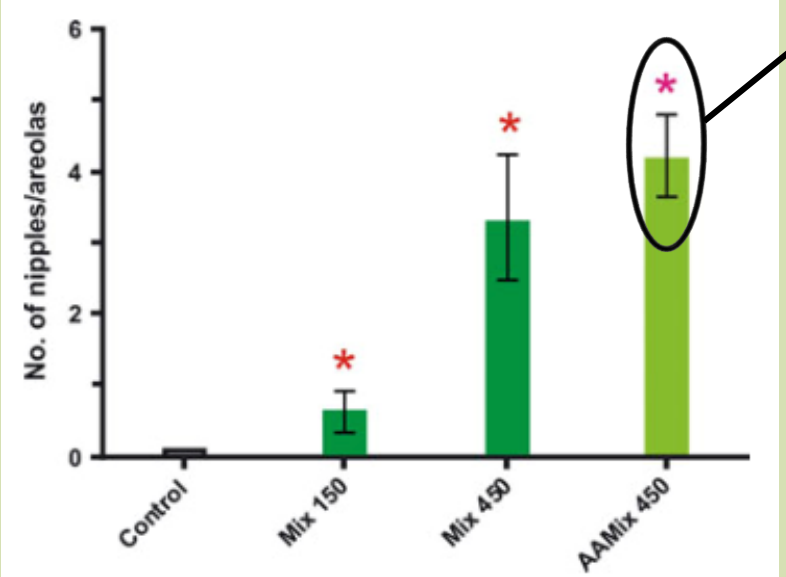
??

PODI (point of departure index)= 0.016

Christiansen S, Kortenkamp A, Axelstad M et al (2012). Mixtures of endocrine disrupting contaminants modeled on human high end exposures: An exploratory study in rats. Int J Androl, **35**:303-316.

Mixture effects – Study 3: Real life exposures

♂ Nipple retention



Only 9 anti-androgens

Christiansen S, Kortenkamp A, Axelstad M et al (2012). Mixtures of endocrine disrupting contaminants modeled on human high end exposures: An exploratory study in rats. Int J Androl, **35**:303-316.

The reality – mother's milk (2006) – 26 chemicals

Personal Care Products & diverse	
UV filters	100 %
Musks	87%
Parabens	25.9%
Phthalates	100%

Industrial POPs	
PCBs	100%
PBDE	100%

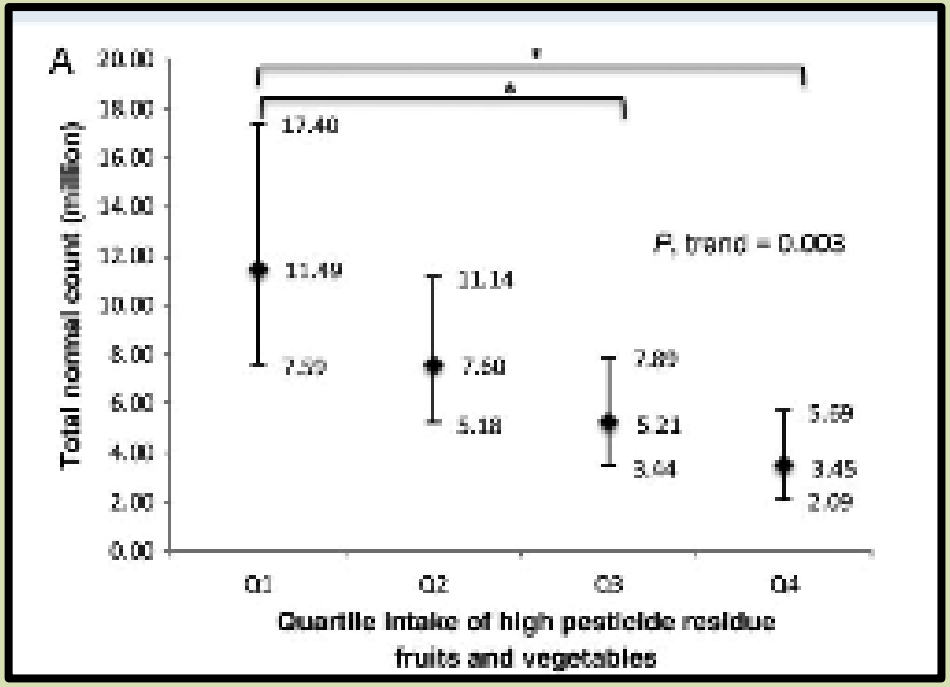
Pesticides	
DDT, HCH, HCB	100%
Chlorpyrifos	37%

Schlumpf M, Kypke K, Wittassek M, et al (2010). Exposure patterns of UV filters, fragrances, parabens, phthalates, organochlor pesticides, PBDEs, and PCBs in human milk: Correlation of UV filters with use of cosmetics. Chemosphere 81:1171-1183

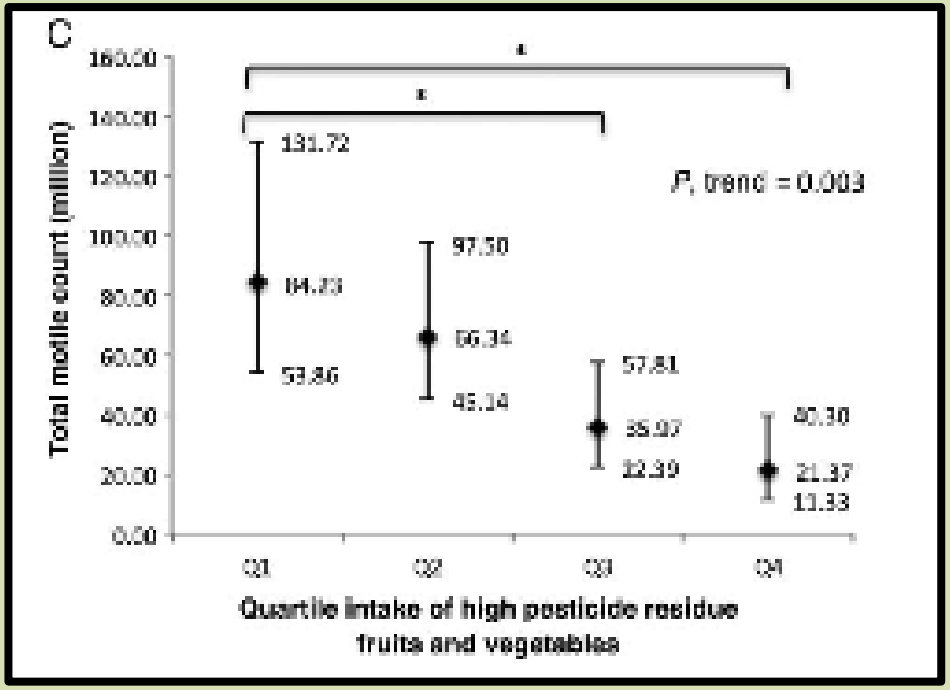
Reality - pesticides

Correlation of pesticide exposure and sperm quality (n=155)

♂ Sperm normal count (n=338)

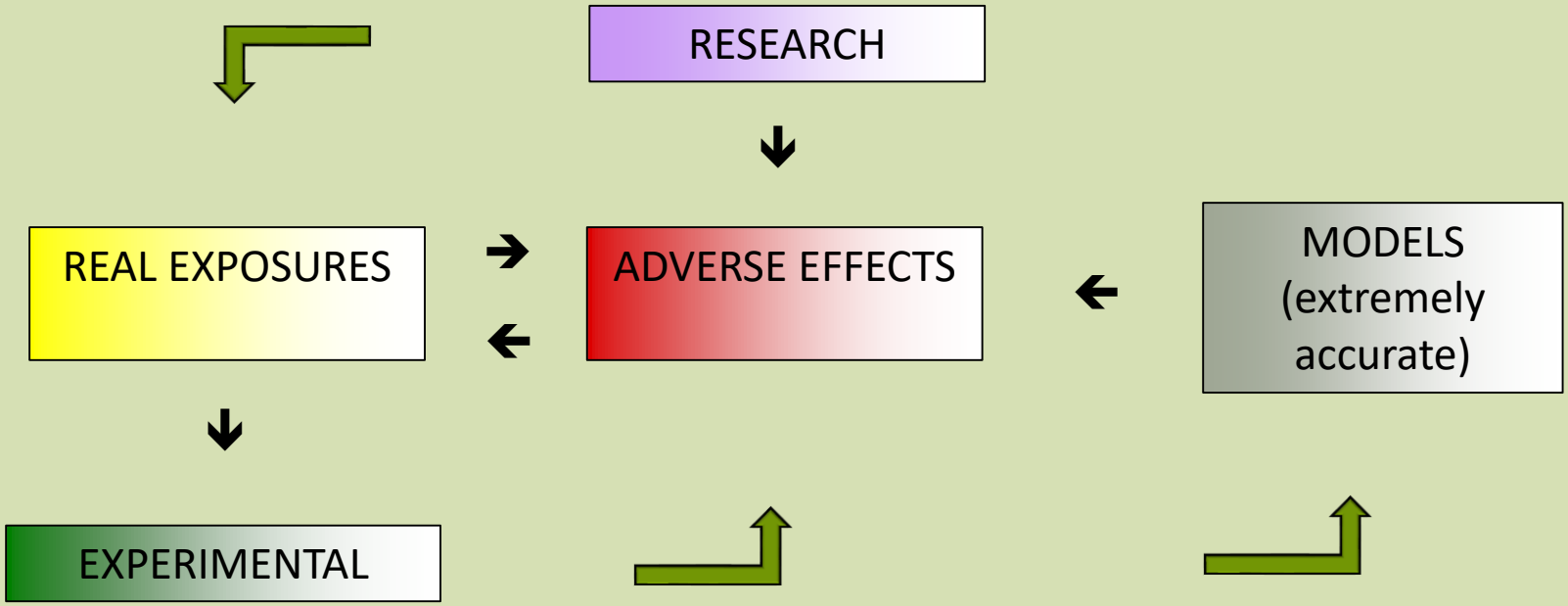


♂ Sperm motility (n=338)



Chiu YH, Afeiche MC, Gaskins AJ, Williams PL et al (2015). Fruit and vegetable intake and their pesticide residues in relation to semen quality among men from a fertility clinic. Human Repro 0:1-10.

Accurate assessment



Accurate assessment = conservative assessment

Final remarks

- Humans are unprotected from mixtures
  - ADI not sufficient ➔ Mixture assessment factor is urgent
- We need field monitoring/clinical data
  - Low dose effects
- Horizontal assessment across types of chemicals
- Avoid over-simplified models
- Urgent need to reduce human and environmental exposure to hazardous chemicals

The dose makes the poison?

The mixture makes the poison!

Thank you!