



**Pesticide
Action
Network**
Europe

Exposure to chemical mixtures: A public concern

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

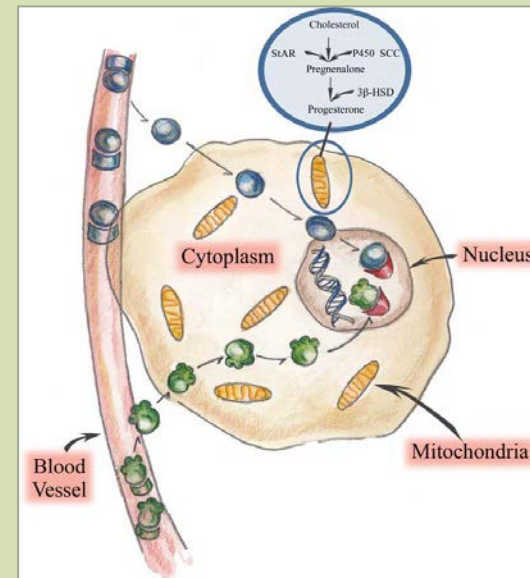


Pesticides

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

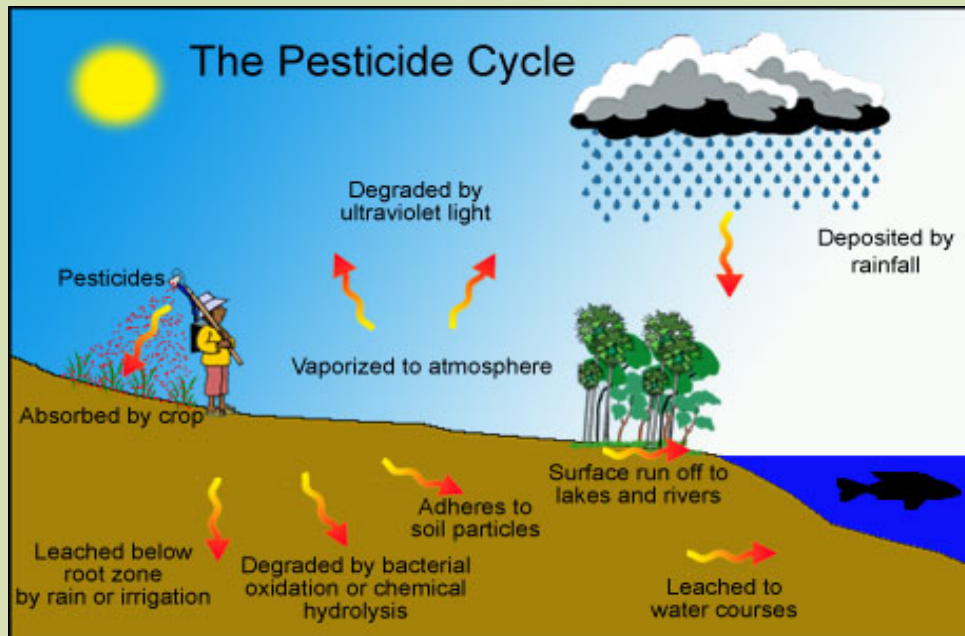


+ Low solubility → Contamination of ecosystems



Pesticides

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



EU sales: 300,000,000 kg/year

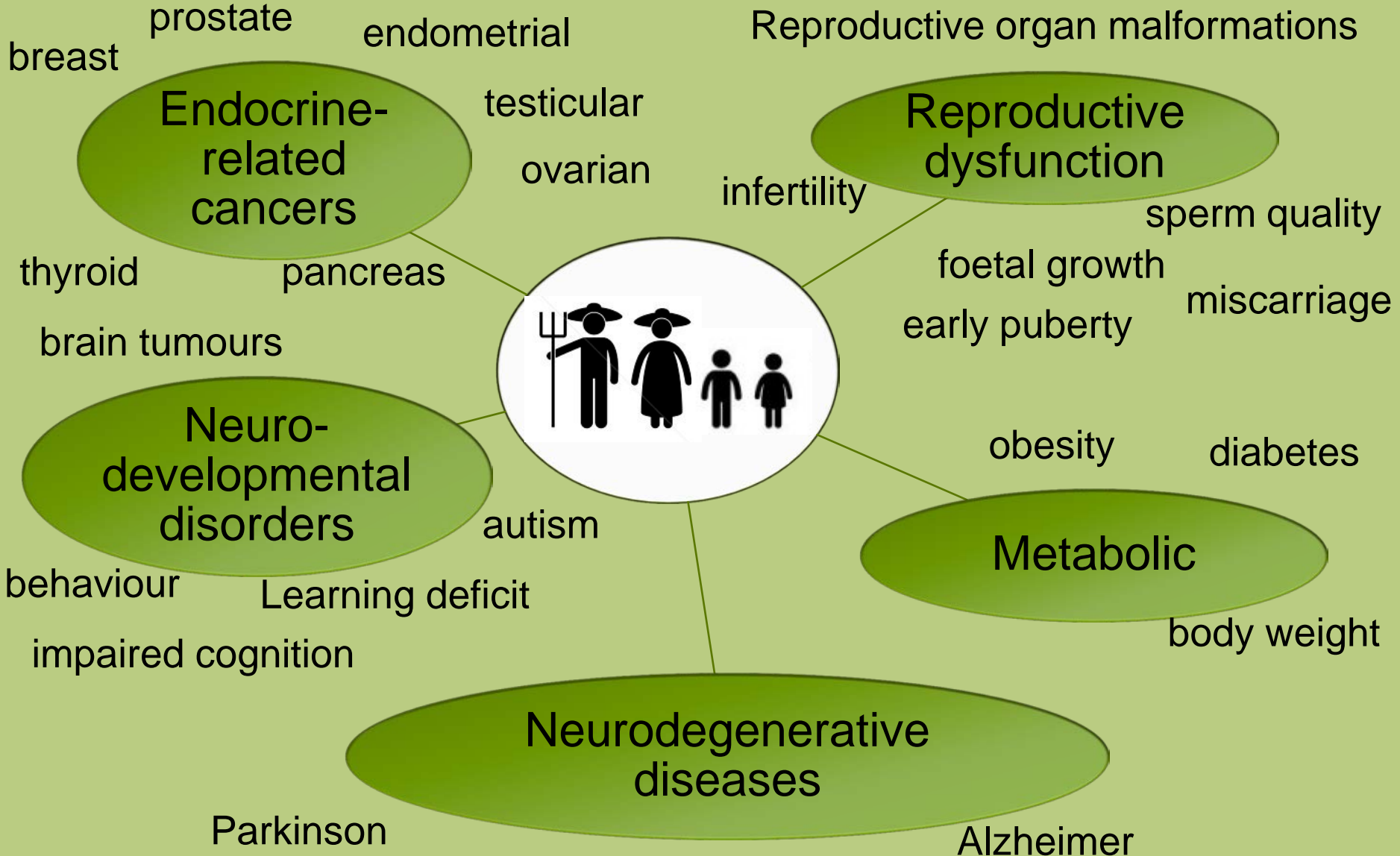
Pesticide residues in food



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

European Food Safety Authority (2015)

ED-pesticides and humans





Exposure to chemicals

Multiple routes of exposure, Multiple chemicals

Inhalation Skin Contact Ingestion

Air

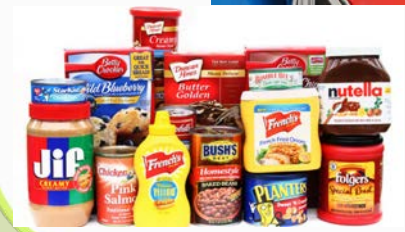
Water

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



Uncertainty factor
(÷100)



No observed adverse effect level
(NOAEL)



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

Highly unrealistic



Legal requirements - pesticides

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

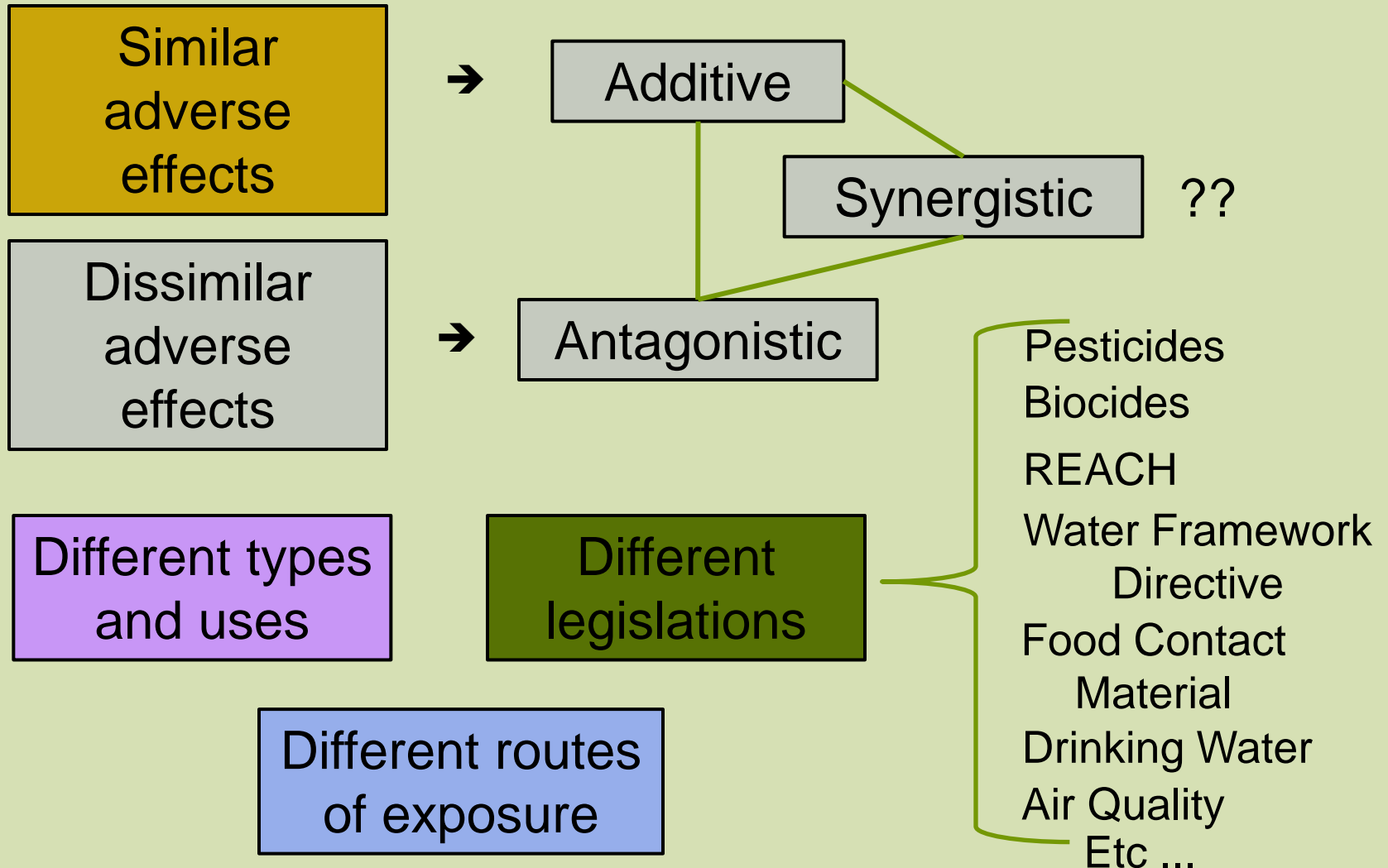
*“it shall have no immediate **or delayed harmful effect on human health**, including that of vulnerable groups, or animal health, directly or through drinking water (taking into account substances resulting from water treatment), food, feed or air, or consequences in the workplace or through other indirect 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 ♂ anogenital distance (AGD)
endpoints: genital malformations, nipple retention

■ Anti-androgens:

- DEHP
- Vinclozolin
- Prochloraz
- Finasteride



< NOAEL or
10 x NOAEL



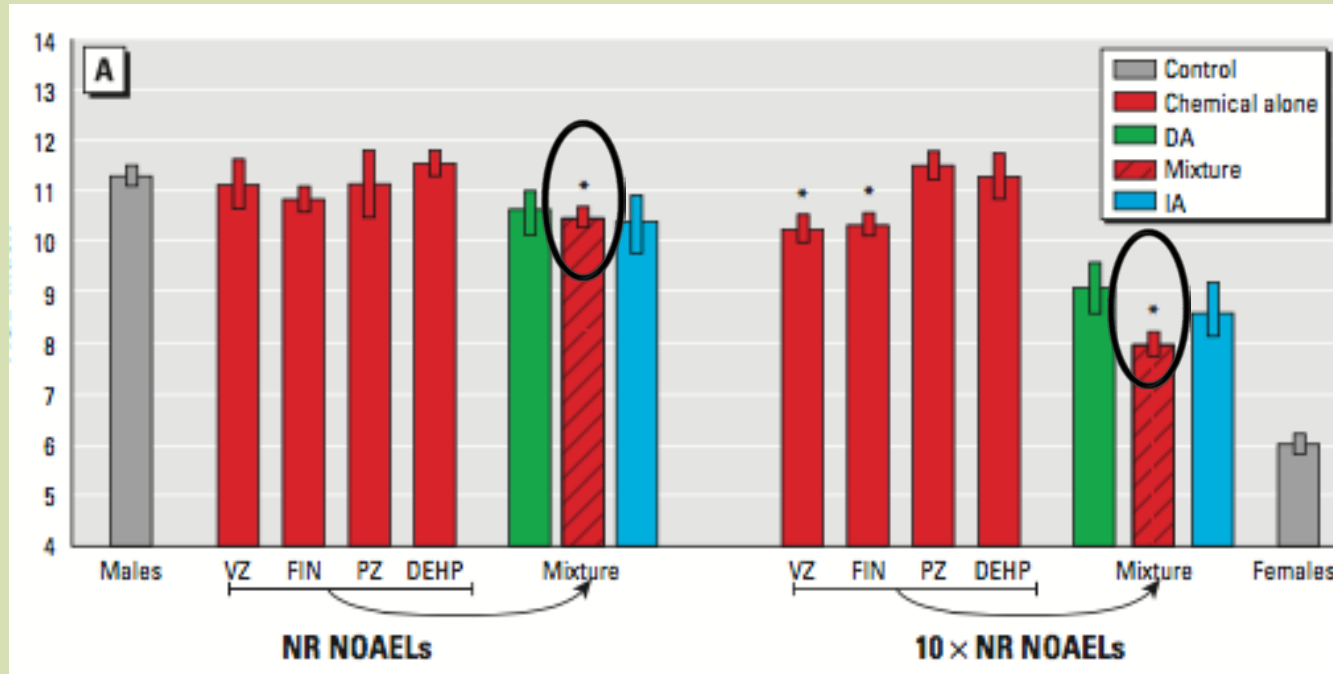
??

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

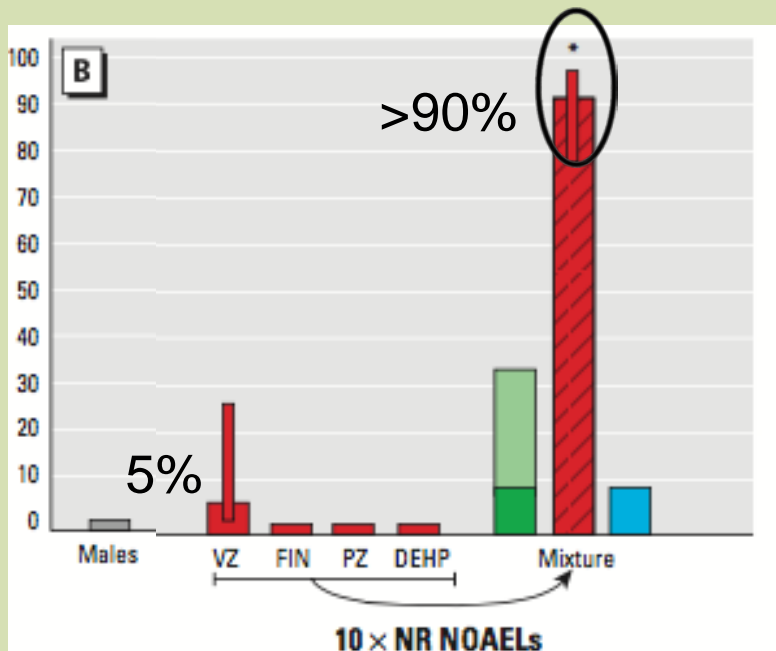
synergistic

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.

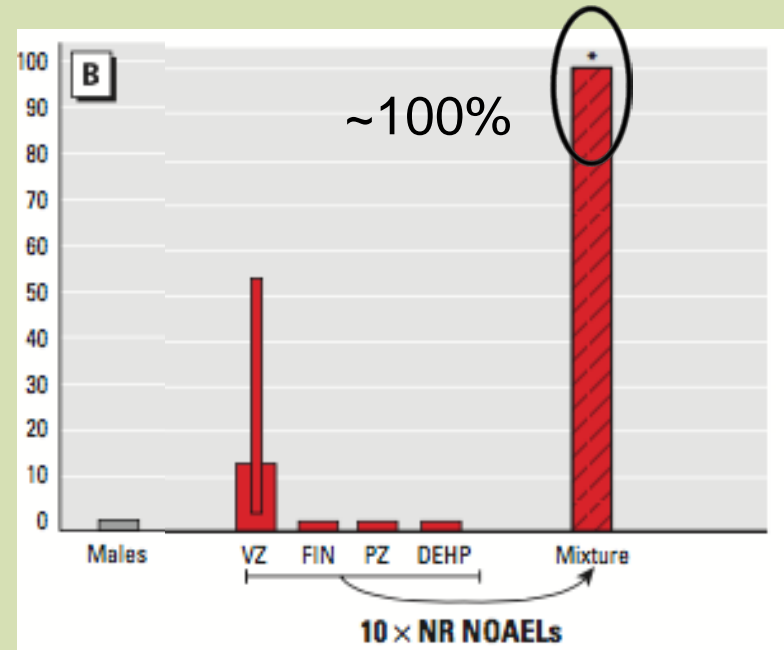
Mixture effects – Study 1: similar adverse effects



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

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

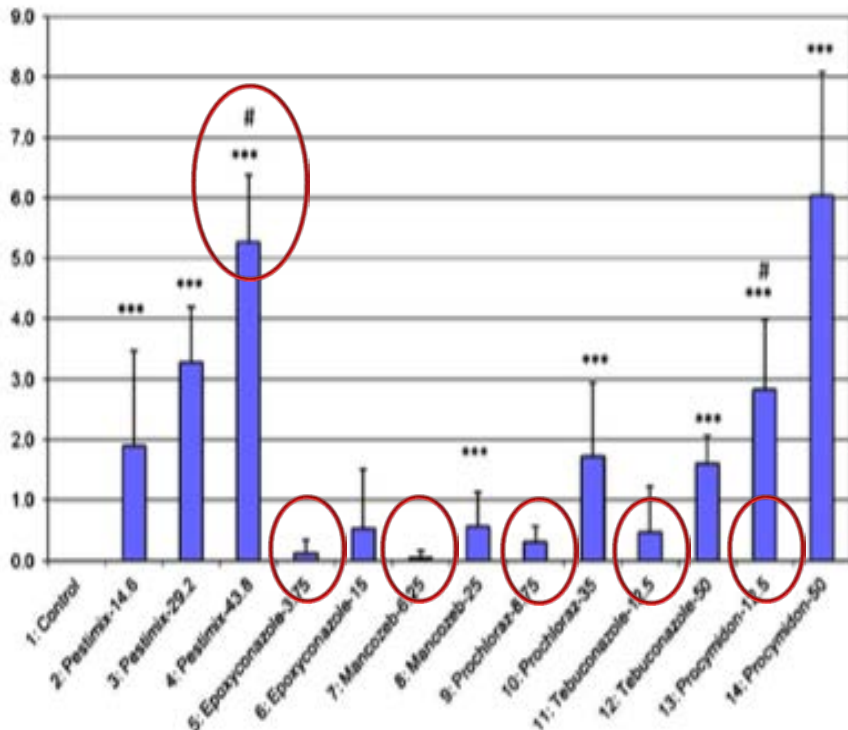


Hass U, Boberg J, Christiansen S, et al (2012). Adverse effects on sexual development in rat offspring after low dose exposure to a mixture of endocrine disrupting pesticides. *Repro Toxicol*, 34:261-274

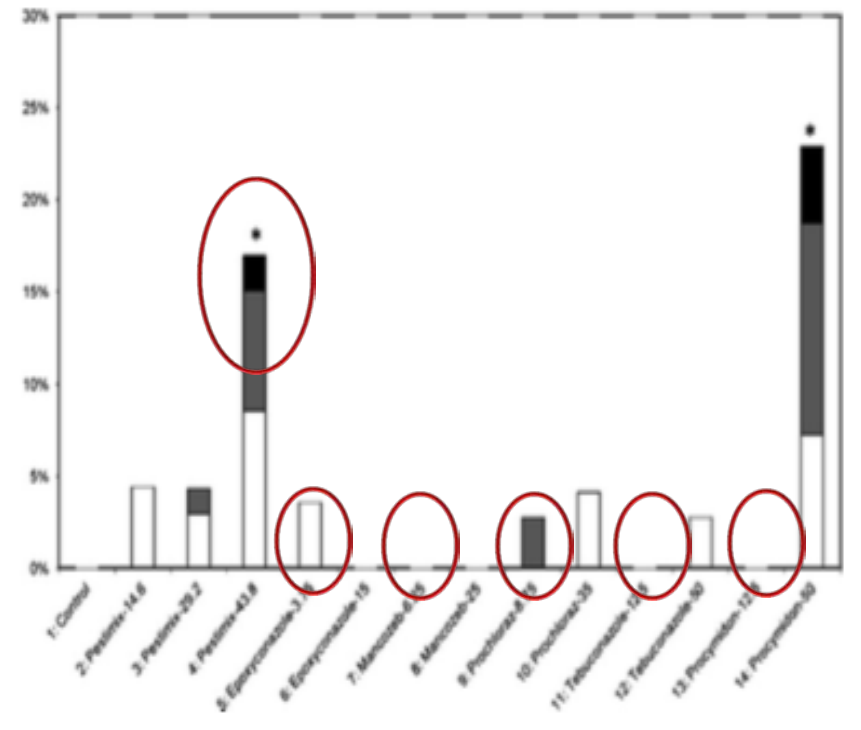
Mixture effects – Study 2: Same uses ≠MoA



♂ Nipple retention



♂ Genital malformations



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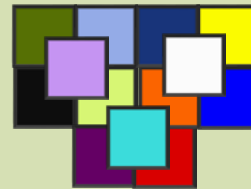
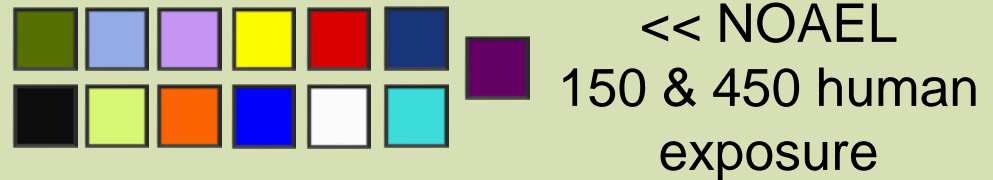
Mixture effects – Study 3: Realistic exposures



developmental toxicity study: gestation → pups

Endocrine endpoints: ♂ nipple retention

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



→ ??

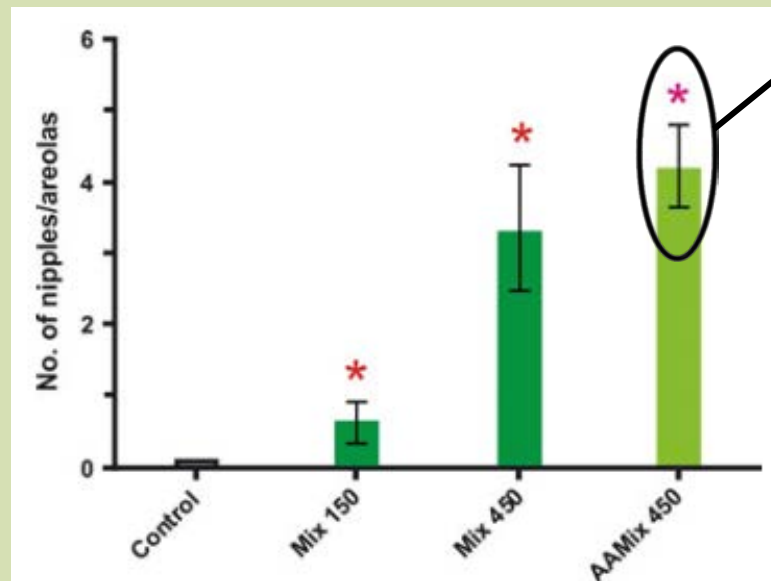
PODI (point of departure index)= 0.016

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

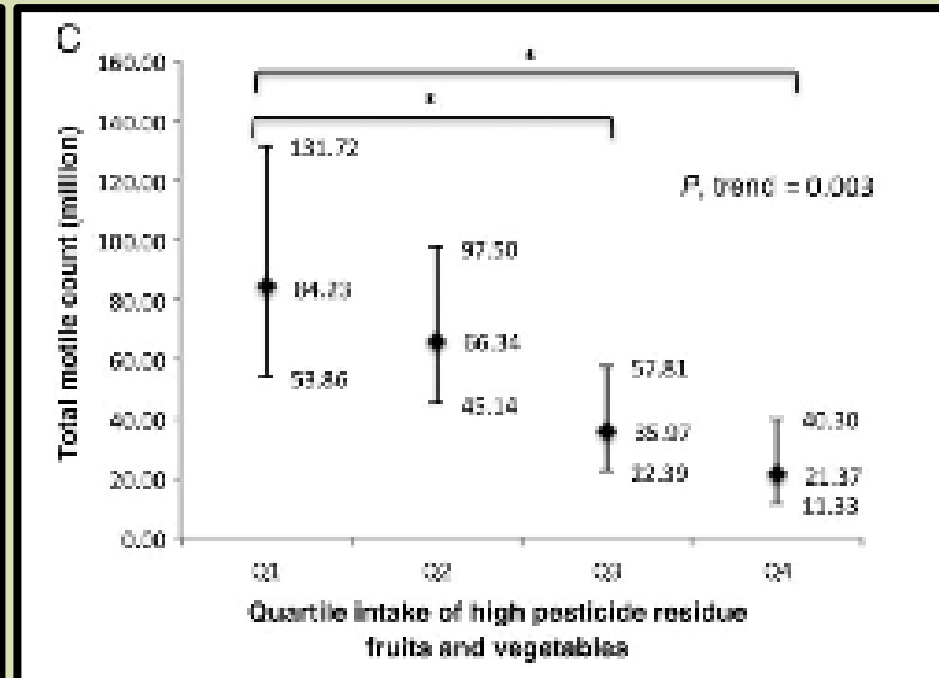
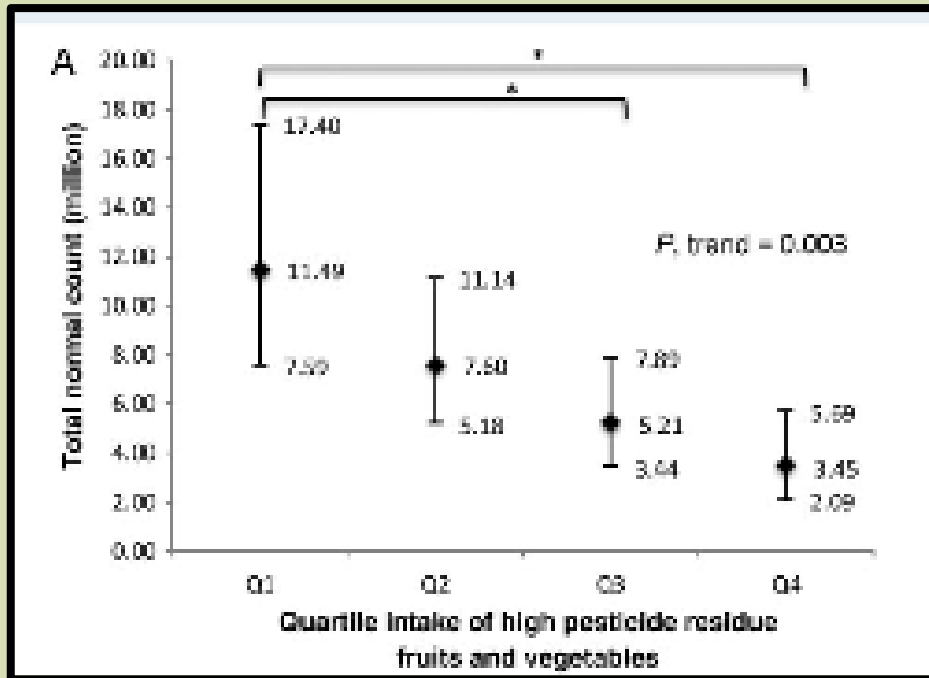
Reality - pesticides



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

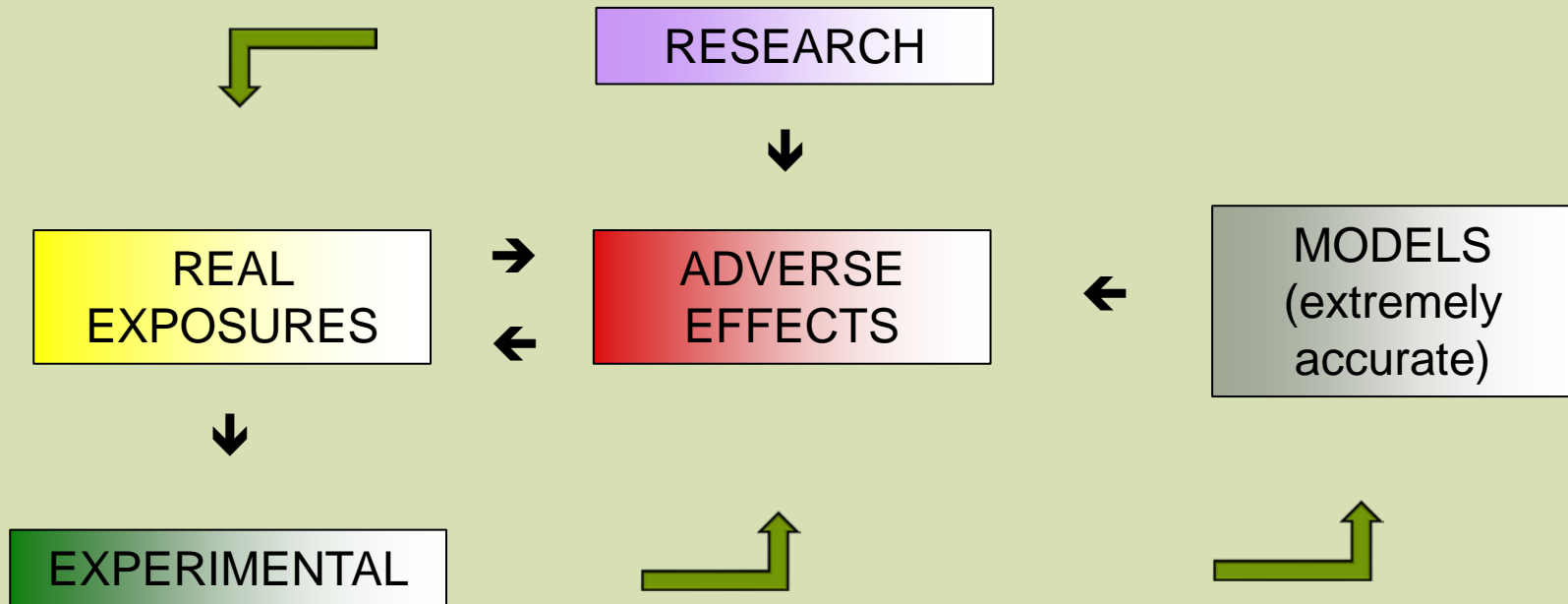
♂ Sperm normal count (n=338)

♂ 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!