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German Federal Institute for Risk Assessment

Diminished semen quality following early exposure to persistent organic pollutants (POPs) as critical effect in health risk assessment?

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Using epidemiological studies in health risk assessment

Associations of biological changes and parameters of exposure in observational studies

Clinical Relevance

Reliability

Overall evidence
Causality

'Effect' size, Adversity?

N (studies, participants)

Biolog. Plausibility

Consistency

Mode of action?
Reverse causation possible?

Variability of effect marker

Exposure assessment in critical window?

Dose range, Dose-Response

Co-Exposure?

Confounder?
Risk of Bias

Overview

Introduction: POPs (Dioxins, PFAS), Semen quality

Early **exposure and semen quality in adulthood: Dioxins and PFAS**
Critical effect of EFSA Dioxin opinion (2018)

Ulm Birth cohort study

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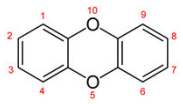
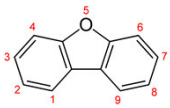
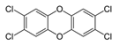
Persistent organic pollutants (POPs)

Polychlorinated Dibenzo-p-Dioxins



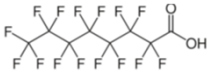
Polychlorinated Dibenzofurans





2,3,7,8-Tetrachlorodibenzo-p-dioxin, TCDD

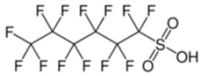
Perfluorinated Alkyl Substances (PFAS)



PFOA

PFOS

PFNA



PFHxS

Important environmental pollutants (high stability)
accumulating in the food chain und in humans (half-lives in the range of years)

Unwanted formation during combustion processes
Mode of Action: Ah-Receptor mediated
TWI: 2 **pg** TEQ per kg bodyweight per week

High volume production for many applications
Mode of Action: different receptors under discussion
TWI: 4.4 **ng** PFAS (EFSA 4) per kg bodyweight per week

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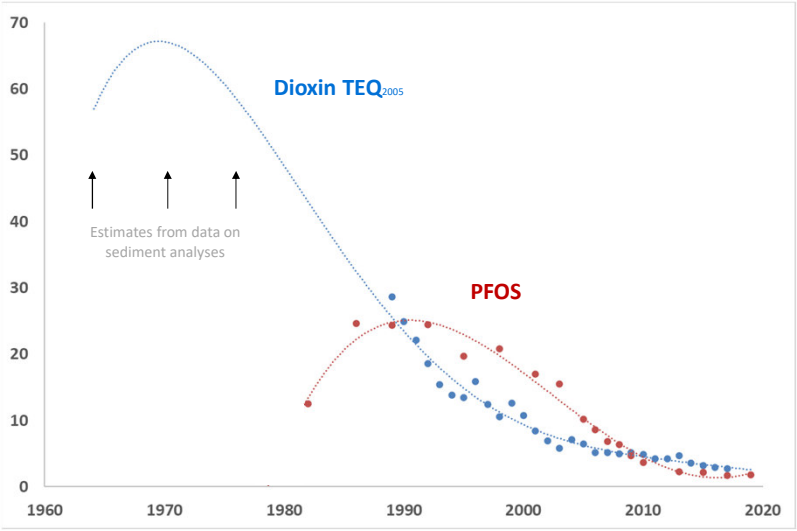
Time trends of internal exposure in Germany

pg/g milk fat ng/mL serum



Data:

Mother's milk (n=20 to 170 per year) measured at the Lebensmittel- und Veterinärinstitut Oldenburg
www.laves.niedersachsen.de

Umweltprobenbank des Bundes (n=20 per year, samples from Münster)
Schröter-Kermani et al., Int J Hyg Environ Health (2013)
Göckener et al., Environ Int (2020)

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Male infertility and 'Sperm crisis'

The Guardian 21.02.2021

Falling sperm counts 'threaten human survival', expert warns

Epidemiologist Shanna Swan says low counts and changes to sexual development could endanger human species

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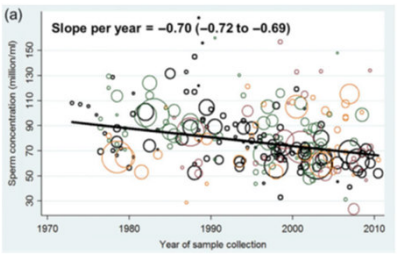
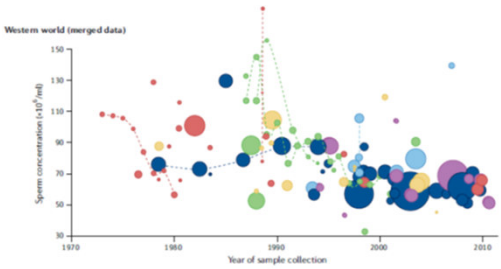
Time trends of sperm concentrations

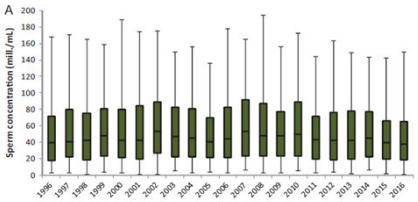


Levine et al., Hum Reprod Update (2017)



Auger et al., Nature Rev Urol (2022)

General population of Denmark: about 300 recruits investigated each year



Priskorn et al., Hum Reprod (2018)

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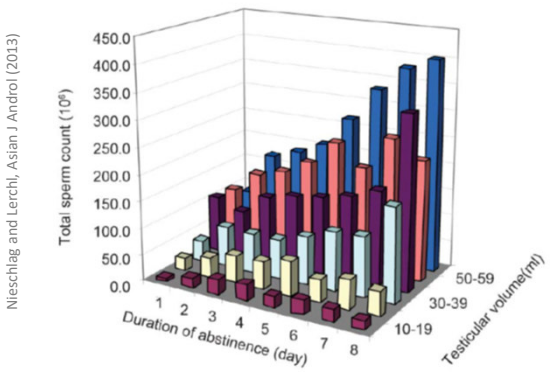
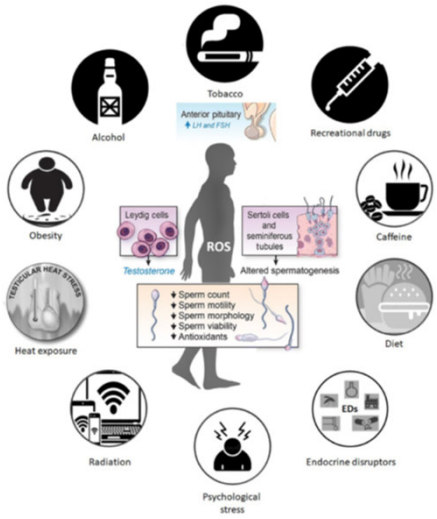
Sperm parameters: robustness?

Huge variability far above that of most other biological parameters
Many factors potentially influence the result. They are difficult to control.





Influencing factors: onset of puberty, age
Technical factors: transport (temperature, duration), experience of the technician

Leisegang and Dutta, Andrologia (2020)

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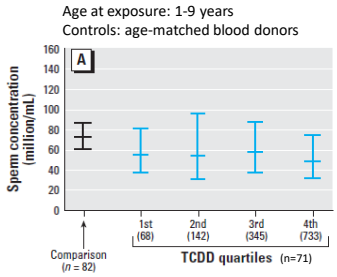
Evidence: *early* dioxin exposure and semen quality in adulthood

Experimental data in animals with exposure during gestation and lactation:
Reduced sperm production in rats and primates

High exposure to TCDD in humans:
Seveso incident 1976

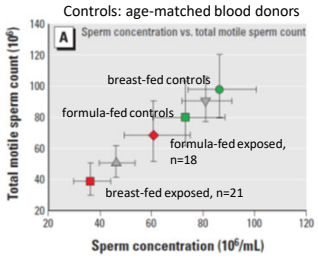
Picture
children with choracne

Impaired semen quality only in those men who were prepubertal at the time of the incident



Mocarelli et al., EHP (2008)

Impaired semen quality only in those men born to exposed mothers who were breast-fed.



Mocarelli et al., EHP (2011)

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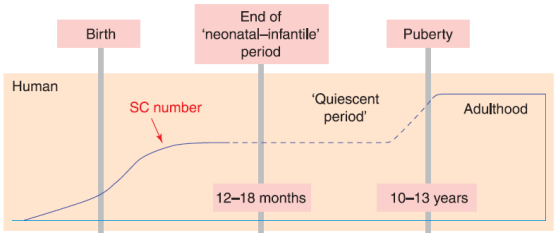
Early dioxin exposure and semen quality: critical window of exposure?

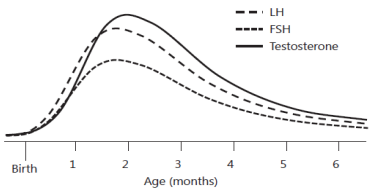
Hypothesis:
Exposure during a critical window in early childhood
leads a permanent effect on semen production measurable in adulthood.

Timing of maturation of Sertoli cells



Sharpe et al., Reprod (2003)

' Minipuberty'



Kuiri-Hänninen et al., Horm Res Paediatr (2014)

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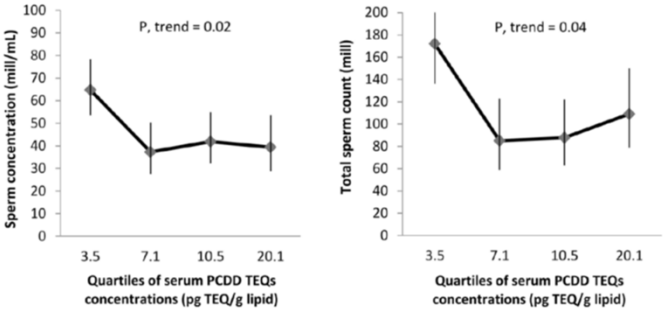
Evidence: *early* dioxin exposure and semen quality (on background level)

Russian Children's Study: Mínguez-Alarcón et al., EHP (2017)

Semen quality measured in 133 young men (age 18-19 years) from Chapaevsk, a Russian industrial city.
They were exposed to high environmental background levels (measured at the age of 8-9 years).

Higher quartiles of dioxin TEQ were associated
with lower sperm concentration and total sperm count.



Mínguez-Alarcón et al., EHP (2017)

Key study of
EFSA Opinion on dioxins (2018)

NOAEL serum level for PCDD/Fs of 7.0 pg TEQ/g fat at the age of 9 years was selected, based on the median level in the lowest quartile.

A toxicokinetic model was used to estimate the daily intake (of 0.25 pg TEQ/kg bw per day) leading to a serum level of 7.0 pg TEQ/g fat at the age of 9 years, taking into account breastfeeding for 12 months. A level in human milk of 5.9 pg TEQ/g fat would result in the NOAEL serum level.

A TWI of 2 pg TEQ/kg bw per week was derived.

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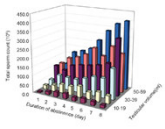
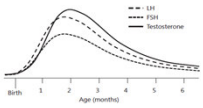
Public Consultation of EFSA: BfR was not convinced by the approach

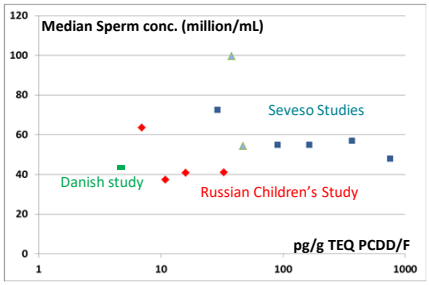
- Parameters of sperm quality: **low robustness, many influencing factors**





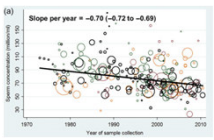
- Russian Children's Study
Critical window of exposure: no justification given for investigations at age of 8-9 years, not reflecting the exposure in the first year of life.

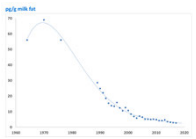
Co-exposure to other chemicals? Site of chemical production



- **Dose-response (overall and within the studies): not convincing**

- **Time trend data on the global 'sperm crisis' do not match** with a relevant negative effect of dioxins.





BfR conclusion:
more data is needed, new study initiated with the Ulm birth cohort

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Evidence: *Early* PFAS exposure and semen quality in adulthood

Danish study on semen quality (FEPOS cohort)
Hærvig et al. EHP (2022)

Semen quality measured in 864 young men (age 19-21 years)
PFAS measured in maternal plasma from early pregnancy

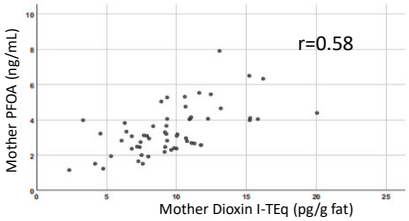
Complex evaluation:
combined maternal PFAS exposure was associated with

- lower sperm concentration (−8%; 95% CI: −16%, −1%)
- lower total sperm count (−10%; 95% CI: −17%, −2%)

Main contributor: Perfluoroheptanoic acid (PFHpA)

Experimental data in animals: not available
Data on high exposure in humans: not available

Dioxins not discussed in the paper, but a relevant correlation of PFAS and dioxins can be expected



Abraham EHP (2023)

Medians: PFOS 27.6 ng/mL PFHpA 0.06 ng/mL
PFOA 4.4 ng/mL

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Ulm Birth cohort

Baseline (2001)
Mothers: n=1066
age 31.0 ± 5.2 years
parity 1 (49%), 2 (36%), ≥ 3 (15%)
Questionnaire data, e.g. on duration of breastfeeding

boys: n=528

Samples stored:
Maternal serum
Breastmilk 6 weeks after delivery

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20-year follow-up (2021/22)
Male participants: n=98
age 20.4 ± 0.4 years
86% breastfed at 6 weeks

provided at least one semen sample (84%: two samples), analysed at the University Center for fertility and endocrinology
human milk samples (n=77 available), analysed for dioxins (Eurofins, HH)
maternal serum sample (n=92 available), analysed for PFAS (BfR)

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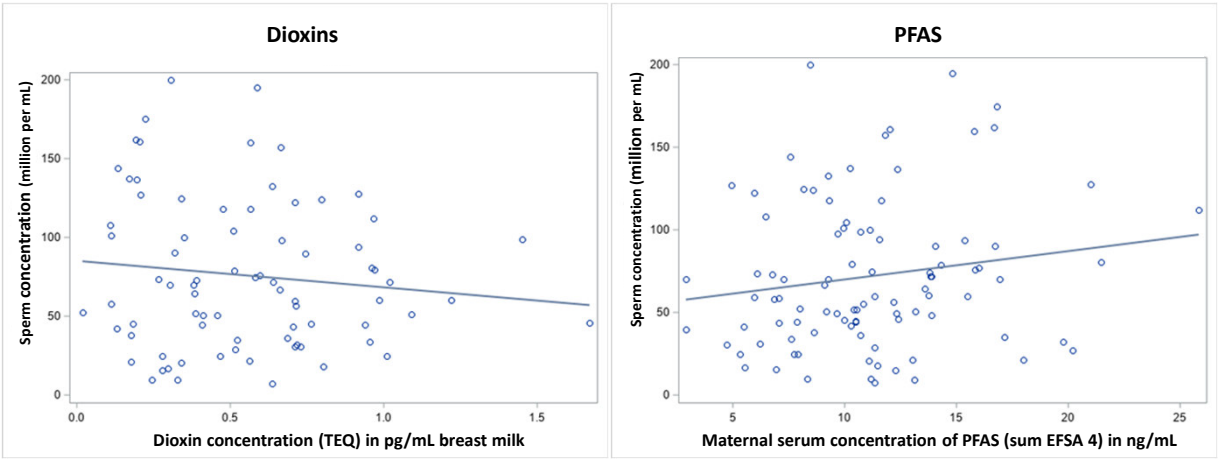
Ulm Birth cohort
First results: trends of sperm concentrations vs. POPs



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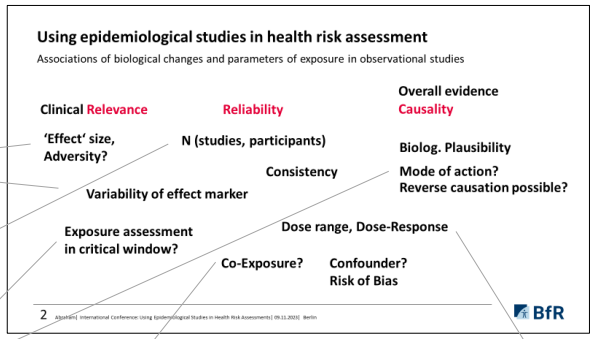
Conclusions
Dioxins and diminished semen quality

Semen quality may be relevant, but is very complex: huge variability, many influencing factors

Only 3 dioxin studies with relatively low numbers of participants

Critical window of exposure in (early) childhood assumed, but exposure measured in different periods of age, mode of action unknown



Dose-response of the 3 dioxin studies not convincing and consistent

Co-Exposure to other relevant POPs?

More data is needed, but it's not easy to conduct new studies: results in about 25 years, exposure meanwhile much lower
Use of old studies: usually not possible to analyse dioxin (not blood/milk available for analysis)

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