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# **Selected Seveso Cohort Papers are Inadequate for Derivation of an RfD**

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# Seveso Cohort Exposures Cannot be Used to Calculate Typical Daily TCDD Doses

- **Seveso exposure pattern is the result of massive exposure over a very brief period, followed by many years of reduced exposure**
- **This is very different from likely daily doses anticipated for U.S. population**

# Mocarelli et al., 2008

- **Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality**
- ***Environmental Health Perspectives* 116:70–77, 2008**

# Claim of Altered Sperm Parameters is Not Well-Substantiated

- **Sample population is not likely representative of general population**
  - Low participation rate
  - Small sample size

Participating Exposed Men			
Years of Age		n (% participate)	TCDD (ppt) Serum lipid basis [1976]
1976	1998		
<b>1-26</b>	<b>22-47</b>	<b>135 (33)</b>	<b>175</b>
1-9	22-31	71 (34)	210
10-17	32-39	44 (34)	164
18-26	40-47	20 (27)	123



# Claim of Altered Sperm Parameters is Not Well-Substantiated *(continued)*

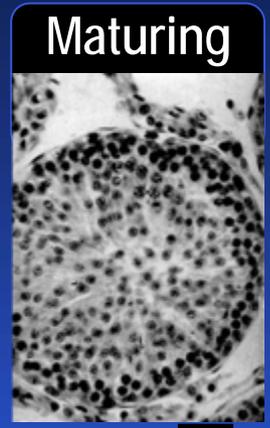
- **Results based on single semen sample per study participant**
  - Clinically, sequential samples are used
  - Collection method is non-uniform
  - Does not account for differences in sexual activity levels among individuals
- **No clinical evidence of impaired male fertility reported**
- **Semen characteristics are all within normal ranges**

# Claim of Altered Sperm Parameters is Not Well-Substantiated *(concluded)*

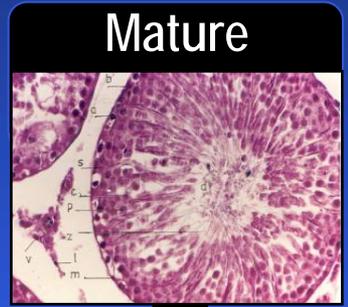
- **Proposed target tissue: Sertoli cells of seminiferous epithelium—unlikely**
  - Development and maturation of seminiferous epithelium does not match up with proposed sensitive stage for exposure

# Natural History Timeline for Sertoli Cell Development

**Sertoli:**  
Cell development  
During last 3 or 4  
months of gestation  
up to ~6-8 months  
of life



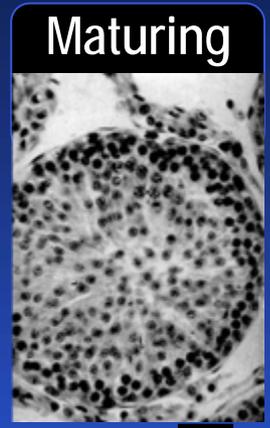
**Spermarche:**  
Development begins  
at approximately  
11 years



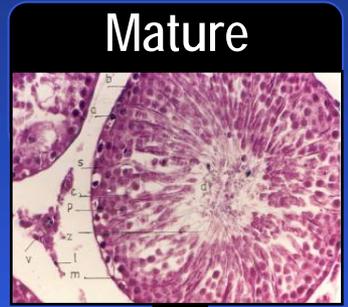
**Sertoli:**  
Cell activity

# Natural History Timeline for Sertoli Cell Development

**Sertoli:**  
Cell development  
During last 3 or 4  
months of gestation  
up to ~6-8 months  
of life



**Spermatogenesis:**  
Development begins  
at approximately  
11 years



Age group that was examined—  
boys who were between 1 and 9  
years of age at the time of exposure

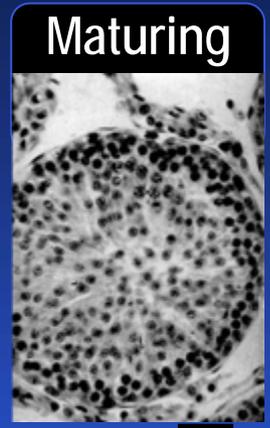
**Sertoli:**  
Cell activity

# Natural History Timeline for Sertoli Cell Development

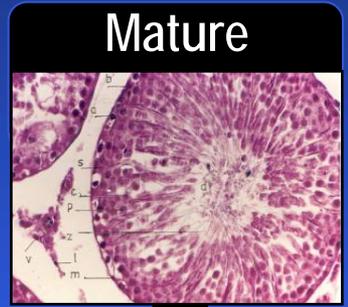
**Sertoli:**  
Cell development  
During last 3 or 4  
months of gestation  
up to ~6-8 months  
of life



Average age  
(6.2 years)  
at explosion



**Spermarche:**  
Development begins  
at approximately  
11 years



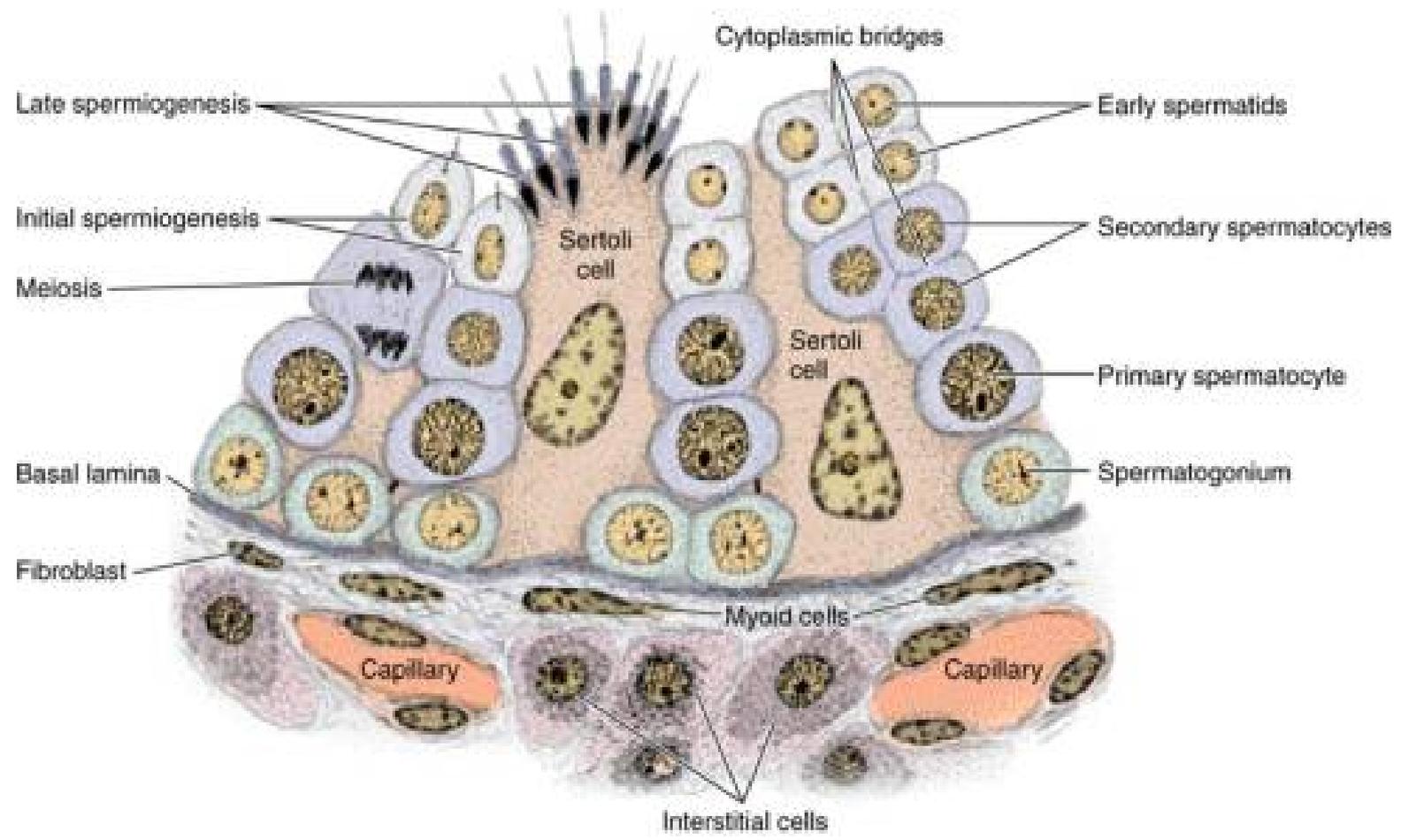
Age group that was examined—  
boys who were between 1 and 9  
years of age at the time of exposure

**Sertoli:**  
Cell activity

# Constituents of Seminiferous Epithelium



# Sertoli Cell



## Baccarelli et al., 2008

- Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin
- *PLoS Medicine* 5:1133–1142, 2008

# Alterations in TSH Levels Likely Transient and of Little Clinical Significance

- Criterion for potential hypothyroidism:  $\geq 10 \mu\text{U/mL}$  TSH
- WHO:  $\leq 3\%$  of children should have TSH  $\geq 5\mu\text{U/mL}$
- Small sample size
  - Likely not representative

Group	Characteristics	Sample size	Mean TSH ( $\mu\text{U/mL}$ )	% > $5\mu\text{U/mL}$ TSH
Zone A	High contamination	56	1.66	16.1
Zone B	Low contamination	425	1.35	4.9
Reference sample		533	0.98	2.8



In high exposure group, an increase of 16% equates to nine individuals (9/56) that had TSH  $\geq 5\mu\text{U/mL}$

# Alterations in TSH Levels Likely Transient and of Little Clinical Significance *(concluded)*

- **During first few days of life TSH levels fall dramatically from  $\sim 30 \mu\text{U/mL}$** 
  - WHO recommends
    - Testing AFTER 3 days of age
    - Population should average  $\leq 5 \mu\text{U/mL}$
  - Variation in time of sampling can affect values, especially with small sample sizes

# Conclusions

- **The subject papers present provocative results that should be followed up**
- **Results are not appropriate for risk assessment**
  - Design problems were unavoidable
  - Sample sizes were small leading to questions about representativeness
  - Biological plausibility remains doubtful
  - High doses incurred by study population not consistent with typical environmental exposures