



Faculty of Health and Medical Sciences



The epidemiological evidence linking endocrine disrupting chemicals and male reproductive disorders

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Legislation on endocrine disrupters in EU. KU-Life
november 9th 2018

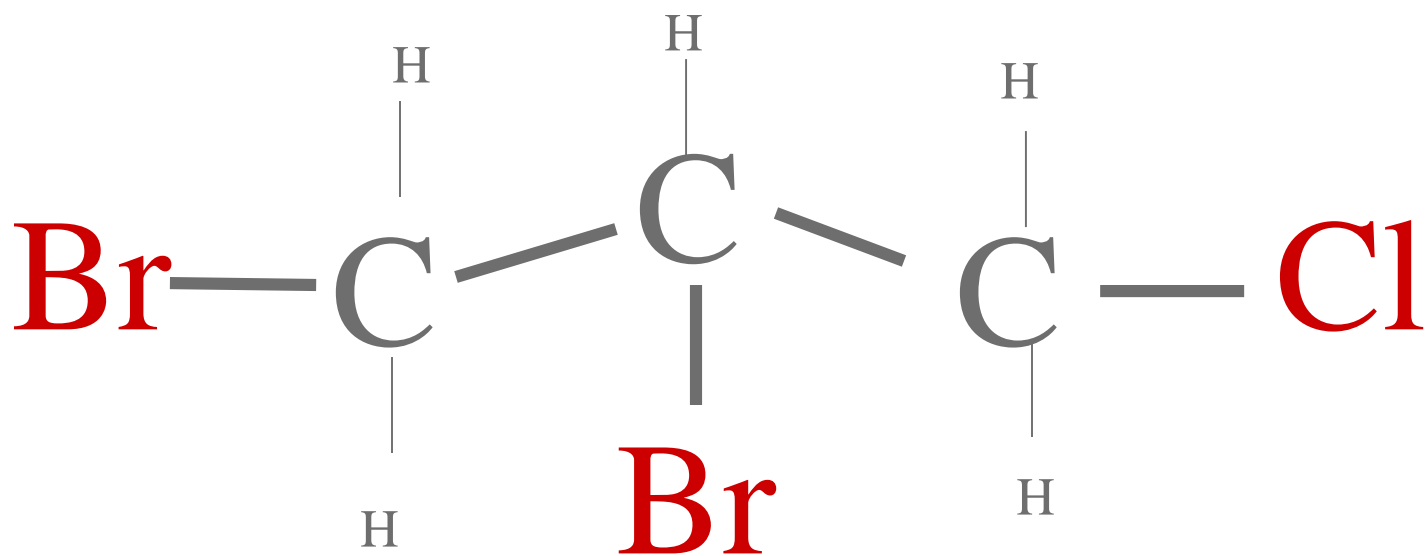
Slide 1



Globule

- ❑ The endocrine disruption hypothesis
- ❑ Systematic review
- ❑ Conclusion







Dibromochloropropane 1977

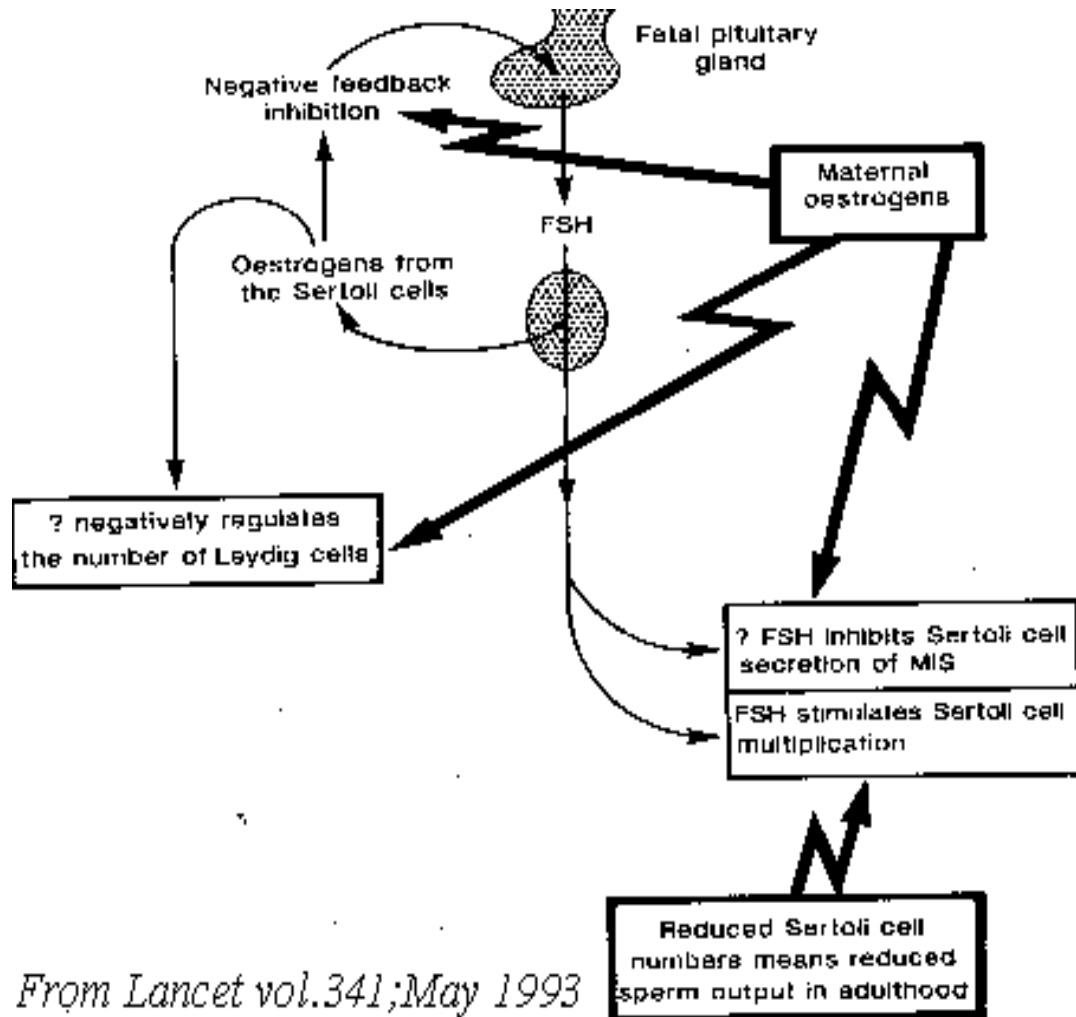
- Severe toxicity at low exposure levels following short periods of exposure (months)
- Irreversible effects (azoospermia or oligospermia)
- Banned in 1978 in US
- Reminder that occupational exposure to toxic compounds may have severe effects





Bussabjerg Hospital 042
Dag 6

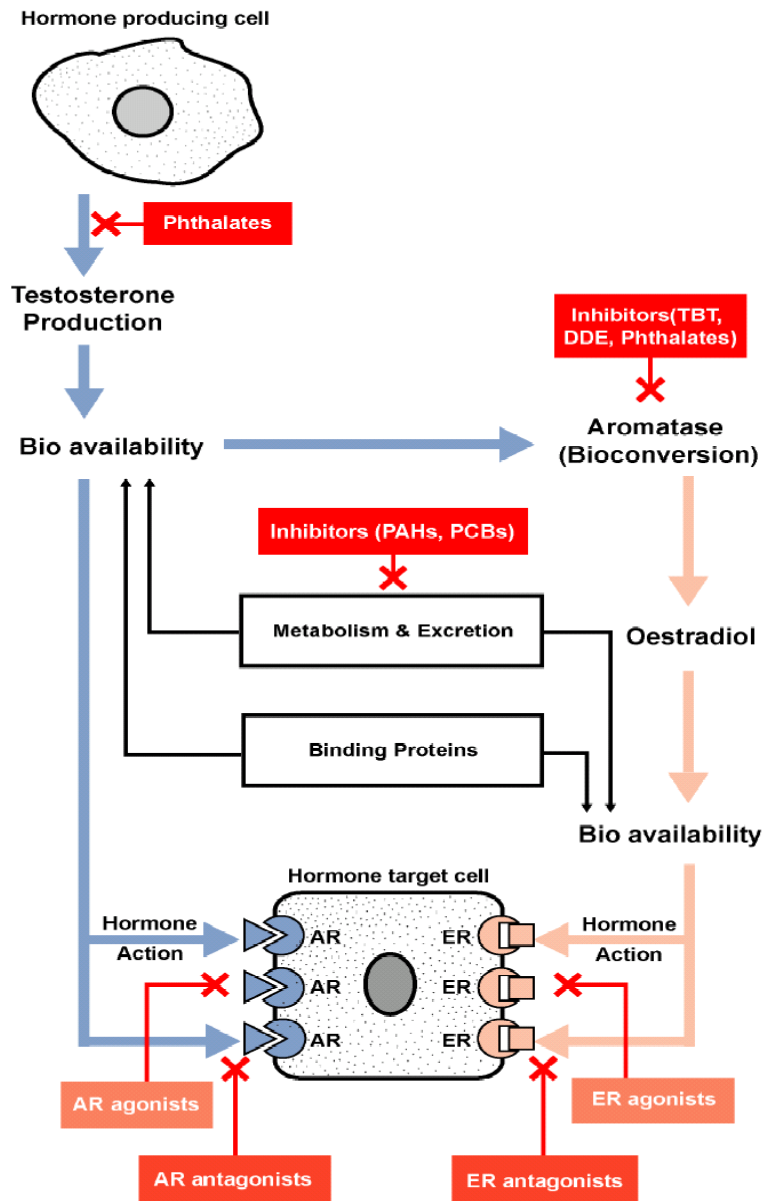
The estrogen hypothesis 1993



From Lancet vol.341;May 1993

**R Sharpe and
NE Skakkebaek**

Lancet 1993:
1392-95



From Sharpe RM and Irvine DS:
How strong is the evidence of a link between
environmental chemicals and adverse effects on
human reproductive health?

BMJ. 2004;328:447-51.

The estrogen hypothesis
is broadened and becomes:

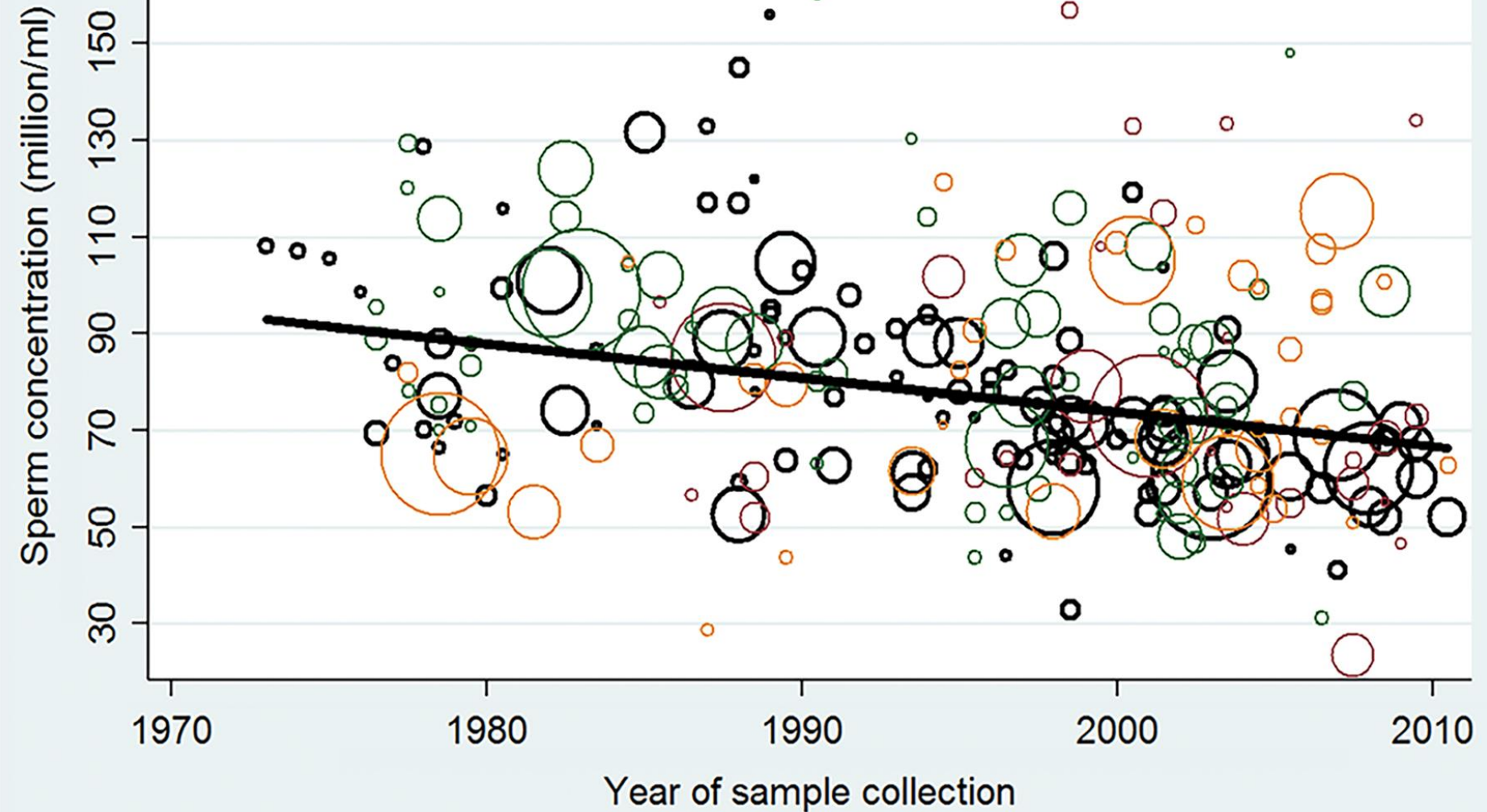
**The endocrine disruption
hypothesis**

The endocrine disruption hypothesis: still controversies



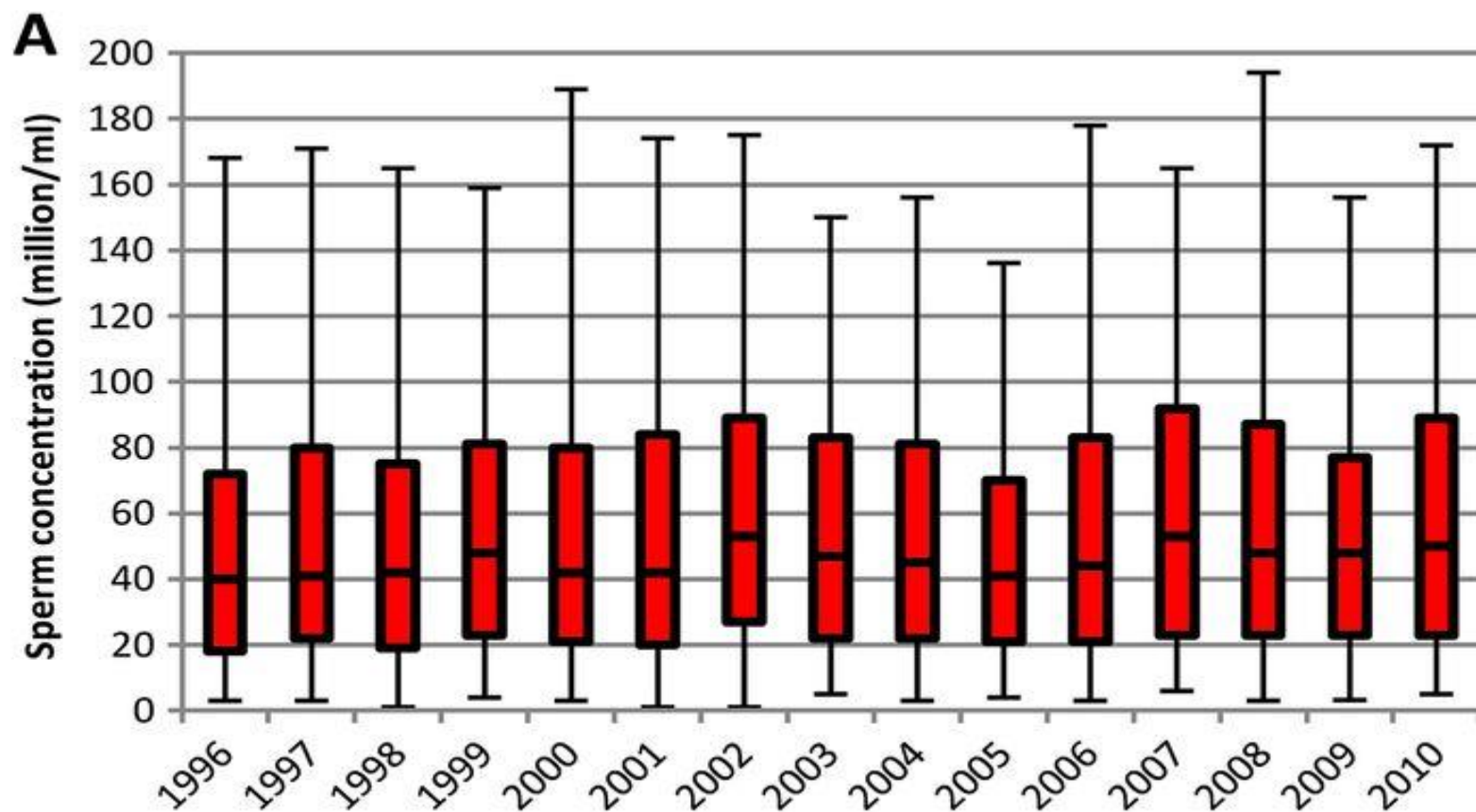
Beronius A and Vandenberg LN. Using systematic reviews for hazard and risk assessment of endocrine disrupting chemicals. *Rev Endocr Metab Disord* 2015; 16:273-287.

(a)

Slope per year = -0.70 (-0.72 to -0.69)

- | | |
|----------------------|--------------------|
| ● Unselected Western | ● Unselected Other |
| ○ Fertile Western | ○ Fertile Other |

Median sperm counts in Danish Army Conscripts 1996-2010 (Jørgensen BMJ Open 2012)



SYSTEMATIC REVIEW WITH META-ANALYSIS

- ❑ risk of male reproductive disorders
 - cryptorchidism
 - hypospadias
 - low sperm counts
 - testicular cancer

- ❑ following in utero or infant exposure

- ❑ chemicals included on the European Commission's list of Category 1 endocrine disrupting chemicals

(documented adverse effects due to endocrine disruption in at least one intact organism)



Definition of an endocrine disrupting xenobiotic substance

- i. Chemicals where at least one study has shown endocrine effects in an intact organism (The European Commission, McCarthy 2011)
- ii. More than 500 compounds fullfill this broad definition
- iii. 60 **category 1 compounds** with high current production volume and/or are highly persistency in nature and in living organisms

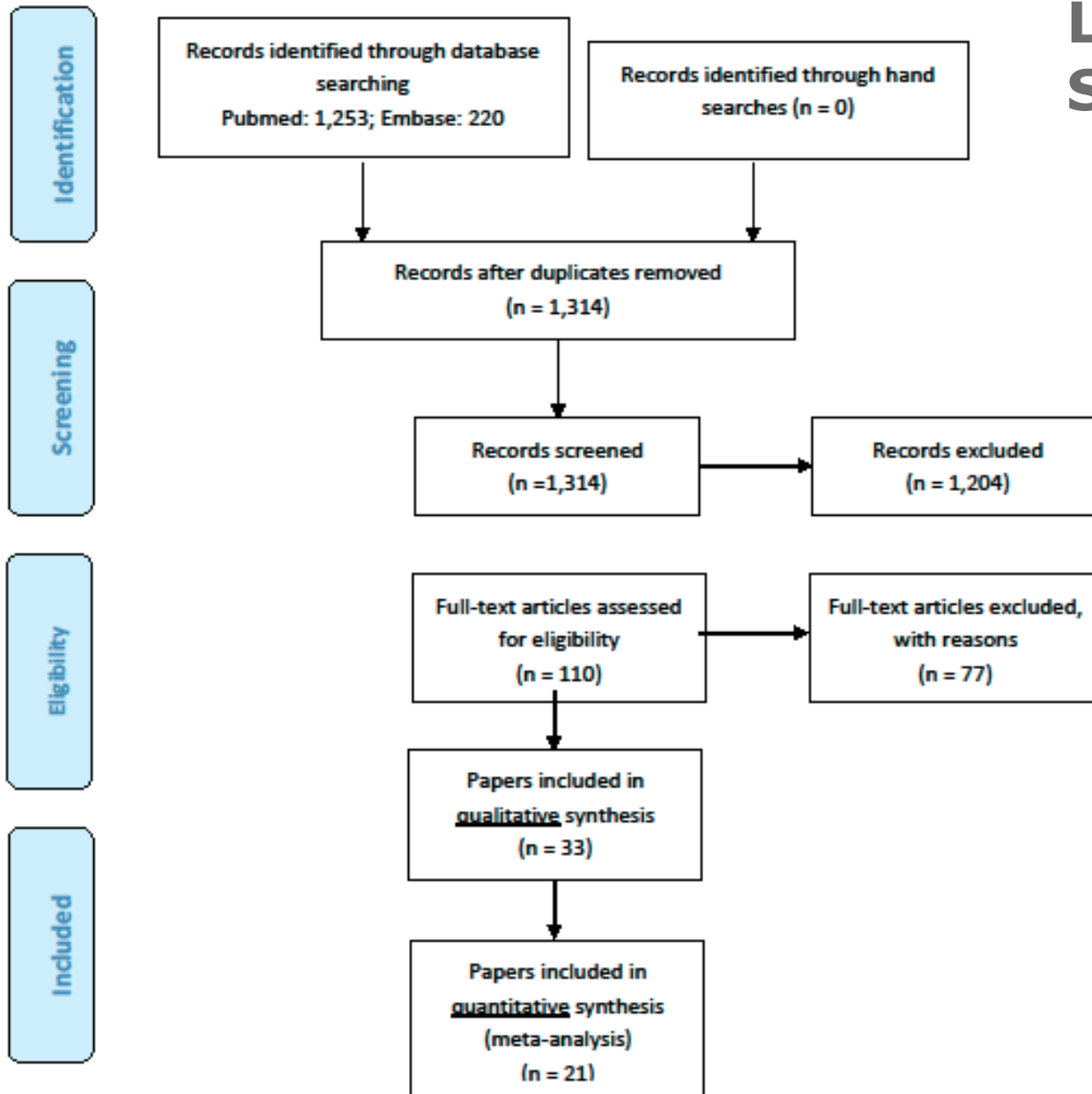


Systematic review: Inclusion criteria

- Category 1 EDC chemicals (60 compounds)
- Outcomes
 - Testicular cancer
 - Cryptorchidism
 - Hypospadias
 - Sperm count
- Prenatal or early postnatal exposure in humans
- Measurements of compounds in biological media**
- Risk estimates or tests of association
- No requests with respect to design or quality



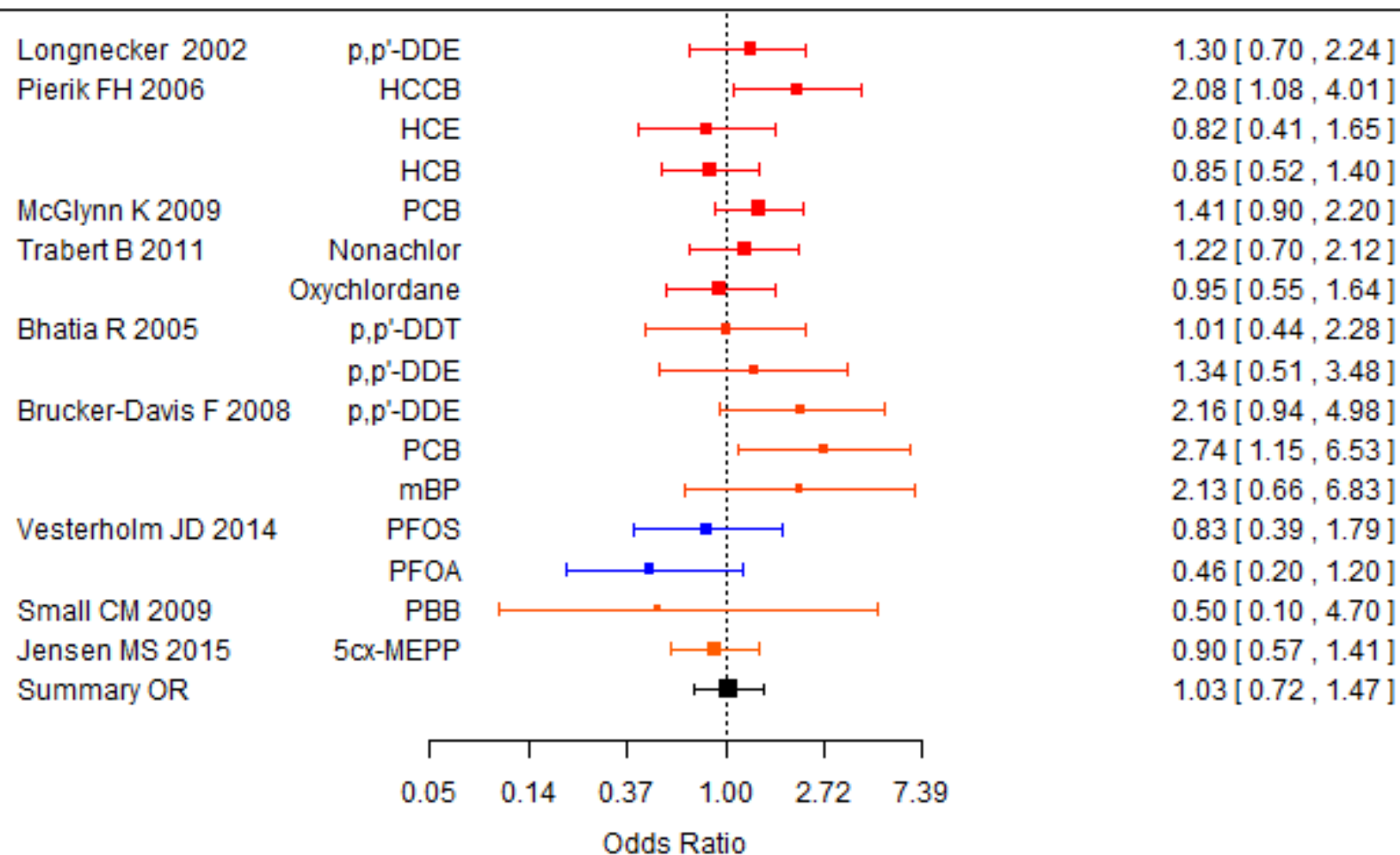
SYSTEMATIC LITERATURE SEARCH



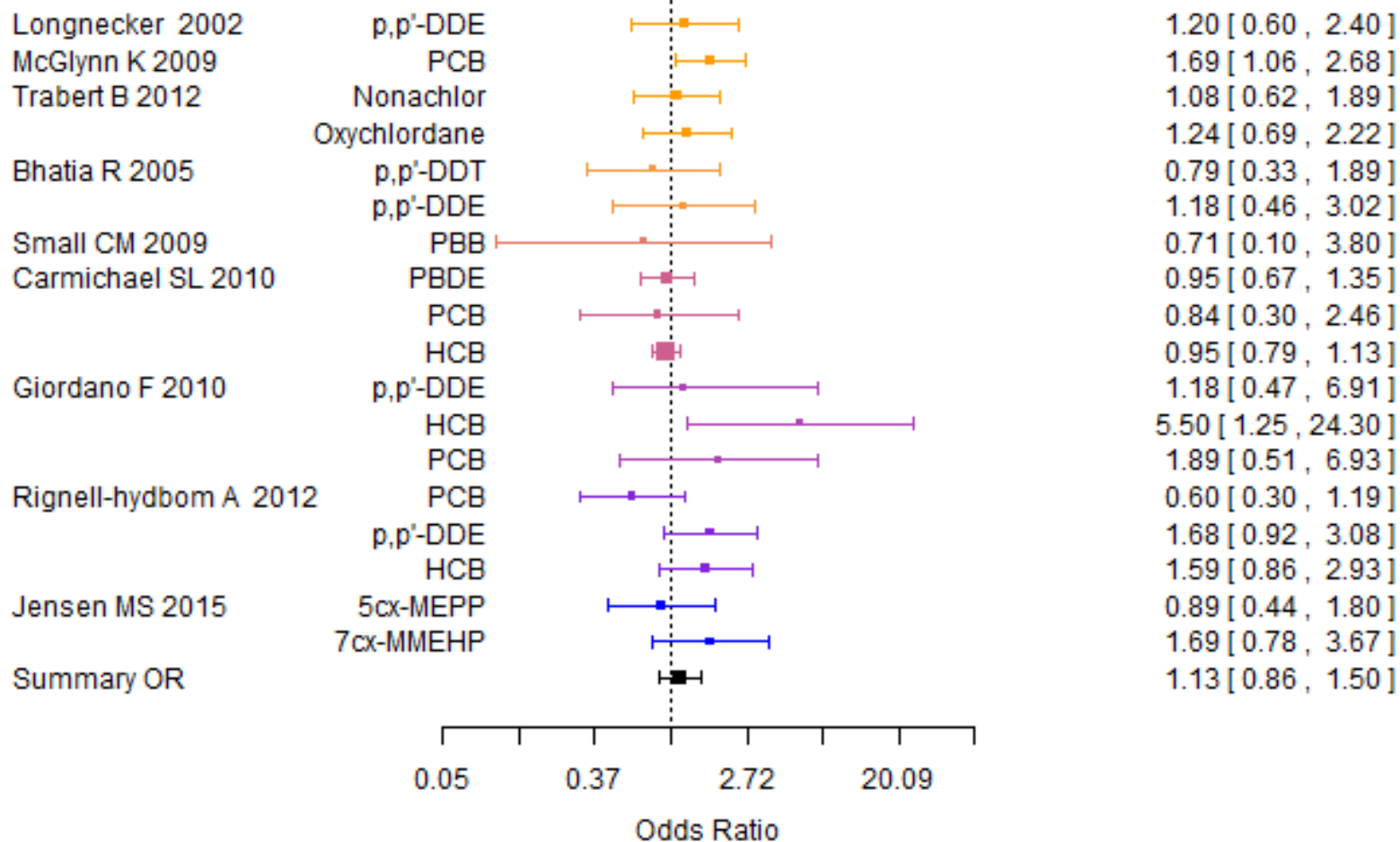
Meta-analysis of risk of cryptorchidism, hypospadias or testis cancer by prenatal EDC exposure

	Studies	Estimates	RR	95% CI
All exposures	21	70 (1-10)	1.11	0.91-1.35
Bias less likely	5	22 (2-7)	1.12	0.81-1.57
Large studies	9	34 (1-7)	1.06	0.85-1.33
Biopersistent EDC	17	66 (1-10)	1.15	0.92-1.44
Not persistent EDC	3	4 (1-2)	1.12	0.71-1.77

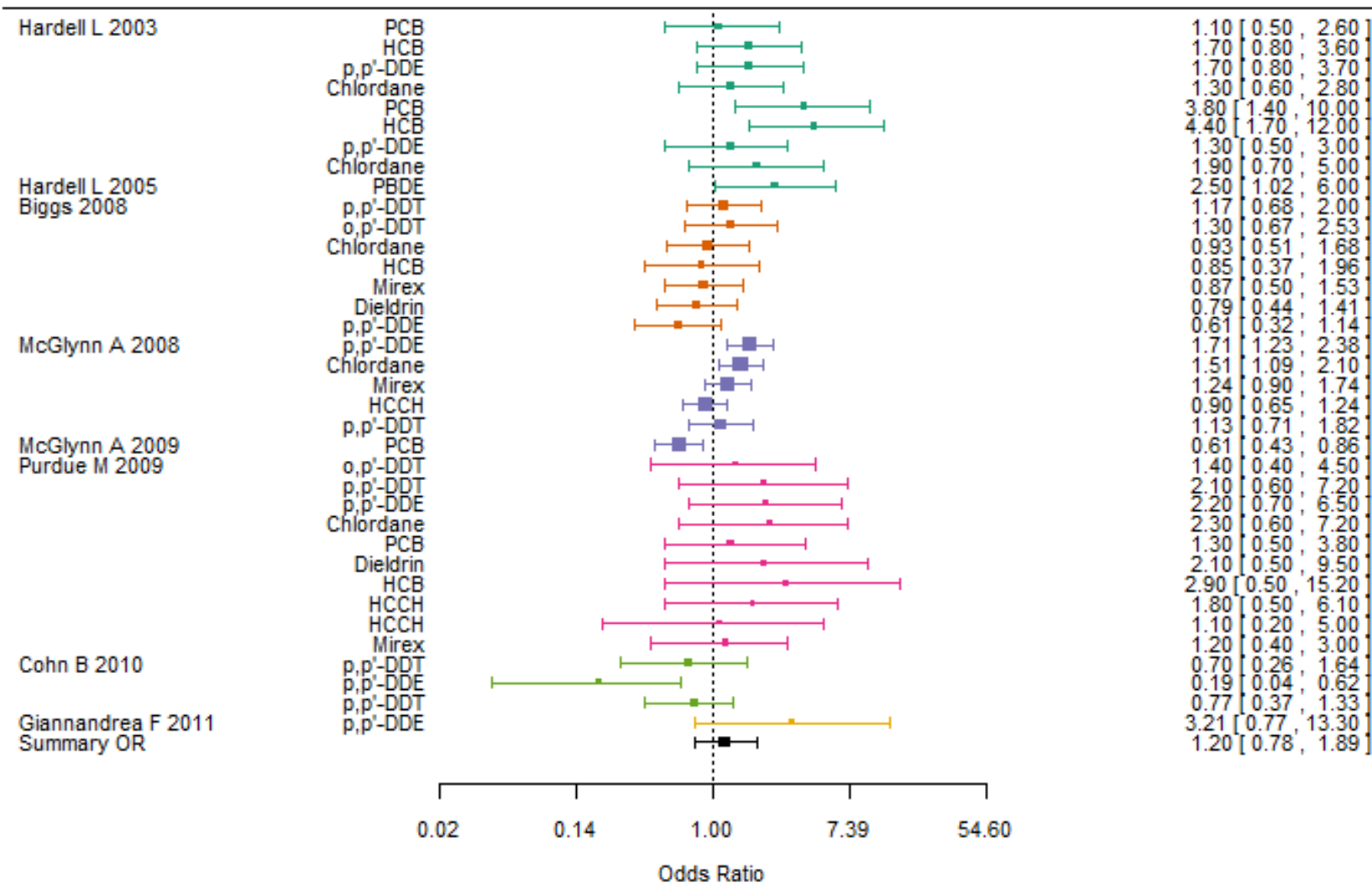
All compounds versus cryptorchidism



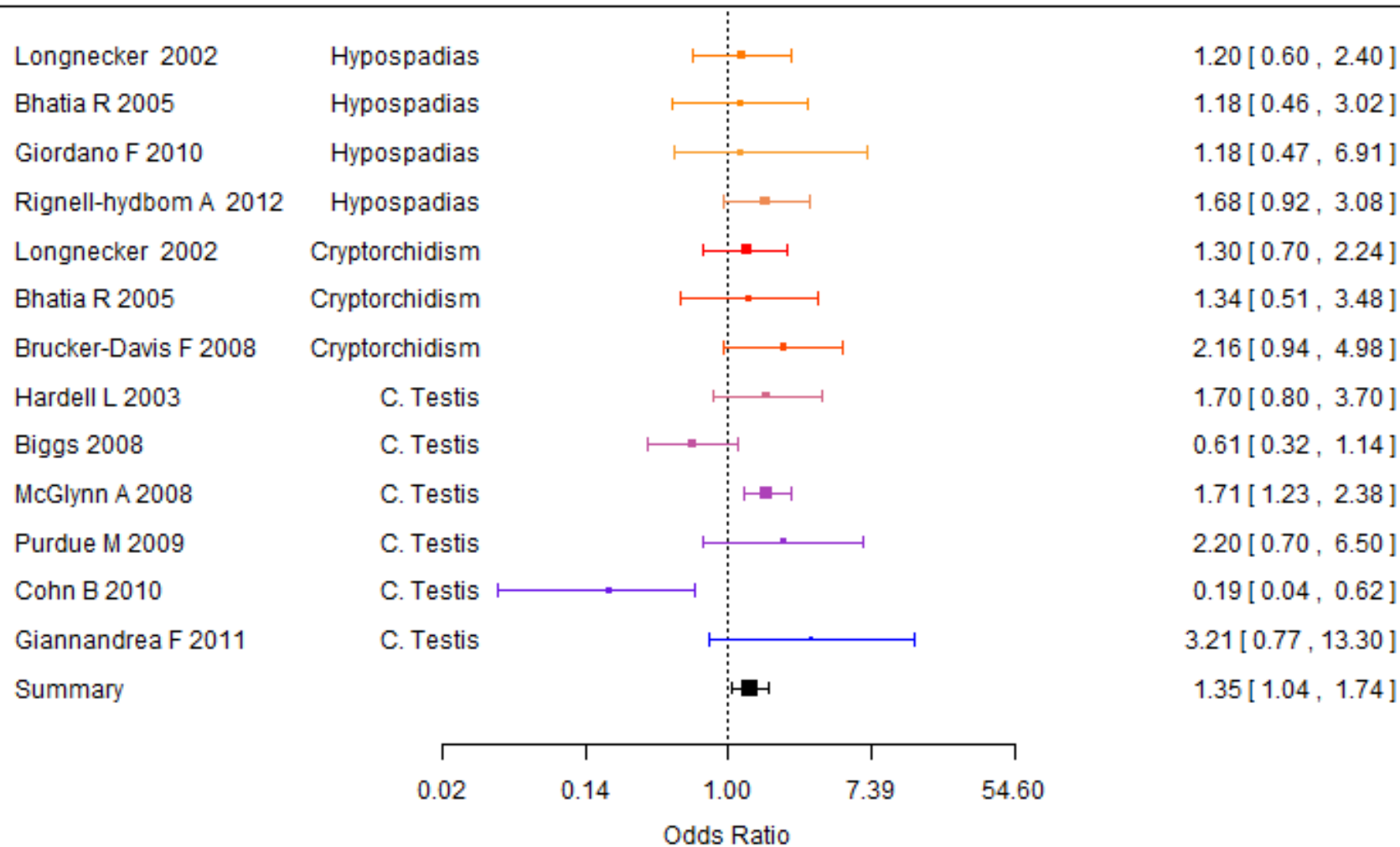
All compounds versus hypospadias



All compounds versus testicular cancer



Meta-analysis: DDE versus all outcomes



Issues

- ❑ The database is limited:
 - One small study with prenatal exposure data and testicular cancer
 - Three studies on sperm count

- ❑ Cocktail effects

- ❑ Non-monotonous exposure-outcome relations



Conclusion

The view that ubiquitous EDC play a **substantial role** for male reproductive disorders through pre- and perinatal mechanisms is challenged by this review

The current epidemiological evidence is **compatible with a small increased risk** of male reproductive disorders following pre- and postnatal exposure to a specific compound - the **DDT metabolite DDE**



Systematic reviews are needed

- All papers on the issue are identified and presented (no selective reporting)
- The process is transparent
- Remarkable few systematic reviews in the field of endocrine disruption
- More are warranted



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THANKS FOR YOUR ATTENTION
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