endocrine disruptive effects of tetrabromobisphenol-A in wistar rats and zebrafish

Leo Van der Ven, Hellmuth Lilienthal, Raoul Kuiper,
Piet Wester, Aldert Piersma

RIVM (Bilthoven, NL), BGFA (Bochum, D),
Utrecht University (NL)

rivm

Br FIRE

Flame retardants
Integrated
Risk assessment for
Endocrine effects

FIRE key issues

- improve risk assessment of BFRs
- for human health & environment
- potential endocrine disruption

FIRE rat studies

- subacute toxicity - 28 day - OECD407

  TBBPA - HBCD - pBDE - dBDE

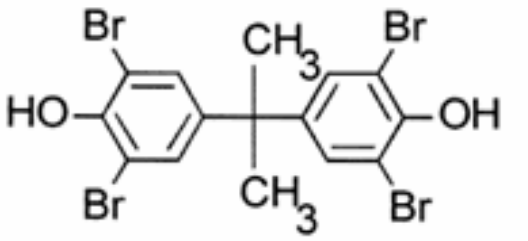
- reproduction / development –

  1-gen - OECD415

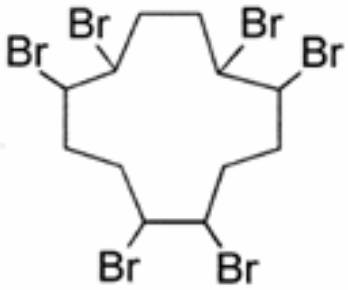
  TBBPA – HBCD

+ endocrine / immune parameters

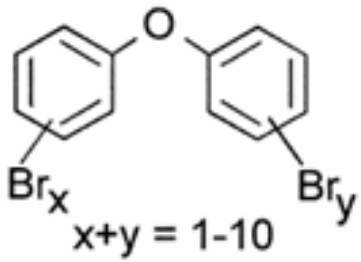
oral dosing (mixed in the feed);
0.3 ..... 3000 mg/kg bw



tetrabromo- bisphenol-A

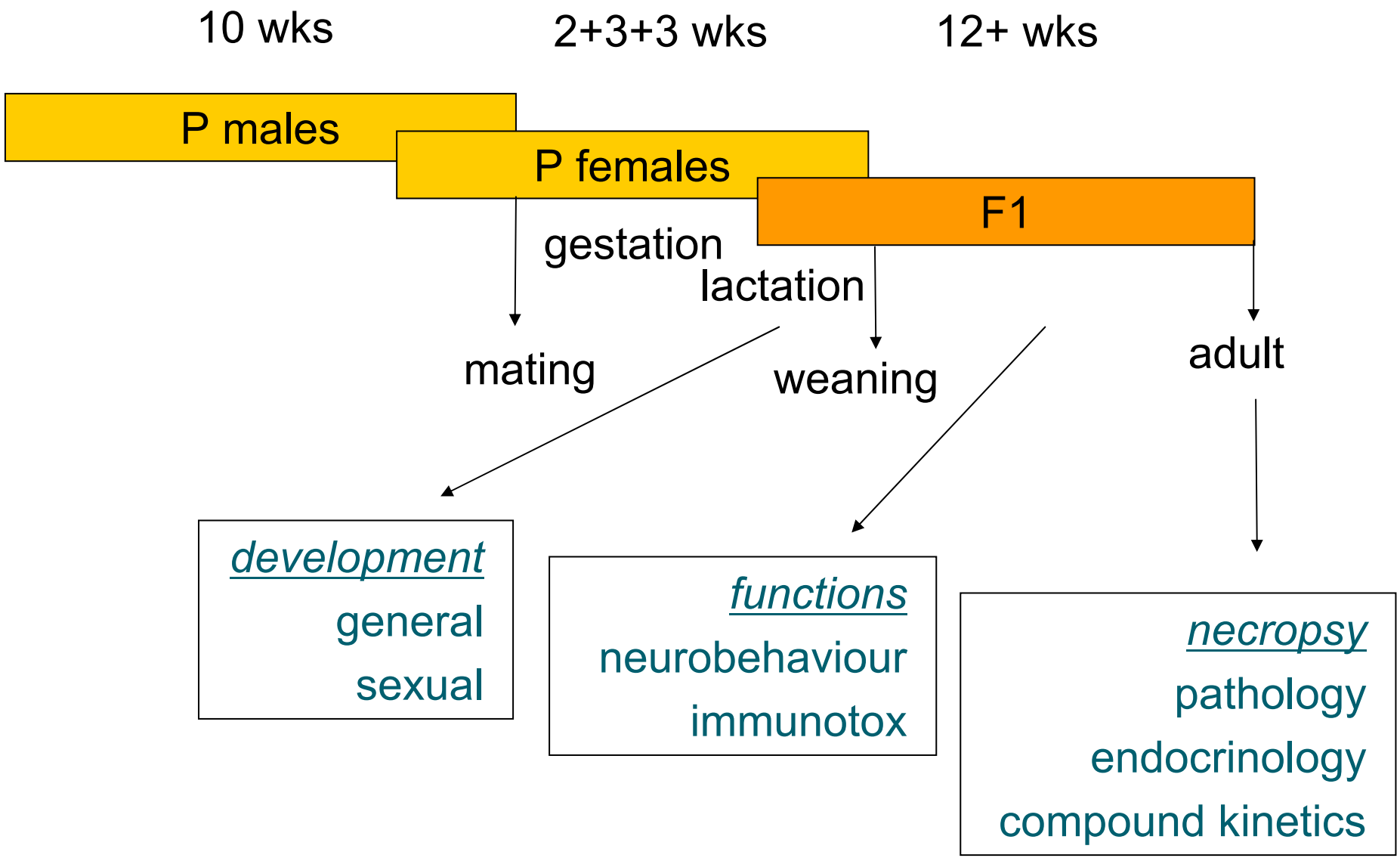


hexabromo cyclododecane



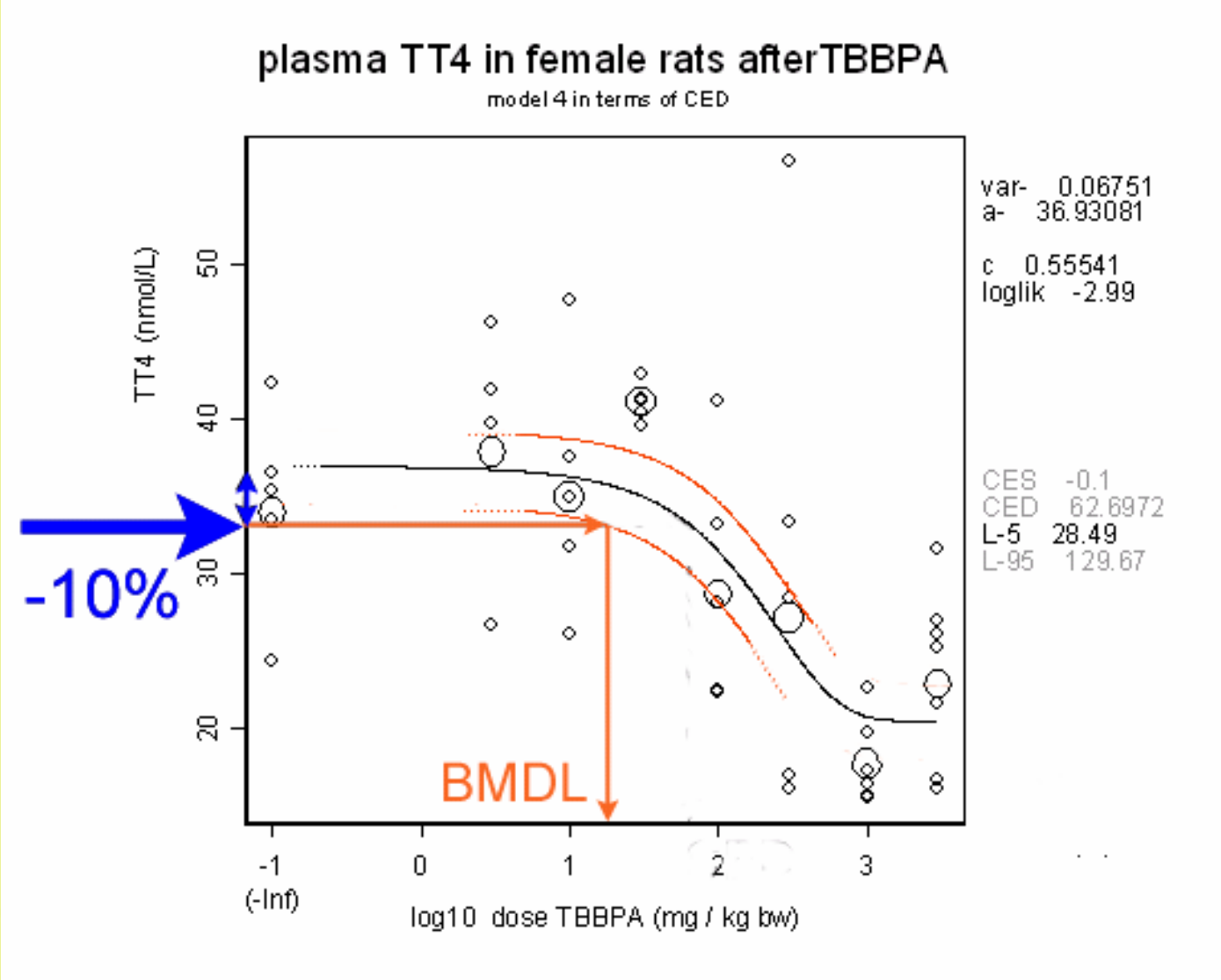
polybrominated diphenylethers

study design



benchmark design

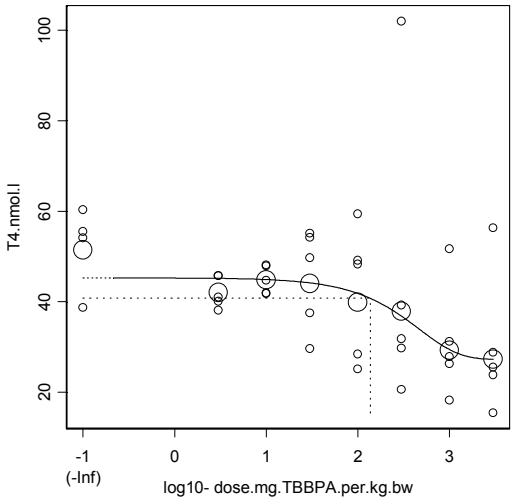
- 8 dose groups
- critical effect size
- benchmark dose @ 5% confidence level = BMDL



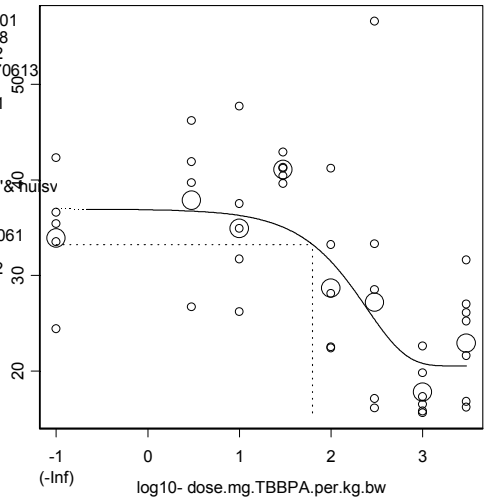
TBBPA affects levels of circulating Thyroid Hormones in F1

	males		*females*	
	BMDL (mg /kg bw)	*max response (%)*	*BMDL (mg /kg bw)*	*max response (%)*
plasma total T3			1.9	27
plasma total T4	17	-60	28	-56

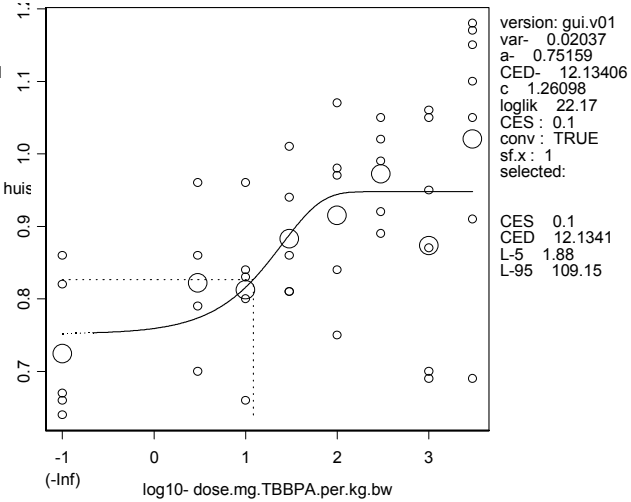
TT4, m



TT4, f



TT3, f



liver weight

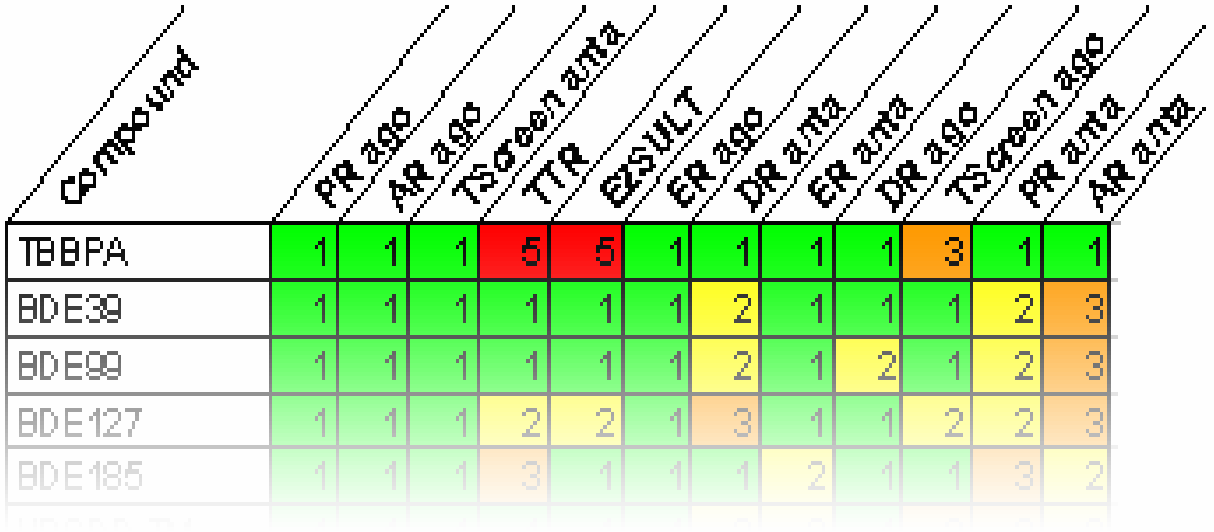
M

- no hepatic P450 enzyme induction

  Germer, Schrenk 2005

- no histopathology

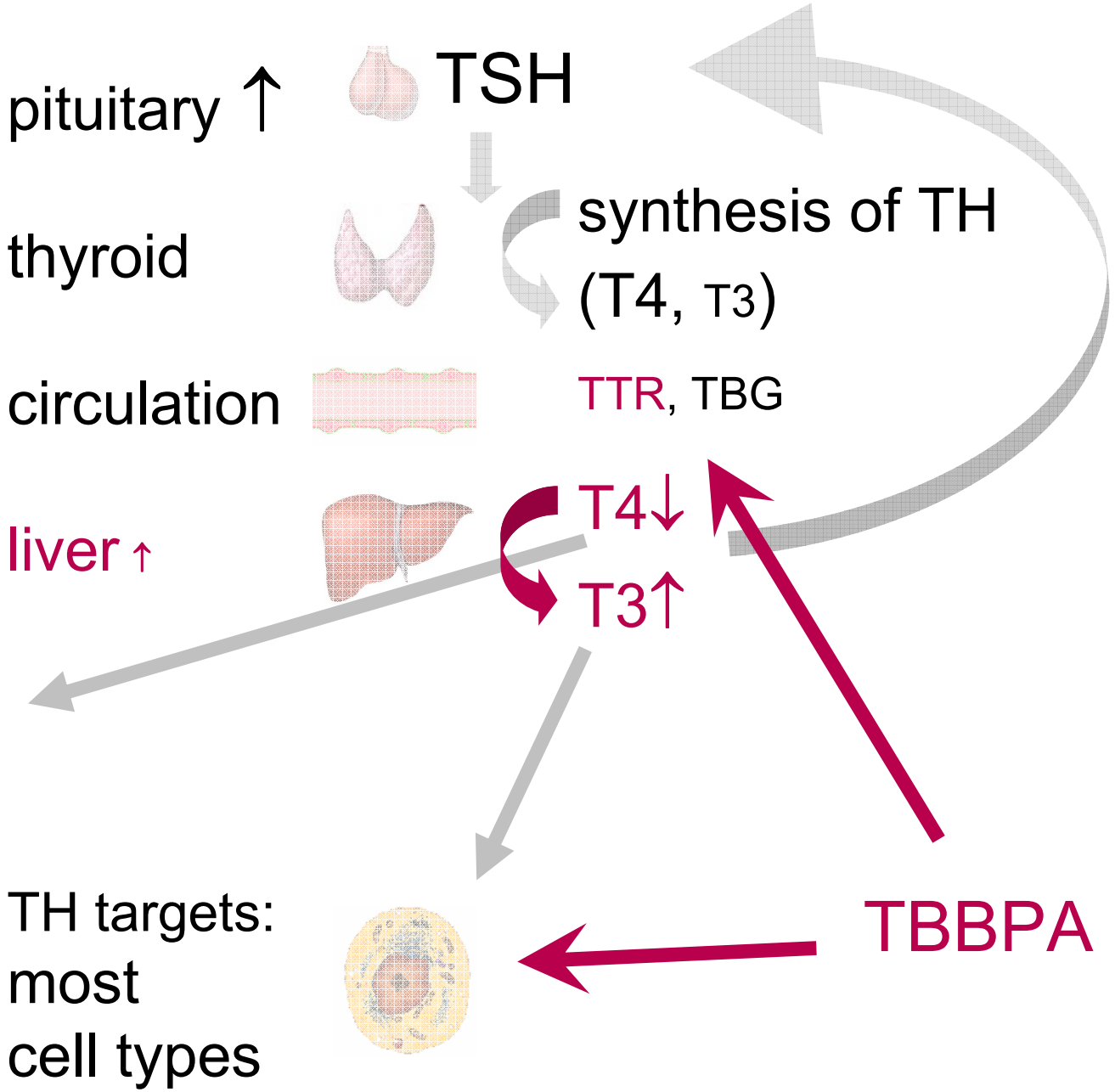
in vitro bioassays for endocrine activity



Compound	PR ago	AR ago	Tscreen anta	TTR	EZSULT	ER ago	DR anta	ER anta	DR ago	Tscreen ago	PR anta	AR anta
TBBPA	1	1	1	5	5	1	1	1	1	3	1	1
BDE39	1	1	1	1	1	1	2	1	1	1	2	3
BDE99	1	1	1	1	1	1	2	1	2	1	2	3
BDE127	1	1	1	2	2	1	3	1	1	2	2	3
BDE185	1	1	1	3	1	1	1	2	1	1	3	2

- transthyretin binding
- TH receptor interaction

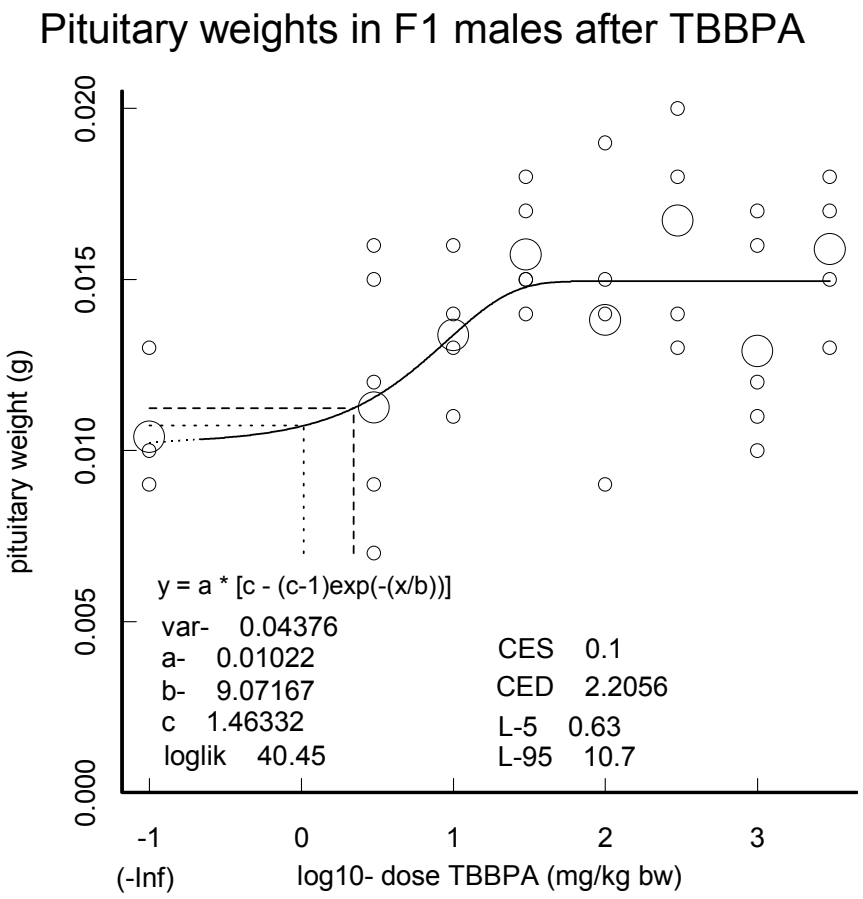
Hamers et al., Toxicol. Sci. 2006



metabolism

- P450 detox
- glucuronidation
- deiodination

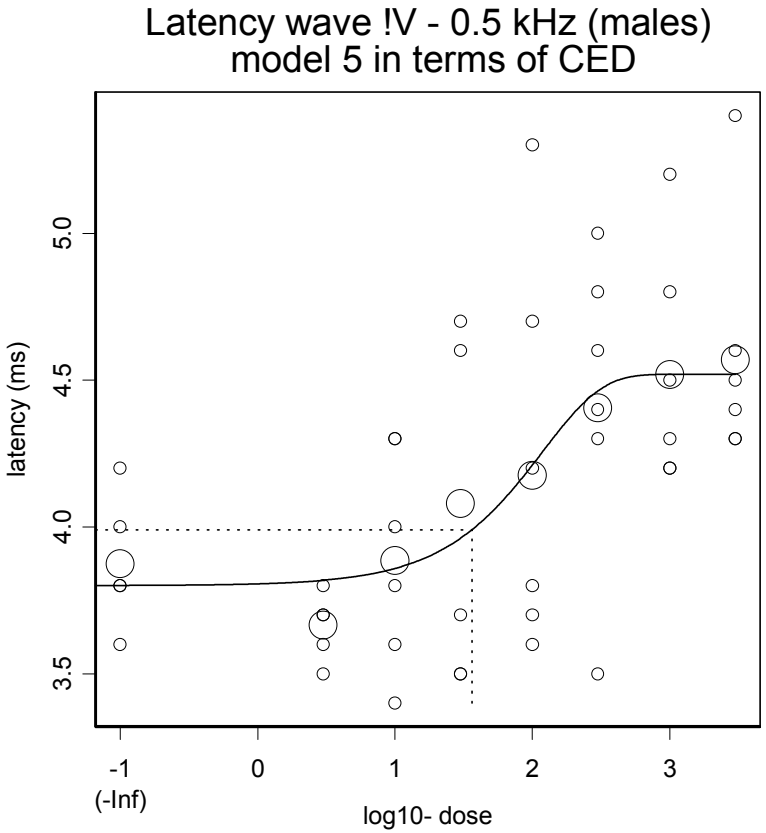
pituitary weight (males)



- statistically not associated with TH effects
- no increased TSH immunostaining
- no effect on thyroid gland

Brainstem auditory evoked potentials (BAEP)

0.5 – 1 – 2 – 4 – 8 – 16 kHz



	females		males	
	BMDL	**size**	**BMDL**	**size**
thresholds				
0.5 kHz	42	12%		
2 kHz	0.9	13%		
latencies – wave II				
0.5 kHz	33	10%		
1 kHz	1029			
8 kHz	10			
16 kHz			1869	
latencies – wave IV				
0.5 kHz	8	11%	**8**	**19%**
1 kHz			19	
2 kHz			56	21%
4 kHz			59	
click 60 dB	34	8%		

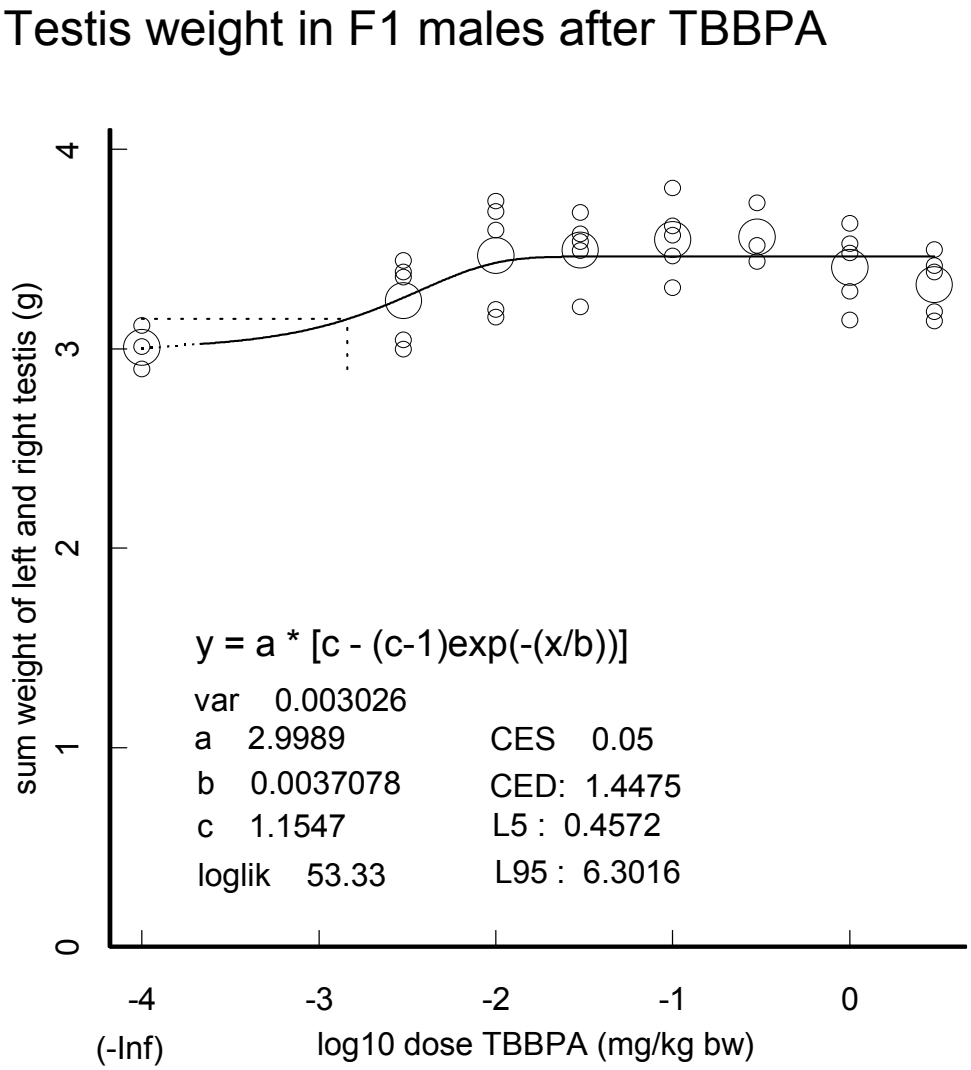
secondary to disruption of TH

TBBPA effects on **sex hormone** related parameters:

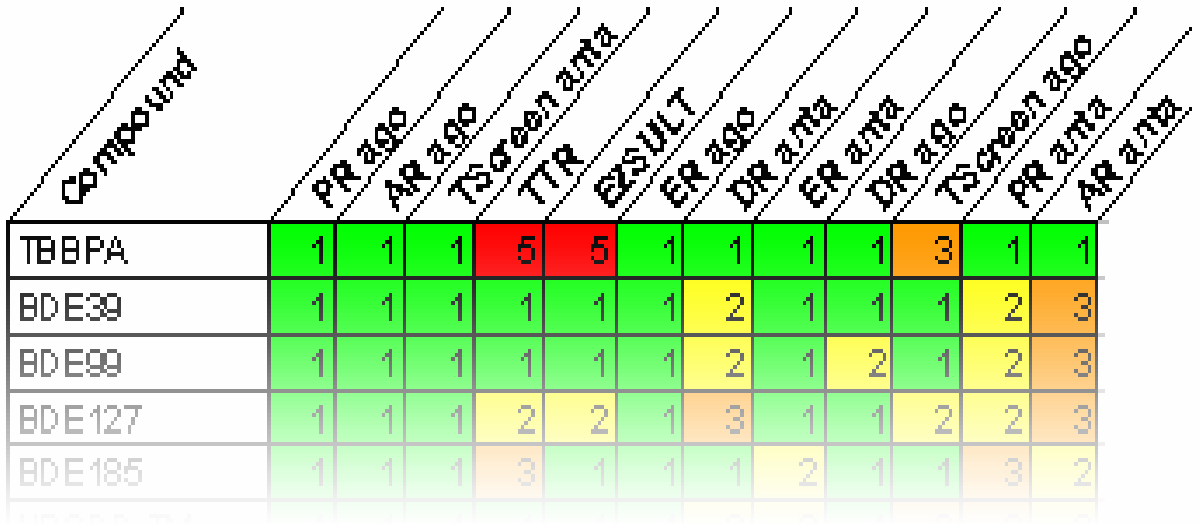
testis weight ↑
pituitary weight ↑
gonad m d21 weight ↑

associated with

gonad f d21 weight
uterus weight
endometrium size
saccharin intake f
testosterone m



in vitro bioassays for endocrine activity



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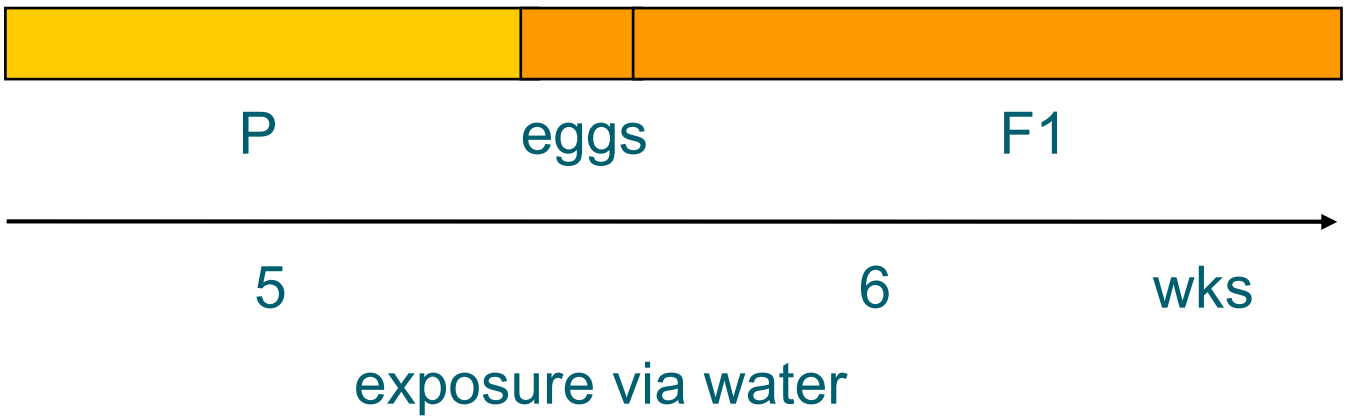
BDE127	1	1	1	2	2	1	3	1	1	2	2	3
BDE185	1	1	1	3	1	1	1	2	1	1	3	2

- E2 sulfation inhibition

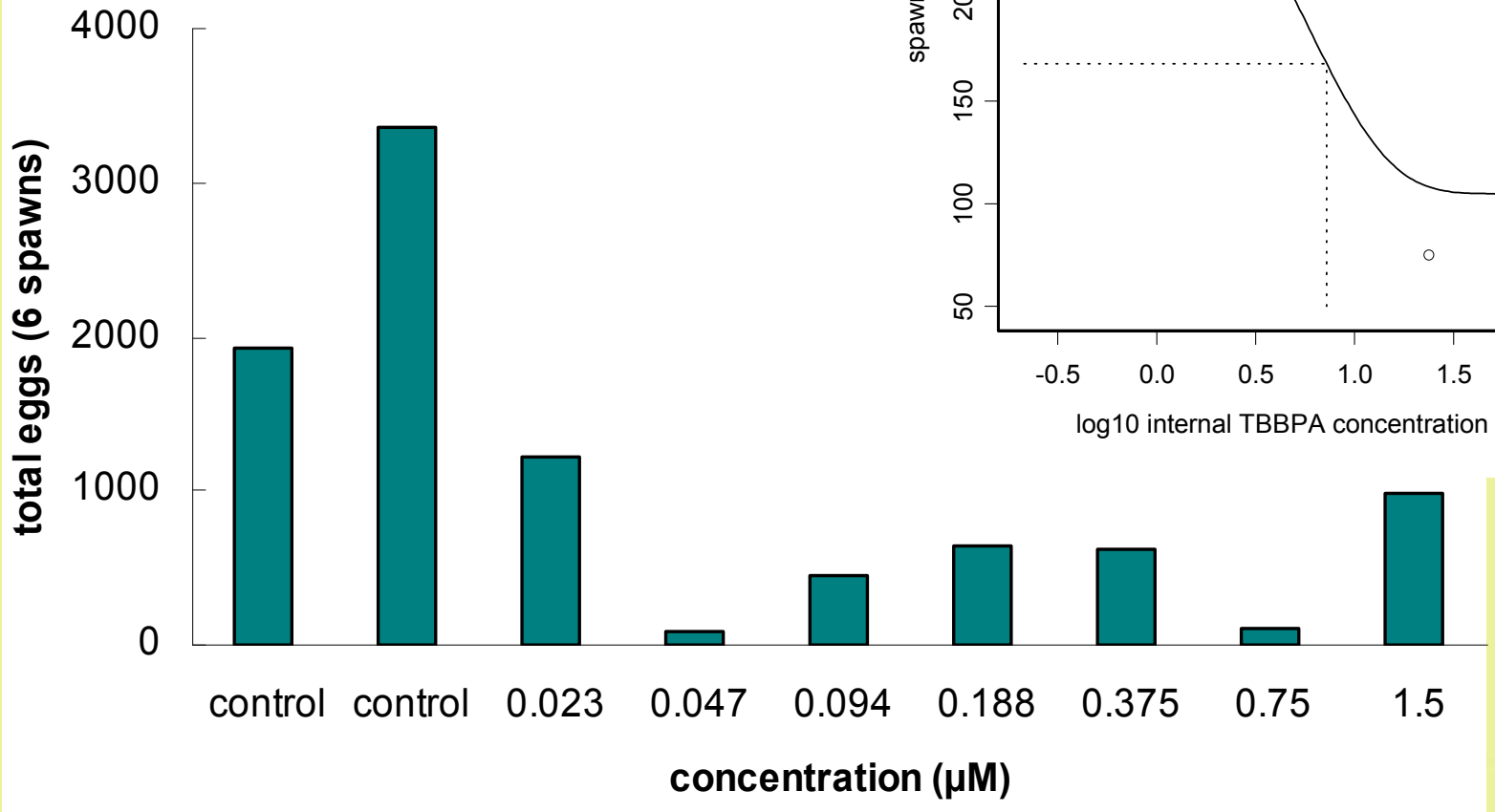
Hamers et al., Toxicol. Sci. 2006

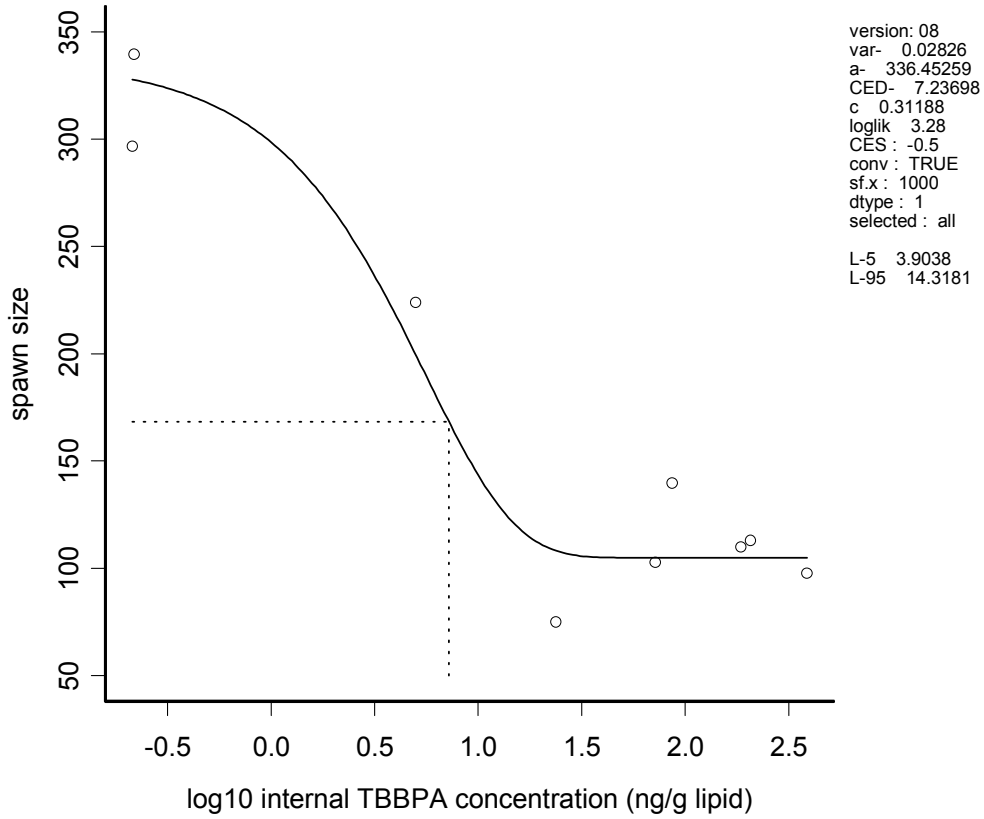
zebrafish partial life cycle assay



- reproductive performance
- juvenile growth & development
- histopathology

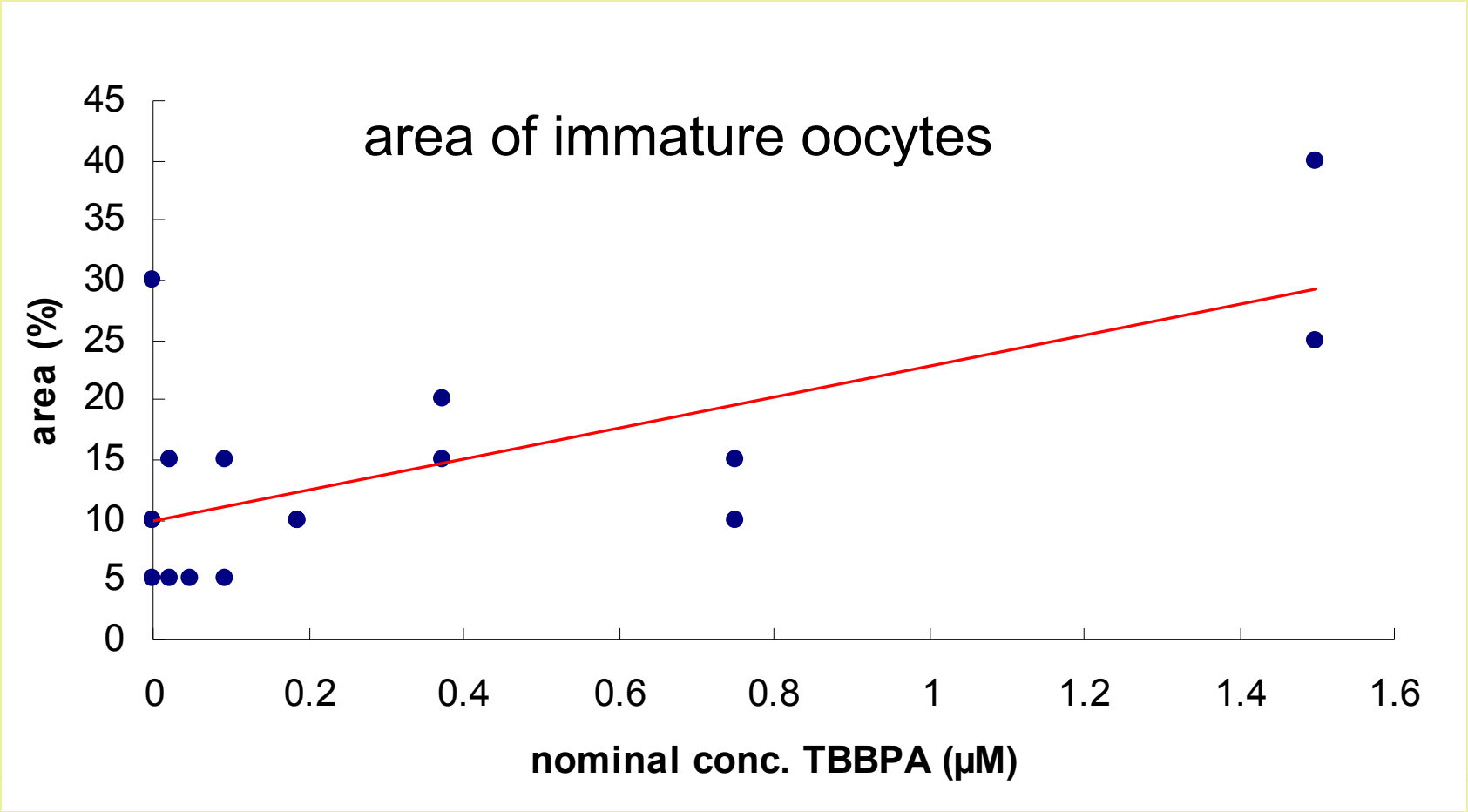
reproductive performance – egg production



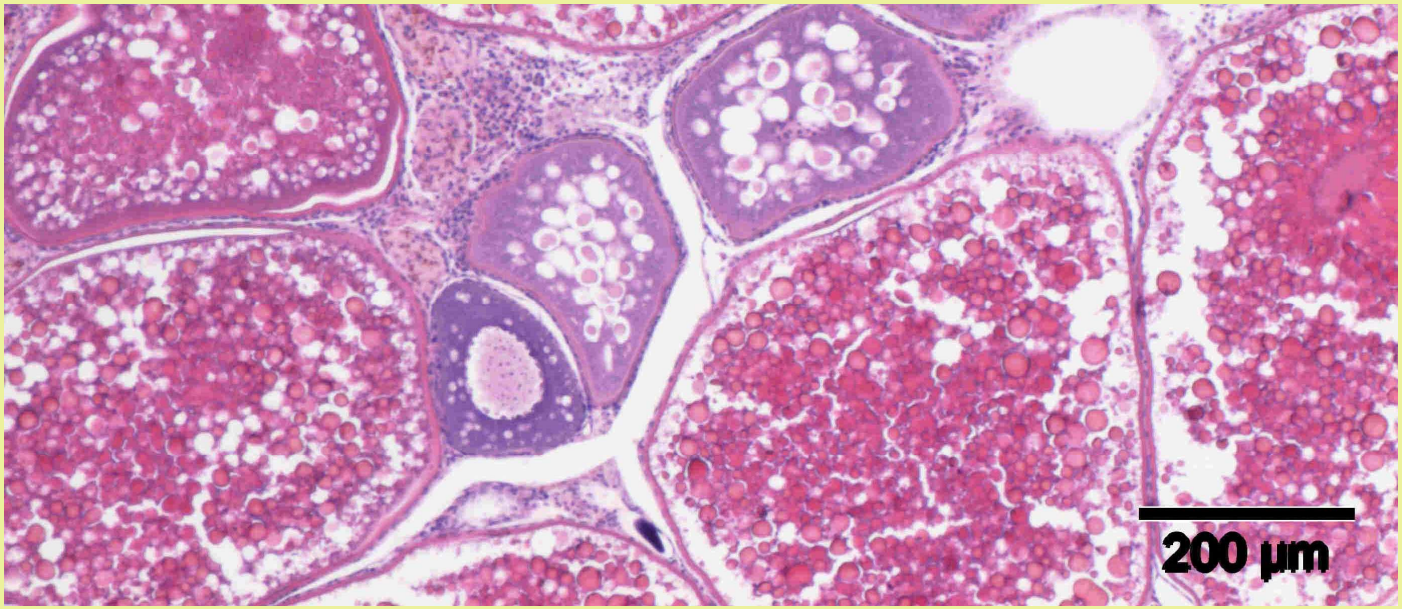


Kuiper et al., Arch. Toxicol. 2007

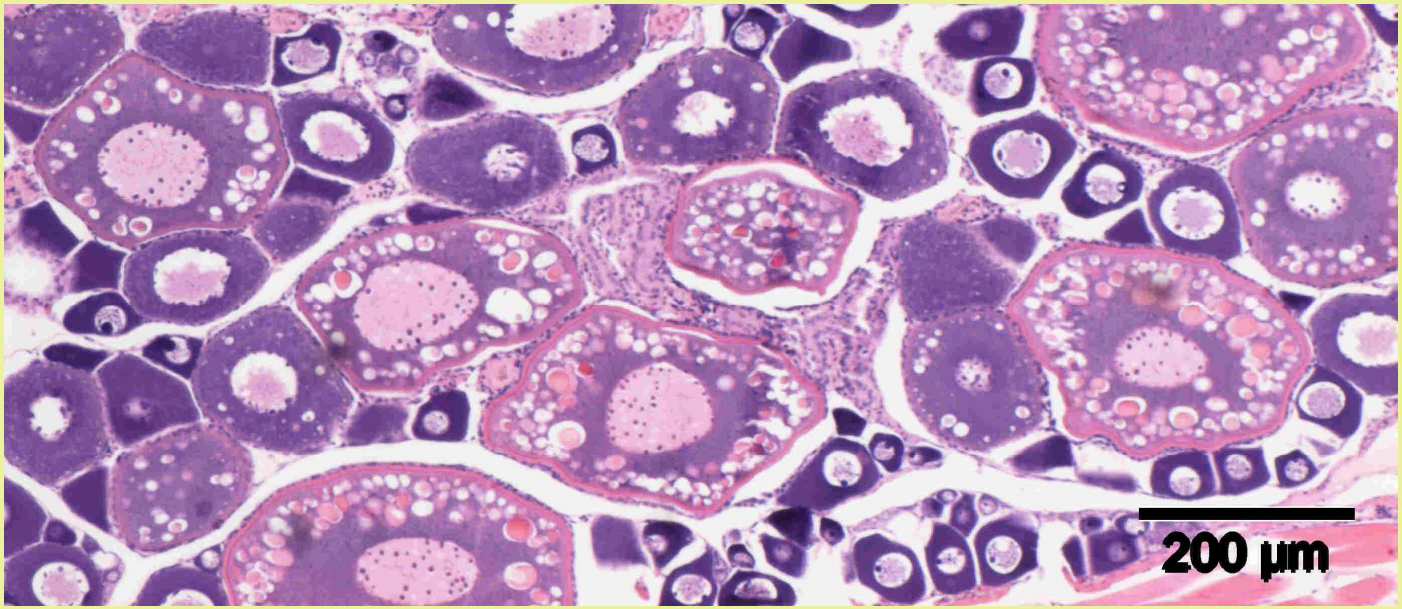
reproduction –
decrease of mature oocytes in the ovary



reproduction - ovary histopathology

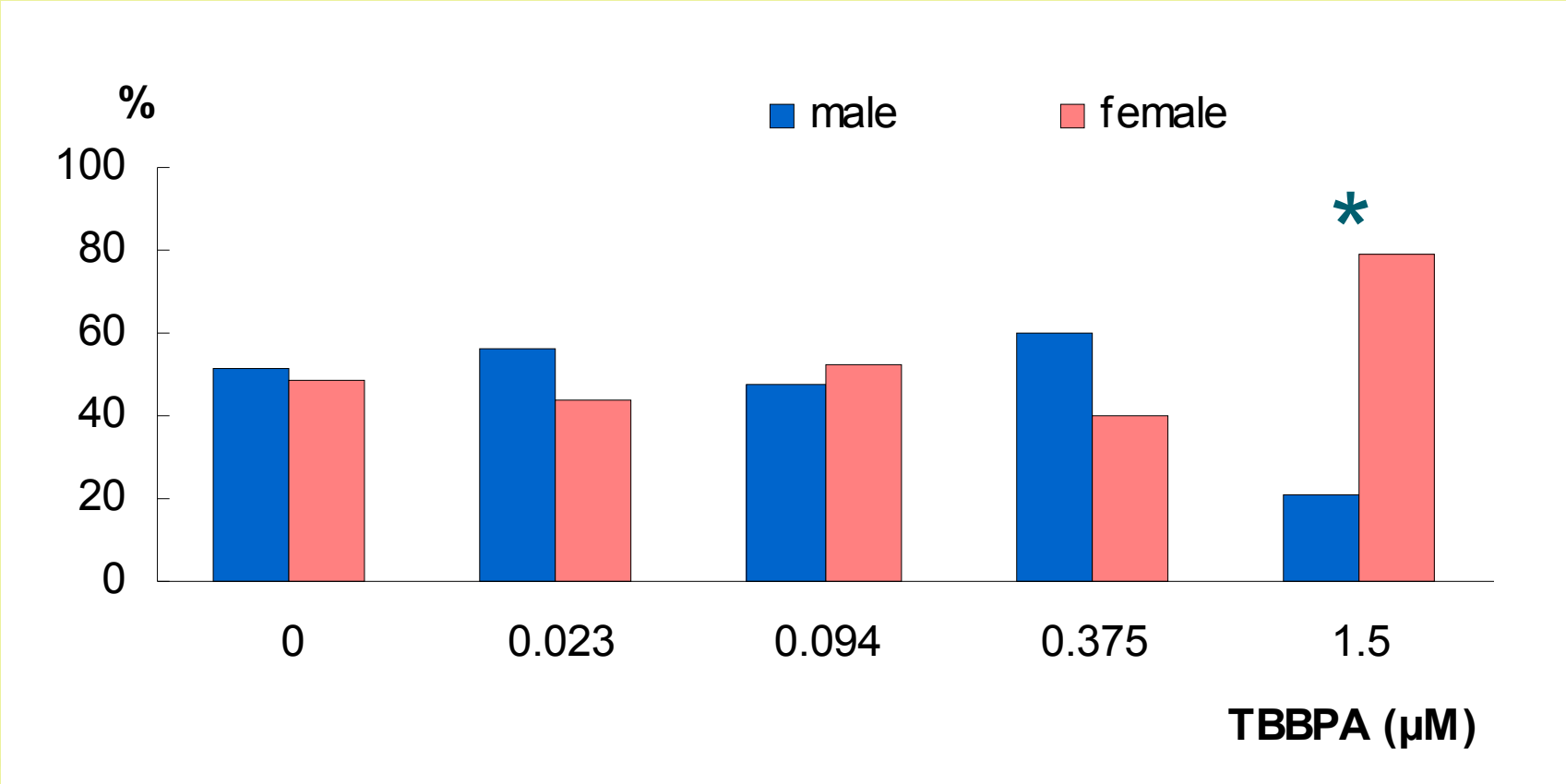


control



1.5 µM TBBPA

F1 development – skewed sex ratio



summary developmental effects of TBBPA

rats

- neurobehaviour, related to TH
- (male) gonads, sex steroid related?

zebrafish

- estrogenic

complementary models

Risk Assessment TBBPA

humans

- **estimated exposure** (EU-RAR)
  - 0.19 mg/kg/d (workers; consumers)
  - 0.024 µg/kg/d (consumers, scenario 2)

- **health effects**
  - testis weight BMDL 0.5 mg/kg/d
  - pituitary weight BMDL 0.6 mg/kg/d

- **margin of exposure** 2.6 (occupational / consumers) → concern!
  or >100 (consumers, scenario 2)

aquatic wildlife

- margin of exposure zebrafish – aquatic environment >100

histotechnique

Bhawani Nagarajah

Frank Slangen

Gerard van Leuveren

Sandra de Waal

Jolanda Vermeulen

clinical chemistry

Rija van Loenen

immunotechnique

Liset de la Fonteyne

Arja de Klerk

Yvonne Wallbrink

Bert Verlaan

biotechnique

Ruud van Kinderen †

Cor Schot

Evert-Jan van den Brandhof

+ team

statistics

Wout Slob

co-ordination, biotechnique, statistical analysis

Aart Verhoef

Ton van de Kuil

Joseph Vos †