Dioxins and dioxin-like PCBs in food: risks for the human health

12th February 2020, Ron Hoogenboom

WAGENINGEN
UNIVERSITY & RESEARCH

100years
1918 — 2018

EFSA Opinion (published 20/11/18)

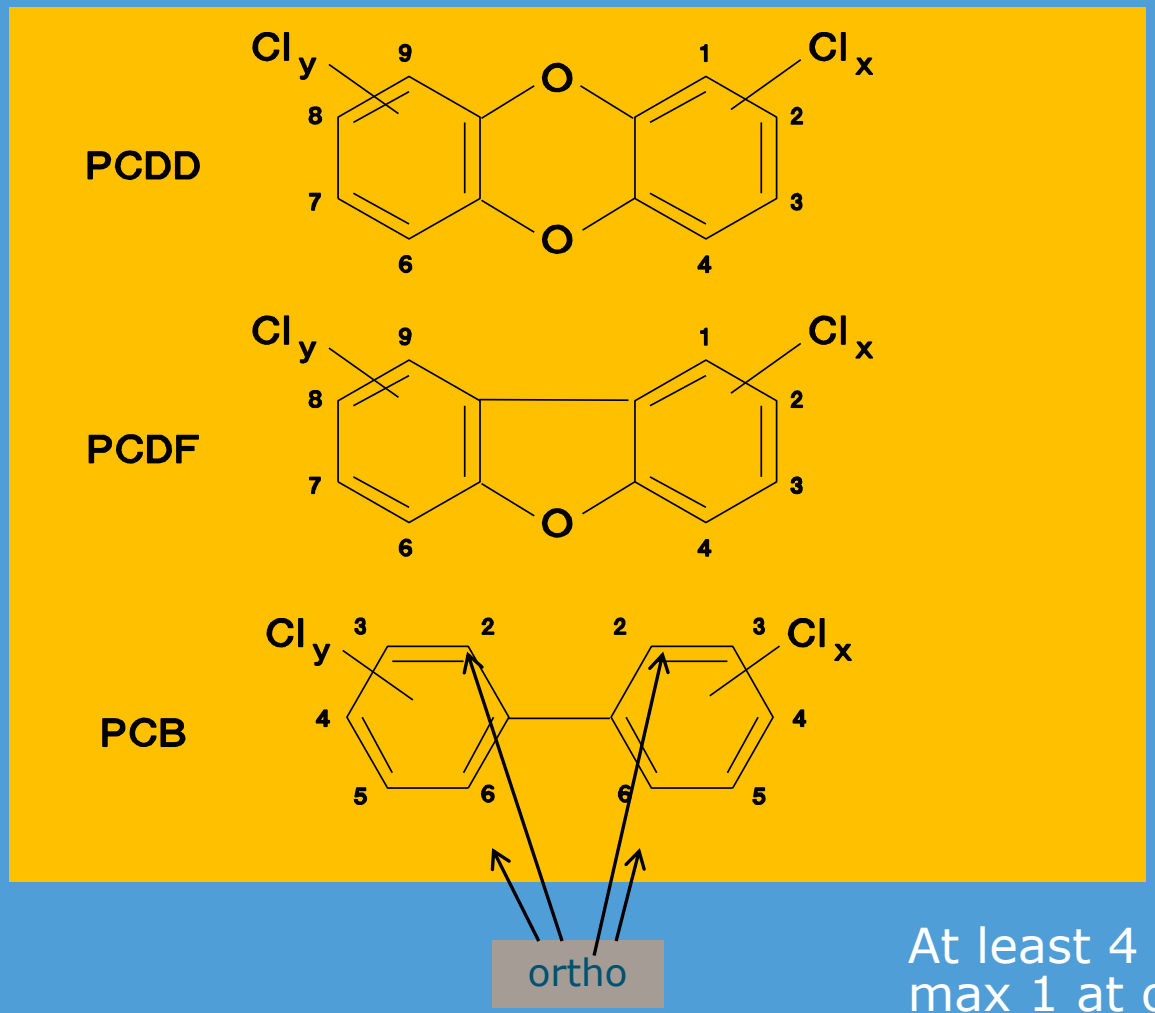
Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food

Knutsen HK, Alexander J, Barregård L, Bignami M, Brüschweiler B, Ceccatelli S, Cottrill B, Dinovi M, Edler L, Grasl-Kraupp B, Hogstrand C, Nebbia CS, Oswald IP, Petersen A, Rose M, Roudot A-C, Schwerdtle T, Vleminckx C, Vollmer G, Wallace H, Fürst P, Håkansson H, Halldorsson T, Lundebye A-K, Pohjanvirta R, Rylander L, Smith A, van Loveren H, Waalkens-Berendsen I, Zeilmaker M, Binaglia M, Gómez Ruiz JÁ, Horváth Z, Christoph E, Ciccolallo L, Ramos Bordajandi L, Steinkellner H and Hoogenboom LR

The EFSA Journal 2018

Dioxins (PCDD/Fs), and dioxin-like PCBs

Different potencies, expressed in TEFs



7 out of 75

10 out of 135

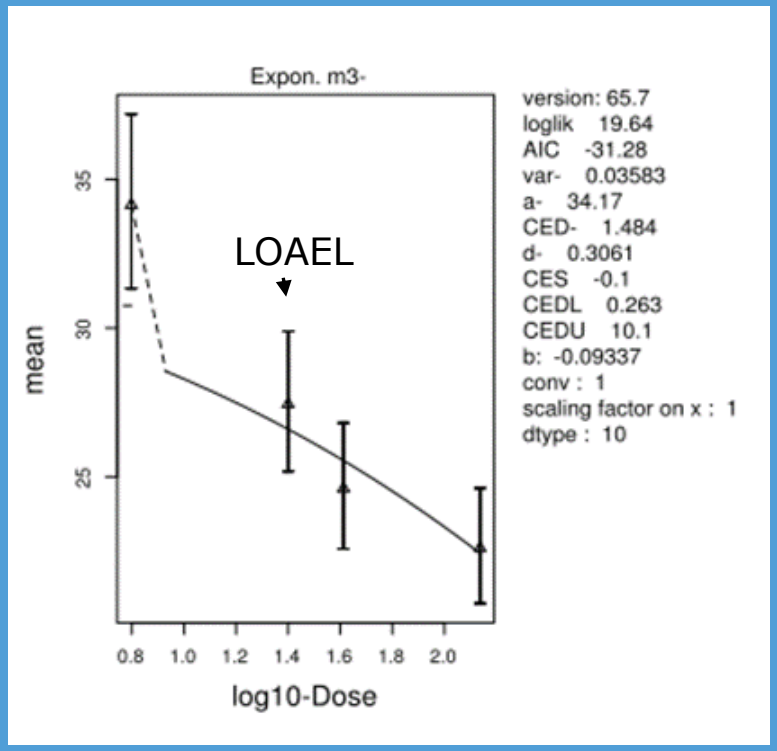
12 out of 209

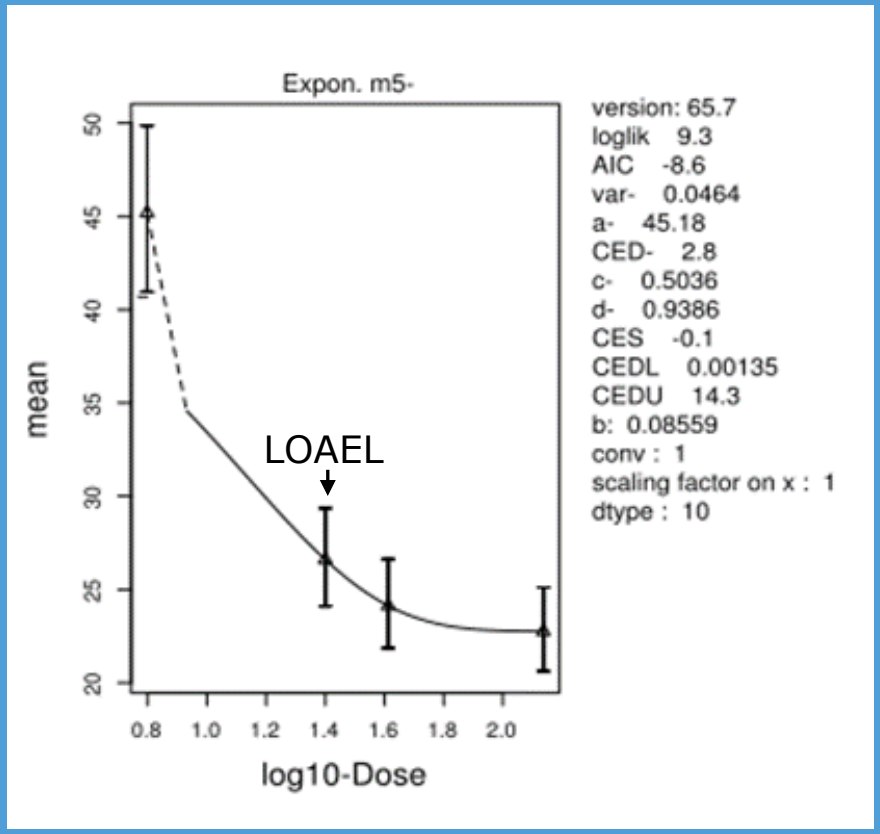
At least 4 chlorines and max 1 at ortho position

TWI set by Scientific Committee on Food (SCF, 2001)

- In 2001 SCF: Tolerable Weekly Intake (TWI) of 14 pg TEQ/kg bw/week
- Based on effects on sperm quality in male rats born to exposed dams (Faqi et al., 1998)

Faqi et al. (1998) BMD modelling





TWI set by Scientific Committee on Food (SCF, 2001)

- Critical body burden (BB) of 40 ng/kg (Lowest Observed Adverse Effect Level (LOAEL))
- Translated to Estimated Human Daily Intake of 20 pg/kg bw/day (LOAEL)
- Converted to 2 pg/kg bw/day using uncertainty factors of 3x3.2 (conversion LOAEL to No Observed Adverse Effect Level (NOAEL) and inter-individual kinetic differences)
- Expressed on weekly base (TWI): 14 pg/kg bw/week

Effects of dioxins in humans

Adverse health effects of dioxins

Victor Yushchenko: poisoned with a few mg of TCDD (2004)
Appearance of chloracne pointed to dioxins

Seveso 1976

- ICMESA chemical plant near Seveso, Italy
  - Production of 2,4,5-trichlorophenol (TCP)
  - On 10 July 1976 emission to an area of 1800 hectares
  - Release of 0.3 – 130 kg dioxins, primarily TCDD
- Consequences
  - First signs were yellow leaves, dead chickens and rabbits
  - Company did initially not warn people
  - After one week, large scale evacuation

Mocarelli et al. 2008: effects on sperm quality exposed boys

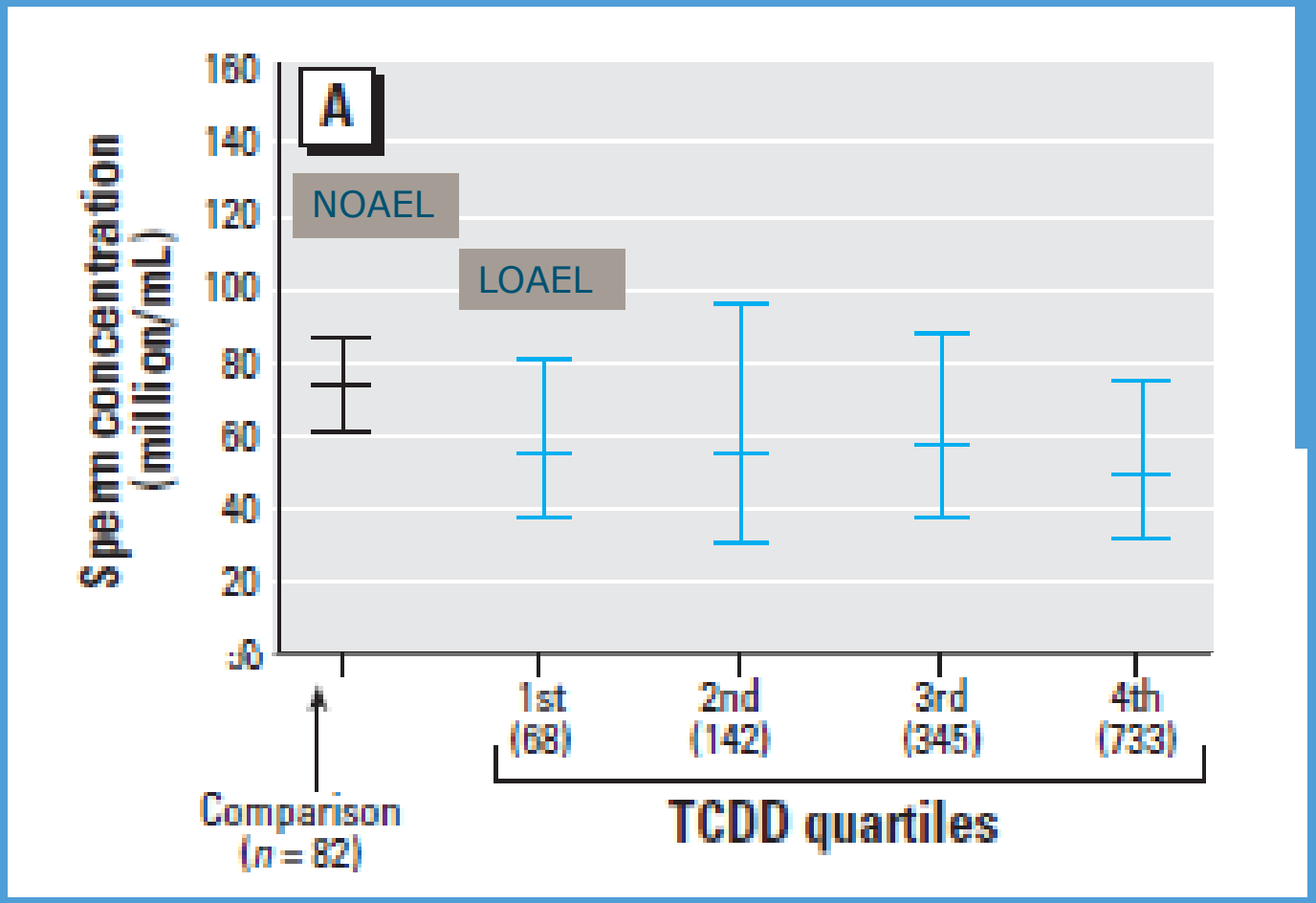
Table 2. Differences in sperm and hormone data between men exposed to TCDD and nonexposed comparison groups by age at time of study (age at dioxin exposure in 1976).

	exposed		control		*p*-Value[a]			
	EG		CG		EG vs. CG		22–31 vs. 32–39	
Characteristic by age group	22–31 (1–9)	32–39 (10–17)	22–31	32–39	22–31	32–39	22–31	32–39
Participants (*n*)	71	44	82	71				
TCDD exposure (ppt[b] level median)								
In 1976	210[c]	164[c]	≤ 15[d]	≤ 15[d]				
In 1998	3.04	4.67	< 6.0	< 6.0				
Sperm concentration (10^6/mL)					0.025	0.213	0.008	0.817
Mean[e]	53.6	81.9	72.5	60.8				
Mean ± SD[e]	21.8–131.8	37.8–177.9	31.7–165.9	24.2–152.8				
Adjusted mean[e]	48.6	87.4	67.1	70.5				
Adjusted mean ± SE	43.1–54.8	74.7–102.3	59.4–75.7	61.3–81.1				

Effects in man exposed at young age (1-9 years),

So not in utero or via breastfeeding

Dose-response? (splitting-up young boys)

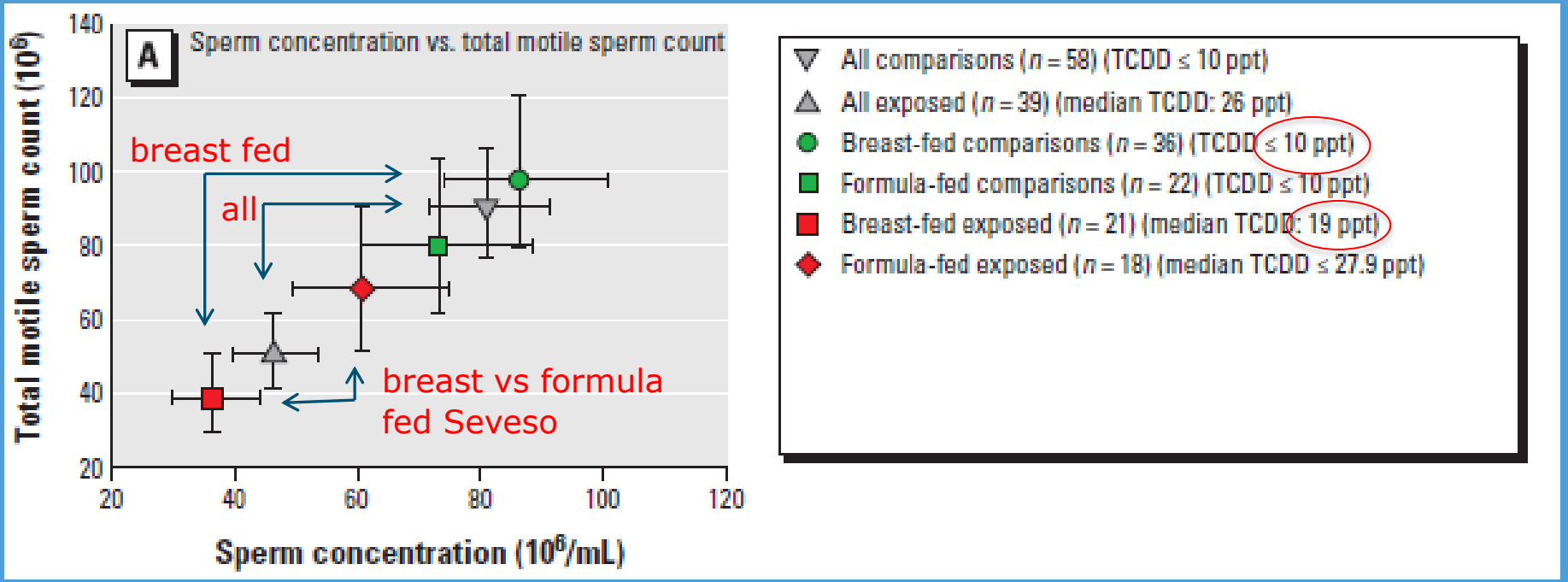


No clear dose-response: actual LOAEL lower than 68 pg/g fat?

Mocarelli et al. 2008

Perinatal exposure (Mocarelli et al. 2011)

Sons born to exposed mothers



- Clear effect, only on breast fed children (effects at lower BB)

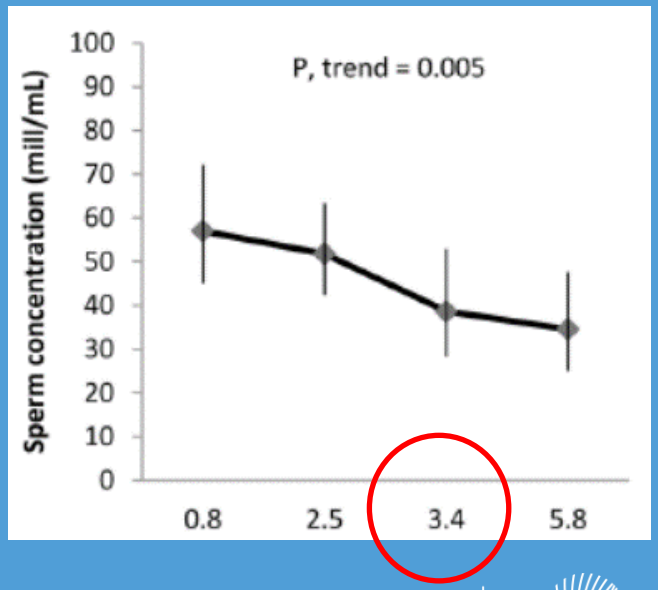
Critical study used by EFSA

- Russian children study from Chapaevsk, Russia
  - Former production chlorinated pesticides
- Levels in boy's blood sampled at 8-9 yrs (2003-2005)
  - Chlorinated pesticides, lead
  - All PCDD/Fs, DL-PCBs and NDL-PCBs
- Observed associations
  - Strong delay in onset of puberty
  - Effects on sperm counts (18-19 years; n=133)
- Confounding by OCPs or lead very unlikely
  - Supported by effects observed in animals

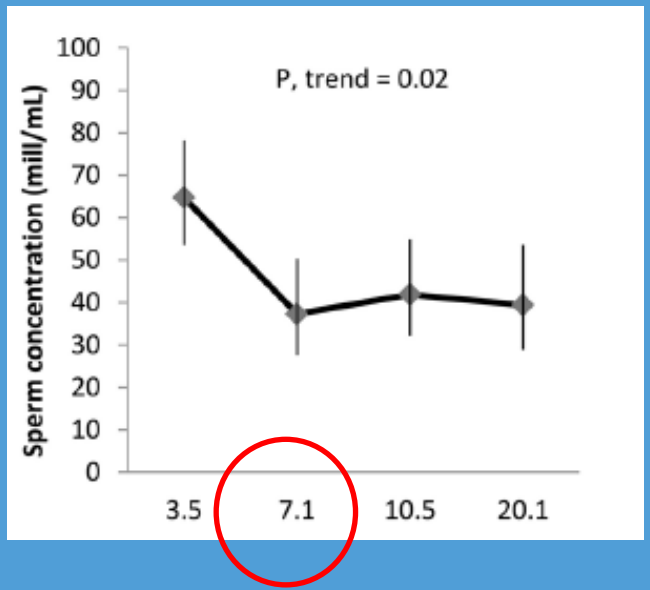
Association dioxins and sperm concentration

Table 3. Multivariable adjusted mean semen parameters by quartiles (Q)[a] of serum dioxins, furans, and PCBs among 133 young men in the Russian Children's Study contributing 256 semen samples.

Toxic equivalent/ concentration	Volume (mL)	Sperm concentration (million/mL)	Total sperm count (million)	Motile sperm (%)	Total motile sperm count (million)
TEQs (pg TEQ/g lipid)					
TCDD					
Q1 (0.35–1.70)	2.7 (2.2, 3.2)	57.0 (45.0, 72.1)	128 (95.6, 173)	61.6 (58.6, 64.7)	78.0 (56.0, 109)
Q2 (1.77–2.45)	2.9 (2.5, 3.4)	51.8 (42.4, 63.3)	136 (105.0, 175)	65.4 (63.4, 67.4)	87.9 (67.1, 115)
Q3 (3.00–3.40)	2.6 (2.1, 2.9)	38.6 (28.2, 52.9)*	85.8 (60.4, 122)	59.5 (56.0, 62.9)	50.1 (33.5, 74.8)
Q4 (4.40–5.80)	3.1 (2.5, 3.7)	34.5 (25.0, 47.7)*	91.6 (63.5, 132)	60.1 (56.6, 63.7)	54.1 (36.0, 81.4)
p-trend	0.55	0.005	0.05	0.17	0.05



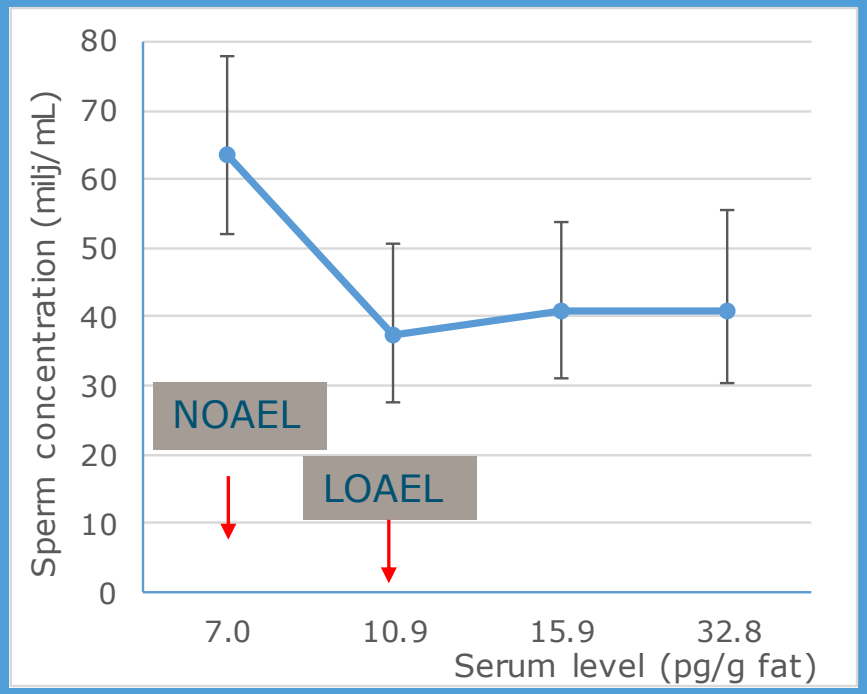
Effect also for PCDD-TEQ



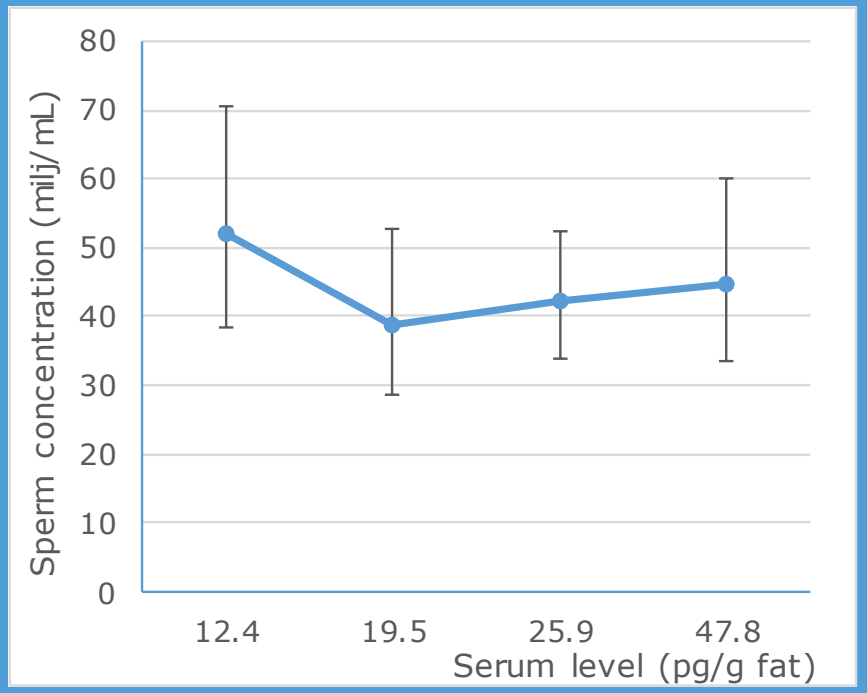
WAGENINGEN UNIVERSITY & RESEARCH

100years 1918 — 2018

Dose-response PCDD/Fs and total-TEQ



PCDD/F-TEQ



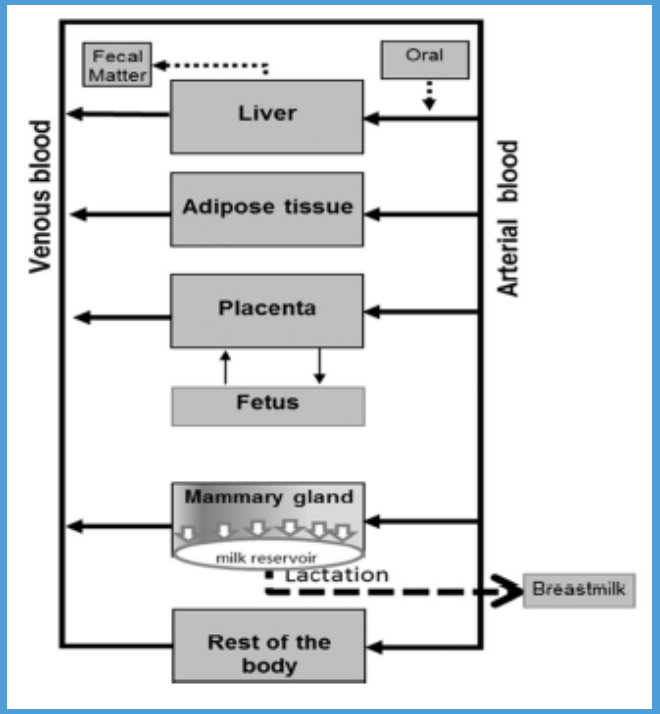
Total-TEQ

- For PCDD/F-TEQ NOAEL 7.0, LOAEL 10.9 pg TEQ/g fat (provided by authors)
- but no significant effect PCDF-TEQ, DL-PCB-TEQ, total-TEQ

From NOAEL serum level to TWI

Toxicokinetic models

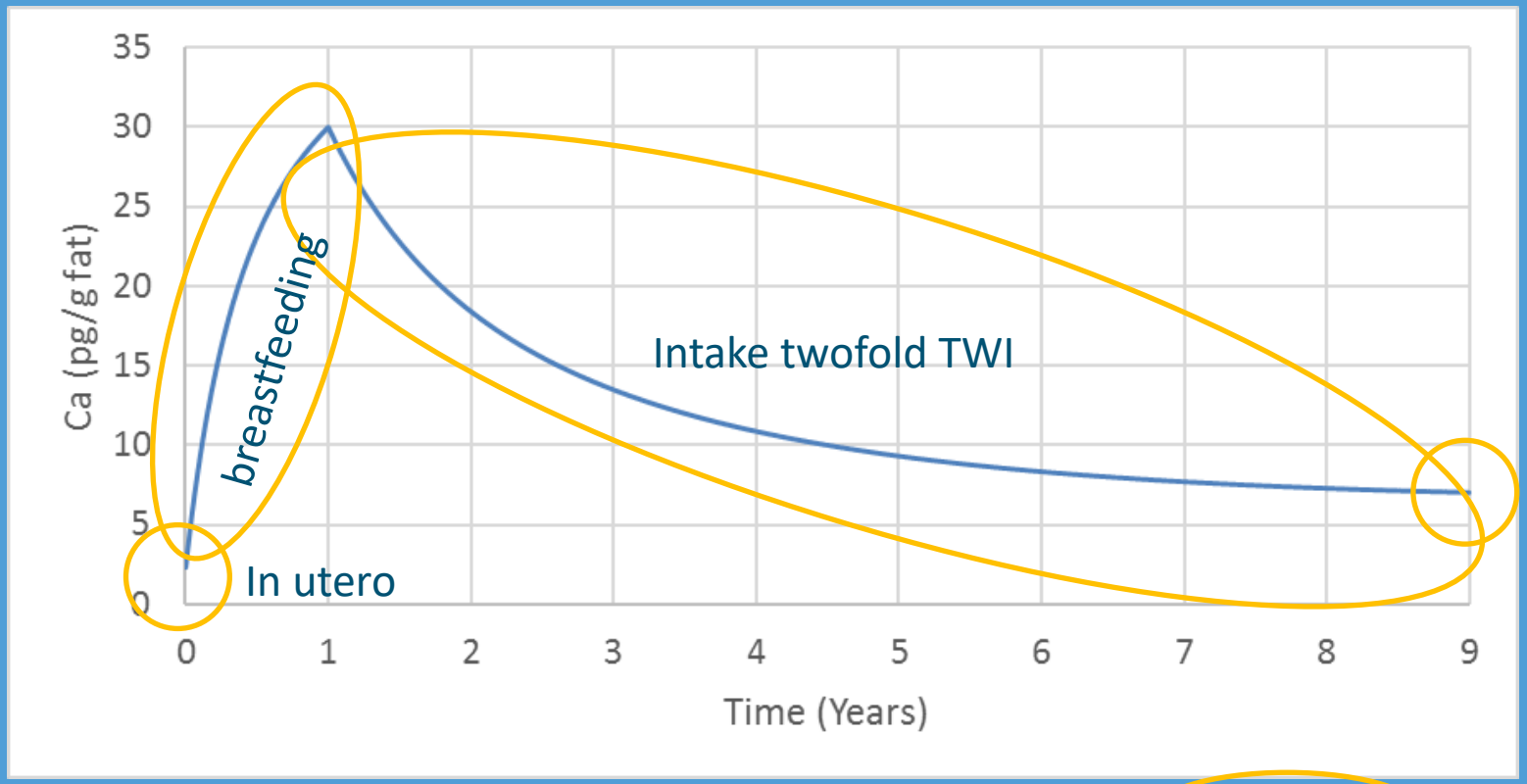
- Use of toxicokinetic rather than one-compartment model
- Available models
  - Emond model, used by US-EPA
  - CADM model, developed by Carrier and Aylward



Toxicokinetic models

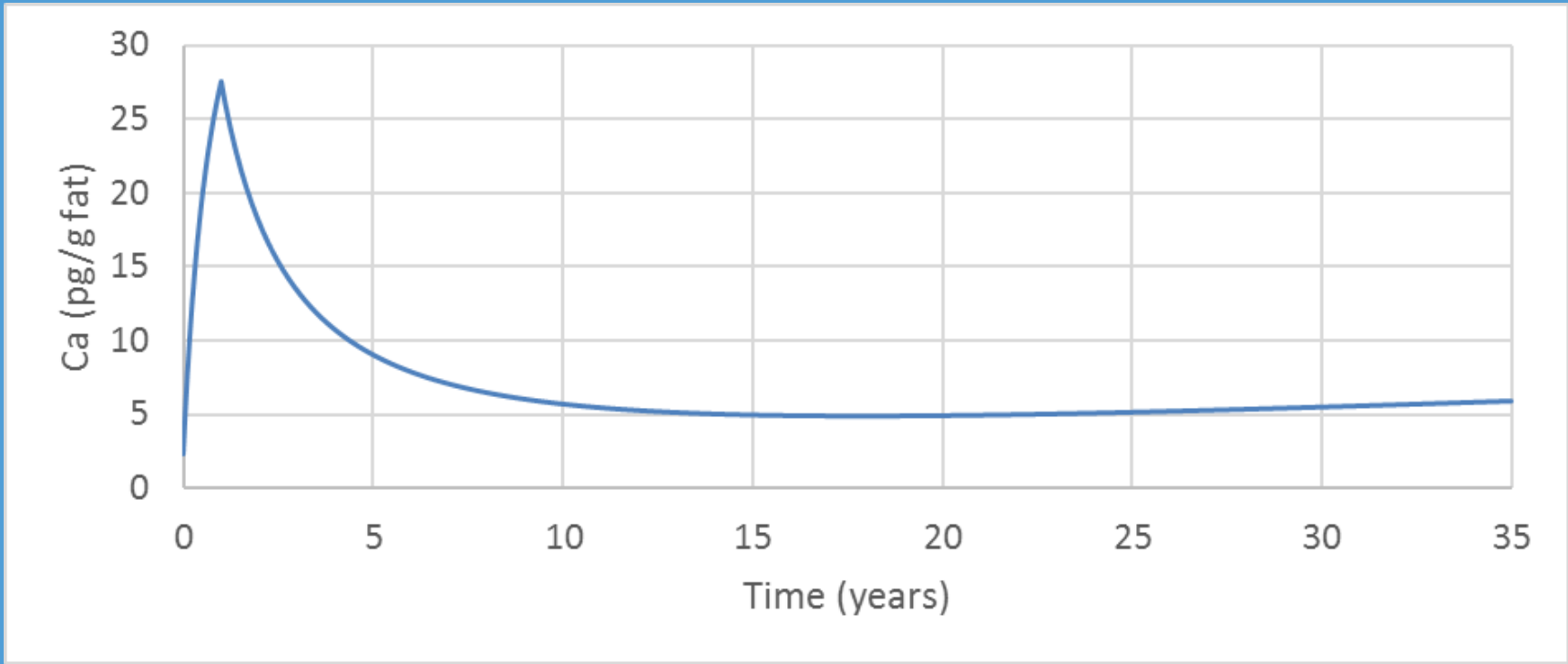
- Half-life dependant on body burden
  - Due to induction liver enzymes (CYPs 1A1 and 1A2)
  - involved in metabolism and liver storage (liver/fat ratio)
- Both models use high absorption rate for TCDD (100%)
  - Calibrated for TCDD, not other PCDD/Fs and DL-PCBs
- Preference for CADM (slightly adjusted)

Modelling boys (CADM)



Serum level (Ca) in boy, breastfed for 12 months with milk with **5.9 pg/g fat** (800 mL per day, 3.5% fat), followed by an intake of **0.5 pg/kg bw per day** for an additional 8 years, resulting in a serum level of 7 pg/g fat.

Modelling mothers (CADM)



Serum levels (Ca) in a woman, breastfed for 12 months in infancy with milk containing 5.9 pg/g fat, and then exposed to **0.25 pg/kg bw per day** for 34 years.

So milk and fat level at birth of son and start of breastfeeding at 35 years: **5.9 pg/g fat**: input for modelling boys

New TWI

- Aim to prevent too high exposure via mother
  - Critical intake: 0.25 pg TEQ/kg bw/day
- Decision to maintain weekly base (TWI)
  - Unclear if longer period (month, year) is safe
- For sum PCDD/Fs and DL-PCBs based on TEQ
  - No doubt that DL-PCBs act dioxin-like
- TWI rounded to **2 pg TEQ/kg bw/week**
- So sevenfold lower than previous TWI
- Lower TWI partly due to different toxicokinetics: higher absorption, longer half-life at lower body burden

What if TWI based on animal studies?

- Faqi study (sperm effects male offspring) most sensitive
  - BB LOAEL 25 ng/kg bw (not 40; s.c. injection)
- Applying same UFs as SCF (2001)
  - UF 3 gives NOAEL of 8.4 ng/kg bw
  - UF 3.2 intraspecies differences: 2.6 ng/kg bw
  - Or 10.4 pg/g fat (based on 25% body fat) (7 pg/g fat in humans)
- Calculating EDHI using CADM
  - EDHI: 0.46 pg/kg bw/day
  - TWI of 3 pg/kg bw/week
- Only slightly higher than new TWI of 2 pg/kg bw/week
  - Much lower TWI due to different kinetic parameters

Exposure assessment

Weekly exposure to PCDD/Fs and DL-PCBs

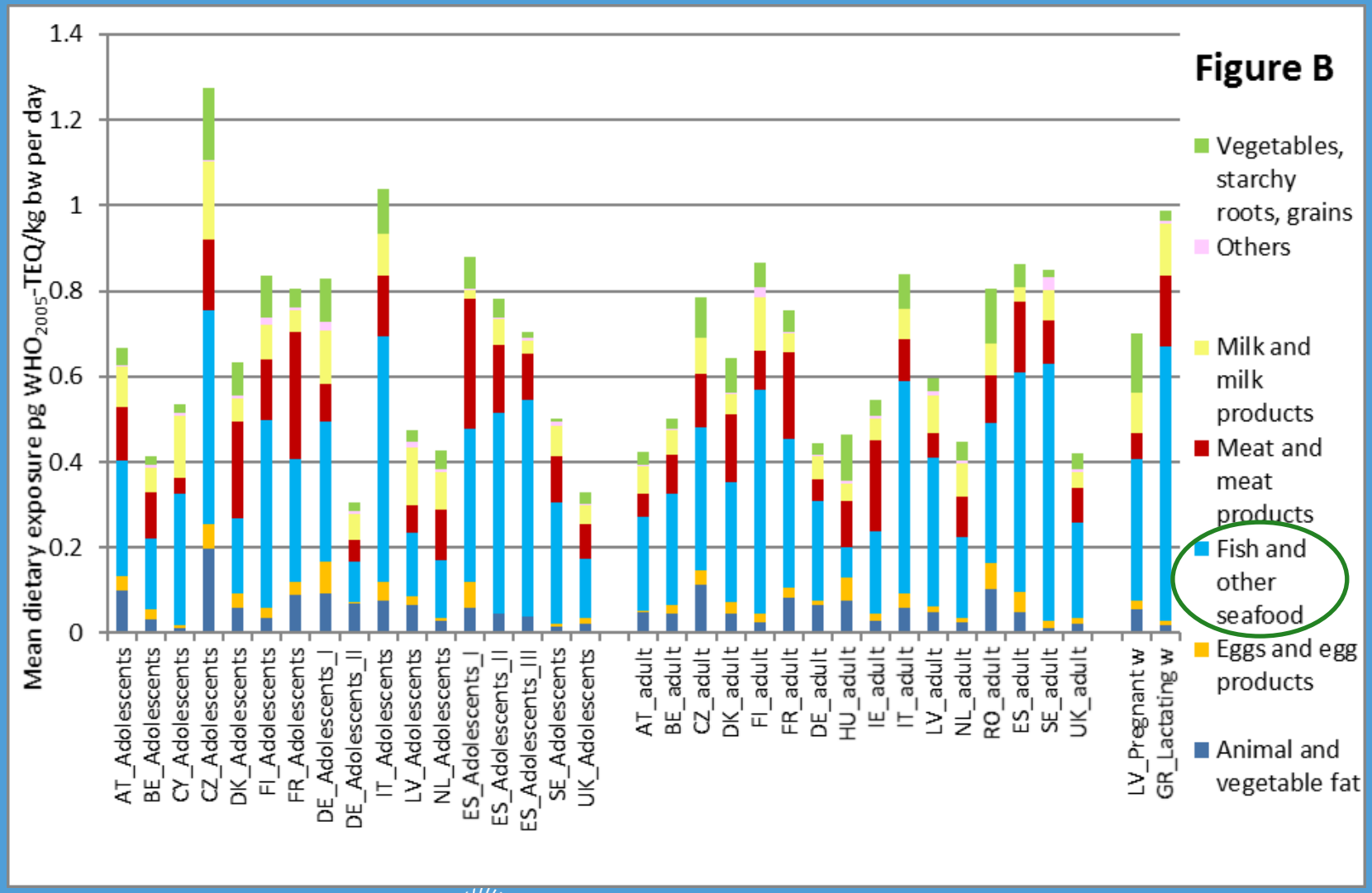
Age class [a]	N	Mean dietary exposure (pg WHO_{2005}-TEQ/kg bw per week)					
		Minimum[b]		Median[b]		Maximum[b]	
		LB	UB	LB	UB	LB	UB
Infants [c]	6	3.1	4.6	4.6	6.5	8.1	9.9
Toddlers	10	4.8	6.2	8.8	10.7	14.8	18.0
Other children	18	3.9	5.0	8.1	9.7	14.1	17.2
Adolescents	17	2.1	2.7	4.6	5.5	8.9	10.5
Adults	17	2.9	3.4	4.5	5.3	7.8	9.1
Elderly	14	2.7	3.6	4.7	5.4	8.9	9.6
Very elderly	12	3.0	4.0	4.5	5.1	8.5	9.2

- Based on food consumption surveys and data from member states
- Small difference UB/LB (low uncertainty)
- Most people below old but above new TWI of 2 pg TEQ/kg bw/week
- Toddlers and other children show 2-fold higher exposure

Observations

- Overall, DL-PCBs contribute 63% to TEQ exposure, PCDFs 23%, PCDDs 14%
- Highest contribution from
  - PCB-126 (54.7%)
  - then 2,3,4,7,8-PeCDF (10.7%)
  - PeCDD (7.4%)
  - TCDF (4.9%), TCDD (3.4%), PCB-169 (3.7%) and PCB-118 (2.7%)
- So exceedance TWI for only PCDD/F-TEQ is less

Relative contribution food groups (at mean exposure)



Major outcomes EFSA Opinion

- New Tolerable Weekly Intake of 2 pg TEQ/kg bw/week
  - Old TWI SCF (2001): 14 pg TEQ/kg bw/week
  - So 7-fold lower
- New TWI exceeded by most consumers
- Major uncertainty: toxic potency of PCB-126,
  - which contributes more than 50% to exposure

Thank you for your attention

Questions?