UNCERTAINTIES IN THE TEF SCHEME

CONTAM Opinion on dioxins and DL-PCBs in food and feed

Roon Hoogenboom
Chair WG Dioxins in food

Info Session – 13 November 2018

efsa
European Food Safety Authority

Risk assessment EFSA CONTAM Panel

- Risk assessment for animals and humans
- Apply current WHO_{05}-TEF scheme

Congener	WHO_{2005}-TEFs		Congener	WHO_{2005}-TEFs
PCDDs			Non-ortho PCBs	
2,3,7,8-TCDD	1		PCB-77	0.0001
1,2,3,7,8-PeCDD	1		PCB-81	0.0003
1,2,3,4,7,8-HxCDD	0.1		PCB-126	0.1
1,2,3,6,7,8-HxCDD	0.1		PCB-169	0.03
1,2,3,7,8,9-HxCDD	0.1		Mono-ortho PCBs	
1,2,3,4,6,7,8-HpCDD	0.01		PCB-105	0.00003
1,2,3,4,6,7,8,9-OCDD	0.0003		PCB-114	0.00003
PCDFs			PCB-118	0.00003
2,3,7,8-TCDF	0.1		PCB-123	0.00003
1,2,3,7,8-PeCDF	0.03		PCB-156	0.00003
2,3,4,7,8-PeCDF	0.3		PCB-157	0.00003
1,2,3,4,7,8-HxCDF	0.1		PCB-167	0.00003
1,2,3,6,7,8-HxCDF	0.1		PCB-189	0.00003
2,3,4,6,7,8-HxCDF	0.1			
1,2,3,7,8,9-HxCDF	0.1			
1,2,3,4,6,7,8-HpCDF	0.01			
1,2,3,4,7,8,9-HpCDF	0.01			
1,2,3,4,6,7,8,9-OCDF	0.0003			

Risk assessment EFSA CONTAM Panel

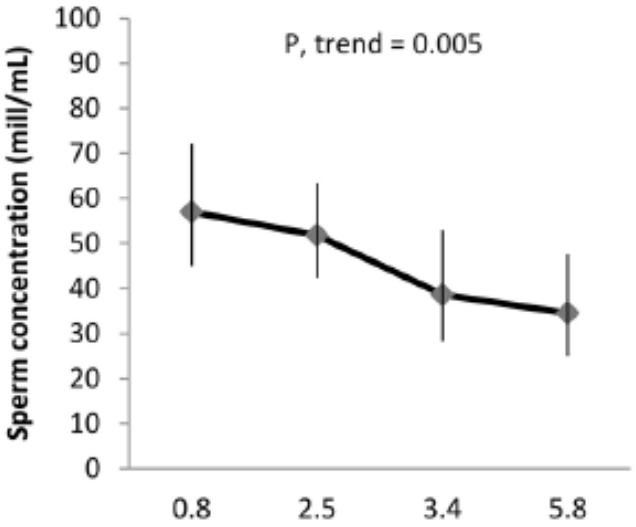
- DL-PCBs contribute 63% to TEQ exposure
  - PCB-126 for 55%
- Critical study used for deriving new TWI of 2 pg TEQ/kg bw/week:
  - Mínguez-Alarcón et al (2017) on effects on sperm quality

A Longitudinal Study of Peripubertal Serum Organochlorine Concentrations and Semen Parameters in Young Men: The Russian Children's Study

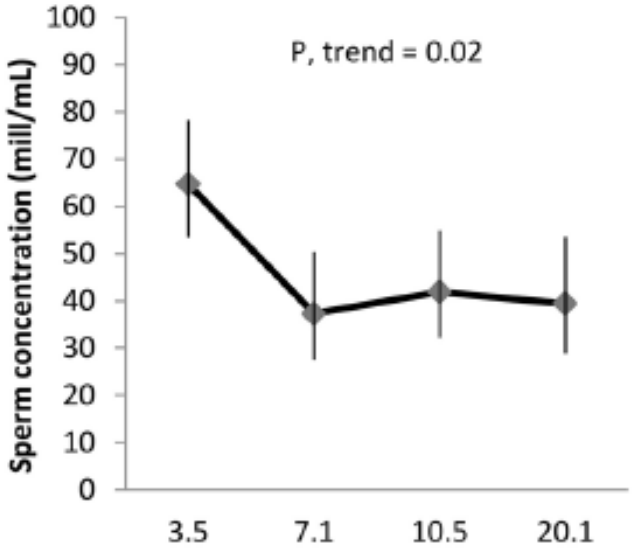
Lidia Mínguez-Alarcón,[1] Oleg Sergeyev,[2,3] Jane S. Burns,[1] Paige L. Williams,[4,5] Mary M. Lee,[6] Susan A. Korrick,[1,7] Luidmila Smigulina,[3] Boris Revich,[8] and Russ Hauser[1,5]

VOLUME 125 | NUMBER 3 | March 2017 · Environmental Health Perspectives

Associations serum levels and sperm concentrations



TCDD



PCDD-TEQ

- Not for PCDF-TEQ, Co-PCB-TEQ or total-TEQ
- Also for PCDD/F-TEQ (not in paper but in EFSA opinion)

Derivation of TWI

- Decision to base TWI on NOAEL serum level for PCDD/F-TEQ
  - So ignore DL-PCBs but include PCDFs

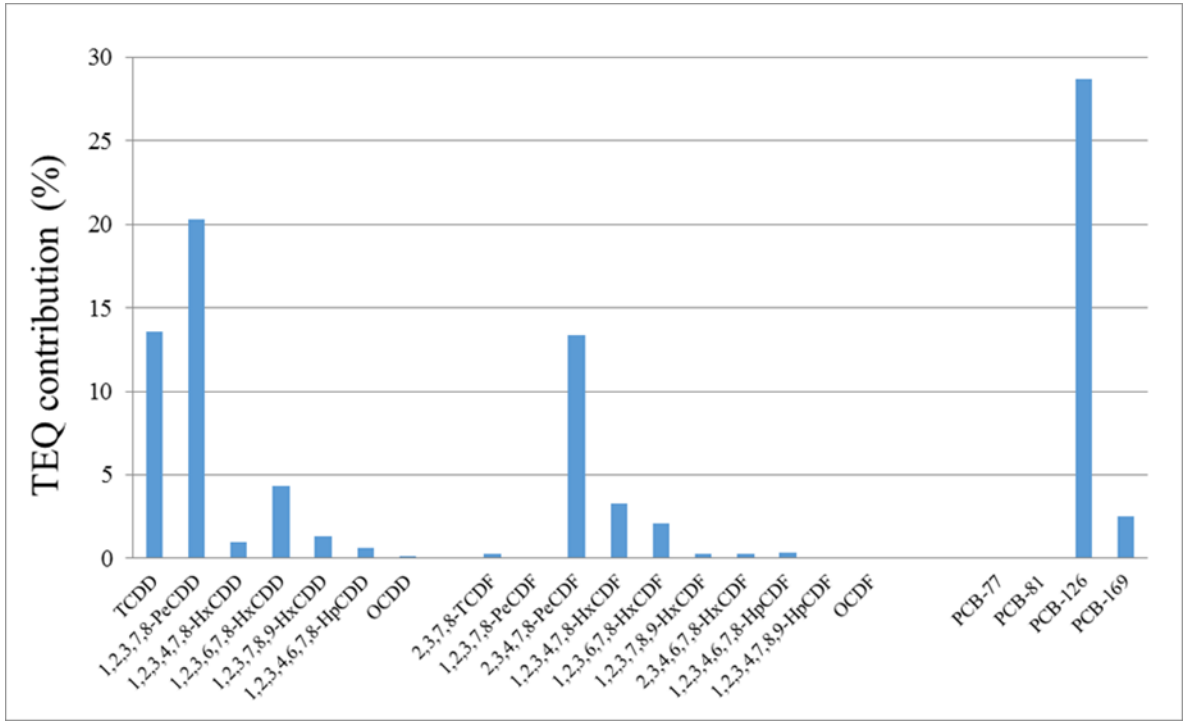
- But TWI considered to be applicable for PCDD/Fs and DL-PCBs
  - No reason to exclude PCDD/Fs or DL-PCBs from TEQ-principle
  - Act on Ah receptor
  - Are persistent, maybe with some exceptions like TCDF and 1,2,3,7,8-PeCDF

How to explain this controversy?

Possible explanations:

- Relative contribution DL-PCBs small
- Role of NDL-PCBs
- Potency DL-PCBs overestimated by WHO_{05}-TEFs

Relative contribution PCDD/Fs & DL-PCBs in serum boys

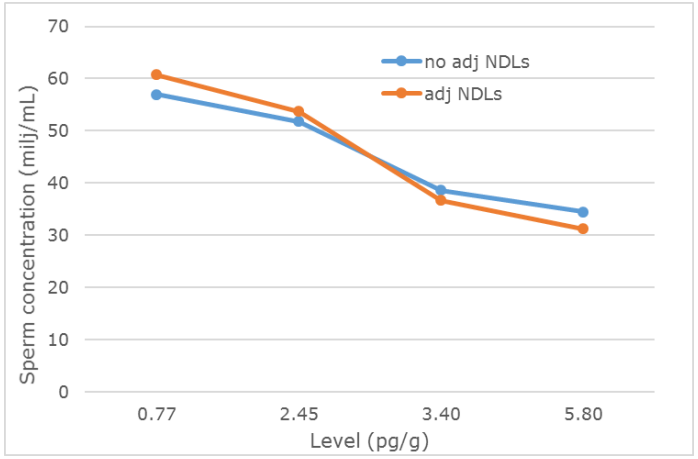


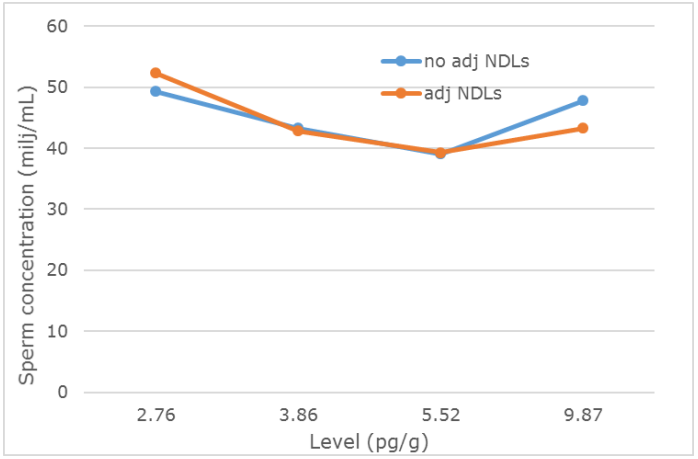
- So DL-PCBs contribute similar as PCDDs to TEQ
- PCDFs contribute less

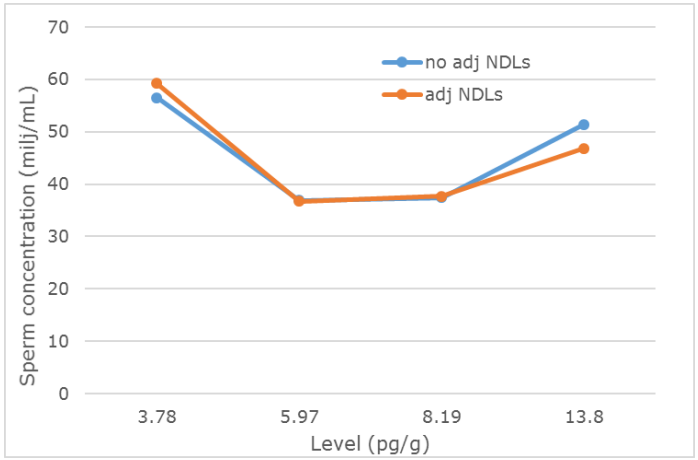
Effect NDL-PCBs

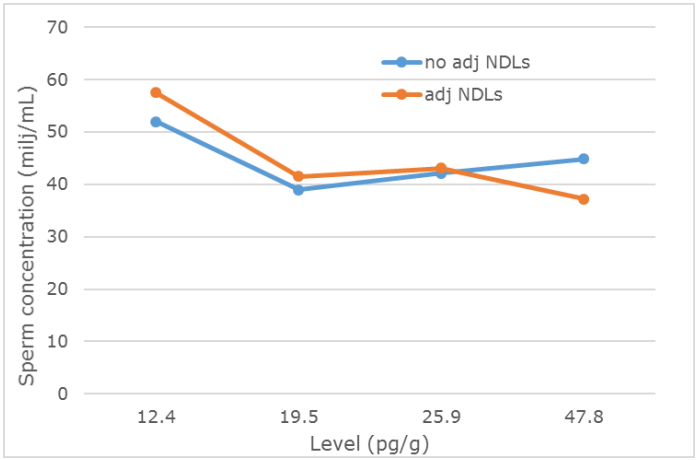
- Association between serum TEQ levels and delayed puberty onset in Russian Children's Study (Burns et al. 2016)
  - Effect stronger when adjusting for NDL-PCBs
  - Opposite association for NDL-PCBs adjusted for TEQ
- Also true for sperm quality?
  - Of interest since association NDL-PCBs with DL-PCBs and also PCDFs expected to be stronger than for PCDDs
- Not in Mínguez-Alarcón et al. (2017), but additional data obtained by EFSA from authors:

Effect NDL-PCBs









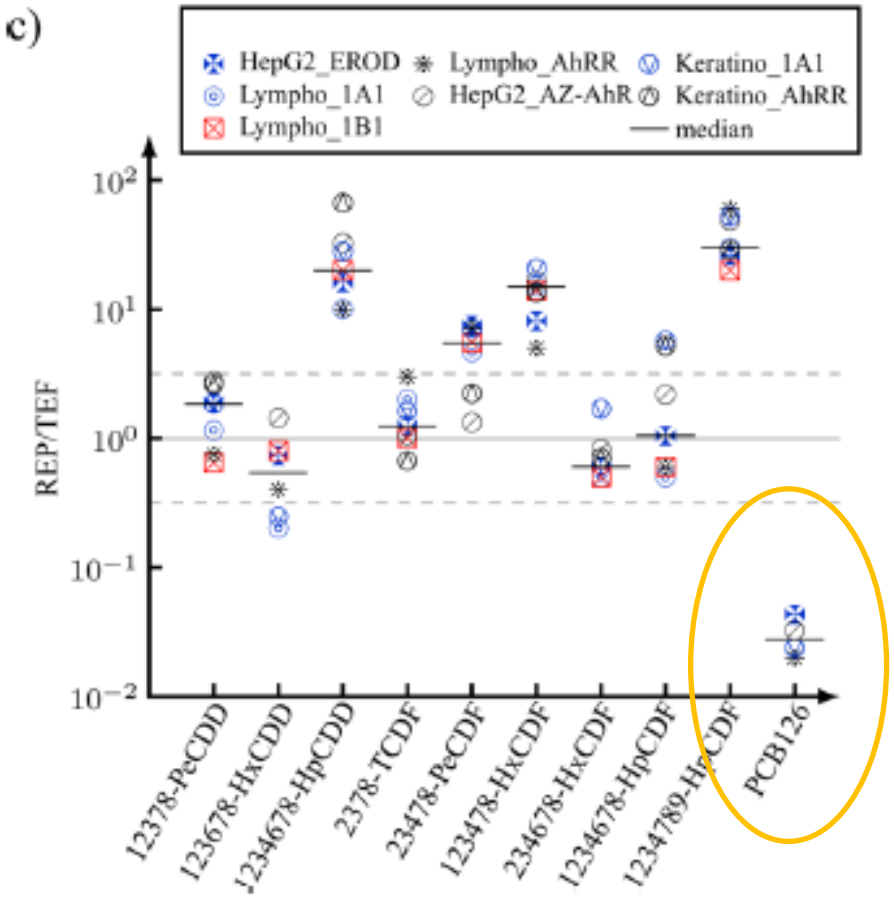
- Slightly better trends, but overall effect not very clear

EU-SYSTEQ project

Consensus Toxicity Factors for Polychlorinated Dibenzo-*p*-dioxins, Dibenzofurans, and Biphenyls Combining *in Silico* Models and Extensive *in Vitro* Screening of AhR-Mediated Effects in Human and Rodent Cells

Malin Larsson,*[,†] Martin van den Berg,[‡] Petra Brenerová,[#] Majorie B. M. van Duursen,[‡] Karin I. van Ede,[‡] Christiane Lohr,[⊥] Sandra Luecke-Johansson,[§] Miroslav Machala,[#] Sylke Neser,[⊥] Kateřina Pěnčíková,[#] Lorenz Poellinger,[§] Dieter Schrenk,[⊥] Simona Strapáčová,[#] Jan Vondráček,[#,∥] and Patrik L. Andersson[†]

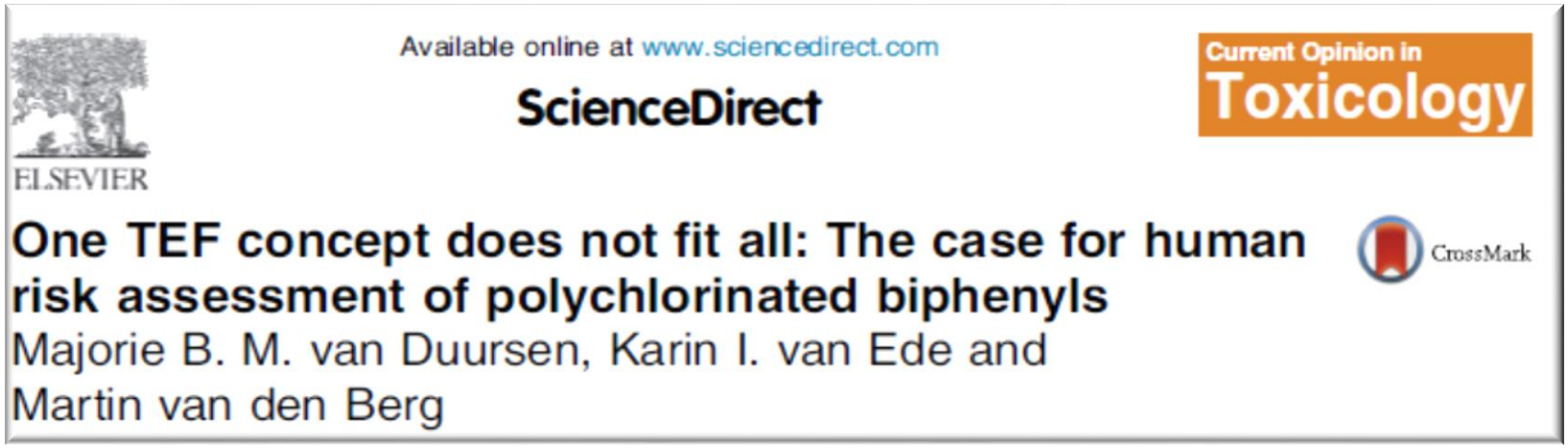
- Relative potency PCB-126 in human cells much less than suggested by TEF of 0.1
- Based on EROD and mRNA CYPs and AHRR
- Confirms previous studies with human hepatocytes and HepG2 cells



EU-SYSTEQ project

- Van Duursen et al. (2017): "*consequently the AHR-mediated risk in humans for DL-PCBs is likely overestimated in the current TEF concept*"

- Median human REP: 0.0033 (TEF = 0.1)



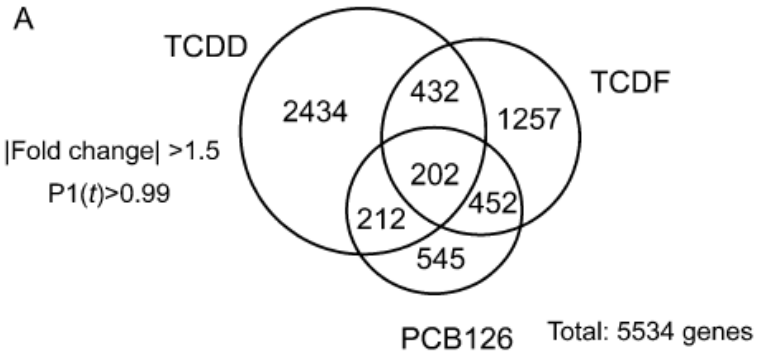
TEF of 0.1 is rodent TEF?

- Kopec et al. (2010) study
- Female OVX mice exposed to various doses of TCDD, TCDF and PCB-126 (large dose range)
  - 11, 8 and 8 doses (n=4, gavage, single dose)
- Gene expression liver
- Overlap for known genes (e.g. various CYPs)
  - Also many genes without overlap

TOXICOLOGICAL SCIENCES 118(1), 286–297 (2010)
doi:10.1093/toxsci/kfq236
Advance Access publication August 11, 2010

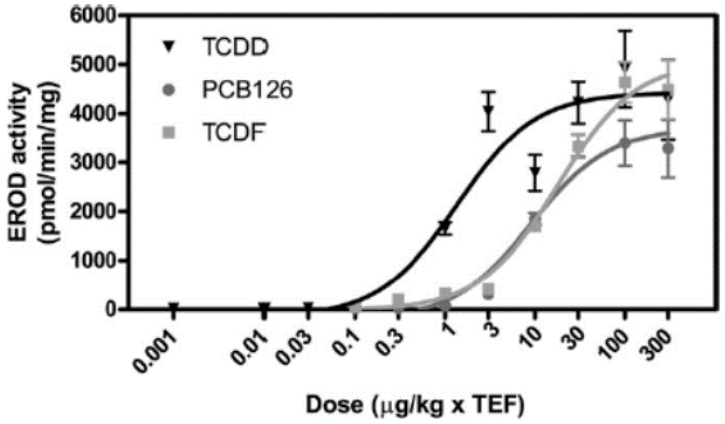
Automated Dose-Response Analysis and Comparative Toxicogenomic Evaluation of the Hepatic Effects Elicited by TCDD, TCDF, and PCB126 in C57BL/6 Mice

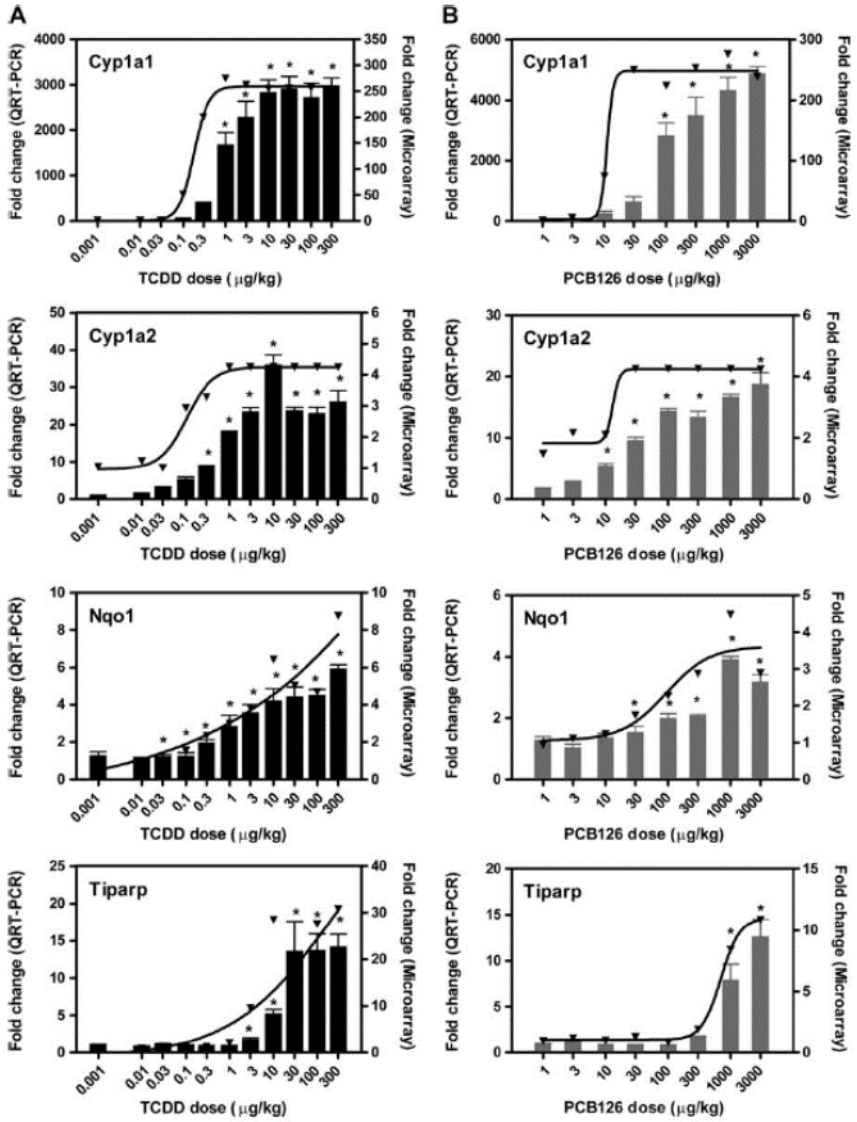
Anna K. Kopec,*·†·1 Lyle D. Burgoon,*·†·‡ Daher Ibrahim-Aibo,†·§ Ashley R. Burg,*·† Andrea W. Lee,*·† Colleen Tashiro,¶ Dave Potter,¶ Bonnie Sharratt,¶ Jack R. Harkema,†·§ J. Craig Rowlands,‖ Robert A. Budinsky,‖ and Timothy R. Zacharewski*·†·1



Kopec et al. study (2010)

- For EROD REP of 0.01
- Also for gene expression, REPs PCB-126 closer to 0.01
- For many genes, dose response not so clear, or at high dose only





Database REPs (Haws et al. 2006)

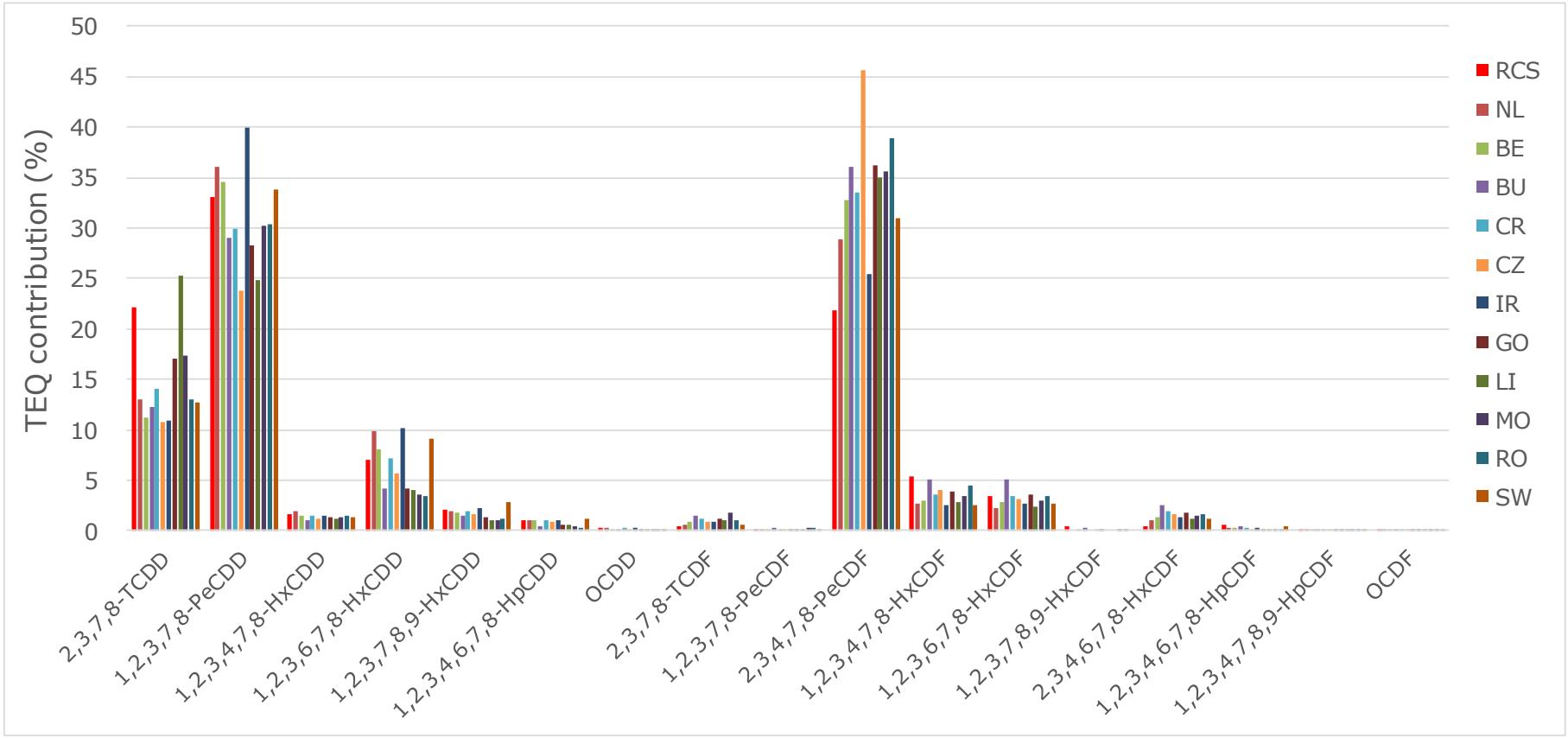
- Primarily data from rats on CYP induction and EROD
- But supported by NTP study on rats
  - Including Liver tumours
- Also some mouse data (e.g. Harper et al.)
  - Relative potency much less for EROD induction liver
- But higher for immunotoxic effects (PFCs)
- Could similar be the case in humans?
  - But immunotoxicity not shown to be critical effect
  - What about sperm quality (studies?)

Conclusions PCB-126

- No human accidents with PCB-126 as major contributor to TEQ
- *In vitro* data with human cells suggest that TEF of 0.1 for PCB-126 is too high for humans
- Associations in Russian Children Study seem to support lower toxicity PCB-126
- PCB-126 contributes significantly to exposure humans
- TEF for PCB-126 should be evaluated

Exposure profile in RCS and Europe

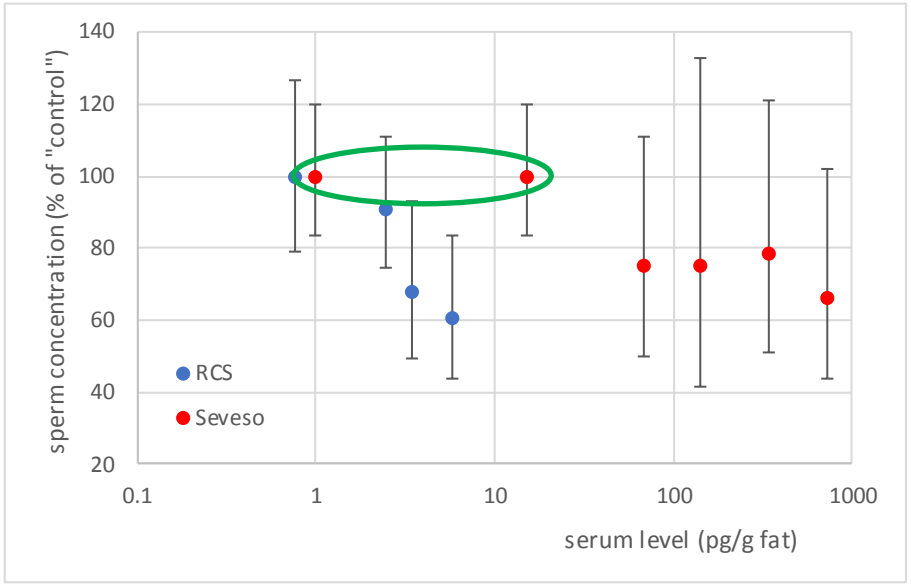
TEQ contribution of the individual congeners in human milk compared to the blood of the Russian boys



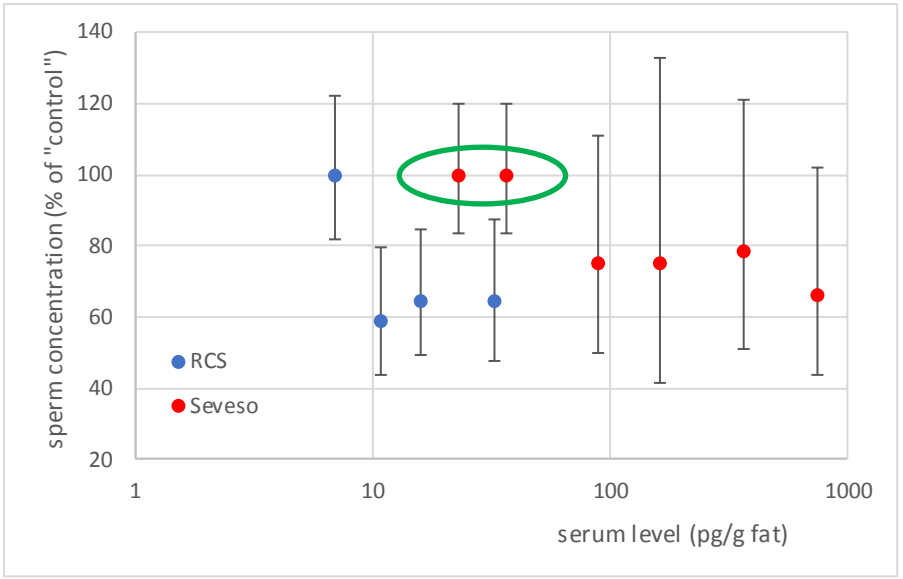
Malisch and Schäechtele, 2018. Selected data from WHO/UNEP-coordinated exposure studies 2000 – 2015 (data submitted to EFSA)

Comparison of dose-response in RCS and Seveso

TCDD

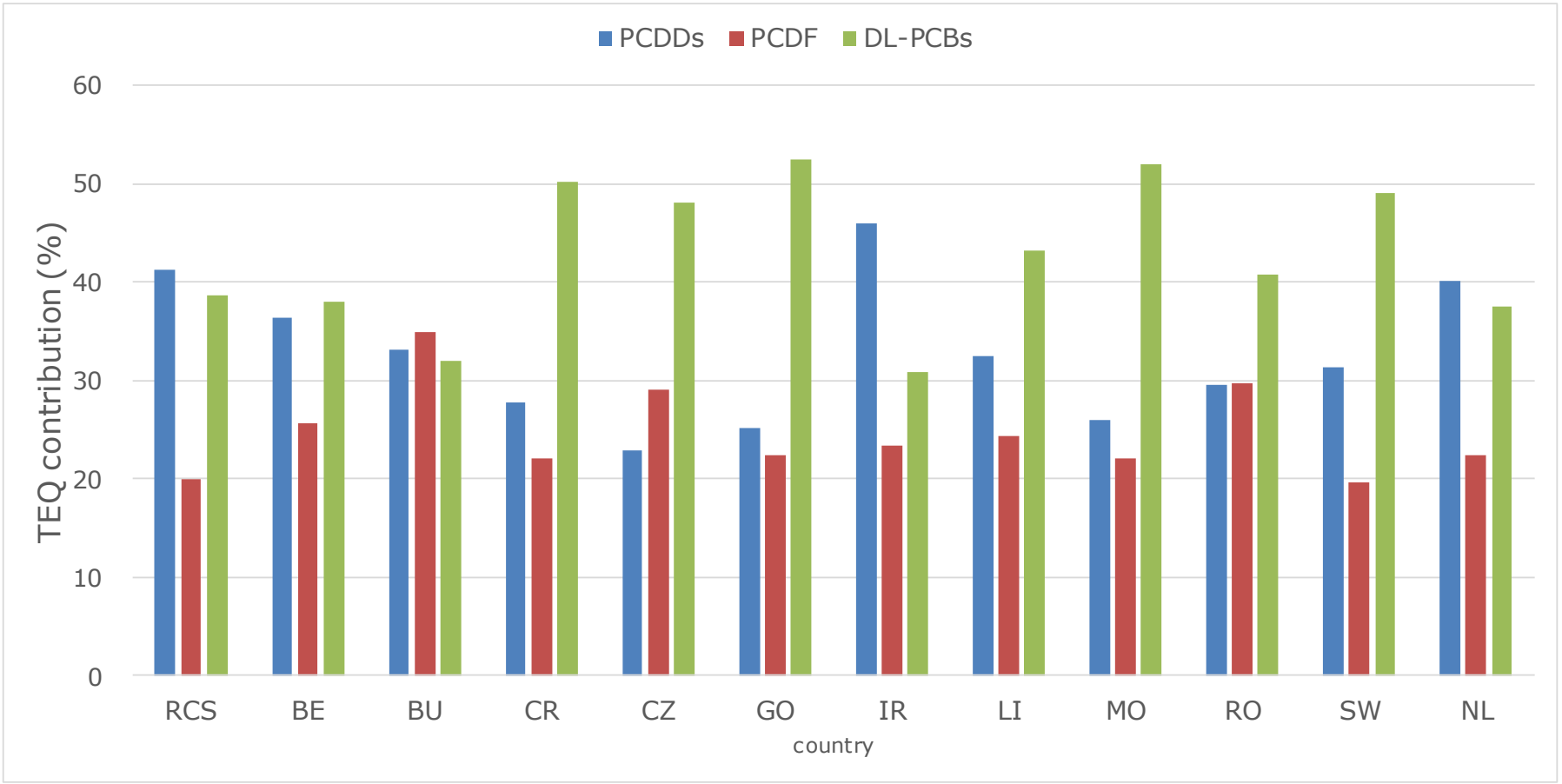


PCDD/F-TEQ



Exposure profile in RCS and Europe

TEQ contribution of PCDDs, PCDFs and DL-PCB in human milk compared to the blood of the Russian boys



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