Risk-benefit assessment for the breastfed infant in relation to the presence of dioxin-like compounds as determined from the WHO and UNEP global human milk surveys.

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Acknowledgments

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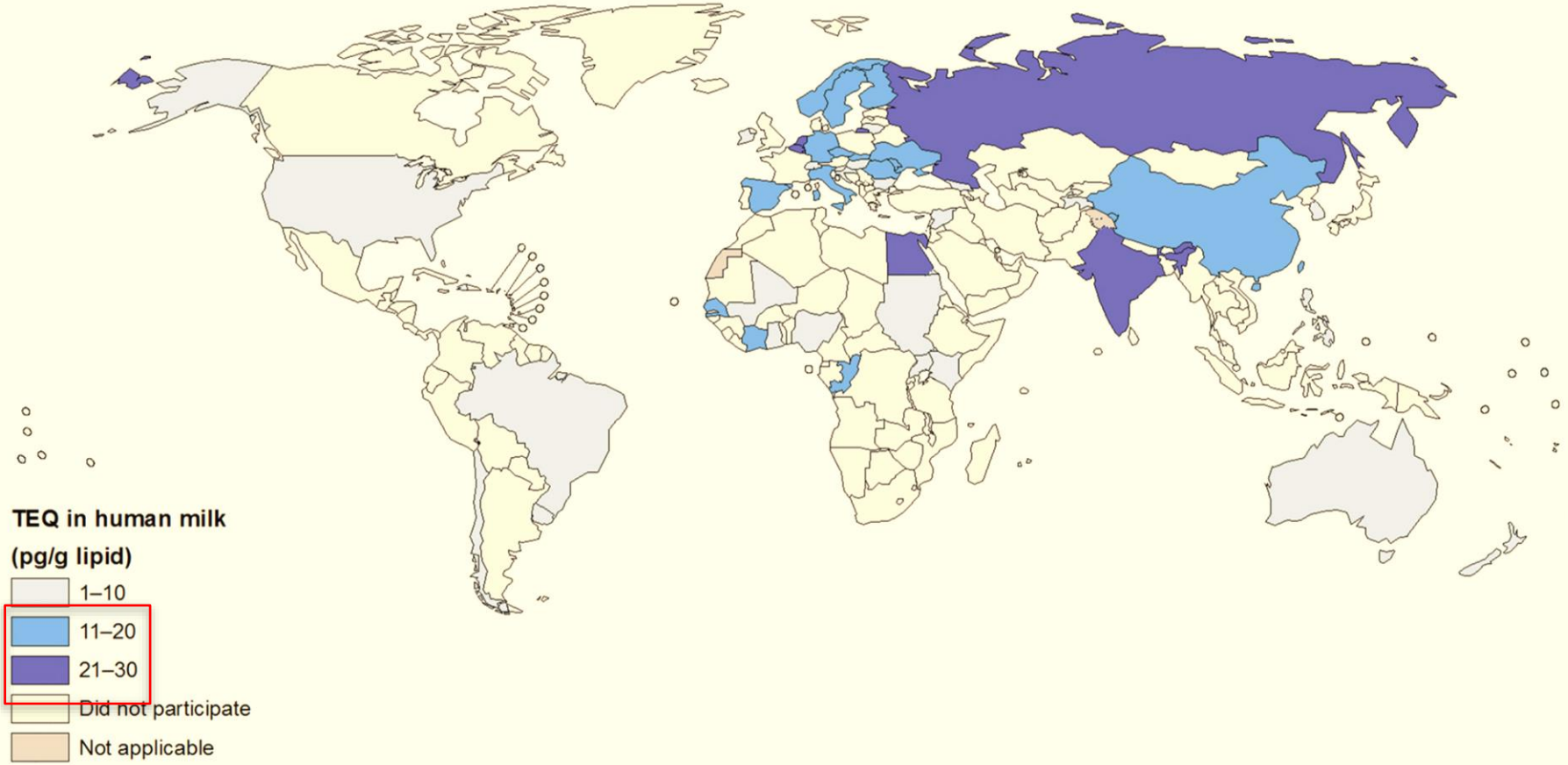
All volunteers worldwide that contributed to the systematic collection of the human milk samples since the 1980's!

Disclaimer: The opinions presented in this presentation do not necessarily reflect those of the United Nations Environment Programme or World Health Organization

Data from European countries are courtesy to these countries (self-paying)

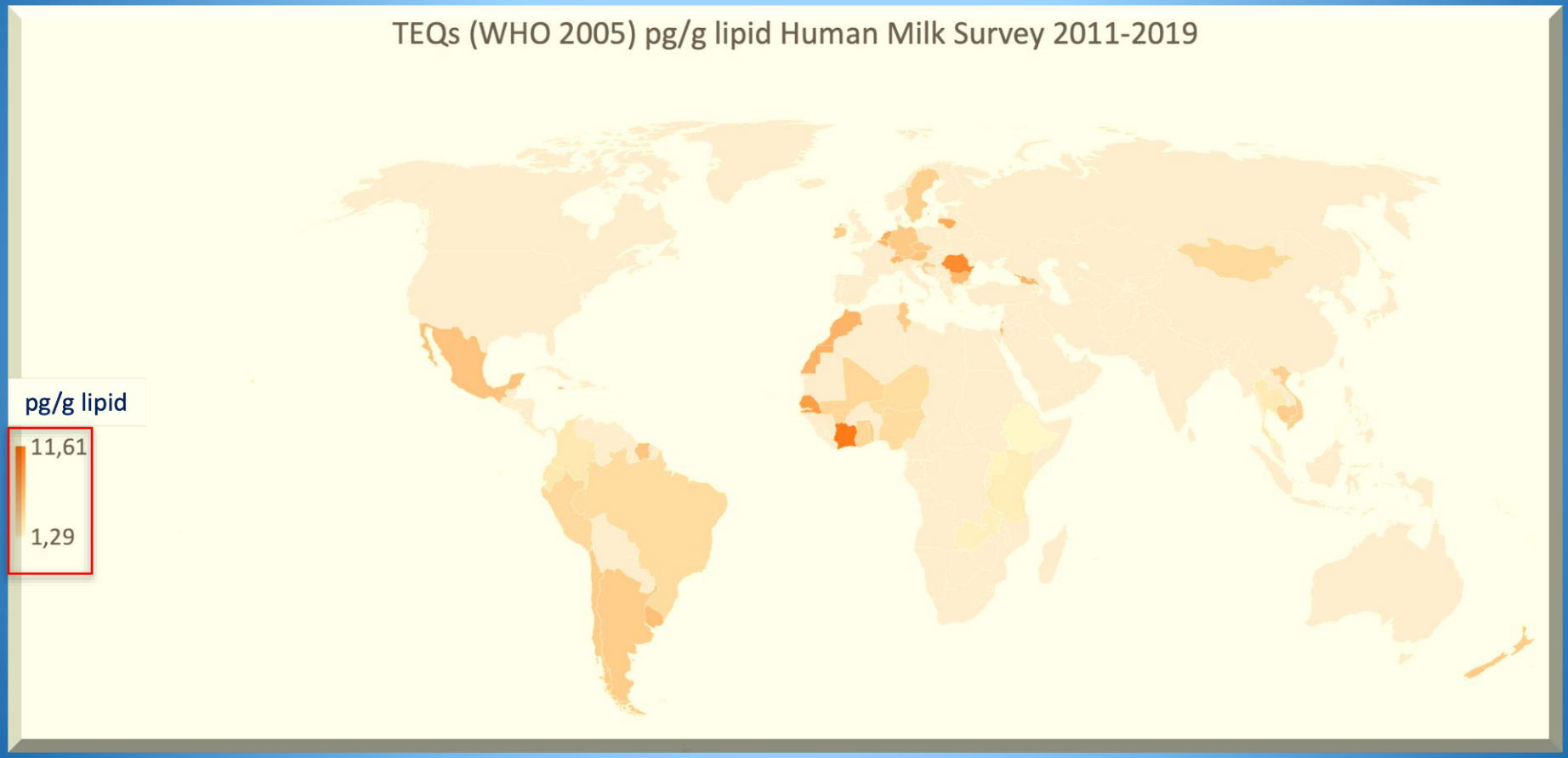
Global distribution PCDD/Fs/DL-PCBs in WHO-TEQs 2000-2010

Toxic equivalents (TEQ) levels for dioxin-like compounds analysed in the period 2000–2010 for specific countries

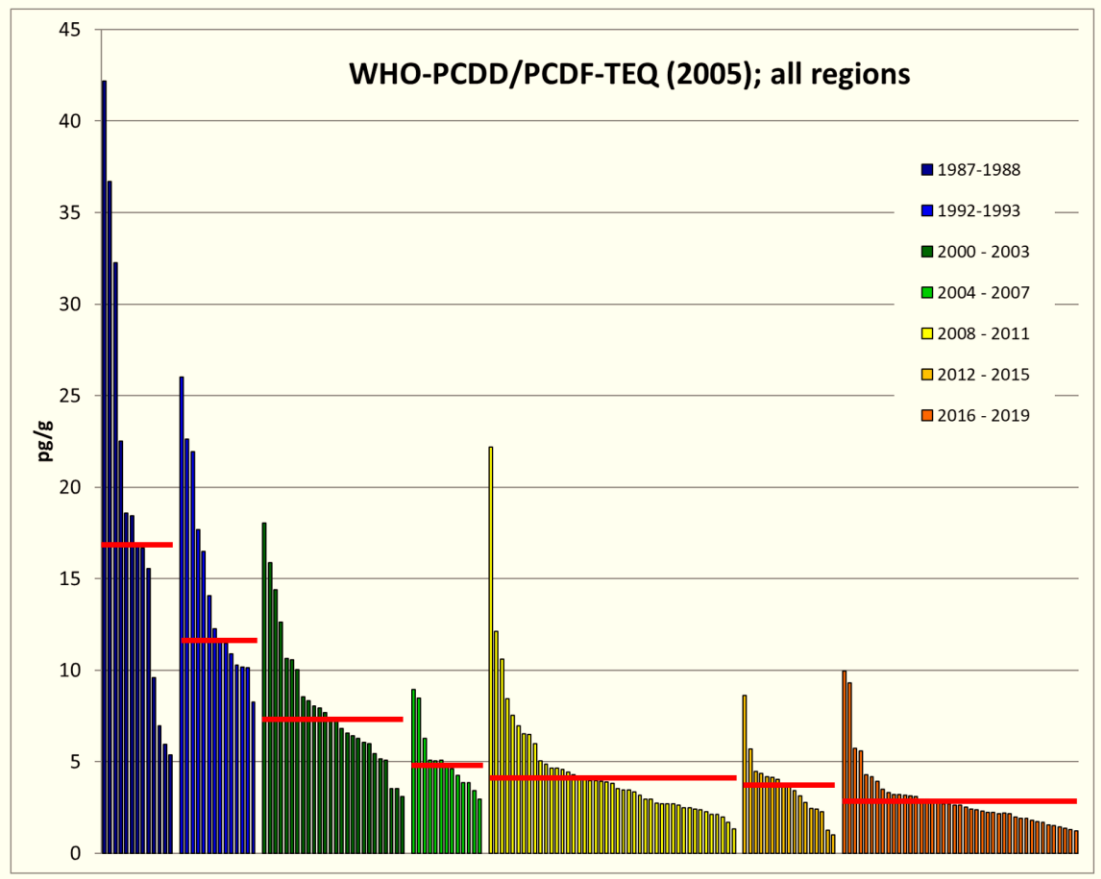


Van den Berg et al., Arch Toxicol (2017) 91:83–96

Global distribution PCDD/Fs/DL-PCBs in WHO-TEQs 2011-2019



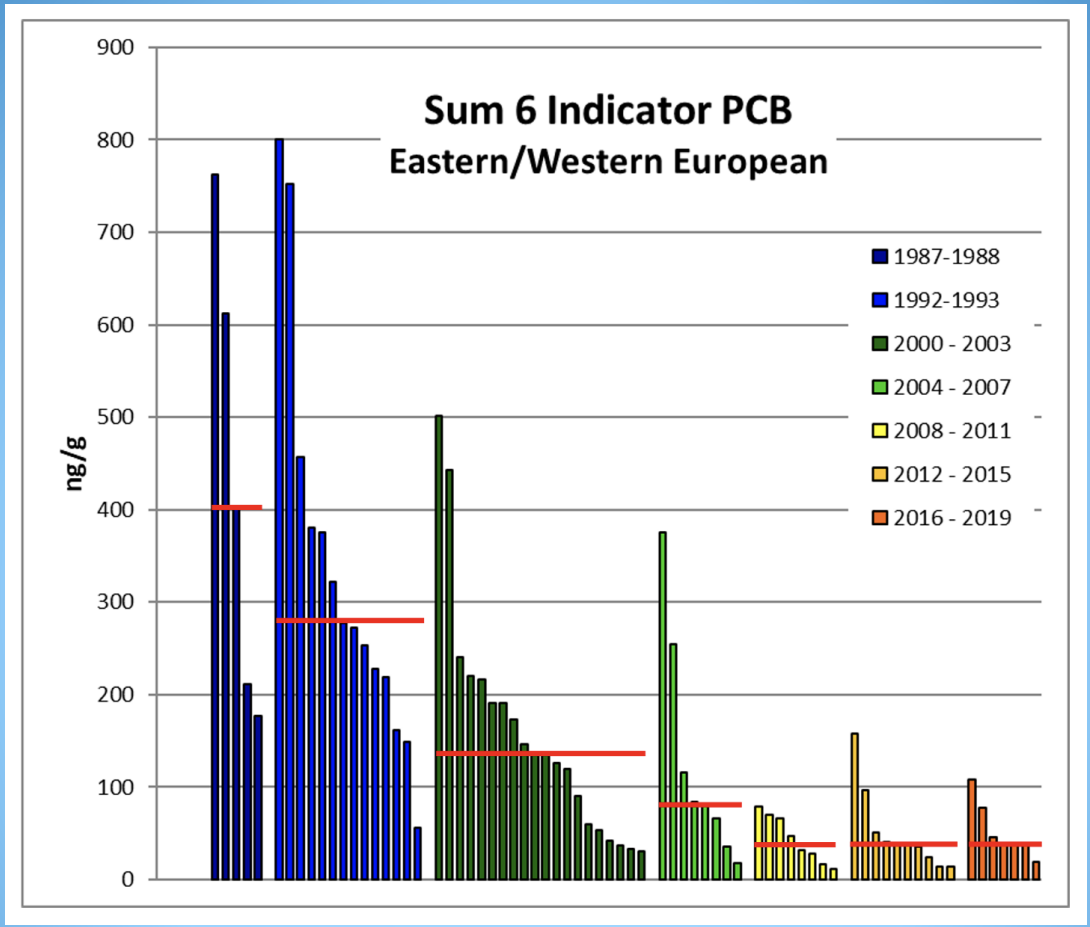
Temporal trend PCDDs and PCDF in human milk



- Concentrations of WHO-PCDD/PCDF-TEQ in the 57 countries
- Between 1987 and 2019, median TEQs concentrations in these seven periods decreased considerably from 16.9 pg /g to 2.68 pg/g (= 84 % decrease).
- In period 2000 – 2019 median concentrations TEQs went down by 63 %

Malisch et al., Time trends estimated in WHO- and UNEP-coordinated exposure studies of persistent organic pollutants in human milk (2022). In: Legacy and emerging persistent organic pollutants in human milk, part 4

Temporal trend PCBs in human milk



Similar trend DL-PCBs

- Between 1987 and 2019 median ΣPCB_6 concentrations decreased from 211 ng /g to 14 ng/g (= 93 % decrease).
- In period 2000 – 2019 the median concentrations ΣPCB_6 went down by 89 %

Rainer Malisch et al., time trends estimated in WHO- and UNEP-coordinated exposure studies of persistent organic pollutants in human milk (2022) in legacy and emerging persistent organic pollutants in human milk, part 4

Temporal trend PCDDs and PCDFs in human milk

Start WHO/UNEP surveys

Round	Period	No of countries / participations	WHO-PCDD/F-TEQ (2005 / UB) Min	Median	Max	Decrease of median over time % relative to round 1	% relative to round 3
1	1987-1988	13	5,38	16,93	42,18	100	-
2	1992-1993	14	8,26	11,93	26,03	70	-
3	2000-2003	24	3,08	7,34	18,03	43	100
4	2004-2007	11	2,94	4,83	8,93	29	66
5	2008-2011	37	1,31	3,92	22,19	23	53
6	2012-2015	15	1,01	3,82	8,61	23	52
7	2016-2019	33	1,02	2,68	9,97	16	37
	1987-2019	147	1,01	4,62	42,18		
	2000-2019	120	1,01	3,96	22,19		

Half way WHO/UNEP surveys

Time trend of WHO-PCDD/PCDF-TEQ concentrations with differentiation of the periods (i) 1987-1988 or (ii) 2000-2003

Individuals may differ one order of magnitude in concentration

Risk assessment for dioxin-like compounds (PCDDs, PCDFs, DL-PCBs) for the breast fed infant only?

Mutiple Issues involved:

- Relevance experimental studies underlying various HBGVs?
- Relevance human studies recently used for HBGVs?
- Present DLCs levels still of concern?
- Time course for decrease DLCs to acceptable levels in human milk?
- Risk-Benefit situation for breastfeeding?

Health Based Guidance Values (HBGVs) determined by various regulatory authorities with underlying health effects observed in animals and humans with an estimated acceptable HBGV in TEQ_{2005} in human milk.

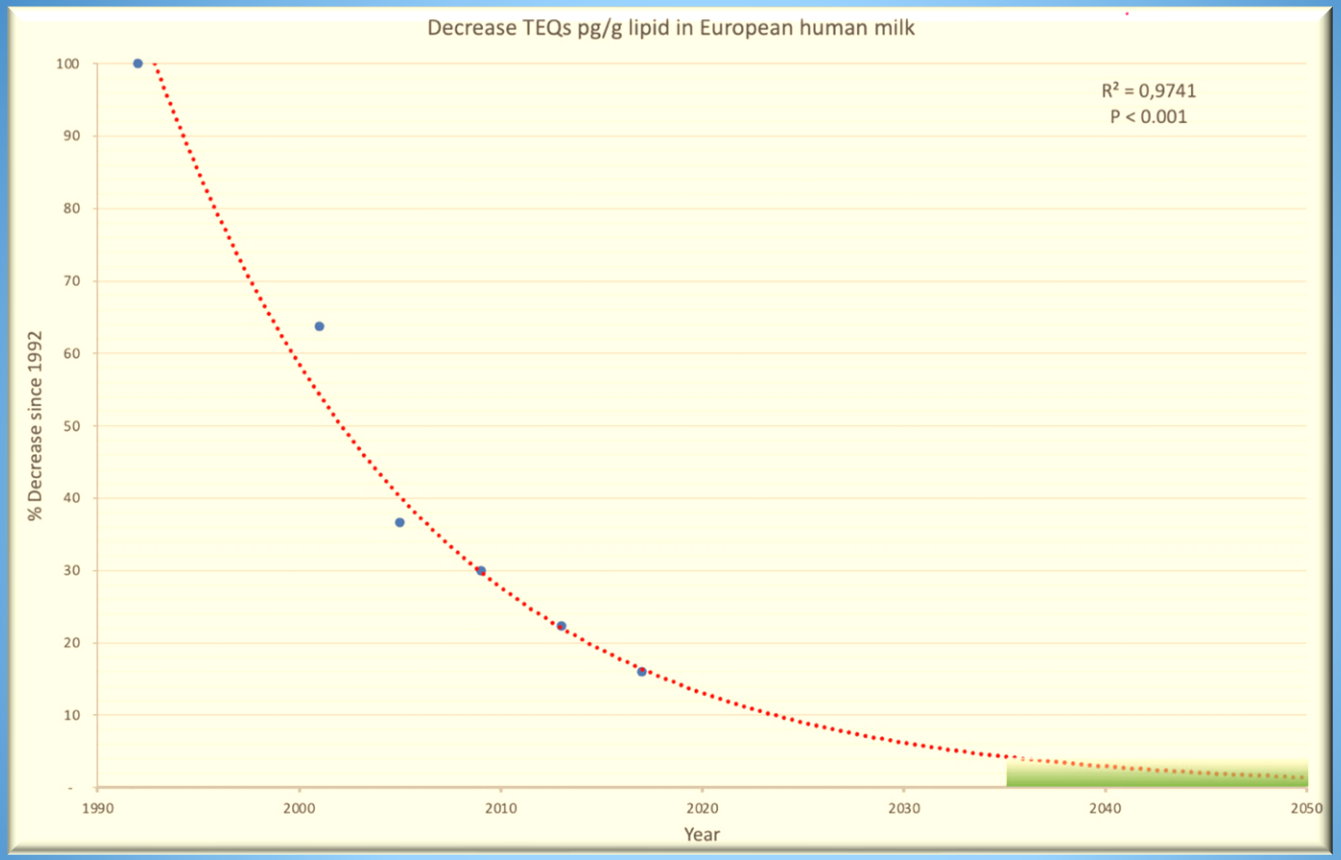
Organization	Health based guidance value (HBGV)		Exceedance HBGV[1,2] (2015-2020)	Associated HBGV milk level in pg TEQs/g lipid[3]	Health endpoints used in offspring
WHO, 2009	TDI	1-4 pg TEQs /kg bw/day	4-14 x	0.2 – 0.9	Offspring monkey, mouse, rat: decreased sperm count, genital malformations, immune suppression, neurobehavioral effects after perinatal exposure
JECFA, 2002	TMI	70 pg TEQs/kg bw/month	6 x	0.5	Male rat: reproductive tract deficits after prenatal exposure
US-EPA, 2010	RfD[4]	0.7 pg TEQs/kg bw/day	19 x	0.2	Human: Decrease sperm count and motility after childhood exposure
ATSDR, 1998	$MRL_{subchronic}$	20 pg TCDD/kg bw/day	0.7 x	4.6	Weanling guinea pig: Immunosuppression after 3 months exposure
ATSDR, 1998	$MRL_{chronic}$	1 pg TCDD/kg bw/day	14 x	0.2	Offspring Rhesus monkey: neurobehavioral effects after perinatal exposure
EFSA, 2018	TWI	2 pg TEQ/kg bw/week	47 x	0.07	Human: Decreased sperm concentration after childhood and perinatal exposure

Multiple ANIMAL studies used for HBGVs relate to early life (pre+postnatal) exposure
Why not applicable for early life risk assessment, besides life time exposure?

If applied, safe levels based on animal experiments approx RANGE 0.1 – 1 PG/G LIPID MILK

[1)]Based on recent median exposure levels of 3 pg TEQs/g lipid
[2)]Based on 3.5% lipid weight in human milk and infant consumption of 125 g milk/kg bw/day, set a 4.5 g lipid/kg bw/d
[3)]HBGV derived level pg TEQs/g lipid (HBGV in pg TEQs/kg bw/day)/4.375 g lipid/kg bw/day
[4)]Reference dose

Average decline in human milk $TEQs_{2005}$ levels* in European countries** since 1992 and expected NOAEL levels based on estimated health-based guidance levels of 0.1 to 1 pg TEQs/g lipid for breastfed infant



* Average for these countries in 1992 set at 25 pg $TEQs_{2005}$/g lipid and 100% with the green bar indicating an HBGV based projected decline of 0.4 to 4 % of the 1992 level.

** Including The Netherlands, Lithuania, Belgium, Germany, Norway, Slovak Rep., Finland, Czech Rep., Croatia

Humans studies also more recently applied to derive HBGVs

- Most sensitive endpoint?
- Are there analogies with animal studies
- Do these studies quantitatively confirm animal data?

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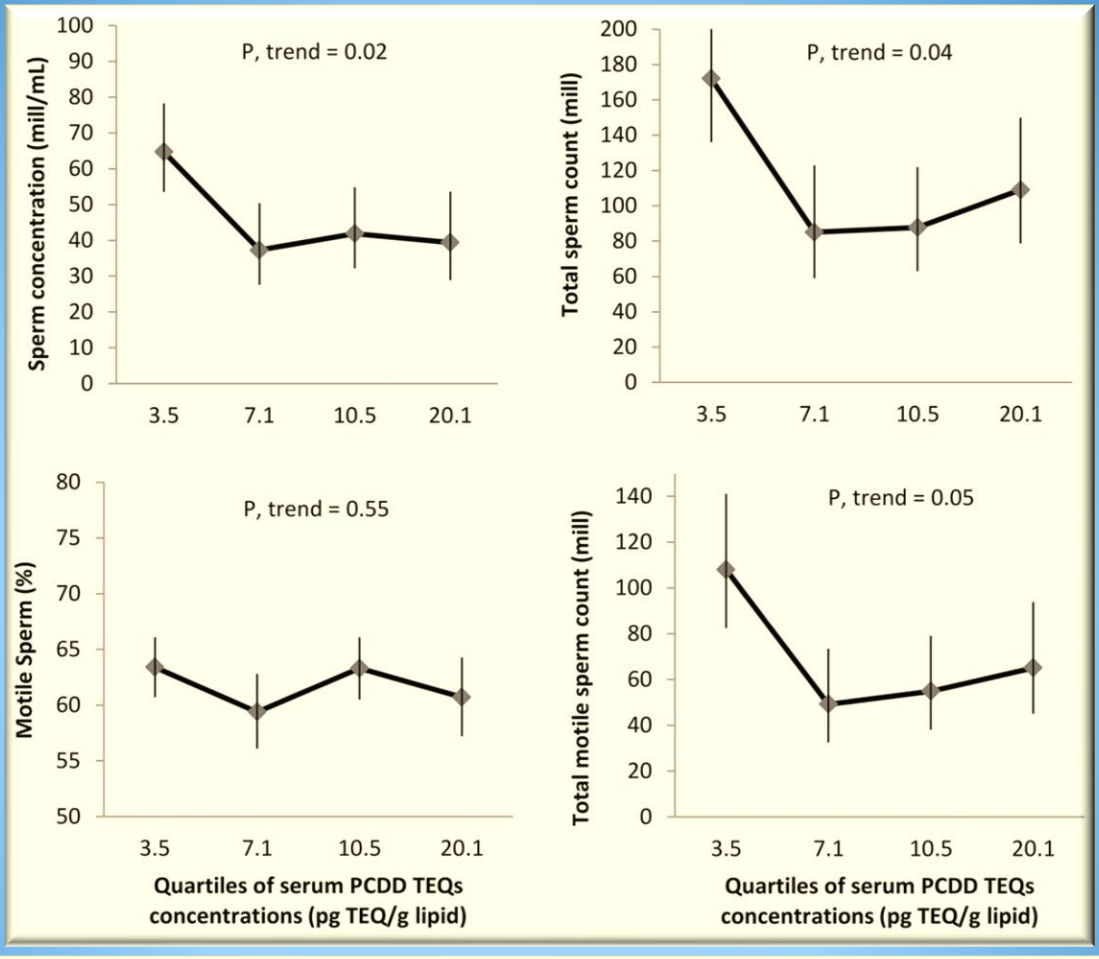
[4)]Reference dose

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]



- Correlation with PCDD/F levels semen quality, NOT total TEQs…… (?)
- Concentrations measured at 8-9 years of age, not in postnatal period
- Backwards calculation EFSA (2018) **estimates 5.9 pgTEQs/g lipid human milk is NOAEL**

Perinatal Exposure to Low Doses of Dioxin Can Permanently Impair Human Semen Quality

Paolo Mocarelli,[1,2] Pier Mario Gerthoux,[1] Larry L. Needham,[3] Donald G. Patterson Jr.,[3,4] Giuseppe Limonta,[1] Rosanna Falbo,[1] Stefano Signorini,[1] Maria Bertona,[1] Carla Crespi,[1] Cecilia Sarto,[1] Paul K. Scott,[5] Wayman E. Turner,[3] and Paolo Brambilla[1,2]

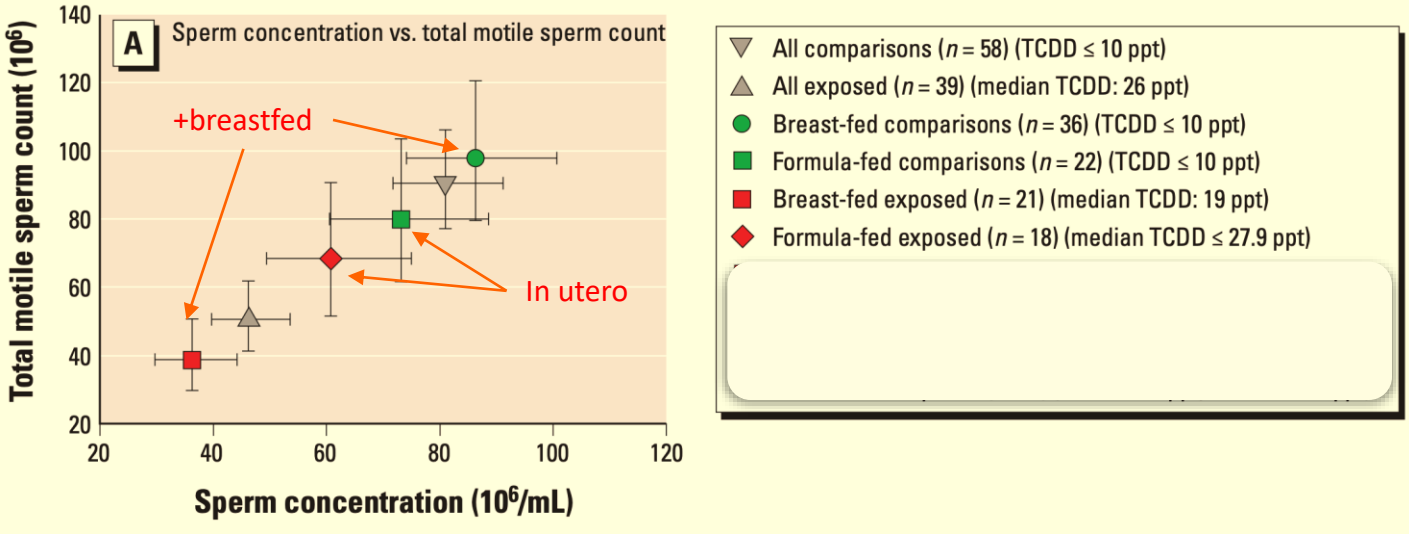


Table 2. Serum TCDD concentrations (percentile distribution) of mothers at exposure in 1976 and extrapolated values at conception of their sons.

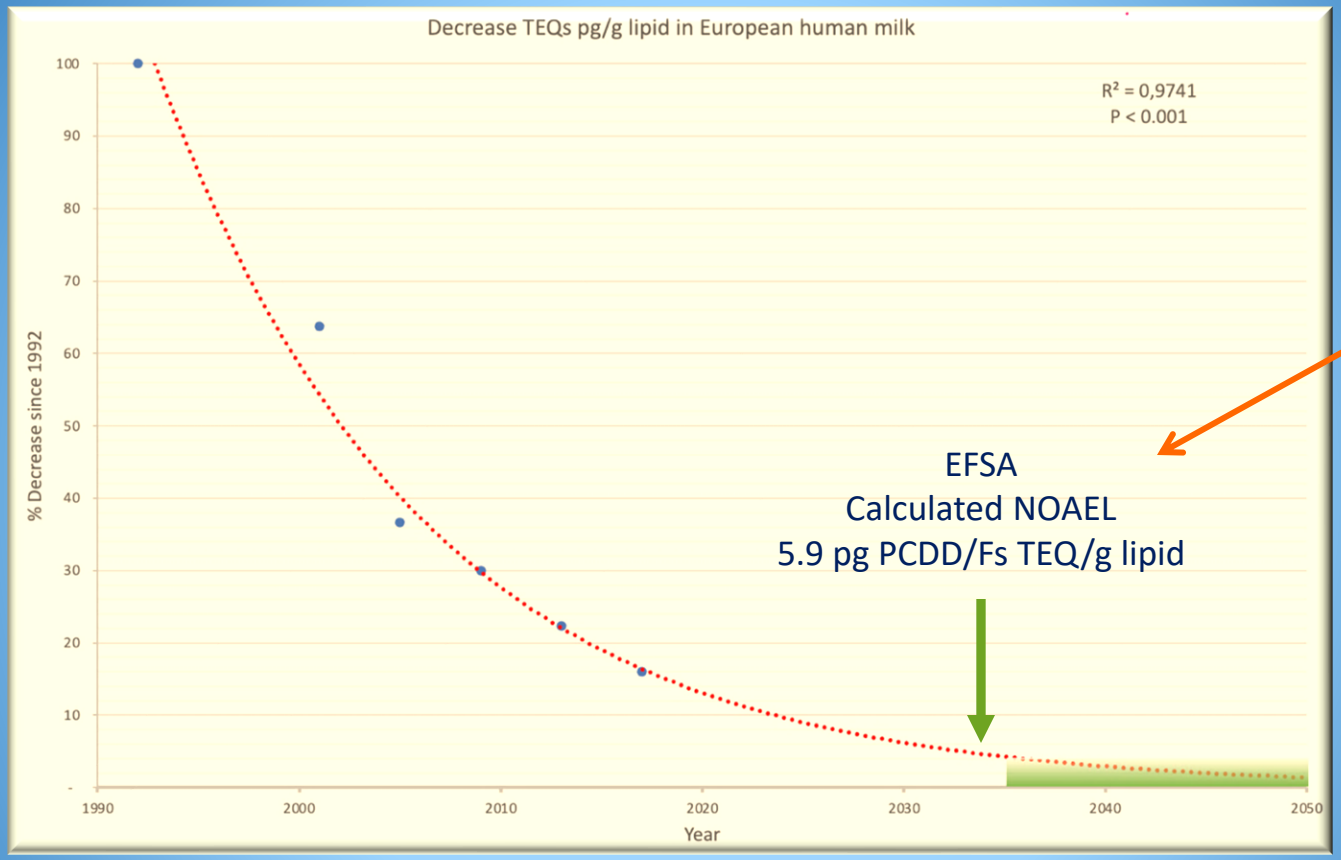
	Percentile (ppt)[a]				
Mothers	5th	25th	Median	75th	95th
At exposure (July 1976)					
All mothers (*n* = 36)	17.0	26.6	51.7	115.0	321.0
Mothers who breast-fed (*n* = 20)	17.0	25.2	46.8	115.0	321.0
Mothers who formula-fed (*n* = 17)	19.0	29.1	55.7	87.6	301.0
At conception (1976–1983)					
All mothers	11.8	16.2	26.0	58.9	232.3
Mothers who breast-fed[b]	11.8	13.1	19.0	58.9	117.1
Mothers who formula-fed[c]	17.0	20.6	27.9	54.6	240.3

Mothers of comparisons were considered as exposed to average background TCDD level of 10 ppt in 1976 (Eskenazi et al. 2004).
[a]Values are parts per trillion TCDD concentration expressed on serum lipid basis. [b]After breast-feeding for 4–5 months, the TCDD value in the child roughly doubles compared with the conception value (Abraham et al. 1998). [c]The formula-fed men were exposed to dioxin only *in utero*.

- In Utero **and** Breastfeeding have effect
- TCDD only, no background measured (TEQs)
- Levels TCDD in blood mother extremely high

MALE FERTILITY VERY SENSITIVE ENDPOINT

Average decline in human milk $TEQs_{2005}$ levels* in European countries** since 1992 and expected NOAEL levels based on backward calculation by EFSA (2018) for breastfed infant



* Average for these countries in 1992 set at 25 pg $TEQs_{2005}$/g lipid and 100% with the green bar indicating an HBGV based projected decline of 0.4 to 4 % of the 1992 level.

** Including The Netherlands, Lithuania, Belgium, Germany, Norway, Slovak Rep., Finland, Czech Rep., Croatia

Both human studies on semen quality show deficiencies with respect due to experimental design or differences in exposure situations compared with everyday exposure situations to dioxinlike compounds

Nevertheless, the EFSA backward calculation using the Russian's Children study does provide an indication of safe level of DLCs in human milk (5.9 pg PCDD/Fs TEQs/g lipid)

Breastfed infant studies with direct comparison with or without breastfeeding

PEDIATRIC RESEARCH
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Effects of Dioxins and Polychlorinated Biphenyls on Thyroid Hormone Status of Pregnant Women and Their Infants

CORINE KOOPMAN-ESSEBOOM, DENNIS C. MORSE, NYNKE WEISGLAS-KUPERUS, INEKE J. LUTKESCHIPHOLT, CORNELIS G. VAN DER PAAUW, LOUIS G. M. T. TUINSTRA, ABRAHAM BROUWER, AND PIETER J. J. SAUER

Table 2. *Spearman rank correlation coefficients between TT_3 and TT_4 levels in maternal plasma and TSH levels in infants' plasma and TEQ of dioxins, planar, and nonplanar PCB in human milk*

	Maternal pregnancy TT_3 (n = 78)	Maternal after delivery TT_3 (n = 77)	Maternal after delivery TT_4 (n = 77)	Infant 2nd wk TSH (n = 78)	Infant 3rd mo TSH (n = 78)
Dioxin TEQ	−0.47*	−0.35†	−0.34†	0.38*	0.41*
Planar-PCB TEQ	−0.39*	−0.38*	−0.33†	0.37*	0.31†
Nonplanar-PCB TEQ	−0.36*	−0.33†	NS	0.38*	NS
Total PCB-Dioxin TEQ	−0.46*	−0.37*	−0.35†	0.40*	0.39*

* $p \leq 0.001$.
† $p \leq 0.01$.

Concentration dependent changes in thyroid hormone levels were within normal clinical range

Effects of Polychlorinated Biphenyl/Dioxin Exposure and Feeding Type on Infants' Mental and Psychomotor Development

Corine Koopman-Esseboom, MD, PhD*; Nynke Weisglas-Kuperus, MD, PhD*; Maria A. J. de Ridder‡; Cornelis G. Van der Paauw§; Louis G. M. Th. Tuinstra, MSc‖; and Pieter J. J. Sauer, MD, PhD*

ABSTRACT. *Objective.* To evaluate the effects of in utero and lactational exposure to polychlorinated biphenyls (PCBs) and dioxins on the mental and psychomotor development of infants.

Design. Prenatal PCB exposure was estimated from the levels in maternal plasma during the last month of pregnancy. Postnatal PCB and dioxin exposure of breastfed infants was calculated from levels in human milk samples and the duration of breastfeeding. Infants were examined at 3, 7, and 18 months of age with the Bayley Scales of Infant Development.

Setting. General community.

Participants. Voluntary sample of 207 mother-infant pairs. One hundred five infants were breastfed and 102 were bottle-fed.

Interventions. None.

Results. Higher in utero exposure to PCBs was associated with lower psychomotor scores at 3 months of age: a doubling of the PCB load resulted in a decrease of 3 points. Breastfed infants scored significantly higher on the psychomotor score at 7 months of age, compared with formula-fed infants. However, when corrected for confounders, the psychomotor score of the 66% highest-exposed breastfed infants (>756 pg total PCB-dioxin toxic equivalent) was negatively influenced by this postnatal exposure to PCBs and dioxins, and was comparable to the psychomotor score of the formula-fed infants. Breastfed infants also scored higher on the mental scale at 7 months of age in a dose-dependent way. There was no significant influence of the perinatal PCB and dioxin exposure on the mental outcome at 3 and 7 months of age. At 18 months of age neither the mental nor the psychomotor score was related to perinatal PCB or dioxin exposure, nor to the duration of breastfeeding.

Conclusions. Prenatal PCB exposure has a small negative effect on the psychomotor score at 3 months of age. PCB and dioxin exposure through breastfeeding has an adverse effect on the psychomotor outcome at 7 months of age. The mental outcome at 7 months of age is positively influenced by breastfeeding *per se;* the perinatal exposure to PCBs and dioxins does not influence this outcome. At 18 months of age the development is affected neither by PCB and dioxin exposure nor by feeding type. *Pediatrics* 1996;97:700–706; *PCBs, dioxins, infants, mental and psychomotor development.*

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ABBREVIATIONS. PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzo-*p*-dioxins; PCDFs, polychlorinated dibenzofurans; PDI, psychomotor developmental index of the Bayley Scales of Infant Development; MDI, mental developmental index of the Bayley Scales of Infant Development; LCPUFAs, long-chain polyunsaturated fatty acids; TEQ, toxic equivalent; HOME, Home Observation for Measurement of the Environment; TEF, toxic equivalent factor.

Polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs), are both widespread, highly-resistant pollutants in the environment with possible adverse health effects on humans.[1,2] PCBs are industrial chemicals that have been used for diverse commercial applications such as dielectric fluids for capacitors and transformers. The production and use of these compounds were mainly banned in the late 1970s. Dioxins are formed as by-products during the process of combustion and manufacturing of organochlorine chemicals. Both toxins are lipophilic and accumulate in the food chain. Adults are mainly exposed through the consumption of dairy products, meat, and fish.[3] Both compounds can pass through the placental barrier and are present in relatively high amounts in human milk.[4] The embryo, fetus, and breastfed infant are exposed to PCBs and dioxins during the critical period of organ growth and differentiation. In formula, milk lipids are replaced by lipids of vegetable origin with a negligible content of PCBs and dioxins. As a consequence, the postnatal exposure to these toxins of formula-fed infants is of no concern. A subpopulation of Taiwanese and Japanese women who were accidentally exposed to high levels of PCBs and PCDFs, through contaminated rice oil, gave birth to infants who were small for gestational age and who showed mainly dermal lesions as chloracne and hyperpigmentation. In follow-up studies a delay in mental and psychomotor development has been described up until 7 years of age, in these prenatally high-exposed children.[5–9] However, at 8 years of age the cognitive development of the exposed Taiwanese children had a tendency to catch up, and did not differ significantly any more from their controls.[10]

Negative effects on both mental and psychomotor development have also been measured after prenatal exposure to PCB background levels in the United

TABLE 3. Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) Scores on the Bayley Scales of Infant Development at 3, 7, and 18 Months of Age

	All	Breastfed	Formula-fed	*P**
MDI-3	N = 201	N = 101	N = 100	
Mean (SD)	127 (13)	128 (13)	126 (13)	
Range	84–149	84–149	84–149	.21
MDI-7	N = 207	N = 105	N = 102	
Mean(SD)	113 (10)	115 (11)	112 (9)	
Range	87–139	87–133	90–139	.03
MDI-18	N = 207	N = 105	N = 102	
Mean (SD)	110 (18)	113 (18)	107 (17)	
Range	68–150	74–149	68–150	.01
PDI-3	N = 199	N = 99	N = 100	
Mean (SD)	117 (12)	118 (12)	117 (12)	
Range	89–155	89–155	89–137	.92
PDI-7	N = 207	N = 105	N = 102	
Mean (SD)	113 (14)	115 (15)	111 (13)	
Range	86–149	91–149	86–149	.05
PDI-18	N = 206	N = 105	N = 101	
Mean (SD)	109 (15)	110 (17)	108 (14)	
Range	51–149	51–149	58–141	.17

* Mann-Whitney Test.

Changes in psychomotoric development were within normal clinical range

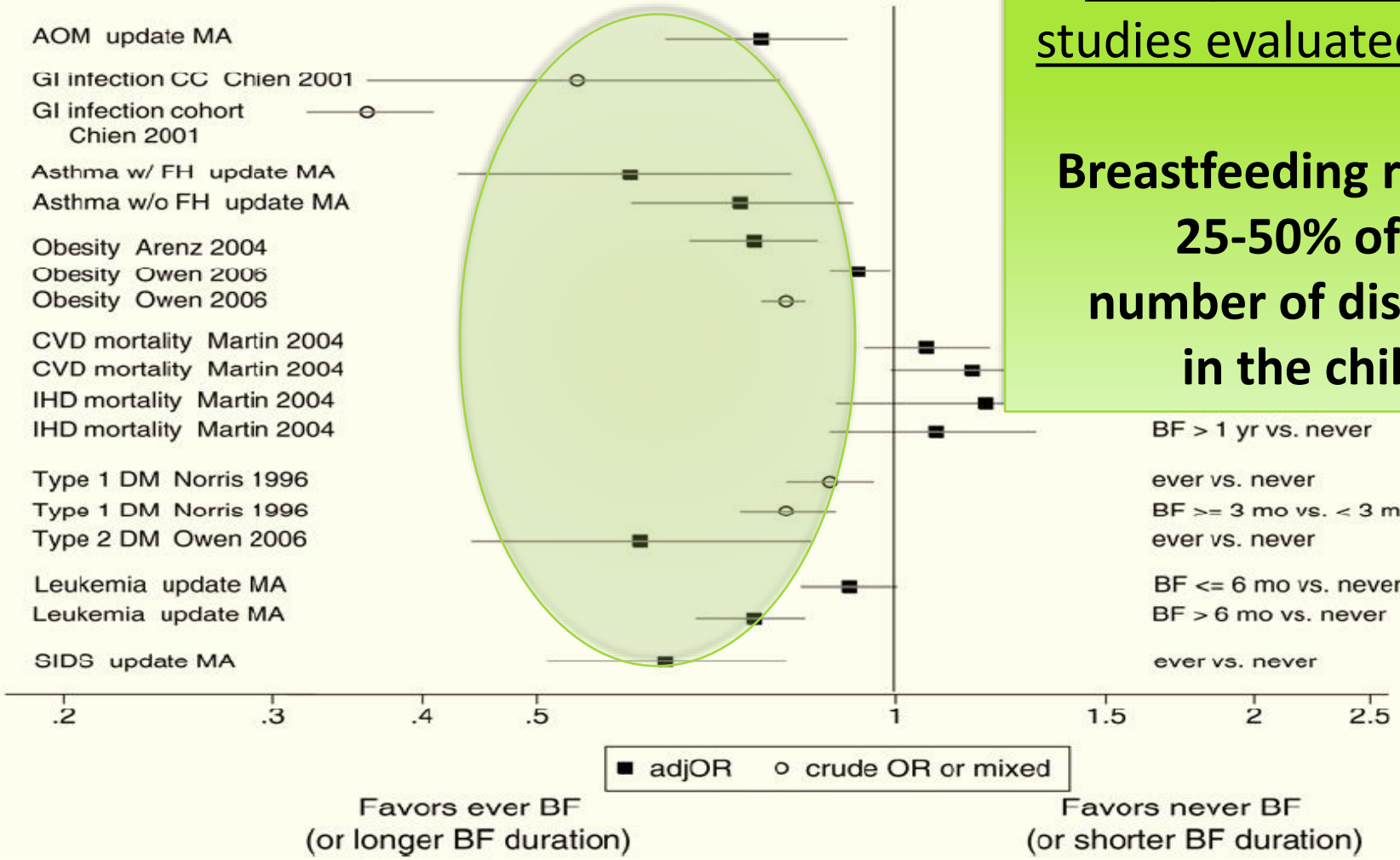
Overall conclusions from these Dutch Cohorts (1990's):

- *Experimental design and exposure situation most appropriate to establish possible negative effects of DLCs in human milk*
- *Postnatal exposure Dutch levels of PCBs and dioxins has small negative effects on thyroid hormone levels and early psychomotor development.*
- *Breastfeeding per se did have an important positive influence on mental and psychomotor development at 7 months of age*
- *Effects are within clinical acceptable range and considered transient (unlike semen quality studies)*

World Health Organization Position for Breastfeeding

- Breastfeeding is one of the most effective ways to ensure child health and survival.
- WHO actively promotes breastfeeding as the best source of nourishment for infants and young children.

Figure 1. The relationship between breastfeeding and health outcome



400 Epidemiological studies evaluated (2007)

Breastfeeding reduces 25-50% of a number of diseases in the child

MA, meta-analysis; AOM, acute otitis media; GI, gastrointestinal; CC, case-control studies; FH, family history; CVD, cardiovascular disease; IHD, ischemic heart disease; DM, diabetes; adj, adjusted

American Dietetic Association (ADA) position paper

J Am Diet Assoc. 2009;109: 1926-1942.

Benefits for the infant:

- Optimal nutrition
- Strong bonding with mother
- Safe milk
- Enhanced immune system
- Reduced risk acute otitis media, gastroenteritis, lower respiratory tract infections, and asthma
- Protection against allergies and intolerances
- Correct development of jaw and teeth
- Association with higher IQ/ school performance
- Reduced risk chronic diseases e.g. obesity, diabetes,heart disease, hypertension, hypercholesterolemia, childhood leukemia
- Reduced risk sudden infant death syndrome
- Reduced risk overall morbidity and mortality

American Dietetic Association (ADA) position paper

J Am Diet Assoc. 2009;109: 1926-1942.

Benefits for the mother:

- Strong bonding with infant
- Increased energy expenditure, faster return to prepregnancy weight
- Faster shrinking of the uterus
- Reduced postpartum bleeding and delay menstrual cycle
- Decreased risk chronic diseases e.g., breast, and ovarian cancer, diabetes
- Improved bone density, decreased risk hip fracture
- Decreased risk postpartum depression
- Enhanced self-esteem in the maternal role
- Time and money saved from preparing and not buying formula, less medical expenses

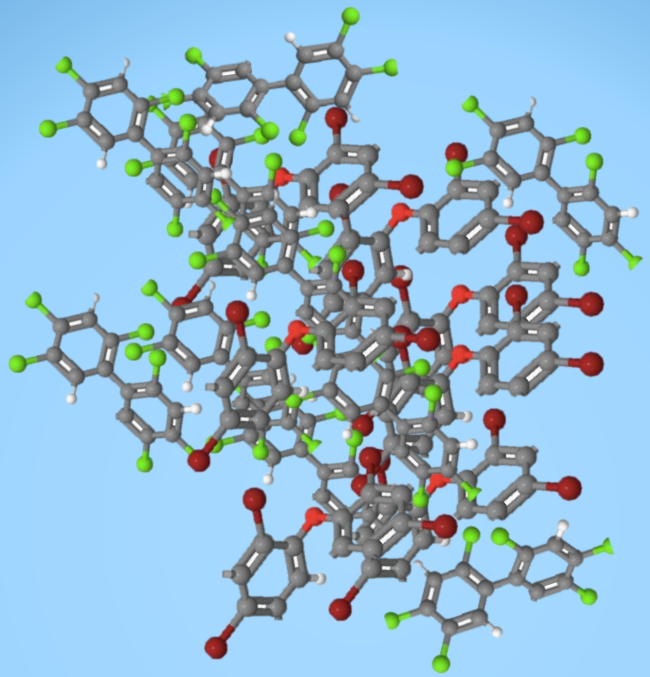
Some more quantitative information regarding the benefits of breastfeeding

- If every child was breastfed within an hour of birth, given only breast milk for their first six months of life, and continued breastfeeding up to the age of two years, about 800 000 child lives would be saved every year (WHO 2015)

- A recent study using meta-analyses of benefits from breastfeeding calculated that it may annually prevent 823 000 deaths in children younger than 5 years and 20 000 maternal deaths from e.g., breast cancer (Victora, Bahl et al. 2016)

Some Concluding Remarks

- Global human milk levels of PCDDs, PCDFs and DL-PCBs are presently one to two orders of magnitude above those considered toxicological safe for the breastfed infant.
- Subtle biological, endocrine or neurological effects can still be expected with levels observed in the period 2000-2020 for dioxin-like compounds, but these may well be transient with the possible exception for neurodevelopmental effects and semen quality.
- Experimental and epidemiological studies indicate that future risk-benefit assessments should focus on **both** the *in utero* situation and lactational period.
- The established benefits of breastfeeding far outweigh the subtle negative effects on the breastfed infant that have been associated with dioxin-like compounds



Thank you