

Perinatal dioxin exposure: 15 years follow up

M.M. Leijds ^{1,2}, J.G. Koppe ³, K. Olie ², W.M.C. van Aalderen ¹,
P. de Voogt ², T. Vulmsma ¹, G.W. ten Tusscher ⁵

¹Department of Paediatrics and Neonatology, Emma Children's Hospital Academic Medical Centre, Amsterdam, The Netherlands

²IBED, Earth Surface Processes and Materials, University of Amsterdam, The Netherlands

³Ecobaby Foundation, Loenersloot, The Netherlands

⁴Department of Paediatrics, Zaans Medical Centre, Zaandam, The Netherlands

⁵Department of Paediatrics and Neonatology, Westfriesgasthuis, Maelsonstraat 3, 1624 NP Hoorn, The Netherlands

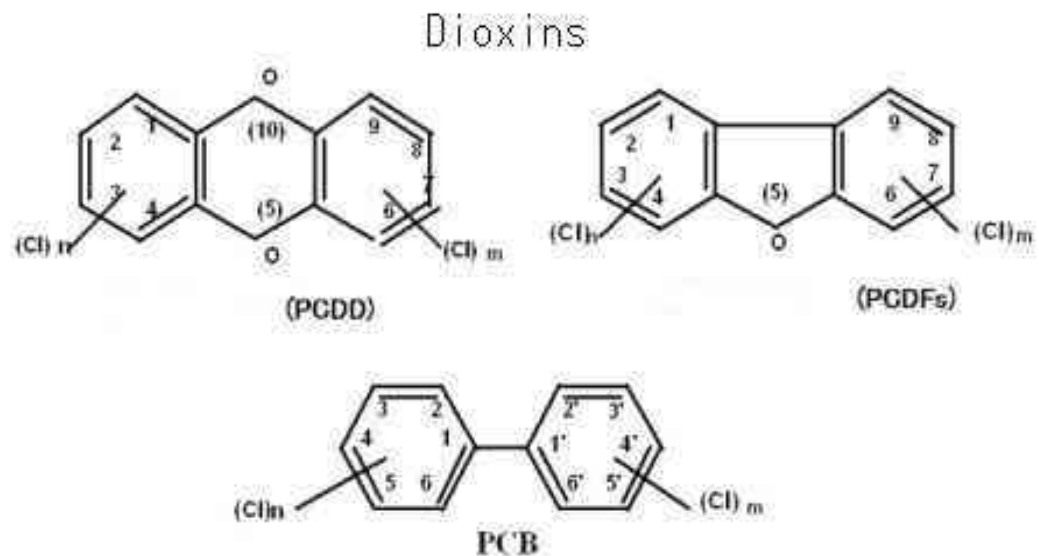


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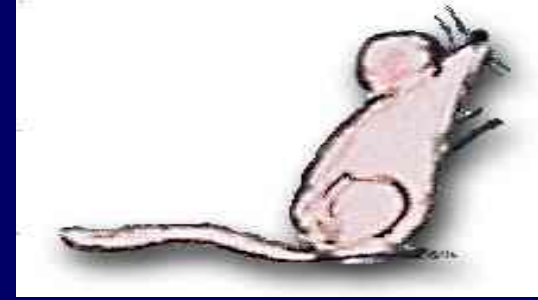
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Dioxins and effects

- Compounds with certain toxicity → Toxic Equivalents (TEQ).
- Able to bind AhR-receptor
- Alter puberty



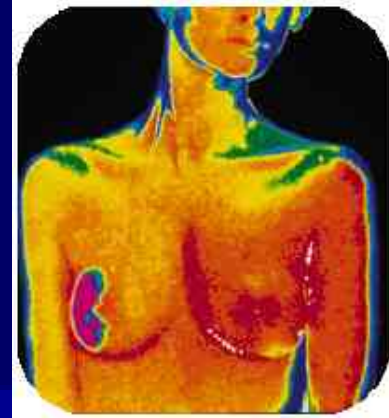
Endocrine disruption; puberty



- Several animal studies:
 - Alteration estrogen receptor and signaling pathways
 - (In)direct action on the ovary
 - Disruption hypothalamus-pituitary-ovary axis (blocking ovulation)

- Thyroid homeostasis

Dioxins and breast cancer



- Developmental toxicants of mammary gland
- Human studies: incidence of mammary tumors
 - Warner detected higher incidence of breast cancer in Seveso women (SWHS) with higher serum TCDD levels (Warner et al 2004)
 - Higher incidence breast cancer after occupational TCDD exposure (Manz et al 1991, Kogevinas et al 1997).
 - Higher incidence breast cancer in Russian town with chemical plant (Revich et al 2001)
 - Higher levels of dl-PCB in women with breast cancer in Canada (Demers et al 2002)

The Zaandam cohort

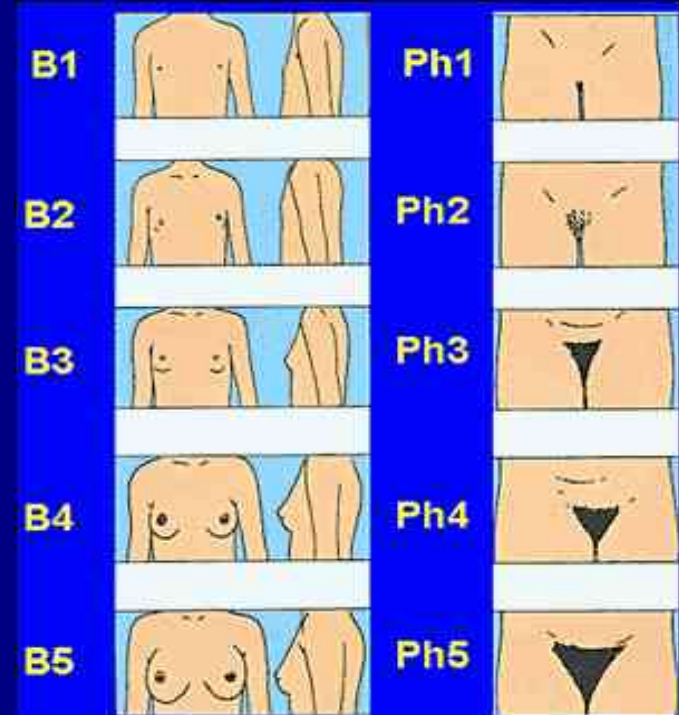
- Longitudinal cohort from 60 mother-baby pairs, evaluated at neonatal (n=60), toddler and pre-pubertal (n=44) age
- 32 boys (n=14) and girls (n=18) aged 14-19 years from 'the Zaandam' cohort
- Relatively high background exposures in perinatal period
- Determined 14-19 years before:
 - PCDD/PCDF concentration in mother's milk: prenatal exposure
 - Total PCDD/PCDF exposure during nursing period: lactational exposure

Objectives current follow-up

- Pubertal development:
 - Questionnaires (age at first breast development, pubic hair, ejaculation, menarche, menses characteristics)
 - Physical examination (tanner scale, length weight)
- Current serumlevels:
 - PCDD/F, PCB and PBDE levels in serum
- Thyroid function, lipid spectrum, leptine, haematology, immunology, glucose metabolism
- Lung function
- Behavioural problems

Methods: Tanner stages

- Physical examination
- Questionnaires during an interview
- Measured compounds:
 - 7 PCDDs/10 PCDFs
 - 3 dl-PCBs
 - 8 PBDEs



Effects seen in earlier follow up

- The neonatal period:
 - Thyroid hormone; TSH↑
 - ↓ polynuclear neutrophils and monocytes, significantly ↓ number of blood platelets
 - ↑ liver enzymes ASAT and ALAT
 - ↓ vitamin K1 levels
 - ↓ Retinol Binding Protein (RBP)

■ Toddler:

- Signs of enhanced neuromotor maturation; Baily Infant Development Test, HEMPEL test
- No effects on thyroid hormone, liver enzymes and haemato- or immunology

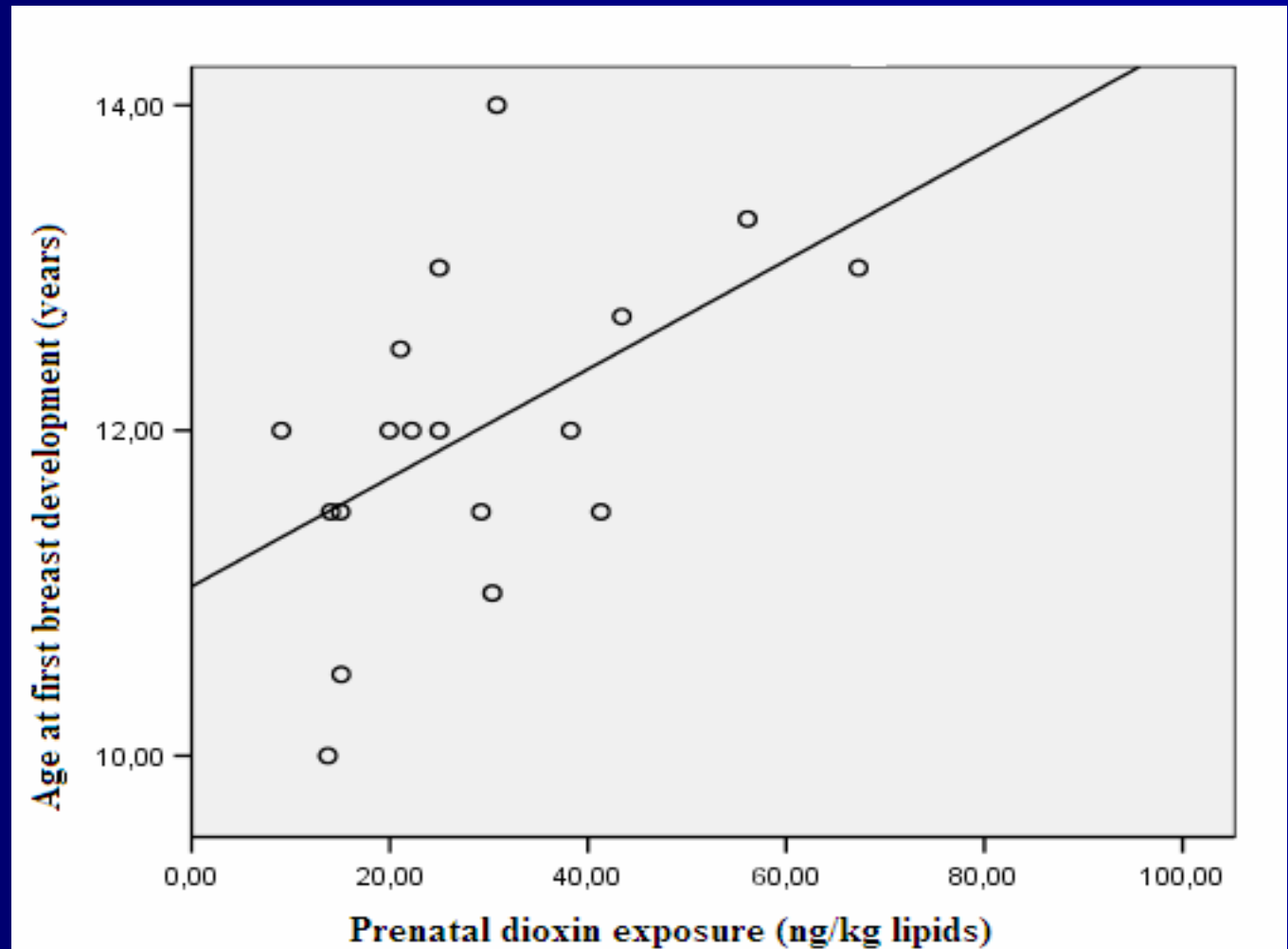
■ Pre-pubertal period:

- Brain function : negative effect latency times and amplitudes; EEG and MEG
- ↓ Trombocytes
- Lung function: more obstruction

Results

	Mean (range)
Age at initiation breast development (years)	12.0 (10-14)
BMI (kg/m ²)	21.0 (17.4-30.9)
Current serum PCDD/F (TEQ) (ng/kg lipid)	2.20 (0.36-6.06)
Current serum dl-PCBs (TEQ) (ng/kg lipid)	2.17 (0.04-7.78)
Current serum PBDE (ng/g lipid)	13.96 (4.85-73.6)
Prenatal PCDD/F exposure (TEQ) (ng/kg lipid)	32.6 (9.1-59.8)
Postnatal (lactational) exposure (TEQ) (ng)	75.4 (4.34-279)

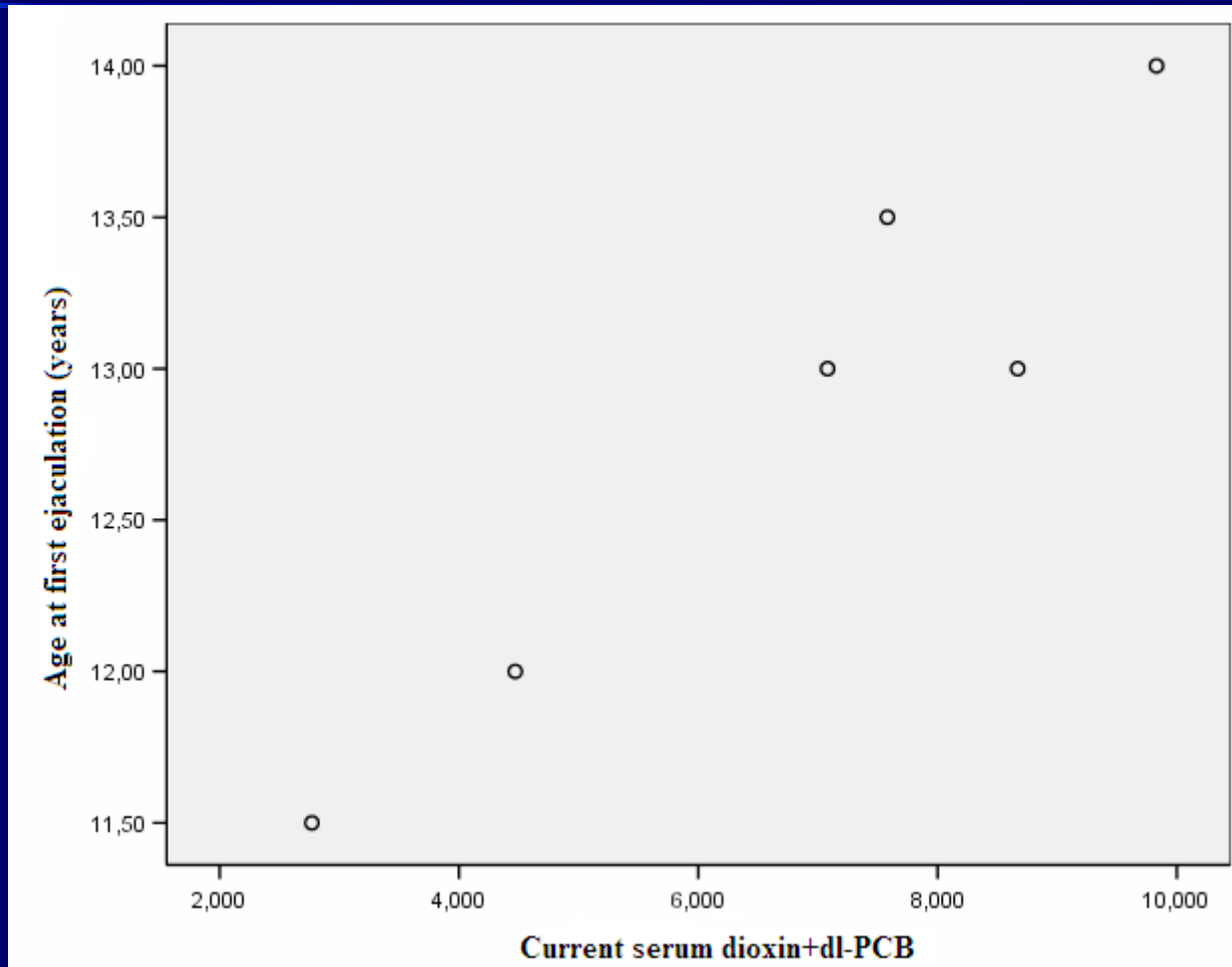
First initiation of breast development (P:0.025)



Summary breast development

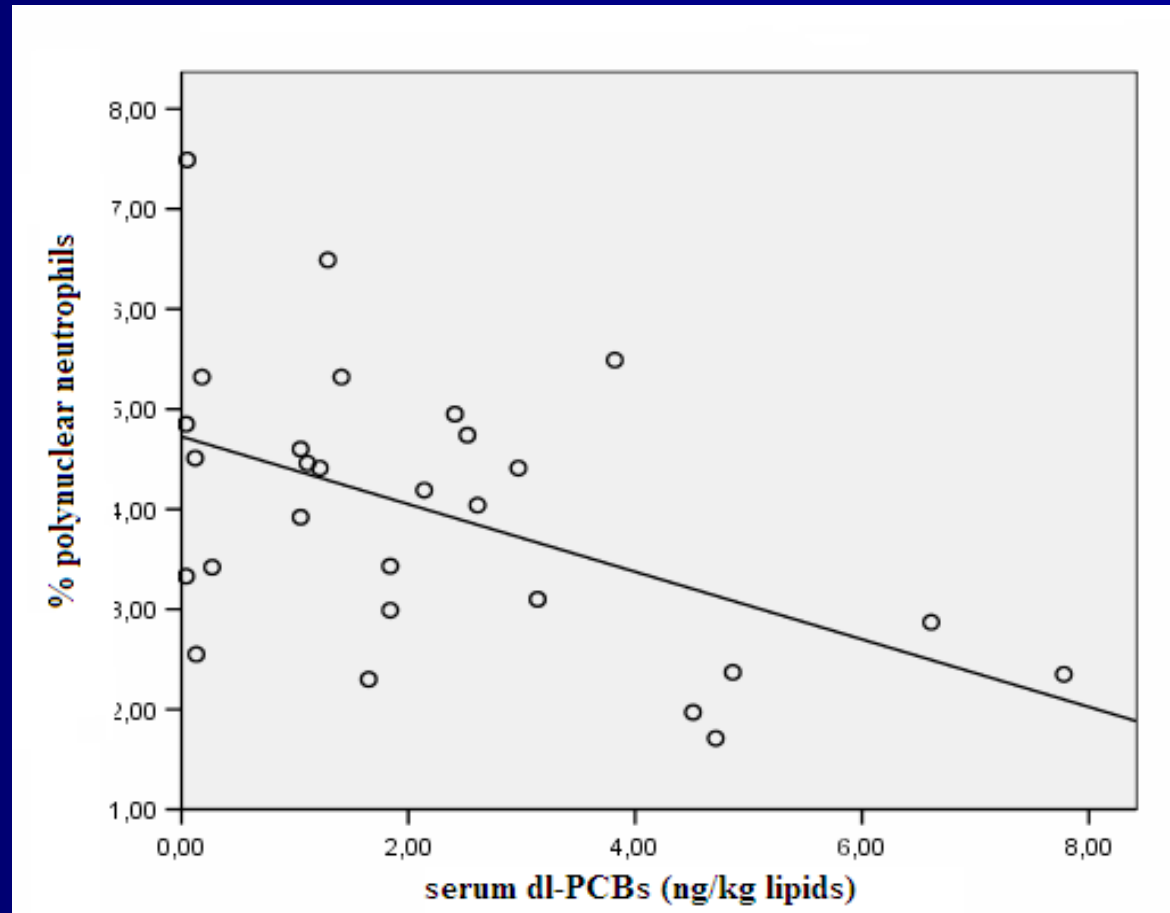
- Prenatal exposure:
 - Age first breast development p: 0.025
 - After correction BMI: p: 0.018
- Lactational exposure:
 - p: 0.097, after correction p: 0.032
- Current serum dioxin:
 - No clear relation
- For current breast development: no relation

First ejaculation ($p=0.003$)



Immunology

- 1 ng/kg ↑ dl-PCB → 0.3 % ↓ polynuclear neutrophils (p=0.017)



Discussion

- Delayed initiation of breast development in relation with prenatal PCDD/PCDF exposure
 - The damaging effects of dioxin on the developing mammary gland in utero
- Belgium: Den Hond et al 2002
 - Delayed breast development in relation to current serum dioxin concentration

Lower polynuclear neutrophils

- immunotoxic effect
- Speculation: disruption of growth in breast development result in a higher incidence of breast cancer

Conclusion

- Delayed initiation of breast development in Dutch adolescents with higher prenatal dioxin exposure
- Decreased polynuclear neutrophils

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