



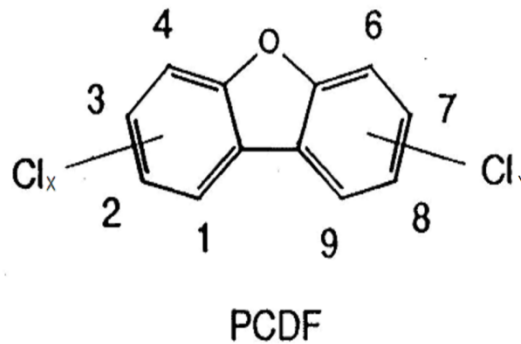
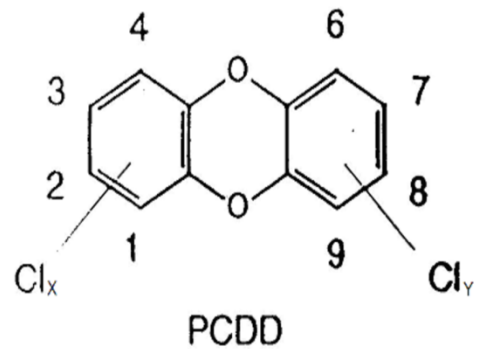
Toxic Effects of Dioxins, PCBs and PBDEs in Adolescents

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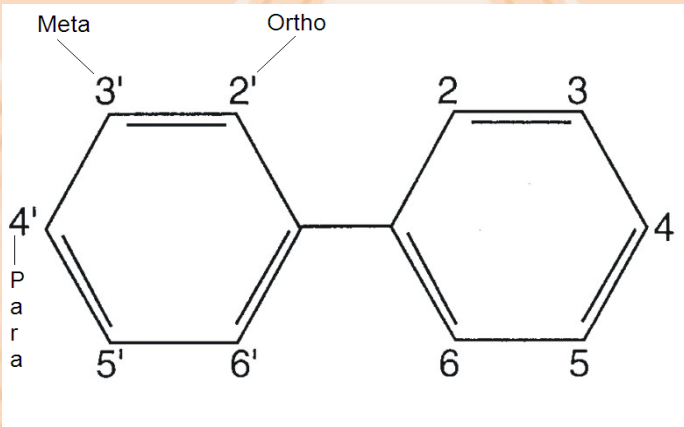


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 - Serum levels, puberty, immunology and haematology, metabolic parameters, thyroid hormone.

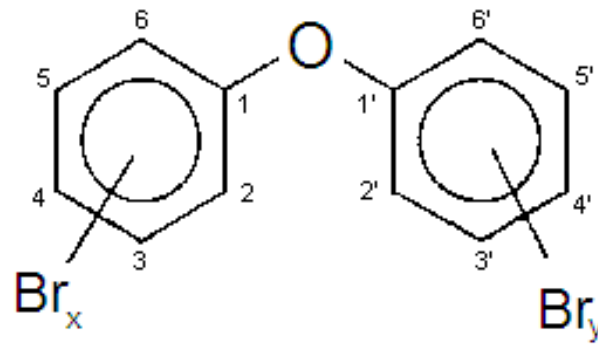


- Sources of dioxines; unintentionally produced
 - Waste incinerators
 - Industry: metal
 - Contaminated pesticides
 - Fuel combustion, diesel, cigarette smoke



- PCBs; forbidden since 1985
 - Isolation liquids, transformers
 - Stabilisator in plastics
 - Paint, glue

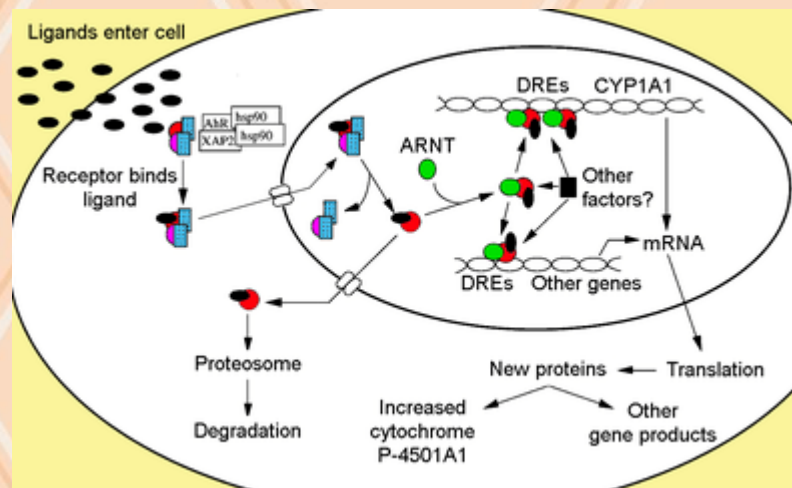
Polybrominated diphenylether PBDE



- PBDEs
Carpet, Curtains, Clothes
Electrical equipments

Dioxins and effects

- Compounds with certain toxicity → Toxic Equivalents (TEQ).
- Able to bind AhR-receptor
- Changes in gene transcription





The Amsterdam cohort

- 33 boys (n=14) and girls (n=19) aged 14-19
- Longitudinal cohort from 60 mother-baby pairs, evaluated at neonatal, toddler and pre-pubertal (n=44) age
- Relatively high background exposures in perinatal period in Western Europe
- Determined 14-19 years before (1987-1991):
 - PCDD/PCDF concentration in mother's milk: prenatal exposure
 - Total PCDD/PCDF exposure during nursing period: lactational exposure

Objectives of this study

- Puberty and Growth
- Blood/serum determinations
 - Levels of Dioxins, PCBs en PBDEs
 - Haematology, Immunology
 - Glucose metabolism (glucose, insuline, HbA1C) leptine, lipidespectrum
- Lungfunction
- Thyroidfunction
- Behavioural problems

Table 1: Means and ranges

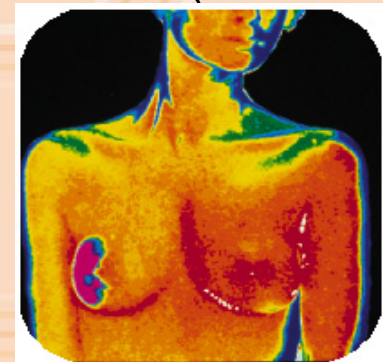
| | Mean | Lowest value | Highest value |
|--|---------------|--------------|---------------|
| Current serum dioxin (TEQ) (pg/g fat) | 2.2 | 0.4 | 6.1 |
| Prenatal dioxin exposure (ITEQ) (pg/g fat) | 32.6 | 9.1 | 59.8 |
| Postnatal (lactational) exposure (ITEQ) (ng) | 75.4 | 4.34 | 279.7 |
| Current PCB levels (TEQ) (pg/g fat) | 2.2 | 0.1 | 7.8 |
| Current PBDE levels (ng/g fat) | 14.0 (8.7) | 4.9 | 73.7 |

Results/discussion

- Lower levels of dioxins (2.2 WHO TEQ pg/g serumfat), low level of dl-PCBs (2.2 WHO TEQ pg/g serumfat) High levels PBDEs (14 ng/g serum fat)
- Retardation in initiation breastdevelopment (p: 0.023)

Are these results of concern?

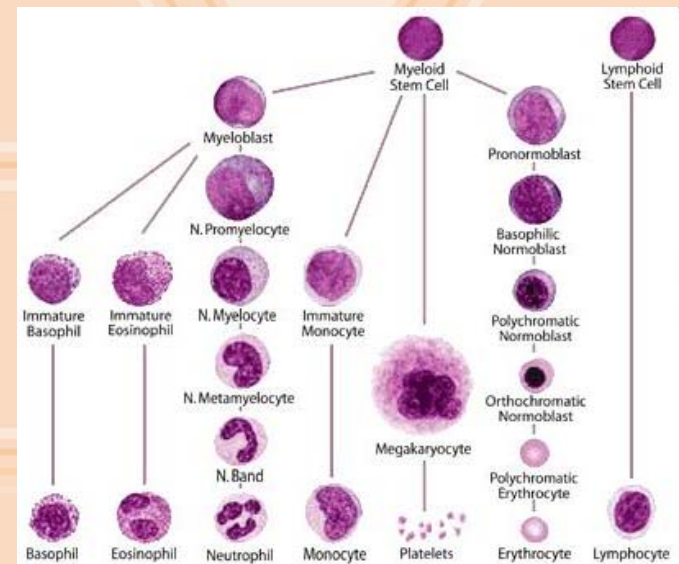
- **Breast development:**
- **Human studies:** incidence of mammary tumors
 - Higher incidence of breast cancer in Seveso women (SWHS) (Warner et al 2004)
 - Higher incidence breast cancer after occupational TCDD exposure (Manz et al 1991, Kogevinas et al 1997).
 - Higher incidence breast cancer in Russian town with chemical plant (Revich et al 2001)
 - Higher levels of dl-PCB in women with breast cancer in Canada (Demers et al 2002)
- **Animal study:** Persistent abnormalities in the rat mammary gland following gestational and lactational exposure to TCDD (Fenton et al 2002)



Immunology and Haematology

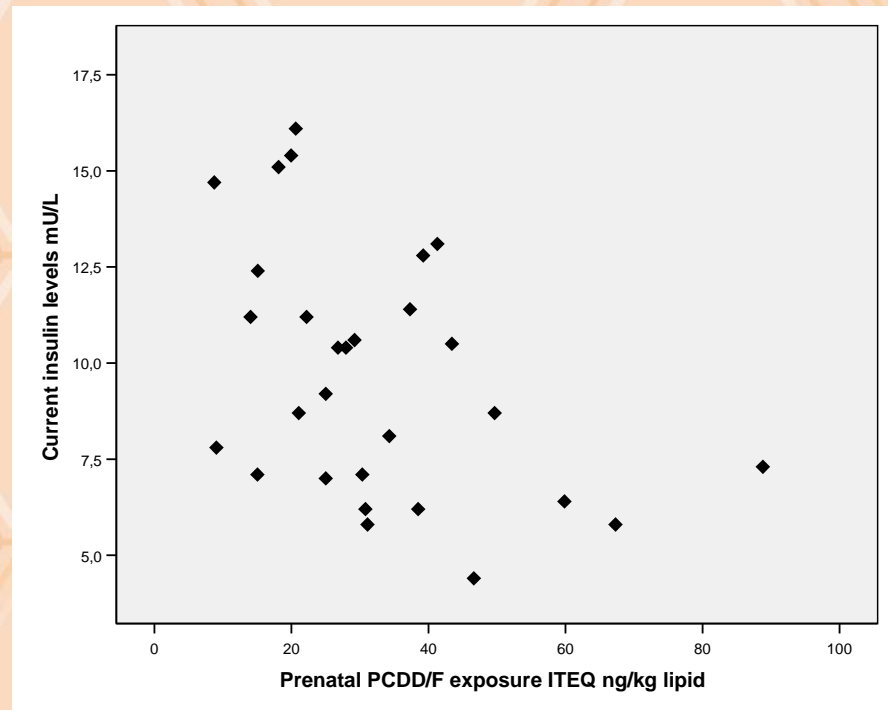
- In earlier study: decrease in polynuclear leukocytes and monocytes, decreased number of thrombocytes
- Now: Effects on innate and adaptive immunology
 - Lower polymorphic neutrophils with higher dl-PCB exposure ($p=0.021$)
 - Negative effects PBDE and number of lymphocytes ($p=0.001$)

- Formation ROS (reactive oxygen species)
- Effects on regulation growth factors in the bone marrow
- Positive effect Hb and PBDEs
 - Effect on differentiation in bonemarrow
 - Release erythropoietin by the kidney
- No effects thrombocytes



Glucose metabolism

- Current dioxin (and total TEQ) levels related with glucose levels ($p=0.015$)
- Prenatal dioxin levels related to glucose:insulin ratio ($p=0.024$)
- And negatively to insulin levels ($p=0.028$)
- No relation leptin or lipid spectrum



Lower insulin levels, higher glucose levels in adolescence:

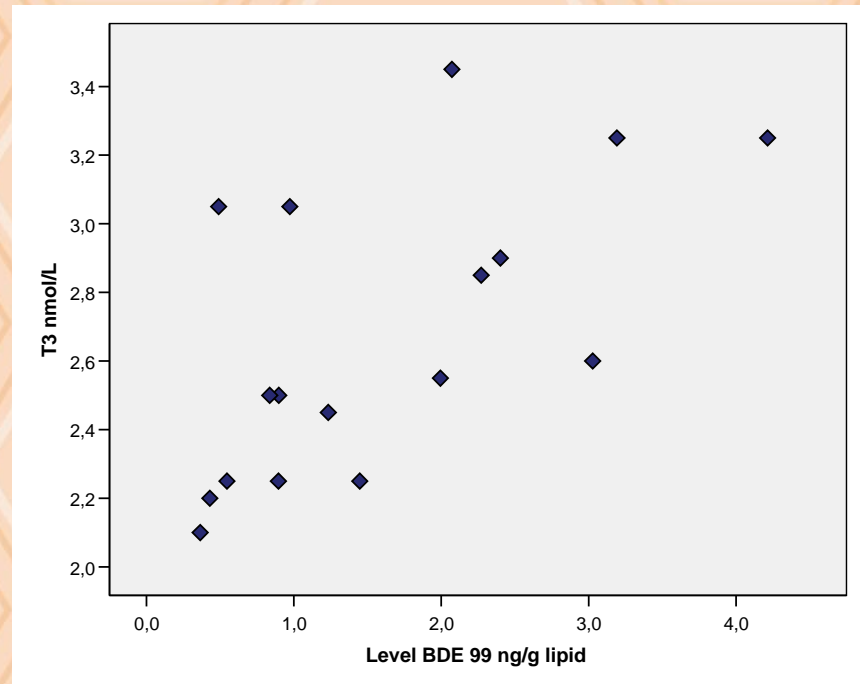
1.(Perinatal) Disruption of Pancreas

2.Adaptation (change in metabolic/hypothalamic setpoints)

3.Altered Gene Expression; Epigenetic changes

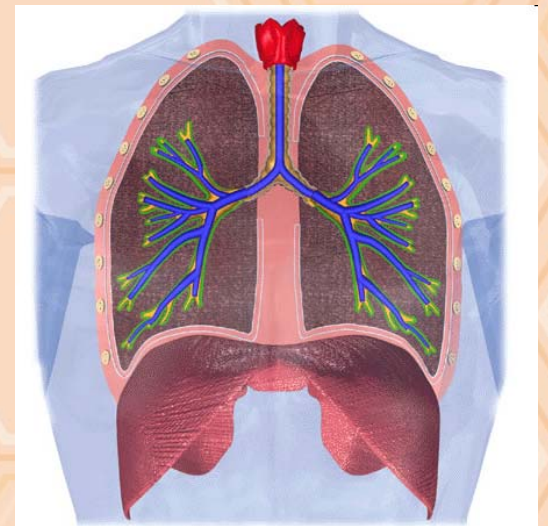
Thyroid hormone homeostasis

- **Function:** Growth and development, metabolism, protein synthesis, catecholamine effect (sympatomimetic; fight or flight, stress, high blood pressure)
- **Previous study (neonatal):**
Dioxins and TSH+T4
- **Current study:**
 - dl-PCB and T3
 - BDE 99 and T3



Lungfunction

- Previous study: Increase in bronchial obstruction and reduction in lung function
- Negative effects lungfunction:
 - sumBDE (FEF50) ($p=0.016$)
 - BDE 100+99 (FEV1/VCMAX) ($p=0.031$ and $p=0.049$)
Indication of increased airway obstruction



Dioxin exposure a thing of the past?

- Maximum allowed combustion levels; 0.1 ng/m³ (Thermphos, Corus)
- New sources of dioxins (melting glaciers)
- Products other countries
- Long term effects background exposure?



Conclusion

- Health effects seen also at very low serum levels
- New effects PBDEs
- Long term effects might indicate disease in later life like breast cancer and diabetes
- Further research necessary