Do Polychlorinated Biphenyls (PCBs) harm the human immune system?
Distribution of total PCBs concentration in serum, 10 studies

- U.S./11 Cities (1959-1965)
- U.S./California (1964-1967)
- Netherlands/2 Cities (1990-1992)
- U.S./Massachusetts (1993-1998)
- Denmark/Faroe Islands (1994-1995)
- Canada/Northern Quebec (1995-1998)

μg/g serum lipid
“Although a number of systems can be affected by environmental contaminants, experimental animal data indicate that the immune system is one of the most sensitive targets for chemical-induced toxicity, especially for the chlorinated compounds TCDD and PCBs”

Tryphonas H. Environ Health Perspectives, vol 109 suppl. 6, 2001
Examples of Environmental Toxicants Influencing Immune Function

• Persistent Halogenated Organic Pollutants (POPs)*
  - Dioxins (TCDDs) (AhR binding)
  - Polychlorinated Biphenyls (PCBs, e.g. Aroclor 1254) (some AhR binding)
  - Pesticides (e.g. hexachlorocyclohexane, chlordane, diazinon, DDT, DDE, carbofuran (AhR binding))
  - Fugicides (e.g. hexachlorobenzene)

• Heavy metals (Hg*, Pb and Cd)

*Levels of Hg exposure often correlate with exposure to POPs
Polychlorinated Biphenyls* (PCBs)

- **Coplanar** (Chlorine in ortho position, dioxin like)
  - AhR binding (Aryl hydrocarbon Receptor)
  - Measured in TEQ (total dioxin equivalents)

- **Non-coplanar** (AhR independent)
  - Probably also immunotoxic by other mechanisms than via AhR
  - Most abundant in human tissues. Longer half life.

*Trade names:Aroclor, Pyranol, Pyroclor, Phenochlor, Pyralene, Clophen, Elaol, Kanechlor, Santotherm, Fenchlor, Apirolio, Sovol.*
Several studies have suggested that PCBs have a negative impact on antibody formation and T-cell function in mammals, fish and birds. Most of these studies were performed in laboratory animals.

- E.G. Reduced Ab response to SRBC by aroclor1254 exposed monkeys (Tryphonas H et al 1991)

- Wild polar bears living in an area with high exposure levels to PCBs have altered antibody responses and lymphocyte proliferative responses. (Skaare JU et al 2002, 2004 and 2005)

**Human: PCBs**

- Yu-Cheng, Taiwan (Chang KJ et al. 1981) suggests focus on of perinatal exposure: **Low IgA and IgM levels** and **total T cells and cytotoxic T cells levels**.
  - Later (1997) decreased **delayed type skin reactions** and **pneumonia, bronchitis and otitis media** more frequently than control infants.

- Great Lakes North America: Mothers with high PCB levels in milk had infants with **increased numbers of infections** first 4 months of life (Swain WR 1991).

- Canada Quebec: Inuit infants highly exposed to marine toxicants have been found to have changes in **T-cell subsets** (Dewailly E et al 1996)

- Canadian Inuit infants. An Increased **risk for otitis media** was observed among those with the highest levels of organochlorine exposure (Dewailly E et al. 2000).

- Dutch children (Weisglas-Kuperus N et al. 2000 and 2004) **Increased risk for otitis media** and **reduced risk for allergic reactions. Post-vaccination antibodies to mumps and rubella** correlated negatively to PCB levels in cord blood.

- Canada St. Lawrence River: Cord blood **T-cell subsets and T-cell proliferative response** influenced by high levels of blood PCBs. Furthermore **in vitro** TNF-secretion correlated negatively with plasma PCBs (Belles-Isles M et al. 2002 and Bilrha et al. 2003).

- Non-coplanar PCBs suppress **in vitro phagocytosis** by human leucocytes (Levin M et al. 2005)
PCBs

- PCBs influence predominantly T-cell function and T-cell composition possibly via an influence on thymic function.
- Antibody production to T-dependent protein antigens is reduced.
“for suppression of immune function, the system is best assessed by vaccination with an antigen to which no prior exposure has occurred …. A strong recommendation is therefore to make a greater use of paediatric vaccination programs.”
Maternal serum and milk for PCB analysis

Breastfeeding

5 m 6 m 15 m 5 y 7 y

Vacc 1 Vacc 2 Vacc 3 Booster TT + DT

Antibodies to tetanus toxoid and diphtheria toxoid Serum PCB

Group A
Group B

Maternal serum and milk for PCB analysis

Breastfeeding

Antibodies to tetanus toxoid and diphtheria toxoid & serum PCB

Vacc 1 Vacc 2 Vacc 3

12 m 18 m

Booster TT + DT

Antibodies to tetanus toxoid and diphtheria toxoid & serum PCB

5 y 5 y +1m

0 m 3 m 5 m

Vacc 3

5 y

Antibodies to tetanus toxoid and diphtheria toxoid & serum PCB

18 m

Booster TT + DT
Correlation between Mono-ortho PCB in Mothers Milk and Infant Serum at age 18 Months.

Pearson r 0.5953
P value (two-tailed) P<0.0001
Dose-effect relationship between PCB exposure and antibody response to antigens from routine childhood vaccinations.

Upper panel: Maternal serum concentration of sum BCBs plotted against serum tetanus antibody concentrations at 7 years of age.

Lower panel: Serum concentrations of sum PCBs against serum diphtheria antibody concentrations, both at 18 months of age.
Change (in %) in Antibody Concentrations after Childhood Vaccinations (18 months) Associated with a Doubling in Prenatal or Postnatal Exposure to Polychlorinated Biphenyls (PCBs).

<table>
<thead>
<tr>
<th>Exposure parameter</th>
<th>Diphtheria tox</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change</td>
</tr>
<tr>
<td><strong>Transitional milk</strong></td>
<td></td>
</tr>
<tr>
<td>Total PCB</td>
<td>-19</td>
</tr>
<tr>
<td>Weighted mono-ortho PCB congeners</td>
<td>-20.7</td>
</tr>
<tr>
<td><strong>Child serum postnatally (18 months)</strong></td>
<td></td>
</tr>
<tr>
<td>Total PCB</td>
<td>-20.3</td>
</tr>
<tr>
<td>Weighted mono-ortho PCB congeners</td>
<td>-17.3</td>
</tr>
</tbody>
</table>
Change (in %) in Antibody Concentrations after (2y) Childhood Vaccinations (5 years) Associated with a Doubling in Prenatal or Postnatal Exposure to Polychlorinated Biphenyls (PCBs).

<table>
<thead>
<tr>
<th>Exposure parameters</th>
<th>Tetanus tox</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change</td>
</tr>
<tr>
<td><strong>Maternal serum</strong></td>
<td></td>
</tr>
<tr>
<td>Total PCB</td>
<td>-16.5</td>
</tr>
<tr>
<td>Weighted mono-ortho PCB congeners</td>
<td>-1.72</td>
</tr>
<tr>
<td><strong>Child serum postnatally (7 years)</strong></td>
<td></td>
</tr>
<tr>
<td>Total PCB</td>
<td>-13.8</td>
</tr>
<tr>
<td>Weighted mono-ortho PCB congeners</td>
<td>-13.8</td>
</tr>
</tbody>
</table>
## Serum antibody concentrations at different time points in relation the source of PCB measurement

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (7 years)</th>
<th>Group B (18 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tetanus</td>
<td>Diphtheria</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>p</td>
</tr>
<tr>
<td><strong>Maternal serum PCB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above median</td>
<td>4.61</td>
<td></td>
</tr>
<tr>
<td>Below median</td>
<td>7.03</td>
<td><strong>0.035</strong></td>
</tr>
<tr>
<td><strong>Current serum PCB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above median</td>
<td>4.74</td>
<td></td>
</tr>
<tr>
<td>Below median</td>
<td>6.70</td>
<td><strong>0.088</strong></td>
</tr>
</tbody>
</table>
Correlation between anti DT Ab and SumPCB 1 month post 5y boost

**Pearson r**

-0.06735

Log(Sum pcb) µg/g lipid

Correlation between anti TT Ab and SumPCB 1 month post 5y boost

**Pearson r**

-0.04421

Log(TT) IU/ml
Variation in Ab Concentration Shortly after Vaccination
TT ab concentrations in relation to numbers of days from booster vaccination

Mean Log(TT IU/ml)

No of days between vacc. and blood test

Diff. birth - boost vacc.: >4.5y And <6y

N:91

60.3 IU/ml

N:113

40.7 IU/ml

N:105

30.2 IU/ml

N:93

25.7 IU/ml

10-28

29 - 34

35 - 41

42 - 90
Conclusions

• Environmental maternal PCB exposure negatively influence antibody response in infants in a dose dependent way.

• Environmental maternal PCB exposure negatively influence recall antibody response in children in a dose dependent way.

• Recall antigen response is probably mainly influenced by a diminished priming of infants elicited by exposure through maternal PCBs intrauterinely and via mothers milk.
Immunotoxicological study on the Faeroe Islands:

Prof. Philippe Grandjean, M.D., Ph.D.
Esben Budtz-Jørgensen, Ph.D.
Flemming Nielsen, Ph.D.
Institute of Public Health, University of Southern Denmark.

Pál Weihe, M.D.
Department of Occupational Medicine and Public Health,
Tórshavn, Faroe Islands