Hormone Disrupting Chemicals and Epigenetica

1. Epigenetics refers to processes that alter gene expression without changes in DNA sequence.
2. Many chronic diseases are the result of epigenetically induced structural changes in DNA, resulting in DNA hypo- en hypermethylation.
3. Epigenetics mediate endocrine disruption.

Dioxins and methylation

1. **Example: Hypermethylation of the progesterone receptor gene.**

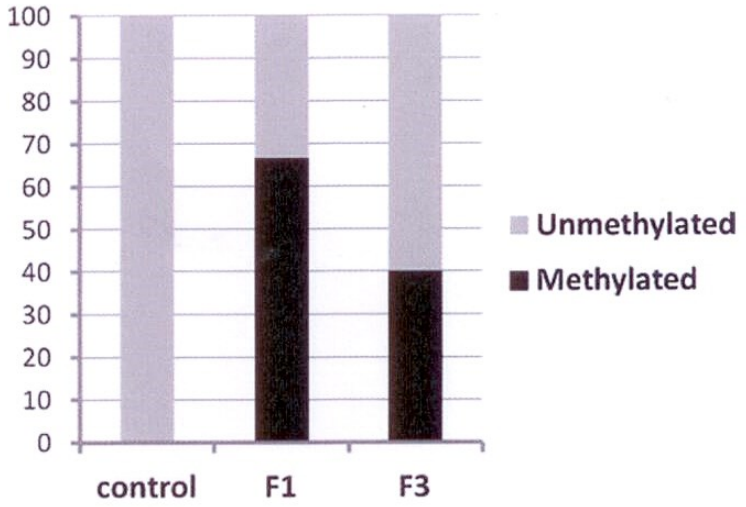


Fig. 1 Methylation-specific PCR of the progesterone receptor gene. Methylation-specific PCR of the progesterone receptor of whole uterine samples obtained from control, F1, or F3 female mice. Extracted DNA was subjected to bisulfite conversion and real-time PCR using methylation-specific primers and standard methodology [52] (n=5 for all groups; mice from multiple litters were used for each group). *PCR* polymerase chain reaction

Ref: Bruner-Tran KL, Resuehr D, Ding T, Lucas JA, Osteen KG. The Role of Endocrine Dusruptors in the Epigenetics of Reproductive Disease and Dysfunction:Potential relevance to Humans. Curr Obstet Gynecol Rep 2012;(1):116-23.

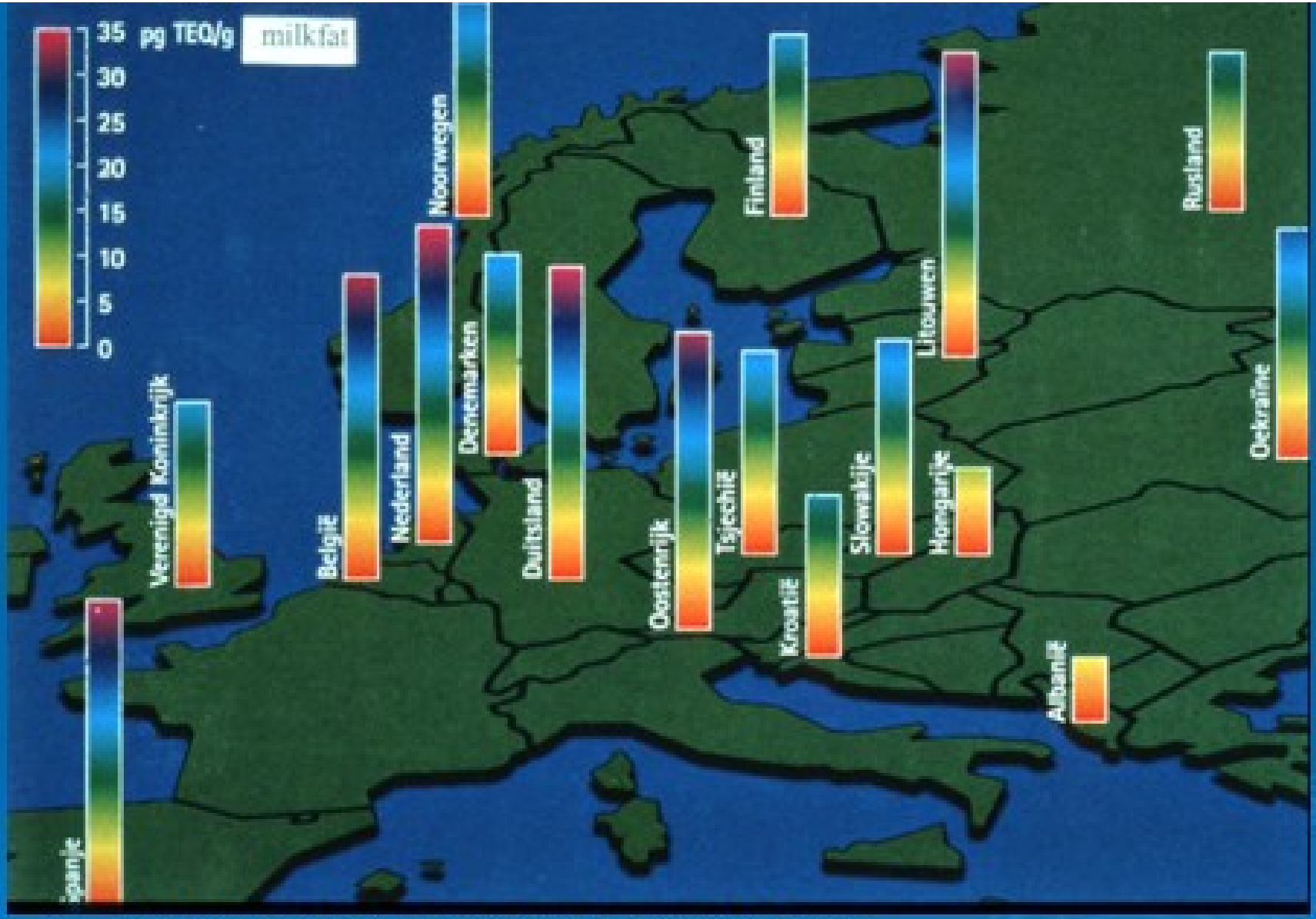
Chemicals causing endocrine disrupting effects

Chemicals with endocrine disrupting effects:

The following chemicals have been related with perinatal exposure and effects in later life:

1. **Dioxins** and PCBs
2. Phthalates
3. Bisphenol-A
4. Chlorpyrifos
5. PFC's

Source TEDX,Theo Colborn



- 1988 levels of PCDD/Fs in different countries in Europe

Perinatal (1987-1991) and current (2005)Dioxin levels in 35 adolescents

- Prenatal PCDD/F level: **32.6** TEQ ng/kg milkfat (range: 9.1-59.8 ng/kg milkfat)
- Postnatal=Lactational exposure:75.4 ng (absolute amount) (range: 4.34-279 ng)
- Current PCDD/F levels: **2.20** TEQ ng/kg fat in serum (range 0.36- 6.06)

Mother-baby pairs

- **1987-1990: 14 Mother-baby pairs were studied, with Dioxin levels (PCDDs and PCDFs) in breastmilk: 29-93 ITEQ PCDD/Fs ng/kg milkfat**

- **1990/1991: 120 Mother-Baby pairs were enrolled, whereby 44 babies exclusively breastfed at 11 weeks post partum remained in the study. Dioxin-levels in breastmilk : 8-63 ITEQ PCDD/Fs ng/kg milkfat**

Long-term follow-up

- **1. at birth (Dr. H. Pluim)**
- **2. at 2 ½ years of age (Dr. A. Ilsen)**
- **3. at 7-12 years of age (Dr. G.W. Ten Tusscher)**
- **4. at 13-18 years of age (Dr. Marike Leijs)**

Mother-baby pairs

Optimal pregnancy according to Prechtl, normal birth and birthweight > 2500 grams.

- **Prenatal dioxin exposure = level in breastmilk**
- **Postnatal dioxin exposure= lactational exposure = level in breastmilk x quantity consumed.**
- **(5.7-385 ng ITEQ PCDD/Fs)**

Findings in the perinatal period

1. **Significant effect on thyroid regulatory system**
2. **Significant decrease in polynuclear cells and monocytes, significantly decreased number of blood platelets at 11 weeks**
3. **An increase in liver enzymes ASAT and ALAT at 11 weeks**
4. **No effect of short maternal diet on dioxin-levels in her breast milk**
5. **A significant decrease in Retinol Binding Protein levels at 11 weeks after birth.**

AT THE AGE OF 2 YEARS AND 7 MONTHS

1. Signs of enhanced neuromotor maturation were found, possibly related to a thyroxin-agonistic action of dioxins
2. No effects on thyroid regulatory system anymore
3. No abnormal liver enzyme levels
4. No decreased number of white cells. Number of blood platelets were not count.

3. AT THE AGE OF 7 – 12 YEARS

- **Brain function was studied in 42 children of the original 14 plus 44 babies : 10% lower IQ**
- **More behavioral problems**
- **Haematologic studies: decreased number of blood platelets**
- **Lung function studies: more obstructive problems=asthma**

Results brain development (MEG and EEG):

- **Increased latencies (10% delay= IQ): defective myelination**
- **Decreased amplitudo, loss of neurons.**
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Lung function

Increase in bronchial obstruction at lung function in relation to both prenatal and postnatal dioxin exposure at the age of 7-12 years

Haematologic and other findings :

1. **Lower number of blood platelets with an increased thrombopoietin level = toxic effect on bone marrow at stemcell level.**
2. **Increased CD4+T-helper cells and increased CD45RA counts**
3. **Less Allergy**
4. **No effect on Cyp 1A2 activity**
5. **No effect on dental enamel**

At 15-18 years:

Pubertal development:

1. **Delay in breast development and first ejaculation.**
2. **Decreased insulin secretion related with higher prenatal dioxin exposure**
3. **Haematology and Immunology:**

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

4. **Lung function: relation with current PBDE's**

What can we expect in this population?

- More breast cancer
- More diabetes
- More auto-immune diseases like thyroid problems and rheumatic diseases
- More social problems
- More prematurity

What to do ? (1)

From a regulating point of view:

Primary prevention:

Zero tolerance for chemicals known to disrupt development and the endocrine system

Secondary prevention :

What can be done to prevent or ameliorate damage?

In general:

Diet: Important to eat lots of vegetables (biologically grown, vegetables better then fruit)

Exercise: more exercise ameliorates damage

What to do ? (2)

Reproduction:

The role of the **“father to be”.**

preconceptional leave of 3 months must be arranged.

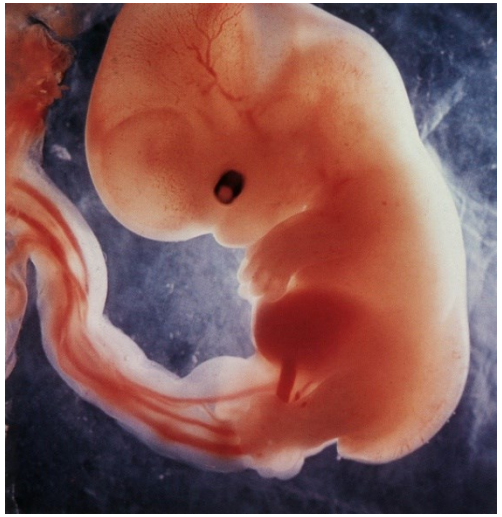
Semen is made in 3 months time. In this preconceptional period the “father to be” must abstain from alcohol, from smoking, from air pollution, eat 30 grams nuts a day and lots of biological grown vegetables. Lots of **exercise.**

b. The role of the **“mother to be”**

Eggs are made during the intra-uterine life of the “mother to be”. So the “grandmother to be ” is already important.

Diet in the beginning of pregnancy (less sugar)is important f.i. to prevent obesity in the child.

Protecting children from Hormone Disrupting Chemicals



Thank you