

**Division of Targeted Research**

National Research Programmes

Wildhainweg 20

CH-3001 Berne

Tel. +41(0)31 308 22 22

Fax +41(0)31 305 29 70

E-Mail nfp@snf.ch

## **NRP Endocrine Disruptors**

### **Intermediate Summary**

<b>Biological activity of complex mixtures of endocrine disruptors</b>
<b>Project leader</b> Prof. Dr. Hanspeter Naegeli
<b>Project number</b> 4050-66572

### **English Summary**

#### **Biological activity of complex estrogenic mixtures**

There is general concern that the permanent low-dose exposure to various man-made chemicals with estrogenic activity may be linked to adverse health effect such as breast cancer, male sterility or other reproductive dysfunctions.

#### **Project description:**

##### **Research questions**

Endogenous estrogens play a fundamental role in human and animal reproduction, as well as in normal development and tissue differentiation. Normal estrogen signaling pathways culminate in the up- or down-regulation of specific genes in target cells. However, a large number of man-made chemicals and naturally occurring phytoestrogens are able to disrupt these physiologic responses. Here, the molecular mode of action of such estrogenic chemicals was recorded by monitoring global alterations of gene function in two human breast cell lines.

##### **Results**

Cultured human breast cells were exposed to the endogenously produced estrogenic hormone 17 $\beta$ -estradiol, and to typical representatives of natural or man-made xenoestrogens, i.e., estrogenic substances that are foreign to the body. These test compounds include the phytoestrogen genistein and the industrial chemicals bisphenol-A and PCB-54. Subsequently, a comprehensive analysis of early genome functions was performed using large-scale oligonucleotide microarrays ("DNA chips") that display the sequences of essentially all known human genes. Surprisingly, these DNA chip experiments showed that all three xenoestrogens induce identical genomic fingerprints by reprogramming exactly the same selection of human genes. Also, the stereotyped genomic signature induced by xenoestrogens was undistinguishable from the effects of the endogenous 17 $\beta$ -estradiol. For example, all xenoestrogens suppressed genes involved in cell-to-cell adhesion while inhibiting cell death and promoting cell growth, DNA replication, and cell division.

**Significance:** Our large-scale molecular analysis revealed identical actions of diverse estrogenic chemicals, down to the level of single human genes. This unexpected functional convergence reinforces the hypothesis that multiple xenoestrogens may act together to produce hazardous effects when combined at low doses. The potential response to mixtures of redundant xenostrogens is likely to be underestimated when risk assessments are based on the separate characterization of single components. Hence, we conclude that new regulatory measures should be introduced to account for the possible impact of multiple low-dose exposures to dietary and environmental estrogens.

### **Perspectives**

We are now planning to assess the overall biological activity of xenoestrogens in relevant biological samples such as human breast milk.