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# Introduction

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*Abstract:* The presence of hormonally active chemicals ('endocrine disruptors') in the biosphere has become a worldwide environmental concern. In 1999, a report released by the Swiss Federal Office for the Environment (FOEN) concluded that such chemicals have already left their mark on the Swiss landscape and implicated them as a general cause of population changes in wildlife. Some of the chemicals involved, for example polychlorinated biphenyls (PCBs) and dibenzo-*p*-dioxins (dioxins), have received wide media attention because of their negative health impact on humans. The potential contribution of endocrine disruptors to the increased incidence of a number of diseases and developmental disorders in humans and animals is alarming, but the establishment of solid cause–effect relationships requires further scientific investigation. In Switzerland, the necessity for a coordinated transdisciplinary approach to the environmental and public health problems caused by endocrine disruptors has now been widely recognized. In 2001, the Federal Government implemented a National Research Programme (NRP) on 'Endocrine Disruptors' which aimed to develop scientific strategies to assess the risks and hazards that arise when endocrine disruptors are processed through ecosystems and cause human and animal exposure. The present issue of CHIMIA presents a selection of research highlights from this program.

**Keywords:** Endocrine disruptors

## Introduction

Chemicals with hormonal activity, also termed endocrine disruptors, can exert a variety of detrimental effects on humans, animals and entire ecosystems.[1] In humans, disturbances of fertility,[2] reproduction,[3] fetal development,[2] metabolism[4] and tumor formation[5] have been reported. In animals, numerous studies attest to reproductive[3] and behavioral[6,7] disturbances across a broad species spectrum ranging from fishes[8] to marine and terrestrial mammals.[9] These deficiencies have already contributed to the local extinction of at least one species. At the level of ecosystems, a major concern is that endocrine disruptors could be a factor in reducing biodiversity in animals.[9]

Principally, the action of endocrine disruptors can result from two different mechanisms: i) receptor-dependent effects and ii) receptor-independent effects. Binding of a ligand to an appropriate receptor can activate or block receptor-mediated hormonal effects. Quantitative and qualitative differences have been observed between constitutive hormonal effects and endocrine disruptors affecting events downstream of receptor binding, *i.e.* the pattern of gene activation/repression (for reviews see refs [9,10]). Moreover, it is known that endocrine disruptors can simultaneously interfere with different hormone systems (*e.g.* estrogens and androgens,[9]). Receptor-independent effects involve interference with the synthesis, metabolism or transport of hormones.[11]

Endocrine disruptors may modulate the function of endocrine systems at concentrations far lower than the levels causing general toxicity and during narrow time windows in the development of an organism.[12,13] Since certain types of hormone receptors, such as the nuclear receptor superfamily,[14] are ubiquitous in the animal kingdom,[15] a large number of species ranging from invertebrates to humans can be affected.

In Switzerland, the necessity of a coordinated transdisciplinary approach to the environmental and public health problems caused by endocrine disruptors has been recognised. In 2001, the Federal Government mandated the Swiss National Science Foundation to implement a National Research Program (NRP50) on 'Endocrine Disruptors: Relevance to Humans, Animals and Ecosystems'.

## Implementation and Focus

An implementation plan was set up by a steering committee with the support of international experts.[16] With regards to endocrine disruption, the following major questions were raised:

- What is the magnitude of exposure of humans, domestic animals, wildlife and environment in Switzerland?
- Which methods and models are suitable to assess the endocrine activity of these chemicals or chemical mixtures, what are the mechanisms of action, and how do they affect developmental and reproductive processes?
- What are the hazards and risks to human and animal health? What is the impact on biodiversity?

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- What measures should be taken for the protection of humans and the environment?

From a broader perspective, the NRP aimed to create a *consensus platform* for industry and regulators on how to avoid the negative impact of today's chemicals of this category.[17] In the pursuit of this goal, the NRP was to define a set of rules for future development of pertinent substances. Finances totalling 15 million CHF were made available over a six-year period for the accomplishment of this multidisciplinary task. The programme and activities of the NFP were continuously adjusted to ongoing international research and regulatory programmes in order to avoid redundancies.

## Research Focus

Endocrine disruptors operate at diverse levels of biological complexity. Consequently, the calls were framed to encompass research from molecular mechanisms to population dynamics. Within this frame, a number of major topics were specified:

### *Assessment of Exposure*

- Development and use of chemical-analytical methods, bioassays and biomarkers to determine the exposure and effects of endocrine disruptors in ecosystems, animals and humans in Switzerland.

### *Processing of Endocrine Disruptors in Ecosystems*

- Application of ecokinetic and toxicokinetic approaches to monitor the fate of individual chemicals and their metabolites in the environment and in organisms; identifying the key mechanisms involved in the bioprocessing of these chemicals.

### *Experimental Toxicology and Ecotoxicology*

- Population studies linking endocrine disruptor exposure and specific end points.
- Identification of indicator species by comparing the effects of endocrine disruptors on various species occupying different ecological niches within particular ecosystems.
- Determination of long-term, low dose effects of endocrine disruptors and mixtures of them on selected indicator species of particular ecosystems; implementation of multigeneration and life cycle studies focussing on reproduction, development, immune system and other organ functions. Input for study design was to come from the aforementioned programme sections.

### *Assessment of Endocrine Disruptor Effects in Animal Models*

- Development of animal models for the study of developmental and endocrine health effects in humans and animals suspected to be caused by endocrine disruptors.

### *Analysis of the Effects of Specific Chemicals and Mixtures*

- Elucidation of how endocrine disruptors could affect mechanisms involved in reproduction, ontogeny, carcinogenesis, immune defence and other health effects. Integration of the signal networks using novel approaches, such as functional genomics, proteomics and quantitative structure activity relationship (QSAR).

### *Integrative Analysis in Model Systems*

- Development of modelling approaches to analyse and predict the effects of endocrine disruptors in ecosystems.

### *Risk Assessment and Implementation*

- This programme section would integrate the results of the entire NRP and generate a decision platform for future actions. Based on a broad inventory of potential hazard and risk scenarios, recommendations were formulated for future regulatory and industrial processes.

## Research Projects

Grants were awarded in three consecutive public calls. In the first round, a conventional submission procedure was announced and scientists were free to choose from any of the topics. In the second grant call, the aim was to recruit junior investigators and attract them to the field. In the third call, the focus was on risk assessment and implementation.

The Table shows an overview of the grant proposals that were awarded by SNF.

## Future Perspectives

What can be done as this national research effort comes to a conclusion? The Steering Committee initiated a series of moderated non-public debates with representatives from the scientific community, industry and authorities. The goal was to establish a consensus platform on the actions of endocrine disruptors as well as on the best measures to be taken to avoid their detrimental impact. The topics of the consensus platforms were chosen to address issues and actions particularly relevant to Switzerland:

- UV Filters in Sunscreens
- Brominated Flame Retardants
- Endocrine Disruptors in Wastewater and in the Aquatic Environment

The procedures and results of the consensus platforms are summarized in the last article of this issue[17] and can be explored in full detail at *http://www.nrp50.ch/consensus-platforms.html*. They represent the consensus of 47 representatives of science, industry and government.[17]

Furthermore, the Federal Office for the Environment (FOEN) will continue to serve as a coordinating anchor for future research efforts in this field. The coordinator will be Dr. Christoph Studer (*christof.studer@bafu.admin.ch*), who also served in the Steering Committee. Likewise, the FOEN will continue to communicate on behalf of the program by maintaining the website of the NRP50 program (*www.nrp50.ch*). A significant step has been achieved with NRP50, but the problems of endocrine disruption will continue to intrigue the scientific community of the world. Let us continue to cooperate on a international level!

### *Acknowledgements*

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Table. Research Projects Funded by NRP50

| **A. Basic Research and Methods** | |
|---|---|
| Grant Title | Prinicipal Investigator |
| **Molecular responses to estrogenic endocrine disruptors** | Rusconi Sandro, Units of Biochemistry, Department of Medicine, University of Fribourg |
| **Biological activity of complex mixtures of endocrine disruptors** | Naegeli Hanspeter, Institute of Veterinary Pharmacology and Toxicology, University of Zurich |
| **Disruption of glucocorticoid- and mineralocorticoid receptor-mediated responses by environmental chemicals** | Odermatt Alex, Institute of Molecular and Systemic Toxicology, Department of Pharmaceutical Sciences, University of Basel |
| **Are organisational effects of estrogens on sexual differentiation, development and growth of fish mediated *via* the Insulin-like growth factor I (IGF-I) system?** | Reinecke Manfred, Institut of Anatomy, Division of Neuroendocrinology, University of Zurich |
| **Mechanisms of action of (xeno)estrogens on the early development and differentiation of brain and gonads in zebrafish (XEBRA)** | Eggen Rik I.L., Swiss Federal Institute of Aquatic Science and Technology (EAWAG), Dübendorf |
| **Environmental disruptor actions in live cells and animals: Elucidating molecular mechanisms of PPAR pathway alterations** | Wahli Walter, Center for Integrative Genomics (CIG), University of Lausanne |
| **Endocrine disruption in soil invertebrates: assessing multigeneration effects and developing a proteomic biomarker approach** | Tarradellas Joseph, Institute of Environmental Science and Technology (ISTE), EPFL, Lausanne |
| **Signaling of estrogenic endocrine disruptors through membrane-associated receptors** | Picard Didier, Deptartment of Cell Biology, University of Geneva |
| **Internet application for the estimation of the binding affinity of small molecules towards the estrogen receptor *in silico*** | Vedani Angelo, Biographics Laboratory 3R, Basel |
| **Development of a mass spectrometry-based assay for the analysis and screening of endocrine disruptors** | Zenobi Renato, Laboratory of Organic Chemistry, ETHZ, Zurich |
| **Development of chemical sensors and affinity-directed fractionation techniques (SENATE)** | Suter Marc J-F, Swiss Federal Institute of Aquatic Science and Technology (EAWAG), Dübendorf |
| **B. Chemicals of Concern** | |
| Grant Title | Principal Investigator |
| **UV filters: Mechanisms of developmental toxicity in mammalian brain and human exposure** | Schlumpf Margret, GREEN Tox, Zurich |
| **Phytoestrogens in food, food complements and medicinal plants: content, pharmacological relevance and metabolic profile** | Hostettmann Kurt, Pharmacognosy and Phytochemistry Laboratory, University of Geneva |
| **Phenolic substances with estrogenic disruptor potential as contaminants in the aquatic environment (PHENCON)** | Kohler Hans-Peter, Swiss Federal Institute of Aquatic Science and Technology (EAWAG), Dübendorf |
| **Endocrine disrupting chemicals in the air – linking emission processes and transport phenomena with effects in wildlife and humans (ENDAIR)** | Gerecke Andreas C., Swiss Federal Institute for Materials Testing and Research (EMPA), Dübendorf |
| **C. Aquatic Systems and Fishes** | |
| Grant Title | Principal Investigator |
| **Hormonal activity of UV screens in aquatic ecosystems (HAUS)** | Fent Karl, University of Applied Sciences Northwestern Switzerland, Muttenz |
| **Endocrine disruption in Switzerland: Assessment of fish exposure and modelling of effects on population level (SAFE I and SAFE II)** | Holm Patricia, Mensch Gesellschaft Umwelt (MGU), University of Basel |
| **Brominated flame retardants and other endocrine disrupting chemicals in the ecosystem of Thunersee - environmental fate and correlation to biological effects (FLEET)** | Kohler Martin, Swiss Federal Institute for Materials Testing and Research (EMPA), Dübendorf |

| Grant Title | Principal Investigator |
|---|---|
| **Gonad malformations of whitefish *(Coregonus lavaretus)* in Lake Thun: are they induced by endocrine-active compounds (EACs)?** | Segner Helmut, Centre for Fish and Wildlife Health, Institute of Animal Pathology, University of Bern |
| **Phenolic and brominated contaminants in wastewaters and in the aquatic environment (PHEBRO)** | Giger Walter, Swiss Federal Institute of Aquatic Science and Technology (EAWAG), Dübendorf |
| **Environmental exposure to estrogenic mycotoxins** | Bucheli Thomas, Agroscope Reckenholz-Tänikon Research Station ART, Zurich |

**D. Human Disease and Disease Models**

| Grant Title | Principal Investigator |
|---|---|
| **Drop of male fertility in various geographic regions of Switzerland: Investigation of the critical parameters usable for prospective repeated evaluations** | Germond Marc, Fondation F.A.B.E.R, Lausanne |
| **Identification of genetic predispositions to oligo-astheno-teratospermia** | Schorderet Daniel, Division of Ophtalmology, University of Lausanne, Hôpital ophtalmique Jules Gonin, Sion |
| **Role of environmental endocrine disruptors in the aetiology of Intrauterine Growth Retardation and its later consequences such as disorders in brain development and adult-onset obesity** | Aubert Michel L., Childrens Hospital, University of Geneva |
| **Endocrine disruptors and breast carcinogenesis: A new mouse model to assess estrogen receptor-dependent and -independent effects** *in vivo* | Brisken Cathrin, Swiss Institute for Experimental Cancer Research (ISREC), Epalinges/Lausanne |
| **Prenatal exposure to endocrine disrupting chemicals: Effects on the male urogenital system** | Nef Serge, Department of Genetic Medicine and Development, University of Geneva Medical School |

**E. Risk Assessment and Consensus Platform**

| Grant Title | Principal Investigator |
|---|---|
| **Ecological risk assessment of UV filters** | Fent Karl, University of Applied Sciences Northwestern Switzerland, Muttenz |
| **Integrative mass flow model for endocrine disruptors in Switzerland – model development, risk assessment and risk management** | Gälli René, BMG Engineering AG, Schlieren |
| **Integrative risk assessment of endocrine disruptors in Switzerland** | Gälli René, BMG Engineering AG, Schlieren |
| **Dynamic substance flow analysis model for selected brominated flame retardants as a basis for decision making on risk reduction measures (FABRO)** | Morf Leo, GEO Partner AG Umweltmanagement, Zurich |
| **Consensus Platform** | Trachsel Marcel, int/ext Communications AG, Basel |

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