

**SCOPE/IUPAC**

**Project on Environmental Implication of  
Endocrine Active Substances**

*Present state of the art and future research needs*

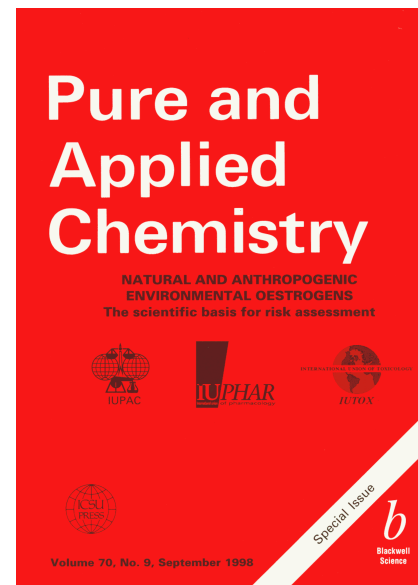
**J. Miyamoto *et al.***

Poster presented at the  
IUPAC Congress/General Assembly  
*July 2001*

# Background

Disruption of endocrine systems by anthropogenic as well as natural compounds has become an **important global issue** during the last decade, because it may encompass not only humans but also a wide range of other organisms, and not only the present generation but also future ones. Massive scientific research efforts are currently underway to assess the significance of reported **adverse effects of exposure to xenobiotics on endocrine systems**.

There are still many scientific uncertainties to be resolved before acceptable testing procedures can be established. As pointed out in the recent reference by IUPAC, IUPHAR, and IUTOX\*, these uncertainties can only be resolved by conducting high-quality scientific investigations and a thorough peer review of the results. In this report, the Unions highlight the need for a better understanding of the mechanisms by which the chemicals produce their effects, and for further examination of the relation between exposure and adverse effects both on humans and the environment. They call for the development of better methods of screening and testing chemicals. Finally, they point out the need for a review of existing and new risk assessment methods.



\* Natural and Anthropogenic Environmental Oestrogens: The Scientific Basis for Risk Assessment, *Pure Appl. Chem.*, Vol. 70, No. 9, 1998

# Objectives

1. To expand and deepen the IUPAC/IUPHAR/IUTOX evaluation of endocrine disruptor issues (1998) by including similar evaluations concurrently underway, and avoiding unnecessary overlapping.
2. To deal with endocrine disrupter issues as scientific problems that have major significance on the world environment scene.
3. To prioritize future research needs and to make the best use of available resources.
4. To facilitate effective risk assessment and risk communication on the problem by offering some manageable action.
5. To deal with the problem highlighted by academia on an international basis, which makes this project quite unique and different from other evaluations that are regional and/or intended for regulatory purposes.

The final report, ca. 600 pages in English, will be published in *Pure Appl. Chem.* A shortened summary for non experts also will be distributed worldwide. The project started in April 2000 and is to be completed in March 2003.

# International Symposium

As a major milestone of the Project, the International Symposium will be held in **November 17 to 21, 2002** in Yokohama (Japan) to present all the draft reports of the Project to discuss them and to receive inputs from external scientists for the final reports in March 2003.

## Supported by:

The following national and international bodies have agreed and/or are solicited to support the Project: ICSU, UNESCO, UNEP, USEPA and FDA, EU, British Government, Japanese Government, US NIEHS, IUTOX, ICCA

## Presentation:

Altogether 60 experts (contributors of the Topics) in USA, UK, Japan, The Netherlands, Denmark, Switzerland, Israel, New Zealand, and France will present the papers including the Topics and Subtopics. All papers will be presented in oral as well as poster sessions. Additionally, a certain number of external papers are invited.

## Calendar:

December, 2001 - Second Circular

June, 2002 - Third Circular, final Program

# Scientific Advisory Committee (SAC)

The Scientific Advisory Committee (SAC) organizes and coordinates all the topics and subtopics in the Project. The SAC is also responsible for the scientific quality of all the manuscripts to be published as part of the final report. There are four areas - *Topics* - to be dealt with in the Project.

The members are:

**Dr. Junshi MIYAMOTO** (Chair), IUPAC/Chemicals Evaluation and Research Institute, Tokyo, Japan

**Prof. Joanna BURGER** (Cochair), Rutgers University, Piscataway, New Jersey, USA

**Dr. William KELCE**, Pharmacia Corporation, Michigan, USA

**Dr. Kenneth S. KORACH**, National Institute of Environmental Health Sciences, Research triangle Park, North Carolina, USA

**Prof. Werner KLEIN**, IUPAC/Fraunhofer Institute for Environmental Chemistry and Ecotoxicology, Schmallenberg, Germany

**Prof. John ASHBY**, Syngenta Ltd., Cheshire, UK

**Dr. James LAMB**, BBL Sciences, Virginia, USA

**Dr. Peter MATTHIESSEN**, Centre for Ecology and Hydrology, Cumbria, UK

# **Topic 1 - *Molecular mode of action of nuclear receptors; Fundamentals for understanding the action of endocrine-active substances***

- Nuclear receptor superfamily
- Mode of action of coactivators and corepressors
- Biological function and mechanism of nuclear receptors; estrogen, progesterone, vitamin D, androgen, glucocorticoid, retinoid, mineralcorticoid, thyroid, and orphan nuclear receptors
- Biological function and mechanisms of non mammalian receptors
- Molecular mechanism of cross-talk between growth factors and nuclear receptor signaling
- Nuclear receptor action through classical and alternate target genes and involved with gonadal differentiation
- Nuclear receptor gene mutation and hereditary diseases
- Interaction of exogenous endocrine-active substances with nuclear receptors

## **Topic 2 - *Environmental fate and metabolism of endocrine-active substances***

- Detection of endocrine-active substances in food and the environment
- Release of natural hormones from humans, wildlife and livestock
- Phytohormones in food and feed, their release into the environment
- Release of industrial chemicals into the environment
- Release of agrochemicals
- Degradation, persistence, and accumulation of endocrine-active substances
- Metabolism in mammals, aquatic and terrestrial organisms
- Environmental exposure modeling
- Prioritization of information needs

## **Topic 3** - *Effects of endocrine-active chemicals in rodents and human and risk assessments for humans*

- Human male reproductive health
- Breast cancer and relationship to environmental hormones
- Hormone-mediated diseases in developing children
- Human health effects: weight of evidence
- Balancing of beneficial and adverse effects
- Plausible relationship to adverse effects on human health
- Biosynthesis, transport, and feedback mechanism: rodent and human differences
- New testing guidelines with endocrine-sensitive endpoints
- Significance of experimental studies in humans
- Critical evaluation of observed adverse effects on reproduction and development, and the nervous and immune systems
- Modification of endocrine-active substances by mixtures
- TDI and PNEC: animal models to ensure human safety



### **Topic 3 (cont.)**

- Dose-response assessment (low dose extrapolations and hormesis)
- NOAEL, benchmark dose, or other models for human health risk assessment
- Current view on the risk assessment of endocrine-active substances

### **Topic 4 - *Effects of endocrine-active substances in wildlife species***

- The TBT story
- Endocrine disruption in freshwater and marine fish
- Deformed frogs and environmental retionids
- Effects on sex determination and differentiation in reptiles
- Animal models for the study of low doses and mixtures
- Full life cycle tests using fish
- Environmental risk assessment
- A government view
- Endocrine disruption in wildlife; the future

# Supplementary workshops

The tentative subjects for the workshops are as follows:

1. Effectiveness of QSAR for prescreening of endocrine disruptors
2. Toxicogenomics as a rational approach to endocrine disruptor research
3. Species specificity (in non mammalian species) related to a rational testing approach
4. Rapid assay for definitive tests of endocrine disruptors
5. Precautionary principle/approach and weight of evidence in endocrine disruptor issues
6. Sound risk assessment of endocrine disruptors in the future

*\* As one of the activities of ICSU, International Council for Science, comprising 22 international scientific unions, committees, and societies, **SCOPE** represents synthesis, assessment, and evaluation of information on environmental changes and their effects on people. IUPAC is one of the members of ICSU, and the mission is to advance the worldwide aspects of the chemical sciences and to contribute to the application of chemistry to the service of mankind.*