



# credo

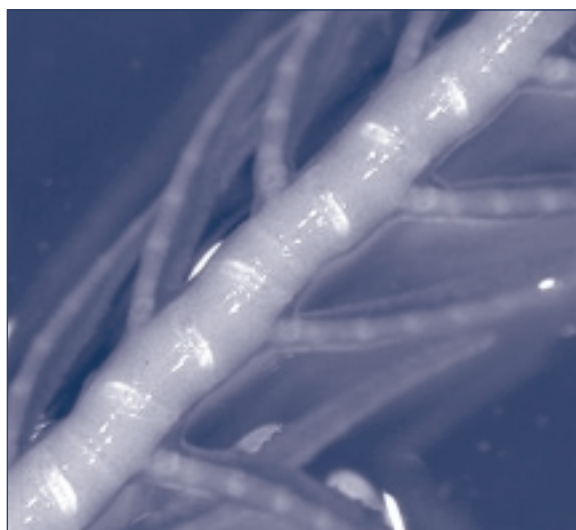
Cluster of research into endocrine disruption in Europe

Coordinating European Environmental and Human Health Research into Endocrine Disruption

## Introducing the cluster

Four projects on endocrine disruption funded by the European Union form the core of the CREDO cluster: EDEN, COMPRENDO, EURISKED and FIRE. Together, these projects represent over 60 research laboratories in Europe, with a total budget of more than €20 million.

The EDEN project has been given the responsibility for overall coordination of the cluster, and a further eight projects that obtained funding in the last round of the Fifth Framework Programme are associated with the cluster.



*Antedon mediterranea is a test species used to study endocrine effects in echinoderms, which is one component of the COMPRENDO project. Photograph courtesy of Daniela Candia Carnevali.*

### Objectives

The main aim of the CREDO cluster is to support the European Union's strategy on endocrine disruptors by producing sound scientific data. In so doing, the European Commission and the cluster are seeking to create a focus for endocrine disrupter research in Europe and beyond.

To achieve this ambitious aim, the cluster projects have agreed to exchange know-how and to set up research collaborations across the boundaries of individual consortia. Four thematic workshops organised by the cluster in 2004 and 2005 will provide the setting for this kind of collaboration and interaction.

Another key aspect of the cluster's activities is to begin a constructive discourse with the public in Europe and with stakeholders and interest groups. These include risk assessors in EU member states, consumer organisations, industry and other non-governmental organisations. Representatives from these groups will be invited to participate in the cluster workshops.

### The newsletter

The CREDO newsletter has been set up as an additional forum for communication between the cluster and interested members of the public and stakeholders. It will provide information about recent developments in the cluster, the outcome of workshops and the results of research collaborations.

We hope that the newsletter will be a lively forum for discussion within the cluster and beyond, and are looking forward to all your future contributions.

*Dr Andreas Kortenkamp, cluster coordinator*

## In this edition

- 2** The cluster projects introduce themselves

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- 5** Dr Claudia Roncancio Pena of the European Commission's DG Environment explains the Commission's strategy on endocrine disruption

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- 6** Dr Michael Faust of Faust and Backhaus Environmental Consulting takes a look at the implications of the new European chemicals policy for endocrine disrupter research

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- 8** Drs Kirsi Haavisto and Tuomo Karjalainen of the European Commission's DG Research provide an overview of endocrine disruption research in the new 6th Framework Programme of Research

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- 11** A report on the first CREDO meeting, held in London in April 2003 and a preview of the cluster workshop on wildlife effects

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- 12** Announcements:  
The CREDO workshop programme

newsletter

## Participating projects

### EDEN

*Endocrine disruptors: exploring novel endpoints, exposure, low-dose and mixture-effects in humans, aquatic wildlife and laboratory animals*

In the EU, there are significant human and wildlife health problems that stem from endocrine disruption. What remains unresolved is whether human/wildlife exposure to endocrine disrupting chemicals plays any causal role in these developmental disorders. EDEN's aim is to address the common problems in wildlife and human hazard assessment in one coherent approach.

The project will produce data about the occurrence of exposures to mixtures of endocrine disrupting chemicals in humans and fish and develop new experimental models that allow more meaningful extrapolations from animals to humans. It will also produce data about low-dose and mixture-effects of endocrine disrupting chemicals that are directly relevant to hazard and risk assessment. The project will provide new insights into indicators of the reproductive health of European citizens and will help to provide the scientific basis for a coherent strategy for dealing with these chemicals in the EU.

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### COMPRENDO

*Comparative research on endocrine disruptors, phylogenetic approach and common principles focusing on androgenic/antiandrogenic compounds*

As an interdisciplinary, integrated approach, COMPRENDO addresses endocrine disruption in human and wildlife species, focusing on androgenic/antiandrogenic compounds (AACs).

The project will identify human and environmental exposures to AACs. A variety of human-relevant models (cell lines, tissues, rodents) and wildlife species (amphibians, fish, echinoderms, crustaceans, molluscs) will be exposed to 13 chemicals and various environmental samples so as to develop new indicators of biological effects, including a molecular screen for genomic AAC effects. Common principles of AAC action will be identified, and new models for the extrapolation on human health developed. Lab cultures of suitable invertebrates will be established and their baseline endocrinology analysed, facilitating the use of these species as standard test organisms. Finally, an evaluation of the risk originating from AACs for humans and wildlife will be carried out.

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### EURISKED

*Multi-organic risk assessment of selected endocrine disruptors*

Endocrine disruptors (EDs) with steroidal or anti-steroidal effects may be of great importance during embryonic development and later for metabolic, brain, cardiovascular, reproductive and bone function. The effects of UV-absorbing chemicals (4-MBC, OMC), characterised recently as estrogenic, and of benzo-phenone (a chemical used in cosmetics), as well as the fungicide procymidone and the pesticide linuron will be studied in rats and gene-targeted mice. High throughput methods will be employed to identify EDs with (anti) estrogenic, (anti) androgenic, (anti) progestational, (anti) glucocorticoid, and (anti) thyroid hormone activities. Gene-targeted cell lines and animals, including the EU-sponsored EUROSTERONE DNA chip, will seek to quantify both EDs and their effects on gene and protein expression in different organs. It is expected that this will lead to clear concepts for clinical trials towards the end of the project.

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### FIRE

*Risk assessment of brominated flame retardants as suspected endocrine disruptors for human and wildlife health*

The overall objective of this multi- and interdisciplinary project is to improve risk assessment of brominated flame retardants (BFRs) for human health and wildlife. BFRs, such as the high production volume chemicals polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA) and hexabromocyclododecane (HBCDD) have been identified as potential endocrine disruptors. PBDE levels have been increasing steadily in biota over the last few decades. Using in vitro cell systems of particular relevance for endocrine effects, BFRs will be selected for rodent and fish toxicity studies, with particular emphasis on endocrine and immune systems. After further selection, reproduction studies will be carried out in rats (with neurobehavioral and immune function tests), and partial life-cycle assays in zebrafish. The exposure part includes congener specific identification, regional distribution and temporal trends of BFRs in the tissue of wildlife and fish, human milk and diet within the EU. By integrating information on exposure, fate and toxicity, this project aims to provide a highly significant contribution to integrated risk assessment for humans and the aquatic environment with respect to endocrine disruption by BFRs.

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## Associated projects

### ACE

*Analysing combination effects of mixtures of estrogenic chemicals in marine and freshwater organisms*

There is growing concern among EU citizens about chemicals that are suspected of disrupting reproduction in aquatic organisms. Natural estrogens and synthetic chemicals with estrogenic activity are now known to have adversely affected a variety of fish. A crucial aspect of identifying the causes of endocrine disruption in aquatic systems is the analysis of how chemicals implicated as causative agents might act when present as mixtures. This project aims to improve our understanding of the combined effects of multiple estrogenic chemicals and other toxicants on aquatic organisms. It brings together expertise from fish biology, endocrinology, biometry, statistics and analytical chemistry. The effects of combining mixtures of multiple estrogenic chemicals will be assessed and predicted at the subcellular, cellular, physiological and organism levels by using a variety of estrogenic assays.

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### BONETOX

*Bone development and homeostasis – critical targets in toxicology. Research to support test-method development and human health risk assessment for dioxins and other endocrine disrupting compounds in the food chain*

The aim of BONETOX is to provide new toxicological and epidemiological data to improve the risk assessment of dioxin and other food-derived endocrine disrupting chemicals (EDCs). The project's focus is to clarify the mechanisms behind functional diseases (such as osteoporosis) and structural malformations induced by EDCs through interactions with components of the nuclear receptor signalling pathways and other cell regulatory systems. It will address the hormonal cross-talk between Ah (dioxin) receptor, retinoid as well as steroid (estrogen) hormone signalling pathways. The results obtained will be used for (i) test method and biomarker development and for (ii) risk assessment purposes.

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### EASYRING

*Environmental agent susceptibility assessment utilising existing and novel biomarkers as rapid non-invasive testing methods*

EASYRING will provide further information on the environmental levels of pollutants, using innovative tools to measure their biological effects on aquatic species and to

assess the risk they present to mammals. The project aims to develop and validate novel non-invasive methods for detecting known and new biomarkers of endocrine disruptors directly in the mucus of aquatic species. The effects of short and long term, and low dose exposure to endocrine disrupting chemicals will be investigated in both aquatic species and mammals. In parallel, integrated testing of in vitro protocols will allow for a wider understanding and evaluation of their effects. New instrumental analytical techniques will be developed and validated for easier and more complete detection of chemicals in water and biota. The project will compare test data developed in this project with both quantitative structure-activity relationships (QSARs) for the prediction of chemicals that may elicit endocrine disruption and quantitative activity-activity relationships (QAARs) to extrapolate the response of different experimental models. The final aim will be to extend mathematical models to human toxicity.

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### EDERA

*Development and implementation of new in vivo and in vitro systems for the characterisation of endocrine disruptors*

Reliable models for toxicological testing of hormonally active compounds are essential for the development of safety assessment programs related to the exposure of animals and humans to endocrine disruptors (EDs). The objective of the EDERA project is to develop a transgenic mouse model for the characterization of environmental estrogens. This model will contain all the genetic elements that may provide a rapid, flexible, sensitive, economic and informative system for the toxicological testing and hazard identification/risk assessment of EDs. The model will exploit novel photon imaging technology to ensure a rapid localization of the activity of EDs in live animals thus allowing the analysis of the long-term effects of environmental contaminants. Moreover, from this model, a reliable 'in vitro' system will be derived.

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### ENDOMET

*Dysregulation of endogenous steroid metabolism potentially alters neuronal and reproductive system development: effects of environmental plasticizers*

Steroids not only regulate endocrine and reproductive systems, they also modulate neuronal development in the foetus and neonate and cognitive function in adults. ENDOMET aims to examine the effects of a range of endocrine disruptors (EDs) which are derived from industrially manufactured plasticizers (EPs). These EPs

(bisphenol-A, alkylphenols, adipate and phthalate esters) are found in foods which are processed or packaged with plastic materials and in dialysis and intravenous drip fluids as contaminants from the plastic tubing. They have teratogenic and feminising effects at low levels in rats and fish. ENDOMET will determine the effects of these EPs on steroid metabolism, steroid function and reproductive potential, using human cell lines and a proteomics/genomics approach. An in vitro range of biomarker tests will be derived to predict potential ED activity of chemical compounds in humans. Public perception of risk will be assessed and compared with that of experts.

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## GENDISRUPT

*Genetic markers and susceptibility to the effects of endocrine disrupters during mammalian testis development*

Endocrine Disrupters (EDs) are a wide group of compounds, mainly environmental contaminants, which could, acting as endocrine deregulators, generate gene deregulation depending on the genetic background of the organisms. Reproductive systems have been considered a crucial target of the impact of EDs. Consequently, the analysis of the genetic effects of these compounds on developing gonads has repercussions on the effects upon the individuals and the progeny of future generations by genetic transmission. The scientific approaches to study the effects of EDs upon testis development will combine animal models and cells, human exposure and new technologies based on microarrays of DNA and bio-informatic resources. The comparative results will help our understanding of endocrine disruption mechanisms, the genetic background driving susceptibility to EDs and the use of genetic markers for testing potential EDs.

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## MENDOS

*Biomimetic optical sensors for environmental endocrine disrupter screening*

The aim of the MENDOS project is to develop new artificial receptor-based optical sensor systems. These systems will then be used to assess and screen endocrine-disrupting compounds in the environment. The combination of optical sensor technology with artificial biorecognition layers (MIP) that mimic the biofunctionality of a receptor or antibody will allow the design of enhanced monitoring schemes.

Biosensors will prove the endocrine disrupting effect of chemicals detected by the MIP sensor and link them to environmental and human health aspects by identifying and quantifying EDCs, and analyzing the effect and risk of endocrine disrupters on humans.

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## SENSPESTI

*Tissue engineering of living biosensors to evaluate risks for health by pesticides affecting the cholinergic neurotransmitter system*

The goal of SensPesti is to carry out investigations on the molecular and functional responses of living cells and developing embryos of simple organisms to cholinergic pesticides, using appropriate cell and tissue models. Neurotoxic pesticides used in Europe for agricultural and domestic purposes represent a growing threat to human and environmental health. The damage starts from gametogenesis and fertilization, as neurotoxic pesticides may act as endocrine disrupters through their action on hyphyseal and epiphyseal cholinesterase activity. The effect on vitellogenesis may affect the embryonic metabolism; the effect on sperms may cause genotoxic damage, which causes reproductive success impairment. Other aspects are during differentiation: neurogenesis, bone formation and hemopoiesis may be affected, and diseases in the adult age (such as ovarian tumours, leukaemia or behaviour disturbance). The project will design a human cell-based biosensor to detect the potential risk for human health by chronic (low-dose) exposure to neurotoxic pesticides. The results of this joint project will permit the development of test systems for biological screening of products and will provide an insight into the signal mechanisms underlying cell-to-cell communication mechanisms leading development. This is a prerequisite for establishing a causal link between exposure to anti-cholinesterase agents and the development of chronic diseases such as anomalies in embryonic development and cell differentiation, and particularly neurogenetic anomalies.

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The logo for credo features the word "credo" in a lowercase, rounded, sans-serif font. The letters "c", "r", "e", and "o" are white, while the letter "d" is a vibrant orange color.



# European Commission Strategy on Endocrine Disruptors

In response to the potential threats that endocrine disruptors pose to humans and the environment, the European Commission adopted a strategy in December 1999 to address this pressing issue. The strategy set out a number of actions that the Commission would take in this area to protect the health of EU citizens and the environment in which they live. An implementation report was published in June 2001 (COM(2001)262).

This strategy is based on three groups of action, designed for the short-, medium- and long-term:

## Short-term action

The majority of short-term activities focused on the need to gather up-to-date information about the science of endocrine disruption, the extent to which it was affecting people and wildlife, and how to identify those substances requiring further evaluation of their role in endocrine disruption. A first report was published in 2000, identifying 553 substances and grouping them according to their persistence in the environment, production volume, evidence from scientific literature suggesting that they could cause endocrine disruption and exposure considerations.

Furthermore, two additional studies are now under way with the aim of implementing this action:

- An in-depth evaluation of nine industrial chemicals which are neither restricted nor currently addressed under existing Community legislation and an analysis of three natural or synthetic hormones.
- A study providing data on the persistence, production volumes and legal status of another 435 substances, with the aim of collecting and analysing their implications for endocrine disruption or potential endocrine disruption.

The Commission's findings are publicly available via a new endocrine disrupter website:

<http://europa.eu.int/comm/environment/endocrine/>

The Commission is preparing an overview of the different initiatives on endocrine disruptors (EDs) that have been launched both by EU Member States and other countries and organisations throughout the world. The survey is due to be published in September 2003.

## Medium-term action

As part of its medium-term approach, the Commission is supporting the process of development and validation of test methods by working closely with Member States to coordinate the European Union's input on EDs for the OECD (Organisation for Economic Co-operation and Development).

In addition, under the Community Framework Programs for Research and Technological Development, the Commission

has financed a number of different projects on endocrine disruption. The Fifth Framework Programme of Research (1998-2002) includes the Quality of Life and Management of Living Resources Thematic Programme which has spent around €43 million on EDs projects and has sponsored 19 large projects. The human health issues associated with EDs are mainly funded through the key action Environment and Health. The Energy, Environment and Sustainable Development Programme (EESD) has financed 7 projects with a total budget of around €16 million touching on EDs via the key actions Sustainable Management and Quality of Water and Sustainable Marine Ecosystems. Details will be available soon at: [http://europa.eu.int/comm/research/endocrine/index\\_en.html](http://europa.eu.int/comm/research/endocrine/index_en.html)

## Long-term action

These include the review and adaptation of existing laws and legislation governing the testing, assessment and use of chemicals and substances within the EU. It is predicted that this will take four years or more to achieve.

The European Commission has taken a number of steps to ensure that EU legislation is adapted or amended to deal with the EDs problem. These include:

- Directive 1999/51/EC (adopted) relating to provisions on tributyltin (TBT).
- Proposals on the Water Framework Directive (Dir 2000/60/EC) and the Drinking Water Directive (Dir 98/83/EC) will be drafted.
- Revision of the annexes to Dir 91/414/EEC on the placing of Plant Protection Products on the market is now in progress.

On 13 February 2001, the Commission adopted a White Paper on a strategy for a future chemicals policy, known as the REACH system, for Registration, Evaluation and Authorisation of CHEMicals. One of the key elements of the proposed strategy is an authorisation procedure for substances that are of very high concern, or CMR (carcinogenic, mutagenic and toxic to reproduction) and substances with POPs (persistent organic pollutants) characteristics. The procedure would require authorities to give specific permission before such a substance could be used for any purpose, or marketed as such or as a component of a product. Given that many of the health effects associated with endocrine disrupting chemicals are CMR effects, it is likely that many endocrine disrupting chemicals will fall under this authorisation procedure.

## Dr Claudia Roncancio Pena

Health and Urban Unit, DG Environment,  
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## The new European Chemicals Policy and its implications on research into endocrine disruption

REACH is a new system of chemicals control. It is the strategic core element of a draft legislative proposal recently launched by the European Commission. Under REACH, the use of substances with endocrine disrupting potencies will become subject to authorization. However, the new system does not provide clear-cut criteria and straightforward testing strategies for identifying endocrine disruptors (EDs) amongst tens of thousands of chemicals. Helping regulators through this dilemma will be one of the most challenging tasks for CREDO projects.

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**REACH** stands for **R**egistration, **E**valuation, and **A**uthorisation of **CH**emicals.

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### Registration

Substances produced in or imported into the Community in quantities of 1 tonne per year and per manufacturer or importer are subject to registration. Registration requirements include information on substance properties and intended uses, risk characterisations derived from these data, and the description of risk management measures that ensure a chemical will be used safely.

### Evaluation

Evaluation of information provided by industry will be automatic in case of production volumes exceeding a threshold of 100 t/a and optional in the case of lower quantities. Standard evaluations will decide on additional substance tailored testing programmes so as to avoid any unnecessary animal testing.

### Authorisation

Any use of substances with intrinsic properties of very high concern, such as CMRs, PBTs, vPvBs<sup>1</sup> and endocrine disruptors, will be subject to authorisation. Authorisation will be granted if it can be shown that the risks will be adequately controlled or that they will be outweighed by the socio-economic benefits of the substance.

REACH was outlined in the European Commission's White Paper on the strategy for a future chemicals policy, published in February 2001. Now, two years later, Commission services have turned the White Paper into a 1,200-page draft legislative proposal, which is available for consultation on the Internet<sup>2</sup>. Over the next few months, it should progress to the status of a formal proposal, which will then be put forward for debate in the European Parliament and the Council of Ministers. This final phase could last another two years.

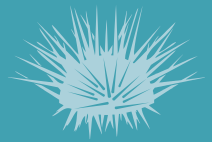
The White Paper was unveiled in the wake of extensive criticism of the current EU chemicals legislation. The key

concerns from the current rules are the different regulatory approach to the so-called 'New Chemicals'<sup>3</sup> which are subject to rigid control, while the regulation of 'Existing Chemicals' has largely failed in its protection goals. During the last ten years, risk assessments have been completed for just 41 out of more than 100,000 existing chemicals<sup>4</sup>. Closing this unacceptable knowledge gap is the prime aim of the REACH system. Under the new approach, around 30,000 existing chemicals exceeding the trigger value of 1 t/a will have to be registered. This ambitious goal is due to be achieved during a phase-in period of 11 years. Industry will take responsibility for this and will bear the costs. 'The new policy introduces a radical paradigm shift,' says European Environment Commissioner Margot Wallström. She estimates the occupational health benefits to be 'between €18 and 54 billion over a 30-year period,' corresponding 'to an ultimate yearly reduction of some 2,200 to 4,300 cancer cases...'<sup>5</sup>.

Representatives of the chemicals industry in Germany and France have countered by presenting business impact studies that predict REACH will result in the loss of hundreds of thousands of jobs and a substantial decline in Gross Domestic Product<sup>6,7</sup>. This ongoing heated debate is dominated by the ritual exchange of pre-defined lobby positions that lean on some rather speculative assumptions. Nevertheless, one thing is clear - risk assessments for tens of thousands of chemicals require advanced methods and strategies that are not only reliable, but also time- and cost-efficient. Developing such methods represents a significant scientific challenge.

One particular challenge will be to draw up more efficient methods for tracing all those substances that need to undergo REACH's authorisation procedure. For CMRs, PBTs, and vPvBs, clear-cut classification criteria have been fixed and corresponding testing or estimation methods are available. There is room for methodological improvements, but there is not major obstacle to widespread acceptance of the basic criteria. For EDs, however, such favourable conditions of regulatory risk management have not yet been given. They will be handled on a case-by-case basis. This means that an EU Member State has to initiate an agreement-finding procedure by preparing a dossier that gives a scientific demonstration of the endocrine disrupting hazard or the risk of a substance of concern. From past experience this may be a long road. Thus, effective control of EDs needs:

- Sound, workable criteria, acceptable to all, for classifying substances as EDs
- Effective strategies for identifying EDs amongst new and existing chemicals
- Cost- and time-efficient screening methods for sorting out potential EDs
- Reliable approaches to low dose and mixture risk assessments of EDs.



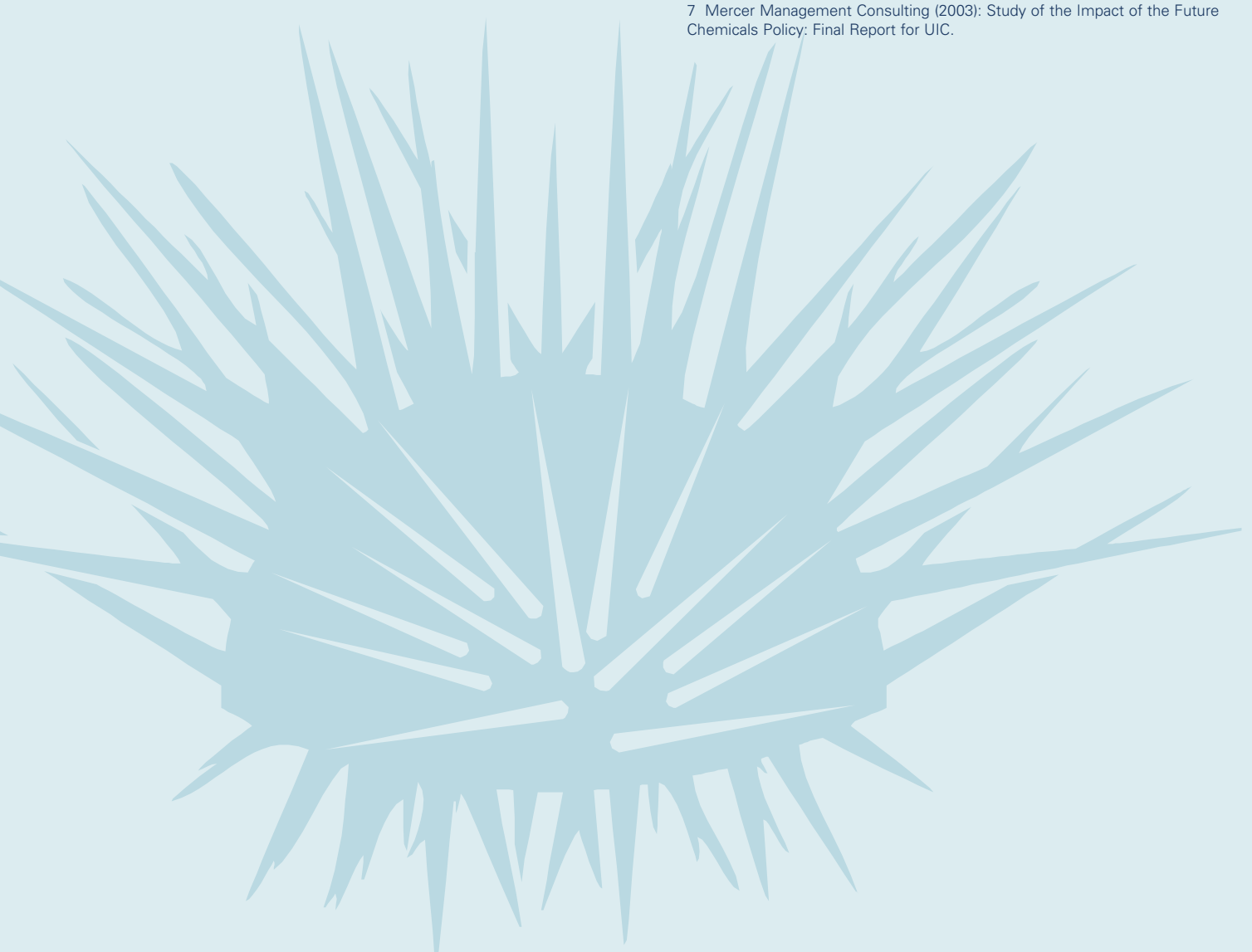
Research performed by the CREDO cluster should provide substantial input towards the fulfilment of these requirements. More specifically, EDEN will address regulatory issues in a work package on testing strategies and risk assessment procedures. This work will start at the beginning of 2005 and deliver a guidance document on regulatory options at the end of 2006.

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*Michael Faust*

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- 1 CMRs are carcinogenic, mutagenic or toxic to reproduction, PBTs are persistent and bioaccumulative and toxic, vPvBs are very persistent and very bioaccumulative.
- 2 CEC (Commission of the European Communities) (2003). Consultation Document concerning the Registration, Evaluation, Authorisation and Restrictions of Chemicals (REACH).  
<http://europa.eu.int/comm/enterprise/chemicals/chempol/whitepaper/reach.htm>
- 3 'Existing Chemicals' are all chemicals which were declared to be on the EU market on or before 18 September 1981 and listed in the EINECS (European Inventory of Existing Chemical Substances). Chemicals introduced after that date are 'New Chemicals' (about 3000 substances up to now).
- 4 Bodar, C.W.M., Berthault, F., de Bruijn, J.H.M., van Leeuwen, C.J., Pronk, M.E.J., Vermeire, T.G. (2002). Evaluation of EU Risk Assessment of Existing Chemicals (EC Regulation 793/93). RIVM (Rijksinstituut voor Volksgezondheid en Milieu) report 601504002/2002, Bilthoven, The Netherlands.
- 5 Wallström, Margot (Member of the European Commission, responsible for Environment) (2003). SPEECH/03/169, Date: 31/03/2003, 'Beyond REACH' European Voice Conference Brussels, 31 March and 1 April 2003.
- 6 ADL (Arthur D. Little) (2002): Wirtschaftliche Auswirkungen der EU-Stoffpolitik. Bericht zum BDI-Forschungsprojekt. Wiesbaden: Arthur D. Little GmbH.
- 7 Mercer Management Consulting (2003): Study of the Impact of the Future Chemicals Policy: Final Report for UIC.





## Endocrine disruption in the 6th Framework Programme of Research (FP6) (2002-2006)

Endocrine disruption has not been forgotten in the 6th Framework Programme of Research (2002-2006). The topic has been specifically addressed by Priority 5 (Food Quality and safety; <http://www.cordis.lu/food/>) and, to a lesser extent, by Priority 6 (Sustainable development, global change and ecosystems; <http://www.cordis.lu/fp6/sustdev.htm>).

# PRIORITY 5

## Priority 5 – Food Quality and Safety

In Priority 5, endocrine disruption is covered especially by the sub-area 'Environmental health risks'. ED is also covered under the sub-area 'Methods of analysis, detection and control'.

### Environmental Health Risks sub-area

The objectives of 'Environmental health risks' are to identify the environmental factors that are detrimental to health, understand the mechanisms involved and work out how to prevent or minimise these effects and risks:

- Risks linked to the food-chain (chemical, biological and physical)
- Combined exposures of authorised substances, including impact of local environmental disasters and pollution on the safety of foodstuffs, with emphasis placed on cumulative risks and health impacts of environmental pollutants, transmission routes to human beings, long-term effects and exposure to small doses, prevention strategies, as well as the impact on particularly sensitive groups, and especially children.

Research will focus on:

- Identifying causal agents including contaminants, and physiological mechanisms, of environmental, and food-linked environmental hazards;
- understanding exposure pathways, estimation of cumulative, low dose and combined exposures;
- long-term effects; definition and protection of susceptible sub-groups;
- environmental causes and mechanisms responsible for the increase in allergies;
- impact of endocrine disrupters;
- chronic chemical pollution and combined environmental exposures, transmission of illnesses linked to water (parasites, viruses, bacteria, etc)

### Methods of Analysis, Detection and Control sub-area

The objective of this sub-area is to contribute to the development, improvement, validation and harmonisation of reliable and cost-effective sampling and measurement strategies for chemical contaminants and existing or emerging pathogenic micro-organisms (such as viruses, bacteria, yeasts, fungi, parasites, and new agents of the prion type including development of ante mortem diagnostic tests for BSE and scrapie) so as to control the safety of the food and feed supply and ensure accurate data for risk analysis.

Research will focus on:

- methods and standards for analysing and detecting food-borne pathogens and chemical contaminants, including pre-normative aspects;
- modelling and approaches to improve existing prevention and control strategies; detection tests and geographical mapping of prions; transfer and longevity of prions.

## Priority 5 – Food Quality and Safety: The 2002 Work Programme

The 2002 Work Programme ([http://europa.eu.int/comm/research/endocrine/pdf/wp\\_foodandsafety.pdf](http://europa.eu.int/comm/research/endocrine/pdf/wp_foodandsafety.pdf)), which describes the topics covered by the 1st call for proposals in December 2002 for which the deadline for applications was April 15, 2003 ([http://fp6.cordis.lu/food/call\\_details.cfm?CALL\\_ID=16](http://fp6.cordis.lu/food/call_details.cfm?CALL_ID=16)), as well as indicative topics for 2004, has several topics with some relevance to endocrine disruption:

### Topics covered in 2003

#### **(T41) Human health implications of exposure to chemical residues in the environment – *Integrated project or network of excellence***

Research will focus on novel or improved analytical techniques for the measurement of inorganic and organic chemical residues, radioactive isotopes and pharmaceuticals in food, water, and the environmental sources linked to the food chain; improved assessment of health effects on humans, in particular sensitive groups. Emphasis will be placed on low dose exposure and non-linear dose response relationships. Harmonisation of the capacities in exposure research should be included in order to produce a series of validated and integrated predictive models for use in assessment frameworks for regulatory risks and for the control of chemical exposure to human.

*Result of evaluation of proposals:*  
*One Network of Excellence to be funded in 2004*

#### **(T43) Neurotoxic effects of environmental contaminants – *Specific targeted research project or coordination action***

Research will aim at developing and providing methods, procedures, and models to detect and characterise environmental factors contaminating food (e.g. persistent organic pollutants and pesticide residues) affecting neuro-endocrine control systems in humans and animals. Special emphasis will be given to neurobehavioural development and neurodegenerative disease. The focus will be on interdisciplinary research approaches engaging neurologists, endocrinologists, (eco)toxicologists, pharmacologists and other relevant specialists.

*Result of evaluation of proposals: One STREP to be funded in 2004*

#### **(T44) Effects of environmental exposure to complex chemical mixtures – *Specific targeted research project or coordination action***

Research will focus on gathering evidence of possible links between combined chemicals exposure related to the food chain and human health effects, including mechanisms, with emphasis on cancers and other chronic diseases and various vulnerable subgroups of the population. Where relevant, effect markers and diagnostic tests will be developed allowing individualised assessment of risks in humans.

*Result of evaluation of proposals: One STREP to be funded in 2004*

### **Indicative topics for 2004 (Work programme under revision)**

#### **(T21) New approaches towards monitoring and preventing chemical contaminants in food products – *Integrated project or network of excellence***

#### **(T45) Environmental factors influencing puberty onset – *Integrated project or network of excellence***

#### **(T47) Food and fecundity – *Specific targeted research project or coordination action***

# PRIORITY 6

## Priority 6 – Sustainable development, global change and ecosystems

Endocrine disruption will be covered by the sub-area 'Global change and ecosystems', and, in particular, by so-called 'complementary research'.

### Complementary research

Complementary research will focus on development of advanced methodologies for risk assessment of processes, technologies, measures and policies, appraisal of environmental quality, including reliable indicators of population health and environmental conditions and risk evaluation in relation to outdoor and indoor exposure. Relevant prenormative research on measurements and testing for these purposes will also be necessary.

### Calls for proposals

The first call, launched in 2002 ([http://fp6.cordis.lu/fp6/call\\_details.cfm?CALL\\_ID=24](http://fp6.cordis.lu/fp6/call_details.cfm?CALL_ID=24)) did not cover topics related to endocrine disruption. A second call for research proposals was launched on July 3rd 2003.

The deadline for applications will be October 9th, 2003. More info on this call can be found at [http://fp6.cordis.lu/fp6/call\\_details.cfm?CALL\\_ID=78](http://fp6.cordis.lu/fp6/call_details.cfm?CALL_ID=78)

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### Two topics have relevance to the ED Community:

#### Topic for up to one Network of Excellence or Integrated Project (IP preferred) to be implemented in 2004

VII.1.1.a) Development of risk assessment methodologies, particularly those requiring conceptual changes and/or developments, such as realistic exposure prediction and assessment tools, and assessments the effects of combined exposures to several stressors including mixtures of chemical and physical/biological agents. The aim is to develop methodologies for assessing the risk of substances and molecules designed for provoking specific interactions with biological structures (e.g. pesticides, biocides, pharmaceuticals). The project shall cover direct exposure routes e.g. water and air (excluding food) and provide efficient risk analysis to protect environmental and human health. The approach should include the development of methodologies for assessing the risk of exposure to chemicals in products.

#### Topic for STREPs and Co-ordination Actions to be implemented in 2004

VII.1.1.b) Methods for risk assessment of pharmaceuticals in the environment. The aim is to advance the scientific knowledge and practice for evaluation of the risks associated with the presence of pharmaceuticals in the environment. This approach should focus particularly on the improvement of data on exposure and effect assessment, and where appropriate, improved assessment tools, and cover different exposure routes e.g. water and soils. The action should stimulate co-ordination and collaboration for information exchange among stakeholders, public authorities, industry and expertise in the fields of exposure assessment, human health and ecological effect assessment. The project should provide science-based contributions to the assessment and development of the European Risk Assessment Schemes for both human and veterinary pharmaceuticals. The participation of SMEs is encouraged.

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## The first cluster meeting April 2003

### A short report

Over 120 delegates attended the first CREDO cluster meeting held at the School of Pharmacy, University of London, in April with the aim of fostering information exchange across project boundaries. The meeting provided an opportunity for the delegates to interact and to think collectively about issues which cut across cluster project areas.

Dr Andreas Kortenkamp (CREDO and EDEN coordinator) introduced CREDO and its aims, while Dr Tuomo Karjalainen (European Commission) presented an overview of EU projects on endocrine disruption. Presentations by the four core cluster projects were followed by talks on low-dose effects, no-observed-effect-levels and the issue of biological variability.

Four parallel thematic sessions stimulated interdisciplinary discussion with the emphasis on exchange of know-how, decision-making and joint ventures across projects. The session on Exposure Assessment, for example, considered interlaboratory studies of organohalogenes and quality assurance / quality control for the validation of analytical methods, aquatic food web modelling and bioassay-directed fractionations.

The session entitled 'Genomics and proteomics – what can it tell us?', focused on the state of the technologies applied in this area and their possible applications to endocrine disruption. Clear areas of exchange were identified for tissues and technologies and a European network for genomics (transcriptomics) in zebrafish was initiated.

In the third session, participants grappled with the question of 'What is low dose?' with talks on low doses and no-observed-effect-levels from a statistical perspective, the issue of experimental reproducibility and the benchmark dose method. Finally, the endpoints and experimental models session included talks on multigeneration studies, a model for testicular dysgenesis syndrome, multiorganic risk assessment and relevant endpoints for endocrine disrupters and their comparability across species.

Presentations, slides and documentation of the cluster meeting are available on-line to cluster participants via the CREDO discussion forum (see back page).

## CREDO workshop July 2004

### Ecological relevance of chemically induced endocrine disruption in wildlife

Although a growing number of toxicological endpoints for effects of endocrine active substances in wildlife species has been identified (eg. induction of vitellogenin or other yolk-precursor proteins in males, shifts of sex ratios) their ecological relevance is not yet fully understood. The cluster workshop Ecological Relevance of Chemically Induced Endocrine Disruption in Wildlife organised by the COMPRENDO consortium, 5th to 7th July 2004, at the University of Exeter, Exeter, UK, will therefore be of central importance for the interpretation of findings in laboratory and field studies.

Whereas human toxicology studies deal with the protection of the individual, the protection target for ecotoxicology is not the single specimen, but the population as a whole. In contrast to this general assumption, the majority of ecotoxicological studies assess endocrine disruption on the organismic or even the suborganismic level (so-called biomarkers) so that the implications for populations and higher levels of biological integration (eg. biocenosis) are mostly unknown.

The central objectives of the workshop are to:

- review the current inventory of endpoints which are used in biological effect monitoring studies and laboratory toxicity testing for endocrine disrupting chemicals and to identify appropriate endpoints for the assessment of population-level effects.
- provide guidance and to suggest appropriate methods for the toxicity assessment of endocrine disrupters in complex mixtures because mostly endocrine disrupting chemicals are present as mixtures in the environment.
- review methods for risk assessment for endocrine disrupters and to identify future requirements for risk assessment strategies considering the precautionary principle.

The workshop is intended to be of interest to CREDO cluster members, industry, governmental and non-governmental organisations. Detailed information on the programme will follow soon and will be available at [www.comprendo-project.org](http://www.comprendo-project.org) and [www.credocluster.info](http://www.credocluster.info)

## CREDO cluster scientific workshops programme

The CREDO cluster will be holding scientific workshops on specific topics to promote the transfer of know-how between scientists, policymakers and network members. The workshops will be open to scientists who are not members of any of the cluster projects. Updates will be posted on the CREDO website at [www.credocluster.info](http://www.credocluster.info)

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Workshop on wildlife effects: Ecological Relevance of Chemically Induced Endocrine Disruption in Wildlife organised by the COMPREDO consortium: 5-7 July 2004, University of Exeter, Exeter, UK

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Workshop on risk assessment organised by the EURISKED consortium: Spring 2004, location to be confirmed.

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Workshop on mixtures/low dose effects organised by the EDEN consortium: April 2005, Prague, Czech Republic.

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Workshop on exposure assessment organised by the FIRE consortium: April 2005, Prague, Czech Republic.

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## The CREDO Internet discussion forum

The CREDO Internet bulletin board has been established as a discussion forum to exchange information and ideas. Announcements and discussion areas are available within a public domain section. The forum also contains a CREDO 'members only' section open for scientific discussion, to advertise assays, exchange samples or experimental plans etc.

The 'members only' section is open to all CREDO cluster project participants and affiliates, and registration is quick and easy. Presentation slides from CREDO meetings and information is available to CREDO members as downloadable files in the documentation area.

The bulletin board is accessible from the CREDO web site at <http://www.credocluster.info/forum/>

## New website on EU funded ED projects

The European Commission's Director General of Research has prepared a website called 'Endocrine Disrupter Research in the European Union': [http://europa.eu.int/comm/research/endocrine/index\\_en.html](http://europa.eu.int/comm/research/endocrine/index_en.html)

It has the following sections:

- Background information
- EU activities (Strategy, activities by Research and Environment DGs, extensive links to various European and international organisations involved in ED research and policies)
- EU funded research projects (ED in the 4th, 5th and 6th frameworks, information on upcoming calls for proposals, completed and ongoing projects, downloadable summaries or progress reports)

More information from Dr Tuomo Karjalainen: [Tuomo.Karjalainen@cec.eu.int](mailto:Tuomo.Karjalainen@cec.eu.int)

## CREDO coordination

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The logo for CREDO, with the word 'credo' in a lowercase, rounded font. The letter 'o' is significantly larger and colored orange, while the other letters are white.

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