



The end of ACE

The start of more realistic risk assessment?

Just as the scientific world is coming to terms with the reality of the endocrine disruption phenomenon, so too are the regulatory bodies recognizing the importance of defining environmentally acceptable limits of endocrine disrupting chemicals in terms of mixtures, as opposed to individual compounds. However, until now, very little has been accomplished in terms of characterizing the activity of multi-component mixtures of endocrine disrupting compounds. The ACE project was formulated in order to take the first steps in filling this gap in the knowledge base. Accordingly, the primary objective of ACE was to contribute to the hazard assessment of EDCs in the aquatic environment, which was to be achieved by 1) analysing multi-component mixture effects of estrogenic chemicals on biological systems (from subcellular assays to populations of fish), and 2) assessing estrogenic mixture effects at low concentrations. These tasks were successfully fulfilled when the ACE project was concluded in June 2005.



Figure 1: Sea bass (*Dicentrarchus labrax*)

A multitude of more specific tasks were undertaken to meet these broad aims, some of which have already been reported in issue 3 of the CREDO newsletter (*Brian, July 2004*). The data in the aforementioned article essentially demonstrated for the first time that multi-component mixtures of different classes of (xeno-)estrogens can be seen to act according to the principles of Concentration Addition (CA) *in vivo*, in a freshwater fish species, the fathead minnow. Subsequent studies with a marine fish species (sea bass; figure 1) have reinforced these findings (figure 2, overleaf), confirming that the CA concept is transferable across species. Although the *in vivo* studies did not involve mixtures of more than 5 chemicals (due to the practical difficulties associated with conducting such experiments), mixtures of up to 19 chemicals were tested in a suite of four *in vitro*

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GENDisrupt reports

In vitro models for detection of genomic effects by endocrine disruptors on germ cells and somatic cells of the developing testis

One of the main aims of the project "Genetic markers and susceptibility to the effects of endocrine disruptors during mammalian testis development" (GENDisrupt) coordinated by Dr Jesus del Mazo (CSIC, Madrid), is to identify genes which could be representative of the action of endocrine disruptors (EDs) over different cell types in the developing mammalian testis. These genetic markers will then be prepared in DNA microarrays. Our purpose within the project is to investigate whether suitable *in vitro* models can be established to identify possible genomic action of selected EDs on specific cell types of the early developing mouse testis.

In animal models, anomalies of the male reproductive system have been associated with exposure *in utero* to estrogenic compounds. During the last decade, there has been an increase in the occurrence in humans of a panel of male reproductive pathologies, such as cryptorchidism, hypospadias and testicular cancers. Environmental estrogenic compounds have been pointed out as one of the factors involved in these pathologies.

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The end of ACE

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assays. These covered various levels of biological complexity, namely binding to the estrogen receptor (HRS), estrogen receptor activation (Yeast Estrogen Screen and ER-CALUX), and stimulation of estrogen-dependent growth (E-SCREEN). It was observed that CA could be used to predict mixture effects in each of these assays, and that this predictability applied to a range of different mixtures, as well as a range of mixture ratios and all effects levels. Although the mixtures used in these studies are somewhat artificial, and cannot be classified as strictly representative of the real world (in that they contained only estrogenic chemicals), these results undoubtedly take us significantly closer towards predicting real-world effects than the current individual chemical-based regulations do.

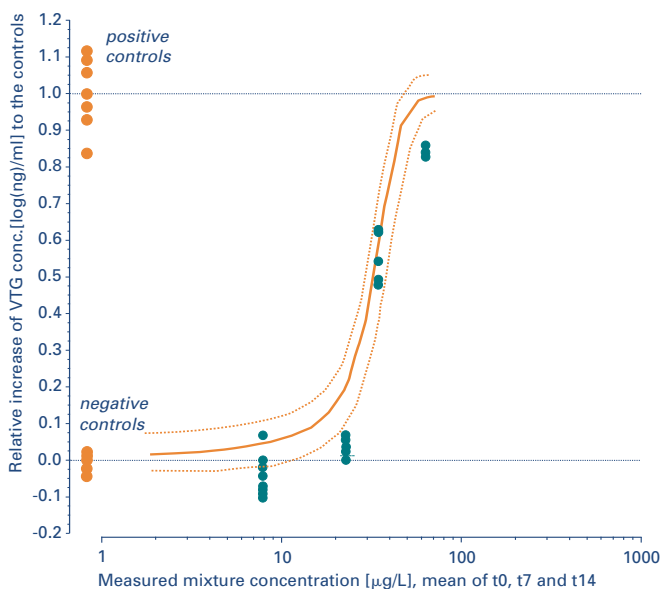


Figure 2: VTG response in juvenile sea bass after a 14-day exposure to a fixed-ratio mixture of ethynylestradiol (EE2), 17 β -estradiol (E2), bisphenol-A (BPA), nonylphenol (NP) and octylphenol (OP). Black dots show the actual responses of the fish, which are in good agreement with the prediction by CA (shown by the red line).

In addition, the theory that a mixture of estrogenic chemicals, each of which is present at extremely low-effect concentrations, can induce a significant response, was tested *in vivo* (figure 3, above right). This confirmed that the “Something from Nothing” phenomenon exists in higher biological systems, and adds strength to the previous *in vitro* data reported on this subject (Silva *et al*, 2002). The significance of these findings for environmental risk assessment cannot be overstated; it is now clear that very low concentrations of estrogenic chemicals, which appear to have little or no effect on their own, are nonetheless biologically active, and, when combined with other estrogen mimics, can exert genuine and measurable effects.

While the majority of work in ACE focused solely on the activity of combinations of estrogenic chemicals, some attention was also afforded to more complex mixtures.

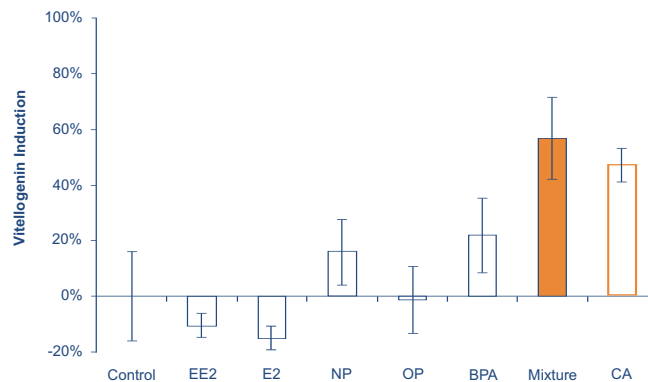


Figure 3: Mixture effects on VTG response of fathead minnows, at low dose concentrations of five estrogenic chemicals. Low doses were based on the EC50 of each chemical divided by five. This was 0.12 and 5 ng/l for EE2 and E2 and 1.4, 9 and 30 μ g/l for NP, OP and BPA, respectively. The response of fish exposed to individual chemicals did not differ significantly from those of the controls, whereas the response to the mixture was marked, being approximately halfway up the concentration response curve. The observed effect of the mixture was consistent with the principles of CA. (Brian *et al.*, 2005).

Specifically, the effect of the presence of non-estrogenic toxicants on the predictability of estrogenic mixture effects *in vitro* was investigated. Perhaps not surprisingly, these confounding chemicals were found to markedly impair predictability of estrogenic mixture effects. Interestingly, however, it was also observed that if these chemicals were accounted for in the assessment of single substance estrogenic activity (which was subsequently used in the model for prediction of combination effects), the predictive capability was restored.

Large amounts of data were generated during ACE, much of which has already been disseminated in peer-reviewed articles, as well as at international conferences. However, work is still ongoing to utilise this extensive database to best effect, specifically with regards to the analysis of concordance between different assays, both within the *in vitro* and *in vivo* sets of data, as well as *in vitro* versus *in vivo*, in the prediction of estrogenic mixture effects. These comparisons will help to clarify to what extent rapid, inexpensive *in vitro* assays can reliably predict estrogenic mixture effects *in vivo*, and hence address the feasibility of replacing costly *in vivo* tests with cheaper *in vitro* alternatives.

Although there is some way to go still in addressing toxicity of more complex mixtures, such as those comprising other types of endocrine disruptors, or indeed, non-endocrine-active chemicals which are nonetheless prolific in the environment, ACE has certainly contributed to the database available to regulatory bodies in their quest for appropriate levels of environmental controls. Feedback from such authorities to date indicates that they welcome this input, and we anticipate seeing a real and positive outcome, in terms of environmental protection, from this project.

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GENDisrupt reports

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The role of estrogen receptors

Development of the male requires activation of specific pathways during embryonic life. This involves the action of hormones, notably androgens and anti-Müllerian hormone. Besides androgens, estrogens which have been known for a long time to be involved in the development of the female reproductive tract, are now believed to be critical also for the development of male reproductive organs. Indeed, studies have shown that exposure to estrogens disturbs the differentiation and/or proliferation of Leydig cells and Sertoli cells (two main somatic cell populations of testis) directly or via perturbation of the hypothalamic-pituitary axis. Some reports have also raised the possibility that testicular gonocytes might be directly affected by estrogens.

During embryo-fetal development, estrogens, estrogen receptors (ERs) and estrogen-inducible transcription machinery are required to affect differentiating tissues. Since no clear information was available, we first aimed to establish whether and which estrogen receptors are expressed by cells of the early developing mouse testis. In the mouse embryo, male and female gonads at embryonic day 11 (E11) are morphologically identical (indifferent gonads) and are formed by the primordial germ cells (PGCs) and the coelomic epithelium. By E13 the testis is twice the size of the ovary and exhibits testicular cords formed by Sertoli cells and prospermatogonia (also called gonocytes, derived from PGCs) (see figure 1). Testicular cords are separated by interstitial cells, including endothelial, Leydig and myoid cells.



Figure 1: Developing mouse testis at embryonic day 11 (top) and day 13 (bottom).

Using RT-PCR and Western blotting, we found that E11-13 male gonadal somatic cells express ER α but not ER β , whereas PGCs do not express either receptors. Moreover, transfection of somatic cells with a reporter of estrogen receptor transcriptional activity (ERE-luciferase) resulted in a significant 2 to 3-fold increase of the reporter activity following 24 hr incubation in the presence of 10 nM 17- β -estradiol (E2) or 10 μ M lindane (one of the selected EDs used in the project) (see figure 2).

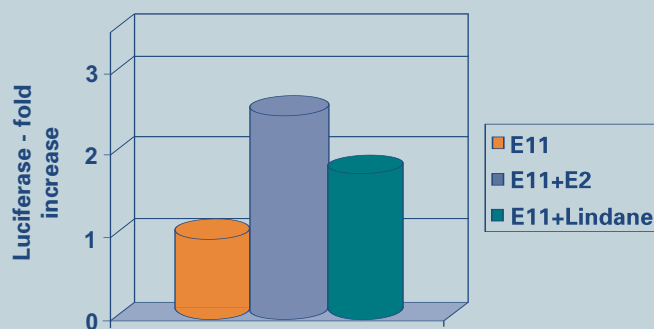


Figure 2: Increase in estrogen receptor transcriptional activity induced in transfected testis somatic cells from embryonic day 11 by E2 and Lindane.

Besides supporting the notion that at a very early stage of differentiation estrogenic pathways can be activated in mammalian testis, this *in vitro* test can be employed to evaluate estrogenicity of test compounds.

Estrogenic chemicals might have diverse effects on testis cell populations. Indeed our *in vitro* results indicate that such compounds, depending on type and concentration, can stimulate or inhibit the proliferation of somatic cells and PGCs or induce apoptosis, making cell cycle controlling and apoptotic genes as likely targets for ED action. In this regard, we found an unexpected effect of E2 and zeralenone (ZEA, another ED used in the project) on PGC proliferation and differentiation. Despite the fact PGCs do not express ERs, when cocultured onto their own somatic cells in the presence of relatively high concentrations of one of these compounds (100 nM E2 and 10 μ M ZEA), they showed increased proliferation. We were able to attribute such effect to increased production of the cytokine Kit Ligand (or SCF) from the estrogen-stimulated gonadal somatic cells. This estrogen action associated with that of other cytokines (i.e. Leukemia Inhibitory Factor, LIF) and with reduced expression of the tumor suppressor gene *Pten* in PGCs, also increased the frequency of PGC transformation in tumorigenic cells in culture. These results give support to the hypothesis that under certain conditions, exposure of the embryo to high levels of estrogens or EDs might disturb normal testis development and favours the development of germ cell tumors from PGCs after birth.

The information briefly summarized here and samples of gonadal cells and PGCs treated *in vitro* with selected EDs are now being employed across the GENDisrupt consortium in the effort to define expression profiling of estrogen and ED-responsive genes in development of the mammalian testis.

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Brominated flame retardants in environmentally relevant test setup

No major endocrine effects found in fish

A major aim of the FIRE project (Flame retardants Integrated Risk assessment for Endocrine effects) is the toxicological characterization of environmentally relevant brominated flame retardants. In this context, we conducted long-term exposure studies using the estuarine flounder (*Platichthys flesus*), an indicator species commonly used in monitoring programs.

Flame retardants were selected for prolonged testing in an environmentally relevant set-up (figure 1) based on large production volume and abundance in the aquatic environment, and the outcome of the *in vitro* hazard identification within the FIRE project (see CREDO newsletter, issue 4). Three studies where flounders were exposed for 3 months to hexabromocyclododecan (HBCD), tetrabromobisphenol-A (TBBPA), and for 1 month to 2,4,6-tribromophenol (2,4,6-TBP), have now been completed including analysis of CYP1A (measured by EROD) and CYP 19 (aromatase, responsible for estrogen synthesis) activities, and levels of thyroid hormones and the estrogen responsive yolk precursor protein vitellogenin (VTG) in plasma. All animals were examined histologically with emphasis on tissues of major endocrine importance (liver, kidney, gonads, thyroid). Chemical analysis was performed on individual muscle samples from all fish for exposure assessment.

Key results

As a relatively water-soluble member of the brominated flame retardant family, TBBPA was administered dissolved in the water via continuous flow-through. Chemical analysis of fish and water samples showed that exposure did not fluctuate and was linear with the nominal range of 0 to 0.8 μM . Levels in fish (based on wet weight) at the end of the study were between 5 to 10 times the actual water concentrations, with an average of 545 ng/g muscle in the top dose. Even at these relatively high levels (TBBPA was reported in estuarine fish to a maximum of 14 ng/g wet weight), general health and toxicity parameters (behavior, survival, growth rate, and relative liver and gonad weight) were not affected. EROD activity in liver did not relate to TBBPA exposure; CYP 19_{arom}, however, showed a mild increase in male gonads (maximum value 9 times the median; figure 2), but did not alter estrogen dependent vitellogenin (VTG) concentrations in plasma. In addition, there was no histological evidence (such as hepatocellular morphology and staining properties) for estrogenic effects. Levels of unbound thyroid hormone (T4) in plasma increased linearly with internal TBBPA concentration, which was possibly caused by competition of TBBPA for plasma protein binding, in line with the strong transthyretin binding found in the pre-screening studies; however, T3 levels were not affected (figure 3) and histology showed no signs of altered thyroid gland activity.

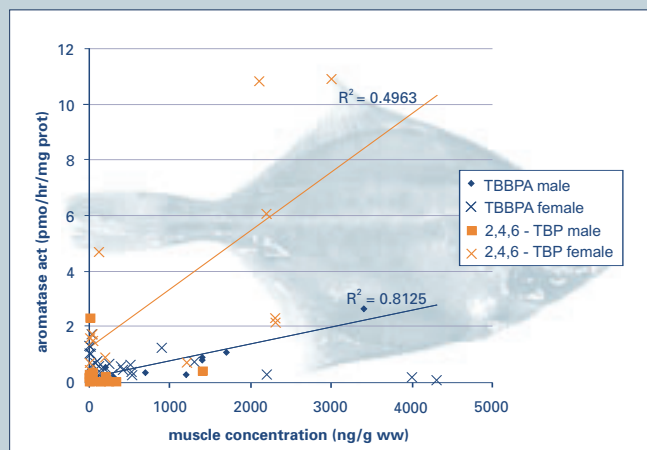


Figure 2: Gonadal aromatase activity in flounder exposed to TBBPA and 2,4,6-TBP.

The more hydrophobic HBCD was administered via spiked sediment and food with a dose range from 0 (background) to 1×10^8 ng/g TOC/lipid, respectively. Σ HBCD levels in this study exceeded reported environmental levels that were usually below the detection limit; the maximum γ -HBCD was 400 times the highest value reported for estuarine fish. General parameters including behavior were unaffected. Histology did not show dose related changes in liver, kidney, thyroid and gonads. Enzyme activities (EROD, PROD, CYP19_{arom}) were unaltered.

2,4,6-TBP was administered via the water in continuous flow through. 2,4,6-TBP concentrations in fish were linear with dose and reached a maximum of 400 times the background level (7.53 ng/g wet weight group average). Growth rates were unaffected, but a slight decrease in relative liver weight was observed with increasing 2,4,6-TBP levels in muscle. EROD activity was unchanged in exposed animals; CYP 19_{arom} activity in female gonads increased linearly with internal 2,4,6-TBP concentrations up to a maximum of 6 times the median (figure 2). Histology gave no indications for the decrease in relative liver weight, nor were signs of

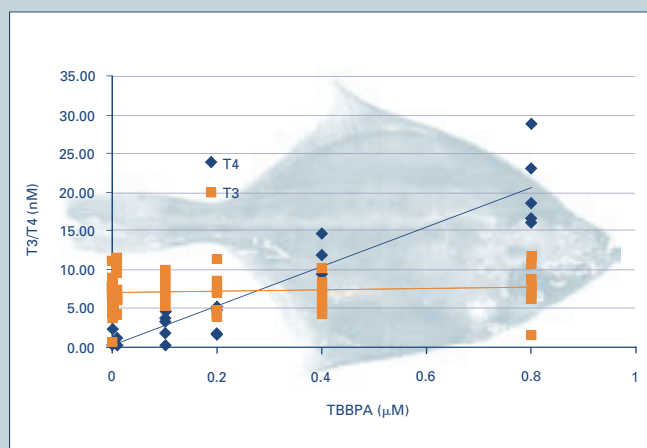


Figure 3: Plasma thyroid hormone concentrations in flounder exposed to TBBPA.

estrogenic effects observed that could be related to the increased aromatase activity. Treatment related effects on renal and thyroid histology were not observed.

The dose-response data from our flounder studies together with data from other FIRE partners will contribute to the integrated risk assessment of BFRs currently under way.

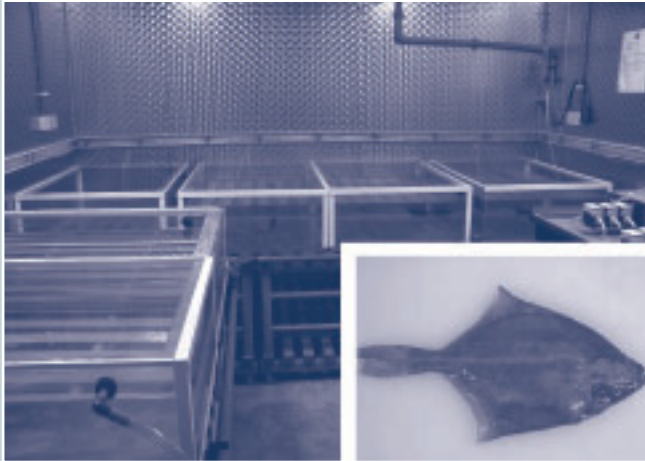


Figure 1: Test system: continuous flow-through with salt water in an air-conditioned room; sediment is added before introduction of animals.

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COMPREDO project final workshop

17 March 2006, Frankfurt, Germany



The COMPREDO consortium for Comparative Research on Endocrine Disrupters is organizing a final project workshop to be held at the Johann Wolfgang Goethe University, Frankfurt, Germany on 17 March 2006. The workshop is devoted to dissemination of the COMPREDO project's research results and will be open to the public.

COMPREDO Research

COMPREDO is funded by the European Commission under the Fifth Framework Programme for research, technological development and demonstration activities and is one of the core projects of the CREDO cluster. The COMPREDO research programme has a strong focus on the evaluation of exposure to, and endocrine-mediated effects of, androgen and anti-androgen mimicking substances (AACs) throughout the animal kingdom, including man. COMPREDO represents a phylogenetic approach, allowing for the exploration of common principles of AAC action across taxa. The project aims to identify new test species and toxicological endpoints to ensure the protection of organisms in the aquatic ecosystems and of human health.

Meeting Objectives

Although biological science is well respected by the public there is a large gap in communicating information, which scientists are trying to address. The COMPREDO consortium therefore intends to inform European citizens about the outcome of its research, scientific innovations and discoveries. With this final project workshop we aim to deliver insight into our work and to improve the means of communication to the public. We will identify the key messages gathered during the project's life time, take up further reflections and basic questions and define implications that can be derived from our research findings. We wish to emphasise that we will aim to reach a wider audience. Therefore the workshop will be open to the public. Stakeholders, including scientists from governmental and non-governmental organizations as well as industry, politicians, journalists, students and interested citizens are all most welcome.

Registration

For registration and further information, please visit the COMPREDO homepage at www.comprendo-project.org. Registration deadline is 15 February 2006.

EDEN and FIRE workshops report

The CREDO workshops on *Exposure assessment, epidemiology, low-dose and mixture effects* took place May 10 to 12, 2005 at Masarykova kolej in Prague, Czech Republic. This event combined the last two workshops in a series of four CREDO workshops aimed at disseminating research results and stimulating debate between researchers in the field of endocrine disruption. The EDEN and FIRE research consortia cooperated to jointly organise and integrate the last two workshops with the aim of broadening dissemination of research, cross-fertilising scientific debate and reducing travel for participants. This cooperation led to a very stimulating and interesting meeting which was attended by more than 170 scientists from academia, industry, government agencies and other stakeholder organisations.

Seven sessions and 38 platform presentations covered topics from male reproductive health to human and wildlife exposure to endocrine disruptors, novel models, endpoints and biomarkers, low-dose and mixture effects as well as options for regulating endocrine disruptors. In addition, a total of 69 scientific posters were presented. The organising committee wish to thank all those who participated and in particular all those who presented their research at the workshop.

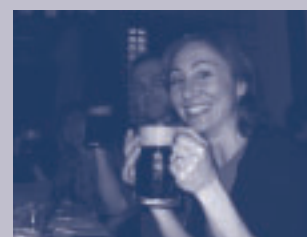
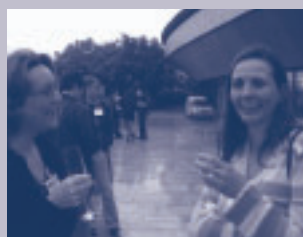
Papers from this workshop will form a special issue to be published in Environmental Health Perspectives (EHP). Publication of this special issue is expected towards the end of 2006.

Ragnor Pedersen

University of London School of Pharmacy, UK

Prague Workshop Sessions

- Male reproductive health in Europe
- Human exposure to endocrine disruptors
- Endocrine disruptors in wildlife and the environment
- Novel models, endpoints and biomarkers
- Low-dose effects of endocrine disruptors
- Mixture effects of endocrine disruptors and their assessment
- Options for regulating endocrine disruptors, knowledge gaps and research recommendations



Scientists call on the EU to take action on endocrine disruption

More than 200 scientists have highlighted the need for the EU to take action on chemicals that interfere with the hormone systems of animals and which may harm the development of unborn baby boys. They are concerned about the rise in reproductive disorders in boys and young men, increases in testis and breast cancer, and harmful impacts on wildlife. "We have identified an extremely disturbing trend that shows a substantial rise in genital disorders in boys and young men in Europe," said Professor Niels E. Skakkebaek M.D, who coordinates EDEN's research into human male reproductive health. "Lifestyle, diet, and environmental contamination all play a role in these disorders. We need to make absolutely sure that research is constantly updated in this area."

Many of the research findings presented at the CREDO scientific workshop in May 2005 in Prague raised concerns about the risks to human and wildlife health posed by endocrine disrupting chemicals. Professor Dr Jörg Oehlmann is coordinating research into wildlife effects produced by endocrine disruptors, as part of the COMPRENDO project into comparative research on endocrine disruptors. "The severity of the endocrine disrupting effects we have observed in wildlife as a direct consequence of exposure to certain chemicals is a cause for concern amongst scientists around the world. We should remember that, while wildlife represents a protection target in its own right, it also provides early warnings of effects produced by endocrine disruptors which may as yet be unobserved in humans."

In the light of these and other research results, scientists have agreed upon a position statement – the Prague declaration on endocrine disruption – which sets out the latest research results in the area, as well as highlighting the inadequacies of existing EU regulations for dealing with endocrine disruptors. Unveiled in June 2005 at a press conference in Brussels, the Prague declaration is intended to update European citizens, policy makers and regulators on research progress in the field of endocrine disruption. Much of this research emanated from the large projects funded by the European Commission and joined together in CREDO.

Although not limited to CREDO projects, the scientists who signed the declaration are all actively engaged in this area of research. They recommend that, in view of the magnitude of the potential risks associated with endocrine disruptors, scientific uncertainty should not delay precautionary action on reducing the exposures to and the risks from endocrine disruptors. Furthermore, they state that meeting the challenges posed by endocrine disruptors will require a long-term commitment to monitoring and research which is dedicated to characterising human and wildlife exposure and their mechanisms of action and interaction. It is envisioned that this will help ensure better protection of the health of European citizens and the environment.

Ragnor Pedersen

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Summary of the Prague declaration

- There is serious concern about the high prevalence of reproductive disorders in European boys and young men and about the rise in cancers of reproductive organs, such as breast and testis. Lifestyle, diet and environmental contamination play a role in the observed regional differences of these disorders and their changes with time.
- Hormone action is important in the origin or progression of the aforementioned disorders. Therefore it is plausible that exposure to endocrine disruptors may be involved, but there are inherent difficulties in establishing such causal links in humans.
- There is a serious gap of knowledge regarding the effects of endocrine disruptive compounds on other serious human diseases such as obesity, neuronal disorders, stress etc.
- Causality is well established for detrimental effects in wildlife as a direct consequence of exposure to endocrine disruptors. In some instances the severity of effects is likely to lead to population level impacts. Wildlife provides early warnings of effects produced by endocrine disruptors which may as yet be unobserved in humans.
- Wildlife represents a protection target in its own right. The severity of endocrine disrupting effects observed in the laboratory indicates that these substances may pose a threat for wildlife biodiversity as already shown for organotin compounds and marine snails.
- Europeans are exposed to low levels of a large number of endocrine disruptors which can act in concert. Many of these chemicals, drugs or natural products are found in human tissues and in breast milk. Humans are exposed to these chemicals from very early on in their lives when the developing organism can be particularly sensitive.
- The existing safety assessment framework for chemicals is ill-equipped to deal with endocrine disruptors. Testing does not account for the effects of simultaneous exposure to many chemicals and may lead to serious underestimations of risk.
- The current safety testing guidelines are based on reproductive effects, and thus do not take into account the deleterious effects of endocrine disruptors in other tissues. New test systems need to be developed to solve this shortcoming.
- In view of the magnitude of the potential risks associated with endocrine disruptors, we strongly believe that scientific uncertainty should not delay precautionary action on reducing the exposures to and the risks from endocrine disruptors.
- The challenges posed by endocrine disruptors require a long-term commitment to monitoring and research which is dedicated to characterising human and wildlife exposure and their mechanisms of action and interaction. This will help ensure better protection of the health of European citizens and the environment.

The full text of the Prague declaration and the list of signatories are available at <http://www.edenresearch.info/declaration.html>. If you are a scientist actively engaged in this area of research and would like to add your name to the declaration, please email Andreas Kortenkamp (andreas.kortenkamp@ulsop.ac.uk) giving your name and affiliation.

CREDO scientific workshops

ENDOMET symposium on the effects of plasticisers on endocrine metabolism

March 3, 2006, Birmingham, UK

For more information see <http://endomet.bham.ac.uk/>

COMPRENDO project final workshop

March 17, 2006, Frankfurt, Germany

For more information see page 5.

Weybridge +10 workshop

November 8-10, 2006, Helsinki, Finland

Ten years on from the 1996 European Workshop on the Impact of Endocrine Disrupters on Human Health and Wildlife (so called Weybridge meeting), a limited number of participants will be invited to attend an ensuing Weybridge +10 workshop. Participants of this expert workshop will review progress made in the ten years since the Weybridge meeting and produce a report on the current knowledge of endocrine disrupting chemicals as well as the limitations to such knowledge. The Weybridge +10 workshop is organised by the Academy of Finland and sponsored by, amongst others, the EU, the European Environment Agency, German Ministry of Environment (UBA), Finnish Ministry of Welfare and Social Affairs, Finnish Ministry of Education and the Finnish Environment Agency. More information will be published in the CREDO newsletter.

Tests and assays for regulatory purposes

Endocrine disrupter testing workshop presentations available online

The workshop on "Endocrine Disrupter Testing and Assays in Commission-sponsored Research Projects: Useful for Regulatory Purposes?" organised by the European Commission's Research Directorate-General Directorate E (Biotechnology, Agriculture and Food) and Directorate I (Environment) took place on November 14 and 15, 2005 at the Centre Borschette in Brussels. Representatives of projects within CREDO presented summaries of their projects' research with regard to regulation and testing, the development of assays and non-animal testing. The presentations are available from European Commission's Directorate-General of Research endocrine disrupter website at http://europa.eu.int/comm/research/endocrine/index_en.html.

PCDD/F and PCB exposure and body burden

Evaluating intake, adipose and breast milk concentrations in Finland



Polychlorinated dibenzo-*p*-dioxins, dibenzofurans (PCDD/Fs) and polychlorinated biphenyls (PCBs) are widespread environmental contaminants associated with mineralisation defects in teeth and suspected of causing neurobehavioral effects, as well as functioning as endocrine disrupters. A new PhD thesis by EDEN researcher Hannu Kiviranta has evaluated the human intake of PCDD/Fs and PCBs in Finland, measured adipose tissue concentrations in the general population and surveyed breast milk samples. Comparisons of contaminants over geographical

areas and changes with time are contrasted with corresponding results from Europe or around the world. The thesis titled *Exposure and Human PCDD/F and PCB Body Burden in Finland* is published by the Finnish National Public Health Institute and available from http://www.ktl.fi/attachments/suomi/julkaisut/julkaisusarja_a/2005/2005a14.pdf or through the EDEN website at <http://www.edenresearch.info/resources.html>.

Erratum. In the previous newsletter article *Male reproductive health in the focus of EDEN* (Jorma Toppari, CREDO Newsletter Issue 4, May 2005, Page 5), it was erroneously reported that the incidence of cryptorchidism at birth is four fold higher in Finland than in Denmark. That was wrong and it should have been *vice versa*. The author and the editors apologise for this error and trust that readers will understand that this was a mistake.

Participating projects

COMPRENDO

Coordinator: Dr Ulrike Schulte-Oehlmann
www.comprendo-project.org

EDEN

Coordinator: Dr Andreas Kortenkamp
www.edenresearch.info

EURISKED

Coordinator: Prof. Wolfgang Wuttke
www.eurisked.org

FIRE

Coordinator: Prof. Joseph Vos
www.rivm.nl/fire

Associated projects

ACE	ENDOMET
BONETOX	GENDISRUPT
EASYRING	MENDOS
EDERA	SENSPESTI

See www.credocluster.info

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A joint project funded by two thematic programmes: Quality of Life and Management of Living Resources Programme, and Energy, Environment and Sustainable Development Programme.