Session 1 Overseas Initiatives

European Community Initiatives in Drafting Policies and Supporting Research in the Endocrine Disrupter Field

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This presentation informs about the European Commission's policies pertaining to endocrine disruption (ED) and initiatives by the European Commission supporting research activities into ED.

In 1999 the European Commission adopted a Communication on a Community Strategy for ED [COM (1999) 706] and in 2001 the European Commission published a follow-up Communication on the implementation of the Community Strategy for ED [COM (2001) 262]. The strategy establishes the need for further research, international cooperation, communication to the public and policy action. Short-term actions focus on the need to establish a priority list of substances for further evaluation of their role in ED and for information exchange and international cooperation. Medium-term actions call for the identification and assessment of endocrine disrupting chemicals including research and development. Long-term activities involve legislative action.

The response of Research Directorate-General of the Commission to EU policies related to ED has been an increased investment in research. In the 4th Framework Programme for Research and Technological Development (1994-1998) over 12M€ was spent on 18 ED projects. The main areas covered were: development of test methods, monitoring of ED chemicals in the environment, ecological effects and human exposure and health effects. The 5th Framework (1998-2002) awarded over 60M€ to ED projects under the Quality of Life and Management of Living Resources (QoL) and Energy, Environment and Sustainable Development (EESD) programmes, including the Cluster of Research into Endocrine Disruption in Europe (CREDO).

In the 6th Framework (2003-2006) ED is specifically addressed in the thematic area Priority 5 (Food Quality and Safety) by the sub-areas 'Environmental health risks' and 'Methods of analysis, detection and control'. The Priority 5 2002 work programme includes topic 41: 'Human health implications of exposure to chemical residues in the environment' resulting in a Network of Excellence (CASCADE) to be funded with a budget of 14.4M?. Topic 43: 'Neurotoxic effects of environmental contaminants' and topic 44: 'Effects of environmental exposure to complex chemical mixtures' each result in a specific targeted research project to be funded with budgets of 2.4M€ (DEVNERTOX) and 1.47M€ (DIEPHY) respectively. Topics covered under Priority 5 for the 2003 work programme include T5.1: 'New approaches towards monitoring and preventing chemical contaminants in food products', T8.1: 'Environmental and endogenous factors influencing puberty onset', T8.3: 'Food and fecundity' as well as initiatives to improve international coordination of research in the field of ED (deadline for applications February 2004). ED is also covered under Priority 6 (Sustainable Development, Global Change and Ecosystems) by the sub-area 'Global change and ecosystems' and by complementary research. Two topics have relevance to ED to be implemented in 2004: VII.1.1.a: 'Development of risk assessment methodologies' and VII.1.1.b: 'Methods for risk assessment of pharmaceuticals in the environment'.

New topics for research are being collected for the 2005-2006 work programme and a new call for proposals will be launched in 2004. New activities will emanate from the Environment and Health Strategy launched by the European Commission in mid-2003 to reduce diseases linked to environmental factors. The action plan to be adopted in 2004 is likely to result in increased funding for research.

USEPA's Endocrine Disruptors Programs: Regulatory and Research

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In 1996, the U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD) identified endocrine disruptors as one of its top six research priorities. In the same year, through enactment of the Food Quality Protection Act, the U.S. Congress directed EPA to develop a screening program to determine whether certain substances may have estrogenic or other hormonal effects in humans. EPA's research program and the development and implementation of a mandated Endocrine Disruptor Screening Program (EDSP) are on parallel, yet highly interactive, tracks.

The blueprint for EPA's research program was published in 1998 as *ORD's Endocrine Disruptors Research Plan*. Since then, ORD has developed a *Multi-Year Plan for Endocrine Disruptors* that identifies the elements of the *Research Plan* that specifically will be addressed over the next five to ten years, intramurally, across three national laboratories and one national center and, extramurally, through a competitive grants program. In the *Multi-Year Plan*, ORD has identified three Long-Term Goals (LTG) to: 1) *Provide a better understanding of science underlying the effects, exposure, assessment, and management of endocrine disruptors*. Research includes determining: dose-response relationships, the effects of exposure to multiple endocrine disruptors, major sources of exposure, and approaches for managing risks; 2) *Determine the extent of the impact of endocrine disruptors on humans, wildlife, and the environment*. Research includes determining what effects are occurring in human and wildlife populations and what chemical classes are responsible; and 3) *Support EPA's screening and testing program*. ORD research is developing/improving *in vivo* and *in vitro* assays in support of the implementation of EDSP. Particular attention is focused on refining mammalian assays for estrogen, androgen, and thyroid activity and in developing and standardizing amphibian and fish bioassays.

The regulatory activities that parallel the research are proceeding in: 1) validating assays for EDSP, 2) seeking counsel on science and technical issues related to assay development and validation through an advisory committee, 3) establishing priorities for selecting chemicals to undergo screening, and 4) outlining procedures the Agency will use to require screening.

The magnitude of the scientific uncertainties about the causes, effects, exposures, and solutions to address the concerns regarding endocrine disruptors require national and international coordination and communication. To facilitate efforts nationally, ORD chairs an interagency working group established under the auspices of the President's National Science and Technology Council. The working group developed a national framework for research, an inventory of federal research programs, identified high priority research gaps, and serves as a vehicle through which to develop and issue multi-agency solicitations for research proposals to help fill in some of these gaps. At an international level, EPA has worked with the European Union, the International Programme on Chemical Safety, the Organization for Economic Cooperation and Development, and with Japan's Ministry of the Environment to promote collaboration among scientists and to develop validated assays.

In summary, EPA's research is providing immediate results by developing new and improved assays for implementing EDSP. The longer-term research is addressing the most critical uncertainties in determining whether humans and wildlife populations are being impacted by levels of endocrine disruptors in the environment and in identifying sources of exposure and approaches to reduce/prevent them. In addition, EPA is working with its US federal partners and other countries to ensure that there is coordination and communication regarding research and testing programs for endocrine disruptors.

The Current OECD Initiative on Endocrine Disrupters Testing and Assessment (EDTA)

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A Task Force on Endocrine Disrupter Testing and Assessment (EDTA) was established to manage the OECD activity on endocrine disrupters in late 1997. The objectives of the EDTA Task Force are to:

* Identify the needs and prioritize the development of new and enhanced guidelines for the detection and characterization of endocrine disrupting chemicals;
* Develop a harmonized testing strategy for the screening and testing of endocrine disrupters;
* Manage validation work for newly developed and enhanced Test Guidelines as appropriate; and
* Provide practical tools for sharing of testing results and assessments.

A major achievement of the EDTA Task Force has been the definition of a Conceptual Framework capturing the potential screening and testing needs for *in vitro*, human health and ecotoxicological areas. The framework attempts to identify tests at different levels of biological and regulatory complexity: from their interactions with hormone receptors to tests in whole animals at different sensitive life stages and tests where effects might be passed to the next generation. The framework is not a testing strategy, but rather a set of tools placed at different levels, depending on the information they can provide. The sexual hormone system (estrogenic and androgenic activities) and the thyroid hormone system are specifically targeted in the EDTA work. In order to share the burden of testing and assessment, a database on endocrine disrupting chemicals is under construction for the sharing of test method development, testing plans, test results and assessment reports conducted by member countries.

The EDTA Task Force validation work of new and enhanced methods aims to ensure the reliability and relevance of testing methods in order to allow regulatory acceptance. All test methods will have to be validated before being formally added to the Conceptual Framework. This validation work is in accordance with the OECD Solna principles, recognized by many centers involved in the validation of test methods (ECVAM, ICCVAM).

The Validation Management Groups (VMG) have been established to co-ordinate and oversee the conduct of method development and validation in three areas: i) mammalian toxicological tests, ii) ecotoxicological tests, and iii) *in vitro* and other non-animal tests. These groups take technical decisions independently, but all report back to the EDTA Task Force.

The VMG for mammalian tests started with three *in vivo* tests as priorities for validation: the rodent uterotrophic assay (estrogen and antiestrogen activities), the rodent Hershberger assay (androgen and antiandrogen activities), and an enhanced Guideline 407 (Repeated dose toxicity) to evaluate several new endocrine related parameters. Validation work is completed for the rodent uterotrophic assay and is now being peer-reviewed by a panel of independent experts. Validation work is well underway for the Hershberger assay: the last phase of experimental work is on-going to demonstrate reproducibility and the rate of false positives. A peer-review of the whole validation work will follow in 2004. The experimental validation work is completed for the enhanced TG 407 (Phase 1 and Phase 2). Several endpoints encompassing sexual hormone and thyroid systems are included, and represent different levels of complexity for the validation exercise. The report is in preparation. The next test on the VMG-mammalian agenda will be the rodent 1-generation test.

The VMG for ecotoxicity tests oversees the development and validation of test methods for fish, birds, amphibians and invertebrates. The Validation effort for a fish screening assay started this year with three fish species widely used in regulatory work; endpoints covering (anti) estrogenic, aromatase inhibitor and (anti) androgenic activities are included. Also on the workplan are a fish partial life-cycle test and a fish full life-cycle test. An Amphibian Prometamorphosis Assay for the detection of thyroid active compounds in Vertebrate organisms is being pre-validated. The development of an avian 2-

generation study is being considered. For invertebrate testing, several development and reproduction or life-cycle tests have been discussed to take into account the diversity of these organisms.

The progress so far in the newly established VMG for non-animal testing is the initiation of Detailed Review Papers in the following areas: thyroid assays (from *in vitro* to mammalian and environmental species), non-animal assays for steroidogenesis assessment, for aromatase assessment and for metabolism assessment. Furthermore, a number of non-animal assays are going through different phases of prevalidation and validation. Results from these validation studies will be presented at the next meeting of the validation management group. A project on the validation of QSAR methods for endocrine disruption will start in the future when an expert group is established.

WHO/IPCS Initiatives on Endocrine-Disrupting Chemicals

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In 1997, the International Programme on Chemical Safety (IPCS) was requested by the Intergovernmental Forum on Chemical Safety and the 1997 Declaration of the Environment Leaders of the Eight (G8) on Children's Environmental Health to undertake a global assessment of the current state of scientific knowledge as it related to endocrine disrupting chemicals. The request was endorsed by the 50th World Health Assembly in 1997. The report was published in August 2002, entitled "Global Assessment of the State-of-the-Science of Endocrine Disruptors", representing the result of a global comprehensive review of the publicly-available scientific literature on EDCs organized by IPCS, a collaborative programme of the World Health Organization (WHO), the United Nations Environment Programme (UNEP) and the International Labour Organization. Over 60 international scientific experts provided input into this document either as IPCS Steering Group Members, chapter leaders, authors, or reviewers. The assessment was unique in providing a global perspective on the endocrine disruptor issue, and in providing a framework by which a strength-of-the-evidence analysis was performed to determine whether there was a causal association between an adverse biological effect and exposure to an endocrine-disrupting chemical (EDC). The report concluded that there was sufficient evidence that adverse effects had occurred as a result of exposure to EDCs in some wildlife species, though the evidence that human health had been adversely affected was generally weak. Therefore, because of continuing concerns and scientific uncertainties, studies on the potential effects posed by these chemicals should remain a high global priority requiring coordinated and strengthened international research strategies. There was, in particular, an urgent need for studies in vulnerable populations, and especially in infants and children, since exposure during critical developmental periods may have irreversible effects. In view of this urgency and because EDC research is a rapidly-moving field, IPCS will be convening a workshop in December 2003 to examine progress made since publication of the state-of-the-science report and to characterize residual data gaps, ongoing research needs and future directions to take in the context of an international research strategy.