

INTERNATIONAL WORKSHOP ON ENDOCRINE DISRUPTORS

Workshop Report
Smithsonian Institution
Washington, D.C., U.S.A.
January 23-24, 1997

This workshop was sponsored by the United Nations Environment Programme, United States Environmental Protection Agency, White House Office of Science and Technology Policy, Homeland Foundation, W. Alton Jones Foundation, and Conservation, Food & Health Foundation, Inc.

INTRODUCTION

An international workshop on endocrine disrupting chemicals was held at the Smithsonian Institution on 23 and 24 January 1997. The workshop had four purposes:

- * review the status of national and regional assessments on the state of the science of endocrine disruptors;
- * explore the perspective of developing countries and countries with economies in transition on the issue of endocrine disruptors;
- * discuss the need for an international science assessment of endocrine disruptors;
- * identify opportunities and open a dialogue for international cooperation that could advance our understanding of the endocrine disruptor issue.

STATUS OF NATIONAL AND REGIONAL ASSESSMENTS AND RESEARCH ACTIVITIES

A group of invited scientists, governmental officials, representatives from industry, international organizations, and intergovernmental entities attended the workshop. The ninety participants represented twenty one countries and four international/intergovernmental organizations including: Australia, Belgium, Brazil, Canada, China, Denmark, England, France, Germany, Israel, Italy, Japan, Mexico, Russia, South Africa, Spain, Switzerland, United Kingdom, United States, Uzbekistan, Zimbabwe, World Health Organization, Organization of Economic and Cooperative Development, Commission on European Union, and United Nations Environment Programme.

At the meeting, information exchange and dialogue occurred in a variety of forms including overview presentations, panel discussions, open microphone sessions, poster presentations, and informal discussions during breaks and meals.

Presentations were made on some major information-gathering and scientific assessment activities underway in North America and Europe.

United States -- Summaries were presented on three efforts in the United States:

(1) a review of federally supported endocrine disruptor research and the development of a research plan; (2) an interim state-of-science report on endocrine disruptors produced by the Environmental Protection Agency (EPA); and (3) a science assessment that is being done through the National Research Council (NRC) of the National Academy of Sciences (NAS). A brief overview of the U.S. industry perspective and efforts was also presented.

Development of a U.S. federal research strategy on endocrine disruptors -- an ad hoc Working Group on Endocrine Disruptors was established by the Committee on Environment and Natural Resources, National Science and Technology Council, to accomplish this goal. This is being done as a three-part activity: (a) development of a conceptual framework to guide both the inventory of extant research and the development of a research plan; (b) building of an inventory of ongoing U.S. government-funded projects, and (c) identification of gaps in the U.S. government's research program on endocrine disruptors and the outlining of a research plan. The first part has been completed and is published as: *The Health and Ecological Effects of Endocrine Disrupting Chemicals: A Framework for Planning*. The second part, an inventory of U.S. government funded research projects, has also been completed. Both the "Framework" document and the inventory can be accessed on the internet (www.epa.gov/endocrine). The analysis of this Committee on Environment and Natural Resources (CENR) inventory of research projects on endocrine disrupting chemicals will be published in a future issue of *Environmental Health Perspectives*. Development of a coordinated federal strategy for addressing critical research needs is the third and final part of the federal planning process. The last product is expected by the end of 1997.

EPA's Interim State of Science Assessment -- The purpose of the interim assessment is to provide an overview of the current state of science on endocrine disruptors. These compounds were defined as "exogenous agents that interfere with the synthesis, secretion, transport, binding, action or elimination of natural hormones in the body, which are responsible for the maintenance of homeostasis, reproduction, development and/or behavior." This definition of endocrine disruptors includes natural products, synthetic chemicals, or mixtures that mimic, enhance, or inhibit the action of hormones. The report reviews the literature on the effects of endocrine disruptors on both humans and wildlife.

The National Research Council's Assessment -- This assessment is scheduled to be completed towards the end of 1997. The statement of work that is guiding the assessment includes the following tasks:

- * Conduct a critical review of the literature on hormonally active agents in the environment
- * Identify known and suspected toxicological mechanisms and impacts on fish,

wildlife, and humans

- * Identify significant uncertainties and limitations of knowledge, and weaknesses in the available evidence
- * Develop a science-based conceptual framework for assessments
- * Identify monitoring, research, and testing priorities
- * Identify specific chemical substances, geographic areas, contaminant sources, etc., where endocrine disruptors are a factor
- * Evaluate the available toxicological evidence for effects of endocrine disruptors

U.S. Industry Research Perspective -- The Chemical Manufacturers Association (CMA) is a non-profit trade association of more than 190 member companies that represent approximately 90% of the product capacity for basic industrial chemicals in the U.S. Over the next three years CMA, through various collaborations with universities, government agencies and industry, will administer a \$4 million generic endocrine research program. This research focus derives from the concept of "Responsible Care," an approach adopted from Canada more than ten years ago.

The CMA's research program will address scientific questions on a broad interest scale and be applicable to a broad range of chemistry. Though CMA supports research on both human health and wildlife populations in this program, it will not conduct testing and research on specific chemicals, the responsibility for which still remains with the prime producers of the chemicals. The research topics pursued will be those that will help industry-product stewardship and provide scientific information as well as assist policy makers in making decisions.

CMA's priorities include:

- * development of tools that will allow industry to evaluate its products (this is particularly important to US chemical companies because of recent mandates laid out by the Food Quality Protection Act and the Safe Drinking Water Act
- * set priorities among chemicals for screening and testing which will be based on a combination of factors including production volume, potential exposure, physical and chemical properties and modeling and structural activity relationships
- * ensure that standardized and validated screening tests are available

- * examine risk assessment methods to see if new approaches are needed for summarizing hazard and exposure information into a form that is useful for decision makers

- * increase industry's understanding of underlying biological mechanisms (i.e. what are the thresholds for adverse effects? what is the shape of the dose-response curve?)

- * to seek further opportunities for collaborations with other interested parties including government agencies, environmental interest groups and universities to foster scientific consensus and help resolve some of the risk management and inventory aspects of the endocrine disruptor issue

CMA also believes that international organizations play an important role in identifying research needs and priorities as well as fostering coordination and collaboration among countries and regions and among industries, government, and environmental organizations. It does have concern, however, about duplication of efforts among the international groups and the impact the duplication has on scientific resources and efforts. Efficient mechanisms must be found for the exchange of information and taking advantage of studies already in progress. There is also the concern that without an increase in coordination among international organizations that industry and the public will become confused on where to direct their attention and resources for information and guidance on this important topic.

Canada -- Canada's research program has a substantial emphasis on multi-disciplinary field studies, chemical mixtures, and wildlife (especially birds and fish). Canada has reached the conclusion that endocrine disruptors are already having an effect on wildlife though they have not undertaken any major assessment activity yet. The Canadians are developing an inventory of research projects and are incorporating the results into an electronic data base patterned after the U.S. model.

Europe -- The European community has taken important steps toward organizing a Pan European program and is working with member states, industry and non-governmental organizations to formulate an appropriate strategy for Europe. A workshop entitled "The Impact of Endocrine Disruptors on Human Health and Wildlife" was held in London on 2 to 4, December 1996. A workshop report is in press. It includes coverage of three major topics: Effects and Mechanisms; Sources and Exposure; and Screening and Testing Methodologies. Germany has taken the lead to conduct an inventory of research projects and already has considerable participation from other European countries.

Japan -- Industry is providing a leadership role on endocrine disruptors in Japan. Two important industry-based organizations (i.e., the Japan Chemical Industry Association and the Japan Chemical Industry Ecology and Information Center) are

involved. At this time, no coordinated program has emerged from academic or government scientists; however, Japan has a long-standing monitoring program for selected compounds in fish, mussels, and birds at 20 locations. These data could prove to be highly useful for retrospective studies of endocrine disruptors in the environment and as a basis for collaborative interactions with scientists from other countries.

Australia -- Recognizing that endocrine disruptors is a major emerging issue, Australia strongly supported the need for a peer-reviewed scientific assessment (not a risk assessment) of endocrine disrupting chemicals. The initial focus of international cooperation should be on agreeing to an appropriate definition of a scientific assessment and the scope of proposed work. To this end, Australia suggested that it may be appropriate to constrain the work to chemicals that interact with the effects on the sex hormones. It was noted that Australia had a strong history in fertility studies but the extent of research in other areas was uncertain as there was no government coordinated program or centralized database of endocrine research in Australia at this stage. The Australian government is not convinced that the case against endocrine disrupting chemicals is sufficiently developed at this stage to give any consideration to international regulatory action particularly given the very high priority Australia placed on the successful completion of UNEP's global legally binding instruments on prior informed consent (PIC) and persistent organic pollutants (POPs).

China -- Although China has no endocrine disruptor research program, development and validation of screening and testing protocols for endocrine disruptors would be of immediate value in China. China faces pressing problems of occupational exposures to pesticides. Also, the Chinese people consume numerous unregulated foods and beverages for alleged health benefits, yet many of these preparations may contain biologically active substances in concentrations sufficiently high to affect growth, development, and reproduction. International scientific agreement on appropriate testing procedures could vastly improve China's ability to protect its people from potentially harmful exposure to endocrine disrupting chemicals.

Russia -- There is no coordinated research program on endocrine disruptors in Russia; however, Russia has many sites that would be highly suitable for field studies. These sites are primarily urban areas that served as chemical manufacturing centers and are now contaminated with a diverse array of chemicals (pesticides, explosives, chemical warfare agents). Also, the presence of municipal incinerators that handle both chlorinated and brominated chemicals may be producing chlorinated and brominated by-products of combustion that are also released to the environment. Russia is willing to work with other countries to study the contaminants at these sites and their potential for endocrine disruption.

Summary -- The value of numerous completed and ongoing assessments as well as specialized data bases was acknowledged. Any future assessments on

endocrine disruptors should take advantage of these initiatives and be certain not to duplicate efforts.

STATUS OF INTERNATIONAL ASSESSMENTS AND RESEARCH ACTIVITIES

Organization for Economic Cooperative Development (OECD) -- A summary was presented on OECD's recent work on the Environment and Health & Safety involving the regulation of chemical management and the possible effects of chemicals on human health. Recent products of the OECD include Guidelines for the Testing of Chemicals and Principles of Good Laboratory Practice which are used for quality assurance of data and harmonized methods for risk assessment of chemicals and co-operative testing and assessment of High Production Volume (HPV) Chemicals. OECD can contribute to a number of areas, development of new test methods, the international organization of risk, development of assessment methods that might be used and the international coordination of assessment. For more information, please visit <http://www.oecd.org.ehs/endocrin.htm>.

The working definition for endocrine disrupters that was adopted by the OECD at a workshop sponsored by the European Union (EU), WHO, and OECD in Weybridge, UK in December 1996 is: An endocrine disrupting chemical (EDC) is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function. A potential EDC is a substance that possesses properties that might be expected to lead to endocrine disruption in an intact organism. @

World Health Organization (WHO) - WHO has one unit dedicated to conducting research on endocrine disruptors entitled Human Reproduction (HRP) and has had an advisory group working together on criteria documents since 1976. WHO hosted a workshop in 1993 which was published in Environmental Health Perspectives and details some problems with active or hormonal chemicals. For more information visit <http://www.who.ch>

International Forum For Chemical Safety (IFCS) - IFCS was formed in 1980 at a meeting in Stockholm on the environment as a scientific response to the problem posed by the increased use of synthetic and natural chemicals. All IFCS work is coordinated through a committee made up of three groups. IFCS is not a United Nations Program that sits on its own. For more information, visit <http://unep.unep.no/unep/partners/global/ifcs>.

PERSPECTIVES OF DEVELOPING COUNTRIES AND COUNTRIES WITH ECONOMIES IN TRANSITION

Workshop participants from developing countries noted that most citizens in their homelands were unaware of the endocrine disruptor issue. In addition, they noted that most governments in developing countries regarded the issue as too ill defined and esoteric to take resources away from other pressing public health problems, though there is some awareness that chemical contamination (e.g., pesticides, industrial, military) poses a threat to human health. The governments have a responsibility to address more basic needs, such as adequate food supplies and clean water. These governments, therefore, have other health and environment research priorities which are far more pressing than exploring the possible effects of chronic exposures to low levels of endocrine disrupting chemicals in the environment. Where awareness of endocrine disruptors is present, concern is most likely to be focused on human impacts, not effects on wildlife.

The participants from developing countries expressed interest in staying informed about the issue of endocrine disruptors and did not want their countries to unwittingly condone practices that would expose citizens to unnecessary or potentially harmful exposures. Special areas of concern in developing countries are occupational exposures of agricultural workers to pesticides and the need for validated screening and testing procedures.

AN INTERNATIONAL SCIENCE ASSESSMENT

A session was held to discuss the need for an international science assessment of endocrine disruptors. At the conclusion of the session, agreement was reached that an international assessment of the scientific underpinnings for endocrine disruptors in the environment would be helpful to scientists and decision makers. Such an assessment could, for example, draw on existing reviews such as those conducted by the U.S. National Academy of Science/National Research Council, U.S. Environmental Protection Agency, and a number of other countries and international organizations. New data could also be considered. There was some concern voiced about the duplication of completed or ongoing regional or national assessment efforts and the current lack of new information to add to already existing assessments.

A basic premise to discussions on the need for an international science assessment is that good science and understanding of what we know and don't know are essential to good policy. Experience has taught that knowledge and understanding of knowns and unknowns is a powerful tool in protecting public health and the environment.

The Need -- The discussion revealed that there are many scientific questions related to international concerns that may never be addressed within the scope of single-nation assessments. Some of these concerns result from the unique cultures, economies, and chemical use practices of specific countries. Other concerns are simply beyond the purview of single nations. Those issues identified as unique to the international arena include endocrine disruptors in the oceans, global transport of endocrine disruptors from contaminated to uncontaminated regions, and the potential movement of endocrine disruptors in migrating wildlife.

Guidelines -- Guidelines for conducting the science assessment were proposed as follows:

- * All products will be peer reviewed
- * There will be broad stakeholder involvement
 - geographic
 - sector (industry, government, academia, NGO, public)
- * Initial terms of reference
 - defined objectives
 - clear scope
 - realistic timetable
 - schedule for updating the assessment
 - work group should have qualified members

ACTION ITEMS FOR THE INTERNATIONAL SCIENCE COMMUNITY

The following two activities were selected as short-term, achievable action items of immediate value to the international community of scientists and decision makers involved in endocrine disruptors.

- * Expansion of the United States inventory of federally funded research projects to become international in scope. This would entail immediate participation of all countries to include each nation's research program in the inventory. Canada and Germany have already begun this process. The European Union's inventory is already international and based in Germany (www.liwa.de/rneed). Subsequent issues to be considered regarding the research inventory are the need to include industry and non-government-sponsored research projects, how to update the inventory on a regular basis, and locating a permanent home for the inventory.

* Selection and validation of screening and testing procedures for endocrine disruptors was widely acknowledged as a high priority need that would benefit all countries. It was suggested that OECD take a lead role in an international exercise to validate screening and testing methods. The Chemical Manufacturers Association expressed its support and willingness to contribute resources to such an international effort. Recent legislation (Food Quality and Safety Act and the Safe Drinking Water Act) has led the EPA to convene a federal advisory committee (Endocrine Disruptor Screening and Testing Advisory Committee -- EDSTAC) to assist EPA in developing a screening and testing strategy for endocrine disrupting chemicals. The purpose is to identify and assess chemicals that have public health impacts and reduce effects on the environment. These include chemicals that are estrogenic, antiestrogenic, androgenic, antiandrogenic, or affect the thyroid or other hormones. The first two years will be used to develop a testing program and the third year used to implement the program.

NEW NETWORKS BEING FORMED

The value of new networks for information exchange on endocrine disruptors was acknowledged. Two candidate topics for international cooperation were identified:

* Semen quality network - An expansion of the European network to share data and research protocols was proposed. Denmark is already doing this with several European partners. Other nations were invited to join the network. (Contact: Niels E. Skakkebaek; Tel: 45-35-45-5086/85; Fax: 45-35-45-6054; Email: rh00654@rh.dk)

* Human indicators network - A network was proposed to facilitate the compilation of existing information on breast cancer, testicular cancer, cryptorchidism, delayed or premature sexual maturity, attention deficiencies, lowered IQ, altered male:female sex ratios, and other indicators of human exposure to endocrine disruptors. (Contact: Devra L. Davis; Tel: 202-638-6300; Fax: 202-638-0036; Email: devra@wri.org)

IDEAS FOR NEW SCIENCE THRUSTS

Several important research topics were identified as highly relevant to the

technical issues surrounding endocrine disruptors, but inadequately addressed at this time. Examples include:

- * Toxicology of endocrine disruptors, including: Non-linear dose-response relations, low dose effects, time of exposure for susceptibility of developing organisms, synergy, metabolism, multi-generational effects.
- * Comparative ecological studies, including: Data bases from reference sites, chemically contaminated field sites, and mesocosms; need to understand ecological effects at the population, community, and ecosystem levels; and the value of biomarkers for predicting these effects; and the role of chemical signals in maintaining critical symbiotic relationships in terrestrial and aquatic ecosystems.

INTERNATIONAL STRATEGY FOR ENDOCRINE DISRUPTORS

The merit of an international research program on endocrine disruptors was recognized as potentially important for bridging the gap between developing and developed countries. The sense of the group was that the concept should be given further thought and consideration. Typically, developing countries do not have active research programs on endocrine disruptors. When they do have such programs, their research efforts may be highly focused on selected topics (sperm count, breast cancer). Effects on wildlife and ecological impacts are more commonly studied in developed countries. Despite these differences, an organized international research program was recognized as a valuable means of building new networks for information exchange and research collaborations beneficial to all nations, thus, an international strategy to coordinate research in these areas was deemed necessary and appropriate.

The recommendations from this international workshop on endocrine disruptors were conveyed to the IFCS at the 10 February 1997 meeting in Ottawa.

By establishing an international strategy for endocrine disruptors early in the debate, there is a unique opportunity to ask what testing requirements and research is appropriate before deciding on suitable international actions. Moreover, by reaching scientific agreement internationally on what is known, what is not known, what data are needed, and the priority of data needs, scientific inquiry can be directed so that critical studies are undertaken in a timely and informed manner. Strong collaboration and coordination in the development of high quality scientific information is a requisite to good public policies in the protection of human health and the environment while ensuring economic development and the availability of beneficial products.

EPILOGUE:

An Update on the Activities of CENR Endocrine Disruptors Working Group
On June 2-3, 1997, representatives of the CENR Working Group on Endocrine Disruptors, briefed representatives of the IPCS and the OECD on the activities of the Working Group. The briefing was followed by discussions on unifying international inventories on endocrine disruptors and possible plans for an international assessment of the science. Agreement was reached that the IPCS and the OECD would take the lead on a proposed outline for an international assessment of endocrine disruptors and that the assessment would take advantage of existing assessments of endocrine disruptors to the maximum extent possible. It was proposed and accepted that a small steering group (8-10 members representing human health, ecological effects, and exposure assessment) would be convened to advise on whether fine tuning of the inventory structure would be needed, and to review a proposed outline for an international assessment. This group would also provide a consultative role throughout its development. Estimates were that it would require 18-24 months for completion. A meeting of the steering group and the existing inventory gatekeepers would be set up in the fall of 1998.

The group also agreed to unify the Canadian, European, and private industry inventories on endocrine disruptors using the format established by the CENR Working Group. The need to update the US federal inventory conducted by the CENR Working Group was emphasized.

The CENR Working Group is scheduled to meet on September 15th at the White House Conference Center to conduct the final phase of its activities, that of identifying gaps and prioritizing research needs in the US to formulate a coordinated research strategy on endocrine disrupting chemicals. In addition, the issues discussed with the IPCS/OECD group (i.e., the need to update the CENR inventory of US federal research on endocrine disruptors, and the proposed plans for an international science assessment of endocrine disruptors) will be considered.