U.S. Environmental Protection Agency CENR Federal Interagency Workshop on Endocrine Disruption in the Environment

U.S. Geological Survey
National Center Auditorium
Reston, VA

February 20-22, 2007

EXECUTIVE SUMMARY

FEBRUARY 20, 2007

INTRODUCTION AND OVERVIEW

The 2007 U.S. Environmental Protection Agency (EPA) Committee on the Environment and Natural Resources (CENR) Federal Interagency Workshop on Endocrine Disruption in the Environment was held February 20-22, 2007, in Reston, Virginia. The goals of this Workshop were to: (1) determine the progress federal agencies have made in addressing the research needs identified in the 1996 CENR document on *The Health and Ecological Effects of Endocrine Disrupting Chemicals, A Framework for Planning*; (2) provide an overview of current federal activities on endocrine disruption research and monitoring; and (3) identify specific areas of potential collaboration and cooperation related to endocrine disruption research and monitoring among government researchers and across programs. This workshop provided an opportunity for various federal agencies to share their experiences and perspectives in this area and to address the future direction of collaborative research efforts.

Welcome
Sue Haseltine, Associate Director for Biology, USGS

Dr. Haseltine welcomed participants to the workshop on behalf of the USGS. The USGS has a major interest in collaborating with other agencies to inform the public and Congress on the issue of endocrine disruption. Over the last 10 years, the USGS has developed research and monitoring programs on the biological response to endocrine disrupting chemicals (EDCs) in the nation's waterways and has identified priorities and opportunities for collaboration with other federal agencies. This workshop will provide a forum to discuss this important issue and to work collectively to respond to public and congressional interest.

Introductions
Sarah Gerould, Coordinator, Contaminant Biology Program, USGS

Dr. Gerould conducted an exercise to introduce individuals according to their areas of interest related to endocrine disruption (e.g., biological methods, chemistry, species, and field study). Participants identified themselves by name and affiliation.

Opening Remarks
Elaine Francis, National Program Director, EPA

Dr. Francis presented an overview of the workshop in the context of the history and mission of the interagency workgroup. The CENR Federal Interagency Workgroup is overseen by the Toxics and Risk Subcommittee of the National Science and Technology Council (NSTC). In 1998, EPA, the National Institute of Environmental Health Sciences (NIEHS), the Department of the Interior (DOI), and the National Oceanic and Atmospheric Administration (NOAA) issued several multi-agency Requests for Applications (RFAs) to study the relationships between exposure to EDCs and adverse outcomes in wildlife populations. In 2000, EPA, NIEHS, the National Institute for Occupational Safety and Health (NIOSH), and the National Cancer Institute (NCI) issued RFAs to investigate reproductive/developmental effects in humans from EDC exposure. A total of 24 proposals were funded and a series of progress review workshops were held. Local and national media coverage of this issue also has drawn the attention of Congress.

Purported effects of EDCs on wildlife include eggshell thinning in bird populations due to dichloro-diphenyl-trichloroethane (DDT), abnormal reproductive development in alligators following a pesticide spill, and birth defects in birds exposed to polychlorinated biphenyls (PCBs) and other chemicals. Human health effects include reproductive tract cancers and abnormalities in offspring of women who used diethylstilbestrol (DES) during pregnancy, neurodevelopmental problems in children exposed prenatally to PCBs, and speculation regarding an endocrine-related basis for increases in certain cancers (i.e., breast, prostate, and testicular cancer). In 2002, the World Health Organization (WHO) International Committee convened to prepare a global state-of-the-science report on endocrine disruptors, which identified specific research requirements, including investigating the biology of underlying endocrine-mediated effects and developing improved dose-response methods and biomarkers. The WHO report also recommended developing monitoring programs to improve international collaboration in the assessment of exposure and effects on wildlife and to monitor trends in human health outcomes across regions and over time.

The key science issues that need to be explored include understanding mixtures of chemicals in the environment, developing methods to characterize exposures and impacts on the environment, and developing methods to reduce or prevent exposures. In terms of risk management, further research is needed to characterize the source of EDC exposure to humans and the ecosystem in wastewater treatment facilities, concentrated animal feeding operations (CAFOs), and the removal of EDCs from drinking water. Research is needed to determine the effectiveness of current risk assessment methods in mixtures that operate through similar and/or different mechanisms of action. Further study is needed in the development of baseline data to understand the significance of findings on aquatic and terrestrial wildlife, biomarkers, and models to extrapolate data from the individual to the population level.

The goals of this workshop are to identify several areas where federal agencies can combine expertise and resources to significantly advance the critical environmental needs related to endocrine disruptors, and to describe the progress in addressing the research needs identified in the 1996 CENR document.

INTERNATIONAL PERSPECTIVE

Glen Van der Kraak, Associate Dean of Research, College of Biological Science, University of Guelph

Dr. Van der Kraak presented the progress and future direction of the issue of endocrine disruption from the perspective of the international science community. Current research activities include the Cluster of Research into Endocrine Disruption in Europe (CREDO), which encompasses several multistakeholder projects as well as the European Union (EU) research program under the 5th, 6th, and 7th Framework Studies. In Canada, the Canadian Network of Toxicology Centres issued two initiatives to address endocrine disruption in the environment: the Toxic Substances Research Initiative and the Children's Heath Initiative. In Japan, the Strategic Project on Environmental Endocrine Disruption (SPEED) includes the Enhanced Tack on Endocrine Disruption (ExTend 2005) and the Hokkaido Study of

Environment and Children's Health. Much progress has been made over the last decade, with thousands of publications written on the topic of endocrine disruption. International research has focused on identifying causative chemicals and exposures; defining effects in humans, laboratory models, and wildlife; and analyzing risks. Science advances have been shown in the application of new methodologies to characterize the properties and effects of endocrine disruptors (molecular biology toolbox), and in the development of new animal models and endpoints. Future research should be directed at exploring the dose-response relationship, extrapolation across species, and linking biomarker responses with developmental endpoints. Data have been obtained on a wide range of affected wildlife species, and future field research could provide an understanding of the genetic basis of susceptibility, establishing cause-and-effect linkages, and developing improved tools for toxicity identification and evaluation. Key issues for test methods include long delays associated with validation and high costs and times required for definitive tests. Genomics and computational modeling can be used to characterize risk. Further research in the area of risk assessments should focus on defining what constitutes an adverse effect, understanding the actions of mixtures, and the validity of safety factors. Endocrine disruption is a mechanism of action and this should be linked to adverse outcomes (e.g., reproduction, development, and neurotoxicity) that are used in regulatory decisions with humans and wildlife. EDCs continue to be a significant topic in terms of regulation of synthetic substances and for protection of the health of wildlife and human populations. The conclusions and research strategy of the 1996 CENR document are applicable today. Over the next decade, strategic partnerships and enhanced communication both nationally and internationally among human health and wildlife researchers are needed to address risks posed by EDCs.

Discussion

A participant asked how the international political and budgetary climates affect the regulatory process. Dr. Van der Kraak replied that funding in Canada for endocrine disruption research has decreased, but is beginning to expand as more researchers become involved. He added that research activities under the 7th framework are lower than those of the 6th and 5th frameworks, which indicates the level of funding is decreasing. In the EU, research activities have been fueled by the 2005 mandate. In Japan, grass roots support has been shown for the study of EDCs at the community and scientific levels, but funding is decreasing overall.

A participant asked what percentage of EDC research is focused on human health and what percentage is focused on wildlife. Dr. Van der Kraak indicated that it is difficult to answer that question without access to specific budgetary information, but he believes that there is slightly more activity on wildlife research than human health research. Some of the proposed long-term studies on children's health, for example, require a different type of commitment. In Canada, it is a difficult issue to balance these long-term studies as part of the children's health initiative, and requires a reprioritization of research activities.

A participant commented that some research organizations focus on adverse effects rather than mode of action for EDCs, which they consider less important. The participant asked if endocrine disruption warrants a different approach to risk assessment, rather than focusing on adverse effects that may be caused by a different mode of action. Dr. Van der Kraak replied that he believes that the focus of attention should be on adverse outcomes.

A participant commented that if we rely on application factors to set safe levels, other endpoints should be included. Dr. Van der Kraak believes that the issue is how gene responses translate to affect the whole organism level. Dr. Van de Kraak is concerned about the use of gene expression changes as a method for risk assessment, and believes in a more conservative approach to better understand some of the linkages.

A participant asked if the EU has a different type of agenda with regard to precautionary principles than Japan and Canada and how this relates to adverse affects. Dr. Van der Kraak replied that he believes that the EU does have a different agenda than Canada, but cannot comment on this issue for Japan.

The participant followed up with the comment that an interest in delayed response requires the need to look at mechanism of action in order to develop shorter-term tests. Dr. Van der Kraak agreed, but emphasized that there is a concern that there can be multiple reasons for changes in genes, and these are not necessarily due to chemical stressors, but may be caused by other stressors that are important to regulate. Dr. Van der Kraak questioned whether we would be making the decision for the right reason.

EDC Poster Session

A poster session was held, which included the display and presentation of 28 posters on EDC research projects.

February 21, 2007

Agency Activities on Endocrine Disruption Research and Monitoring

Each agency was asked to address the following questions in their presentations:

(1) What is your organization's mission as it relates to the EDCs issue in the environment?

(2) What are your agency's regulatory tools for assessing or managing EDC risks? What laws and/or regulations are currently available to manage EDCs?

(3) What are your agency's activities or research related to sources of EDCs? What progress has your agency made since the publication of the 1996 framework?

(4) What are your agency's monitoring and methods development activities for detecting and assessing exposure and effects for aquatic and terrestrial systems?

(5) What is your agency doing to identify ecological populations that may be at risk and to what extent are these populations at risk in aquatic and terrestrial systems?

(6) What is your agency doing to identify or implement remediation of identified risks to ecological receptors?

(7) What current or past collaborations has your agency had with other federal agencies?

CENR Perspective, Recommendations on How To Increase Federal Collaboration on Endocrine Disruption
Christopher Portier, Associate Director, NIEHS
Director, Office of Risk Assessment Research, Co-Chair, Toxics and Risk Subcommittee

As co-chair of the Toxics and Risk Subcommittee, which oversees the interagency workgroup, Dr. Portier discussed endocrine disruption in the context of its importance in informing public health decisions. The issue has become part of mainstream science and is the subject of routine media coverage. Among the news reports related to EDCs are the possible link between scented oils and breast growth in boys (reported by *Scientific American*, February 1, 2007), chemicals in cosmetics (reported by 9NEWS, February 1, 2007), and intersex fish in the Potomac basin (reported by the Associated Press, January 19, 2007). Because the issue has been identified as a priority, it is important for scientists and regulators to work closely to ensure that they are moving in the same strategic direction. EDC issues currently under debate include low dose effects, nonmonotonic dose-response relationships, and the relevance of animal findings for humans. For example, the responsibility for addressing endocrine disruption has been divided among many federal agencies. Research to understand basic biology and toxicology is being conducted by EPA, NIEHS, U.S. Food and Drug Administration's (FDA) National Center for Toxicological Research (NCTR), and National Toxicology Program (NTP). Screening programs to detect endocrine disruptors are currently being conducted by EPA, NTP-HTS, and FDA. Monitoring programs are being conducted to measure levels in the environment by USGS and in humans by the Centers for Disease Control and Prevention (CDC). All of these research efforts lead to the need for remediation programs. Endocrine disruption has been linked to a variety of different diseases, not solely related to reproduction. EDCs have developmental, neurological, immunological, and metabolic implications. It is important for government agencies to collaborate and cooperate to translate research into information that can be used appropriately in guiding public health decisions. Also, it is important to understand what has been accomplished since 1996 and to understand where efforts have failed. In addition, there is a need to know the current activities, specifically regarding collaboration and cooperation, to find out what research organizations are conducting complimentary research, what partnerships will yield better science, and what partnerships will advance public health and ecological health. The Toxics and Risk Subcommittee is interested in coordinating a strategic direction to balance this issue against other priorities. By understanding current activities and the future direction of research initiatives, the subcommittee can define the scope of the problem and report back to Congress.

U.S. Geological Survey
Sarah Gerould, Coordinator, Contaminant Biology Program, USGS

Dr. Gerould highlighted the USGS' progress in endocrine disruption research. The mission of USGS is to provide reliable, unbiased science information to enhance the quality of life; the USGS is not a regulatory agency. USGS' research efforts in the area of endocrine disruption have included the study of water and effluent, soil, biosolids, bed sediment, and tissue using analytical techniques, chemical screening, and biomarkers to address exposure and effects on fish and wildlife. The USGS measures exposure using environmental and tissue concentrations and assesses the occurrence, distribution, transport, and fate of chemicals. New exposure technique methods are underway to measure exposure by extracting chemicals from water and air using a screening process to identify compounds that are endocrine active. The USGS also develops new methods to measure exposure by extracting chemicals from water and air using a membrane device coupled with a yeast estrogen screening process to identify compounds that are endocrine active. Another exposure technique developed by the USGS is an avian and fish dosing system to inject pure compounds or mixtures of compounds into eggs. The critical needs for future research include understanding the complete mixtures of hormonally active compounds in U.S. stream ecosystems and wastewater and understanding what chemicals in commonly encountered mixtures are the most potent endocrine disruptors. A series of emerging contaminant surveys related to wastewater treatment plants, septic systems, and CAFOs have been completed. In the laboratory, the USGS is evaluating a variety of different endpoints, species, single EDCs, and mixtures to understand the different effects in different organisms. For example, salmon were studied to understand the effects, and in some cases, the delayed effects, of a variety of chemicals on immune suppression, smoltification, and osmoregulation. Several studies include a laboratory component and a field component. One example is a study of the effect of perchlorate exposure on thyroid function in the leopard frog. Another study assessed polybrominated diphenyl ether (PBDE) flame retardant levels at a computer waste dump site and used a chemical analytical method to determine concentrations in a variety of different organisms. Research is needed to identify the species that are most vulnerable to EDCs, and how sewage treatment systems can be improved to remove EDCs from wastewater effluents. Additional outstanding issues include developing causal links between a chemical and endocrine disruption, developing a national database/Geographic Information System (GIS) of endocrine measurements, and developing biomarkers to determine the significance of endpoints. It would be useful to list all of the endocrine disruption studies being conducted by different federal agencies on a single map.

Discussion

A participant asked where the study of PBDE computer contamination occurred. Dr. Gerould responded that it was in Missouri.

A participant asked about pharmaceuticals in the water supply, specifically in terms of how their location is determined and the remediation methods used. Dr. Gerould answered that it is obviously expensive to remediate everywhere that chemicals exist. The important issue is determining how to expedite the natural attenuation of chemicals and promote the natural degradation of chemicals because of the damage that results from removing chemicals. Source reduction is the best hope for reducing pharmaceuticals in the water supply. Perhaps a multi-agency collaboration can address public education regarding this issue.

U.S. Environmental Protection Agency
Elaine Francis, National Program Director, EPA

Dr. Francis provided an overview of EPA's progress since the 1996 CENR report. In 1996, two legislative mandates, the Food Quality Protection Act and the Safe Drinking Water Act, raised specific scientific questions regarding endocrine disruption, which strongly affected EPA's research program. Chemicals of concern (i.e., pesticides and industrial chemicals) are EPA's responsibility. There is global concern that exposures to some environmental agents interfere with endocrine systems. EPA's Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) has spent $9 million in research to screen a broad universe of chemicals for their human and ecological effects on estrogen, androgen, and thyroid function. The screening program uses a two-tiered approach: Tier 1 includes *in vitro* assays and *in vivo* assays to detect the potential for chemicals to interact with endocrine systems, and Tier 2 includes multigeneration studies covering a broad range of taxa for hazard assessment.

The diverse nature of the endocrine disruption issue requires a multidisciplinary set of research areas for both human health and wildlife that cuts across the risk assessment/risk management paradigm. EPA developed a set of long-term goals that focus on the most critical uncertainties in determining whether humans and wildlife populations are being impacted by levels of EDCs in the environment, identifying the sources of those exposures, and developing approaches to reduce and prevent them. The purpose of the first long-term goal is to provide a better understanding of the science underlying the effects, exposure, assessment, and management of endocrine disruptors. The second long-term goal is to determine the extent of the impact of endocrine disruptors on humans, wildlife, and the environment. The third long-term goal supports EPA's screening and testing program. Examples of laboratory research include determining classes of chemicals that act as EDCs and their potencies, investigating the mode of action of certain EDCs, studying approaches to cumulative risk to EDCs, and determining the dose-response curves for EDCs at environmentally relevant concentrations. It is important to study the impact of developmental exposures in the short term and later in life by characterizing cellular and molecular mechanisms of abnormal reproductive development. The ability to extrapolate across species is an important research activity. EPA is collaborating with other federal agencies and other countries on screening and testing as well as research programs. An example of a collaborative study with the U.S. Fish and Wildlife Service is the assessment of the potential for estrogenic exposure of an endangered species (pallid sturgeon) in the Missouri River. EPA's future direction in addressing endocrine disruption includes considering the recommendations by the external scientific panel at Program Reviews, continuing to develop new methods and tools and applying them to environmentally relevant issues, and expanding EPA's partnerships and collaborations.

Discussion

A participant asked if results from EPA's screening program have driven any changes in laws and regulations. Dr. Francis responded that funded research related to pesticide assessment has been used to set tolerance levels for particular pesticide compounds and has had an impact on understanding the relevance for setting endpoints. The development of the screening and testing assays will be part of the Agency's screening and testing program to be implemented later this year. Additionally, some of the research on perfluorinated chemicals has had an impact on Agency decisions and risk assessments, and EPA is working with industry on developing enforceable consent agreements.

A participant referred to the October 2006, hearing of the House Committee on Government Reform, where EPA was questioned on the status of the testing program, and asked if any changes may have occurred as a result of the hearing. Dr. Gerould asked Gary Timm of EPA to respond. Mr. Timm indicated that the hearing did not have a direct impact on EPA's activities. The development of assays is a slow process and EPA has been trying to put Tier 1 assays in place. EPA has a list of 79 chemicals that will be published in the next few months. Based on recommendations from the scientific advisory panel, EPA will screen the initial list of targets, tweak assays, and complete mid-course corrections before further screening is attempted.

A participant asked if the list of receptor targets will be expanded. Mr. Timm responded that the list will not be expanded at this time. EPA is focusing on its initial goals and it would be difficult to include additional targets.

U.S. Food and Drug Administration
Dave Hattan, Acting Director, Division of Health Effects Evaluation, FDA

Dr. Hattan provided an overview of the FDA's role in the research and monitoring activities of EDCs. The FDA has no legislative mandate to fulfill the mission regarding EDCs in the environment, and little or no budgetary allocations for these purposes. The most significant program that FDA has to study EDCs is an interagency agreement for collaborative studies between FDA, NIEHS, NCTR, and NTP. The NTP supports the program, which includes a multigenerational research and testing program at its research facility in Arkansas. Within this program, FDA has conducted range-finding studies, reproductive studies, and a chronic 2-year study on a range of chemicals, including methoxychlor, vinclozolin, genistein, ethinyl estradiol (EE2), and nonylphenol. These studies assessed the low-dose effects of chemicals believed to have endocrine activity, including the dosing of parents and offspring. Other research included a study of the standard reproductive-developmental toxicity end-points, as well as gross organ and typical NTP tissue histological assessments. The endpoints studied included male mammary glands as well as estrous cycles in the chronic studies. The genistein studies were reviewed by the NTP Board of Scientific Counselors (BOSC) Technical Reports Subcommittee and the Technical Report will be published in 2007. The research on EE2 is scheduled to be reviewed by the NTP BOSC Technical Reports Subcommittee in May 2007, and the report of nonylphenol will be published as an NTP Toxicology Series Report in May 2007.

FDA's Center for Veterinary Medicine also is conducting research (pending funding), in collaboration with the Lombardi Cancer Center at Georgetown Medical Center, to study the genetic markers predictive of endocrine disruption and breast cancer risk in humans. FDA's Center for Drug Evaluation and

Research (CDER) is not currently involved in any specific research on EDCs; however, CDER and all of the FDA centers monitor EPA activities, literature, and news reports of pharmaceuticals and cosmetics with EDC effects. Routine testing of drugs and food additives includes an evaluation of developmental and reproductive effects, as the effects of EDC on species can be extrapolated to humans. When this occurs, various agencies can make a stronger case for implementing legislation to increase budgetary allocation for research and monitoring. FDA's Center for Devices and Radiological Health (CDRH) is conducting preliminary research on phthlates, and has found evidence of low estrogen receptor potency. A study of Bisphenol A (BPA), which is a cross-linking agent in polymers added to many products, has shown positive results on uterotropic assay in addition to changes in heat shock proteins in embryos in this system. A gene activation study in conjunction with George Washington University on the hippocampus of the embryo showed methodological difficulties.

Discussion

A participant commented that no mention was made of monitoring for dietary exposure. A participant from FDA replied that under the National Environmental Policy Act, the FDA has a mandate to look at the environmental impact in the approval process of drugs and food additives. FDA recognizes that it is responsible for assessing EDCs as part of the investigation process. The Center for Veterinary Medicine (CVM) is currently in discussions with FDA's Office of the Commissioner to more thoroughly address the possible endocrine disruption activity of pharmaceuticals as part of the drug approval process. It is not clear whether FDA has the ability to review the endocrine disruption activity of pharmaceuticals retroactively. FDA is currently working with EPA's Office of Water to identify sources of EDCs and with the Office of Science and Technology Policy in their Pharmaceuticals in the Environment Working Group, which includes endocrine disruption in the environment.

Dr. Hattan questioned whether the money is available to investigate these issues to the extent needed; a watershed event is often required to serve as the vehicle for Congress to extend legislative mandates and budgetary allocations.

A participant asked whether industry is required to provide endocrine disrupting activity of pharmaceuticals to FDA. A participant from FDA clarified that environmental assessments are required by pharmaceutical companies as part of the drug approval process as required by the Center for Food Safety and Applied Nutrition (CFSAN), the CDER, and the CVM. The pharmaceutical industry has been conducting environmental impact studies, and it is feasible to ask industry to expand their studies to look at endocrine disrupters, if deemed necessary. The industry has been supportive of FDA's activities surrounding pharmaceuticals in the environment. FDA discontinued the review of pharmaceutical manufacturing effluents and has limited the scope of environmental assessment studies to the use and disposal of pharmaceuticals, which includes assessing the environmental impacts.

Dr. Francis asked to what extent FDA is assessing levels of natural estrogenic compounds, which enter the environment through digestion. Dr. Hattan responded that there are hundreds of naturally occurring estrogenic compounds and FDA is currently studying some of the more common active compounds, such as genistein and daidzein. Most of these compounds are less potent than naturally occurring etiological hormone substances, so it is important to look at the metabolic fate of the materials as well as their effects in the tissue. FDA needs to reconcile the complex issue of the relative contribution of the man-made hormones compared to the naturally occurring hormones, which requires time and effort.

National Institute of Environmental Health Sciences
Jerrold Heindel, Scientific Program Administrator, NIEHS

Dr. Heindel presented the human health-related research efforts of the NIEHS specific to EDCs. NIEHS' mission is to understand the role of gene-environment interactions in disease and dysfunction. They are interested in these areas to provide data that may translate to human health effects. Therefore, funding in these areas is focused on comparative biology and translation to other animal species and humans, with ecological studies as "sentinels" for human health. Thirty NIEHS studies have focused on the impact of exposure of agents on fertility/reproduction, growth and development, puberty, breast cancer, thyroid function, and endometriosis. Exposure agents of specific interest include atrazine, organochlorine pesticides, dioxin/PCBs/polybrominated biphenyls (PBBs), dichloro-diphenyl-trichloroethane (DDT), phthalates, BPA, and phytoestrogens. The NIEHS is interested in how genes are altered by exposure to EDCs during the developmental period, when early exposure causes a greater incidence of disease later in life. In contrast, exposure to EDCs in adulthood may not have long-lasting effects. The NIEHS has solicited several fetal grants to study the epigenetic effects of dioxin, environmental estrogens, phthalates, and PCBs on a variety of diseases.

The NIEHS believes collaborating with other agencies will further the understanding of the degree to which ecological studies with wildlife are consistent with laboratory studies in similar and different species. For example, the vitellogenin response is a common biomarker in wildlife and nonmammalian laboratory species to BPA found in sewage treatment effluent, landfill leachate, and the watershed and marine environments. Responses seen in wildlife (vertebrates) include decreased male reproduction as exemplified by changes in steroidogenesis and/or spermatogenesis. These results are qualitatively consistent with controlled laboratory studies in a variety of species. The NIEHS recommends that the future direction of research focus on several concepts: epigenetics, transgenerational effects, lifespan approach, mixture studies, translation of animal endpoints to humans, improved exposure assessments, and the development of biomarkers of exposure. Specifically, epidemiological studies should focus on exposure (internal doses and biomarkers), mixtures, single nucleotide polymorphisms (SNPs), developmental focus-latent effects, cause and effect, syndromes, biomarkers, and low dose. The issue of endocrine disruption has an image problem resulting from a lack of proper exposure data in humans, the lack of a human "poster child," the lack of focus on diseases in animal models, and the lack of translation of animal data to humans.

Discussion

Dr. Christopher Portier briefly mentioned other studies within the NIEHS that include EDCs, including the Agricultural Health Study and the National Children's Study. In addition, the Sister Study is the only long-term study of women aged 35 to 74 whose sister had breast cancer. It is a national study to learn how environment and genes affect the chances of getting breast cancer. The NTP program is screening known toxicants.

U.S. Fish and Wildlife Service
Roger Helm, Chief, Division of Environmental Quality, FWS

Dr. Helm presented an overview of the U.S. Fish and Wildlife Service's (FWS) research efforts. The Natural Resource Damage Assessment (NRDA) provisions within the Superfund law are used extensively to address significant releases of contaminants and a number of the legacy organochlorine chemicals, which are known as EDCs, such as dioxins, furans, DDT and its metabolites, and the various PCB congeners. The contaminants have been a major focus of several damage assessment cases, and hundreds of millions of dollars have been paid by the companies responsible for their release to clean them up and restore injured natural resources across the United States. Approximately $3 million annually is set aside for field investigations of contaminant effects on FWS trust resources and two-thirds of that amount is specifically earmarked for studies on FWS refuge property. Therefore, the FWS EC program has a budget of $1 million annually for all contaminant-related investigations on nonservice lands and this includes paying for all analytical analyses. As several people have noted, wildlife is clearly being impacted by EDCs and FWS field biologists have played a significant role in documenting those impacts. Nearly all of these studies have centered around field-collected samples which represent direct information about what is going on in the natural world. The FWS has been collaborating with partners to understand the nature and magnitude of the impact of EDCs on wildlife, to identify sources, and to eliminate pathways of exposure. Affected species include migratory birds, certain marine mammals, inter-jurisdictional fishes, threatened and endangered plants, and the animals and habitats that support them. It is now clear that many contaminants are of concern, including many EDCs that are spread worldwide via aerial deposition, as well as legacy chemicals with long-lasting effects. The FWS is a regulatory agency that operates under several laws, including the Endangered Species Act. Over the past 10 years, EDCs have been included as part of a larger study in approximately 10 percent of the studies conducted; few studies are solely focused on EDCs. Research is limited by small sample sizes and a lack of published data. Because of budgetary constraints, the FWS relies on partners to co-lead studies, to provide long-term monitoring efforts, and to develop tools for measuring exposure and detecting effects. The FWS uses an ecosystem-focal area approach to concentrate efforts on restoration, and is primarily focused on marine and freshwater aquatic systems. As a result of data that established highly polluted areas, the FWS conducted a series of Natural Resource Damage Assessments (NRDAs) to restore Lake Apopka in Florida, Fox River in Wisconsin, and resources affected by the Montrose Superfund Site in Southern California. EDCs are negatively affecting wildlife populations, and the FWS has an interest in collaborating with EPA on establishing nontraditional endpoints of ecological risk. The FWS also is working with the American Pharmaceutical Association to develop a media campaign to modify consumer behavior regarding the disposal of unwanted or unused medications. People will be encouraged to dispose of medications in the trash rather than flushing them down the toilet and thereby relatively directly into water courses.

Discussion

A participant noted the lack of studies devoted to EDCs and asked if there are any better opportunities to study them. Dr. Helm responded that budgetary constraints prohibit EDC-related research. He added that virtually all of the data collected by the FSW is of high quality, is published in internal reports, and peer reviewed literature, and is used in making management recommendations and decisions. The FSW is in the position to bring field biology research to other federal agencies as a great resource in addressing the issue.

U.S. Department of Agriculture
Cliff Rice, Research Chemist, Agricultural Research Service, USDA

Dr. Rice presented the Agricultural Research Service's (ARS) role and priority interests related to endocrine disruption in the environment. Many suspected EDCs are used in agriculture (e.g., DDT, lindane, and pyrethroid pesticides). The U.S. Department of Agriculture's (USDA) priority interest is to maintain healthy and productive farming operations in a sustainable way. The USDA has focused on the EDCs that are natural products, such as endogenous hormones in animals and animal wastes. The USDA is not a regulatory agency; therefore, its primary role is to recommend, advise, and quarantine. In cooperation with land-grant universities, the ARS has completed multistate research on pesticides, CAFOs, and veterinary pharmaceuticals. In collaboration with EPA, USDA has been involved in the remediation of agricultural risks, such as total daily maximum loads (TMDLs). The USDA has an interest in furthering the understanding of how compounds used and produced in agriculture move and are changed in the environment, such as the reuse of animal wastes (fertilizer) as a source of endocrine disruptors in the environment. ARS research projects include frog deformity studies (investigating possible links to water chemistry); manure management to mitigate natural and anthropogenic contaminants, including nutrients and pathogens; and groundwater leaching of animal wastes.

ARS has collaborated with EPA and the USGS to study nonylphenol ethoxylates in effluent-dominated streams. To identify ecological populations that may be at risk, especially in aquatic and terrestrial systems, ARS is collaborating with USGS and EPA on a study of fish as biomarkers and chemical measurements in the North Channel of the Chicago River. USDA's monitoring activities and methods development for the detection and assessment of EDC exposure and effects are minimal; however, the Natural Resources Conservation Service (NRCS) and Farm Service Agency (FSA) are incorporating the monitoring of EDCs, especially for CAFOs, into their best management practices (BMPs). Methods development is mostly done in concert with FDA or EPA, such as those developed for alkylphenol ethoxylates, roctopamine, and LC/MS steroids. The USDA does not directly sponsor environmental research on EDC effects on wildlife, but does utilize tools developed by other agencies (e.g., vitellogenin and measure of natural hormone pools). Remediation is a major focus of research as demonstrated by animal waste studies (pathogens and hormones), the use of composting to remove nutrients and other pollutants, and the use of natural wetlands to mitigate animal wastes. The challenges to ARS include a need to analyze EDCs at the tissue level and to understand mixture effects, including synergism, enhanced availability (surfactant interactions), and beneficial interactions.

National Oceanic and Atmospheric Administration
Tony Pait, National Ocean Service, NOAA

Dr. Pait presented an overview of NOAA's research and monitoring activities related to the impact of EDCs on the developmental and reproductive biology of marine and estuarine species. Endocrine disruptor research cuts across NOAA's strategic objectives of building sustainable fisheries, recovering protected species and promoting healthy coastal ecosystems. Understanding the impact of EDCs on the developmental and reproductive biology of marine and anadromous fish, marine mammals, sea turtles, and marine invertebrates is especially relevant. NOAA's responsibilities include acting as a trustee for marine resources, including fish, shellfish, and marine mammals, for marine protected areas (e.g., sanctuaries). NOAA also is responsible for protection and recovery of marine species listed under the Endangered Species Act (ESA), such as pacific salmon and killer whales. Natural resource damage assessment and restoration is another area of responsibility. Contaminants are a potential source of damage to marine resources. NOAA is particularly interested in understanding if EDC exposures are sufficient to affect critical processes such as growth, development, metabolism, reproduction and disease resistance, and the threshold concentrations associated with effects. Another area of interest is the human health concerns resulting from the consumption of seafood contaminated with one or more EDCs. Typical projects include assay development and application (e.g., vitellogenin, pituitary hormones, and analytical methods for contaminants); laboratory studies (e.g., exposure to contaminants); environmental monitoring (concentrations in sediment, water, biota); and ecological studies. A laboratory study of Coho salmon has shown that ethynyl estradiol suppresses FSH and increases LH gene expression. Environmental monitoring efforts by NOAA include measuring PBDEs in salmon. The Mussel Watch Project has focused its efforts on monitoring contaminants over a 20-year period at approximately 250 sites in coastal and estuarine waters. Approximately 120 organic and inorganic compounds, including PAHs, PCBs, and chlorinated pesticides, are measured on a regular basis. Field studies of English sole have shown contaminant-related impacts on spawning as well as on percentage of fertile eggs and larval development. NOAA will continue to work with other federal agencies to optimize the use of resources and expertise to evaluate endocrine disruption in the Nation's coastal waters. NOAA is currently collaborating with USGS, USDA, and FWS on research.

Discussion

A participant asked how information is translated into action, specifically in terms of how the information is used. Dr. Pait responded that NOAA's work is published in scientific journals and the Internet. In terms of action, information is provided to decision makers. For example, technical support is provided to NOAA's regulatory office for siting and permitting of sewage treatment plants.

U.S. Department of Defense
Mark Johnson, Aberdeen Proving Ground, U.S. Army

Dr. Johnson discussed the U.S. Department of Defense's (DoD) efforts related to investigating the potential for reproductive or endocrine disrupting effects of chemicals. The mission of the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM)is to provide health promotion and preventive medicine leadership and services to identify, assess, and counter environmental, occupational, and disease threats to health, fitness, and readiness in support of the National Military Strategy. The DoD's environmental toxicology research laboratories conduct the following activities related to endocrine disruption: exposure, risk characterization, monitoring, and collaboration. Environmental contamination occurs from explosives manufacturing, load and pack plants, ranges, and open burn/open detonation areas. Significant amounts of money are spent on cleanup efforts. Funding has been relegated to reactive toxicology methods to respond to public concerns and includes addressing data gaps and improving chemical analysis methods, though these efforts are not specifically focused on endocrine disruption. The DoD has made progress only recently in developing proactive methods for investigating the endocrine disrupting potential of military-specific substances before they are used. Wildlife toxicity is often determined for new and legacy compounds using a controlled laboratory design. New efforts are underway to collect information needed to understand the environmental effects from the use of new compounds using model projection (e.g., Quantitative Structural Activities Relationships [QSARs]). QSAR predictions are used to help ascertain toxicity targets *a* priori and to help focus histopathological assessments. Data from these models are used to address relative toxicity, determine lethal and sublethal exposure endpoints, and develop monitoring efforts and safe levels of exposure. These data are regularly published as peer-reviewed reports, and summarized in Wildlife Toxicity Assessments published by the USACHPPM New models for estimating exposure and calculating risk include the Adaptive Risk Assessment Modeling System (ARAMS), and the incorporation of fate and transport models, exposure models, and toxicity values in a single interface. Spatially explicit models for wildlife show promise in providing greatly enhanced estimates of exposure and risk from environmental exposures. New advances in analytical chemistry methods have resulted in lowering detection limits of many compounds and have fueled additional research, such as studies on perchlorate.

Few DoD laboratories have the mission and the resources to conduct wildlife toxicity studies. The Strategic Environmental Research and Development Program (SERDP) and the Environmental Security Technology Certification Program (ESTCP) are two DoD mechanisms dedicated to funding such efforts; however, they typically do not fund laboratory animal studies relevant to human health extrapolation. The Army Environmental Quality Technology Program and the Defense Environmental Restoration Program have been instrumental in providing funding for toxicity studies aimed at specific applications, with the focus on restoration, pollution prevention, conservation, and compliance.

BREAKOUT GROUPS

Participants attended four different breakout sessions, each representing a different area of study related to endocrine disruption: Chemistry/Analytical Methods, Exposure/Monitoring, Effects/Physiology, and Risk Assessment. Each breakout discussion group was instructed to address the following questions:

(1) Summarize what collaborations exist or have occurred across federal organizations within each breakout group category.

   (a) Identify what things work best to develop successful interagency collaborations.
   (b) Identify what are the most significant impediments to successful interagency collaborations.

(2) Identify what we know (federal and non-federal science) and have documented very well within each breakout group category.

(3) Identify what the data gaps are, what questions still need to be answered, and what still needs to be done within each breakout group category.

(4) What expertise do we have within each federal organization that can address these data gap questions within each of the breakout group categories?

(5) If possible, develop specific interagency research proposals that might develop during the breakout group discussion.

FEBRUARY 22, 2007

FINALIZATION OF BREAKOUT SESSION FINDINGS AND RECOMMENDATIONS

The following summaries were provided by a moderator from each breakout discussion.

Chemistry/Analytical Methods Group

Moderators: Marc Mills, EPA
James Gray, USGS

The chemistry/analytical methods group used the five questions as a framework for their discussion. The group identified two key issues for successful collaborative efforts: face-to-face meetings with scientists and bottom-up collaborations. Another successful approach is to develop analytical methods for a class of compounds and then present them to other agencies for collaboration. Defining data quality objectives at the onset of a project, collaborating informally, and providing "in-kind" services also are important for interagency collaborations. A meeting of potential collaborators can facilitate a discussion of mutual benefits and eliminate the formal process of exchanging funds, which can delay the project.

Impediments to successful collaborations are interagency agreements, which can be difficult to execute due to government sole sources. A lack of integrated planning also can be a severe impediment to collaborations. Joint planning is necessary to provide management support and the best allocation of resources, including funding, personnel, and equipment. Without this step, the project could become an "unfunded mandate" and would have to be wedged between other projects. Authorship is an important discussion that needs to be addressed at the onset of a study. Roles and responsibilities need to be defined to facilitate a fair and even exchange. The final impediment noted was the different stresses that agencies face, which can impact their schedules and ability to collaborate (i.e., fire drills and administrative burdens).

Examples of interagency collaborations include:

- Global Water Research Coalition (GWRC) inter-comparison, in-kind interagency agreement (EPA, USGS, International Community)
- Fee-for-service analytical support (EPA, USGS)
- Pharmaceuticals in wastewater in-kind interagency agreement (EPA, USGS
- Enzyme linked immunosorbent assay (ELISA) evaluation round robin, in-kind interagency agreement (EPA, USGS, Industry)
- Wastewater treatment fate study (EPA Great Lakes National Program Office, USGS, USDA)
- Land application of CAFOs effluent interagency agreement (EPA, USDA, RARE)
- Ground water impacts of poultry CAFOs in-kind interagency agreement (EPA ORD, Region 4, USGS)

In terms of identifying data gaps, many participants mentioned methods that have been used within their own agencies, but concluded that a proactive approach is best (e.g., compiling a list of compounds for targeted analysis). Several other challenges exist regarding clean-up: instrumentation, hydrolysis for conjugates, and sample preparation. Because of these clean-up issues, results can be very difficult to reproduce from laboratory to laboratory. Collaborating on the synthesis of standards between agencies would help.

Developing interagency personnel agreements to foster collaboration and to transfer knowledge between agencies would expedite methods development. Expanding round-table discussions internationally should also be considered, as the United States can benefit from research conducted by other nations.

Proposals for specific interagency collaboration include an interagency work group or discussion forum to keep the lines of communication open and maintain the momentum. An important issue that was discussed was the need for a centralized federal laboratory to analyze tissues. All participants agreed that this is a difficult objective to achieve, in part because of the lack of flexibility needed to conduct effective research. Another solution would be to develop a core analytical group. The group concurred that collaborative planning and integrated research would be a better solution for dividing and conquering the analytical methods development between agencies.

Discussion

A participant asked about the possibility of collaborating with the National Institute of Standards and Technology (NIST) for assistance with standards. Another participant responded that NIST currently provides contaminant analyses and conducts interlaboratory comparisons (nationally and internationally) for marine mammal tissue for NOAA's National Marine Fisheries Service. Dr. Mills clarified that the idea is not to reinvent methods for standards. If information is available or if mechanisms are currently in place, then they should be used.

A participant commented that the Consumer Product Safety Commission (CPSC) has been involved with FDA and EPA on projects that involve methods development. It was a positive experience for everyone involved. With regard to international collaboration, the United States has guidelines for the mutual acceptance of data with the Organization for Economic Cooperation and Development (OECD) countries. Once the OECD countries have accepted data, the United States also is required to accept the data.

A participant commented that FDA has associations with the mutually acceptable data package and test guidelines promulgated by the OECD; however, FDA has additional latitude that obligates them to accept that information, but it does not mean that FDA cannot accept additional information.

Exposure/Monitoring Group

Moderators: James Lazorchak, EPA
Dana Kolpin, USGS

The exposure/monitoring group discussed ongoing collaborations and the effects of chemical exposures and monitoring efforts on fish populations in rivers and streams. The group included participants from EPA, USGS, FDA, NOAA, and USDA. Collaborations have occurred between many of these agencies and within agencies to examine the biochemistry of hormones and the adverse effects of EDCs, primarily on fish. Examples of recent or current collaborations include:

- EPA and the Nebraska U.S. Fish and Wildlife Association to study the habitats of sturgeons and possible exposure to estrogens;

- A national study with EPA Region 5, USGS, and USDA to examine pharmaceuticals in fish fillets and fish livers;

- EPA's Office of Research and Development (ORD), National Center for Environmental Assessment (NCEA) and National Health and Environmental Effects Research Laboratory (NHEERL) to study recent fish kills in the North Fork, Virginia, area;

- USDA and the University of Maryland to study the effects of poultry waste on fish;

- EPA and USGS to study pesticides, particularly atrazine, in surface water;

- NOAA, USDA, USGS, and EPA to study the effect of pharmaceuticals on fish and wildlife in streams; and

- USGS and the FWS to monitor large rivers, including the Mississippi and Rio Grande, for chemistry data and tissue analysis on fish.

Although many of these collaborations focus on chemical effects in rivers and streams, intersex conditions also are a priority. Causes of intersex in fish, background rate of intersex, and normal rates of intersex within specific fish populations currently are being examined through collaborative work.

Successful collaboration depends on many factors. Local support from state agencies and publicly owned treatment works (POTW) is needed, and agencies must be flexible and willing to negotiate among parties to address broad research goals. Collection of samples and subsequent research will be affected by the responsiveness of the collaborators involved. Clear objectives also are needed when planning collaborative projects.

Planning cycles should be identified and better synchronized to give researchers time to plan collaborative projects far in advance, which can help ensure enough field study time and prevent duplicate research efforts. Specific lists of tissue and other samples enable a more efficient and effective collaboration. Geographic proximity of researchers often facilitates collaboration, but regular conferences and briefings to coordinate and link information also can be effective. Web sites should be developed to introduce and track new and current studies, with regional or local information shared through listservs. GIS and interactive mapping, with all sites georeferenced, also could be used to keep agencies informed of collaborative efforts.

Impediments to effective collaborations include difficulties in transferring funds between and within agencies. Currently, forums for discussion are lacking, and there are few mechanisms for communication within and across agencies. Better interagency briefings also are needed. Too often, similar studies by a single agency are being developed, which can be more costly and less effective than collaborative efforts. Several characteristics of the federal effort make collaboration difficult, such as multiple disciplinary areas; broad geographical distributions of agencies; and varied priorities, missions, and cultures.

Monitoring programs and tools are needed to study conditions before problems occur. Many existing monitoring programs could be linked to similar areas or conditions, and information could be synchronized. This effort would facilitate methods sharing among federal and state agencies and help eliminate the current database gap, as well as encourage preliminary research on areas under threat. Networks should be developed to communicate existing research and data gathering methods to agencies so that opportunities for collaborative projects are not lost. One option is a centrally managed database or clearinghouse of methods that is regularly updated and maintained.

Better methods are needed to share exposure data, and integrated research results should be readily available. Agencies should be encouraged to establish consistent approaches concerning EDC assessments, with integrative analysis on the effects of EDCs on fish. Currently, there is a lack of research on terrestrial routes of chemical exposure. Biosolids create chemical exposure issues for fish, but this problem has not been researched thoroughly because there are few existing comprehensive monitoring EDC programs for wildlife and terrestrial routes. Intersex—its causes and effects on fish populations and communities—represents a reproductive health data gap that should be more thoroughly addressed. Other "hot spots" and possible sensitive populations also must be considered.

Questions remain concerning the best way to search for cumulative and mixture exposure and how to link such exposures to effects seen in fish populations. The effect of different chemical compounds on fish populations has not been determined. Linking chemical and biological approaches using biomarkers could help move the research forward. One such program, Biomonitoring of Environmental Status and Trends (BEST), may soon be discontinued, but researchers hope to use the endpoints from the program to advance EDC research.

Effects/Physiology Group

Moderators: Joe Tietge, EPA
Don Tillitt, USGS

The effects/physiology group agreed that a solid body of evidence is needed to determine whether EDCs have a specific effect on organisms, if this effect is transmitted to the population or community level, and the sources of EDCs. A number of data gaps regarding this issue exist and must be addressed. Current research focuses on androgen, estrogen, and thyroid hormone receptor activity, but other steroids may need to be examined. There is a lack of clean references, controls, and standards for determining "baseline" EDC levels. There also is a lack of clean, laboratory-based experiments; fish are contaminated at sites and by food or plastics containing EDCs.

Other challenges to understanding the effects of EDCs on organisms and populations include determining the effects of life histories and migration patterns on exposure with respect to dose and sensitive exposure periods. This cannot be studied in the laboratory, but could be addressed through field research. Although models exist that hypothesize the effects of exposure, there is a lack of data linking exposure markers to biological effects. Additionally, wildlife (and humans) usually is exposed to mixtures of EDCs and these mixtures may have different compositions at different times of exposure. The phenomenon of EDC affects on fish is associated with effluents, but the identities of all chemicals contained in these effluents are not known, which hinders researchers' abilities to perform diagnostic tests in the field. A battery of high throughput screening assays for different EDCs that can be used to assess sensitivity across species would be useful.

Expertise to address some of the specific issues in understanding the effects of EDCs on organisms and populations exists in several federal agencies, underscoring the need for collaboration and an integrated approach to this issue. To create enthusiasm for a cross-agency initiative to advance research on the effects of EDCs, a project with high visibility exploring potential wide-ranging effects on human health is needed. An issue around which to build this collaboration is the phenomenon of intersex fish. EDCs are believed to be involved in this phenomenon, but there is a lack of conclusive data regarding mechanisms, population effects, and effects on ecosystems/wildlife and human health. Because humans drink the water that may contain EDCs, this issue is highly relevant to human health; fish may be the proverbial "canaries in the coal mine." Intersex fish and EDCs are found in water sources across the nation and this issue is a matter of interest to numerous federal agencies and political constituencies. Addressing this situation will require many kinds of scientific expertise and research activities from a number of agencies, including those with regulatory mandates; the dearth of conclusive data connecting EDCs to population-level effects could make regulation of these chemicals difficult. Therefore, a multiagency collaboration is needed to address the issue of EDCs in water sources, focused on the phenomenon of intersex fish. Differences between federal agencies, including differences in funding, cultures, and mandates may make collaboration challenging, but the potentially wide-ranging and multilevel impact of EDCs make it likely that research issues around this problem will fit with most agencies' mandated activities. A united interagency voice to address Congress regarding funding issues might help prevent some budget cuts. Agencies also should consider working together to develop a set of slides describing activities across agencies that can be used as working materials for meetings with Congress or can be provided to advocacy and grassroots organizations to aid their efforts. Other ways to improve communication across agencies include developing workshops, teleconferences, webcasts, listservs, and bloglists as forums for scientists to share their research.

A specific proposal to build this collaboration was developed by the group. A 2002 report by World Health Organization (WHO) on human and ecological health assessed EDCs and their potential effects on breast cancer, prostate cancer, semen quality changes, and behavior (for PCBs). The report writers worked with epidemiologists to develop a set of criteria to determine whether these were true effects of EDCs. This report represents a useful data source and starting point for a new analysis of EDC effects centered on the existence of intersex fish in the nation's water bodies. This new report will summarize the current state of knowledge and will be a basis for future research plans. The goal of this effort is to focus and coordinate current knowledge and research activities across agencies. Using the 2002 WHO report as a framework, this report will provide a new synthesis of existing information, coordinate existing federal research, identify and recommend new research and next steps, and suggest ways for agencies to collaborate and commit existing resources to efficiently address knowledge gaps and reduce redundancy and duplication of efforts. The highlights of the proposed effort, The National Evaluation of EDCs and Intersex in Fish: An Integrative Assessment of Reproductive Health in Humans and Wildlife, are detailed below.

The presence of intersex in fish suggests that there may be EDC effects in the environment. Numerous federal agencies are conducting relevant studies, but there is no current effort to coordinate research and integrate the results. An integrative analysis of EDC effects on fish, combined with data from published literature, is needed to provide a comprehensive analysis on the effects of EDCs on reproductive health and assessment of implications for human health and wildlife. Numerous federal agencies have existing EDC-related programs, which can generate relevant data using their unique capabilities. For example, the FWS has many research sites, allowing data to be gathered from a large geographical context.

There are several aspects to the federal effort that makes conducting such an analysis difficult, yet necessary. Federal agencies focus on multiple disciplinary areas, have broad geographical distributions, and have different priorities, missions, cultures, and funding status.

Topics to consider in this integrated analysis include:

1. Mixtures
2. Chemical representation in laboratory effects studies
3. Laboratory to field linkages
4. Field effects and population assessments/modeling
5. Inter-species extrapolation
6. Incorporation of new endpoints

7. Inter-chemical extrapolation
8. Low dose effects
9. Dose-response types
10. *In vitro/in vivo* extrapolation
11. Endpoint sensitivity
12. Risk relevancy
13. Linkage to exposure information
14. Absorption/distribution/metabolism/excretion (ADME)
15. Implications of species specific life history strategies—dose-response, sensitive periods.

These topics should be prioritized and focused based on the Hill Criteria of Causation. This effort is focused largely on potential reproductive impairment in fish, but a strong comparative approach with human health must be maintained to ensure relevancy, provide for extrapolative potential (particularly with conserved elements of endocrine systems), and maintain engagement of health expertise (to maintain a relationship to human health).

Implementation of this project includes convening an initial committee with broad disciplinary and organizational representation and a strong technical character followed by the development of a document surveying existing data and refining objectives, roles, and responsibilities, and describing a detailed plan for conducting analyses. A phased approach calls for review of the 2002 WHO report as a baseline; a new evaluation and synthesis of existing data; identification of specific framework needs; development of a framework for case study analysis; coordination of existing federal research with existing resources; and recommendations for new research and next steps.

Discussion

A participant asked if the intent of the proposal was to analyze existing data or to collect new data. Dr. Tietge responded that the initial phase of the project would use the WHO 2002 data as a platform for the evaluation of new data as well as the synthesis of existing data. He indicated that the approach will be "smarter" to be able to identify the data gaps.

A participant asked why the group targeted only one endpoint (i.e., intersex fish), instead of considering a broader scope of endpoints that could create a national resource and also be economically advantageous. Dr. Tietge responded that the group considered expanding the research to study the effects of EDCs on reproductive health, but because of limited resources, decided to focus on the issue of intersex. Dr. Tietge acknowledged that more information is better, provided that there are no cost implications. If you collaborate with people from four or five organizations, the idea of expanding the scope becomes an exponentially complicating factor.

A participant asked why the group decided to conduct this analysis on a national scale rather than approach the issue on a local scale (using detail-oriented process studies). Dr. Tietge responded that the intent was to conduct a larger analysis as a meta approach, rather than a site-specific approach. A participant suggested selecting certain pilot areas that would allow detailed analyses of field monitoring to establish relationships measured in the laboratory with effects in the field to correlate the effects of exposure. If the focus is on one local area, the focus can be used as a proof of principle that is then distributed nationally to discuss the implications across the nation. This is a national issue, so it has to be addressed on that scale. The national survey has the power to provide resources. A suggestion was made to use a smaller spatial scale and then develop a compelling argument on a national basis.

Dr. Francis commented that in 2005, the WHO convened a smaller panel for the purpose of updating data from some of the smaller case studies. EPA participated in these discussions, which resulted in a plan for a larger followup workshop to assess all of the case studies to see where additional data can contribute to either strengthen or weaken the associations of the findings made in 2002.

Risk Assessment Group

Moderators: Charles Eirkson, FDA
Les Touart, EPA

The risk assessment group focused on identifying data gaps and developing research proposals to address the issue of risk assessment as it relates to endocrine disruption. The risk assessment implications of several issues emerged and the discussion was geared towards research needs and the appropriate interagency collaborative efforts. The issues raised took into consideration those that are required to protect human health and the environment.

One important issue that was discussed was the requirement for data-sharing tools for assessing risk. The group strongly agreed that databases, surveys, and archives are needed to make information more accessible. From the human health perspective, the quality of the data is important as a means to leverage further study. A specific recommendation for increased collaboration is to create a central clearinghouse for information. It was acknowledged that issues of confidentiality are inherent in this effort.

The dose-response relationship was viewed as another important area that would benefit from a collaborative research effort. The group recommended conducting an interagency workshop to discuss how to interpret dose-response relationships, specifically for low dose and nonmonotonic dose issues. In terms of the risk assessment framework and problem formulation, the group recommended establishing consistent approaches across agencies for EDC assessments. To this end, it was proposed to establish an interagency risk assessment advisory work group (NTP executive committee subgroup or lead agency group) to manage risk assessment issues across agencies.

Another important issue is defining what constitutes an adverse effect, and the consensus recommendation was to conduct a detailed analysis on a single defined system (such as a reproductive system in fish) to improve understanding. This type of study would create an opportunity for dialogue across agencies, such as a colloquium to understand agency concerns.

The cause-and-effect relationships from the molecular level to the organism level to the population level is another issue that was raised. The question becomes how we interpret or characterize the effect to determine causal effect. Collaboration across agencies is needed to further an understanding of how a particular effect correlates with one particular level of organization.

The issue of risk characterization was discussed in terms of how risks are communicated. The group recommended cross-agency comparisons for targeted compounds in an effort to identify compounds that have common interests and to promote interagency collaboration (i.e., a risk assessment toolbox).

Other issues that would benefit from collaborative efforts include species extrapolation (including human/wildlife), data gaps and lack of knowledge, particularly in terms of data quality, and exposure (source/fate). These items were identified, but no specific recommendations were provided.

Discussion

A participant asked if the issues were listed in any priority order. Dr. Touart answered that the list was narrowed down from a larger list of issues, but the issues are not ranked in any specific order of priority.

A participant asked if the discussions pertain to EDCs. Dr. Touart acknowledged that these issues cross over to other areas, but they are specific to EDCs, such as the need to address dose-response relationships and low dose issues.

A participant commented that all of the discussion groups have mentioned the fragmented bioevaluation programs that need to be coordinated into a national database.

WORKSHOP CONCLUSIONS AND NEXT STEPS

Elaine Francis, National Program Director, EPA

Dr. Francis stated that the overall objective of the workshop—to understand the progress of individual agency research activities related to endocrine disruption over the past 10 years—was successfully met through the research summary presentations, as well as through the posters and abstract presentations. Important information was gathered from the inventories completed by participants concerning the current research on the ecological effects and exposure assessments, as well as from the last 5 years. The third objective of the workshop was to identify opportunities for interagency collaboration, and the plenary discussions from each of the breakout groups were successful in providing a framework for the best approaches for continuing collaborations.

The next steps include: (1) identifying individuals to develop the framework and draft the report; (2) compiling an integrated bibliography of published federally supported research studies (intramural and extramural) over the last 10 years; and (3) compiling an interagency monitoring database with locations and layered information. A complementary workshop on human health will be held August 26-29, 2007, in Durham, North Carolina, and outcomes from this workshop will be integrated into the program. A report will be provided at the next Toxics and Risk Subcommittee meeting on March 22, 2007. Dr. Francis thanked all of the speakers, the agency representatives, the moderators of the breakout discussion groups, the participants, the poster presenters, the organizing committee, and the planners for their participation and valuable input. The meeting adjourned at 12:00 p.m.

U.S. Environmental Protection Agency
CENR Federal Interagency Workshop on Endocrine Disruption in the Environment

U.S. Geological Survey
National Center Auditorium
Reston, VA

February 20-22, 2007

Participants List

<u>Presenters</u>

Suzanne Fitzpatrick
U.S. Food and Drug Administration

Elaine Francis
U.S. Environmental Protection Agency

Sarah Gerould
U.S. Geological Survey

James Gray
U.S. Geological Survey

Sue Haseltine
U.S. Geological Survey

Dave Hattan
U.S. Food and Drug Administration

Jerrold Heindel
National Institutes of Health

Roger Helm
U.S. Fish and Wildlife Service

Mark Johnson
U.S. Army

Dana Kolpin
U.S. Geological Survey

James Lazorchak
U.S. Environmental Protection Agency

Marc Mills
U.S. Environmental Protection Agency

Tony Pait
National Oceanic and Atmospheric Administration

Christopher Portier
National Institutes of Health

Cliff Rice
U.S. Department of Agriculture

Joseph Tietge
U.S. Environmental Protection Agency

Donald Tillitt
U.S. Geological Survey

Leslie Touart
U.S. Environmental Protection Agency

Glen Van Der Kraak
University of Guelph

<u>Participants</u>

Carolyn Acheson
U.S. Environmental Protection Agency

William Allaben
U.S. Food and Drug Administration

David Alvarez
U.S. Geological Survey

Gerald Ankley
U.S. Environmental Protection Agency

Layla Batarseh
U.S. Food and Drug Administration

Elizabeth Bayne
ASPH/EPA Fellow
U.S. Environmental Protection Agency

Joseph Beaman
U.S. Environmental Protection Agency

Don Bergfelt
U.S. Environmental Protection Agency

Patricia Bittner
U.S. Consumer Product Safety Commission

Vicki Blazer
U.S. Geological Survey

Raanan Bloom
U.S. Food and Drug Administration

Michael Bolger
U.S. Food and Drug Administration

Bryan Boulanger
U.S. Environmental Protection Agency

Herb Buxton
U.S. Geological Survey

Tracy Collier
National Oceanic and Atmospheric Administration

Octavia Conerly
U.S. Environmental Protection Agency

Tara Conrad
U.S. Department of the Interior

Ralph Cooper
U.S. Environmental Protection Agency

Kevin Crofton
U.S. Environmental Protection Agency

Andrew Draxler
National Oceanic and Atmospheric Administration

Diana Eignor
U.S. Environmental Protection Agency

Charles Eirkson
U.S. Food and Drug Administration

Brian Englert
U.S. Environmental Protection Agency

Mike Focazio
U.S. Geological Survey

Jack Fowle
U.S. Environmental Protection Agency

John French
U.S. Geological Survey
Mary Gilbert
U.S. Environmental Protection Agency

Steven Goodbred
U.S. Geological Survey

Christiana Grim
U.S. Environmental Protection Agency

Chris Guy
U.S. Fish and Wildlife Service

Rosemary Hall
U.S. Environmental Protection Agency

Stephen Hutchins
U.S. Environmental Protection Agency

Abigail Jacobs
U.S. Food and Drug Administration

Jill Jenkins
U.S. Geological Survey

Natalie Karouna-Renier
U.S. Geological Survey

Abu Khan
U.S. Food and Drug Administration

Susan Laessig
U.S. Environmental Protection Agency

Michael Mac
U.S. Geological Survey

Susan Makris
U.S. Environmental Protection Agency

Greg Masson
U.S. Fish and Wildlife Service

Alec Maule
U.S. Geological Survey

Annette McCarthy
U.S. Food and Drug Administration

Jesse Meiller
U.S. Environmental Protection Agency

Lesley Mills
U.S. Environmental Protection Agency

Donna Myers
U.S. Geological Survey

Todd Nettesheim
U.S. Environmental Protection Agency

George Noguchi
U.S. Fish and Wildlife Service

Edward Ohanian
U.S. Environmental Protection Agency

Diana Papoulias
U.S. Geological Survey

Reynaldo Patino
U.S. Geological Survey

Hardy Pearce
U.S. Geological Survey

Fred Pinkney
U.S. Fish and Wildlife Service

Michael Quinn
U.S. Army

Lou Reynolds
U.S. Environmental Protection Agency

Bruce Rodan
Office of Science and Technology Policy

Mary Ann Rozum
U.S. Department of Agriculture

Suzanne Rudzinski
U.S. Environmental Protection Agency

Kathy Schenck
U.S. Environmental Protection Agency

Carl Schreck
U.S. Geological Survey

Leanne Stahl
U.S. Environmental Protection Agency

Tammy Stoker
U.S. Environmental Protection Agency

Shirlee Tan
U.S. Environmental Protection Agency

Gary Timm
U.S. Environmental Protection Agency

Michelle Twaroski
U.S. Food and Drug Administration

John Wathen
U.S. Environmental Protection Agency

Janet Whaley
National Oceanic and Atmospheric Administration

Katrina White
U.S. Food and Drug Administration

Vickie Wilson
U.S. Environmental Protection Agency

K. R. Young
U.S. Environmental Protection Agency

John Zogorski
U.S. Geological Survey

Contractor Support

Lauren Firestone
The Scientific Consulting Group, Inc.

John Hare
The Scientific Consulting Group, Inc.

Nanci Hemberger
The Scientific Consulting Group, Inc.

Laura Kramer
The Scientific Consulting Group, Inc.

Stefanie Nelson
The Scientific Consulting Group, Inc.