Board of Scientific Counselors

Office of Research and Development
United States Environmental Protection Agency

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Endocrine Disrupting Chemicals (EDC) Research Program Review

Final Report of the Subcommittee on Endocrine Disrupting Chemicals

March 4, 2005
Revised April 21, 2005

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PROGRAM REVIEW REPORT
OF THE
BOARD OF SCIENTIFIC COUNSELORS

ENDOCRINE DISRUPTING CHEMICALS (EDC) RESEARCH PROGRAM

Office of Research and Development
U.S. Environmental Protection Agency

MARCH 4, 2005
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I. EXECUTIVE SUMMARY

Overall Goals and Charge

The National Academy of Sciences has recommended independent expert review for evaluating federal research programs. The U.S. Environmental Protection Agency's (EPA's) Office of Research and Development (ORD) is committed to independent expert review of its environmental research programs for objective evaluation of research at the program level, to establish "best practices" in federal research program design, management, and evaluation, and to assist the Agency in preparing performance and accountability reports to Congress under the Government Performance and Results Act of 1993.

The Board of Scientific Counselors (BOSC) Executive Committee agreed in May 2004 to undertake two pilot program reviews—the Endocrine Disrupting Chemicals (EDC) Program and the Global Change Program reviews. The BOSC formed a subcommittee to provide a program review of the EDC research program of EPA's ORD. This subcommittee was charged with reviewing ORD's EDC program and providing a report to the BOSC Executive Committee. The results of these pilot reviews will guide future BOSC program reviews.

This pilot program review differs from previous Multi-Year Plan (MYP) reviews in that it includes a retrospective as well as a prospective evaluation, examining progress made to date and the future direction of the EPA research in this program. The program review is intended to provide guidance that will help ORD: (1) assess the progress and direction of the EDC research program; (2) plan, implement, and strengthen the program; (3) make research investment decisions over the next 5 years; (4) compare the program with programs designed to achieve similar outcomes in other parts of EPA and in other federal agencies; and (5) prepare EPA's performance and accountability reports to Congress under the Government Performance and Results Act (GPRA) of 1993.

The objective of the EDC program review was to review the relevance, quality, performance, scientific leadership, and resources of the program (see Appendix A). The subcommittee responded to a series of questions organized into five broad charge questions, which were framed to solicit comments on the program's: (1) design; (2) relevance; (3) progress in addressing key scientific questions and impacting environmental decisionmaking; (4) contributions to scientific leadership; and (5) resource allocation. The subcommittee chose to organize the review around the three long-term goals presented in the MYP, commenting and responding to the questions and factors noted in the first three charge questions (i.e., program design, program relevance, program progress/performance) for each long-term goal. Charge questions four and five (leadership and resource allocation) were evaluated separately, as they crosscut the overall program.

Background for the EDC Research Program

In the early 1990s, a number of scientists began to synthesize information about the potential impacts of endocrine-mediated toxicity on humans and wildlife, arriving at the hypothesis that weakly endocrine-active compounds in the environment were having significant adverse effects on public and environmental health (Colborn and Clement, 1992)[1]. In response, EPA convened two international workshops in 1995 (Kavlock, et al., 1996; Ankley, et al., 1997)[2,3] at which uncertainties and research needs relative to future risk assessments for EDCs were highlighted. These workshops identified effects on reproductive, neurological, and immunological function and carcinogenesis as the major endpoints of concern and made a number of recommendations for research. The workshops served as the basis for establishing national research efforts that spanned the entire federal government, as well as international efforts. The *Multi-Year Plan (FY2000-2012) for Endocrine Disruptors* covers a considerable fraction of the research identified by the scientific community as being important for understanding the impact of endocrine disruptors. Collectively, chemicals with the potential to interfere with the function of endocrine systems are called endocrine disruptors or endocrine disrupting chemicals.

A recent publication by experts in the field identifies 10 key areas of uncertainty that must be addressed to determine the significance of endocrine disruptors as public and ecological health threats (Daston, et al., 2003).[4] The key uncertainties are:

What effects are occurring in exposed humans and wildlife populations?
What are the chemical classes of interest and their potencies?
What are the dose-response characteristics in the low-dose region?
Do our testing guidelines adequately evaluate potential endocrine-mediated effects?
What extrapolation tools are needed?
What are the effects of exposure to multiple EDCs, and will a Toxicity Equivalency Factors approach be feasible?
How, and to what degree, are human and wildlife populations exposed to EDCs?
What are the major sources and environmental fates of EDCs?
How can unreasonable risks be managed?
What approaches are needed to assess risks to humans and wildlife?

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1 Colborn T., Clement C. 1992. Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection. Princeton, NJ: Princeton Scientific Publishing Co.

2 Kavlock RJ, Daston GP, DeRosa C, Fenner-Crisp P, Gray LE, Kaattari S, Lucier G, Luster M, Mac MJ, Maczka C, et al. 1996. Research needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the U.S. EPA sponsored workshop. Environ Health Perspectives 104 (Suppl 4):715-740.

3 Ankley GT, Johnson RD, Toth G, Folmar LC, Detenbeck NE, Bradbury SP. 1997. Development of a research strategy for assessing the ecological risk of endocrine disruptors. Rev Toxicol 1:71-106.

4 Daston GP, Cook JC, Kavlock RJ. 2003. Uncertainties for endocrine disruptors: our view on progress. Toxicol Sci 74:245-252.

In 1996, EPA's ORD identified endocrine disruptors as one of its top six research priorities. In the same year, through the enactment of the Food Quality Protection Act (FQPA), the U.S. Congress directed EPA to screen pesticides for estrogenic activity in humans using validated studies or other scientifically relevant information and gave the Agency discretionary authority to screen for other endocrine effects as well. The Safe Drinking Water Act (SDWA) Amendments passed in the same year, authorized EPA to screen drinking water contaminants for similar activities. To implement the legislation, a number of scientific questions needed to be addressed and resolved through research. As a result, EPA's Endocrine Disruptors Research Program and the development and implementation of a mandated Endocrine Disruptor Screening Program (EDSP) by the Office of Prevention, Pesticides and Toxic Substances (OPPTS) are on parallel, yet highly interactive, tracks.

The peer-reviewed blueprint for EPA's research program was published in 1998 as *ORD's Endocrine Disruptors Research Plan* (EDRP) and took into consideration the advice, provided to OPPTS, on the implementation of the legislation by an independent expert advisory panel. Since then, ORD has developed a *Multi-Year Plan (FY2000-2012) for Endocrine Disruptors* that identifies the elements of the EDRP that will be addressed intramurally over the next 5 to 10 years across three national laboratories and one national center and extramurally through a competitive grants program.

The purpose of the MYP is to provide a framework that: (1) integrates research across ORD's laboratories and centers to produce scientifically credible results in accordance with the GPRA goals; and (2) supports the Agency's mission to protect human health and the environment. ORD's MYP identifies long-term goals (LTGs) and presents annual performance goals (APGs) and associated annual performance measures (APMs) for a planning window of approximately 5-10 years. ORD's MYP also fosters the integration of strategic risk-based environmental protection and anticipation of future environmental issues by communicating the research approach and timing for responding to environmental issues. ORD's MYP is intended to be a living document that is updated every 2 years to reflect the current state of the science, resource availability, and Agency priorities.

The MYP for EDCs is in its third iteration and reflects ORD's most recent interpretation of Agency research needs in addressing key areas of uncertainty. The plan includes research activities implemented and planned for fiscal years (FY) 2000 through 2012. Resources for the implementation of these research activities for FY 2003 to 2005 have decreased from $12.7 million to $8 million per year; the program includes approximately 55 full-time equivalent (FTE) personnel per year.

In the MYP for EDCs, ORD has identified three LTGs that will provide the methods the Agency needs to implement the EDSP and the scientific underpinnings to interpret data from EDSP and incorporate them into risk assessments and Agency decisions. The LTGs are:

- ✧ LTG 1: Provide a better understanding of science underlying the effects, exposure, assessment, and management of endocrine disruptors.

- ✧ LTG 2: Determine the extent of the impact of endocrine disruptors on humans, wildlife, and the environment.

- ✧ LTG 3: Support EPA's screening and testing program.

In addition to the MYP for EDCs, which identifies the research directions for all of ORD's laboratories and centers, some of the laboratories and centers have developed their own implementation plans. For example, ORD's National Risk Management Research Laboratory (NRMRL) has developed a Risk Management Evaluation (RME), and the National Health and Environmental Effects Research Laboratory (NHEERL) has developed a Research Implementation Plan to guide that laboratory's specific activities related to EDCs. These documents are consistent with the EDRP and the MYP.

The magnitude of the scientific uncertainties about the causes, effects, exposures, and solutions in addressing the concerns relating to endocrine disruptors clearly require national and international coordination and communication. To facilitate efforts nationally, ORD chairs an interagency working group established under the auspices of the Committee on Environment and Natural Resources. This working group developed a national framework for research and an inventory of federal research programs, identified high priority research gaps, and serves as a vehicle through which to develop and issue multi-agency solicitations for research proposals to help fill in some of these gaps. At an international level, ORD is working with the European Union, the International Programme on Chemical Safety/World Health Organization (WHO), the Organization for Economic Cooperation and Development (OECD), and Japan's Ministry of the Environment to promote collaboration among scientists and to develop validated assays.

Structure of the Program Review

The EDC Subcommittee, chaired by Dr. Anna Harding from Oregon State University, had broad and considerable expertise in the area of EDC research. Dr. George Daston of The Proctor & Gamble Company served as Vice-Chair of the subcommittee. Other members included Drs. Glen R. Boyd, Tulane University; George W. Lucier, private consultant; Stephen H. Safe, Texas A&M University; Juarine Stewart, Morgan State University; Donald E. Tillitt, U.S. Geological Survey (USGS) Columbia Environmental Research Center; and Glen Van Der Kraak, University of Guelph, Canada. The panel's expertise included research specific to EDCs in the areas of developmental toxicology, fate and transport, wastewater treatment, hormone receptor mechanisms and receptor-mediated processes, risk assessment, molecular epidemiology, molecular biology and carcinogenesis, environmental toxicology, reproductive development in fish, aquatic ecosystems, and screening and testing. The subcommittee also has expertise in the areas of public health and xenobiotic metabolism in mammals. Biographical sketches of the subcommittee members are included in Appendix B.

The subcommittee was sent ample review material in stages; the first package arrived approximately 7 weeks prior to the face-to-face meeting held December 13-15, 2004. A second mailing was received several weeks prior to the December meeting. Overall, the materials included the *Research Plan for Endocrine Disruptors*, the *MYP for Endocrine Disruptors*,

NHEERL's *Research Implementation Plan*, a bibliography of publications by intramural and extramural researchers, proceedings and abstracts from recent EDC workshops (2002 *Endocrine Disruptors Program Review Workshop Abstracts* and the 2003 *Proceedings of the Endocrine Disruptors Research Program Review Workshop*), abstracts of the posters to be presented at the December meeting, and biographical sketches of the intramural and extramural researchers. Additional reports (WHO, *Global Assessment of the State-of-the Science of Endocrine Disruptors*; American Chemistry Council (ACC), *Endocrine Issues Research Summary*; Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), *Endocrine Disruptor Screening and Testing Advisory Committee Final Report*; and the CD-ROM, *Effective Risk Management of Endocrine Disrupting Chemicals Workshop*) were sent about 7 weeks prior to the face-to-face meeting. The subcommittee members also were sent the CD-ROM, *Endocrine Disruptors Program Progress Review Workshop,* held at Tulane University in October 2004, which included abstracts of the presentations from the Tulane conference, bibliographies of the presenters, and a summary of the panel discussion. Finally, the subcommittee members were provided a synopsis of EDC research and screening programs, including the logic model showing the interrelationship between the research program and the screening and testing program. At the December meeting, the subcommittee members received copies of the miniaturized posters, copies of the oral presentation slides, and summaries of the Science To Achieve Results (STAR) projects.

The face-to-face meeting included a series of introductory/welcome presentations followed by a brief overview of the EDC Research Program and LTGs. The overview of each of the three LTGs was followed by a poster session of the research conducted by intramural and extramural researchers, program and regional office scientists, and grantees. The poster sessions were followed by a discussion period, in which the subcommittee members were given the opportunity to have one-on-one discussions with the principal investigators. Discussion and work sessions for the subcommittee were allotted throughout the 3-day face-to-face meeting. The meeting concluded with presentations that addressed the relevance of the research program from Agency program and regional offices that use the resulting science. Closing remarks were followed by a draft oral report from the BOSC EDC Subcommittee. The meeting also included an opportunity for public comment.

Throughout the meeting, the presentations and posters were important to help clarify materials provided to the BOSC subcommittee. The presentations overviewing the goals and the posters presented by the investigators and grantees describing the research effort conducted under all of the LTGs were excellent. The enthusiasm, dedication, and excellence of the scientists within the program clearly were evident. The BOSC subcommittee thanked those who participated in these aspects of the face-to-face meeting, as they were critical for the BOSC's evaluation of the EDC research program.

Overarching Conclusions and Recommendations

The subcommittee's evaluation of the research plan and the MYP resulted in the conclusion that the goals and scientific questions are appropriate and represent an understandable and solid framework for setting research priorities for EDCs. The research plan was formalized in 1998 following a series of workshops, interagency considerations, and meetings that embraced all relevant stakeholders. The program is recognized nationally and internationally as a multidisciplinary set of research areas for both human health and wildlife and it cuts across the risk assessment/risk management paradigm. Key research areas are aligned closely to the LTGs and to the APGs.

The EDC program is a combination of "problem-driven" and core research and has stood the test of time; however, progress reviews are encumbered, to some extent, by the difficulty in defining the scope of activities considered to be part of endocrine disruptor research. There are a large number of toxic mechanisms that could be categorized as endocrine disruptors; therefore, EPA should clarify what is and what is not covered by the EDC program whenever the program is reviewed. Confusion regarding the classification and scope of endocrine disruptors is common in many assessments of these compounds.

In general, the BOSC subcommittee is favorably impressed with the quality and relevance of the work and the progress to date, although it recognizes that much remains to be done. The APGs are highly ambitious and should be viewed as the time when significant progress should be evident but progress on those goals should, in most cases, continue well past the initial timeline. The subcommittee also is impressed with the enthusiasm of the investigators and their commitment to researching the difficult and controversial problems that surround EDCs. The poster presentations were exceptionally well done and served to consistently address potential problems raised by the reviewers after reading the written material.

One of EPA's main functions is providing risk assessment and risk management of chemicals in commerce and the environment. LTG 1 provides a solid scientific foundation for conducting risk assessments and making risk management decisions for endocrine disruptors. The research that falls under this goal covers the major questions in the key areas of the risk paradigm. Although there are many challenges to fully defining the nature of possible biological effects and the extent of exposure, the research being conducted under this LTG will put EPA in a strong position to make scientifically grounded decisions.

EPA's research program, relevant to the science questions contained in LTG 2 has been productive, of high quality, and relevant to the mission of EPA. Available resources have been used efficiently, and there is a high degree of enthusiasm for the projects by both the intramural and extramural investigators. In general, greater progress has been made on the ecological effects of EDCs compared to human health effects, although several appropriate human health projects are underway.

The progress on LTG 3 within the EDC program has been excellent. Two mammalian tests already have been examined through a validation program administered by the OECD. These should be available for use by the EDSP very soon. Development of the other two tests

recommended by EDSTAC is in progress, and publications emanating from this work indicate that the work is on track. ORD has articulated clear goals for the development of screening and testing methods for endocrine disruptors and is fulfilling those goals in an admirable fashion. The research is directly relevant to legislation that EPA administers and is serving the program offices well. EPA's research is well coordinated with that of other federal agencies and with international efforts on the standardization and validation of endocrine screening assays.

In particular, Dr. Elaine Francis (EDC National Program Director) and Dr. Lawrence Reiter (Executive Lead for EDC and Director of NHEERL) have provided outstanding leadership necessary for this integrated program to thrive. The EDC program scientists are highly sought as consultants and provide technical assistance to EPA program offices, other federal agencies, and the broader scientific community. EDC scientists are engaged in intramural and extramural research within ORD, and program scientists have provided exemplary leadership in the field at the national and international levels. EDC scientists disseminate their research in top-tier scientific journals, a strong indicator of the quality of their research and respect among professional peers. The EDC researchers are a group of highly esteemed scientists who are at the forefront of EDC research in screening and testing methodologies for mammalian and ecological tests, source identification, effects on wildlife, and ecological health.

EPA's future success in meeting the specified goals of the EDC program will depend on a number of factors including continued funding, support from EPA management, multidisciplinary intramural research spanning ORD and other EPA entities, extramural grants, and continued interagency collaborations, especially with respect to identifying new sources of environmental and human exposure (e.g., National Institute of Environmental Health Sciences [NIEHS], Centers for Disease Control and Prevention [CDC], Food and Drug Administration [FDA], U.S. Department of Agriculture [USDA], USGS, and others). To date, ORD has been very astute in leveraging its EDC program resources by collaborating with other federal agencies, and these collaborations have extended the EDC research program.

The continuation of the grants program is vital because it provides a mechanism for EPA to more efficiently evaluate new technologies and innovations for use in the risk assessment and risk management arenas.

Recommendations:

- ✧ **Progress reviews are encumbered, to some extent, by the difficulty in defining the scope of activities considered "endocrine disruptor research." There are a large number of toxic mechanisms that could be categorized as endocrine disruptors; therefore, EPA should clarify what is and is not covered by the EDC program whenever the program is reviewed.**

- ✧ **The following are recommendations that would allow the Program Director to negotiate for needed research expertise from a position of strength and enhance the laboratories that participate in EDC program research: (1) hire additional personnel to share the workload of the participating laboratories; (2) elevate the position of the EDC Program**

Director to the level of the Laboratory/Center Directors; and (3) provide the EDC Program Director budget authority.

Strengths and Challenges of Long-Term Goals

Brief summaries of the overall strengths and challenges of each LTG are presented below.

LONG-TERM GOAL 1

LTG 1: Provide a better understanding of science underlying the effects, exposure, assessment, and management of endocrine disruptors.

The research being carried out under this LTG will strengthen the foundation of EPA's risk assessment practices and risk management decisions for endocrine disruptors. The research plan plays to the strengths of EPA's research laboratories, which are organized along risk assessment/ management themes. EPA already has been a leader in characterizing the effects of endocrine disruptors in mammalian systems and has expanded its capabilities in ecological toxicity by bolstering its laboratory capabilities and partnering with other agencies, and through judicious use of STAR grants to expand its expertise beyond its own walls.

Strengths:

The scientific expertise available in ORD and some of the external STAR recipients is a primary strength. The research program structure and implementation are logical and well designed. Additionally, the models that are being characterized to evaluate EDCs under LTG 3 will complement the ongoing efforts in this area.

The EDC program and scientists within ORD provide strong leadership in the design and execution of research efforts. The models, which have been designed or modified to evaluate endocrine disruption, will provide the data required to develop risk assessments. The models have been the subject of harmonization efforts to be compatible with OECD guidelines.

The risk management program provides important information for the regulated community with regard to identifying and prioritizing EDCs of concern and leadership in developing risk management approaches.

***Challenges*:**

The complexity of endocrine systems, in conjunction with the diversity of potentially endocrine-active chemicals, makes evaluation of the combined effects of EDCs a daunting task. Even with a solid approach, good laboratory models, and adequate funding, it is likely that it will take some years for ORD to fully evaluate this question.

Intramural scientific expertise for the areas of human and aquatic species (i.e., fish, invertebrates, and amphibians) is very good; however, this is not the case in the area of wildlife toxicology.

Consequently, much of the experimental research and expertise resides in the STAR grant recipients. It is advantageous to utilize the expertise of these scientists from outside the Agency; however, more expertise in the area of wildlife toxicology within the Agency may be required to fully attain the program's goals. Application of the wildlife models that are being developed may require Agency personnel to meet the exact needs of regulatory concern. Also, the evaluations of EDCs on wildlife within a risk assessment paradigm, including evaluation of uncertainties, almost certainly would require full-time EPA personnel. It is not clear from the review of information presented to this subcommittee that adequate personnel exist to address wildlife concerns of EDCs.

Recommendations:

- ✧ **To meet the program goals and fulfill the exact needs of regulatory concern, the BOSC recommends that the EDC program dedicate full-time EPA personnel to work in this area.**

- ✧ **Because of the complexities in extrapolating among the many species in the environment that may be affected by endocrine disruptors, it will be important for ORD to continue to collaborate with other federal, academic, nongovernmental organization (NGO), and industry partners to characterize better the range of variability among species.**

A major challenge for risk assessment will be to form definitions of what constitutes an adverse effect, and what defines a biological indicator. This challenge does not reside exclusively within ORD, but ORD research will need to support decisions in this area.

The development of analytical methods is a significant challenge and was not identified clearly as an APG and/or APM for this research. The subcommittee believes that this may be slowing down the progress of the risk management program.

Selected water and wastewater treatment technologies have been studied by other investigators and reported in peer-reviewed literature but do not seem to be integrated into the EDC program.

Recommendation:

- ✧ **Studies have been reported regarding the use of predictive tools that can be used to prioritize the focus of specific treatment technologies and compounds. These findings could be integrated into EPA's EDC program.**

There is no current (i.e., as of 2004) ongoing research or specific plan for future research regarding natural processes in sediments.

LTG 2: Determine the extent of the impact of endocrine disruptors on humans, wildlife, and the environment.

EPA's research program relevant to the science questions contained in LTG 2 has been productive, of high quality, and relevant to the mission of EPA. Available resources have been used efficiently, and there is a high degree of enthusiasm for the projects by both the intramural and extramural investigators. In general, greater progress has been made on ecological effects of EDCs compared to human health effects, although several appropriate human health projects are underway. Several strengths and challenges were identified by the BOSC in the review of the projects listed under LTG 2, as indicated below.

Strengths:

Many of the models required for studying effects of EDCs on fish and invertebrates have been developed, modified and/or applied. Ongoing studies have set appropriate priorities for determining sources of EDC exposures including concentrated animal feedlot operations (CAFOs), combustion processes, and pulp mills.

The ecological studies have effectively coupled field studies, biomarker measurements, analytical chemistry, laboratory studies with whole organisms, and cultures of hormone-responsive cells with effluents suspected of possessing hormonal activity.

EPA scientists have made good decisions on how best to use genomics in their EDC studies; the information that is being generated by the studies should produce important data that address critical knowledge gaps. There is a good balance between molecular toxicology and effects on aquatic species and experimental animals.

Interactions between ORD and the regional offices are strong, effective, and frequent in regards to the EDC studies. Such interactions provide a good model for EPA to use in other areas. EPA's research regarding LTG 2 is consistent with the overarching research plan developed by EPA and other agencies in 1998, and the research priorities reflect the high-priority goals identified by that plan.

***Challenges*:**

Although priorities for the chemicals studied have been appropriate, EPA should continue to improve its interactions with other agencies that have a strong interest in EDCs (i.e., CDC, NIEHS, National Toxicology Program [NTP], National Institute for Occupational Safety and Health [NIOSH], and FDA) to identify new sources of environmental and human exposures to EDCs. Moreover, EPA should mine data made available from the OECD High Production Volume (HPV) Program and work with FDA to investigate the role of pharmaceuticals in the environment as a source of endocrine disruptors.

Recommendation:

- ✧ **EPA should continue to improve its interactions with other agencies that have a strong interest in EDCs to identify new sources of environmental and human exposures, including investigating the role of pharmaceuticals as sources of EDCs.**

It was not feasible for scientists conducting epidemiologic studies to attend the face-to-face meeting. Although the EDC Subcommittee members were provided a CD-ROM of the Tulane conference and one of the subcommittee members attended the conference, the subcommittee members thought it would be helpful to include poster presentations by each of the scientists funded by this interagency program for subsequent program reviews.

Recommendations:

- ✧ **It will be important for EPA to take a leadership role in the application of the "omics" technologies to address many of the science questions critical for evaluating environmental and human health effects of EDCs. This will require a strong commitment to a systems biology approach and computational toxicology as well as effective interactions with those generating much of the basic data.**

- ✧ **EPA should continue to investigate the common ground between ecological and human health because the Agency is in a unique position to do so.**

LONG-TERM GOAL 3

LTG 3: Support EPA's screening and testing program.

ORD has articulated clear goals for the development of screening and testing methods for endocrine disruption, and is fulfilling those goals in an admirable fashion. The research is directly relevant to legislation administered by EPA and is serving the program offices well. With regard to LTG 3, EPA's research is well coordinated with that of other federal agencies and with international efforts on the standardization and validation of endocrine-screening assays.

The progress on LTG 3 within the EDC program has been excellent. Two mammalian tests already have been through a validation program administered by OECD. These should be available for use by the EDSP very soon. Development of the other two tests recommended by EDSTAC is in progress, and publications emanating from this work indicate that the work is on track.

Strengths:

ORD has clearly defined its objectives for research to support the development, standardization, and validation of alternative methods that can be used by the program offices.

ORD's research is mechanistically driven, which provides a solid scientific foundation for the test methods that are developed. Because of this mechanistic focus, it is highly likely that the methods ORD develops will be valid, broadly applicable, and easily interpreted.

ORD has used its leadership role in the fields of reproductive, developmental, endocrine, and aquatic toxicology to adapt and develop methods that have high relevance to the needs of the program offices and to the protection of public and environmental health.

Challenges:

The major challenge that ORD has faced with regard to the screening and testing program is handing off its research to the program offices so that validation and implementation can occur in a timely way. It should be noted, however, that much of the delay in validation and regulatory acceptance is because this process takes place largely outside the Agency.

ORD has a large number of research accomplishments within NHEERL that have contributed significantly to a basic understanding of the toxic responses to estrogens, anti-androgens (within the Reproductive Toxicology Division [RTD]) and thyroid toxicants (within Experimental Toxicology Division [ETD]), which in turn has led directly to the development of improved methods for endocrine disruptor detection. This research is not centralized and may not be captured adequately in the list of annual performance goals and accomplishments. It would be worthwhile to identify this research as important support for LTG 3.

Recommendation:

- ✧ **ORD is beginning to develop core competencies in genomics and quantitative structure activity relationship (QSAR) methods, both of which hold promise in endocrine disruptor identification. Because these areas are so data intensive, it will be important for ORD to train or hire experts in bioinformatics to work with the life sciences experts already on staff.**

Program Leadership

Dr. Lawrence Reiter serves as the Executive Lead for the EDC program and also is the Director of NHEERL. Dr. Reiter has been the Executive Lead since the inception of the program in 1995, and Dr. Elaine Francis serves as the National Program Director. She is extremely effective as the Program Director and has done an outstanding job of providing the leadership necessary for this integrated program to thrive. Her FTE and institutional support comes from the National Center for Environmental Research (NCER), and her role is to oversee the planning and execution of the intramural and extramural EDC research program. Dr. Francis works closely with Dr. Reiter to resolve EDC issues and reports to the NCER Director, Dr. Jack Puzak (Acting Director). Dr. Francis has responsibility for program oversight but does not have budgetary authority.

The EDC program is unique in that no other U.S. federal agency has such a program. The EDC program is not just an umbrella for a series of independent projects but is a fully integrated program across all ORD laboratories and centers (with the exception of the National Homeland Security Research Center). The program is recognized nationally and internationally as a multidisciplinary set of research areas for both human health and wildlife and it cuts across the risk assessment/risk management paradigm.

EDC scientists are highly sought out as consultants to EPA program offices (such as the Office of Coordination and Science Policy and OPPTS), other federal agencies, and the broader scientific community. EDC scientists provide technical assistance to the program and regional offices. ORD supports research on EDCs in both its intramural and extramural programs, and scientists carrying out this research have provided leadership in the field at the national and international levels. These individuals are involved in organizing meetings on EDCs sponsored by governments and industry and scientific societies, and they also play an important role in these conferences by reporting their research on EDCs in terms of model development, mechanisms of action, and assay validation. The leadership of EPA scientists in the development of screening and testing methods for EDCs also is attributable in part to the long history within the Agency of studying the possible actions of chemicals as reproductive and developmental toxicants. The EDC researchers are a group of highly esteemed scientists who are at the forefront of research in EDC screening and testing methodologies for mammalian and ecological tests, source identification, effects on wildlife, and ecological health. EDC scientists are a tremendous resource and asset for the Agency.

Program Resources

The EDC program was projected to have an average annual budget of $12 million. This includes the STAR grants program, which averages $4 million per year in those years it is funded. The average annual budget from FY 2003 to 2005 has ranged from $12.7 million enacted in FY 2003 to the FY 2005 request of $8.0 million. The EDC Program Director does not have direct access to human or financial resources to carry out the program's objectives; rather, the Director must negotiate with the Division Directors of the laboratories and centers (her peers) of ORD to recruit the time and effort of scientists with the needed expertise.

The laboratories and center that contribute resources to the EDC program are NRMRL, NCER, NHEERL, and National Exposure Research Laboratory (NERL). Although the total budget for the program has decreased since FY 2003 (from $12.7 million to an $8.0 million request for FY 2005), the percentage of resources provided by each of these laboratories has been relatively stable (except for NCER) during the past 2 years and is proportionate to the number and extent of tasks that they perform for the EDC program across the LTGs. The STAR grants program adds significant value to the research portfolio of the EDC program in that it assists in filling identified research gaps, brings in research expertise that is not found among intramural scientists, and assists ORD in responding to new issues that the laboratories and centers may not be able to readily address.

The manner in which this program is funded, though indirect and possibly cumbersome, does not appear to hinder the quality of the research conducted under the program. It is apparent that the EDC Program Director has had success in convincing Division Directors to loan scientist time to the EDC program. It does make it more difficult, however, for the Program Director to do forward planning or to plan the investigation of emerging issues. ORD has been very astute in leveraging the EDC program's resources by collaborating with other federal agencies. The amount of research conducted by the EDC program has been expanded by collaboration with agencies such as NIOSH, NIEHS, and the National Cancer Institute (NCI); however, the fragmentation of scientists' time without extra compensation raises concern about whether the productivity (e.g., number of published manuscripts, etc.) of these scientists is negatively impacted by participation in the EDC program.

Recommendation:

- **The situations cited above (insufficient funding and the mechanism used to provide resources to the EDC program) can be remedied by several courses of action: (1) hire additional personnel to share the workload of the participating laboratories; (2) elevate the position of the EDC Program Director to the level of the Laboratory/Center Directors; and (3) give the EDC Program Director budget authority.**

These actions would allow the Program Director to negotiate for needed research expertise from a position of strength and will allow the Program Director to enhance the laboratories that participate in EDC program research. The subcommittee understands that ORD has plans to enact the latter two of these actions in the near future for all newly hired National Program Directors. The BOSC recommends the speedy implementation of that plan.

Report Overview

In addition to the Executive Summary, the progress review report contains five chapters and three appendices. Chapters II through IV focus on the three long-term goals of the program, and Chapters V and VI cover program leadership and program resources, respectively. These five chapters provide a more detailed account of the subcommittee's deliberations. The three appendices include the charge questions to the EDC Subcommittee, biographical sketches of the subcommittee members, and a list of acronyms used in the report.

II. LONG-TERM GOAL 1

Provide a better understanding of science underlying the effects, exposure, assessment, and management of endocrine disruptors.

Introduction

LTG 1 of ORD's EDRP strives to provide the science underlying the effects, exposure, risk assessment, and risk management of endocrine disruptors. The information generated under this LTG will help address key issues for the regulatory needs of EPA. The key issues and research questions to be answered are related to understanding: (1) characteristics of the dose-response relationships for EDCs, particularly in the low-dose region; (2) development of risk assessment approaches for EDCs, including interspecies extrapolations for EDCs; (3) the effects of multiple exposures of EDCs; (4) management of risks associated with EDCs; and (5) characterizing the nature and manifestations of latent effects from developmental exposures to EDCs.

Program Design

The goals set forth in the EDRP and the MYP to address the underlying science needs for risk assessment and management of EDCs continue to be appropriate. The research and implementation plans to achieve these goals are well founded and provide a logical framework for attaining the EDRP goals.

EPA's MYP takes advantage of existing core competencies in reproductive toxicology, mechanistic toxicology, ecotoxicology, and risk assessment and risk management methodology to address these questions. The capabilities of these scientists are unique in breadth, depth, and scope within the federal government. No other federal agency is equipped to provide answers regarding both risk assessment and management of EDCs; however, the outcomes of the EDC program continue to be essential for other regulatory and resource management agencies, both federal and state, as well as external investigators and industry.

The program also has relied on the STAR program to conduct research and provide expertise to achieve program-related outcomes. STAR grant recipients have provided important findings on interspecies differences in steroid receptors, avian and invertebrate models for EDC evaluations, and the effects of multiple EDC exposure. The EDC program also has utilized the skills and abilities of scientists from other federal agencies to complement some activities in this research area. Because the EDC program relies on this outside expertise, programs such as the STAR program are essential for the program to continue to meet its goals in this area. One example of the EDC program's reliance on extramural expertise is in avian toxicology. This particular expertise and ability to conduct avian toxicology studies in the laboratory or in the field does not reside within EPA.

Dose Response. The most significant question in dose-response assessment is whether low doses (i.e., below the no-observed-effect level for traditional reproductive toxicity studies) of endocrine-active compounds produce qualitatively different responses than are observed at the exaggerated dose levels commonly used in hazard identification studies. There are reports in the literature of such low-dose effects, but these reports have not been corroborated in replicate studies. Unfortunately, because of the variability in the parameters being measured (e.g., organ weights) and the difficulty in controlling the many factors that may influence study outcomes, the participants in an NTP workshop (Melnick, et al., 2002)[5] found that the possibility of low-dose effects could not be discounted (although it is believed that the weight of evidence weighed against the possibility). The issue is an important one because the presence of such effects would challenge the validity of our current approaches to hazard identification and risk assessment for endocrine disruptors.

The MYP describes a number of research objectives that consider the low-dose question. The program is designed to evaluate effects on a number of target tissues at different life stages and with different model compounds. In addition to intramural research, a request for extramural grant proposals also was issued for this research.

Risk Assessment. The identification and application of key risk assessment tools for humans and wildlife is one of the practical goals of the EDC program. The ability to obtain this goal is directly dependent on the success achieved in the other goals of the program. As the uncertainties of dose-response models and endpoints, interspecies differences, and cumulative effects of multiple exposures are clarified, the approaches required for risk assessment of EDCs will be elucidated. A key to attaining this goal is communication and cooperation among ORD personnel and staff in the regional and program offices.

A number of products have resulted from ORD's EDC program and ongoing efforts of the program will be used to develop risk assessment tools for EDCs in humans and wildlife. The structure of the program is well suited to develop information on mode of action, interspecies differences, multiple chemical exposures, critical life stages, dose response, evaluation of multiple levels of biological organization, establishment of linkages among assessment endpoints, and low-dose effects of EDCs, all required for risk assessments. Work on development of models (mammalian, fish, amphibian, and avian) is ongoing and the endpoints are appropriate to help identify and evaluate uncertainties for risk assessment of EDCs. Model compounds include traditional organochlorine pesticides and industrial compounds, positive controls (estrogens and androgens), current-use pesticides (e.g., atrazine), and thyroid-active agents.

Multiple EDC Exposures. A key research need in the area of EDCs effect assessments is to develop a better understanding of potential impacts of multiple chemical exposures in both wildlife and humans. Unintentional environmental exposures to EDCs almost always involve more than one chemical. A better understanding of the interactions at the molecular, cellular,

5 Melnick R, Lucier G, Wolfe M, Hall R, Stancel G, Prins G, Gallo M, Reuhl K, Ho SM, Brown T, et al. 2002. Summary of the National Toxicology Program's report of the endocrine disruptors low-dose peer review. *Environmental Health Perspectives* 110:427-431.

and organism levels will provide the required information for risk assessment and risk management activities within EPA and across federal and state regulatory agencies.

Additive, synergistic (i.e., "more than additive"), and antagonistic (i.e., "less than additive") interactions are known to occur with EDCs. These interactions can occur through direct interactions with receptors (e.g., estrogen, androgen, thyroid, etc.), effects on metabolic pathways (i.e., steroid pathways), and signal transduction pathways (e.g., kinases or phosphorylases). The interactions of EDCs on endocrine function often are species-specific, life-stage specific, and tissue-specific, thereby increasing the potential complexity of these issues. Therefore, research efforts to address potential effects and population impacts of multiple EDC exposures must encompass a variety of animal models, measurement endpoints, and chemical classes.

The program design within ORD to address this issue is appropriate given the state of knowledge and the funds available. The intramural EDC program incorporates aspects of QSAR models, computational toxicology, mechanistic laboratory models (*in vitro* and *in vivo*) with multiple endpoints, and field evaluations that address these issues. Some of the research that applies to this issue can be found under other LTGs (e.g., QSAR and computational chemistry), but there is good integration across research lines to ensure the appropriate application of the findings. Results from all of these lines of research will be required to address the scientific and regulatory issues of multiple chemical exposures.

The models currently under active development or use to evaluate the effects of multiple exposures include mammalian models with endpoints of reproductive function and sexual differentiation, a short-term mammalian model evaluating thyroid function, *in vitro* approaches with cell culture, and a STAR grant to evaluate effects in a gastropod. Endpoints of the models include multiple levels of biological organization from genomic analysis to reproductive function.

The 1996 FQPA mandated EPA to investigate the effects of multiple chemical exposures within the same class (mode of action) of chemical. Most of the research efforts within EPA on multiple chemical exposures have been testing chemical mixtures with a similar mode of action. Major research efforts have been undertaken on Ah-R agonists (polychlorinated biphenyls [PCBs], dioxins, and furans), chlorotriazine pesticides, AR antagonist fungicides (viclozolin and procymidone), and phthalate esters. There also has been research on the effect of mixtures that contain chemicals with different modes of action.

Risk Management. The risk management program aims to develop strategies for determining how unreasonable risks can be managed by minimizing exposure of humans and wildlife to suspected EDCs. Risk management strategies focus on modifying existing technologies for controlling the release of EDCs at the source and in developing new tools for mitigating exposure to EDCs. Risk management research is conducted in parallel with risk assessment research to identify and develop effective risk management approaches based on exposure and effects information as it becomes available.

Chemicals that currently are considered known or highly suspected endocrine disruptors and present in environmental situations associated with significant exposure to humans or wildlife are identified and discussed in the updated RME. The target compounds included in the current RME are alkylphenolics, PCBs, reproductive hormones, chlorinated dioxins and furans, and DDT and DDE. The risk management program relies on information generated by LTG 2 and is driven by three APGs with target completion dates of 2008 to 2009.

Latent Effects From Developmental Exposures. Estrogens, androgens, and thyroid hormones are active during development and may produce effects that are organizational and permanent. Whereas some of these effects are obvious (e.g., structural malformations observable at birth), others are latent and are manifested as functional changes or increased susceptibility to disease states later in life. The research portfolio has a number of programs that evaluate the potential latent effects of developmental exposure to a variety of endocrine disruptors on a number of target tissues and functions. The program is a well-designed survey of the organ systems that are most likely to be affected by early life exposure.

Relevance

The science conducted under this LTG is unique and provides the foundation required for future risk assessment and risk management activities required by EPA. Important models are being developed and characterized, and the choice of endpoints is relevant for the ecological risk assessment process. The choice of chemicals is timely and important relative to exposure. Important issues such as low-dose and latent effects are being addressed in a rigorous manner. Thus, a considerable amount of high-quality data is being developed under this LTG; these data will provide the foundation for environmental risk assessments and risk management of EDCs.

Dose Response. This aspect of the LTG is directly relevant to a central mission of EPA, which is the appropriate assessment of hazard and risk of chemical substances. EPA's entire chemical regulation framework is based on the presumption that as dose increases, so does the prevalence and severity of adverse effects. Hazard identification test designs and risk assessment practices to establish reference doses are based on this fact. The purported low-dose phenomenon challenges the existing paradigm. The program as described in the MYP is robust and directly addresses the key issue of whether these low-dose effects are real and does so with a combination of internal and external research.

Risk Assessment. Research conducted under the EDC program is highly relevant to human and ecological risk assessments of EDCs. As stated above, many important models are being developed and characterized. The choice of endpoints is relevant for the ecological risk assessment process, and the choice of chemicals is timely and important relative to exposure. Important issues such as low-dose and latent effects are being addressed; thus, high quality data are being developed that will provide the foundation for environmental risk assessments of EDCs.

Multiple EDC Exposures. The previous and ongoing work in this research area is very relevant, and the approach of first investigating interactions of chemicals within the same mode of action

is a sound approach. A thorough understanding of within-class interactions and development of predictive models stemming from within-class interactions are required before more complex interclass (i.e., across mode of action) effects of EDCs may be evaluated. The chemicals and classes represented in the ORD and STAR investigations are appropriate and timely based on the known concerns of exposure and observed effect. The research models encompass a variety of endocrine pathways and the evaluations have metrics at multiple levels of biological organization.

Risk Management. The risk management program is unique in that it covers a breadth of research areas (i.e., water and wastewater treatment, septic systems, CAFOs, air quality, sediments, etc.) and aims to provide the foundation for developing approaches for pollution prevention and control. The program evaluates existing technologies (typical treatment operations and processes) and aims to develop new risk management approaches (e.g., treatment optimization, site remediation, chemical substitutes, and predictive computational tools) to reduce exposure to EDCs. The selection of target compounds is relevant based on available risk assessment and exposure data and information; thus, deliverables generated by this LTG will provide the foundation for developing effective environmental risk management approaches for EDCs.

Latent Effects. EPA is charged with protecting the public from harmful chemical exposures. In so doing, it is necessary to identify the possible outcomes of toxicity that should be evaluated during the risk assessment process. The research goal on latent effects after developmental exposure evaluates the possibility that more needs to be done to test for latent effects of developmental exposures.

Program Progress

The EDC program has developed important and relevant information on mode of action, interspecies differences, multiple chemical exposures, critical life stages, dose-response characteristics, effects at multiple levels of biological organization, linkages among assessment endpoints, and low-dose effects of EDCs. All of these findings are required for the appropriate evaluation and risk assessments of EDCs. Work on the development of models (mammalian, fish, amphibian, and avian) is ongoing and the endpoints are appropriate to help identify and evaluate uncertainties for risk assessment of EDCs. Model compounds include traditional organochlorine pesticides and industrial compounds, positive controls (estrogens and androgens), current-use pesticides (e.g., atrazine), and thyroid-active agents.

Dose Response. Much of the work in this area has been completed; however, the extramural work is still in progress. This is a problem that has generated much interest and activity outside EPA, especially in the private sector. It may be time for EPA to evaluate the literature, along with its own progress, to determine whether there is enough information available to reduce the uncertainty associated with dose response, or to alter its research plans.

Risk Assessment. Progress has been good on the basic research needs that are required to clarify uncertainties in risk assessment. Good models are being developed with endpoints important for

risk assessment needs. Progress and efforts to develop an integrated framework for human or environmental risk assessment of EDCs, however, appear to be limited. Some or most of this work may be the focus of other groups within EPA such as the Risk Assessment Forum. The model and framework for the development of critical information on EDCs for risk assessment is well established and progress is being made. Efforts now should focus on development of risk assessment paradigms for EDCs and application of the research findings.

Multiple EDC Exposures. Although the challenges faced by ORD to address the issues of effects from multiple chemical exposures are tremendous, progress has been excellent. ORD has been methodically evaluating a number of relevant models and endpoints as well as relevant chemical classes. Moreover, the models that are being developed and validated in LTG 3 (e.g., fish reproduction, amphibian development, avian reproduction, etc.) will provide the foundation for testing and evaluation of combined effects in future years.

Risk Management. Careful consideration must be paid to progress on risk management issues to meet the schedules provided in the MYP for the EDRP. An RME was prepared to identify EDCs of concern and major EDC sources and to develop a comprehensive risk management research program based on available risk assessment and exposure information to date. This RME is intended to identify opportunities of greatest need and greatest potential for making significant impacts on the reduction of EDC releases and exposures. Additional resources are needed to adequately consider the EDC compounds included in the current RME. Upcoming revisions of the RME are targeted for FY 2005 and FY 2008 based on information regarding new EDCs of concern. Future risk management research on new EDCs of concern will require additional resources to meet the schedules in the MYP.

Latent Effects. Most of the milestones in this area have been achieved on time.

Strengths and Challenges

Strengths:

The scientific expertise available in ORD and through the STAR grants is a primary strength. The research program structure and implementation are logical and well designed. Additionally, the models, which are being characterized to evaluate EDCs under LTG 3, will complement the ongoing efforts in this area.

The EDC Program and scientists within ORD provide strong leadership in the design and execution of research efforts in this area. The models, which have been designed or modified to evaluate endocrine disruption, will provide the data required to develop risk assessments. The models have been the subject of harmonization efforts to be compatible with OECD guidelines.

The risk management program provides important information for the regulated community with respect to identifying and prioritizing EDCs of concern and leadership in developing risk management approaches.

Challenges:

The complexity of endocrine systems, in conjunction with the diversity of potentially endocrine-active chemicals, makes the evaluation of combined effects of EDCs a daunting task. Even with a solid approach, good laboratory models, and adequate funding, it is likely that it will be some years before ORD can fully evaluate this question.

Scientific expertise in the areas of human and aquatic species (i.e., fish, invertebrates, and amphibians) is very good, but this is not the case in the area of wildlife toxicology. Consequently, much of the experimental research and expertise comes from STAR grant recipients. It is advantageous to utilize the expertise of these scientists from outside the Agency, but ORD will need more internal expertise in the area of wildlife toxicology to fully attain the program's goals. Application of the wildlife models that are being developed may require Agency personnel to meet the exact needs of regulatory concern. Also, the evaluations of EDCs on wildlife within a risk assessment paradigm, including evaluation of uncertainties, almost certainly would require full-time EPA personnel. It is not clear from the review of information presented to this subcommittee that adequate personnel exist to address wildlife concerns of EDCs. Because of the complexities in extrapolating among the many species in the environment that may be affected by endocrine disruptors, it will be important for ORD to continue to collaborate with other federal, academic, NGO, and industry partners to better characterize the range of variability among species.

A major challenge for risk assessment will be to settle on definitions of what constitutes an adverse effect and a biological indicator. This challenge does not reside exclusively within ORD, but ORD research will need to support decisions in this area. In addition, the development of analytical methods is a significant challenge and was not identified clearly as an APG and/or APM for this research. The subcommittee members believe that this may be slowing down the progress of the risk management program.

Selected water and wastewater treatment technologies have been studied by other investigators and reported in peer-reviewed literature. These findings could be integrated into ORD's work. Studies have been reported regarding the use of predictive tools that can be used to prioritize the focus of specific treatment technologies and compounds.

As of 2004, there is no ongoing research or specific plan for future research regarding natural processes in sediments.

Recommendations:

- ✧ **The model and framework for development of critical information on EDCs for risk assessment is well established and progress is being made. Efforts now should focus on the development of risk assessment paradigms for EDCs and application of the research findings.**

- ✧ **Studies have been reported regarding the use of predictive tools that can be used to prioritize the focus of specific treatment technologies and compounds. These findings could be integrated into EPA's EDC program.**

- ✧ **To meet the program goals and fulfill the exact needs of regulatory concern, the BOSC recommends that the EDC program dedicate full-time EPA personnel to work in the area of wildlife toxicity.**

- ✧ **Because of the complexities in extrapolating among the many species in the environment that may be affected by endocrine disruptors, it will be important for ORD to continue to collaborate with other federal, academic, NGO, and industry partners to better characterize the range of variability among species.**

III. LONG-TERM GOAL 2

Determine the extent of the impact of endocrine disruptors on humans, wildlife, and the environment.

Introduction

The BOSC EDC Subcommittee examined this goal in relation to the specific charge questions on design, relevance, and progress and the four specific research questions comprising this LTG. The key areas of uncertainty related to LTG 2 include: (1) how and to what degree human and wildlife populations are exposed to EDCs; (2) effects that are occurring in exposed human and wildlife populations; (3) chemical classes of interest and their potencies; and (4) major sources and environmental fates of EDCs.

The subcommittee evaluation of the research plan and the MYP concluded that the goals and science questions are appropriate and represent an understandable and solid framework for setting research priorities for endocrine disruptors. The research plan was formalized in 1998, following a series of workshops, interagency considerations, and meetings that embraced all relevant stakeholders. This plan has stood the test of time and it is reflected appropriately in the MYP for LTG 2; however, progress reviews are encumbered, to some extent, by the difficulty in defining the scope of activities considered endocrine disruptor research. There are a large number of toxic mechanisms that could be categorized as endocrine disruption, so EPA needs to clarify what is and is not covered by the EDC program whenever the program is reviewed. Confusion regarding the classification and scope of endocrine disruptors is common to many assessments of these compounds.

In general, the subcommittee is favorably impressed with the quality and relevance of the work and the progress to date, although it is recognized that much remains to be done. The subcommittee also is impressed with the enthusiasm of the investigators and their commitment to understanding the difficult and controversial problems that surround EDCs. The poster presentations were exceptionally well done and helped to address issues raised by the reviewers after reading the written material provided for the review.

EPA's future success in meeting the specified goals of the EDC program will depend on a number of factors including continued funding, support from EPA management, multidisciplinary intramural research spanning ORD and other EPA entities, extramural grants, interagency collaborations (with NIEHS, CDC, USGS, FDA, USDA, and others), and partnerships with other government and industrial research funding agencies and groups. Continuation of the EPA-funded grants program is vital because it provides a mechanism for EPA to more efficiently evaluate new technologies and innovations for use in risk assessment and risk management arenas, and for resolving key scientific issues.

The APGs are highly ambitious and should be viewed at the time when significant progress should be evident, but progress on those goals should, in most cases, continue well past the initial timeline.

The presentations and posters under LTG 2 appear to represent primarily issues of environmental and human exposures to actual and suspected EDCs and the spectrum of effects that might be produced from those exposures. There is obvious overlap with the other LTGs; for example, one of the key science questions in the MYP for LTG 2 is to "determine how and to what degree human and wildlife populations are exposed to EDCs." This question also is relevant to LTG 1, which deals with dose response and exposure to mixtures of EDCs. This overlap is desirable if it is understood that the success of each of the LTGs is dependent on continued productive interactions among all the projects covered under the EDC umbrella as well as related activities in the human health, computational toxicology, risk assessment, and risk management programs and the needs of the regional offices. To date, EPA appears to have been successful in linking different components of the EDC program as evidenced by both the oral and poster presentations.

Program Design

In the case of environmental releases and ecological effects, EPA has taken two approaches: (1) studying chemicals with known EDC activity; and (2) evaluating the endocrine activity of emissions and releases from different sources followed by attempts to identify the chemicals responsible for the observed activity.

Both approaches are needed but EPA should not lose sight of the goal of determining chemical classes of interest and the sources of EDCs. The process for selecting chemicals studied under the EDC program should take advantage of the HPV program and other EPA activities and information obtained from NTP, FDA, CDC, NIOSH, and other relevant programs. It always is tempting to focus on chemicals that can be analyzed using validated methodologies; however, such an approach limits the ability of EPA to address some important science questions that define LTG 2. The BOSC recommends that EPA establish a procedure for determining which chemicals and/or exposure circumstances are of high priority for study. This procedure should incorporate material generated from CDC's "report card"; recent results from the NTP, including data on the toxicity of herbal medicines; and information generated by the HPV Program on screening and emissions data. Consideration of studies on the release of pharmaceuticals and their metabolites into wastewater and other federal activities relevant to identifying chemical classes of interest also is recommended. It is clear that EPA is doing much of this on an *ad hoc* basis; however, success in meeting the objectives of LTG 2 will require a more focused approach.

Priority setting for chemical classes evaluated for human and ecological effects of EDCs should take into account newer methodologies that detect a wide range of endocrine-active compounds including dietary phytoestrogens. The consequences of human and wildlife exposures to environmental estrogens must be assessed in conjunction with parallel dietary exposures to phytoestrogens.

Research on the potencies of several chemical classes of EDCs is ongoing and is dependent on having adequately characterized experimental models. Many of the models required for mammalian, fish, invertebrate, and avian species models appear to have been developed or are under development. As the models are characterized and evaluated, it will be important for EPA to use these models to determine potencies of a wider range of chemicals. Current efforts using samples from the Ohio River and surface waters in California are tractable and address specific concerns. EPA needs to determine if the EDC program should systematically evaluate (in collaboration with FDA) releases of pharmaceutical compounds into the environment.

Simple models of effects are required; however, EPA also should strive to develop models that permit evaluations across multiple levels of biological organization. *In vitro* models are valuable for obtaining detailed knowledge on discrete biological/molecular events important for endocrine disruption, but they do not capture and integrate the multiple events essential for normal as well as altered endocrine function. Therefore, the BOSC recommends that EPA continue to focus on systems biology approaches and develop biologically based models that identify hazards and reduce uncertainties in risk assessment. The development and refinement of reliable models will require a cohesive multidisciplinary approach involving EPA scientists and collaborators from other scientific agencies and organizations.

Several sources of environmental releases of EDCs are being evaluated including CAFOs, wastewater treatment, combustion processes, and paper and pulp mills. These projects are well designed and should produce important data. The CAFO studies would benefit from collaborations with other agencies working on new technologies designed to minimize environmental discharges. For example, North Carolina has a well-funded effort to develop environmentally superior technologies for dealing with hog wastes from CAFOs; this includes testing new technologies on model farms to determine if toxic emissions and releases can be minimized in a cost-effective manner. The subcommittee was impressed with EPA's priority setting for evaluating endocrine activity of environmental releases and the strong science emerging from the studies.

The human health studies include a children's exposure program, the National Children's Study (interagency), and a series of epidemiology studies on known endocrine disruptors. The epidemiology studies represent a large and important component of the EDC program relevant to LTG 2. The epidemiology research was reviewed at the Tulane conference held in October 2004. Given the travel expenses incurred by the researchers to attend that conference in New Orleans, it was not feasible for them to attend the BOSC's EDC program review meeting in Research Triangle Park (RTP) 6 weeks later. As a result, a member of the EDC subcommittee was invited to attend the Tulane conference. To disseminate the epidemiology information to the subcommittee, each subcommittee member was given a CD-ROM with all of the abstracts of the presentations from the Tulane conference, bibliographies of the presenters, and a summary of a panel discussion. These are large studies that address reproductive and developmental effects as well as cancer. EPA is encouraged to continue these kinds of interagency activities and to use the exposure results to set priorities for future epidemiology studies so that the same substances are not tested repeatedly.

EPA also is encouraged to collaborate with the National Institutes of Health (NIH) and other agencies to ensure that appropriate markers of genetic predisposition are included in the epidemiology studies for the purpose of identifying sensitive subpopulations. With respect to human and rodent toxicogenomic studies, EPA should rely primarily on other groups to generate the basic human and rodent toxicogenomic data; however, EPA scientists could play a significant role in metabolomics. It will be important for EPA to take a leadership role in applying these data to hazard identification, systems biology, and computational toxicology strategies and the development of the next generation of biologically based models to estimate interindividual variation in risks. EPA should aggressively pursue ecogenomics through its extramural grants program and in-house research.

Relevance

The major research questions covered under LTG 2 are:

- ✧ How and to what degree are human and wildlife populations exposed to EDCs?
- ✧ What effects are occurring in exposed human and wildlife populations?
- ✧ What are the chemical classes of interest and their potencies?
- ✧ What are the major sources and environmental fates of the EDCs?

These questions are consistent with the overarching EDRP, and they are relevant to EPA's scope of interests and responsibilities. The results emerging from studies addressing these goals have been essential in identifying EPA as a leader in the arena of endocrine disruption. The fact that EPA conducts research on both ecological and human health issues places the Agency in a unique position to study the common ground between ecological and human health. It is important that EPA continues to be vigilant in mining this common ground for environmental chemicals, pharmaceuticals, and substances administered to farm animals.

Chemicals selected for testing and calibration of models for endocrine dysfunction represent important classes of EDCs based on their known or potential exposures. The proposed and ongoing human and wildlife studies are highly relevant to EPA's mission and will be critical for future decisionmaking and regulatory measures for EDCs. Several studies address the endocrine-disrupting activities of trenbolone, a potent synthetic androgen used as a growth promoter in livestock. This is an excellent example of careful priority setting and well-conducted research relevant to the endocrine disrupting potential of CAFO emissions.

The research presented at the review struck a good balance between molecular toxicology and ecological evaluations. This balance will be essential for EPA to continue to address the science questions covered under LTG 2. Good examples of this are the studies investigating aquatic invertebrates as indicators of EDC exposures in aquatic systems, in which diagnostic indicator data from multiple aquatic organisms are being integrated to characterize the intensity and duration of exposures to EDCs. The molecular profiles from this research may permit simultaneous monitoring of exposure to multiple classes of EDCs, and thereby provide data useful for determining cumulative risks and chemical interactions.

The relevance of the EDC to goals expressed in the research plan and MYP will require EPA to continue to improve interactions with federal and state agencies and the scientific community to leverage resources and to set appropriate priorities. Some suggestions were made previously under Charge Question 1 for LTG –2, including the need to mine data from programs such as the HPV Program, wherein industries are making available screening level toxicity data for chemicals that are produced or used in volumes greater than 1 million pounds per year in the United States. These data frequently reveal which chemicals are being released into the environment in substantial quantities and have the potential to be endocrine disruptors. This program is centered in OPPTS and should involve a systematic review by EPA for relevance to the EDC program. Although interactions between OPPTS and ORD have been strong regarding the congressional mandates of the FQPA and SDWA, improved interactions are needed in other areas relevant to the EDC program. Likewise, the ability of EPA's EDC program to address emerging ecological and human health issues and to identify new classes of EDCs will require continued active interactions with CDC, NIEHS, NTP, NIOSH, FDA, and USGS.

The EPA-supported research is well connected to risk assessment and risk management needs and addresses local problems identified by the regional offices. This approach will clarify which classes of EDCs may adversely affect human health and the environment and thereby facilitate identification of sources and eliminate or reduce their release. The subcommittee was impressed by the effective interactions between ORD and the regional offices. These interactions seem to be working very well for the EDC program and as such may serve as a model for other programs within EPA. Specific examples include assistance in evaluating gender disruption in native fishes in the Arkansas River, assessment of endocrine disruption in fish in the Potomac River, and surface water monitoring programs in California that measure the magnitude of environmental estrogen signals in fish.

Program Progress

Good progress has been made in both the intramural and extramural projects, and they appear to be complementary; therefore, the BOSC recommends that EPA continue to fund EDCs research through the STAR program and that regular meetings continue between the extramural and intramural investigators for the purpose of fostering collaborative research and maximizing the effectiveness of the available resources.

Several highly relevant studies are underway on the potential adverse effects of various classes of chemicals in humans and ecological systems. These studies include evaluations of PCBs, polybrominated biphenyls (PBBs), pesticides, dioxin-like compounds, synthetic and steroidal androgens and estrogens, anti-androgens, thyroid-active agents, phthalate acid esters, and polybrominated diphenyl ethers (PBDEs). Whereas some of these compounds do not directly activate hormonal systems via hormone receptor mechanisms, they do modulate hormone pathways through other mechanisms, and adverse health effects are hormonally mediated. Projects presented during the review are making reasonable progress, although it may be difficult to meet the designated timelines in all cases. The children's health initiatives and the interagency epidemiology studies will take time to reach fruition.

The subcommittee notes that specific APGs have been met for the ecological studies, with timelines for significant accomplishments due by 2004. These APGs are to: (1) develop field methods to assess environmental exposures in tissues and environmental compartments; (2) determine the efficacy of various wildlife species as sentinels; and (3) evaluate several classes of chemicals suspected of being endocrine disruptors in field studies and ascertain the degree to which they are, or have the potential to, adversely affect wildlife at the population level.

The subcommittee was impressed with the progress on studying CAFOs as a source of EDCs. These studies have demonstrated that estrogen conjugates are released into groundwater from swine operations, and the potential for release of trenbolone also has been demonstrated. The coupling of field studies to biomarker measurements (i.e., vitellogenin), analytical chemistry, and laboratory studies with whole organisms and hormone-responsive cells in effluents is yielding important results used to address specific problems identified by the regional offices. This strategy is a good model for EPA to follow in evaluating endocrine-disrupting activities in ecological systems at multiple levels of biological organization. In addition, good progress has been made on the identification of androgenic substances in pulp and paper mill discharges, the National Effluent EDC Screening Study, and the screening for emissions of EDCs from combustion processes. Progress has been made on developing assays to assess endocrine disrupting toxicity in invertebrates using a wide range of chemicals known or suspected to be EDCs.

ORD also has made progress on the APG for evaluating several classes of chemicals suspected of being EDCs and determining their potencies in laboratory studies, especially with respect to ecological studies. Progress has been slower in mammalian systems based on the projects identified under LTG 2; however, some of the projects under LTG 1 are relevant to this APG. Likewise, the APG for determining the critical biological factors during development resulting in toxicities later in life are addressed in LTG 1. The APG for determining the extent to which exposures to EDCs contribute to the onset or increase the severity of diseases is an important goal that will require the collaboration of toxicologists, molecular biologists, and epidemiologists. It is not clear how EPA will address this APG, which stipulates the need for significant accomplishments by 2007.

The deadline for the APG for determining whether adverse developmental/reproductive effects are occurring in human populations following exposures to EDCs is 2008. It was not feasible for scientists conducting the epidemiologic studies to attend the face-to-face meeting. Although the subcommittee members were provided with a CD-ROM of the Tulane conference and one of the subcommittee members did attend the conference, it was difficult for the subcommittee to critically review the progress in meeting this APG. The subcommittee determined that it would be helpful for subsequent reviews of this program to include poster presentations by each of the scientists funded by this interagency program.

The deadline for the APG for determining sources of exposure and environmental fates of EDCs also is 2008; nevertheless, good progress has been made for a wide range of chemical classes of EDCs.

It will be important for EPA to carefully review progress to determine when and how to take advantage of new methodologies and innovations such as gene arrays, proteomics, and metabolomics. The reviewers were pleased with the attention given the "omics" to date.

It also will be important for EPA to make decisions regarding the ending of projects once goals have been achieved.

Strengths and Challenges

EPA's research program relevant to the science questions contained in LTG 2 has been productive, of high quality, and relevant to the mission of EPA. Available resources have been used efficiently and there is a high degree of enthusiasm for the projects by both the intramural and extramural investigators. In general, greater progress has been made on ecological effects of EDCs compared to human health effects, although several appropriate human health projects are underway. Several strengths and challenges were identified by the subcommittee in the review of the projects listed under LTG 2, as indicated below.

Strengths:

- ✧ Many of the models required for studying fish and invertebrate effects of EDCs have been developed, modified, and/or applied. Ongoing studies have set appropriate priorities for determining sources of EDC exposures including CAFOs, combustion processes, and pulp mills.

- ✧ The ecological studies have effectively coupled field studies, biomarker measurements, analytical chemistry, and laboratory studies with whole organisms and hormone- responsive cells with effluents suspected of possessing hormonal activity.

- ✧ EPA scientists have made good decisions on how to best use genomics, and the information generated should produce important data that address critical knowledge gaps. There is a good balance between molecular toxicology and effects on aquatic species and experimental animals.

- ✧ Interactions between ORD and the regional offices on EDC problems are strong, effective, and frequent and provide a good model for EPA to use in other areas.

- ✧ EPA's research regarding LTG 2 is consistent with the overarching EDRP developed by EPA and other agencies in 1998, and research priorities reflect the high priority goals identified by that plan.

Challenges/Recommendations:

- **Although priorities for chemicals studied have been appropriate, EPA should strive to continue to improve its interactions with other agencies that have a strong interest in EDCs such as the CDC, NIEHS, NTP, NIOSH, and FDA. This will facilitate identifying new sources of environmental and human exposures to EDCs. Moreover, EPA should mine data made available from the HPV Program and work with FDA to investigate the role of pharmaceuticals in the environment as a source of endocrine disruptors.**

- **It was not feasible for scientists conducting epidemiologic studies to attend the face-to-face program review meeting. Even though the subcommittee members were provided information from the Tulane conference and one of the subcommittee members attended the conference, the BOSC recommends that subsequent reviews of this program include poster presentations by each of the scientists funded by this interagency program.**

- **It will be important for EPA to take a leadership role in the application of "omics" technologies to address many of the science questions critical for evaluating environmental and human health effects of EDCs. This will require a strong commitment to a systems biology approach and computational toxicology as well as effective interactions with those generating much of the basic data.**

- **EPA should continue to investigate the common ground between ecological and human health, as no other agency is in a position to do this.**

- **Progress reviews are encumbered, to some extent, by the difficulty in defining the scope of activities considered endocrine disruptor research. There is a large number of toxic mechanisms that could be categorized as endocrine disruptors; therefore, EPA should clarify what is and is not covered by the EDC program whenever the program is reviewed.**

IV. LONG-TERM GOAL 3

Support EPA's screening and testing program.

Introduction

EPA's screening and testing program was established to comply with the FQPA and SDWA, both of which called for the establishment of screening programs for estrogenic activity and other endocrine activity that EPA deemed appropriate to evaluate. Principles for screening and testing of chemicals for potential endocrine-disrupting activity were developed by the EDSTAC, a federal advisory committee convened by EPA to provide recommendations on how to implement the endocrine disruptor assessment aspects of the FQPA and SDWA. EDSTAC recommended that the evaluation of chemicals proceed in a tiered manner: prioritization for assessment followed by screening for putative endocrine activity, which then would be confirmed by definitive testing. EDSTAC recommended that the screening encompass effects on estrogen, androgen, and thyroid hormone (EAT) function.

EDSTAC developed a number of principles for screening and testing, including that these tiers evaluate every known mechanism of action that alters the EAT function, including binding to the estrogen or androgen receptor, interference with hormone synthesis or metabolism, and interference with hormonal action. EDSTAC also concluded that the screening and testing tiers be representative of the vertebrate classes known or suspected to be responsive to EAT disruptors. Because these recommendations cannot be accommodated in a single assay, a battery approach to screening and testing was recommended, and EDSTAC proposed a series of test methods with sufficient options. Although many of the assays in the proposed screening battery were in existence, there were no standardized, validated protocols for the purpose of EDC screening. Other assays had never been conducted, although the individual parameters of the test had been the subject of research. Most of the assays in the testing tier were already in use but required modification to include endpoints that were more sensitive to EAT activity.

Regarding the prioritization tier of the screening program, EDSTAC recommended that consideration be given both to exposure and to the potential to cause biological effects. Because there is not a lot of existing information on the potential for biological effects, methods that are conducive to prioritization need to be developed. These methods may include QSAR approaches or high-throughput biological/ biochemical approaches.

Program Design

EDSTAC's recommendations have served as the basis for EPA's EDSP. Given the state-of-the-art at the time the recommendations were made, it became apparent that: (1) further methods development was required; (2) a better understanding of assay performance and reproducibility was needed; and (3) in some cases, additional studies of the mechanistic aspects of endocrine toxicity were needed to make the evaluation of endocrine disruptors more functional. ORD has

taken the appropriate steps through its MYP for endocrine disruptors to develop tools for prioritization, has standardized and validated assays for screening, and has added sensitive endpoints to traditional assessments of reproductive toxicity that enable a more complete understanding of the mechanisms of EDCs.

ORD has been highly responsive to the needs of the EDSP and has provided technical expertise to the Office of Science Coordination and Policy (OSCP). ORD also has participated extensively with the OECD and other nations, notably Japan, in the harmonization of methodology for screening and testing methods. This has included the design of screening and testing methodologies through participation in the round-robin testing of proposed methodologies. ORD also has responded with the development of new approaches (e.g., the H295R adrenocortical tumor cell line for evaluating chemical effects on steroidogenesis) and by addressing technical issues via further experimentation (e.g., effects of loss of body weight on the applicability of the mammalian short-term reproduction assays and evaluation of additional endpoints for effects on the thyroid hormone axis). There also are several examples in which ORD has integrated some of the newer genomic and proteomic methodologies into the tests that are central to LTG 3 in an effort to define sensitive markers of response to different classes of EDCs.

Relevance

The ORD research on screening and testing is essential to EPA's mission and to the mandates given to EPA under the FQPA and SDWA. Virtually all of the short-term goals (i.e., those in the first several years) identified in the MYP are fully aligned with the recommendations of EDSTAC and EPA's efforts to comply with the nature and timing of its FQPA/SDWA mandates. Research support and expertise from ORD has been at the forefront of developing, standardizing, and validating screens for endocrine disruptors.

The LTGs go beyond the explicit recommendations of EDSTAC but are highly relevant in that they anticipate and will take advantage of improvements in the science, especially in the realm of computational biology. EPA recently has launched a national, multilaboratory computational toxicology program, which stands to contribute significantly to endocrine disruptor screening, particularly through the development of QSAR models.

Program Progress

There has been significant progress by ORD and its scientific partners in the development and validation of several relevant bioassays important for the screening and testing requirements for LTG 3. There were a number of mammalian assays proposed by EDSTAC as being useful for screening: the uterotrophic assay for estrogenic effects, the Hershberger assay for androgenic effects, and the pubertal male and female assays, which evaluate the attainment of puberty in rodents and are semi-apical in that they assess the integrated function of a number of mechanisms of action (i.e., hormone synthesis, hormone action, endocrine axes). Of these, only the uterotrophic protocol was sufficiently developed to be placed immediately into a

standardization and validation program. Therefore, ORD identified the need to further develop the other assays and included these as short-term goals in its MYP.

The inclusion of new endpoints into traditional toxicity tests was another major recommendation of EDSTAC and it clearly has been the subject of research within ORD laboratories. This research is diffuse and is occurring in multiple divisions within NHEERL—development of sensitive markers of estrogenicity within the RTD and research on thyroid-mediated effects on development in the ETD and Neurotoxicology Division (NTD). Many of the accomplishments in these areas have been difficult to capture in the list of APGs. The BOSC recommends that EPA try to summarize this research and its relevance to EDC identification in subsequent reports and revisions of the MYP.

In vitro assays for androgen receptor (AR) and estrogen receptor (ER) binding have been developed and validated. Moreover, *in vitro* AR- and ER-dependent transactivation assays in transformed cell lines now are available and these use both stable and transiently transfected cells. These assays, coupled with ongoing studies in other laboratories, suggest that this important screening component of LTG 3 is nearly complete. In addition, an *in vitro* assay for determining the effects of EDCs on steroidogenesis has been developed, and the approach will be capable of measuring both modulation of steroidogenic gene expression and activity. This bioassay seems highly promising and requires further validation using more extensive sets of test EDCs and possibly development of alternate cell lines to determine potential intercellular differences in response to EDCs. Excellent progress also has been made on validation of short-term *in vivo* assays for the determination of estrogenic/antiestrogenic and androgenic/anti-androgenic chemicals using the rat as a model.

Computational QSAR models also have been developed as part of the tier-I assays for the identification of EDCs. These approaches complement high-throughput screening assays, and their predictive nature will continually improve as new data on EDCs become available. It also is recommended that genomic/proteomic and metabolomic approaches for characterizing the various subtypes of EDCs be developed because this eventually should provide specific "omics" signatures for different structural and functional classes of EDCs. The bioinformatics expertise required for these approaches must be developed.

Considerable progress has been made in the development of tier-I screening methods for wildlife. This includes: (1) an *in vivo* test for examining thyroid physiology in *Xenopus laevis*; and (2) a short-term *in vivo* reproductive test with the fathead minnow. The former assay is 14 days in duration and is sensitive to thyroid hormone synthesis inhibitors and exogenous thyroid hormones. The basic assay is being modified for the evaluation of molecular and biochemical endpoints of relevance to the thyroid axis in an effort to shorten the assay and develop diagnostic indicators of thyroid hormone system dysfunction. EPA has made considerable progress in the development and application of the short-term fathead minnow reproduction assay for testing chemicals that exert effects by diverse modes of action (estrogens, androgens, anti-androgens, and inhibitors of steroid metabolism). Both test methods have been developed through the stage of prevalidation and are ready for validation by OPPTS. Both methods also have been communicated in the peer-reviewed literature and made available to the OECD.

Considerable progress has been made with the development of tier-II test methodologies for wildlife species. An amphibian growth and reproduction test is under development to enable evaluation of the chronic effects of chemicals on the development and maturation of the amphibian HPG axis. This test involves *X. tropicalis* and takes advantage of the rapid maturity of this species (approximately 6 months). One negative issue is that the original intent was that this test would employ a native North American frog, but to date, no suitable candidate species has been identified.

Two fish species have been identified for lifecycle testing. These take advantage of their short generation times and unique aspects of their life history that can be exploited. The sheepshead minnow is an estuarine species and represents an important link to the marine environment. Considerable progress has been made with respect to basic husbandry conditions and in establishing genomic and proteomic markers of response to EDCs. The second species is the medaka, which affords the possibility of using the DMY gene expression to determine genotypic sex and relate this to phenotypic sex. These tests respond to requests from the OPPTS and OECD for alternate test methods for fish reproduction and development.

Considerable progress has been made in the development of tier-II tests for invertebrates. This includes the development and validation of a lifecycle test using mysids and a rapid bioassay using copepods. The latter test involves the rearing of a meiobenthic copepod in a 96-well microplate format. This method has been applied to the evaluation of molecular markers of response (vitellogenin and ecdysteroid production) and has application in population-based assessment through the use of the Leslie-Matrix population growth model. Both test methods represent an important link to invertebrates and the opportunity to look at modulators of endocrine disruption beyond the E, A, and T axes.

There are a number of challenges associated with the delivery of the testing protocols to OPPTS. Some of the protocols have been in place for many years, yet the transfer to contract laboratories has been problematic. This has led to a substantial commitment by EPA staff to refine and troubleshoot assays. This also has had a negative effect on other core research activities that are the responsibility of EPA staff. A mechanism is needed to ensure the timely transition of protocols to OPPTS, or this will continue to be a major commitment of time and resources by ORD staff. This will become even more problematic when there is more emphasis on whole animal test methodologies.

Strengths and Challenges

The progress on LTG 3 within the EDC program has been excellent. Two mammalian tests already have been through a validation program administered by OECD. These should be available for use by the EDSP very soon. Development of the other two tests recommended by EDSTAC is in progress, and publications emanating from this work indicate that the work is on track.

ORD has articulated clear goals for the development of screening and testing methods for endocrine disruption and is fulfilling those goals in an admirable fashion. The research is

directly relevant to legislation that EPA administers and is serving the program offices well. EPA's research is well coordinated with that of other federal agencies and with international efforts on the standardization and validation of endocrine screening assays.

Strengths:

ORD has clearly defined its objectives for research to support the development, standardization, and validation of alternative methods that can be used by the program offices.

ORD's research is mechanistically driven, which provides a solid scientific foundation for the test methods that are developed. Because of this mechanistic focus, it is highly likely that the methods ORD develops will be valid, broadly applicable, and easily interpreted.

ORD has used its leadership role in the fields of reproductive, developmental, endocrine, and aquatic toxicology to adapt and develop methods that have high relevance to the needs of the program offices and to the protection of public and environmental health.

Challenges:

The major challenge that ORD has faced is handing off its research to the program offices so that validation and implementation can occur in a timely way. In fairness, it should be noted that much of the delay in validation and regulatory acceptance is because this process takes place largely outside the Agency.

Recommendation:

- ✧ **The transfer of protocols to contract laboratories has been problematic. This has led to a substantial commitment by EPA staff to refine and troubleshoot assays, and it has had a negative effect on other core research activities that are the responsibility of ORD staff. The BOSC recommends that there be a mechanism in place to ensure the timely transition of protocols to OPPTS.**

ORD has a large number of research accomplishments within NHEERL that have contributed significantly to a basic understanding of the toxic responses to estrogens, anti-androgens (within RTD), and thyroid toxicants (within ETD), which in turn has led directly to the development of improved methods for endocrine disruptor detection.

Recommendation:

- ✧ **This research is diffuse and is occurring in multiple divisions within NHEERL, and many of the accomplishments in these areas have been difficult to capture in the list of APGs. The BOSC recommends that EPA try to summarize this research and its relevance to EDC identification in subsequent reports and revisions of the MYP.**

ORD is beginning to develop core competencies in genomics and QSAR methods, both of which hold promise in endocrine disruptor identification.

Recommendations:

- **It will be important for EPA to take a leadership role in the application of the "omics" technologies to address many of the science questions critical for evaluating the environmental and human health effects of the EDCs. This will require a strong commitment to a systems biology approach and computational toxicology as well as effective interactions with those generating much of the basic data.**

- **Because these areas are so data-intensive, it will be important for ORD to train or hire experts in bioinformatics to work with the life sciences experts already on staff.**

V. PROGRAM LEADERSHIP

Dr. Lawrence Reiter serves as the Executive Lead for the Endocrine Disruptors Research Program and also the Director of NHEERL. As the lead senior administrator, he does not attend to the day-to-day activities, but does follow the issues and serves as a resource for the Program Director if problems arise. Dr. Reiter has been the Executive Lead since the inception of the Program in 1995. Dr. Elaine Francis is extremely effective as the National Program Director, and has done an outstanding job of providing the leadership necessary for this integrated program to thrive. Her FTE and institutional support comes from NCER, and her role is to oversee the planning and execution of the intramural and extramural research program. Dr. Francis works closely with Dr. Reiter on EDC issues and reports to the Acting NCER Director, Dr. Jack Puzak . With the current organizational arrangement for the National Program Directors, Dr. Francis has responsibility for program oversight but does not have budgetary authority.

A new organizational structure has been proposed and presented to the BOSC Executive Committee at a meeting in 2004, in which the National Program Directors will be afforded stature within EPA comparable to the Laboratory and Center Directors. With the new organizational structure, National Program Directors will report to the Deputy Assistant Administrator for Science (the position currently held by Dr. William Farland) and the Deputy Assistant Administrator for Management. The new reporting structure might provide more management and budgetary authority. The proposed model probably would be more desirable than the current structure, which requires the EDC Program Director to negotiate with various Center and Laboratory Directors for FTEs and resources to work on the EDC program. Because the new organizational model appears to present advantages in program leadership that are absent in the current model, the BOSC recommends that EPA implement the new organizational paradigm for National Program Directors that was presented to the BOSC Executive Committee at the May and September 2004 meetings.

The EDC program is unique in that no other U.S. federal agency has such a program. The EDC program is not just an umbrella for a series of independent projects but is a fully integrated program across all laboratories and centers (with the exception of the National Homeland Security Research Center). In addition, research partners from academia, other federal agencies, and industry participate in the program and contribute to a diverse set of talents to address various research questions. The program is recognized nationally and internationally as a multidisciplinary set of research areas for both human health and wildlife and it cuts across the risk assessment/risk management paradigm.

There is ample evidence documenting the leadership EDC scientists provide both within EPA and external to the Agency. Examples of leadership internal to the Agency are: (1) service on national and international workgroups such as providing the lead in various aspects of the dioxin reassessment; (2) service as chairs and members on numerous laboratory steering committees; and (3) service on various validation and implementation groups. EDC scientists are highly

sought out as consultants to EPA program offices (such as OCSP and OPPTS), other federal agencies, and the broader scientific community. EDC scientists provide technical assistance to the program and regional offices. There also are numerous examples of EDC scientists providing scientific leadership external to the Agency. EDC scientists are recruited to lead national and international collaborative efforts, including organizing national and international conferences and symposia. They are invited speakers to international symposia, chair sessions at research symposia, serve on scientific review panels for other federal agencies and universities, and chair interagency working groups.

EDC scientists also have been recognized for their leadership in the field through their contributions as elected officers and members of professional societies. The scientists serve as reviewers for an impressive number (well over 100 of peer-reviewed journals. EDC scientists boast impressive vitas, with publications in top-tier scientific journals, a strong indicator of the quality of their research and their respect among professional peers. In addition, EDC scientists have been successful in being awarded additional funding from other federal agencies (i.e., NIH, NSF, NIEHS, and National Oceanic and Atmospheric Administration [NOAA]), private industry, and research foundations, and also have received STAR grants. Scientists in the program serve as adjunct professors or research fellows in academia, Branch Chiefs, Division Directors, and Program Directors. They contribute to the pipeline of new scholars in the field by serving as mentors to and sponsors of postdoctoral fellows. Finally, EDC scientists are the recipients of numerous scientific and technical achievement awards, commendable service awards, publication awards, EPA bronze medals, and other research awards. The EDC researchers are a group of highly esteemed scientists who are at the forefront of research in EDC screening and testing methodologies for mammalian and ecological tests, source identification, effects on wildlife, and ecological health. EDC scientists are a tremendous resource and asset for the Agency.

VI. PROGRAM RESOURCES

The EDC program was projected to have an average annual budget of $12 million. This includes the STAR grants for EDCs, which average $4 million per year in the years when the program is funded. In actuality, the average annual budget from FY 2003 to 2005 has ranged from $12.7 million enacted in FY 2003 to the FY 2005 request of $8.0 million.

The EDC Program Director does not have direct access to human or financial resources to carry out the program's objectives. Instead, the Program Director must negotiate with the Division Directors of the laboratories and centers (her peers) to recruit the time and effort of scientists with the required expertise. The sum of the fractions of FTEs of individual scientists who are devoted to the EDC program then is calculated as the EDC budget. There are 55 FTEs devoted to the EDC program throughout ORD in the FY 2004 and FY 2005 budgets.

Four ORD laboratories/centers contribute resources to the EDC program—NRMRL, NCER, NERL, and NHEERL. Although the total budget for the program has decreased since FY 2003 (from $12.7 M to a $8.0 M request for FY 2005), the percentage of resources provided by each of these laboratories has been relatively stable (with the exception of NCER) over the past 2 years and is in proportion to the number and extent of tasks that they perform for the EDC program across the LTGs. In FY 2003, NCER provided 44 percent and 48 percent of the total budgets for LTGs 1 and 2, respectively. These percentages were slightly decreased in FY 2004 but were reduced drastically in the FY 2005 request. The FTEs contributed to the EDC program by NCER, however, have been relatively steady (one for LTGs 1 and 2 in FY 2003; one for LTG 1, and two for LTG 2 in FY 2004 and the FY 2005 request). NCER has not made a significant contribution to LTG 3 in any year. Even with these variations, the distribution of tasks and resources across appropriate laboratories and centers and across the LTGs appears to be appropriate, although there was concern expressed that the total budget was not sufficient.

The STAR grants program adds significant value to the research portfolio of the EDC program. The research sponsored by the STAR program assists in filling identified research gaps, brings in research expertise that is not found among intramural scientists, and assists ORD in responding to new issues that the laboratories and centers may not be able to readily address. The value of the STAR program to the EDC program was evident during this review because at least 25 percent of the poster presentations selected to demonstrate the sound science done by the EDC program were from STAR grant recipients. The STAR grants program, however, is not always funded at a level that allows maximum utility by the EDC program. The consequences of these actions is that ORD has learned to forward-fund STAR recipients. This allows the funded STAR recipients to be confident in receiving funding for the entire period of their awards; however, it significantly reduces the number of awards that can be made.

The manner in which this program is funded, though indirect and possibly cumbersome, does not appear to hinder the quality of the research being conducted under the program; this could, however, make it more difficult for the Program Director to do forward planning or to plan the investigation of emerging issues. The Program Director currently must rely on the willingness

of Laboratory/Center Directors and Division Directors to "release" scientists to the EDC effort. Again, this does not diminish quality, but it may not be the best way to operate a program from which so much is expected.

It should be noted that the scientists (both intramural and extramural) involved in the EDC program are some of the best in their respective fields. From the oral and poster presentations given and discussions with the investigators, it is apparent that scientists with the most relevant skills to EDC research are involved in this program. It also is apparent that the mix of skills on each project and in each subject area is appropriate for the research questions to be addressed.

The EDC program has been very astute in leveraging its resources by collaborating with other federal agencies. The amount of research conducted by the EDC program has been expanded by collaboration with agencies such as NIOSH, NCI, and NIEHS. This leveraging of resources has allowed the EDC program to get involved in areas of research, such as epidemiological studies, that it does not have sufficient intramural expertise to handle and to increase the output in other research areas.

From the research progress made in the EDC program in the past 5 years, it is apparent that the EDC Program Director has had success in convincing Division Directors to lend scientists' time to the program. It also is apparent that the Division Directors have been very cooperative in participating in the EDC program. The fragmentation of scientists' time without compensation (e.g., the addition of a technician to the laboratory to either carry out the scientist's originally assigned research or to perform the research necessary for the EDC program) raises concern about whether the productivity (e.g., number of manuscripts published) of these scientists is negatively impacted by participation in the EDC program.

The situations cited above (insufficient funding and the mechanism used to provide resources to the EDC program) can be remedied by several courses of action: (1) hiring additional personnel to share the workload of the participating laboratories; (2) elevating the position of the EDC Program Director to the level of the Laboratory/Center Directors; and (3) giving the EDC Program Director budget authority.

These actions would allow the Program Director to negotiate for needed research expertise from a position of strength and will allow the Program Director to enhance the laboratories that participate in EDC program research.

The ORD has plans to enact the latter two of these ideas in the near future for all newly hired National Program Directors. The BOSC recommends the speedy implementation of that plan.

It should be noted, however, that the BOSC's recommendations about the hierarchal placement of the position of the National Program Director and the granting of budgetary authority to the holder of that position is based solely on its observations of the performance of the EDC Program Director. Dr. Elaine Francis has demonstrated the ability to work cooperatively with Laboratory/Center Directors and has used the resources provided to her in a responsible manner. Thus, the BOSC's recommendation is based solely on the exemplary model established by Dr. Francis.

The subcommittee subsequently discussed possible disadvantages to the elevation of the position of National Program Director. One disadvantage may be that giving the National Program Director the authority to unilaterally select ORD scientists to participate in the program may undermine the authority of the Laboratory/Center Directors. Another possible disadvantage may be that funds given directly to a National Program Director may further restrict the funding of a laboratory or center in times of fiscal retrenchment. The subcommittee is confident that ORD has worked through all possible problems involved in the elevation of the position.

Recommendation:

- **The BOSC recommends the following courses of action: (1) hire additional personnel to share the workload of the participating laboratories; (2) elevate the position of the EDC Program Director to the level of the Laboratory/Center Directors; and (3) give the EDC Program Director budget authority.**

VII. APPENDIX A—CHARGE QUESTIONS

In your review of the Endocrine Disruptors Research Program, please use the Endocrine Disruptors Research Plan (EDRP), Multi-Year Plan (MYP), NHEERL's Research Implementation Plan, and other submitted documents as background information. In your review, providing comments on the following areas would be very helpful in assessing the program's relevance, performance, quality, and leadership, retrospectively, and its proposed directions, prospectively:

CQ #1. Program Design

A. Please comment on the goals and priorities of the EDRP and MYP, including whether the MYP's long-term goals (LTGs) represent appropriate outcome measures for this program.

B. Please comment on whether the research program has appropriately implemented the EDRP and MYP, tracking the key science questions closely and describing clearly the expectations for providing answers to the key science questions.

   - Factors to consider: the appropriateness of the key science questions; the appropriateness of the LTGs in providing a logical framework for organizing the EDC Program to best meet the Agency's needs; the degree of clarity to the path of annual research products aimed at accomplishing each of the LTGs; and the scientific soundness of the approaches used.

C. Please comment on whether the EDRP and MYP make it clear what ORD's unique research niche is in the context of endocrine disruptors research being conducted across the federal government and internationally. Please comment on whether the rationale is sound for supporting the choices that ORD has made in the past and for the future regarding what to emphasize over the next 5 to 7 years. If it is not, what arguments need to be more clearly stated and what additional evidence and information need to be included? Have the potential public benefits of the program been clearly articulated? Also consider and comment on the interagency collaborations that should and can be improved to advance the Agency's research agenda. To what extent has EPA established and utilized other agencies (inside and outside the government) in advancing EPA's research agenda? What are the impediments to collaboration with other organizations?

   - Factors to consider: research activities of other federal agencies, industry, academic institutions, and other countries; and the degree of collaboration and coordination with other research organizations.

D. Please comment on whether the research products (annual performance measures [APMs]) and their sequencing and emphases over the next 5 to 7 years are appropriate, especially in light of needs for the Endocrine Disruptor Screening Program (EDSP) by

OPPTS. Does the program have a complete schedule with annual milestones for decisions and termination points, highlighting changes from previous schedules?

- Factors to consider: the appropriateness of the research products identified in the MYP to focus on the highest priority research for each LTG; and the adequacy/sufficiency/necessity of the sets of APMs under the annual performance goals (APGs) to accomplish the intended goals.

E. Please comment on whether the MYP is sufficiently flexible to adapt to anticipated future science and policy direction changes.

CQ #2. Program Relevance

Please comment on the extent to which the research program, as evidenced by the EDRP, the MYP, the NHEERL Implementation Plan, and other submitted documentation plans to be responsive to Agency and other stakeholder needs and priorities. Please comment on the role the program scientists have had in providing technical support to Agency program and regional offices.

- Factors to consider: the degree to which the research is driven by EPA priorities; the degree to which this research program has had (or is likely to have) an impact on Agency decisionmaking; and the extent to which research program scientists participate on or contribute to Agency work groups and transfer research to program and regional customers.

CQ #3. Program Progress in Addressing Key Scientific Questions and Impacting Environmental Decisionmaking

The ORD MYP has identified three LTGs under which the key science questions are aligned. Please comment on the degree of progress that has been made in addressing each of the LTGs and associated key research questions. Please comment on the degree to which scientific products are being used in environmental decisionmaking. Has the research program met its APGs?

- Factors to consider: the scientific soundness of the approaches used; the degree to which scientific understanding of this problem has been advanced; the degree to which scientific uncertainty has been reduced; and the impact and use of research results in implementing the EDSP by other EPA program and regional offices and by other organizations.

CQ #4. Program Contributions to Scientific Leadership

Please comment on the leadership role the program and its scientists have in contributing to advancing the state of science on endocrine disruptors.

- Factors to consider: the degree to which this program is identified as a leader in the field; the degree to which endocrine disruptor scientists serve/are asked to serve on national/international workgroups, officers in professional societies, and publication boards; the degree to which endocrine disruptor scientists lead national/international collaborative efforts, organize national/international conferences/symposia, and are awarded for their contributions/leadership; and benchmarking of scientific leadership relative to other programs, agencies, and countries.

CQ #5. Program Resource Allocation

The MYP was developed based on an assumption of level resources (approximately $12 M including approximately 55 full-time equivalent personnel) over the period covered by the plan. Please comment on: (1) the appropriateness of the relative allocation of resources across the LTGs based on a consideration of scientific and programmatic needs; and (2) the manner in which resources are allocated. Do these funding processes maintain program quality?

- Factors to consider: the degree to which resources are allocated across LTGs and across laboratories/centers; the appropriateness of the skill mix devoted to this program; intramural funds, allocated based upon ORD's risk-based priority setting process; matching finite resources with finite in-house expertise; and extramural funds, allocated based upon competitive solicitation with only those achieving a rating of "excellent" or "very good" by an external peer panel considered for funding by an internal program panel.

VIII. APPENDIX B—BIOGRAPHICAL SKETCHES OF THE EDC SUBCOMMITTEE MEMBERS

Anna K. Harding (Chair) is an Associate Professor in the Department of Public Health at Oregon State University. Dr. Harding received her Ph.D. in Public Health from Oregon State University in 1990. Dr. Harding's research expertise is in environmental health, including water quality and public health outcomes, and the effects of environmental contamination on at-risk populations. Dr. Harding also serves as a member of EPA's Board of Scientific Counselors (BOSC).

George P. Daston (Vice-Chair) is a research fellow at the Proctor & Gamble Company in Cincinnati, Ohio. Dr. Daston has expertise in developmental biology, teratology, toxicology, and risk assessment. He received his Ph.D. in Developmental Biology and Teratology from the University of Miami in 1981. Dr. Daston also serves as a member of EPA's BOSC.

Glen R. Boyd is a registered professional engineer with a background in engineering consulting. Currently, he is an Assistant Professor in the Department of Civil and Environmental Engineering at Tulane University. Dr. Boyd's research interests include occurrence and treatment of low-level EDC and pharmaceuticals and personal care products (PPCPs) in the environment, water quality in drinking water distribution systems, and remediation of dense nonaqueous phase liquid (DNAPL) contaminated groundwater. He received his Ph.D. in Environmental Systems Engineering from Clemson University in 1991.

George Lucier is an environmental consultant who retired from the National Institute of Environmental Health Sciences (NIEHS) in 2000. While at NIEHS, he served as Director of the Environmental Toxicology Program and Associate Director of the National Toxicology Program (NTP). Dr. Lucier received his Ph.D. in Entomology in 1970 from the University of Maryland. He has expertise in hormonally active chemicals and risk assessment models.

Stephen H. Safe is a Distinguished Professor in the Department of Veterinary Physiology and Pharmacology at Texas A&M University and the Director of its Center for Environmental and Genetic Medicine. He received his doctorate in 1965 from Oxford University. Dr. Safe's research interests include: toxicology, molecular biology of estrogenic and antiestrogenic compounds, and molecular mechanisms of estrogen receptor and Ah receptor action.

Juarine Stewart is the Interim Dean at Morgan State University's School of Computer, Mathematical, and Natural Sciences. She received her Ph.D. in 1978 in Biomedical Sciences from the University of Tennessee. Her expertise includes chemistry, biochemistry, and management of research. Dr. Stewart also serves as a member of EPA's BOSC.

Donald E. Tillitt is the Branch Chief for the Biochemistry and Physiology Branch at the U.S. Geological Survey's Columbia Environmental Research Center in Columbia, Missouri. He is also an Adjunct Assistant Professor in the Departments of Biochemistry and Fisheries and

Wildlife Sciences at the University of Missouri. Dr. Tillitt's research interests include developmental and reproductive toxicology of environmental contaminants in fish and wildlife, techniques to assess the effects of complex mixtures on environmental contaminants, and biochemical effects on aquatic organisms. He received his Ph.D in Environmental Toxicology in 1989 from Michigan State University.

Glen Van Der Kraak is Associate Dean for Research of the College of Biological Science at the University of Guelph. He also is the Leader of the Reproductive and Endocrine Ecotoxicology Program, Canadian Network of Toxicology Centres. He received his Ph.D. from the University of British Columbia in 1984. Dr. Van Der Kraak's current research includes the regulation of ovarian function in fish and evaluation of reproductive fitness in fish and amphibians.

IX. APPENDIX C—LIST OF ACRONYMS

ACC	American Chemistry Council
APG	Annual Performance Goal
APM	Annual Performance Measure
AR	Androgen Receptor
BOSC	Board of Scientific Counselors
CAFO	Concentrated Animal Feedlot Operation
CDC	Centers for Disease Control and Prevention
DNAPL	Dense Nonaqueous Phase Liquid
EAT	Estrogen, Androgen, and Thyroid Hormone
EDC	Endocrine Disrupting Chemical
EDRP	Endocrine Disruptors Research Plan
EDSP	Endocrine Disruptor Screening Program
EDSTAC	Endocrine Disruptors Screening and Testing Advisory Committee
EPA	U.S. Environmental Protection Agency
ER	Estrogen Receptor
ETD	Experimental Toxicology Division
FDA	U.S. Food and Drug Administration
FQPA	Food Quality Protection Act
FTE	Full-Time Equivalent
FY	Fiscal Year
GPRA	Government Performance and Results Act
HPV	High Production Volume
LTG	Long-Term Goal
MYP	Multi-Year Plan
NCER	National Center for Environmental Research
NCI	National Cancer Institute
NERL	National Exposure Research Laboratory
NGO	Nongovernmental Organization
NHEERL	National Health and Environmental Effects Research Laboratory
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NOAA	National Oceanic and Atmospheric Administration
NRMRL	National Risk Management Research Laboratory
NTD	Neurotoxicology Division
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
OPPTS	Office of Prevention, Pesticides and Toxic Substances
ORD	Office of Research and Development
OSCP	Office of Science Coordination and Policy
PBBs	Polybrominated Biphenyls
PBDEs	Polybrominated Diphenyl Ethers

PCBs	Polychlorinated Biphenyls
PPCPs	Pharmaceuticals and Personal Care Products
RME	Risk Management Evaluation
RTD	Reproductive Toxicology Division
RTP	Research Triangle Park
SDWA	Safe Drinking Water Act
STAR	Science To Achieve Results
USDA	U.S. Department of Agriculture
USGS	U.S. Geological Survey
QSAR	Quantitative Structure Activity Relationship
WHO	World Health Organization