UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

September 8, 2005

OFFICE OF
RESEARCH AND DEVELOPMENT

Dr. James H. Johnson, Jr.
Chair, Board of Scientific Counselors
Dean, College of Engineering, Architecture and Computer Sciences
Howard University
2366 6th Street NW
Washington, DC 20059

Dear Dr. Johnson:

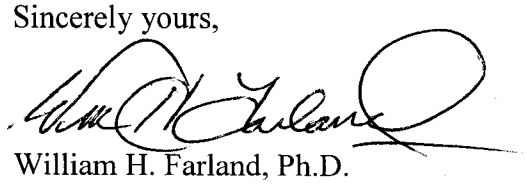
On December 13-15, 2004, Dr. Harding chaired the Endocrine Disruptors Subcommittee of the Board of Scientific Counselors' evaluation of the Office of Research and Development's (ORD) Endocrine Disruptors Research Program in Research Triangle Park, NC. Following that review, the Subcommittee presented a report of its findings and recommendations about program relevance, quality, performance, and scientific leadership to the Executive Committee of the Board of Scientific Counselors. After a receiving a copy of the final report, the Endocrine Disruptors Research Program generated a response to the BOSC's report, which is now transmitted to you for your consideration.

The response of the Endocrine Disruptors Research Program to the reviewers' comments and recommendations is based on input from members of the Endocrine Disruptors Research Working Group, program and regional office stakeholders, and the National Program Director for Pesticides and Toxics. The enclosed narrative identifies specific recommendations made by the reviewers for each of the three Long-Term Goals, provides a brief comment in response, and indicates how the Endocrine Disruptors Research Program will incorporate the BOSC's findings into its operations. Also attached is a table summarizing each recommendation, the action to be taken, and a schedule for completion of the action. The Program benefited considerably from your insight and advice, and your recommendations were greatly appreciated.

As indicated in the Charge for the Endocrine Disruptors Research Program, ORD intends to conduct periodic evaluations of its program's progress at intervals of four to five years. The purpose of the reviews is to determine progress with regard to relevance, quality, performance, and scientific leadership; identify when clients are applying research to strengthen environmental decisions; and evaluate client feedback about the research. In addition to a formal review every four to five years, ORD intends to conduct an interim evaluation of the Program's progress

midway through the review cycle. Within the next year or so, a subset of the Endocrine Disruptors Research Program Subcommittee will be invited to participate in a one-day review to evaluate the status of the changes the Program has agreed to implement. In this context, we look forward to the possibility of working with you again.

Sincerely yours,



William H. Farland, Ph.D.
Acting Deputy Assistant Administrator for Science

Enclosure

cc: Dr. Anna Harding (Endocrine Disruptors Subcommittee, Chair)
Dr. George P. Daston (Endocrine Disruptors Subcommittee, Vice-Chair)
Dr. Glen R. Boyd
Dr. George W. Lucier
Dr. Stephen H. Safe
Dr. Juarine Stewart
Dr. Donald E. Tillitt
Dr. Glen Van Der Kraak

Office of Research and Development (ORD) Response to the Board of Scientific Counselors (BOSC) April 2005 Final Report That Reviews ORD's Endocrine Disruptors Research Program

BOSC Endocrine Disruptors Subcommittee:
Dr. Anna K. Harding, Chair
Dr. George P. Daston, Vice-Chair
Dr. Glen R. Boyd
Dr. George W. Lucier
Dr. Stephen H. Safe
Dr. Juarine Stewart
Dr. Donald E. Tillitt
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Submitted:
Dr. Elaine Z. Francis
National Program Director
Pesticides and Toxics Research Program
Office of Research and Development

The following is a narrative response to the recommendations and observations offered by the Subcommitee on Endocrine Disrupting Chemicals of the Board of Scientific Counselors' review of ORD's Endocrine Disruptors Research Program. The review was held on December 13-15, 2004, in Research Triangle Park, NC. Overall, the Subcommittee found that the Endocrine Disruptors Research Program was of high scientific quality and of direct relevance to legislation that the Environmental Protection Agency (EPA) administers and that it serves the Program Offices well. The goals and scientific questions of the Research Program were deemed to be appropriate. In addition, the Program was found to be nationally and internationally recognized as a multi-disciplinary set of research areas for both human health and wildlife that cuts across the risk assessment/risk management paradigm. The Subcommittee offered a number of observations and recommendations, which are being used to guide the Program during the annual planning cycle and revision of the Multi-Year Plan (MYP) for Endocrine Disruptors. The following response outlines actions that are being taken by the Research Program in response to the review.

Actions being taken or planned are described for each section of the Report of the Subcommittee on Endocrine Disrupting Chemicals Research. Several recommendations were repeated in multiple sections. In such cases, overlapping recommendations have been combined and discussed in the order in which they first appeared in the review document. Peer review comments or recommendations are shown below in *italics.* ORD comments, where needed for clarification, are in plain format, while actions underway or planned are in **bold-faced type.**

EXECUTIVE SUMMARY

Overarching Conclusions and Recommendations

1. The EDCs 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 (p. 6, 7, 30, 41).

Comment: ORD recognizes this issue. The Research Plan and MYP for Endocrine Disruptors Disruptors used the definition developed through an internationally convened workshop (Kavlock et al., EHP 104 (Suppl 4): 715-740, 1996). Since then the World Health Organization has developed another definition (WHO, 2002) which will be considered in the updating of the MYP. But the crux of this issue appears to be a request to better clarify what the scope of the ORD EDCs Research Program is. As evident from the Program Review, the emphasis of ORD's Program has been on mechanisms related to impacts on estrogen, androgen, and thyroid systems. However, in addition, there are activities on other mechanisms such as through steroidogenesis, aromatase, the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-thyroid axes, retinoids,

and ecdysoids. The emphasis on a systems approach to the EDCs' issue and the realization that the central nervous system, liver, and other mechanisms are all critical components of any endocrine system, may compel us to look at a broader research scope. The challenge in the MYP update will be to balance clarifying the scope but leaving the door open to address critical gaps in endocrine mechanisms known or suspected to be involved in adverse effects in humans and wildlife that may not be addressed through other ORD or outside Research Programs.

Action: ORD's Research Plan for Endocrine Disruptors and the MYP for Endocrine Disruptors reference the definition that is used to guide this Research Program. The guiding definition, what research is included, and how this relates with other ORD research will be further clarified in the next update of the MYP and in future Program Reviews

Time Line: The Endocrine Disruptors research planning team is updating the MYP. A draft of the update will be available in early 2006. A mid-course review of the Research Program will take place in late 2006.

2. *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. (p. 7-8, 14).*

Comment: ORD recognizes the priority of the EDCs Research Program in providing the support needed for the Agency to carry out its mandates. The National Program Director (NPD) for Pesticides and Toxics, who now oversees the EDCs Research Program, will make the best use of the available resources to implement a scientifically sound and highly relevant Research Program. (1) Agency resource limitations, including the ceiling on the number of personnel (Full Time Equivalents - FTEs), make hiring additional personnel unlikely at this time. Other options for supplementing the scientists in the EDCs Research Program will be explored. (2) In May 2005, ORD announced the establishment of NPDs for eight Research Programs. One of those was for Pesticides and Toxics research, which includes the EDCs Program. There was much discussion among ORD's senior leadership regarding the relationship of the NPDs to the Laboratory/Center Directors. (3) "Budget authority" resides with the Senior Budget Officer (SBO) in ORD.

Action: (1) The EDCs Research Program will be bringing on board several new postdoctoral fellows to fill critical gaps and help advance the Research Program. The NPD will encourage the Laboratories/Centers to pursue other Fellows (e.g., AAAS, ASPH) and will work with ORD's Office of Resources and Management Administration to explore the possibility of using other vehicles (e.g., recent graduate contract) to supplement the number of scientists in this Research Program. (2) The NPDs report individually to the Assistant Administrator (as do the Laboratory/Center/Office Directors) through the Deputy Assistant

Administrators and work together as a group to assist in planning and implementing ORD's Research Programs. They are awarded senior level stature and make recommendations to the Laboratory/Center Directors, the Assistant Administrator, and Deputy Assistant Administrators (i.e., collectively the Executive Council) regarding research priorities. The details regarding the relationship of the NPDs, to the Executive Council, Science Council, and other Agency groups are being delineated in a document under development. (3) "Budget authority" resides with the SBO in ORD. The Executive Council decided that budget advice and recommendations will be sought from the NPDs who would be responsible for working closely with the Laboratory/Center/Office Directors

Time Line: (1) Finding innovative ways to supplement the existing EDCs workforce is an ongoing effort. Furthermore, as the NPDs begin to work together, they may be in a better position to characterize leveraging of personnel across the Research Programs. (2) and (3) Details of the relationship of the NPDs within the ORD management structure are being worked out in a document under development by ORD and will be available by January 2006.

STRENGTHS AND CHALLENGES OF LONG-TERM GOAL 1:

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

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.

3. 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 [wildlife toxicity] area (p. 9, 22).

Comment: ORD had a wildlife toxicology program which ended in 1994. Currently, in general, ORD has a very limited program in the area of wildlife toxicity since other Agencies have greater

depth and breadth there. Given our limited resources, ORD has determined where EPA's research can have its greatest impact and has carved out our niche to address 3 areas: 1) developing mechanistically based approaches for extrapolating toxicological data across wildlife species, media, and individual level response endpoints, 2) developing approaches for predicting population level responses to stressors, and 3) developing approaches for evaluating the relative risks from chemical and non-chemical stressors on spatially structured wildlife populations across large areas or regions. Further detail is given in the National Health Effects Research Laboratory's Wildlife Research Strategy (http://www.epa.gov/nheerl/publications/). Some of this research, which is conducted under the Safe Pesticides/Safe Products (SP2) MYP is looking at endocrine disruptors. Furthermore, there are wildlife toxicologists in EPA's Office of Prevention, Pesticides and Toxic Substances who are responsible for reviewing data on pesticides and other toxic chemicals for Agency decisionmaking.

Action: As noted in the BOSC review, ORD has complemented its strengths in the areas of aquatic and human health related toxicity by engaging academic wildlife toxicologists through the extramural STAR program and will continue to do so, where appropriate. It is anticipated that some of the new post doctoral fellows that will be sought will be in the area of aquatic or invertebrate toxicology which will strengthen our ecological portfolio but will not move into other wildlife research. We will increase our efforts to collaborate across federal agencies to leverage the talent of their wildlife toxicologists. The EDCs Research Program is working with a contractor to have a synthesis document developed that is integrating the published results from ORD's extramural STAR and intramural programs on the impacts of EDCs on wildlife, including aquatic, amphibian, invertebrate, avian, reptile species.

Time Line: The NPD will work through the Interagency Working Group (IWG) on Endocrine Disruptors to increase sharing of information and leveraging research activities. One collaboration already underway is the organization of a multi-Agency sponsored workshop to look at the impact of wastewater treatment plants and concentrated animal feeding operations (CAFOs) on ecosystems. It will be held in 2006. The synthesis report on wildlife will be completed late in 2005.

4. 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 (NGO), and industry partners to characterize better the range of variability among species (p. 9, 22).

Comment: ORD appreciates the fact that the BOSC has recognized its long history of research on species-to-species extrapolation. In fact, this topic is of paramount importance in several of ORD's MYPs. Improving our understanding regarding extrapolation across species is one of the

ten questions that the EDCs Research Program is aimed at addressing. We are doing this through both our intramural and extramural programs. By pursuing research on mechanisms of action, the EDCs Research Program will provide significant information that is important in improving our ability to extrapolate (e.g., homology at the mechanistic level). ORD agrees that establishing collaborations and partnerships with other Federal and non-Federal research organizations ultimately strengthen ORD's overall Research Programs.

Action: Our intramural Research Program will continue to evaluate potential interspecies differences and similarities among the various cellular mechanisms of action of current interest in the EDCs Research Program. Currently, these efforts include identifying the androgen receptor and estrogen receptor of different species, examining the response of these receptors to the same compounds using *in vitro* methods, as well as conducting a comparison of the *in vivo* response in several species. This work is being conducted in conjunction with investigators at two universities and a chemical company in Germany. In addition, our scientists will continue to collaborate with scientists from other organizations. This will be done on a scientist-to-scientist basis as well as under the auspices of the IWG.

Time Line: Our Research Program on species extrapolation is scheduled to continue through FY07. The topic of extrapolation across species will be raised at a meeting of the IWG in the fall of 2005 to determine whether there is any interest in having a future workshop on this topic.

5. 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 (p. 9, 22).

Comment: One of the objectives of EPA's Computational Toxicology (Comp Tox) Research Program is to develop and apply predictive tools to prioritize chemicals for testing. An early proof of concept using EDCs as the chemicals of interest was implemented in our in-house laboratories, as well as through the STAR program. The directions of the Comp Tox Program were under development and the program itself was in its infancy when the current EDCs MYP was being developed. Regardless, the MYP for EDCs identifies a number of these tools as Annual Performance Measures.

Comp Tox work is progressing. For example: 1) There is on-going work to develop a hypothalamic-pituitary-thyroid (HPT) model providing a rational framework to organize and interpret toxicological data from the molecular to the organismal levels that will serve as a basis for development of predictive tools related to thyroid toxicity. This will enhance the Agency's use of quantitative structure activity relationships (QSARs), thus, providing a basis for sorting chemicals by mode of action (MOA). 2) Work on using a combination of genomics, proteomics,

metabonomics, computational modeling, and whole animal endpoints to identify new molecular biomarkers of exposure to EDCs representing several MOAs is also progressing. These markers are then linked to biomarkers of effects that are relevant for both diagnostic and predictive risk assessments using small fish models.

Action: The NPD and the EDCs and SP2 planning teams will work with the Director of the National Center for Computational Toxicology (NCCT) to ensure greater linkages among the EDCs, Comp Tox, and SP2 Research Programs. These will be better characterized in the updated MYPs.

Time Line: Comp Tox research is making progress in developing predictive tools for EDCs. The directions of the Comp Tox Program underwent a review by a Subcommittee of the BOSC in April 2005. A workshop that brought together STAR grantees and EPA scientists was held on July 17-18 to share their research and build collaborations. A draft of the EDCs MYP will be ready by early 2006 and will include clearer linkages among the EDCs, Comp Tox, and SP2 programs.

6. 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 (p. 21).

Comment: EPA's position is that current approaches for risk assessment under specific endpoints (e.g., developmental, reproductive, cancer) are appropriate for use in evaluating endocrine disrupting chemicals. There are some relevant activities that are discussed in greater detail in responses to other recommendations that apply here as well, for example, the efforts in developing data and approaches to incorporate 'omics information into Agency decisions and consideration of the MOA approach (page 10).

Action: EPA will continue to monitor research results that may affect current risk assessment practices, as they get published. If, and when, the Agency determines that risk assessment approaches need modification, they would convene a cross-Agency committee (as has been done with the development of other risk assessment guidelines) to deliberate and develop guidelines. In keeping with the guideline development process, there will be opportunity for public involvement, through workshops and solicitation of public comments.

Time Line: Research that may affect current risk assessment practices will be monitored on an ongoing basis.

STRENGTHS AND CHALLENGES OF LONG-TERM GOAL 2:

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

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.

7. 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. EPA should mine data made available from the HPV Program (p. 11, 30).

Comment: The NPD chairs the IWG on Endocrine Disruptors and will use this opportunity to strengthen our relationships with the other Agencies. EPA is engaged in the topic of pharmaceuticals in the environment in a number of ways. There is a small research effort under the Water Quality Research Program (WQRP). ORD is also participating on a steering committee for an International Workgroup on "Pharmaceuticals in the Environment" sponsored by Society of Environmental Chemistry and Toxicology (SETAC). This workgroup is composed of members from academia, government and industry and is focused on pharmaceuticals impacts and potential risks in the environment. In addition to the intramural research, a solicitation through STAR resulted in the award of six grants. Finally, under the auspices of the Office of Science and Technology Policy, an interagency task group on Pharmaceuticals and Personal Care Products (PPCP) was established in late Fall, 2004. This workgroup is co-chaired by ORD and FDA and reports to the Toxics and Risk Subcommittee under the Committee of the Environment and Natural Resources. The PPCP task group is working closely with the chair of the IWG on EDCs. The charge to the PPCP task group is to develop a strategic Framework document that would identify: 1) work currently underway across the Federal government; 2) areas of common interest to explore collaboration; and 3) data gaps which would be prioritized relative to greatest impact. It is unclear as to what extent data from the HPV program will shed some light onto the effects of these chemicals on the endocrine system but the opportunity to evaluate will be pursued. Knowledge regarding he potential sources of these chemicals will provide insights regarding potential exposures and may assist in the determination of screening priorities.

Action: The NPD chairs the IWG on Endocrine Disruptors and will use this opportunity to strengthen our relationships with the other Agencies. Efforts are already underway to

organize a multi-Agency sponsored workshop related to sources of exposure. The IWG decided to focus this workshop on looking at the impact of two exposures, wastewater treatment plants and concentrated animal feeding operations (CAFOs), on ecosystems. The NPD will continue to work closely with the co-chairs of the interagency PPCP task group and look for opportunities for joint efforts. The NPD will work with the NPD for WQRP to explore leveraging PPCP activities. In updating the EDCs MYP, the planning team will consider linkages with the WQRP's PPCP efforts. The NPD will work with OPPTS to make the data not only from HPV but also from VCCEP, available to ORD for data mining and research hypothesis generation.

Time Line: The interagency workshop on wastewater treatment plants and CAFOs will be held in 2006. A STAR grantee and EPA scientist-to-scientist meeting on pharmaceuticals in the environment was held August 23-25. Some of the ORD EDCs research was presented at the workshop. The proceedings of this workshop are being distributed. The interagency Task Force also held a workshop on July 25-26 that was attended by some of ORD's EDCs researchers. The products of the workshop will contribute to the development of the Framework document, whose first draft is anticipated by December 2005. The SETAC workgroup will convene at the annual meeting in Baltimore in November 2005 to discuss organization and workgroup activities, including establishing potential subgroups on environmental effects, environmental risk assessment, fate and PEC, water treatment and management, future criteria for risk management, and mixtures. The NPD will be meeting with the OPPTS Office Directors in September about ways in which to improve communications of research results and will use that opportunity to request access to HPV and other data for the EDCs scientists. The NPD and MYP team will consider opportunities for incorporating the HPV and VCCEP data base mining activities in the next update of the MYP scheduled for completion in early 2006.

8. 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 (p. 11, 30).

Comment: A symposium for the epidemiology grantees had been planned eight months prior to knowing that a Program Review of the EDCs research would be planned. The symposium took place just 6 weeks before the Program Review. It was decided that rather than have grantees come to the review that we would invite the Reviewers to the symposium, provide the results of the symposium to the Reviewers, and have a single poster at the Program Review that integrated the status and progress that each grantee was making.

Action: The grantees will be brought together next summer for another grantees progress

review. In the future the NPD and the planning team will avoid scheduling progress reviews of grantees near the time of anticipated Program Reviews. For the next Program Review, an invitation to the epidemiology grantees will be extended requesting their participation.

Time-line: The NPD and planning team and the IWG will continue to track the research of this group of epidemiologists. Another progress review is being planned for next summer. The grantees will be invited to participate in the 2008 EDCs Program Review.

9. It will be important for EPA to take the 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 (p. 11, 30, 36).

Comment: ORD has initiated a Research Program in the area of Computational Toxicology which is using EDCs for its proof of concept pilot. The program has three objectives: 1) improve linkages across the source to outcome paradigm, 2) develop predictive tools, and 3) improve quantitative risk assessments and is being implemented intramurally and extramurally through STAR. Through the Comp Tox program ORD is collaborating with many other federal agencies (e.g., NIEHS, DOE), private companies (e.g., Gene Logic, Iconix, IBM), and universities. Some of this research is being conducted through the SP2 program, e.g., development of systems biology models for fish and amphibian. One project in particular is addressing the question, "Can existing toxicogenomics data improve Environmental Protection Agency (EPA) chemical health risk assessments?" To address this question, a case study will be performed in which toxicogenomics data for dibutyl phthalate, a chemical with endocrine activity, will be incorporated qualitatively in the hazard characterization step of a recent or ongoing EPA chemical health risk assessment. Integrating toxicogenomics data into an assessment case study will identify areas that may be impacted by toxicogenomics data, and contribute to the development of criteria and approaches for incorporating toxicogenomics data in assessments.

Other research is being conducted through the EDCs Research Program. For example, 'omics tools are being used to develop and evaluate semi-high throughput approaches for screening chemicals for endocrine activity. One of these has been so successful already that OPPTS is including it among the battery of assays under consideration for EDSP. Data from similar efforts are also feeding into improving QSAR models for prioritization of chemicals for testing. ORD's in-house capability has been complemented through the STAR extramural program by issuing three Requests for Applications in the areas of high throughput screens, systems biology approaches (using the HPG and HPT axes), and Environmental Bioinformatics Research Centers (EBRCs).

EDCs researchers participate in a cross-Agency Genomics Task Force that is lead by the Office of

the Science Advisor. Subgroups of this Task Force are developing guidance on data submission, data quality, data management, data analysis, data storage and training. The goal is to begin to position the regulatory side of the Agency to handle the types of data that are likely to become part of submissions of toxicological dossiers. For example a Genomics Action Plan has been developed that is addressing incorporation of genomics information in activities such as prioritization and monitoring, both of which are relevant to the EDCs Research Program. Other links to the EDCs program are the application of genomics data in identification of stressor modes of action, identification and assessment of impacts on susceptible subpopulations and life stages, and improving mixtures assessments.

Action: EPA is positioning itself as a leader in the 'omics field through research and policy developments. EDCs scientists will continue to play a critical role in both of these areas. The Director of NCCT and the NPD will continue to hold frequent meetings to coordinate activities. They will work with the planning team to ensure that the linkages among the Comp Tox, EDCs, and SP2 programs are captured in the updated MYPs.

Time Line: The update of the MYP will be available in early 2006. Interaction with the Office of the Science Advisor's Genomic Workgroups is expected to continue for the foreseeable future, as confirmed at the Genomics Training and Tools collaboration meeting with FDA/NIEHS/ICCVAM held on August 4, 2005. The use of toxicogenomics data in risk assessment case study will have a draft for internal review by June 2006. A Workshop review of the case study will be completed by September 2007.

10. *EPA should continue to investigate the common ground between ecological and human health because the Agency is in a unique position to do so (p. 11, 30).*

Comment: The NPD and the planning team agree that the EDCs program is in a unique position to develop approaches that integrate human health and ecological assessments. The assessment portion of our Research Program has been relatively small. However, a case study was developed using mode of action (MOA) information across animal species and humans determining the relationship between MOA and species relatedness (i.e., evolutionary relationships). A case study assessing the utility of this approach was performed for Bisphenol A (BPA), a chemical shown to have endocrine disrupting activity. For the tested vertebrate species, the data support a relationship between species relatedness and the estrogen agonist MOA. Thus, the cross-species MOA approach holds promise for predicting the MOA among untested species for toxic agents. Such predictions could be useful for applying MOA information in an integrated ecological and human health risk assessment as well as for screening and toxicity testing prioritization of chemicals such as the EDSP since the program is concerned with protecting human and wildlife health. The STAR extramural program was used earlier this year to solicit proposal on methods to characterize exposures to mixtures which would be of relevance to human and ecological health.

Currently, several intramural laboratory projects are looking at impacts of exposures on aquatic species and rodent models used for human health.

Action: The NPD and the planning team will take on the challenge to develop approaches that integrate human health and ecological assessments. We will consider improving the integration of projects that will contribute to evaluate human and ecological health (e.g., using the MOA approach). A pilot for this consideration may be centered around CAFOs, where we will be increasing our intramural efforts and issuing a STAR solicitation.

Time Line: Discussions regarding the directions of the EDCs Research Program are ongoing. Within the next year, several post docs will be brought on board to expand our research efforts on CAFOs. In addition, an RFA is under development to issue this fall to engage the academic community to focus on CAFOs. The update of the MYP will be available in early 2006. The MOA case study was finalized in June 2005.

STRENGTHS AND CHALLENGES OF LONG-TERM GOAL 3:

Support EPA's screening and testing program

11. ORD is beginning to develop core competencies in genomics and quantitative structure activity relation (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 (p. 8, 24, 36)

Action: ORD is addressing the need for increasing our competency in bioinformatics in two ways. The first is with new hires. The National Exposure Research Laboratory already has hired two bioinformaticians. The NCCT has issued job announcements for an additional two intramural bioinformaticians. Second, we have issued a solicitation through STAR for an Environmental Bioinformatics Research Center. The award for the EBRC will be made in the form of a cooperative agreement so that there will be strong interactions between extramural intramural scientists.

Time Line: Two hires have been made. Two additional positions have been advertised and applications received. It is expected that selections for the latter two positions will be completed by October 15, 2005 with the persons joining the staff of NCCT soon thereafter. The awards for the EBRCs will be made by September 30.

The major challenge that ORD 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 (p. 12).

12. 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 transfer of protocols to OPPTS (p. 35).

Comment: The problem has been with the type of contracts and the contractor to whom OPPTS transfers the protocols once ORD has transferred them to OPPTS. As a result, OPPTS is seriously behind in their validation effort. Furthermore, OPPTS has had to rely on ORD's EDCs scientists to help analyze data developed through the contractor. This results in ORD staff being diverted from their planned experiments to serve as consultants to OPPTS.

Action: OPPTS senior management and the NPD will be meeting with NHEERL senior management to emphasize OPPTS' priorities and time lines and to reach agreement on how to meet their expectations.

Time Line: Meetings are being set up in Research Triangle Park and Duluth in September.

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

13. 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 (p.35).

Comment: The NHEERL Implementation Plan for Endocrine Disruptors identifies the directions of NHEERL's research and provides integrated summaries of the projects' efforts as of Fall 2004. The Implementation Plan was included in the background material that was sent to the EDC Subcommittee peer reviewers prior to the Program Review and was cited in the charge questions for review.

Action: The EDCs planning team is beginning to update the MYP. It will develop a more coherent way in which to summarize the accomplishments to date and characterize their impact and cite linkages to other relevant documents, such as the NHEERL Implementation Plan, the National Risk Management Research Laboratory's Risk Management Evaluation for Endocrine Disruptors, the Comp Tox Implementation Plan, and the MYPs of other Research Programs, e.g., SP2, Human Health, WQRP. The research is also being summarized in three topical synthesis documents (Effects in Wildlife, Effects on Development, Screening & Testing) that will compile and integrate the intramural and STAR extramural research accomplishments.

Time-line: The NHEERL Implementation Plan on Endocrine Disruptors was updated in October 2004 and included in the background materials for the Program Review. The synthesis documents will be available late in 2005. A draft of the updated EDCs MYP will be available early in 2006.

Endocrine Disruptors Research Program
Summary of BOSC Comments From April 2005 Final Report and Proposed ORD Actions

Recommendations	Action Items
1). 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 (p. 7, 30, 41).	**Action**: ORD's Research Plan for Endocrine Disruptors and the MYP for Endocrine Disruptors reference the definition that is used to guide this Research Program. The guiding definition, what research is included, and how this relates with other ORD research will be further clarified in the next update of the MYP and in future Program Reviews **Time Line**: The Endocrine Disruptors research planning team is updating the MYP. A draft of the update will be available in early 2006. A mid-course review of the Research Program will take place in late 2006.
2). 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. (p. 7-8, 14).	**Action:** (1) The EDCs Research Program will be bringing on board several new postdoctoral fellows to fill critical gaps and help advance the Research Program. The NPD will encourage the Laboratories/Centers to pursue other Fellows (e.g., AAAS, ASPH) and will work with ORD's Office of Resources and Management Administration to explore the possibility of using other vehicles (e.g., recent graduate contract) to supplement the number of scientists in this Research Program. (2) The NPDs report individually to the Assistant Administrator (as do the Laboratory/Center/Office Directors) through the Deputy Assistant Administrators and work together as a group to assist in planning and implementing ORD's Research Programs. They are awarded senior level stature and make recommendations to the Laboratory/Center Directors, the Assistant Administrator, and Deputy Assistant Administrators (i.e., collectively the Executive Council) regarding research priorities. The details regarding the relationship of the NPDs, to the Executive Council, Science Council, and other Agency groups are being delineated in a document under development. (3) "Budget authority" resides with the SBO in ORD. The Executive Council decided that budget advice and recommendations will be sought from the NPDs who would be responsible for working closely with the Laboratory/Center/Office Directors **Time Line:** (1) Finding innovative ways to supplement the existing EDCs workforce is an ongoing effort. Furthermore, as the NPDs begin to work together, they may be in a better position to characterize leveraging of personnel across the Research Programs. (2) and (3) Details of the relationship of the NPDs within the ORD management structure are being worked out in a document under development by ORD and will be available by January 2006.

Recommendations	Action Items
3). 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 [wildlife toxicity] area (p. 9, 22).	**Action**: As noted in the BOSC review, ORD has complemented its strengths in the areas of aquatic and human health related toxicity by engaging academic wildlife toxicologists through the extramural STAR program and will continue to do so, where appropriate. It is anticipated that some of the new post doctoral fellows that will be sought will be in the area of aquatic or invertebrate toxicology which will strengthen our ecological portfolio but will not move into other wildlife research. We will increase our efforts to collaborate across federal agencies to leverage the talent of their wildlife toxicologists. The EDCs Research Program is working with a contractor to have a synthesis document developed that is integrating the published results from ORD's extramural STAR and intramural programs on the impacts of EDCs on wildlife, including aquatic, amphibian, invertebrate, avian, reptile species. **Time Line**: The NPD will work through the Interagency Working Group (IWG) on Endocrine Disruptors to increase sharing of information and leveraging research activities. One collaboration already underway is the organization of a multi-Agency sponsored workshop to look at the impact of wastewater treatment plants and concentrated animal feeding operations (CAFOs) on ecosystems. It will be held in 2006. The synthesis report on wildlife will be completed late in 2005.
4). 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 (NGO), and industry partners to characterize better the range of variability among species (p. 9, 22).	**Action:** Our intramural Research Program will continue to evaluate potential interspecies differences and similarities among the various cellular mechanisms of action of current interest in the EDCs Research Program. Currently, these efforts include identifying the androgen receptor and estrogen receptor of different species, examining the response of these receptors to the same compounds using *in vitro* methods, as well as conducting a comparison of the *in vivo* response in several species. This work is being conducted in conjunction with investigators at two universities and a chemical company in Germany. In addition, our scientists will continue to collaborate with scientists from other organizations. This will be done on a scientist-to-scientist basis as well as under the auspices of the IWG. **Time Line**: Our Research Program on species extrapolation is scheduled to continue through FY07. The topic of extrapolation across species will be raised at a meeting of the IWG in the fall of 2005 to determine whether there is any interest in having a future workshop on this topic.

Recommendations	Action Items
5). 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 (p. 9, 22).	**Action**: The NPD and the EDCs and SP2 planning teams will work with the Director of the National Center for Computational Toxicology (NCCT) to ensure greater linkages among the EDCs, Comp Tox, and SP2 Research Programs. These will be better characterized in the updated MYPs. **Time Line**: Comp Tox research is making progress in developing predictive tools for EDCs. The directions of the Comp Tox Program underwent a review by a Subcommittee of the BOSC in April 2005. A workshop that brought together STAR grantees and EPA scientists was held on July 17-18 to share their research and build collaborations. A draft of the EDCs MYP will be ready by early 2006 and will include clearer linkages among the EDCs, Comp Tox, and SP2 programs.
6). 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 (p.21).	**Action**: EPA will continue to monitor research results that may affect current risk assessment practices, as they get published. If, and when, the Agency determines that risk assessment approaches need modification, they would convene a cross-Agency committee (as has been done with the development of other risk assessment guidelines) to deliberate and develop guidelines. In keeping with the guideline development process, there will be opportunity for public involvement, through workshops and solicitation of public comments. **Time Line**: Research that may affect current risk assessment practices will be monitored on an ongoing basis.
7). 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. EPA should mine data made available from the HPV Program (p. 11, 30).	**Action**: The NPD chairs the IWG on Endocrine Disruptors and will use this opportunity to strengthen our relationships with the other Agencies. Efforts are already underway to organize a multi-Agency sponsored workshop related to sources of exposure. The IWG decided to focus this workshop on looking at the impact of two exposures, wastewater treatment plants and concentrated animal feeding operations (CAFOs), on ecosystems. The NPD will continue to work closely with the co-chairs of the interagency PPCP task group and look for opportunities for joint efforts. The NPD will work with the NPD for WQRP to explore leveraging PPCP activities. In updating the EDCs MYP, the planning team will consider linkages with the WQRP's PPCP efforts. The NPD will work with OPPTS to make the data not only from HPV but also from VCCEP, available to ORD for data mining and research hypothesis generation. **Time Line**: The interagency workshop on wastewater

Recommendations	Action Items
	treatment plants and CAFOs will be held in 2006. A STAR grantee and EPA scientist-to-scientist meeting on pharmaceuticals in the environment was held August 23-25. Some of the ORD EDCs research was presented at the workshop. The proceedings of this workshop are being distributed. The interagency Task Force also held a workshop on July 25-26 that was attended by some of ORD's EDCs researchers. The products of the workshop will contribute to the development of the Framework document, whose first draft is anticipated by December 2005. The SETAC workgroup will convene at the annual meeting in Baltimore in November 2005 to discuss organization and workgroup activities, including establishing potential subgroups on environmental effects, environmental risk assessment, fate and PEC, water treatment and management, future criteria for risk management, and mixtures. The NPD will be meeting with the OPPTS Office Directors in September about ways in which to improve communications of research results and will use that opportunity to request access to HPV and other data for the EDCs scientists. The NPD and MYP team will consider opportunities for incorporating the HPV and VCCEP data base mining activities in the next update of the MYP scheduled for completion in early 2006.
8). 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 (p. 30).	**Action**: The grantees will be brought together next summer for another grantees progress review. In the future the NPD and the planning team will avoid scheduling progress reviews of grantees near the time of anticipated Program Reviews. For the next Program Review, an invitation to the epidemiology grantees will be extended requesting their participation. **Time Line**: The NPD and planning team and the IWG will continue to track the research of this group of epidemiologists. Another progress review is being planned for next summer. The grantees will be invited to participate in the 2008 EDCs Program Review.

Recommendations	Action Items
9). It will be important for EPA to take the 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 (p. 11, 30, 36)	**Action**: EPA is positioning itself as a leader in the 'omics field through research and policy developments. EDCs scientists will continue to play a critical role in both of these areas. The Director of NCCT and the NPD will continue to hold frequent meetings to coordinate activities. They will work with the planning team to ensure that the linkages among the Comp Tox, EDCs, and SP2 programs are captured in the updated MYPs. **Time Line**: The update of the MYP will be available in early 2006. Interaction with the Office of the Science Advisor's Genomic Workgroups is expected to continue for the foreseeable future, as confirmed at the Genomics Training and Tools collaboration meeting with FDA/NIEHS/ICCVAM held on August 4, 2005. The use of toxicogenomics data in risk assessment case study will have a draft for internal review by June 2006. A Workshop review of the case study will be completed by September 2007.
10). EPA should continue to investigate the common ground between ecological and human health because the Agency is in a unique position to do so (p.11, 30).	**Action**: The NPD and the planning team will take on the challenge to develop approaches that integrate human health and ecological assessments. We will consider improving the integration of projects that will contribute to evaluate human and ecological health (e.g., using the MOA approach). A pilot for this consideration may be centered around CAFOs, where we will be increasing our intramural efforts and issuing a STAR solicitation. **Time Line**: Discussions regarding the directions of the EDCs Research Program are ongoing. Within the next year, several post docs will be brought on board to expand our research efforts on CAFOs. In addition, an RFA is under development to issue this fall to engage the academic community to focus on CAFOs. The update of the MYP will be available in early 2006. The MOA case study was finalized in June 2005.
11). ORD is beginning to develop core competencies in genomics and quantitative structure activity relation (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 (p. 8, 24, 36)	**Action**: ORD is addressing the need for increasing our competency in bioinformatics in two ways. The first is with new hires. The National Exposure Research Laboratory already has hired two bioinformaticians. The NCCT has issued job announcements for an additional two intramural bioinformaticians. Second, we have issued a solicitation through STAR for an Environmental Bioinformatics Research Center. The award for the EBRC will be made in the form of a cooperative agreement so that there will be strong interactions between extramural intramural scientists. **Time Line**: Two hires have been made. Two additional positions have been advertised and applications received. It

Recommendations	Action Items
	is expected that selections for the latter two positions will be completed by October 15, 2005 with the persons joining the staff of NCCT soon thereafter. The awards for the EBRCs will be made by September 30.
12). 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 transfer of protocols to OPPTS (p. 35).	**Action**: OPPTS senior management and the NPD will be meeting with NHEERL senior management to emphasize OPPTS' priorities and time lines and to reach agreement on how to meet their expectations. **Time Line**: Meetings are being set up in Research Triangle Park and Duluth in September.
13). 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 (p.35).	**Action**: The EDCs planning team is beginning to update the MYP. It will develop a more coherent way in which to summarize the accomplishments to date and characterize their impact and cite linkages to other relevant documents, such as the NHEERL Implementation Plan, the National Risk Management Research Laboratory's Risk Management Evaluation for Endocrine Disruptors, the Comp Tox Implementation Plan, and the MYPs of other Research Programs, e.g., SP2, Human Health, WQRP. The research is also being summarized in three topical synthesis documents (Effects in Wildlife, Effects on Development, Screening & Testing) that will compile and integrate the intramural and STAR extramural research accomplishments. **Time Line**: The NHEERL Implementation Plan on Endocrine Disruptors was updated in October 2004 and included in the background materials for the Program Review. The synthesis documents will be available late in 2005. A draft of the updated EDCs MYP will be available early in 2006.