

ENDOCRINE DISRUPTING CHEMICALS (EDCs) MID-CYCLE REVIEW SUBCOMMITTEE

**Conference Call Summary
Tuesday, August 21, 2007
1:00 p.m. – 3:00 p.m. Eastern Time**

Welcome

Dr. Deborah Swackhamer, University of Minnesota, Subcommittee Chair

Dr. Deborah Swackhamer, Chair of the EDCs Mid-Cycle Review Subcommittee, welcomed the Subcommittee members to the conference call and thanked them for their participation in the review. Dr. Swackhamer reminded the Subcommittee members that their objective is to evaluate the progress made by the U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD) relative to the commitments made in the program review that was conducted in December 2004 and to obtain advice and feedback on issues related to the future direction of the Program. The mid-cycle review is a relatively new process within the Board of Scientific Counselors (BOSC), but program reviews are common activities of the BOSC. All programs now undergo mid-cycle reviews to provide advice on mid-course corrections. This is the first mid-cycle review for the EDCs Research Program. Dr. Swackhamer asked Ms. Heather Drumm to discuss the administrative procedures for the call.

Administrative Procedures

Ms. Heather Drumm, U.S. Environmental Protection Agency (EPA)/ORD, Designated Federal Officer (DFO)

Ms. Drumm thanked Dr. Swackhamer and the Subcommittee members for their participation in this mid-cycle review. She discussed the BOSC and Federal Advisory Committee Act (FACA) guidelines for the benefit of those who were not on the earlier administrative call. The BOSC is a Federal Advisory Committee that provides independent, scientific peer review and advice to EPA's ORD, and as such, is subject to the rules and requirements of FACA. The EDCs Mid-Cycle Review Subcommittee was established by the BOSC to review the progress made by the EDCs Program since the program review that was conducted in December 2004. There are four members of the Subcommittee, and information on their affiliations can be found on the BOSC Web Site at <http://www.epa.gov/osp/bosc>. The Subcommittee has been asked to respond to a set of charge questions and provide a report for the BOSC Executive Committee's deliberation. The Executive Committee has the authority to evaluate the Subcommittee's report and revise it as necessary before submitting the report to ORD. Ms. Drumm stated that the role of the BOSC is to provide advice and recommendations to ORD. The rights to decision-making and program implementation remain with the Agency.

This is the first public conference call for this Subcommittee. A second conference call is scheduled for September 14, 2007, and a face-to-face meeting will be held on September 18, 2007, in Arlington, Virginia.

As the Designated Federal Officer (DFO) for the Subcommittee, Ms. Drumm serves as the liaison between the Subcommittee and ORD. Ms. Drumm stated that it is her responsibility as the DFO to ensure that the Subcommittee's conference calls and meetings comply with all FACA rules. All meetings and conference calls involving substantive issues—whether in person, by phone, or by e-mail—that include one-half or more of the Subcommittee members must be open to the public, and a notice must be placed in the *Federal Register* at least 15 days prior to the call or meeting. The Subcommittee Chair and DFO must be present at all conference calls and meetings. All advisory committee documents also are made available to the public. To ensure that all appropriate ethics requirements have been satisfied, each Subcommittee member has filed a financial disclosure report. In addition, all Subcommittee members completed the required annual ethics training prior to today's call. Ms. Drumm reported that no requests for public comment were submitted prior to the call, but the agenda allows time for public comment at 2:30 p.m.

Dr. Swackhamer asked Dr. Elaine Francis to discuss the materials the Subcommittee members had received.

Material Overview

Dr. Elaine Francis, EPA/ORD, EDCs Research Program National Program Director (NPD)

Dr. Francis welcomed Dr. Swackhamer as Chair of the Subcommittee and thanked the Subcommittee members for their participation in this review. She stated that the EDCs Research Program appreciates the opportunity to work with outside peer panels to improve the quality of the research and welcomes recommendations to help strengthen the Program.

Dr. Francis discussed the background materials that were sent to Subcommittee members. The materials were designed to assist the Subcommittee members in addressing the charge questions.

Dr. Swackhamer added that Ms. Drumm had recently sent an e-mail with three PowerPoint presentations to the Subcommittee members. These PowerPoint files included a materials overview presentation, a progress review presentation, and a presentation on the progress of Long-Term Goal (LTG) 3. She clarified that Dr. Francis would be discussing those presentations next.

Dr. Francis began the materials overview discussion. The first document included in the Subcommittee members' notebooks was the draft charge (Tab C), which outlines the purpose and the background behind the charge questions. Behind Tab E was a list of available materials; some of these were in the notebooks, while others will be sent in a second mailing. Additional background materials that Subcommittee members might find helpful were listed in this section. The Research Plan for Endocrine Disruptors (www.epa.gov/ord/htm/documents/ORD-EDR-Feb1998.pdf) is the overall blueprint for the Endocrine Disruptors Research Program. Despite being published in 1998, it is still relevant. The next document listed was the most recent (2003)

Multi-Year Plan (MYP) for the Endocrine Disruptors Research Program (www.epa.gov/osp/myp/edc.pdf). Dr. Francis explained that the development of the MYPs began in 1999. The MYPs offer greater detail on Program plans, including when products will be produced, which Laboratory or Center is responsible for producing which products, and so on. The MYPs are living documents and are updated every 3 to 4 years. The Computational Toxicology Research Framework (www.epa.gov/comptox/publications/comptoxframework06_02_04.pdf) also was included in this list. Computational Toxicology is one of the newer programs within ORD, and some of the early work of this program targeted endocrine disruptors. A portion of the research currently being performed in the EDCs Research Program is related to the work in the Computational Toxicology Research Program. The other program that might be of interest to Subcommittee members is the Safe Pesticides/Safe Products Research Program. Complementary research is being conducted in this program, so the Safe Pesticides/Safe Products MYP (www.epa.gov/osp/myp/sp2.pdf) might be a valuable resource as well.

The bibliography under Tab K was a list of all peer-reviewed publications from the EDCs Research Program organized by LTG. It included both intramural and extramural research; if the research was intramural, the laboratory/center of the principal investigators (PIs) for the research were identified in the bibliography. Also included was the report from the previous BOSC review, which was held in December 2004 (Tab F). This report was finalized by the BOSC Executive Committee in April 2005. The ORD response to the report from September 2005 also was included in the notebook (Tab G).

Three documents will be included in the next mailing to be sent out in approximately 7 to 10 days. These documents include a Progress Report (Tab I) that will follow a narrative and tabular format similar to the ORD response. This report summarizes the progress made regarding ORD commitments in its response to the BOSC recommendations from the 2004 program review. The next item is the updated MYP (Tab H); this document is a working draft. Lastly will be a synthesis document (Tab J), which will summarize the progress made in the EDCs intramural and extramural research programs in three areas: screening and testing assay development, impacts of developmental exposures, and exposures and effects on wildlife.

Performance rating materials in the notebook included the Program Performance Measures and Goals (Tab L), which identified the long-term outcomes agreed upon with the Office of Management and Budget (OMB) in the 2004 Program Assessment Rating Tool (PART) review. These are the outcomes on which the 2009 BOSC review will rate the research program. The current mid-cycle review is an opportunity for the Subcommittee to review and rate the progress made since the 2004 program review. The Program Performance Measures and Goals document also identified annual outputs reported to OMB since 2001 that were planned and those that were met (actual). The Annual Performance Goals (APGs) document (Tab L) outlined the Program's success in meeting the APGs on time. If a goal was not met, an explanation was included. Lastly, Tab M consisted of a bibliometric analysis; this was an analysis of the quality and impact of the peer-reviewed publications resulting from the Program. Publications were evaluated according to citation rates and the impact of the journals in which they were published, among other parameters.

Over the course of this and the next call and the face-to-face meeting, these documents will be discussed in greater detail.

Dr. Swackhamer thanked Dr. Francis for the overview and asked the Subcommittee members if they had any questions on the materials. There were no questions.

Overall Progress Review

Dr. Elaine Francis, EPA/ORD, EDCs Research Program NPD

Dr. Francis gave a brief overview of the Endocrine Disruptors Research Program. EPA's strategic plan includes five goals. The EDCs Research Program falls under Objective 4.4 of the Agency's Healthy Communities and Ecosystems goal. The EDCs Research Program is consistent with both EPA's overall strategic plan and with ORD's strategic plan, which was last updated in 2000. In 1996, EDCs were identified as a high priority research area. As discussed earlier, a research plan was published in 1998. Since then, a number of MYPs have been developed. Laboratories and centers often develop their own implementation plans, which provide even greater detail about the research to be conducted. The National Health and Environmental Effects Research Laboratory (NHEERL) developed an implementation plan in 2000; this plan was updated in 2004. The National Risk Management Research Laboratory (NRMRL) developed an implementation plan in 2003. All research also is reviewed at the division level; these division-level reviews occur every 3 to 4 years and are in addition to the BOSC mid-cycle reviews.

Input for the EDCs Research Program comes from the EPA strategic plan, customers (including the Office of Prevention, Pesticides, and Toxic Substances [OPPTS]), regional offices, the Office of Water (OW), other federal agencies, planning teams, and high-level administrators. Outside advice comes from groups like this Subcommittee, from products that are reviewed, scientific advisory panels, OMB, and Congress. Research products often are incorporated into decisions that are made within the Agency.

The budget for the EDCs Research Program at its highest was \$13 million. The extramural funding for the Science To Achieve Results (STAR) Program was eliminated from the budget in 2005. For Fiscal Year (FY) 2008, the Program has 41 full-time equivalents (FTEs); this number includes PIs, technicians, and administrative support personnel. Funding has been fairly stable over the last few years. Although the STAR Program component of the Program was eliminated, in each of the last 3 years, Congress has allocated additional funding above the amount allocated in the President's Budget. This funding has been used to help address some of the shortfalls in the intramural program. In addition, funds have been used to continue to fund STAR grants.

Dr. Francis summarized the progress made since the 2004 program review. In 2005, an exposure-related Request for Applications (RFA) was issued. Five projects working to develop models and methods to assess or characterize exposures in complex mixtures were funded. A Concentrated Animal Feeding Operations (CAFOs) RFA was issued in 2006. That same year, a meeting was held that brought together grantees and the Program's intramural scientists. In 2007, an interagency workshop was held that brought together scientists from 13 different federal agencies to discuss the research being conducted across agencies on the effects of

endocrine disruptors. ORD is in the process of updating the MYP, and a CAFOs workshop is currently underway. The face-to-face meeting for this review will be held in September 2007.

Input considered in the MYP update includes:

- ✧ Recommendations from the OMB PART Review in April 2004 to revise the Program's LTGs to be more outcome-oriented and to better evaluate how the Program's research products are used in decision-making. This OMB Review was unique because the Research Program and the Program Office were jointly assessed; a rating of Adequate was given.
- ✧ BOSC program review (December 2004) recommendations. These will be discussed in more detail later in the call.
- ✧ Regular meetings between staff from the EDCs Research Program and senior management from the Office of Science Coordination and Policy (OSCP)/OPPTS and various advisory committees.
- ✧ Recommendations from OW senior management; the EDCs Research Planning Team (ORD, OPPTS, Regions, OW); NPDs for Human Health, Ecological, Drinking Water, Safe Pesticides/Safe Products, and Water Quality Research Programs; the Director of the National Center for Computational Toxicology; and interagency working groups under the Committee on the Environment and Natural Resources (CENR) Office of Science and Technology Policy (OSTP).

The BOSC program review in December 2004 assessed the EDCs Research Program in the areas of design, relevance, research progress, leadership, and resources.

- ✧ Design. The goals and scientific questions of the research Program were deemed appropriate. The Program consists of a multidisciplinary set of research areas for both human health and wildlife that cut across the risk assessment/risk management paradigm.
- ✧ Relevance. The work of the EDCs Research Program is of direct relevance to legislation that EPA administers, and it serves the program offices well.
- ✧ Progress. Research has been productive and of high scientific quality. Of particular note is the excellent progress made under LTG 3.
- ✧ Leadership. The Program's leadership is nationally and internationally recognized. Research is disseminated in top-tier scientific journals. Program scientists are at the forefront of EDCs research in screening and testing methodologies.
- ✧ Resources. Resources have been used efficiently. The Program is particularly astute in leveraging with other federal agencies. The continuation of the extramural grants program is vital.

The Program's LTGs were updated, taking into consideration OMB's advice to make the research more outcomes-oriented. New language that was added as a result of OMB's input is in bold type. The intent of the LTGs has not changed. The updated LTGs follow:

- ✧ LTG 1. Reduction in uncertainty to provide a better understanding of the science underlying the effects, exposure, assessment, and management of endocrine disruptors so that EPA has a sound scientific foundation for environmental decision-making.
- ✧ LTG 2. Reduction in uncertainty to determine the extent of the impact of endocrine disruptors on humans, wildlife, and the environment so that EPA has a sound scientific foundation for environmental decision-making.
- ✧ LTG 3. OPPTS uses endocrine disruptor screening and testing assays developed by ORD to create validated methods that evaluate the potential for chemicals to cause endocrine-mediated effects in order to reduce or prevent risks to humans and wildlife from exposure to EDCs. (Support EPA's screening and testing program.)

Thirteen unique recommendations were made as a result of the December 2004 BOSC program review.

An overall recommendation was for the EDCs Research Program to clarify what is and is not covered by the Program. EDCs now are defined more clearly in the MYP. Specifically, it is noted that the Program's research is focused on the estrogenic, androgenic, and thyroid processes as opposed to the entire endocrine system.

Another recommendation was to strengthen the NPD's ability to oversee the Program. Specific recommendations included: hiring additional personnel, elevating the position of the EDCs Program Director to the level of the Laboratory/Center Directors, and providing the EDCs Program Director budgetary authority. Hiring additional personnel has been a challenge. The budget of the EDCs Research Program has been decreasing over the last several years, requiring some innovative approaches to supplementing the intramural workforce. Three new staff members have been hired, but the Program has largely relied on hiring postdoctoral fellows, other fellows, and graduate students using a mechanism known as a recent student contractor; this allows for the hiring of recent graduates (within the last 2 years) as independent contractors. Much effort has been put toward better leveraging of personnel across programs. For example, some EDCs personnel are now working under the Safe Pesticides/Safe Products (SP2) Program; these individuals are still working on EDCs research. In addition, the roles and responsibilities of the NPDs currently are under review. In fact, a draft document on the roles and responsibilities of the ORD senior managers was recently released. Some of that information will be included in the narrative. The draft document has not been fully reviewed by the Agency, so the full document cannot yet be shared with the Subcommittee.

At the time of the program review, much of the Program's wildlife research was conducted through the extramural program. A recommendation was made to increase intramural wildlife research. Unfortunately, because of FTE ceilings, additional personnel could not be hired. Efforts have been made to better leverage across the research programs in ORD and work more

with other federal agencies. For example, an interagency workshop that brought together approximately 100 scientists from 13 federal agencies was held earlier this year. In addition, the CAFOs workshop that currently is underway in Chicago, Illinois, includes representatives from other federal agencies including the U.S. Department of Agriculture (USDA) and the U.S. Geological Survey (USGS). The wildlife research being conducted in the EDCs Research Program is summarized in the Progress Report that Subcommittee members will receive in the next mailing. Although the EDCs Research Program would like to increase the number of staff working in this area, there is no funding to support such research. The Program is using its current staff to leverage with other programs to address this data gap.

It was recommended that the EDCs Research Program expand its work with other federal agencies and work more with new partners. The Program has made great strides in this area. A number of topical collaboration opportunities have been identified through interagency workshops. The Computational Toxicology Program is developing databases to further the development of physiologically based pharmacokinetic (PBPK) models that would incorporate information on the variability of species. This information, if it can be extrapolated to other species, could theoretically reduce the need for animal testing. The ToxCast project, also spearheaded by the Computational Toxicology (CompTox) Program, will integrate data on toxic chemicals, allowing for more accurate forecasting of the toxicity of chemicals.

The 2004 BOSC program review recommended that new predictive tools be used to help prioritize the EDCs Research Program. Research in this area is ongoing across a number of ORD's research programs such as EDCs, SP2, and CompTox. The EDCs Research Program's new MYP identifies and makes clearer the linkages with other programs. Both the CompTox and SP2 Programs have been reviewed by the BOSC; thus, the evaluation of the work on prioritization of tools is being conducted across a number of programs. Recently, an RFA was issued through the CompTox Program to support new centers to work on the development of predictive environmental and biomedical computer-based simulations and models. This is another good example of the EDCs Research Program leveraging its work across other research programs.

It was recommended that the EDCs Research Program's efforts focus on the development of risk assessment paradigms for EDCs and the application of research findings. Work currently is underway related to the issue of cumulative exposure or aggregate exposures and cumulative risk, looking at groups of chemicals with similar modes of action. Research on both the androgenic and thyroid systems is being conducted. Results from research on exposure to chemicals that act in a similar fashion and ones that act by different modes of action are being published. In addition, a number of the Integrated Risk Information System (IRIS) assessments that are underway in the Agency's National Center for Environmental Assessment are for EDCs with similar mechanisms of action. The EDCs Program has developed a case study on the incorporation of toxicogenomics data into a risk assessment. EPA's position remains the same—current approaches for risk assessment under specific endpoints are appropriate for use in evaluating EDCs.

The EDCs Research Program is developing tools to study interactions and the impact of exposure. In addition, researchers are looking at the role of pharmaceuticals as sources of EDCs

as well as mining data from the Agency's High Production Volume (HPV) Program. As previously mentioned, an interagency workshop to discuss collaboration opportunities was held earlier this year. In fact, there is a separate interagency working group focused on pharmaceuticals and the environment. This group is developing an inventory of the research currently underway across federal agencies. The working group's ultimate goal is to identify a research data gap framework; a report is expected to be released by the end of 2008. The updated MYP for EDCs research will include research on endocrine-active pharmaceuticals. The Program plans to leverage with other research programs as well. The CompTox Program is coordinating international efforts on molecular screening initiatives and is working to bring together and mine data that might be available from other programs.

Another recommendation made was that the EDCs Program could explore what might be happening to ecological systems as well as human health, given the fact that the Program recognizes that there is concern for both wildlife and human health and that the endocrine systems are similar. There has been some limited progress in addressing this recommendation. Specifically, the Program took part in a case study of the mechanism of action of bisphenol-A (BPA) that was published in 2005. Researchers are targeting Aromatase as one of the common modes of action; they are using both fish and rats to explore the bridge that might exist between ecological and human health. The BOSC December 2004 program review suggested that this was an area ripe for the application of "omics" technology. The EDCs Research Program is conducting research under the Agency's genomics taskforce. In addition, the EDCs Program has developed a repository for array data and is holding an EPA-wide training workshop to help scientists better understand what these data mean and how to apply the data in assessments. The Program also is developing approaches for incorporating these data into its own assessments.

The next recommendation was to add bioinformaticians to the staff. To date, two bioinformaticians have been hired and a job announcement has been posted for two more.

It was recommended that there be a better mechanism in terms of relaying Program protocols to the program office to ensure appropriate validation. Much progress has been made in this area; Dr. Cooper will address this in a subsequent presentation.

Lastly, it was recommended that the Program improve the identification of its research products and the tracking of product use. This is an evolving area, as capturing the wealth of information that has been generated over the past decade is a difficult task. Some of this information will be incorporated into the MYP. As indicated earlier, however, there is no separate document summarizing the work from the EDCs intramural and extramural programs.

The narrative will include much greater detail on each of the recommendations.

Dr. Swackhamer thanked Dr. Francis for her overview and asked if there were any questions or comments. There were no questions.

Dr. Swackhamer introduced Dr. Ralph Cooper, Chief of the Endocrinology Branch in the Reproductive Toxicology Division of NHEERL.

ORD: Scientific and Technological Support for the Agency's Endocrine Disruptors Screening Program (EDSP)

Dr. Ralph L. Cooper, EPA/ORD/NHEERL, Reproductive Toxicology Division

Dr. Cooper discussed the work that has been performed related to LTG 3 of the MYP: "ORD will develop protocols that the Agency will validate and use in implementing its mandated screening and testing program. ORD scientists will also provide scientific expertise through the transfer of the protocols and their validation. This is a 'problem-driven' research area. The Agency needs this research in order to implement its Congressionally-mandated program on Endocrine Disruptors Screening Program (EDSP)."

Dr. Cooper gave an overview of the linkages and timelines for the APGs within LTG 3. He began with these for a number of reasons. First, one of the Program's major landmarks occurred in FY06 when it was scheduled to produce a protocol for various assays for screening and testing programs. Some issues arose around the different species or types of tests as opposed to the screens that would be developed. Because of concerns for some other species, the final dates for some of those protocols were extended to the end of FY10. Still, many screening protocols have been developed since 2004. Final dates for some tests have been extended, but significant progress has been made.

ORD has a long history of identifying and evaluating EDCs; much of this work predates the Food Quality Protection Act and the Safe Drinking Water Act, two Congressional acts that mandated testing for EDCs. ORD scientists were on the Endocrine Disruptor Screening and Testing Committee and played a key role in FACA providing guidance to EPA. Early on, NHEERL developed multiple implementation plans to identify the strategic needs for EDCs research and to match these needs with resources. A broad approach was taken and resources were focused in particular areas—estrogen, androgen, thyroid, and hypothalamic-pituitary-gonadal (HPG) axes. Research in these areas contributes to the development of a variety of screens and tests.

ORD and NHEERL scientists have contributed to the EDSP work in many ways, but most of their work has been focused on developing Tier 1 screens and more recently, on finalizing Tier 2 assays. ORD and NHEERL scientists have attended domestic and international workshops on screening and testing and have delivered presentations at several FACA meetings. ORD scientists also have played key roles in the Organisation for Economic Co-operation and Development's (OECD) work addressing the need for these tests and screens. ORD scientists were involved in both the BOSC program review and the PART review; they have worked to incorporate the recommendations made by these groups. Overall, Program scientists continue to assist in developing and validating these protocols.

ORD scientists work with several different organizations and labs. Information derived from this work is provided to the advisory committee; the advisory committee then provides feedback on the approaches being taken, and adjustments are made based upon this feedback. All information is sent to OSCP; they conduct the studies and are responsible for validation of the assays.

Since 2004, ORD scientists have been focused primarily on completing the Tier 1 screens, which were designed to identify substances for further testing. This work involves both *in vitro* and *in vivo* assays. The Tier 2 protocols should provide more refined information that will allow for the identification of truly adverse effects of a chemical; the Tier 2 protocols also can help establish a dose-response relationship for hazard assessment. These are all multi-generational studies covering a broad range of taxa.

Dr. Cooper discussed the progress made on the Tier 1 and Tier 2 assays. The assays are separated into two groups, *in vitro* and *in vivo*, and there are five stages in the process—protocol development, writing a detailed review paper (DRP), pre-validation, writing an integrated summary report (ISR), and peer review. The ISR includes all information gathered during the pre-validation phase. It is peer reviewed, and then the assay moves forward as a peer-reviewed assay that can be considered for inclusion or exclusion in the battery. The pre-validation phase involves the demonstration of the relevance of the protocol, review of sensitivity and specificity, further standardization, and determination of the readiness of the assay to proceed to multi-lab studies.

Protocols were in place for the majority of the *in vitro* assays in 2004. Some were developed within ORD, while others were the result of collaboration with other groups. For example, the H295-R Cell Lines were achieved through work with OECD and different contract labs were involved in the development of the protocols for Aromatase. Most of the DRPs were written in 2004. All of the assays were at different stages of pre-validation. Much progress has been made in the past 3 years. The pre-validation phase for some of the assays has been completed. The hER Binding, AR (rat cytosol), and Aromatase assays have all been through pre-validation and the ISRs currently are being drafted. The three ISR reports are expected to be completed in the fall of 2007; they then will be peer reviewed, which should be completed by December 2007. The H295-R Cell Line has shown great progress. The H295-R DRP has been published. Pre-validation is in the interlab study phase, which is the last of the three phases in pre-validation. It is expected that the ISR will be written in early 2008 and the final peer review will occur in 2008. The Steroidogenesis Rat Sliced Testes assay was reviewed and presented to the Endocrine Disruptor Methods Validation Advisory Committee. There were many issues with variability, so the Committee suggested that the assay be put on hold.

Dr. Cooper described the status of the 2004 *in vivo* assays. These assays included the Hershberger and the Uterotrophic assays. The Uterotrophic assay was exclusively an OECD effort and in 2004, had completed the pre-validation phase and the ISR was being drafted. The Hershberger assay also was an OECD effort, but with an ORD lead laboratory running the development of the pre-validation studies. In 2004, the ISR for the Hershberger assay was being drafted. The DRPs for the Pubertal Male and Pubertal Female assays were being drafted and the pre-validation phase had begun. The Frog Metamorph and the Fish Screen assays were in pre-validation as well. There were no DRPs for these assays at the time. It is important to note that the stages do not have to be completed in order. By 2007, substantial progress had been made. The Hershberger and the Uterotrophic assays have been published and guidelines are being written for the Hershberger assay. The Pubertal Male and Pubertal Female assays were just going into the pre-validation process in 2004 and have now completed that phase. The rough drafts of the ISRs have been completed and are expected to be sent for peer review in September

2007. Peer review should be completed by December 2007. The same is true of the Frog Metamorph and the Fish Screen assays. The Frog Metamorph assay completed the pre-validation phase, but scientists are performing additional work to answer some specific questions about that assay. The ISRs for the Frog Metamorph and the Fish Screen assays are at different stages of completion. Peer review is scheduled for December 2007.

In 2004, the Tier 2 assays were not as far along in the process as were the Tier 1 assays. Protocol work was in progress for the Mammalian Extended 1 Generation, the Avian 2 Generation, the Amphibian Development Repro, and the Fish 2 Generation assays. The Mysid Lifecycle assay was further along than the others; the protocol and DRP were completed and demonstration and guidance document work was in progress. The Utero/Lactational assay was originally classified as a Tier 1 assay, but was reclassified as a Tier 2 assay after it was reviewed in January 2007.

Much progress has been made since 2004. There now is a protocol for the Mammalian Extended 1 Generation assay and a DRP was published in April 2006. It is now in the demonstration stage. It would be very difficult and expensive to have a pre-validation stage for these assays; however, some volunteer laboratories currently are running the Mammalian Extended 1 Generation studies. There is a draft guidance document for this protocol; it should be sent for review at the end of August 2007. It also will be reviewed at a meeting in Berlin in October 2007. The hope is that it will be peer reviewed in 2008. A DRP has been completed for the Avian 2 Generation assay. For the Amphibian Development Repro assay, there is not yet a finalized protocol, but the DRP is being drafted and some demonstrations are in progress. The DRP currently is being drafted for the Fish 2 Generation assay. The Mysid 2 Generation assay is in the demonstration stage; planning has begun for an interlab comparison study. The Utero/Lactational assay was reviewed in January 2007 as a Tier 1 assay. The protocol was determined to be too complex to classify as Tier 1, so it was recommended that the protocol be abbreviated, used in conjunction with the Mammalian Extended 1 Generation assay, or substituted by the Mammalian Extended 1 Generation assay. Further work on the Utero/Lactational assay is on hold.

Even though the protocols have been completed, ORD scientists continue to consult with OSCP on the final validation of the assays. A lot of work must be done to take the assays to the final stages. Many ORD scientists will continue to work on the Tier 2 protocols with the different species. The screening battery is scheduled to be reviewed in early 2008 and ORD scientists will act as consultants during that process. In addition to the assays discussed, there are many alternatives or second generation assays on which scientists within ORD have been working. The hope is that these assays will provide improved *in vitro* alternatives and also will help to prioritize chemicals.

Dr. Swackhamer thanked Dr. Cooper for his presentation and asked if the Subcommittee members had any comments or questions. Dr. Glen Boyd asked if the Steroidogenesis Rat Testes assay had been eliminated as a potential assay. Dr. Cooper responded that, at the moment, he would agree that it has been eliminated. Dr. Boyd pointed out that the 2004 slide indicated that there were guidance documents for the Mysid Lifecycle assay, but the 2007 slide did not. Dr. Cooper replied that the guidance documents were checked in error on the 2004

slide. Dr. Cooper offered additional comments on the Steroidogenesis Rat Testes assay. The variability and the fact that male rats were required for that assay made it somewhat unattractive. The work done on the H295-R Cell Line since then has made it very unlikely that there will be any additional work on the Steroidogenesis Rat Testes assay. Dr. Swackhamer noted that as science advances newer assays may replace older ones. She thanked Dr. Cooper for his clear and concise presentation.

Overview of Charge

Dr. Deborah Swackhamer, University of Minnesota, Subcommittee Chair

Dr. Swackhamer wanted to ensure that the Subcommittee members understood the charge questions. If members have any concerns or clarifications, they should be addressed at this time. A copy of the charge questions for the mid-cycle review was included in the materials sent to the Subcommittee. Dr. Swackhamer summarized the charge questions:

- ✧ How responsive has the EDCs Program been to the 2004 program review?
- ✧ To what extent does the updated draft MYP provide a coherent framework and rationale for addressing priority research needs?
- ✧ Are there performance metrics the EDCs Program should be using in addition to the current indicators?
- ✧ What advice could the BOSC provide regarding the narrower focus since the 2004 review and, given budget constraints, in what direction should the Program be headed?
- ✧ Rate the progress using the standardized rating tool. Ratings include Exceptional, Exceeds Expectations, Meets Expectations, or Not Satisfactory.

Dr. Swackhamer asked if there were any questions on the charge questions or on the rating categories. There were no questions.

Public Comments

Dr. Deborah Swackhamer, University of Minnesota, Subcommittee Chair

At 2:30 p.m., Dr. Swackhamer called for public comments. There were no comments offered.

Rating Program Performance

Ms. Lorelei Kowalski, DFO, BOSC Executive Committee

Ms. Drumm stated that she sent Subcommittee members a one-page guidance document on the BOSC review mid-cycle performance rating. She asked Subcommittee members who had not yet reviewed the document to do so. She noted that the performance rating tool is relatively new to the BOSC; it was implemented earlier this year.

Ms. Kowalski stated that the 2004 review of the EDCs Research Program was the first program review conducted for ORD by the BOSC. Since then, eight additional program reviews have been completed and two are underway. The BOSC began conducting mid-cycle reviews this year; the purpose of the mid-cycle review is to check the progress made by the Program with respect to the recommendations from the previous BOSC program review. The program review process has evolved over time. The BOSC Executive Committee has tried to standardize and streamline the approach to these reviews to promote consistency across reviews. For example, last year the BOSC approved a template set of charge questions. These charge questions serve as a starting point and then are modified based on the specific program being reviewed. The rating tool is another component of the process that has evolved over time. The rating tool was added to the process in 2007 and has been applied to two program reviews and three mid-cycle reviews. When the rating tool was originally developed, it was intended for the program review process, similar to the 2004 BOSC program review of the EDCs Research Program. The rating tool is used to evaluate performance by LTG, so the number of ratings will vary depending on the number of LTGs for a program. After the rating tool was implemented for the BOSC program reviews, it was decided that it would be included in the mid-cycle reviews as well. Because the mid-cycle reviews are not in-depth technical evaluations, however, the focus of the rating is not on the technical aspects, but on the progress made by the Program in responding to the previous BOSC recommendations. The Program overall is evaluated; a rating is not given for each LTG. The Chair of the BOSC Executive Committee has begun incorporating feedback on the ratings from BOSC members. Based on this feedback, the Chair is drafting brief guidance documents on how to apply the rating tool in both the program review and mid-cycle review contexts. These guidance documents will be discussed at the BOSC Executive Committee meeting on September 17, 2007, which is the day before this Subcommittee's face-to-face meeting. Ms. Drumm will inform those in attendance at the face-to-face meeting of the results of that discussion. Ms. Kowalski concluded her overview of the rating tool and asked if there were any questions. Dr. Glen Van Der Kraak asked why the Program received an Adequate rating in 2004, when there is no Adequate rating option listed in the rating tool charge question. Ms. Kowalski clarified that Adequate is OMB terminology for the PART review. This mid-cycle review rating is not an element of the PART review, and the terminology is different.

Dr. Swackhamer asked if there were any additional comments or questions and there were none.

Preparation for Next Call and Face-to-Face Meeting

Dr. Swackhamer, University of Minnesota, Subcommittee Chair

Dr. Swackhamer asked if the Subcommittee members needed any additional information. Dr. Glen Boyd commented that in the previous review, the Subcommittee members received a preliminary report on risk management. He asked if an update to that report would be included in the materials. Dr. Francis responded that, unfortunately, the document would not be updated. Dr. Safe asked Dr. Francis to bring her most engaging speakers to the face-to-face meeting. Dr. Francis explained that the face-to-face meeting would be different from the 2004 program review because this is a mid-cycle review. The meeting will consist mostly of Subcommittee discussion. She expects all of the presentations to be completed after the next conference call, but there may be a brief presentation at the face-to-face meeting before the discussions. Dr. Swackhamer said that the majority of the face-to-face meeting will consist of Subcommittee

discussion of the five charge questions. That is why it is important to make sure that all Subcommittee members are comfortable with the charge questions and have all the information they need before the face-to-face meeting. Given the materials provided and the PowerPoint presentations, Dr. Swackhamer thought the Subcommittee had sufficient information to answer the charge questions. The rest of the Subcommittee members agreed.

Dr. Swackhamer thought it was premature to discuss the writing assignments until the group had discussed the charge questions. Nevertheless, she asked anyone who had a preference for certain question(s) to let her know. Dr. Safe suggested that the Subcommittee members think about this before the next call and let Dr. Swackhamer know which question(s) they prefer. Dr. Swackhamer agreed. Dr. Boyd said that he would like to review the additional materials being sent to the Subcommittee members before he made that decision. He also would like to refresh his memory on the overall framework. When there were no additional questions or comments, Dr. Swackhamer asked Ms. Drumm if there was anything else that needed to be addressed on the call. Ms. Drumm did not have anything to add, but she reiterated that within the next week or two she would be sending out another package of information for the binders. Dr. Swackhamer thanked everyone for attending and adjourned the call.

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EDC MID-CYCLE SUBCOMMITTEE**AGENDA****Tuesday, August 21, 2007****1:00 pm – 3:00 pm Eastern Time****Participation by Teleconference Only****866-299-3188****code: 2025648239#**

1:00–1:10 p.m.	Welcome - Roll Call - Overview of Agenda	Dr. Deborah Swackhamer Subcommittee Chair
1:10–1:15 p.m.	Administrative Procedures	Heather Drumm Subcommittee DFO
1:15–1:30 p.m.	Material Overview	Dr. Elaine Francis Office of Research and Development
1:30–1:50 p.m.	Overall Progress Review	Dr. Elaine Francis Office of Research and Development
1:50–2:10 p.m.	Long Term Goal 3 Progress	Dr. Ralph Cooper Office of Research and Development
2:10–2:30 p.m.	Overview of Charge/ Rating Program Performance	Dr. Deborah Swackhamer Subcommittee Chair Phillip Juengst Office of Research and Development
2:30–2:35 p.m.	Public Comment	
2:35–3:00 p.m.	Preparation for Next Call and Face-to-Face Meeting - Discuss Writing Assignments - Identify Additional Information Needs	Dr. Deborah Swackhamer Subcommittee Chair
3:00 p.m.	Adjourn	