

**ENDOCRINE DISRUPTING CHEMICALS (EDCs) MID-CYCLE REVIEW  
SUBCOMMITTEE  
MEETING SUMMARY**

**Key Bridge Marriott  
Arlington, VA  
September 18, 2007**

**Welcome and Outline of Purpose**

*Dr. Glen Van Der Kraak, University of Guelph, Acting Chair, Endocrine Disrupting Chemicals (EDCs) Mid-Cycle Review Subcommittee*

Dr. Glen Van Der Kraak, Acting Chair of the Endocrine Disrupting Chemicals (EDCs) Mid-Cycle Review Subcommittee of the Board of Scientific Counselors (BOSC), welcomed everyone and thanked the Subcommittee members for their participation in the mid-cycle review. He explained that he was serving as the Acting Chair because Dr. Deborah Swackhamer, Chair of the Subcommittee, was unable to attend the meeting in person due to a family emergency. Dr. Swackhamer was on the telephone for the day's meeting. He noted that this was the first in-person meeting of the Subcommittee members.

Dr. Van Der Kraak explained that the Subcommittee had been charged with evaluating the progress made by the U.S. Environmental Protection Agency's (EPA) Office of Research and Development's (ORD) EDCs Research Program relative to the commitments made as a result of the December 2004 BOSC program review. The Subcommittee also has been asked to offer advice and feedback on the future direction of the Program.

Dr. Van Der Kraak explained that all Subcommittee members had been provided a copy of the draft charge questions to be addressed in the mid-cycle review. He summarized the draft charge questions as follows:

- ✧ How responsive has the EDCs Research Program been to the recommendations from the 2004 BOSC program review?
- ✧ To what extent does the updated draft Multi-Year Plan (MYP) provide a coherent framework and rationale for addressing priority research needs?
- ✧ Are there performance metrics the EDCs Research Program should be using in addition to their 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.

**Designated Federal Officer (DFO) Welcome and Charge**

*Ms. Heather Drumm, ORD, EPA, Subcommittee Designated Federal Officer (DFO)*

Ms. Heather Drumm thanked the Subcommittee members for their participation in this mid-cycle review. She reviewed the BOSC and Federal Advisory Committee Act (FACA) guidelines. The BOSC is a Federal Advisory Committee that provides independent, scientific peer review and advice to EPA's Office of Research and Development (ORD), and as such, is subject to the rules and requirements of FACA. The EDCs Mid-Cycle Review Subcommittee was established by the BOSC Executive Committee to review the progress made by the EDCs Research 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.

Today's meeting is the face-to-face meeting for the EDCs Mid-Cycle Subcommittee. A conference call was held prior to this meeting on August 21, 2007. There will likely be one or more conference calls after today's meeting to finalize the draft report. The dates are yet to be determined, but they will be published in the *Federal Register*.

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 *Federal Register* notice for today's meeting was published in July 2007. All advisory committee documents also are made available to the public. The Subcommittee Chair and DFO must be present at all conference calls and meetings. A DFO must approve the agenda and attend all meetings. Meeting minutes must be certified by the Chair within 90 days of the meeting. To ensure that all appropriate ethics requirements have been satisfied, each Subcommittee member has filed a financial disclosure report. In addition, all Subcommittee members have completed the required annual ethics training.

Ms. Drumm reported that no requests for public comment were submitted prior to the call, but the agenda allows time for public comment at 2:00 p.m. Public comments will be limited to 3 minutes each.

**Long-Term Goal 1: Neurodevelopment and Thyroid Homeostasis**

*Dr. Mary E. Gilbert, Neurotoxicology Division, National Health and Environmental Effects Research Laboratory (NHEERL), ORD, EPA*

Dr. Mary Gilbert's presentation began with a brief discussion of the changes made to the EDCs Research Program Multi-Year Plan (MYP) since 2004. The wording for Long-Term Goal (LTG) 1 was updated but the overarching goal remains the same. LTG 1 originally read, "Provide a better understanding of the science underlying the effects, exposure, assessment, and management of endocrine disruptors." The updated wording reads, "Reduction in uncertainty regarding effects, exposure, assessment, and management of EDCs so that EPA has a sound scientific foundation for environmental decision-making." The Annual Performance Goals (APGs) under LTG 1 were redefined into three main goals to: (1) improve information on the shape of the dose-response curve, (2) provide models to test and predict the vulnerability of neuroendocrine systems, and (3) investigate molecular approaches to define mechanisms of action, improve extrapolation across species, and improve risk assessments of EDCs. Dr. Gilbert reiterated that the overarching goal for LTG 1, which is to reduce uncertainty regarding EDCs to provide EPA with a sound scientific background for environmental decision-making, had not changed.

Dr. Gilbert explained that her presentation was organized by five different topic areas:

- ✧ Low-dose effects, developing appropriate animal models
- ✧ Evaluation of mixtures of EDCs
- ✧ Species extrapolation
- ✧ Toxicogenomics in risk assessment
- ✧ Biomarkers and screening tools.

Dr. Gilbert discussed a project examining the effect of low-level thyroid hormone disruption on brain development. It is well established that severe hypothyroidism leads to altered brain structure and function. What is not known is the affect modest perturbations in the thyroid axis might have on brain development. One of the first studies conducted by ORD's National Health and Environmental Effects Research Laboratory (NHEERL) examined low-level thyroid hormone disruption. An abnormal brain was observed, with malformation in the corpus callosum, which is the primary fiber system that connects the two hemispheres of the brain. During development, the corpus callosum acts as a pathway for migrating particle neurons. The study found that the malformation was comprised of neurons and was dose-dependent and permanent. These findings support the theory that there is an abnormal migratory error occurring during gestation. NHEERL scientists believe that studying the cell types and the signals that precede the formation of this abnormal cell cluster may lead to information about sensitive biomarkers that underlie brain development disturbed by thyroid hormone disruption. In humans, the main concern is decreased IQ function in children born to mothers who had an altered thyroid status during critical periods in pregnancy. The hippocampus is a part of the brain that is critical for many types of learning and memory. A permanent dose-dependent reduction in the synaptic transmission was observed in this important brain region in response to graded levels of two different thyroid hormone disruptors, propylthiouracil (PTU) and perchlorate. The response of serum hormones in the dams was modest. The researchers found significant positive correlations between the degree of thyroid hormone disruption and the degree of impairment in synaptic transmission. Because reduced IQ function is the primary health

outcome of concern in humans, extrapolation to humans from animal models is facilitated if common endpoints are assessed in both species. In addition to electrophysiological indicators of “learning” being impaired, the researchers also detected behavioral deficits in tasks of learning and memory in adult offspring of dams treated with thyroid hormone disruptors.

In the 2004 BOSC review of the EDCs Research Program, it was recommended that EPA partner with other government agencies, industry, and academia to further improve its research program. Two grants on low-level thyroid hormone disruption awarded through EPA’s Science To Achieve Results (STAR) Program were converted to cooperative agreements and strong collaborative efforts were cultivated between the academic laboratories and EPA scientists. The goal of one project was to identify sensitive biomarkers of effect on central nervous system (CNS) development in response to low-level thyroid hormone disruption. It is well-known that myelination is a process in normal brain development that is severely impacted by hypothyroidism. The data from this study are the first to show that this process also is impacted by very modest alterations in the thyroid axis at critical periods. Dr. Gilbert presented a slide showing an *in situ* hybridization image of mRNA for myelin-associated glycoprotein. The reduction in the expression of this gene is dose-dependent at modest levels of hormone disruption. The number of oligodendrocytes, the cells that actually make this protein and form the myelin sheath of neurons that contribute to synaptic transmission, also is reduced in a dose-dependent manner. Some other NHEERL research is consistent with these observations. In particular, microarray data have been used to show that there are a number of myelin-associated genes that are downregulated in a dose-dependent manner as a function of thyroid hormone disruption. In this study, animals were exposed in a manner similar to those from the other study. It is possible that the biomarkers in these genes in the myelin family represent sensitive biomarkers of brain development that are disrupted by thyroid hormone insufficiencies. In addition, other studies have shown that morphological abnormalities resulting from transient exposure to adrenergic receptor (AR) antagonists delay puberty and reduce fertility.

Data from another STAR-funded grant have indicated that even longer term changes may be associated with endocrine disruption. These data showed an indication of altered testes morphology in response to very low doses of EDCs three generations later. In other words, the great-great-grandmother of the rat with altered testes morphology was exposed to a very low dose of vinclozolin during a critical period in reproductive development. The incidence of persistence across generations suggested to the researchers that there may be an epigenetic reprogramming of the germ line. These are very provocative and controversial findings. If these findings can be duplicated in other laboratories, it will likely change how EPA performs its risk assessments for this class of chemicals. Two recently published abstracts, however, have failed to replicate these findings. To date, ongoing efforts within NHEERL also have failed to replicate these findings. Ongoing research efforts within the Reproductive Toxicology Division (RTD) of NHEERL to either support or refute these findings are critical.

Dr. Gilbert discussed research on EDC mixtures. Until recently, EPA performed risk assessments on a chemical-by-chemical basis, not by concurrent exposure. Since 1986, the dose additivity statistical model has been the default model for risk assessment for chemicals with a common mechanism of action. Response additivity was the default model used when chemicals with different mechanisms of action were assessed. Data from three different experiments suggest that response additivity severely underestimates risk and that dose additivity may be sufficient for the evaluation of chemicals with both similar and dissimilar mechanisms of action.

There also may be a new generation of models on the horizon that incorporates both the dose additivity and response additivity components.

Research from one laboratory shows that when two phthalates are administered at effective concentrations, both the hormonal genomic as well as the structural indices of disruption of the reproductive system behave in a dose additive fashion. Thus, for these data, with this group of compounds at these specific doses, the dose additivity model works very well. At non-effective doses, however, the dose additivity model fails to predict the observed effect.

In the thyroid axis, there are different sites of action where chemicals may serve to reduce circulating levels of thyroid hormone. One of these sites is the liver and the other is at the level of the thyroid gland. When a low-level mixture of chemicals that acts through the liver was subjected to the additivity model, this model was very predictive of the effects. There was a deviation from additivity at higher concentrations of the mixture that may be an example of synergism. The combined dose and effect additivity model then was used to evaluate a mixture of chemicals that acted at two different target sites. There are three different components of this combined dose effect additivity model: one to evaluate the dose addition-associated thyroid target, another dose addition to evaluate the components associated with the liver, and a third effect addition component used to assess the different target sites over which these two different classes of chemicals act. Using the mixed model resulted in a good prediction of the empirical data.

In sum, dose additivity appears to work well for both chemicals with similar and dissimilar mechanisms of action. It is possible that combined mixture models may prove to be more predictive. One of the important lessons learned from this work over the last 4 years is that precise knowledge of the mechanism of toxicity is not necessary to predict these interactions. What is necessary is having extensive dose-response data for each chemical within the mixture.

There are still many unknowns about extrapolation across species in toxicology. Dr. Gilbert highlighted two projects that were designed to directly address species extrapolation. Hormones binding to androgen and androgen receptors are critical for sexual differentiation. EDCs also bind to these receptors using the same mechanism and can disrupt reproductive development. One of the primary assumptions in screening methodologies is that binding assays performed in fathead minnow or in rats will be sufficient to screen for EDCs that may impact humans. One of the drawbacks, however, is that this assumption of species sequence homology of these receptors has never been directly tested. The study that Dr. Gilbert described was designed to test this assumption. A series of androgen and estrogen receptors were collected from a wide variety of species, from *Daphnia* to humans, expressed in the same expression cell system, and performance to binding was compared for the receptors from the distinct species. Data collected to date indicate that the androgen receptors in the fathead minnow and the human are fairly comparable. Other recent data demonstrate that the chimpanzee androgen receptor is more than 99 percent homologous with the human androgen receptor such that the chimpanzee androgen receptor could be substituted for the human androgen receptor in the *in vitro* screening.

The second project addressing species extrapolation resulted from a series of controversial studies that indicated that the proposed mechanism of action for atrazine increase in aromatase activity was responsible for the feminization seen in some frogs. Atrazine is a widely used herbicide and these claims were made on the basis of less than parts per billion (ppb) exposure

levels. Despite a number of studies showing the impact of EDCs on aromatase *in vitro*, there have been no *in vivo* studies demonstrating that atrazine affects sex through this mechanism of action. NHEERL scientists have shown that in rats, the administration of atrazine leads to an increase in serum hormones, but this was not associated with an increase in aromatase activity in either the testes or the brain. In fish, reproductive viability was decreased by atrazine. This was associated with an increase in aromatase activity in the brain but not in the gonads of the fish and was only evident at low depth levels of exposure. There are significant differences in the metabolism of atrazine between these two species. Contrary to recent claims, the induction of aromatase is not the primary mechanism of action for atrazine-induced toxicity *in vivo* in rats or in fish.

Dr. Gilbert discussed the use of biomarkers and screening techniques. She mentioned again the cooperative agreement EPA has initiated to develop sensitive biomarkers of CNS development associated with low-level thyroid hormone disruption. Another project using proteomics as potential biomarkers for detecting reproductive toxicity is underway in RTD. One of the problems with the thyroid hormone screening assay is its throughput. It is a 21-day assay for tail resorption in the tadpole. Scientists in the EDCs Research Program have been working to identify alternatives, searching for molecular and biochemical markers in the thyroid glands and serum of tadpoles and relating those to structural defects in an attempt to identify biomarkers that may be incorporated into the next generation of screening assays.

Dr. Gilbert discussed a toxicogenomics study that is a joint collaboration between the National Center for Environmental Assessment (NCEA) and NHEERL scientists using risk assessment for dibutyl phthalate as a case study. There has been an increase in the use of “omics” technology in science and the risk assessor often is unsure what to do with the data. NCEA and RTD scientists worked together to develop a number of recommendations for conducting toxicogenomics studies that would improve their utility in a risk assessment context. These recommendations include using parallel study designs in genomics and toxicity assessments, increasing sample numbers to improve power, and incorporating multiple doses, especially low doses, to address dose response.

There are a number of additional projects underway in the EDCs Research Program. One project is developing a quantitative biologically based dose-response model for thyroid hormone disruption in the rat fetus and neonate. This is the other cooperative agreement sponsored through EPA’s STAR Program. Future work will focus primarily on binary mixtures. Multiple chemicals need to be added to the mixtures and statistical models need to be assessed under those conditions. To date, the work on reproductive function has focused only on androgens and male reproductive function; in the future, both sexes will be included. The EDCs Research Program would like to continue developing animal models of human neurodevelopmental outcomes of concern. The work with the androgen and estrogen receptor binding assays needs to be expanded. There also is a need to identify biomarkers for thyroid hormone disruption that are sensitive at low levels of exposure. Proteomics and toxicogenomic profiles of reproductive toxicants need to be incorporated into the research. Finally, the development of more sensitive and predictable screening assays for androgens, estrogens, and thyroid hormone disrupting chemicals is needed.

Dr. Gilbert thanked everyone who contributed to the science she discussed and also those who helped put the presentation together.

**Long-Term Goals 1 and 2: Exposure Assessment and Risk Management of EDCs**

*Dr. Marc A. Mills, Land Remediation and Pollution Control Division, National Risk Management Research Laboratory (NRMRL), ORD, EPA*

Dr. Marc Mills explained that he would be covering Long-Term Goals (LTGs) 1 and 2 from the aspect of exposure assessment and risk management of EDCs. The objective of his presentation was to provide an update on and examples of the progress of the research to support LTGs 1 and 2. Dr. Mills pointed out that he would be discussing only a few examples; much more research currently is underway.

Dr. Mills explained that his presentation would cover four APGs from the 2003 version of the EDCs Research Program MYP. LTG 1 reads, "Provide a better understanding of the science underlying the effects, exposure, assessment, and management of endocrine disruptors." Dr. Mills presented a diagram showing how the four APGs fit together and most importantly, how they fit under LTG 1.

The first APG reads, "Evaluate exposure methods, measurement protocols, and models for the assessment of risk management efficacy on EDCs (2008)." One of the recommendations from the 2004 BOSC review was to incorporate bioinformatics into the EDCs Research Program. This effort has been led by the National Exposure Research Laboratory (NERL), which has hired a bioinformatician. The objective is to prioritize future ecological monitoring research by focusing on key aspects of analytical chemistry, occurrence and monitoring, and ecotoxicity. A process has been developed to harvest the data from databases, organize the data, and then prioritize them. This work is guiding future ORD, industry, and science community research efforts in EDCs and emerging contaminants.

One project in this area is developing analytical methods for ecologically relevant pharmaceuticals and metabolites/degradation products. The project objective is to develop methods for waters, sediment, and tissues to conduct fate and occurrence studies. Target analytes were identified using the bioinformatics approach described previously and program office priorities were incorporated. The results of this work will assist the program offices, regions, industry, and the scientific community in designing and implementing exposure monitoring and assessment programs for selected emerging contaminants. This research eventually will be transferred to ORD's National Risk Management Research Laboratory (NRMRL), where efficacy studies will be conducted. The EDCs Research Program has begun some efficacy studies as well.

Another project is examining the potential use of proteomics to identify exposure issues from mixtures. The objective of this project is to identify protein indicators resulting from exposures to mixtures of EDCs and, ultimately, to link protein indicators to biomarkers of exposure and biomarkers of effects. Researchers are working to determine if upregulation, downregulation, or no change in protein expression is occurring. This work will provide regional and state risk assessors with proven, rapid methods for characterizing early indicators of exposure to EDCs.

Another project is assessing the occurrence and potential risks of EDCs in discharges from Concentrated Animal Feeding Operations (CAFOs). This is a collaborative, multi-laboratory effort between NHEERL, NERL, NRMRL, and a number of academic collaborators from the STAR Program. The goals of this project are to determine how and to what degree human and

wildlife populations are being exposed to EDCs, the effects of these exposures, the major sources of environmental EDCs, and ultimately, how unreasonable risk can be managed.

Another project is examining possible EDC exposures to endangered and declining fish populations (pallid sturgeon and silvery minnow). This project aims to identify sources of EDCs to endangered species habitats. If sources are found, researchers will deploy fathead minnows (FHMs) in endangered species habitats below sources and measure gene expression in indigenous fish in these habitats. This project is a collaborative effort between NERL, EPA Region 7, the State of New Mexico, and the U.S. Fish and Wildlife Service. This work will help federal and state services develop recovery programs for endangered species and water quality standards for these EDCs.

The next APG under LTG 1 reads, "Identify risk management EDCs research (2008)." This effort has been discontinued because of funding reductions; however, planning is continuing as part of a larger, more collaborative effort between the ORD laboratories. The need for separate NRMRL planning also has been reduced due to a growing body of literature for EDCs and risk management.

The next APG reads, "Evaluate at least three existing risk management tools to reduce exposure to EDCs (2008)." An ongoing project in the EDCs Research Program is evaluating drinking water treatment technologies for removal of EDCs. In fact, some of the early project work was reviewed in the 2004 BOSC program review. Since that time, work has progressed at a good pace. The objective of this work is to determine the ability of conventional and advanced drinking water treatment processes to remove EDCs from source waters. By the time of the 2004 BOSC review, the analytical methods had been developed and a few bench-scale processes had been evaluated (e.g., granular activated carbon and powdered activated carbon [PAC]). Work continues and has moved on to the processes of coagulation and flocculation. Currently, the researchers are studying the effects of chlorination on EDCs. This work will eventually progress to advance treatment options for drinking water treatments and their effects on EDCs and other emerging contaminants.

Another project under this APG is a study of the persistence of wastewater compounds during drinking water treatment and removal and potential exposure. NERL scientists have taken the lead and are collaborating with U.S. Geological Survey (USGS) scientists. This project is examining drinking water facilities impacted by human wastewater (due to proximity to wastewater treatment plant [WWTP] discharges, or reclaimed water facilities) to determine the "worst case scenario" of persistence of wastewater compounds (especially pharmaceuticals) through drinking water treatment. USGS is developing two new methods. The first will incorporate pharmaceuticals not currently included in their methods; the second will focus on disinfection/degradation byproducts of compounds known to be present in the raw/source waters. Sampling is occurring in two rounds. First, the raw and finished water from 10 to 15 drinking water treatment facilities will be sampled to determine gross removal. Second, at least quarterly for 1 year, two to four drinking water treatment facilities will be sampled throughout the treatment process to gauge the effectiveness of each step and to determine any effects of seasonality on the compounds found in the water.

The National Wastewater Treatment Plant Endocrine Disrupting Chemicals Screening Study was partially reviewed in the 2004 BOSC program review and work continues on this study.

This effort is evaluating 50 effluents in 9 regions in 23 states. FHMs were exposed to effluents for 24 hours. Vitellogenin (Vg) was measured by quantitative polymerase chain reaction (QPCR) on RNA extracted from the livers of the exposed fish. Chemical analyses for natural and synthetic estrogens were performed by NRMRL scientists. These analyses were in progress at the time of the 2004 BOSC program review and have now been completed. Findings include:

- ✧ 26 percent of effluents caused upregulation of Vg expression in male FHMs estrogenic exposure.
- ✧ 4 percent of effluents caused downregulation of Vg expression in female FHMs androgenic exposure.
- ✧ Chemical analysis confirmed estrogenic compounds in WWTP effluents.

A more rigorous statistical approach is being evaluated. Additionally, EPA's Office of Water (OW) has requested that some additional work focusing on these facilities be performed.

The OW Publicly Owned Treatment Works (POTW) Wastewater Survey was initiated by OW, and NRMRL and NERL were asked to participate. This project will evaluate nine POTWs each year for as many as 450 different chemical and biological parameters, of which NRMRL will be contributing the steroid hormones and alkylphenol analysis. NERL will contribute the exposure assays for endocrine activity. To date, work has been completed for eight plants. This project will continue for at least another year, with the potential to expand this to a much broader survey based on the preliminary data.

The Anaerobic Digester Project is a joint project of NRMRL, EPA Region 5, the Great Lakes National Program Office, and the Metropolitan Reclamation District of Greater Chicago. Unfortunately, some obstacles were encountered early on in this project. First, the funding for this project was reduced. In addition, the digesters to be used for this project had some unexpected maintenance needs. The maintenance has now been completed and NRMRL is working with the district to move this project along.

The next APG reads, "Develop at least two new risk management tools to reduce exposure to EDCs (2009)." The Strategies to Suggest Substitutes for Endocrine Active Substances Study is led by NRMRL with collaborators in academia. The objective is to develop substitutes for existing EDCs. The substitutes developed must maintain the chemical properties needed for desirable performance and significantly lower undesirable endocrine activity. A computational approach was developed, and the methodology was tested using alkylphenol ethoxylate surfactants; satisfactory substitutes were found. Unfortunately, funding has been discontinued under the updated EDC MYP. This project will continue, however, in some form under the Computational Toxicology Program.

Onsite wastewater treatment (WWT) research is being led by NRMRL with some support from NERL. This work is being leveraged to include the Drinking Water Program and other water quality programs within NRMRL. For example, a constructed wetland that was being used for nutrient/pathogen removal for domestic waste is now being evaluated for stability to manage EDCs. In the future, this research will be expanded to include other onsite wastewater treatment

options. NRMRL scientists are constructing, fabricating, and testing some pilot-scale septic systems. Other innovative treatments will be evaluated as well.

Dr. Mills summarized the EDC Program's plans for future work on exposure and risk management of EDCs for LTG 1. The occurrence of EDCs from pharmaceuticals and from CAFOs will continue to be a focus area. Work on the development of "omic" and chemical measures of exposure to characterize fate and transport of EDCs also will continue. The Program will further enhance its collaborations with STAR researchers. Additional research will be performed on source identification of EDCs and pharmaceuticals and on the supporting analytical chemistry and biomarkers of exposure. The Program's work will continue to be leveraged against some of the endangered species work that is ongoing within NERL and other laboratories to evaluate their exposure to EDCs and other emerging contaminants. Finally, the Program will continue to expand the informatics approach that was developed to identify veterinary pharmaceuticals from CAFOs as well as over-the-counter (OTC) pharmaceuticals in wastewater. In addition, work will be conducted to further evaluate bioavailability and clearance in wildlife.

NRMRL will continue its work evaluating existing treatment technologies or management practices. Eventually, this information will be used to develop or evaluate innovative treatment options. This work will continue for four theme areas, including CAFOs, onsite wastewater treatment, centralized wastewater treatment, and drinking water.

LTG 2 reads "Determine the extent of the impact of endocrine disruptors on humans, wildlife, and the environment." The first APG under LTG 2 reads, "Characterize sources of exposure and environmental fates of EDCs (2008)." Dr. Mills presented a diagram showing how this APG fit with the others and how it fit under LTG 2.

The Ohio River EDC Instream Effects Study is an example of research supporting this APG. It is a joint project between NERL Cincinnati, NRMRL Cincinnati, the Ohio River Valley Sanitation Commission (ORSANCO), and USGS that is evaluating the upstream and downstream effects of EDCs in the Ohio River. Initial proof-of-concept studies have been completed and work is in progress to plan a larger scale study on the Ohio River.

Research on the land application of biosolids is being led by NRMRL scientists who are collaborating with scientists from academia and USGS. The first effort in this area focused on a project in North Carolina using anaerobically digested and lightly limed biosolids. The EDC side of the project was a subset of a much larger project focused on the water quality aspects of pathogens and nutrients. The work showed that the heterogeneity of the application of these biosolids was so high that the chemistry in some of the supporting data was indeterminate. Additional work is needed to develop sampling protocols and evaluate additional biosolids. This work will eventually be expanded to include hormones and the alkylphenol work that was mentioned earlier. The Program will continue to leverage this work against the biosolids water quality program.

Another study is evaluating the potential for EDCs from CAFOs to contaminate groundwater. This is a substudy of the CAFOs EDC Program, with most of the work being performed in the NRMRL laboratory in Ada, Oklahoma. In some cases, limited field data have shown that swine CAFOs can contaminate groundwater. The field sites chosen for this initial study were, in many instances, worst-case scenarios (i.e., facilities known to be leaking). There is a need for

additional long-term monitoring of these facilities, but also for evaluation of additional facilities not under these worst-case scenarios. Additional work is needed, especially on the conjugated forms of hormones and sample preservation and storage.

### **Endocrine Disruptors Research Program: Long-Term Goal 2 Progress Report**

*Dr. Susan A. Laessig, National Center for Environmental Research (NCER), ORD, EPA*

Dr. Susan Laessig explained that she would be covering additional APGs under LTG 2. LTG 2 reads, "Determination of the extent of the impact of endocrine disruptors on humans, wildlife, and the environment to better inform the federal and scientific communities." Over the last several years, EPA scientists have moved from developing field methods and conducting laboratory studies to using the results of these studies in field-based pilot studies and human studies. Much of this work has been leveraged through the STAR Program.

Dr. Laessig explained that she would be discussing three APGs under LTG 2. The first APG is to "Characterize sources of exposure and environmental fates of EDCs." Scientists are working to characterize the occurrence and ecological impacts of estrogenic and androgenic chemicals in the environment. EPA has developed: *in vitro* and analytical methods to identify EDCs, measure activity of EDCs, and collect samples; methods to assess ecological impacts with a variety of techniques; and molecular biomarkers in aquatic species using genomic approaches. These methods will be brought together to evaluate fate, transport, and metabolism of EDCs in surface and ground waters. In addition, different risk management techniques, technologies, and approaches to reduce exposure will be examined.

NERL, NHEERL, NRMRL, and National Center for Environmental Research (NCER) scientists are collaborating on a number of projects examining the sources of EDCs from CAFOs. Analytical methods to determine estrogens and conjugates in swine waste have been developed and have been used to characterize groundwater contamination from swine lagoons. A number of cell-based assays for estrogens and androgens and biomarkers of androgen exposure in fathead minnows also have been developed. One biomarker is the morphology seen in FHMs. Dr. Laessig showed a slide with images of a normal male, a normal female, and a female that had been exposed to  $\beta$ -trenbolone (a synthetic steroid given to cattle). The exposed female had tubercles on the nose and a larger head and appeared to be more similar to the male FHM than the unexposed female. A number of additional biomarkers have been developed in the FHM. Assays have been used to determine the androgenicity of runoff from feedlots. This is just some of the preliminary work that has been done that has made this collaborative project possible. In addition, researchers have developed a reproductive fecundity model and a population dynamics model that look at the effects of trenbolone in the FHM that can be tested when data from the field are collected.

Even though this work is just beginning, the collaborative project already has made an impact. Both  $\alpha$ -trenbolone and  $\beta$ -trenbolone have been demonstrated to masculinize female FHMs with a similar response profile in plasma steroids and Vg. Water samples associated with a typical operating beef CAFO consistently exhibit androgenic activity. Both  $\alpha$ -trenbolone and  $\beta$ -trenbolone have been measured and confirmed in the samples. A simple estimate of the risk ratio (exposure/effects) indicates that trenbolone concentrations in effluent are sufficient to adversely affect egg production in fish.

The population dynamics model has been used to estimate the ecological effects of EDCs. A joint project between the EDCs Program and the Computational Toxicology Program has developed a modeling construct incorporating data from toxicity, life history, carrying capacity, and habitat to predict population dynamics of FHM exposed to the endocrine disruptor 17 $\beta$ -trenbolone and also to relate changes in biomarkers, such as Vg or steroid levels, to changes in fecundity. Dr. Laessig presented an example of what the population model under one scenario would show. Population trajectories for the FHM population were forecasted at carrying capacity initially. The population then was exposed to chemicals that depress Vg or 17 $\beta$ -trenbolone. Over time, with the increase in Vg levels in males, the population would be drastically reduced. This research has resulted in three publications to date and has been used to forecast population levels of FHMs exposed to chemicals that either depress Vg or 17 $\beta$ -trenbolone.

Seven STAR awards have been made to study the fate and effects of hormones and waste from CAFOs. Several of the grants have been converted to cooperative agreements whereby EPA scientists can work in collaboration with academic scientists on these projects. This allows for the leveraging of these projects and should result in greater impact of the research program. Research goals for the collaborative projects include increasing knowledge of the amount and fate of steroid hormones associated with animal waste under various conditions, determining the extent of the impact of hormones in CAFO waste on aquatic and terrestrial habitats, and evaluating new or improved animal waste handling systems and risk management options for steroid hormones in animal waste.

The EDCs Research Program recently held a workshop on the fate and effects of hormones in waste from CAFOs that served as the kickoff of the collaborative projects. This workshop included EPA scientists, representatives from the U.S. Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), USGS, and participants from federal, state, and academic communities. This meeting brought together key stakeholders and served as a starting point for future collaborations. A workshop summary report was drafted and will be made available on the EPA Web Site ([http://es.epa.gov/ncer/publications/workshop/08\\_20\\_07\\_caf0.html](http://es.epa.gov/ncer/publications/workshop/08_20_07_caf0.html)). This meeting had an overall positive effect on interactions between EPA and other agencies with a focus on communicating and involving the right players at the beginning of a project.

Anticipated impacts from this work include:

- ✧ Understanding risks associated with CAFOs as a potential source of hormones in soil, surface water, and groundwater.
- ✧ Support of the activities of EPA's OW and regional offices with respect to the regulation of CAFOs.
- ✧ Support of site-specific risk assessments and development of risk management options for hormones in waste from CAFOs.

Five STAR research awards began in 2006 to develop exposure methods with application to monitoring and were presented at a 2006 workshop. The methods that will be developed include

a number of different activity-based methods and biomarkers in various species for rapid detection and monitoring of EDCs. Examples of progress to date include the following:

- ✧ Evaluation of five polymers for their ability to extract EDCs from water.
- ✧ Testing of an array of known EDCs in relevant matrices for surface enhanced Raman spectroscopy (SERS) response characteristics to create a quantitative spectral library.
- ✧ Establishing methodology for determining exposure effects through a newly developed bioassay, the physiological response of diatoms to estrogens 4-nonylphenol, but not 17 $\beta$ -estradiol, results in cell mortality.
- ✧ Cloning and characterization of the retinoid X receptor from *Daphnia magna*.
- ✧ Determination of the environmental-endocrine basis of intersex in a crustacean.
- ✧ Evaluation of estrogens singularly (E1, E2, EE2) and in mixture for effects on reproduction and brain of fathead minnows.

One STAR project is studying genomic markers in invertebrates, specifically in *Daphnia*, and there also is a related project in NERL searching for molecular biomarkers of exposure, differentially expressed genes, in *Daphnia* after exposure to atrazine or nonylphenol. A number of candidate genes were observed after exposure to nonylphenol, but not atrazine, so researchers are testing these targets. Identifying biomarkers in invertebrates would be a great way to decrease the time and effort needed to test environmental samples. The biomarkers that were developed for fish were applied in the Experimental Lakes Study, which took place from 1999 to 2004 in a remote lake in Canada and was a collaboration among NERL, Fisheries and Oceans Canada, and USGS. EPA applied the biomarkers to assess exposure and effects of endocrine disruptors in wild fish populations. Baseline data were collected from a reference lake and a study lake prior to adding up to 5  $\mu\text{g/L}$  of ethinylestradiol to the entire lake. Increased Vg gene expression occurred in male FHMs in the lake. There was a drastic decline in the population of FHMs and pearl dace in the lake after 1 or 2 years, depending on the species. This study shows that low levels of ethinylestradiol impact fish populations and it strengthened EPA's environmental monitoring capabilities. The study has been cited by EPA as justification for developing Ambient Water Quality Criteria for EDCs and by FDA as a basis for Environmental Assessments.

EPA recently co-sponsored two interagency workshops focused on the impacts of EDCs on ecosystems and human health. One workshop examined biomarkers of ecological effects and exposure and effects monitoring. The other examined translation of basic and animal research to understand human disease. These workshops are another means of improving EPA's interactions with other agencies and identifying research priorities and collaboration opportunities.

EPA is synthesizing EDC research results from the last decade into a report on research accomplishments. Subcommittee members received a draft of this report, and the EDCs Research Program would appreciate feedback on this document.

A second performance goal under LTG 2 is to determine the extent and impact of EDCs in human populations. EPA released a joint interagency solicitation for STAR grants to support studies to examine the health effects of EDCs. Twelve studies were funded in 2001, of which EPA funded five. In 2004, a progress review workshop included presentations on all 12 of the epidemiology studies and in 2006, an EPA endocrine disruptors progress review meeting included presentations from the five EPA-funded studies. Results are starting to emerge from these research projects, but work is still being conducted to complete sample and data analyses. The grantees will be invited to the next full BOSC review.

Key results from this research are highlighted in the 2007 EDC Accomplishments Report. One study that examined phthalates in pregnant women and reproductive development of the children already has had a significant impact and has been highly cited. Another study of a highly contaminated industrial area in Russia has found that dietary exposure is the main route of exposure for dioxins. In the Great Lakes Fish Study, polybrominated diphenylethers (PBDEs) have been found to have some effect on thyroid hormones, possibly through the thyroid binding globulin protein. Effects varied by gender and menopausal status in women.

Continued impacts of these epidemiological grants include the highly cited paper examining anogenital distance among male infants with prenatal phthalate exposure. Many of the PIs funded through this program have received subsequent grants from other federal agencies. The Russian study has had a very positive impact on the community there; a children's hospital has been built and people are able to make better informed food choices.

The next APG under LTG 2 is to "Determine the extent to which EDCs contribute to the severity or onset of disease." EPA scientists studied the effects of EDCs on mammary gland development, looking at different critical exposure periods of development for the mammary gland and also at a number of potential health impacts. Depending on the chemicals they studied, the researchers found different effects on development of the mammary gland. Some chemicals were associated with delayed development, impaired lactation, transgenerational effects, and precocious development. A critical window of mammary gland development was determined for atrazine, mixture of atrazine metabolites, dioxin, and perfluorooctanoic acid (PFOA). A number of papers, including a review paper, have been published or are pending publication. One of the research papers won a "Best Paper of the Year" Award from the Specialty Section of the Society of Toxicology.

As the 2007 MYP is implemented, EPA expects to continue monitoring the STAR studies on epidemiology, exposure methods and applications, and the fate and effects of hormones in waste from CAFOs until they are completed over the next few years. EPA also is involved in federal projects studying pharmaceuticals in the environment (including EDCs). EPA is participating in a Pharmaceuticals in the Environment Interagency Workgroup that has developed an interactive project inventory database and is developing two documents on strategic research directions. One is a research strategy for human and veterinary pharmaceuticals in the environment, expected to be completed around December 2007. The other is a research strategy for antibiotics in the environment focusing on the question of antibiotic resistance, estimated to be completed in December 2008. Lastly, the Global Water Research Coalition is conducting an international effort to characterize tools for analyzing estrogenicity in the environment. Members of the coalition are performing an analytical round robin, comparing cell-based endocrine assays using both EPA developed and non-EPA developed assays. Water samples have been collected from

participating countries around the world. It is anticipated that this work will result in recommendations for selecting the appropriate bioassay for a given water source.

## Discussion

Dr. Glen Boyd asked Dr. Mills about the water treatment facility project he discussed. Were the researchers studying the source of EDCs coming from a water treatment plant? Obviously, one source from a wastewater treatment plant would be the discharge or the CAFOs discharge into the receiving water body. Dr. Boyd asked if the researchers were studying EDCs that may pass through the plant without being removed by treatment. Or are the researchers studying how EDCs are being transformed as they move through the plant? Dr. Mills responded that their focus is on evaluating how wastewater contaminants or CAFOs contaminants that reach source waters flow through the system. Dr. Boyd asked if Dr. Mills meant whether or not EDCs were being removed or transformed into other chemical species that may be EDCs themselves. Dr. Mills confirmed that Dr. Boyd was correct. Dr. Boyd pointed out that Dr. Mills had mentioned water treatment plants, but that another way to approach the issues would be to study it from the perspective of the whole water system. He asked if the researchers were studying what occurs after the water is treated and enters the distribution system. Dr. Mills asked if Dr. Boyd was referring to conducting tap surveys. Dr. Boyd confirmed that he was asking about studies examining the water after it has reached the consumer. According to Dr. Mills, there currently is no plan for that type of work. EDCs Program researchers are collaborating with the water division to begin work on a water infrastructure. The water division is interested in studying EDCs and pharmaceuticals from an emerging contaminants perspective. Dr. Boyd asked Dr. Mills if lead is considered an EDC. Dr. Mills responded that the EDCs Research Program does not focus on lead as an EDC, but there is a lead program within EPA. Dr. Boyd mentioned lead because, if it is an endocrine disruptor, then maybe there already is some research being performed that could be integrated into the EDCs Research Program.

Dr. Boyd asked if air particulates work had been eliminated from the Program. Dr. Mills confirmed that it had been eliminated because of funding limitations. The EDCs Research Program had to identify the core capabilities and drinking water, wastewater, and CAFOs were the areas identified. The work on air particulates was focused on air emissions and was being performed in the internal EPA laboratory. Dr. Mills said that he thought the work was continuing in some form. Dr. Boyd asked if Dr. Mills thought the Program needed to be redefined to focus, for example, on just the aqueous and soil environment. Dr. Mills responded that in the current MYP the Program has been redefined to focus on the four core theme areas. Dr. Boyd asked how the drinking water treatment technologies for removal of EDCs work is integrated with work being done by the American Water Works Association Research Foundation (AWWARF) and the Water Environment Research Foundation (WERF). Is the Program looking to collaborate more in the future? Dr. Boyd mentioned this because risk management funding is decreasing and working with others is a good way to leverage resources to continue the work. Dr. Mills agreed and said that the EDCs Research Program would continue to look for more collaboration opportunities. Program representatives are starting to participate in these groups' planning workshops to help guide their research. The EDCs Research Program has had a long-term relationship with WERF, exchanging research plans and ideas. One limitation to working directly with these groups is that EPA cannot receive funding from them; however, the Program certainly can leverage their efforts. Dr. Boyd suggested that

EPA take the lead in connecting the different disciplines and also lead the effort to look at the whole integrated water cycle. Dr. Mills agreed that this would be a good approach.

Dr. Boyd asked if the EDCs Research Program was using bioinformatics and proteomics as quick assays for evaluating the occurrence of EDCs and cross-checking those with a specific compound to have a rapid assessment. Dr. Mills explained that the EDCs Research Program has been working to make its research more quantitative. For example, the FHM assay was adapted for the Program's risk management research. More data are needed (occurrence data are not sufficient) to perform efficacy studies, and Program researchers are working with others on this.

Dr. Van Der Kraak asked Dr. Stephen Safe if he had any questions. Dr. Safe said that he was impressed with the presentations. He also added that many of the issues in the 2004 BOSC program review were being addressed, particularly the wildlife issue. He commented that there is still a dearth of human research; however, papers like the one by Dr. Swann were helping to get the dialogue started. He hoped to see more studies on that particular issue, so the question could finally be answered. He thought the EDCs Research Program had made good progress since the 2004 review. Dr. Safe mentioned that the animal studies in which mice are used to study transgenerational effects might prove to be very useful. The next question to answer is if the same effects are seen in humans. Dr. Safe said he was very impressed with the presentations and the progress made by the Program.

Dr. Van Der Kraak asked Dr. Swackhamer if she had any questions or comments. She agreed with Dr. Safe's comments. The presentations have been extremely helpful. She did not have any questions.

Dr. Van Der Kraak stated that all three presentations showed the quality of the science in the Program to be very high. He asked how EPA achieves balance through the Program. He saw very strong research on the animal side. When it comes to LTG 2, however, there does not seem to be as much interconnectedness with the basic science and in trying to make some of the models developed for thyroid or some of the reproductive endpoints applicable to humans. Is this because it is difficult to study some of these disease processes in the human population? Dr. Laessig confirmed that many of the endpoints are difficult to study in human populations, but that animal research is helping to provide better models for human effects. Dr. Francis also agreed that human studies are a challenge. The budget for the STAR Program component of the Program has basically been eliminated since the 2004 program review. Fortunately, Congress, over the last few years, has allocated some additional funding, allowing the Program to release the Request for Applications (RFA) that Dr. Laessig mentioned on developing exposure methods to look at occurrence in terms of complex mixtures, and also the RFA on the CAFOs work. When the RFA on epidemiology was released in 2000, the intent was to periodically release an RFA on epidemiology and to tailor future RFAs as more was learned from the previous studies. Unfortunately, there is no funding available for epidemiologic studies. EPA does not have the capability to conduct epidemiology studies in its own laboratories. As in other research areas, the Program is always looking for opportunities to leverage its work with others. The EDCs Research Program recently co-sponsored a workshop with the National Institute of Environmental Health Sciences (NIEHS) on translational science. One topic covered at this meeting was how to translate the results from toxicology studies to support public health decision-making. A number of research needs were identified in this workshop. Dr. Laessig stated that the EDCs Research Program will continue to leverage its work with others.

**Performance Measures and Directions of Endocrine Disruptors Research**

*Dr. Elaine Z. Francis, National Program Director (NPD), Pesticides and Toxics Research, ORD, EPA*

Developing performance measures for research is difficult. At the same time, it is crucial that these measures be developed. Because there is no perfect measure, ORD has developed a “suite” of performance indicators for each of its major research programs, including the EDCs Research Program. These indicators include LTG ratings, milestones, APGs, and bibliometric measures. Tab L of the notebook the Subcommittee members received includes two fact sheets that describe these performance measures. LTG ratings were introduced recently and are recognized as one of the best ways to qualitatively measure research performance. Specific well-defined ratings are assigned by an expert peer-review panel (i.e., the BOSC) to each programmatic LTG. In a full review, each LTG receives a rating. For this mid-cycle review, the Subcommittee members will rate the program overall on the progress made since the 2004 BOSC program review. APGs are used as a planning and communication tool. Aligned under the APGs are a number of milestones. One of the fact sheets in the notebook describes the milestones in more detail. It is important to note that there is not necessarily a one-to-one match between the APMs from the 2003 MYP and the Program’s anticipated milestones. As a result of discussions with the Office of Management and Budget (OMB), the APGs were aggregated across laboratories. For example, there is one APG on risk management and the areas of exposure and effects were combined. There is a separate APG on screening and testing because of the high visibility of this work. Tab L of the notebook includes more detail on how the Program has performed in terms of meeting its milestones. Lastly, a bibliometric analysis was performed. When the bibliometric analysis was first performed in December 2003, the Program had produced more than 300 publications; to date the Program has produced more than 500 peer-reviewed publications.

Several benchmarks that are well accepted in the scientific community are used in the bibliometric analysis. One is Thompson’s Essential Science Indicators (ESI) and the other is the Journal Citation Reports (JCR). The bibliometric analyses begin with searches of Thomson Scientific’s Web of Science or Elsevier’s Scopus. These databases indicate the number of times a publication has been cited in journals covered by these databases. JCR is consulted for the impact factor and immediacy index of each journal. ESI categorizes each journal into one of 22 research fields and reports average citation rates as well thresholds for the top 10%, 1%, 0.1%, and 0.01% papers in each category. Times cited data are compiled on the Program’s publications and compared with the 10%, 1%, 0.1%, and 0.01% annual threshold values from ESI to determine if the publication meets any of these thresholds and can be classified as “highly cited.” Detection of “hot papers” is accomplished by determining the citation rate in 2-month increments over a period of 2 years from the paper’s publication date and applying In-cites “hot paper” thresholds to determine if the paper is hot. The bibliometric analyses also account for primary author self-citation, which is the referencing of one’s own previously published documents in a publication. EDCs publications are highly cited. Over one-quarter of the EDCs Research Program publications are in the top 10 percent of highly cited publications. This is 2.8 times what is expected. Papers from the EDCs Research Program cover 15 of the ESI fields, demonstrating the multidisciplinary research being conducted under the Program. For 11 of the 15 fields, the citation rate was greater than expected. Combining the fields, the Program’s citation rate is double what would normally be expected. In terms of the impact, more than 40 percent of the Program’s papers are published in high impact journals. Again, more than 40 percent appear fairly quickly in the top 10 percent of journals. While only 0.8 percent of

Program papers are considered “hot” papers, this is actually eight times what would normally be expected for a program of this size. The Program has a low self-citation rate of about 4.6 percent (the accepted range is 10-30%). Another measure is the list of the world’s most influential researchers; 17 authors from the EDCs Program are included in that list.

The EDCs Research Program has had to make adjustments for a number of reasons. First, many advances in the science have taken place since the last review. In addition to this, the Program has worked to address the recommendations that have come from different external reviews. One major change is that there is much more collaboration and interaction with OW. The elimination of funding for the extramural research (i.e., STAR Program) also has resulted in program adjustments.

The EDCs Research Program has made these adjustments in a number of ways. First, the Program has increased its application of molecular and computational approaches. As stated previously, the Program has increased collaborations at multiple levels. One of the most important changes has been to improve leveraging within the Agency, across divisions, across laboratories, and so on. Collaboration with other Agency research programs such as the Water Quality Program, the Drinking Water Program, the Computational Toxicology Program, the Safe Pesticides/Safe Products Program, and the Human Health Program has greatly increased. Much of the work developing screens and tests has been completed. As this work is completed, the Program will shift its attention from LTG 3 to LTGs 1 and 2. The Program will continue to work to improve the scientific foundation to help the Agency interpret the data that will be produced by the Endocrine Disruptor Screening Program (EDSP) and other programs. Program scientists continue to work on cumulative risk, on characterizing dose-response curves, and on cross-species extrapolation. Program scientists are working to better characterize sources of exposures and their impact on the environment.

There have been a number of changes to the Program’s APGs and milestones. In most cases, this is because the milestones have been met. In some cases, decreased funding forced the elimination of some programs. New goals and measures for future directions have been added. In some cases, it was determined that the research should continue, perhaps in a different form, because of the results of early work. In other cases, the research is taking longer than anticipated because there are fewer resources. In some cases, the program offices have asked the EDCs Research Program to conduct specific research as in the case for LTG 3. The researchers thought that the Tier 2 tests had been completed, but the Program was asked to develop tests for additional species (e.g., the sheepshead minnow in addition to the FHM). The Program’s research has been aggregated, so there are fewer APGs. This is a result, in part, of the recommendation from the Agency to reduce the number, as it is resource intensive to keep track of them. Additionally, having fewer of these shows how the research is leveraged across research projects. The previous MYP included APGs that built on each other. In the updated MYP, however, the focus was changed to the next 7 years.

The number of appendices to the MYP has increased and their content has been enhanced. The EDCs Research Program hopes to list the most significant accomplishments of the Program by APG. A separate appendix provides detail on the research themes and identifies the goals and approaches that will be taken, as well as the intended outcomes. Information on linkages with other research also is included. Key ORD researchers for each theme are identified. Improved examples of where the EDRP is cross-linked to other ORD research programs are included. As a

result of the PART review and recommendations by OMB, the titles of the LTGs have been reworked to make them more “outcome-oriented.”

Since the last review, the APGs have been updated. In terms of the shape of the dose-response curve, the Program has completed the research goals that were set in 2004. This is an area where much additional work is needed, however. Another area is the neuroendocrine work, which was originally scheduled to end in 2012; this work has been extended another year. This is an area where much collaborative work has been done, allowing for more productivity in a shorter period of time. Collaboration also allows EPA to branch out to other areas for which the Agency may not have in-house capability.

Three APGs were combined. Some of the work on critical biological factors during development has been aggregated with the work on mechanisms and modes of action. Also, some of the computational work has been aggregated and is now covered by a single APG. The EDCs Research Program is applying some of the newer technologies in terms of “omics” and testing to better define mechanisms of action and extrapolating across species. Previously, there was a small program working on research in the area of risk assessment. Unfortunately, that work has largely been discontinued. This does not mean, however, that ORD is no longer performing research in the area; it means that efforts in terms of developing guidance have been discontinued. The risk management and exposure individual APGs have been combined in one APG.

The same principle applies for LTG 2. The work related to human populations has been extended; this is largely done through the extramural grants program. Those grants have been given no-cost extensions and work is expected to continue for several years. The work related to impacts on the development of the mammary gland described by Dr. Laessig earlier is really the only work remaining for this APG. The work being performed on sources of exposure and environmental fates has expanded considerably and will continue for another 4 years.

For LTG 3, the APG is about providing the tools for the Agency’s screening and testing program. Basically, the APG to develop screening assays has been met; it was decided that any further development of the next generation of screening assays would fit under LTG 1, under the APG on the use of molecular approaches. After the last two assays—the fish and the frog lifecycle assays—are finalized, LTG 3 will be completed. As indicated earlier, the program office has EDCs Program researchers performing additional work on those assays. Hopefully, those will be completed by Fiscal Year 2011.

### **Overall Summary of Progress**

*Dr. Elaine Z. Francis, NPD, Pesticides and Toxics Research, ORD, EPA*

The introduction section of the draft MYP clarifies what is and is not covered by the EDCs Research Program. One section of the 2004 BOSC program review dealt with strengthening/defining the National Program Director’s (NPD) role. At that time, the NPDs had not been officially integrated into the organization of ORD. A draft document defining the role of the NPDs was recently produced. Another suggestion made in the 2004 BOSC program review was to hire additional personnel. With shrinking resources, the EDCs Research Program has had to use other approaches to leverage the research and to complement and supplement the intramural expertise. There has been an increase in leveraging work across research programs.

The Program has hired 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. These are ways to bring on additional expertise that do not count against the personnel ceiling.

LTG 1 focuses on providing the underlying science for EDCs. Leveraging within the Agency and with other federal agencies has improved. In addition, the Program has made a consolidated effort to better communicate research results. For example, the draft accomplishments report includes all the results from both the internal and external wildlife research programs. Another recommendation made was to focus on cross-species extrapolation and on developing predictive tools for prioritization. Again, the EDCs Research Program is working collaboratively with other ORD research programs to achieve this. Much of the collaboration is with the Computational Toxicology Program, which has taken a leadership role in the development of predictive tools for prioritization. In addition, it was recommended that research on developing new risk assessment paradigms be conducted. The Program is focusing on issues like cumulative risk and incorporating “omics” into its assessments.

LTG 2 focuses on determining the impact of EDCs. An incredible amount of work has been performed to improve interagency interactions in this area. Also, it was suggested that there might be some lessons to be learned regarding pharmaceuticals. This issue has come to the forefront in recent years. In fact, an interagency working group on pharmaceuticals in the environment has been established and EPA, along with FDA and USGS, is a co-chair. As Dr. Laessig pointed out, this working group will soon issue two reports on the state of the science regarding veterinary pharmaceuticals and antibiotic resistance. Again, the Program is using some of its cross-agency collaborations to feed into these interagency working groups. If the group produces research recommendations, the work likely will be distributed across multiple programs in ORD as compared to creating a separate research program for pharmaceuticals. This is an area of great interest to a number of federal agencies; EPA will work with other agencies to define the research needs. Another recommendation was related to the mining of data and in particular, the data in the high production volume (HPV) program. Although the EDCs Research Program has not accomplished a lot in this area, other elements of the Program have been mining these data. Most recently, the Computational Toxicology Program worked collaboratively with the Office of Pollution, Prevention, and Toxics (OPPT) to access the data, mine it, and feed that information into some of their databases. Research from the epidemiology grantees is closely monitored. The grantees are brought together every few years. They will attend the next review, which probably will take place in early 2009. Investigating the common ground between ecological and human health has been accomplished through the development of case studies through the Program’s interagency activities. Examples include the work being conducted on cross-species extrapolation, the work being supported through the extramural grants program on exposure methods development, and workshops held with other federal agencies. All of these examples bridge the divide between health and ecological science. Lastly, the EDCs Research Program plays a role in both research and policy developments regarding the application of “omics” technologies. This is largely done under the auspices of the Agency’s Office of the Science Advisor, which has taken a leadership role on this issue.

LTG 3 focuses on supporting the screening and testing program. The EDCs Research Program has been working to enhance the Program’s capabilities in the area of bioinformatics. A number of strategic hires have been made. In fact, since the last Subcommittee conference call, the

Program has received Title 42 Authority, which allows EPA to hire up to five people each year for the next 5 years at a pay scale greater than the General Schedule pay scale. This will assist Program leadership in bringing in needed talent to help move the research forward. The Program has made significant progress in completing research to develop and standardize assays for the EDSP; all Tier 1 and all but two Tier 2 assays have been completed and transferred to the program office. The program office currently is working to complete the validation and peer review of these assays, and they should be ready for implementation in early 2008. Some work remains on two of the Tier 2 assays, largely because the Program has been asked by the program office to perform some additional work. The Program is working to improve the way research results are communicated. An accomplishments report has been drafted toward this end. The Program has a bibliography with more than 500 published articles. An appendix to the MYP that aligns the products under the APGs is being developed. The Program also is in the process of developing a Web site. All NPDs are in the process of developing linked Web sites that should be launched by the end of 2007.

One major change has been the building of major collaborative relationships. Despite the fact that there is no longer an official extramural grants program, the Program has successfully used funding from Congress to continue the research in some form. Separately, EDCs Program scientists have been working with scientists at academic institutions. Another lesson learned is the value of making awards in the form of cooperative agreements where there is complementary work being performed in the EPA laboratory. This is a win-win situation—outside scientists can work more closely with EPA scientists and vice versa. Additional collaborators include other federal agencies, international agencies, state and city agencies, water industry foundations, and industry. There also is much collaboration within EPA, whether it is across laboratories, across divisions, or across research programs.

The next steps for the Program include collecting feedback from the Subcommittee members on the updated MYP and on the accomplishments report. There are plans to solicit comments from program and regional office scientists as well. After their feedback has been integrated, the two reports will be finalized, and then the Web site will be finalized. The EDCs Research Program also plans to bring together senior managers from ORD, representatives from the Office of Prevention, Pesticides, and Toxic Substances (OPPTS), EPA regional offices, and other EPA offices; this meeting is in the early planning stages and will cover the research progress made by the Program in recent years. It will be an opportunity to solicit feedback on the future direction of the Program and for others to share their research needs.

## **Discussion**

Dr. Boyd asked about integrating more work on pharmaceuticals. Is the focus on the hormonal compounds or on pharmaceuticals in general? Dr. Francis responded that any work being performed in the EDCs Research Program is focused on hormonal pharmaceuticals.

Dr. Boyd noted that some parts of the Program have been eliminated. With the funding reductions and the reprioritization of different programs, it seems that the Program is looking for projects that can be retired, looking to consolidate work where possible, and seeking opportunities to collaborate. He asked how it is determined which programs will be eliminated. Dr. Francis responded that, on an annual basis, the EDCs Program leadership examines the research program, keeping in mind the projected future budget, and prioritizes the research and

makes decisions on which research areas are the highest priorities. Of course, all of the research is high priority, but the reality is that there is not enough funding to support all of the research needed. Research areas of less immediate priority and those areas in which other programs or other organizations are working are deemed to be lower priorities. The EDCs Program leadership works with client offices to make these decisions. Client offices have an immediate need for effects and exposure data. Although the client offices recognize that risk management research is important, it is still a lower priority when compared to their immediate needs. Dr. Boyd said it sounded like when the data are there, the focus can move to the applied research to reduce the risk. Dr. Francis responded that it was more like the client offices think that they have the legislative mandates needed to take an action, so they can do so without the benefit of the research. Clearly, the research would help them make decisions on the different options available to them. Research would offer them additional tools to consider, but the bottom line is that the program offices are the ones that implement and make risk management decisions. They can make these decisions either with or without research, depending on the authority they have been granted.

Dr. Boyd noted that in the revised MYP, it is stated that the purpose of the EDCs Research Program is to provide the scientific information to reduce exposure to EDCs. It appears that the EDCs Research Program is effectively providing the scientific information, but not helping to reduce exposure, which is the domain of these other offices. Is that correct? Dr. Francis replied that reducing exposure is up to the offices; however, with some of the work being performed currently, the program offices could take some of these methods and the science being developed and begin applying it.

Dr. Boyd commented on the bibliometric analysis. He wondered if it might put engineering at a disadvantage because it might not have the same level of publications in the sciences. Dr. Francis stated that engineering was one of the 22 ESI fields.

Dr. Francis asked Dr. Mills if he wanted to comment on any of Dr. Boyd's questions. In response to Dr. Boyd's first question, Dr. Mills explained that Dr. Francis had been referring to OPPT's interests. OW's interest is continuing to increase and this will require a driver for the engineering side as well. Historically, OPPT has been the primary client. As the interest of OW and other offices increases, things will change. Dr. Francis agreed. Until recently, OPPTS was the EDCs Research Program's main client, but OW has played a larger role in recent years. As the work is completed on LTG 3 with the screening and assays, the focus will return to LTG 1, which includes the area of risk management.

Dr. Boyd followed up with Dr. Mills' comment, adding that a White House directive suggesting that drugs be flushed down the toilet instead of put in landfills was released in early 2007. That directive caused some concern within the operating wastewater treatment facilities because it meant they would be responsible for treating water for those pharmaceuticals. Unfortunately, the work is not being done to help the utilities understand which drugs they need to treat for and what they need to be concerned about. As this issue gains more visibility, these types of things will begin to impact the water and wastewater treatment communities more and more.

Dr. Safe indicated that LTG 3 supported the screening and testing program. He thought he recalled that there was a mandate for EPA to develop the assays by a certain date. Dr. Francis responded that they were to be implemented 3 years after the Food Quality Protection Act

(FQPA) was enacted in 1996. Dr. Safe asked for an explanation of the delay. Dr. Francis confirmed that the FQPA did mandate that the screening program be implemented in 3 years. The program office response is that the word implementation can be interpreted broadly. A program was implemented; this included developing the framework to determine what would be tested and determining how each chemical would be tested. The procedures were in development, but were in use at the same time. All of this was completed within the 3-year time period. A major challenge has been the Congressional mandate that all assays be validated. At the time, there was little understanding of what was involved in validating an assay. Most of the assays that had been recommended by the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) had not yet been standardized. Some of the assays like the Uterotrophic and the Hershberger assays had been used by pharmaceutical companies for many years, but they were not standardized even across the pharmaceutical industry. Furthermore, although they could detect pharmaceuticals that were fairly potent, the assays had to be optimized to detect environmental chemicals, which have a much lower potency. It has been a challenge to update existing protocols, and in many cases, new protocols had to be created. The process is a long one as it includes the development of assays, optimizing the assays, review of the assays by advisory committees, incorporating advisory committee input, and developing standardized protocols. The protocols then are transferred to the program office where they are reviewed again.

Dr. Laessig mentioned two positive developments. First, the Office of Science Coordination and Policy (OSCP), which oversees the validation of the assays, has begun working with the Organisation for Economic Co-operation and Development (OECD) validation management group on validating some of the *in vitro* assays. This is much quicker than going through a contractor, which requires considerable paperwork. Dr. Van Der Kraak commented that one of the problems appears to be what occurs after the work has been passed on for validation. He asked if the events that occur after the transfer might jeopardize the Program's ability to sunset LTG 3. Dr. Francis reiterated some of the points made by Dr. Laessig. Many of the issues have been resolved through working with OECD on the validation. Many lessons have been learned throughout the process. Short-term *in vitro* types of screens are needed to move away from testing for every chemical, and the EDCs Research Program has adjusted its focus accordingly. In 2000, a law was passed requiring all new assays developed to be validated before use. Prior to this law, an assay could be disseminated and was validated as it was used.

Dr. Van Der Kraak pointed out that one of the difficulties in developing an MYP is that it depends on personnel. He asked if there was a plan or a proposal in place for replacing personnel as they retire. Dr. Francis responded that this is an issue across ORD, as a significant number of ORD's scientists will be eligible for retirement in the next 5 years. This is one reason the Program has been working to bring in postdoctoral fellows and younger employees, which will help to build the Agency's next generation of scientists.

Dr. Swackhamer asked Dr. Francis how the Program determines that an APG has been met. In the presentations, it was noted that some of the APGs have been met. In some cases, however, it appears the goal was met with respect to one particular outcome related to one particular EDC. Dr. Francis responded that it has been difficult to determine when an APG has been met. In developing the MYP, specific milestones are developed. The nature of research, however, is such that as more research is completed, more questions arise. The work then focuses on refining these additional questions and moving forward with the research to answer them.

Program leaders work to identify the science questions and also the milestones that will address those questions, but things often change. Dr. Swackhamer asked Dr. Francis if she thought there was sufficient information about the shape of the dose-response curve or if there was enough information about interactions among mixtures of EDCs. Dr. Francis responded that the Program had accomplished what it set out to accomplish in the last 3 years. Regarding Dr. Swackhamer's questions, there is not enough information available. This is why most of the work continues. The EDCs Program is committed to completing a certain amount of work in a given period of time. The work has been completed and that is why that milestone or APG technically has been met. She suggested looking at it in terms of where the Program was in 2004 and where the Program said it would be in 2007. Dr. Swackhamer stated that she thought the work performed by the Program was excellent. She did not intend to criticize the Program; her criticism was directed more toward EPA's limited investment in it.

### **Public Comments**

*Dr. Glen Van Der Kraak, University of Guelph, Acting Chair, EDCs Subcommittee*

At 2:00 p.m., Dr. Van Der Kraak called for public comments. There were no comments offered.

### **Program Rating Discussion**

*Dr. James R. Clark, Exxon Mobil Research & Engineering Co., Chair, BOSC Executive Committee*

Dr. James Clark thanked the Subcommittee members for their participation in the mid-cycle review. BOSC program reviews have included a lot of information on the Program under review, including comments on specific program areas and suggestions for improvement. One question often not addressed in these reviews, however, was how the program as a whole was performing. Thus, a rating tool was implemented by the BOSC Executive Committee. The rating tool makes the process more quantitative because it allows for comparison across reviews. The rating tool was originally created for the BOSC program reviews and each LTG was to be rated. Subsequently, it was decided that the rating tool also would be useful for the mid-cycle reviews. In the case of the mid-cycle review, the overall progress made by the Program, relative to the recommendations made in the previous BOSC program review, is rated. The Subcommittee members are asked, at the end of their deliberations, to step back and decide on an overall program rating. The program review subcommittees and, in particular, the mid-cycle review subcommittees, have encountered some difficulty in applying the rating tool. To avoid these difficulties, Dr. Clark suggested that the Subcommittee members discuss and work through the charge questions, develop their responses, and then come to a consensus on the overall rating. It is important to remember that the true value of the report is in the words written in response to the charge questions. Based on these responses, the Subcommittee can arrive at an overall rating.

Dr. Van Der Kraak stated that he envisioned the report as a commentary on each of the three LTGs and then a comment on each of the charge questions. He asked if Dr. Clark was suggesting the Subcommittee not comment on each of the LTGs. Dr. Clark responded that it is up to the Subcommittee to decide on how to structure its report. He was simply asking the Subcommittee members to arrive at an overall rating.

## Subcommittee Discussion

The Subcommittee members discussed whether they should address each LTG. As the LTGs were included in the 2004 program review, it was decided that they already were embedded in the charge questions and would be addressed as the questions were answered.

Dr. Van Der Kraak began discussion of Charge Question 1. He thought that the Program had been highly responsive to the 2004 BOSC program review recommendations. The Program has been faced with fiscal challenges and has used creative approaches to implement the recommended changes. Dr. Boyd agreed that the Program had, for the most part, been responsive to the recommendations. If progress was not made with respect to a recommendation, there always was a good reason, such as a lack of funding. He thought that the ratings had to be qualified. The reason the Program had not met some of the recommendations was because of budgetary constraints, and the Program had very sound reasons for cutting back in those areas. Dr. Boyd stated that, in general, he thought the Program was meeting expectations, but in some areas it was not. Dr. Van Der Kraak responded that part of the difficulty lies in how to judge each recommendation. Should they be judged equally? Or should the parts of the Program that have been emphasized be given more weight? Dr. Boyd gave the example of the risk assessment paradigm that was discussed as one of the charges. The EDCs Research Program did not specifically do what was recommended in the 2004 BOSC program review, but they gave a very sound rationale for not doing it. This is true of other areas as well. In this case, did the Program not meet the expectations? Or did they meet the expectations because they had a good reason for not implementing the recommendation? Dr. Van Der Kraak asked Dr. Swackhamer for guidance. Would she recommend reviewing each of the specific recommendations and identifying specific examples where the Program had been exceedingly proactive in addressing the recommendations and then identifying where the Program (for good reason) had not addressed those concerns? Dr. Swackhamer stated that she thought the BOSC was looking for an overall assessment, so the Subcommittee would not need to assess each recommendation from the program review. She stated that she would probably rate the Program as meeting expectations overall. Still, there are examples where the Program has exceeded expectations and there are examples where the Program has not met expectations, largely for reasons beyond its control.

The report from this mid-cycle review should be about 7-10 pages in length. Ms. Drumm confirmed that the other mid-cycle review reports were of similar length. Dr. Van Der Kraak stated that he was having difficulty because he was coming out with a higher rating than meets expectations; the difference might be in relation to the value or the weight that is put on different aspects of the Program. From Dr. Van Der Kraak's perspective, some aspects of the Program have been eliminated for good reason. Dr. Safe stated that from his perspective, looking at the biological work, he would give the Program a rating of exceeds expectations. Dr. Swackhamer stated that because she is not a toxicologist, she did not think she could judge whether the science was of such high quality that it would make up for the fact that the Program did not meet all of its milestones. Dr. Van Der Kraak stated that he thought in some areas the Program had more than exceeded expectations or had even performed exceptionally. One example may be in the area of environmental genomics. Dr. Van Der Kraak thought that another area where the Program had done a particularly good job was in its dose-response research. In addition, the Program has established EPA as a leader in the scientific community in many areas, one of which is CAFOs. Dr. Van Der Kraak was impressed by the major change that occurred from

working as individual laboratories to working as one unit. These are some factors that, in Dr. Van Der Kraak's opinion, would warrant an exceeds expectations rating. Dr. Swackhamer said that she agreed with Dr. Van Der Kraak's assessment, particularly regarding how the research performed fit into the overall progress and the movement within the scientific community. EDCs is one of the fastest growing scientific fields and the Program seems to have adapted quite well. She asked the toxicologists if this was an accurate assessment. Drs. Van Der Kraak and Safe confirmed that it was.

Dr. Safe mentioned that it would be interesting to look at interagency laboratory collaborations in terms of the number of reports and publications produced. How many were produced previously and has there been an increase? Also, it would be interesting to know the number of EPA-academic collaborations. Has the number increased since the last review? Dr. Francis stated that she could provide those data in the future. Dr. Van Der Kraak suggested that those could be two new performance metrics to suggest under Charge Question 3.

Dr. Boyd agreed with all the comments; he was very impressed with the Program's work. Looking at the progress overall, Dr. Boyd would give the Program an exceeds expectations rating. If the Program were examined in detail, it would show that some goals had not been met but there was always a sound reason for this. Dr. Swackhamer said that she would agree with an exceeds expectations rating for Charge Question 5.

Dr. Van Der Kraak discussed the different options for writing the Subcommittee's responses to the questions. The Subcommittee members could each write a response to Charge Questions 1 through 4 and then the responses could be combined or each person could be assigned a specific Charge Question. Dr. Boyd said he preferred the first option as it would allow for all of the different perspectives to be incorporated throughout the response. Dr. Safe agreed. He suggested that each Subcommittee member write 2-3 pages. Then someone could eliminate the common statements and combine the responses. This document then could be circulated to the Subcommittee members for review. Dr. Swackhamer agreed that this would be a good approach. Dr. Van Der Kraak asked if there were any restrictions on the correspondence between Subcommittee members after the meeting. Ms. Drumm explained that any discussion of the report writing among the Subcommittee members must occur in a public forum. Other review subcommittees have had each member write a few pages and then send their individual drafts to one person who compiles them into a single document. Dr. Swackhamer offered to compile the document and stated that Ms. Drumm should be copied on the e-mails when Subcommittee members submit their comments to her. Dr. Swackhamer asked if the Subcommittee members could submit their drafts to her by the week of October 1. For the next conference call, the individual responses from the four members as well as the next draft would be available. Ms. Drumm suggested scheduling two future conference calls and stated that the next conference call could be scheduled for the week of October 15, 2007, at the earliest. Dr. Van Der Kraak was unable to access his calendar on his computer, so Ms. Drumm said she would send an e-mail to the Subcommittee members and each person could respond with the dates that worked best for them.

Dr. Van Der Kraak asked for suggestions on how to use the last 15 minutes of the meeting and the Subcommittee decided to discuss Charge Questions 2, 3, and 4. Dr. Boyd reminded the members that Charge Question 2 asked if the updated draft of the MYP provided a coherent framework and rationale for addressing priority research needs. Dr. Boyd stated that he thought

the updated MYP was excellent. The updated MYP includes the history of the Program and details on the modifications and revisions made over the years. The Program has made the necessary revisions while still keeping an eye on the LTGs. With respect to this Charge Question, Dr. Boyd would rate the Program as exceptional. Dr. Swackhamer agreed. She thought the updated MYP demonstrated a very mature level of thought, as it detailed the Program's move to the next level.

Dr. Van Der Kraak explained that Charge Question 3 focused on performance metrics. Dr. Swackhamer said she agreed with Dr. Safe's suggestions for new measures of collaboration. She wondered if there was a way to measure the impact of the research on decision-making. Dr. Boyd suggested that it might be possible to establish a baseline on the occurrence of EDCs. Once the methods are in place, validated, and ready for use, a baseline on the occurrence of EDCs and the exposure levels to humans and ecosystems is needed. Dr. Swackhamer suggested recommending that the Program consider developing these metrics in the future. Dr. Boyd proposed that it might be useful to tie the indicators to the budget. For example, the impact factor of the publications could be assessed as a function of the budget. Dr. Swackhamer agreed that this would be useful. Dr. Safe mentioned that most of the biological studies are associated with risk at a certain time point (i.e., *in utero* exposure or early postnatal exposure). Is that the major area of risk? It is assumed to be, but it may not be. Another question would be, are there endocrine disruptors that improve human health? These types of questions are important and may be worth looking at in the future. Dr. Boyd added that he would encourage the Program to collaborate with industry organizations involved in EDCs work.

Dr. Van Der Kraak moved to Charge Question 4, which asked about the streamlining of the focus in direction. Has that been done in a sound way and are there other, higher priority emerging areas on which the Program should focus? He commented that the Program's work to address mixture toxicology was a solid strategic decision.

Dr. Van Der Kraak asked if there were any additional comments. When there were none, Dr. Swackhamer thanked Dr. Van Der Kraak for acting in her absence and said that she very much appreciated everyone accommodating her schedule. Dr. Van Der Kraak expressed his gratitude to Dr. Francis and all of the presenters and Ms. Drumm for the incredible amount of work they put into the review. Ms. Drumm also thanked Dr. Van Der Kraak for serving as the Acting Chair and stated that she would be in touch regarding the next conference call.

### **Action Items**

- ✧ Ms. Drumm will e-mail the Subcommittee members to inquire about their availability for the next two conference calls. After the dates and times have been determined, Ms. Drumm will e-mail this information to the Subcommittee members.
- ✧ Each Subcommittee member will write a 2- to 3-page response to Charge Questions 1 through 4 and e-mail it to Dr. Swackhamer and Ms. Drumm by the week of October 1, 2007.
- ✧ Dr. Swackhamer will compile the responses into a draft report and distribute this report to the Subcommittee members.
- ✧ The Subcommittee members will discuss the draft report on the next conference call.

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**EDC MID-CYCLE SUBCOMMITTEE  
FACE-TO-FACE MEETING  
AGENDA**

**September 18, 2007**

Key Bridge Marriott  
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**Tuesday, September 18, 2007**

9:30-10:00 a.m.	Registration	
10:00-10:10 a.m.	Welcome and Outline of Purpose	Dr. Glen Van Der Kraak Acting Chair, EDC Mid-Cycle Subcommittee
10:10-10:15 a.m.	DFO Welcome and Charge - Administrative Procedures/FACA Rules	Heather Drumm (EPA) DFO, EDC Mid-Cycle Subcommittee
10:15-10:50 a.m.	Goal 1 Progress	Dr. Mary Gilbert and Dr. Marc Mills Office of Research and Development
10:50-11:10 a.m.	Goal 2 Progress	Dr. Susan Laessig Office of Research and Development
11:10-11:25 a.m.	Overview of Performance Measures and the Updated MYP	Dr. Elaine Francis Office of Research and Development
11:25 a.m.-12:10 p.m.	Overall Summary of Progress - Discussion and Q&A	Dr. Elaine Francis (EPA) and Research Planning Committee EDC Mid-Cycle Subcommittee
12:10-12:40 p.m.	Break for Lunch	
12:40-2:00 p.m.	Working Lunch/	EDC Mid-Cycle Subcommittee Subcommittee Discussion
2:00-2:10 p.m.	Public Comment	
2:10-2:40 p.m.	Program Rating Discussion	EDC Mid-Cycle Subcommittee
2:40-3:00 p.m.	Next Steps, Wrap-Up	EDC Mid-Cycle Subcommittee
3:00 p.m.	Adjournment	