MULTI-YEAR PLAN (FY2000-2012) FOR

ENDOCRINE DISRUPTORS [1]

OFFICE OF RESEARCH AND DEVELOPMENT

US ENVIRONMENTAL PROTECTION AGENCY



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The Office of Research and Development's (ORD) multi-year plans (MYPs) present ORD's proposed research (assuming constant funding) in a variety of areas over the next 5-8 years. The MYPs serve three principal purposes: to describe where our research programs are going, to present the significant outputs of the research, and to communicate our research plans within ORD and with others. Multi-year planning permits ORD to consider the strategic directions of the Agency and how research can evolve to best contribute to the Agency's mission of protecting human health and the environment.

MYPs are considered to be "living documents." ORD intends to update the MYPs on a regular basis to reflect the current state of the science, resource availability, and Agency priorities. ORD will update or modify future performance information contained within this planning document as needed. These documents will also be submitted for external peer review.

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I. INTRODUCTION

It has been suggested that humans and domestic and wildlife species have suffered adverse health consequences resulting from exposure to chemicals in the environment that interact with the endocrine system. However, considerable uncertainty exists regarding the relationship(s) between adverse health outcomes and exposure to environmental contaminants. Collectively, chemicals with the potential to interfere with the function of endocrine systems are called endocrine disrupting chemicals (EDCs). EDCs have been defined as exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes.

To date, these problems have primarily been identified in wildlife species with relatively high exposures to specific compounds, including organochlorines such as DDT and its metabolites, PCBs and dioxins, or in domestic animals foraging on plants with high levels of phytoestrogens (Kavlock et al., 1996). Effects noted in wildlife that have a documented or presumed relationship to altered endocrine function include imposex in molluscs exposed to the alkyltins, vitellogenin induction in fish living near sewage outfalls (recently linked to concentrations of ethynyl estradiol), changes in sex steroids in fish near kraft-mill outfalls, abnormal reproductive development in alligators in Lake Apopka following a pesticide spill, nearly complete mortality of Lake Ontario lake trout in the sac-fry stage presumably resulting from exposure to dioxin-like compounds, eggshell thinning in birds from exposure to DDT and its metabolites, and birth defects in Lake Michigan cormorants exposed to PCBs and other Ah-receptor ligands. Also, a variety of adverse effects on reproductive development have been observed in laboratory rodents exposed to very low levels of dioxin.

In humans, the consequences of prenatal exposure to DES on the reproductive tract of both females and males are well known and developmental neurological problems have been identified in children exposed to PCBs and/or PCDFs. In addition, reports of declines in the quality and quantity of sperm production in humans over the last four decades, and increases in certain cancers that may have an endocrine-related basis (breast, prostate, testicular) have led to speculation about environmental etiologies.

While there is a large wealth of data available on some endocrine disruptors, much more research is needed in order for the Agency to carry out its large number of mandates. For example, despite the above mentioned effects, we know little about their causes and the concentrations of EDCs that would induce effects at the population level . Nevertheless, it is known that the normal functions of all organ systems are regulated by endocrine factors. Small disturbances in endocrine function, especially during certain stages of the life cycle such as development, pregnancy and lactation, can lead to profound and lasting effects.

Given EPA's overall mandate to protect both public-health and the environment, it is in a unique position to provide leadership in this area. Individual scientists across EPA's laboratories and centers had

been doing research related to endocrine disruptors for many years. Then, in response to increasing public health concerns in the early to mid-nineties, the Office of Research and Development decided to integrate and expand its ongoing efforts into a consolidated endocrine disruptors research program. To initiate the program, two workshops were held in 1995 where the opinions of international experts were sought to help formulate a national research plan for endocrine disrupting chemicals (Kavlock et al., 1996; Ankley et al., 1997).

Research on endocrine disruptors was identified as one of the six high-priority topics in the ORD Strategic Plan (USEPA, 1996; USEPA, 1997, USEPA, 2000). This was based upon recognition of: *1) the potential scope of the problem, 2) the possibility of serious effects on the health of populations, 3) the persistence of some endocrine-disrupting agents in the environment, and 4) the widespread global concern about the fate and transport over national borders.*

ORD's *Research Plan for Endocrine Disruptors* (**www.epa.gov/ORD/WebPubs/final/revendocrine.pdf)**, published in 1998, was developed from the recommendations provided by the USEPA-sponsored workshops, the scientific judgement of the ORD Research Planning Committee, and reviews and input from the chairpersons for the risk assessment breakout groups of the Raleigh workshop, internal peer reviewers from across the Agency, the ORD Science Council, and an external peer review panel convened by the Agency's Risk Assessment Forum. The framework for ORD's EDCs research program is designed around the risk assessment/risk management paradigm. The objectives of the EDCs research program are to improve our knowledge and understanding of endocrine disruptors in the environment so that we can improve our methods of assessment and risk management. This, in turn, will assist the Agency in identifying the chemicals that pose an unreasonable risk, developing ways to prevent or reduce their release into the environment, and developing means to remediate in-place EDCs that pose an unreasonable risk. Further, the research plan specifically addresses scientific questions that have arisen as a result of legislation enacted in 1996. The Safe Drinking Water Act Amendments (SDWAA) and the Food Quality Protection Act (FQPA) mandate the development of a screening and testing program to evaluate the potential of chemicals found in drinking water sources and food, respectively, to have estrogenic or other hormonal activity. Thus, EPA's research program strikes a balance between "problem-driven" and "core" research. It includes areas that are uniquely of importance to EPA in helping the Agency meet its legislative mandates and includes research areas that serve to improve the basic understanding of EDCs, in general.

The research described in this MYP assumes annual resources of approximately $11-12 million. It should be noted that throughout the document ORD describes research that it is conducting either on EDCs, in general, or on specific chemicals or classes of chemicals. It should not be construed that just because ORD is studying specific chemicals or classes of chemicals that this means that the Agency has determined that these chemicals or classes are officially designated as "endocrine disruptors." Those determinations will be made by the Agency through the implementation of the Endocrine Disruptors Screening Program.

ORD's research on endocrine disruptors falls under EPA's Goal 4 Objective 4 Subobjective 4.1: **Goal 4,Healthy Communities and Ecosystems**, commits the Agency to protect, sustain, or restore the health of people, communities, and ecosystems using integrated and comprehensive approaches and partnerships. Objective 4: **Through 2010, provide and apply a sound scientific foundation to EPA's goal of healthy people, communities, and ecosystems by conducting leading-edge research and developing a better understanding and characterization of environmental outcomes under Goal 4. Subobjective 4.1.** Through 2012, conduct research that contributes to the overall health of humans, their communities, and ecosystems. Research will provide a foundation for protecting, sustaining, or restoring human and ecological health. Research will focus on pesticides and toxics, global climate change, cross-cutting research on the health of humans, their communities, and ecosystems.

II. BACKGROUND

Agency's priorities and regulatory programs

The authorities and responsibilities of EPA are mandated primarily by thirteen major environmental statutes (CRS Report to Congress, 1995). These statutes direct EPA to perform a wide variety of activities with the goal of protecting human health and the environment. Chemicals that are known or suspected of being endocrine disruptors are included in these mandated activities. In order to meet the needs of its mandates, EPA needs the tools to be able to: 1) identify EDCs, 2) evaluate their potential effects on human health and the environment, 3) discern when additional data are needed, 4) develop the appropriate protocols, should additional data be required, 5) set allowable levels of exposure or releases to the environment that are protective of human health and the environment, 6) develop technological controls to prevent/reduce releases, in the first place, and 7) remediate the risks associated with in-place EDCs. The *Research Plan* and this MYP set forth the research that is needed by program and regional offices to carry out their legislative requirements.

Science questions from research strategy

The *Research Plan* identified a number of key areas of uncertainty, in the form of questions, that needed to be addressed. The Multi-Year Planning Committee considered the nine questions from the *Research Plan* as still valid and critical and augmented the list with an additional question to address risk assessment methodologies. Addressing these key science issues is critical to give the Agency program and regional offices the tools they need to meet mandates as related to EDCs. The key questions are not in any order of priority, but rather follow the order identified in the *Research Plan*.

- What effects are occurring in exposed human and wildlife populations?
- What are the chemical classes of interest and their potencies?
- What are the dose-response characteristics in the low-dose region?
- Do our testing guidelines adequately evaluate potential endocrine-mediated effects?
- What extrapolation tools are needed?
- What are the effects of exposure to multiple EDCs and will a TEF approach be applicable?

- How and to what degree are human and wildlife populations exposed to EDCs?
- What are the major sources and environmental fates of EDCs?
- How can unreasonable risks be managed?
- What approaches are needed to assess risks to humans and wildlife?

Non-EPA research

The broad nature of the EDCs issue necessitates a coordinated effort on both the national and international level. In November 1995, the Committee on Environment and Natural Resources (CENR), under the President's National Science and Technology Council (NSTC), identified endocrine disruptors as an initiative. The CENR established a working group on endocrine disruptors that is chaired by ORD/EPA with vice chairs from the Department of the Interior (DOI) and the National Institute of Environmental Health Sciences (NIEHS). In addition to the three aforementioned agencies, participants include: the National Oceanic and Atmospheric Administration (NOAA), the National Science Foundation (NSF), the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), the Agency for Toxic Substances and Disease Registry (ATSDR), the National Cancer Institute (NCI), the Smithsonian Institution, the Department of Energy (DOE), the Department of Agriculture (USDA), the Department of Defense (DOD), and the Office of Science and Technology Policy (OSTP).

The CENR working group: 1) Developed a framework for federal research related to the human health and ecological effects of EDCs. The document reviews the state of the science and major uncertainties related to endocrine disrupting chemicals and established a framework for research areas that need attention. This framework categorizes major research needs into three groups; methods development, model development, and laboratory and field data acquisition. 2) Developed an internet-accessible searchable data base of on-going federally funded research on EDCs (htpp://www.epa/gov/endocrine). 3) Overlaid the framework with the inventory to identify high priority research gaps in the federal portfolio (Reiter et al., 1998). The inventory and the analysis point out what research is ongoing across the federal government that relates to the various LTGs and APGs identified in this Multi-Year Plan. These activities, along with the recognition that the key uncertainties regarding endocrine disruptors are complex, that interests across the agencies are overlapping, and that federal resources are limited, have helped ensure that there is close cooperation and collaboration on endocrine disruptors research across the federal government.

Additionally, many of the endocrine disrupting chemicals are persistent in the environment so there is widespread global concern about their fate and transport over national and international boundaries. While evidence for a global concern is growing, the breadth of the current scientific uncertainties related to what effects are actually attributable to environmental exposures, what chemicals are responsible for the effects, and what risk management steps need to be taken to protect public health and the environment necessitate international cooperation and communication. To begin to address this issue from a global perspective, several key collaborative efforts have been undertaken. The US federal inventory of research was updated and expanded in 1998 to include research projects from Europe, Canada, and Japan and,

thus, establish a Global Endocrine Disruptors Research Inventory (GEDRI) that includes almost 800 projects. The inventory provides us with a searchable database as to what research is ongoing across continents that relates to the various LTGs and APGs identified in this Multi-Year Plan. In addition, the US chaired a steering committee under the auspices of the International Programme on Chemical Safety/World Health Organization/Organization for Economic Cooperation and Development that developed a "Global State-of-the-Science Review," (WHO, 2002). Both the inventory and the international assessment are a result of recommendations made at the 1997 G-8 Environmental Ministers' Meeting.

In addition to ongoing research across the US federal government and those of other countries, the chemical industry is also engaged in research in this area. The American Chemistry Council (ACC) is a trade association of more than 190 member companies that represents the majority of the manufacturers of industrial chemicals in the US. ACC coordinates the chemical industry's research and testing programs. Under the auspices of an Endocrine Issues Science Forum, ACC supports an annual compilation of industry-sponsored endocrine research projects (www.endocrinescience.com/background.cfm). A number of these research efforts have been incorporated into GEDRI. They have ongoing research activities in many areas that complement EPA's intra- and extramural programs, e.g., studies on testing and testing methodology, mechanisms of action, epidemiology, animal toxicology, wildlife studies, aquatic toxicology, environmental exposure, and environmental chemistry.

Focus of EPA's contribution

In ORD's *Research Plan*, those areas where EPA should be playing at least a moderate role were selected first, taking into consideration the research activities of other agencies and organizations. Priorities for both the *Research Plan* and the Multi-Year Plan were assigned based upon an assessment of the importance of the research to the EPA program and regional offices, on the magnitude of the uncertainties in the knowledge base, the sequence of research needed to obtain the final answer, the possibility that the research would result in a significant product for hazard identification, risk characterization or risk management and, finally, the technical feasibility of conducting a successful project.

EPA's program strikes a balance between "problem-driven" and "core" research. It includes areas that are uniquely of importance to EPA in helping the Agency meet its legislative mandates and includes research areas that serve to improve the basic understanding of EDCs, in general, that is complementary to research programs conducted at other federal agencies, in other countries, or by industry. ORD has significant expertise in the areas of toxicology, endocrine effects, behavioral sciences, and environmental exposures, relating to both humans and ecological systems and in providing solutions to solving environmental problems. ORD scientists are respected members of the scientific community and leaders in the field. Therefore, ORD can make a significant contribution in the areas of improving our understanding of endocrine disruptors, their impact on human health and the environment and the management of the risks they pose.

III. PROGRESS TO DATE/CHANGES FROM PREVIOUS VERSIONS

Progress to Date - Research Highlights 2000-2002 (Note: Highlights are aligned by Long Term Goal (LTG), which are defined in Section IV. Some highlights may fit under more than one LTG but are aligned here under the single most appropriate one.)

LTG 1: PROVIDE A BETTER UNDERSTANDING OF SCIENCE UNDERLYING THE EFFECTS, EXPOSURE, ASSESSMENT, AND MANAGEMENT OF ENDOCRINE DISRUPTORS

- Determined that the nature of estrogen and dioxin interaction in birds (chickens) is quite different than that observed in mammals. (NCER)
- Determined that neonatal exposure of male rats to low and high concentrations of nonylphenol or bisphenol A failed to show any effect on prostate growth - i.e., could not reproduce the U-shaped growth response curve observed to occur when animals are exposed *in utero*. (NCER)
- Determined that TCDD and related compounds delay ovulation in rats by one or two days in a dose and time dependent manner and that mechanism is occurring at two levels: hypothalamus and ovary. (NCER)
- Discovered a new (third) estrogen receptor in vertebrates (Atlantic croaker) and demonstrated that estrogens and xenoestrogens can act on cells at the membrane level. (NCER)
- Determined that some mixtures of EDCs (e.g,. PCBs and methoxychlor) may be of lesser toxicity than either agent by itself. (NCER)
- Reported initial development of first fathead minnow Cy3/Cy5 glass-based microarray platform using exposure-specific cDNA targets including those discovered by subtraction cloning following exposure to ethinyl estradiol. Development was enabled by collaboration in microarray production and bioinformatic analyses with the University of Cincinnati Department of Environmental Health Sciences (Dr. Craig Tomlinson), and Children's Hospital Medical Center Department of Pediatric Bioinformatics (Dr. Bruce Aronow). Presentation of genomics approach (including EDCs) was made at the first International Workshop and Consortium on Technology and Application of Ecotoxicogenomics, Pensacola Florida (Sept. 2002)(To be published in Ecotoxicology in 2003). (NERL)
- Published two articles in Environmental Toxicology and Chemistry focused on the development of molecular diagnostic indicators of exposure of aquatic species to estrogens (2001, 2002). (NERL)
  - "Vitellogenin gene transcription; A relative quantitative exposure indicator of environmental estrogens" Lattier, D.L., Gordon, D.A., Burks, D.J., and Toth, G.P. 2001. Environmental Toxicology And Chemistry. 20:1979-1985.
  - "17a-Ethynylestradiol induced vitellogenin gene transcription quantified in fathead minnow (pimephales promelas) adult male livers, embryo larvae and gills." Lattier, D.L., Reddy, T.V., Gordon, D.A., Lazorchak, J.M., Smith, M.E., Williams, D.E., Wiechman, B., Miracle, A.L., Flick, R.W., and Toth, G.P. 2002. Environmental Toxicology And Chemistry. 21(11):2385-2393.

- Facilitated technology transfer of estrogenic molecular diagnostic indicators to EPA Regional scientists and water resource managers. Classroom and laboratory training occurred during August of 2002 (Region 9, San Francisco). Followup with Region 9 Tribal Scientists and State of California scientists occurred in February, 2003. Scientists from Regions 1, 2 and 3 were trained in Spring 2003. (NERL)
- Collaborated with NHEERL-MED and RTD on exposure and effects of androgenic compounds associated with Confined Animal Feeding Operations (CAFOs)- joint posters presented at 2002 SETAC describing chemical and biological evidence of androgenic substances found in several CAFO effluents. (NERL)
- Collaborated on a cosponsored Region 3/5 RARE Research Project to develop and validate analytical methods for alkylphenols and corresponding ethoxylates. (NERL)
- Conducted research to characterize the transformation, bioavailability and occurrence of selected enantiomers of chiral pesticides in environmental matrices and food products. (NERL)
- Published report on the use of internet resources for the study of ecological effects of anthropogenic chemicals released into the environment, including endocrine disrupting chemicals. (NHEERL)
- Reported that the anabolic steroid trenbolone acetate, a growth promotor used in cattle and found in waste sites, had significant androgenic activity in vivo and in vitro. (NHEERL)
- Reported on models to extrapolate risks of endocrine disrupting chemicals from individuals to wildlife populations. (NHEERL)
- Reported on development of cancer associated with developmental exposure to endocrine disruptors. (NHEERL)
- Reported on consensus toxic equivalency factors to predict reproductive effects of endocrine disruptors in mixtures. (NHEERL)
- Published review on the health effects of dioxin and dioxin-related compounds. (NHEERL)
- Found that environmental agents that inhibit aromatase can act as endocrine disruptors . (NHEERL)
- Reported that some organophosphate insecticides have direct effects on the androgen receptor. (NHEERL)
- Reported on effects of diphenylether compounds on nervous system function and thyroid gland function following developmental exposure in animal models. (NHEERL)
- Reported on persistent sensory and cognitive effects of developmental exposure to polychlorinated biphenyl compounds in animals. (NHEERL)
- Completed internal peer review of the document, *Risk Management Evaluation of EDCs*, and preparing for external peer review. (NRMRL)
- Used the *Risk Management Evaluation of EDCs* to identify and prioritize initial risk management research projects. (NRMRL)
- Conducted a workshop in January 2002 to complement the *Risk Management Evaluation of EDCs*. The workshop established the current state of risk management research on EDCs. The proceedings of the workshop was published as a multimedia CD-ROM (EPA/625/C-02/015). (NRMRL)

- Initiated risk management research on remediation of environmental reservoirs contaminated with suspected EDCs including aquatic sediments and drinking water.
- Began to adapt analytical chemistry and bioassays methods to evaluate the performance of risk management processes. (NRMRL)
- Formed a NRMRL/NERL collaboration on wastewater treatment research. (NRMRL)

LTG 2: DETERMINE THE EXTENT OF THE IMPACT OF ENDOCRINE DISRUPTORS ON HUMANS, WILDLIFE, AND THE ENVIRONMENT

- Determined levels of phytoestrogens in human amniotic fluid and effects of exposure to those levels in rats on markers of sexual development. (NCER)
- Identified androgenic compounds (male hormone mimics) in paper mill effluent using a screening assay developed using mosquitofish. (NCER)
- Found no evidence for immunosuppression in developing and hatchling American alligators exposed to a range of concentrations and combinations of EDCs (DDE, dieldrin, endosulfan, methoxychlor, toxaphene, chlordane). (NCER)
- Determined exposure to high levels of polybrominated biphenyls (PBBs) prenatally and via breast milk may impact puberty in girls. (NCER)
- With NRMRL, completed sampling of 50 waster water treatment plants (WWTP) for a survey of estrogenic activities to compare the relative effectiveness of treatment processes (Summer, Fall 2002). (NERL)
- Collaborated with the State of New Mexico Department of the Environment to determine the exposure potential of 27 EDCs on the Gallinas River, above and below the City of Las Vegas, NM water supply. The State of New Mexico split samples with ORD-EERD and analyzed 27 potential Endocrine Disrupting compounds while ORD-EERD assessed the estrogenic potential of the same samples using the fathead minnow Vitellogenin gene expression assay. (NERL)
- Completed large scale exposure study assessing 260 young children's aggregate exposures to pesticides, EDCs, and other persistent organic pollutants (Children's Total Exposure to Pesticides and other Persistent Organic Pollutants. Study conducted in NC and OH. Samples analyzed. Final analyses planned for FY03/04. (NERL)
- Completed joint HUD/CPSP/EPA assessment of children's exposures in >160 daycare centers randomly selected across the US. Samples being analyzed. Final analyses planned for FY03/04. (NERL)
- Developed and had externally peer reviewed study design and protocol for assessing very young children's exposures to pesticides and EDCs (study to start in FY03/04, pending OMB approval). Pilot study conducted in Jacksonville, FL in collaboration with CDC, NHEERL, and Duval County. (NERL)
- Completed exposure assessment of >120 farm applicators and their families in NC and IA to produce data to evaluate the NCI exposure algorithms in support of the Interagency AHS. Final analyses planned for FY03/04. (NERL)

- Reported that although androstenedione was present at detectable quantities in contaminated river water, the compound was not associated with androgenic activity of water from the site. (NHEERL)
- Report of masculinized female juvenile alligators from Lake Apopka, suggesting juveniles of both genders exhibit altered endocrine and reproductive dysfunction. (NHEERL)
- Launched risk management research on characterizing suspected EDC sources to the environment including investigations of wastewater treatment plants, concentrated animal feeding operations and combustion processes. (NRMRL)

LTG 3: SUPPORT EPA'S SCREENING AND TESTING PROGRAM

- Developed an estrogen-responsive transgenic zebrafish whose expression can be monitored by fluorescence capture of reporter gene activity. (NCER)
- Developed, characterized, and optimized/standardized an *in vitro* spermatogenesis model for detecting spermatotoxicants, including EDCs, using dogfish shark testis. (NCER)
- Developed/refined an *in vivo* model using medaka to identify EDCs. (NCER)
- Developed integrated array of computational tools undergoing validation by OPPTS for setting priorities for screening and testing (S&T) program. (NCER)
- Reported on a Short-term Test Method for Assessing the Reproductive Toxicity of Endocrine-Disrupting Chemicals Using the Fathead Minnow (EPA Document). (NHEERL)
- Reported on a model using a 3-D structural approach to predict chemicals for their ability to bind to the estrogen receptor. (NHEERL)
- Provided an overview on the use of structure-activity relationships for ranking and prioritizing large chemical inventories, including endocrine disruptors. (NHEERL)
- Reported that the estrogen-responsive reporter gene assay in trout was responsive to estrogen over a wide range of environmentally relevant temperatures. (NHEERL)
- Reported on a novel cell ine that can be used to detect hormone receptor agonists and antagonists for screening purposes. (NHEERL)

Changes from Previous Versions

As the result of an FY 2002 appropriations redirect of funds for research in the development of alternatives to animal testing, ORD has given rise to an innovative program, entitled Computational Toxicology (CT). The intent of this program is integrate modern computing and information technology with the technology of molecular biology and chemistry to improve EPA's prioritization of data requirements and risk assessments for toxic chemicals. As "proof-of-concept," ORD will first develop methods for the immediate priority-setting issues facing OPPTS in evaluating endocrine disruptors as mandated by Congress in FQPA. This version of the MYP includes an APG and related APMs that are associated with the CT research that is implementing this "proof-of-concept" program.

In addition, in the Appendix Potential Additional Research, we have taken the methods, tools and approaches we described in the previous version and describe how we propose to apply them to a case-study that would be conducted in an integrated fashion using the expertise from all of ORD's Laboratories and Centers.

IV. LONG-TERM GOALS

The *Research Plan* is the road map that identifies the research that is needed to improve our understanding of endocrine disruptors. It should be referred to in order to understand the overall research program that is envisioned. This Multi-Year Plan identifies the elements of the *Research Plan* that ORD will be working on in an integrated fashion, across branches, divisions, Laboratories, and Centers, over the next five to ten years. the Water Quality, Safe Communities, and Ecosystem Protection MYPs, 5) developing integrated risk assessments will be of value to Goals 3, 4, 8.1 and 8.2 research under Safe Food, Safe Communities, Ecosystem Protection, and Human Health Risk Assessment MYPs, and 6) developing risk management approaches, including pollution prevention methods, will be valuable to research under the Pollution Prevention MYP.

As noted previously, the *Research Plan* identified nine key areas of uncertainty and the MYP Committee added a tenth area. The Committee used these areas as a basis to derive three Long-Term Goals (LTGs). The three LTGs with the key areas of uncertainty they address are as follows:

1) Provide a better understanding of the science underlying the effects, exposure, assessment, and management of endocrine disruptors
   - Determine what are the dose-response characteristic in the low-dose region
   - Determine what extrapolation tools are needed
   - Determine what are the effects of exposure to multiple EDCs and will a TEF approach be applicable
   - Determine how can unreasonable risks be managed
   - Determine what approaches are needed to assess risks to humans and wildlife
2) Determine the extent of the impact of endocrine disruptors on humans, wildlife, and the environment
   - Determine how and to what degree are human and wildlife populations exposed to EDCs
   - Determine what effects are occurring in exposed human and wildlife populations
   - Determine what are the chemical classes of interest and their potencies
   - Determine what are the major sources and environmental fates of EDCs
3) Support EPA's screening and testing program
   - Determine whether our testing guidelines adequately evaluate potential endocrine-mediated effects

It should be noted that the LTGs identified by the Multi-Year Planning Committee are consistent with not only the key areas of uncertainty identified by EPA's *Research Plan*, but also assessments conducted by the following organizations: 1) the research needs framework and priority data gaps identified

by the Endocrine Disruptors Working Group (Reiter et al., 1998) of the Committee on Environment and Natural Resources (CENR) under the President's National Science and Technology Council (NSTC), 2) research needs identified by the National Research Council in its 1999 report "Hormonally Active Agents Environmental Agents," (NRC, 1999), 3) research needs developed at a joint US-European Union workshop held under the auspices of US-EU Science and Technology Agreement (JRC, NIEHS, EPA, 1999), and 4) the internationally developed document *Global Assessment of the State-of-the-Science of Endocrine Disruptors* (WHO, 2002). Therefore, it is well-recognized and accepted that resolution of these goals are key to being able to: 1) improve our understanding of the science regarding endocrine disruptors - *specifically in the areas of effects, exposure, risk assessment, and risk management*, 2) determine the extent of the problem endocrine disruptors are causing to humans and the environment, and 3) develop scientifically valid methods to screen and test for agents in the environment that may be endocrine disruptors.

ORD is committed to addressing particular aspects of each of these LTGs. These aspects are reflected in the Annual Performance Goals (APGs) and their respective Annual Performance Measures (APMs) described in greater detail in Section V and in attached supporting Tables 1-3. The attached flow diagrams for each of the LTGs (Figures 1-3) depict the time line for completion of the APGs and their interrelatedness and should help put the information in Section V into simpler context.

The degree of emphasis for each LTG is based on criteria similar to those used when assigning priorities in the *Research Plan*: 1) an assessment of the importance of the research to the EPA program/regional offices, 2) the magnitude of the uncertainties in the knowledge base, 3) the sequence of research needed to obtain the final answer, 4) the possibility that the research would result in a significant product for hazard identification, 5) risk characterization or risk management , 6) the technical feasibility of conducting a successful project, and 7) legislatively mandated time frames. The following table summarizes the relative emphasis of each LTG over the period of FY2000 through 2012.

LTG	**Emphasis from 2000 through 2012**
1	Level through 2008 and then increasing
2	Level through 2008 and then increasing
3	Level through 2008 and then decreasing

Successfully addressing these LTGs will require a highly coordinated effort. It is anticipated that each Laboratory and Center within ORD will develop an implementation plan for EDCs that will further facilitate the coordination and sequencing of the research elements to occur. The Implementation Plans will be consistent with the *Research Plan* and the Multi-Year Plan. These documents should be considered collectively when trying to understand the overall endocrine disruptors research program, what specific research the Laboratories and Centers will be carrying out, and when. Recognizing the dynamic nature of

research, the Multi-Year Planning Committee recommends that the priorities and sequencing in the *Research Plan*, in the Multi-Year Plan, and in the individual Implementation Plans be revisited periodically so that the overall research program can be modified as the knowledge base increases.

The following section on Description of the Flow Diagrams will lay out which specific aspects of the LTGs ORD plans to address. However, given the breadth of the goals and the complexity of the issue, it will require coordinated efforts across the federal government, academia, industry, non-governmental organizations, and with our international counterparts to fully address these goals. The mechanisms for collaboration are highlighted in Section II.

The endocrine disruptors research program is one of a few ORD research programs that includes a diverse multi-disciplinary set of research areas for both human health and wildlife. This set includes: 1) evaluation of effects in human health and wildlife, 2) determining exposures in human and ecosystems, 3) development of integrated risk assessment approaches for human and wildlife populations and 4) development of risk management approaches to mitigate exposures in human and wildlife populations. Meeting these high level goals will enable us to achieve the Goal 4.4.1 GPRA sub-objective, as it relates to endocrine disruptors, to "conduct research that contributes to the overall health of humans, their communities, and ecosystems" by combining human health and ecological considerations.

The EDCs MYP does not rely directly on research conducted under other MYPs and other MYPs do not rely directly on research conducted under the EDCs MYP. However, it should be noted that the research conducted under this MYP will provide results that are indirectly valuable across a number of MYPs and Agency Goals. A few of the examples where endocrine disruptors research will be of value to other Agency Goals and MYPs are provided in the following table.

Examples of EDCs Research - Goal 4.4.1	**Goals and MYPs that benefit indirectly**
Exposures to multiple endocrine disruptors	Goals 4 aggregate exposure and cumulative risk issues - Safe Food, Ecosystem Protection, and Human Health Risk Assessment MYPs
Development of protocols for screening and testing	Goal 4 test methods development program - Safe Communities MYP
Understanding critical biological factors during development	Goals 2, and 4 sensitive subpopulation issues - Drinking Water, Safe Food, and Human Health Risk Assessment MYPs
Understanding impacts of endocrine disruptors on wildlife	Goals 2, and 4 ecological methods, models, and measures research - Water Quality, Safe Communities, and Ecosystem Protection MYPs

Developing integrated risk assessment methods	Goals 4, risk assessment methods development programs - Safe Food, Safe Communities, Ecosystem Protection, and Human Health Risk Assessment MYPs
Developing risk management approaches, including pollution prevention methods	Goal 5 pollution prevention methods - Pollution Prevention MYP

V. DESCRIPTION OF THE FLOW DIAGRAMS

The flow diagrams, as noted previously, depict the APGs that will support the LTGs, the time frame for their completion, and how they are interrelated. In the development of the Multi-Year Plan, the Committee took the following into consideration when determining the Annual Performance Goals (APGs): 1) the key questions identified in the *Research Plan*, 2) the original 33 subissues identified in the *Research Plan*, 3) the research themes that were being identified within several laboratory implementation plans (specifically NHEERL's Multi-Year Implementation Plan and NRMRL's Risk Management Evaluation), and 4) an assessment of ongoing and anticipated ORD research efforts. As a result, 20 discrete research areas (APGs) were identified in which ORD can make a significant impact, between the intramural and extramural STAR grants programs, in advancing the state of the science on endocrine disruptors within the next 7 years. Schedules for these research areas were estimated based upon knowledge of: 1) existing resources, 2) intramural capacity and capability, 3) projected timelines for awarded grants, 4) the complexity of the area, and 5) in several cases, Congressionally-driven deadlines.

Annual Performance Measures (APMs) representing discrete segments of research to be completed within the defined schedule were developed for each APG. The APMs (Tables 1-3) will help to determine progress made towards completing the APG. The APMs in the Tables represent the expected product from a given research area. Therefore, the Tables, for the most part, do not necessarily show continual progress of a research area from start to finish, but rather just the major "milestones." Each APM is attributed to one of ORD's Laboratories or Centers. It should be noted that, for the most part, those that are attributed to NCER are products of STAR grants. Some APMs (those in italics) appear in multiple MYPs. It is important to note that the Tables capture the APGs and APMs currently anticipated. The Committee recognizes the need to update the matrix periodically, as new Milestones are anticipated and as emphases shift. However, the Committee agrees that the current APGs will drive the development of the Laboratory- and Center-specific Implementation Plans and the projects/topics on which their efforts will be focused for the next five to seven years.

Please note that guidance for the development of the MYP called for the use of the term "Annual Performance Measure" to acknowledge those activities that collectively would address an APG. However, the APMs described in this MYP should not be confused with or ever designated as ORD or Agency APMs used in cross-Agency planning and accountability activities. It is anticipated, that APMs from the

MYP will be aggregated and integrated to derive "Annual Performance Measures" for Agency accountability activities when required.

The 21 APGs for the Multi-Year Plan are described below. For each APG, the objective, the significance/impact, and the schedule of the research are described. It is assumed that the various APMs, when aggregated, will lead to the achievement of the APG. In order to facilitate understanding how the achievement of the APGs will lead to achieving LTGs, the descriptions for the APGs are aligned chronologically under the LTG(s) they support. Please note that in a couple of cases an APG may support more than one LTG. Similarly, in Tables 1-3, an APM may support more than one APG. Since the Multi-Year Plan identifies which areas of the *Research Plan* our efforts will focus on for the next 7 years, the descriptions below include the cross-reference to the relevant subissues in the *Research Plan*. For more detail and context, the reader should refer to the *Research Plan* itself.

LTG 1: PROVIDE A BETTER UNDERSTANDING OF SCIENCE UNDERLYING THE EFFECTS, EXPOSURE, ASSESSMENT, AND MANAGEMENT OF ENDOCRINE DISRUPTORS

The products of the research conducted under this LTG will: 1) improve our understanding regarding environmental exposures and effects of EDCs and 2) result in the development of improved methods for risk assessment and risk management. In other words, this LTG will result in the development of tools that can be applied in the conduct of research under LTG 2 in trying to determine the extent of the impact of EDCs. The LTG 1 research can be thought of, therefore, as basic or "core" research. Therefore, the results will be of value to most of EPA's program and regional offices, other federal agencies, agencies in other countries, and the scientific community at large.

APG: Characterize the effects of exposure to multiple EDCs, in various combinations such as those with similar and different mechanisms of action (FY03)

Objective: To understand the impacts on humans and wildlife of exposures to mixtures of EDCs at environmentally relevant levels.

Significance/Impact: Understanding whether effects following exposures to mixtures of EDCs will be additive, synergistic, cancel each other out (estrogens and anti-estrogens), or otherwise, will lead to improved human health and ecological risk assessments.

Schedule: The question of the interactions of mixtures of EDCs is a critical one for both human and ecological risk assessments. There are efforts ongoing intramurally with PCBs, PHAHs, dioxins, phthalates, and triazines, and through STAR looking at tributyltin in combination with other contaminants. We anticipate being able to complete the ongoing research to address this APG by FY03. However, based upon the results of these data it may be necessary to conduct additional studies in later years.

Research Plan Subissue: EFF.6.1

APG: Determine the shape of the dose-response curve in a variety of species exposed to ambient levels of endocrine disruptors (FY05)

Objective: To develop a more complete understanding of specific chemical mechanisms of action particularly for mechanisms that operate in the low end of the dose-response curve.

Significance/Impact: Understanding of how EDCs elicit toxicity through receptor-based interactions, membrane receptors, enzyme alterations, and other non-nuclear receptor-based pathways, will lead to improved methods to interpret data (particularly from the screening and testing program) and, thus, improved risk assessments. Most of what we know about endocrine disruptors is a result of laboratory studies or as a result of environmental spills/accidents where exposures in both types of studies were relatively high. Understanding how EDCs operate at the low end of the dose-response curve is particularly relevant to evaluating effects at ambient environmental levels of exposure. Gathering this information in a variety of species will lead to improved methods for extrapolating data across species.

Schedule: Because data from this research are critical to help interpret the results from the screening and testing program, this research is ongoing now in both our intramural and STAR programs. Because of the complexities associated with elucidating mechanisms of action, the ongoing research that is addressing this APG will not be completed until FY05. However, it appears warranted to issue a STAR solicitation for additional research in this area, based upon the recommendations that came out of the "Low-Dose Peer Review Panel on Endocrine Disruptors" sponsored by EPA and NIEHS. Therefore, once awards are made for those grants, in all likelihood it will be necessary to push back the date for completion of this APG.

Research Plan Subissue: EFF.3.1

APG: Identify key risk assessment issues and develop guidance for assessing endocrine disruptors (FY06)

Objective: To work collaboratively across ORD laboratories and centers to: 1) identify, characterize, prioritize, and assess the potential exposures and effects to selected suspect EDCs, and 2) develop a framework to integrate experimental and observational data for both human health and ecological effects in order to conduct holistic risk assessments for EDC modes of action (MOAs)

Significance/Impact: The development of tools that factor in how best to incorporate MOAs, multiple chemical exposure, critical life stages, criteria for adversity, dose-response relationships and inter-species comparisons are critical for the development of improved human health and ecological

risk assessments for EDCs. The methods that will be developed also will have broader impact on Agency risk assessments beyond EDCs.

Schedule: These tools will be needed as the knowledge base on EDCs increases, particularly with the screening and testing program. Limited efforts are ongoing. While we have designated its completion in FY06, program/regional offices are asking that the work be completed even earlier, if possible, because of its importance to the screening and testing program. Further, the research should be evaluated periodically to ensure it is addressing key data gaps that remain/develop as the knowledge base increases and risk assessments are performed routinely.

Research Plan Subissue: LNK.1.1

APG: Determine the critical biological factors during development resulting in toxicities occurring later in life (FY06)

Objective: To determine the critical factors that account for exposures during development resulting in toxicities occurring later in life (e.g. windows of vulnerability, developmental tissue dosimetry, modes of action) to inform appropriate human health and ecological risk assessments for these effects and the chemicals involved.

Significance/Impact: To address a critical issue in the controversies over potential endocrine disruption linked to environmental chemical exposure, that is, the impact of developmental exposures on function later in life. Development is a period when hormone-mediated changes in gene expression can have permanent consequences that may not be apparent until later in life because functional changes do not occur until puberty or adulthood and during which extraordinary changes occur. Thus, the developing organism may be more vulnerable to toxic effects at lower doses than would produce adverse effects in adults. It also has been suggested that there are processes for which there may be no apparent threshold due to limitations in the kinds of regulatory, surveillance, and repair processes that create biological thresholds in adults. Research in this area will provide the critical information needed for assessing the potential consequences of *in utero* and childhood exposures, both representing periods of sensitivity of human and wildlife populations. Since, EDCS research focuses on the mode of action of a compound, the impact of these effects on developmental processes is critical to risk assessment. The determination of developmental anomalies caused by a compound, the identification of the dose required to produce such effects and an understanding the mode and mechanism of action involved provides information that can allow for informed decisions on the potential risk to the developing human and wildlife species. Furthermore, mode of action analyses of the low-dose issue could have a major influence on the Agency's approach to risk assessment of endocrine disruptors.

Schedule: Because of the importance of addressing this uncertainty, the breadth of the research that will be needed, and the complexity of the issues, although there is ongoing research in this area, it

will take 5-6 years before we can make a significant impact in this area. However, our in-house expertise is highly capable of addressing this issue as it relates to both human health and wildlife. In addition, there are several ongoing grants that are contributing to our being able to meet this challenge.

Research Plan Subissue: LNK.2.3

APG: Determine the degree to which the effects of EDCs with defined mechanisms/modes of action can be extrapolated across classes of vertebrates (FY07)

Objective: To determine the degree to which the effects of EDCs with defined mechanisms/modes of action (MOAs) can be extrapolated across classes of vertebrates.

Significance/Impact: 1) To reduce the uncertainty associated with extrapolating effects of chemicals across species. 2) To understand the degree to which quantitative extrapolation is defensible/possible, comparative toxicological studies using chemicals with well-defined MOAs are necessary. The EDC program, because of its focus on systems controlled by endocrine function which appear to be highly conserved and, in some cases, reasonably well-characterized across species, offers a logical opportunity around which to formulate and test hypotheses related to across-species extrapolation of chemical toxicity. Research will have a direct and, potentially, relatively immediate impact on the regulation of EDCs in terms of defining the degree to which screening and testing based on an assumption of similar MOAs across species is technically and scientifically defensible. Of broader significance, the development of approaches to evaluate and conduct inter-species extrapolation research should ultimately help reduce uncertainties in both human health and ecological risk assessments.

Schedule: Currently there are limited intramural efforts ongoing in this area. However, since this was one of the focus areas identified in NHEERL's implementation plan it is anticipated that more efforts will commence. Because data from this research is critical to help interpret the results from the screening and testing program, the conduct of this research should be from now and should be evaluated periodically as data become available from the S&T to ensure that it focuses on questions that require addressing. Because of the complexity of the issues being addressed, the need for developing physiologically-based toxicokinetic (PBTK models), and the fact that there are limited efforts currently ongoing, indicate that this APG will not be addressed until FY07.

Research Plan Subissue: EFF.4.2; EFF3.1

APG: Evaluate exposure methods, measurement protocols, and models for the assessment of risk management efficacy on EDCs (FY08)

Objective: Develop exposure methods, measures, and multimedia, multi-pathway models to assist in the measurement of risk management success.

Significance/Impact: As risk management approaches are identified and/or developed there will be a need to identify and adapt and/or develop bioassay screening tools and other analytical methods to assess their efficacy. Measurements research will be performed to define the extent of the exposure issue (e.g., bioavailability/uptake) and assist in defining risk management needs. In addition to serving as tools on risk management approaches, exposure measures (e.g., chemical and biological indicators) will be valuable to screen and characterize exposures, improve exposure estimates in future epidemiological studies, and assist in developing and verifying exposure models. This effort will entail cross laboratory participation from NRMRL, NERL, and NHEERL.

Schedule: Research has begun on this effort and is being coordinated with projects of similar scope in the other ORD laboratories and centers. Molecular biological indicators are being developed through FY07 to measure exposure of aquatic species to single and multiple EDCs. These are DNA microarray-based indicators and offer the potential to measure exposure to specific endocrine-disrupting components of chemical mixtures. . Innovative analytical methods are being developed and field validated for some pesticides, alkylphenols, phthalates, and other classes of suspected EDCs. Multimedia, multi-pathway models are being developed to characterize EDC exposures, identify critical gaps, and define further research. The exposure, effects, and risk management research programs will develop in an iterative approach with future tools defined through the analysis of past and current research results.

Research Plan Subissue: EXP.2.3

APG: Computational Toxicology Program: Provide at least one computational model for assessing endocrine disruptor compounds (FY08)

Objective: The scientific approach consists of first describing in detail the endocrine systems in representative species and identifying primary pathways by which a chemical could disrupt these systems. Employing this diagnostic approach, an expanded series of *in silico*, *in vitro* and *ex vivo* models and assays will be employed to discriminate specific pathways and develop models for specific classes of chemicals that exert toxic effects through each of the pathways.

Significance/Impact: If successful, these models could facilitate priority-setting among large numbers of chemicals by ranking each chemical sequentially for its similarity to the chemical classes that disrupt each pathway. In the near-term, the program will provide high quality databases that can be used to develop, in the mid-term, additional predictive, computer-based structure activity models. In the longer-term, the research efforts will refine existing *in vivo* assays to increase the amount of diagnostic information gained for the invested resources by eliminating redundancies among these assays and reducing the number of animals needed.

Schedule: ORD anticipates developing over the next three to five years additional computer models, and associated *in vitro* assays that will predict, from chemical structure, the potential for a compound to elicit the initial chemical-biological interactions that trigger molecular, biochemical, and physiological events that can ultimately lead to adverse reproductive or developmental outcomes. The computer models will be developed, and iteratively evaluated and improved, by employing data sets derived from *in vitro* assays that are responsive to, and diagnostic of, specific toxicological pathways. The employment of genomics will comprise the next generation of techniques to identify chemical-biological interactions that initiate endocrine disruption to further define the subsequent biological events diagnostic of specific pathways. These techniques will efficiently expand knowledge bases to support new computer models that predict 'keystone' events from chemical structure.

In the next three to five years, additional *in vitro* assays will be developed and evaluated to broaden the means of identifying pathways of endocrine disruption. Over the long term (five to ten years) new *in vivo* approaches will be developed and evaluated for their ability to capture increased information, with a reduction in the number of separate tests that are conducted and a decrease in animal usage. Again, the use of genomics tools will be essential to meeting this objective. While we indicate that this APG will be completed in FY08, we recognize the need to re-evaluate this date as the research program unfolds.

Research Plan Subissue: EFF.1.1, EFF.3.1, EXP.2.3, LNK.4.1, LNK.4.2

APG: Identify risk management EDC research (FY08)

Objective: To evaluate the state of science of EDCs and identify risk management research opportunities to reduce EDC exposure to human populations and ecosystems.

Significance/Impact: A risk management evaluation (RME) will allow ORD to identify major EDC sources and to develop a comprehensive risk management research program that is focused on the major sources of EDCs, employs research results from other ORD laboratories and center, and is coordinated across ORD. This RME will identify opportunities of greatest need and greatest potential for making significant impacts to the reduction of EDC releases and exposures.

Schedule: Research that addresses this APG will be continuous. Although the matrix lists this APG to be addressed in FY08, as more information becomes available on sources of EDCs, the need for additional risk management research will be evaluated to ensure it is focused on the most appropriate sources.

Research Plan Subissue: LNK.4.1; LNK.4.2

APG: Develop at least two new risk management tools to reduce exposure to EDCs (FY09)

Objective: To develop new risk management tools for addressing EDCs.

Significance/Impact: If existing methods are deemed inadequate to address the risks posed by EDCs, new tools will be developed. Development of new tools will lead to cost-effective approaches to mitigating exposures to EDCs; pollution prevention approaches to minimize the use, release, or production of EDCs; and site remediation methods.

Schedule: Once major sources of EDCs have been identified and an evaluation of existing tools is underway, research on developing tools to manage unreasonable risks will begin. Therefore, this research effort is scheduled to begin a few years into the 2000-2012 time frame. As more information becomes available on sources of EDCs and data become available as to the feasibility of using existing tools, research for this APG will be evaluated to ensure it is focused on the most appropriate sources. It is anticipated that initial research to address this APG will be completed in FY09 and that its impact on the reduction of EDC releases to the environment and the need for additional new RM tools will be re-evaluated.

Research Plan Subisssue: LNK.4.2

APG: Evaluate at least three existing risk management tools to reduce exposure to EDCs (FY09)

Objective: To determine whether existing risk management tools can be applied to major sources of EDCs to mitigate exposures

Significance/Impact: There are a number of existing risk management tools that possibly could be applied to reduce exposures to EDCs. This research will determine which existing technologies can be applied or modified to reduce exposure. If technologies exist that can be applied to major sources of exposure, the impact could potentially be a major reduction of EDC release to the environment (e.g., revision to the waste water treatment process that would remove EDCs from effluent and/or sludge).

Schedule: Once major sources of EDCs have been evaluated, research on the potential application of existing tools to manage unreasonable risk will begin. Current thinking has early efforts focusing on the following sources: sewage treatment plants, sources of combustion, drinking water treatment plants, sediments, and CAFOs. As more information becomes available on sources of EDCs, research for this APG will be evaluated to ensure it is focused on the most appropriate sources. Given the current sources of concern, it is anticipated that research to address this APG will be completed in FY09.

Research Plan Subissue: LNK.4.2

APG: Develop systems models to test and predict vulnerability of the neuroendocrine system to contaminant-induced effects

Objectives: Disruption of neuroendocrine systems in invertebrates, aquatic, and amphibian species is a potential target for environmental chemicals. However, such effects may be mediated via different biological pathways within and across species. In addition, it is possible that environmental chemicals with different modes of action could interact in a nonadditive manner by affecting different, but converging, neuroendocrine pathways. The scientific approach consists of developing a basic understanding of the neuroendocrine systems in non-mammalian species and using emerging toxicogenomic and proteomic techniques to identify potential common pathways of action. This research will focus on potential reproductive or developmental effects across various non-mammalian species because they are crucial to understanding chemical effects in non-mammalian species at the population level.

Significance/Impact: This research will result in the identification of key biological events across multiple non-mammalian species that are sensitive to neuroendocrine disruption. This information is important for reducing uncertainties associated with extrapolation across non-mammalian species and for predicting potential non-additive interactions among chemicals that affect the neuroendocrine system by different pathways. Ultimately, this research could lead to models that would facilitate priority-setting among large numbers of environmental contaminants having effects on the neuroendocrine system in non-mammalian species.

Schedule: ORD will first conduct research to understand how the neuroendocrine system in target non-mammalian species is associated with normal reproductive and developmental outcomes. Research will then focus on using emerging toxicogenomic and proteomic techniques as a means of identifying common molecular endpoints that could be perturbed by environmental contaminants. Once common molecular endpoints of neuroendocrine function are identified across different species, effects of contaminants will be studied. These results will be used to develop computational or other predictive models to test for effects of contaminants and to provide the basis for extrapolation across non-mammalian species. Eventually, this research will lead to the development of a model to predict contaminant-induced effects in non-mammalian species associated with multiple and potentially interacting neuroendocrine modes of action.

Research Plan Subissue: LNK.2.3; EFF.4.2; EFF.3.1; EFF.3.4; EFF.5.3

LTG 2: DETERMINE THE EXTENT OF THE IMPACT OF ENDOCRINE DISRUPTORS ON HUMANS, WILDLIFE, AND THE ENVIRONMENT

The products of the research conducted under this LTG will improve our understanding regarding the extent to which current environmental exposures to EDCs impact human and wildlife populations and the environment. As noted above, the methods, approaches, and tools developed through LTG 1 and elsewhere will be applied under LTG 2 in trying to determine the extent of the impact of EDCs. The LTG 2 research can be thought of, therefore, as more "applied" research. The results of this research will be of value to most of EPA's program and regional offices, other federal agencies, agencies in other countries, and the scientific community at large.

APG: Develop field methods to assess environmental exposures in tissues and environmental compartments (FY02)

Objective: To develop improved field and analytical methods to collect, separate, characterize and identify EDCs in environmental media and tissues.

Significance/Impact: Improved methodologies will optimize monitoring and analytical throughput. Results of this research will provide improved sample extraction methods, extract preconcentration, chromatographic separation, and analyte detection.

Schedule: Efforts have been ongoing for several years intramurally to develop improved methods to detect EDCs in water, sediment, soil, and animal tissue. These efforts are expected to be completed in FY02.

Research Plan Subissue: EXP.2.2

APG: Determine the efficacy of various wildlife species as sentinels (FY04)

Objective: To select appropriate sentinel species for context-specific studies.

Significance/Impact: To address the need to identify appropriate animal models for different scenarios that require testing - e.g., 1) representation of different life history strategies; 2) species vagility with respect to exposure distribution; 3) representation of multiple taxonomic and trophic levels; 4) manipulability of species in laboratory tests; 5) availability of baseline information; and 6) the degree of distribution of a species.

Schedule: A number of research activities are underway as a result of previously announced solicitations through the STAR extramural grants program and some intramural efforts. The research cuts across a variety of species including fish, birds, reptiles, and invertebrates. Another request for proposals may be announced in the future, pending the outcome of these studies. Reports from current studies are expected to be completed in the FY03-FY04 timeframe.

Research Plan Subissue: EFF.5.3

APG: Evaluate several classes of chemicals suspected of being endocrine disruptors in field studies and ascertain the degree to which they are, or have the potential to, adversely affect wildlife at the population level (FY04)

Objective: 1) To develop and interpret measurement endpoints collected at lower levels of biological organization that could be extrapolated into understanding impacts at population or community levels and 2) to use specific chemical classes to ascertain the degree to which EDCs are, or have the potential to adversely affect wildlife at the population level.

Significance/Impact: One of the biggest unanswered questions in assessments of ecological risk, in general, is the "So what?" one. That is, what does it mean, in terms of a population or community, to observe an adverse effect in an individual or groups of individual fish and wildlife. This research will improve the ability to quantify the significance of effects observed at individual levels, to impacts at a larger scale. Results of this research will not only be of value specifically to the issue of EDCS, but also across ecological risk assessment, in general. The field research in this APG will complement results of the laboratory-based studies being conducted for the previous APG. Collectively, data from these two APGs will provide us with much needed information for between-chemical and between-species extrapolations.

Schedule: Research in this area will have broader impact on ecological risk assessments than just for EDCs. There are ongoing efforts within the intramural program to address this APG such as studying the effects of retinoids in amphibians and effects of EDCS in South Florida wildlife populations. This research is complemented by studies funded through the STAR program, as a result of a solicitation specifically focused on population-level effects. The extramural research cuts across a variety of species, such as fish, alligators, amphibians, crustaceans, birds, and a variety of chemicals including PCBs, PAHs, tributyltin, and pesticides. The intramural and extramural efforts are scheduled for completion by FY04.

Research Plan Subissue: EFF.5.2; also to some extent EFF.4.1 and EFF.4.2

APG: Evaluate several classes of chemicals (e.g., triazines, phthalates, organochlorines) suspected of being endocrine disruptors and determine their potencies in laboratory studies (FY04)

Objective: To conduct laboratory studies on several agreed upon classes of chemicals suspected of being endocrine disruptors.

Significance/Impact: To be able to definitely understand the mechanisms of action, potencies, dose-response relationships of several agreed upon classes of suspected EDCs. The research addressing this APG is the laboratory component of the complementary field studies in the following APG and will help elucidate understanding potential impacts on human health. Collectively, data

from these two APGs will provide us with much needed information for between-chemical and between-species extrapolations.

Schedule: Efforts are underway through our intramural and STAR programs to conduct studies in laboratory animals on a number of environmental agents suspected of endocrine disruption, e.g., phytoestrogens, certain PHAHs, triazines, methoxychlor, dioxins, PCBs. This APG is expected to be addressed in FY04.

Research Plan Subissue: Related to EFF.3.1, EFF.3.4, EFF.3.5

APG: Determine the critical biological factors during development resulting in toxicities occurring later in life (FY06)

See description under LTG 1.

APG: Determine the extent to which exposure to EDCs contribute to the onset or increase in the severity of diseases (FY07)

Objective: 1) To determine the extent to which exposure to EDCs contribute to the onset or increase in the severity of diseases and 2) to develop adequate, validated animal models that would enhance the ability to assess the potential of EDCs to produce disease in human populations.

Significance/Impact: 1) The extent to which EDCs induce or influence the emergence of endocrine-related disorders such as endometriosis, prostate and testicular cancers, functional male and female reproductive disorders, and other diseases such as those of the cardiovascular, immunological, or neurological systems yet to be determined. 2) Once developed, the animal models will be valuable to test hypotheses that low, environmentally relevant doses of EDCs can induce similar conditions in humans. Many of the issues surrounding EDCs center on the possibility that these chemicals can lead to or predispose the organism to various disease states. Diseases associated with the endocrine system impact millions of Americans and their impact on the economy is in the billions of dollars annually. By appropriately examining specific hypotheses raised in this research area and developing better models, information concerning the extent to which EDCs can induce or modify disease conditions will be provided.

Schedule: One of the biggest unanswered questions related to EDCs is whether they are impacting human health. The development of animal models to test hypotheses could help us address that question. There are a few limited ongoing efforts in this area within our intramural program. Since this area has been identified by NHEERL as a key focus area it is anticipated that more research will be conducted in the future. Given the current limited efforts and the complexity of the issue, significant impacts in this area are not anticipated until FY07.

Research Plan Subissue: EFF.3.3

APG: Determine whether adverse developmental/reproductive effects are occurring in human populations following exposures to EDCs (FY08)

Objective: To determine the extent to which human development/reproduction is being adversely affected by exposure to EDCs

Significance/Impact: To address one of the biggest unanswered questions related to EDCs, that is, whether humans are being adversely impacted by exposure to EDCs. Given that development and reproduction appear to be highly sensitive endpoints in laboratory animal and wildlife studies and that there are reported alterations in particular endpoints (e.g., hypospadias, cryptorchidism, sperm quality), if any adverse effects are to be found, then evaluating these endpoints in humans appears to be logical.

Schedule: One of the biggest unanswered questions related to EDCs is whether they are impacting human health. Work under this area is, by nature, exclusively through the STAR program. Currently there are six studies that are aligned with this APG , five of which are the result of an FY00 joint solicitation with NIOSH/CDC, NIEHS, and NCI The epidemiology studies are examining the effects of exposures of a variety of environmental contaminants on a variety of endpoints. Specifically they are evaluating the effects of: 1) PBBs on puberty in girls, 2) heptachlor on reproduction and immune function, 3) phthalates on breast and genitalia development, 4) dioxin on male reproductive development, 5) organochlorines and PCBs on endometriosis, and 6) PBDEs on thyroid function. The other federal partners are funding an additional total of seven studies as a result of the joint RFA. This group of 12 grants from the same solicitation will be followed closely. Given length of time to conduct studies in human populations, significant impacts in this area are not anticipated until at least FY08.

Research Plan Subissue: LNK.2.3; LNK.2.4

APG: Determine sources of exposure and environmental fates of EDCs (FY08)

Objective: To determine the extent of environmental and human exposures to EDCs, characterize the sources and factors influencing these exposures, and develop and evaluate risk management strategies to reduce exposures.

Significance/Impact: It is important to understand the extent of EDC exposures and the factors influencing the source-to-exposure-to-dose relationships in order to develop effective risk management strategies. Gaining improved understanding regarding the fate and transport processes, the interactions of EDCs from the source to the receptor, and collecting high quality exposure data for the development of multimedia, multi-pathway models are critical for ecological and human health risk assessments. Application of newly-developed biological indicators of exposure to the study of components of mixtures offers the potential to validate and refine these models.

Schedule: Efforts are already underway through our intramural program to identify key sources of EDCs and characterize the extent of EDC exposures. Emphasis is being placed initially on: 1) contaminated sediments, 2) sources of combustion, 3) consolidated animal feeding operations (CAFOs), 4) waste water treatment plants, 5) drinking water treatment plants, and 6) pesticide applications. Biological and chemical indicators of exposure, developed under Long Term Goal 1, are being applied to field studies to characterize the spatial and temporal vatioation associated with these issue-related exposure scenarios. Characterization of children's exposures to EDCs is also being emphasized. Intramural research on studying transport, transformation, and fate of EDCs in environmental media is also underway. A series of multimedia, multi-pathway models are being developed, evaluated and refined to investigate the physical, chemical and metabolic processes associated with environmental exposures (e.g., sorption/desorption processes) and human exposures (e.g., source-to-exposure-to-effects modules). Risk management strategies will be developed and evaluated for specific sources of EDC exposures. The results of the exposure, effects, and risk management research will be fully integrated. Research related to this APG will be completed in FY08. It may be necessary to periodically review data as the knowledge base increases to ensure that all state of the art information on the major sources are considered in the risk management research program.

Research Plan Subissue: LNK.4.1; EXP.2.1

LTG 3: SUPPORT EPA'S SCREENING AND TESTING PROGRAM

The products of the research conducted under this LTG will result in the evaluation of current testing protocols and the development of new ones to evaluate the potential endocrine effects of environmental agents. This research is critical to OPPTS and OW in their meeting the Congressional mandates in FQPA and SDWAA for development of a screening and testing program. Development of protocols will also be of value to other federal agencies, agencies in other countries, and international organizations, such as the OECD under which protocol development for industrial countries are harmonized. Furthermore, research under this LTG will result in the development of improved methods for risk assessment that will also be of particular value to OPPTS and OW, as well as to other EPA program and regional offices, other federal agencies, agencies in other countries and the scientific community at large.

APG: Evaluate existing testing guidelines for their adequacy to evaluate endocrine mediated effects (FY01)

Objective: To determine whether testing guidelines already in place are adequate to evaluate chemicals for their potential to induce endocrine effects.

Significance/Impact: To support the legislative mandates of the Food Quality Protection Act (FQPA) and the Safe Drinking Water Act Amendments (SDWA) of 1996 that require EPA to develop and implement a screening and testing program for endocrine disruptors**.** Before

developing new methods for evaluating the potential of chemicals to disrupt the endocrine system it is important to evaluate the existing methods for their adequacy. Based on this assessment, either additional parameters may be added to the existing protocols to better assess the potential activity of chemicals or, as noted in APGs below, new methods will need to be developed.

Schedule: Many of the existing protocols, (e.g., for developmental toxicity, reproductive toxicity, developmental neurotoxicity, neurotoxicity), have recently undergone a harmonization effort within the Agency and with the Organization for Economic Cooperation and Development (OECD). Since the enactment of FQPA, ORD's scientists have been evaluating the existing protocols for human health and wildlife and determining what, if any additional parameters, could improve their ability to detect potential endocrine disruptors. Since this effort has been ongoing for several years, it is anticipated that this APG will be addressed in FY01.

Research Plan Subissue: EFF.2.1; EFF.5.1

APG: Develop standardized protocols for screening chemicals for their potential endocrine mediated effects to meet FQPA requirements (FY06)

Objectives: To develop short-term methods to screen for EDCs with specific modes of action (MOAs) and to develop quantitative structure activity relationship (QSARs) models to serve as screening/priority setting tools.

Significance/Impact: To support the legislative mandates of the Food Quality Protection Act (FQPA) and the Safe Drinking Water Act Amendments (SDWA) of 1996 that require EPA to develop and implement a screening and testing program for endocrine disruptors. This research is addressing the recommendations made by an advisory panel (EDSTAC, 1998) convened following the enactment of the legislation regarding the need for several short-term *in vivo* and *in vitro* mammalian and several *in vivo* non-mammalian assays as part of a Tier 1 or screening battery. The research leading to the development of protocols is critical to the success of the Agency in fulfilling its Congressional mandates to develop and implement a screening and testing program. After the development, standardization and validation, these screening and testing protocols will be used not only by the USEPA to require the testing of chemicals, but also internationally through the OECD's test guidelines program and possibly by other regulatory agencies. The process to develop and implement screening and testing program has a high profile and the products will be closely scrutinized by the US Congress, stakeholders, and the scientific community within the US and internationally.

Schedule: Because of the timetables of the Congressional mandates, the research for this APG has been (since 1997) and will continue to be of highest priority until achieved in FY03. There is a significant amount of research ongoing intramurally to address this APG - studies aimed at finalizing the development of in vitro methods, in vivo studies, and QSAR approaches. Furthermore,

NHEERL's implementation plan identified this as a focus area, and, therefore, even greater effort is anticipated shortly. In addition, there are a number of projects through STAR (from early solicitations) that are resulting in the development of potential screens for EDCs.

Research Plan Subissue: EFF.1.1; EFF2.1; EFF.5.1

APG: Identify key risk assessment issues and develop guidance for assessing endocrine disruptors (FY06)

See description under LTG 1.

APG: Develop standardized protocols for testing chemicals for their potential endocrine mediated effects to meet FQPA requirements (FY08)

Objectives: To develop Tier 2 level methods to test chemicals for their potential to elicit endocrine-mediated effects.

Significance/Impact: To support the legislative mandates of the Food Quality Protection Act (FQPA) and the Safe Drinking Water Act Amendments (SDWA) of 1996 that require EPA to develop and implement a screening and testing program for endocrine disruptors. This research is addressing the recommendations made by EDSTAC (1998) regarding the need for Tier 2 tests in a variety of species, i.e., mammalian, avian, fish, amphibian, and invertebrates. (See APG immediately above for additional information on Significance/Impact.)

Schedule: Because of the timetables of the Congressional mandates, the research for this APG has been (since 1997) and will continue to be of highest priority until achieved in FY05. Research is ongoing intramurally to develop improved Tier 2 assays in fish, amphibians, and mammals. Furthermore, NHEERL's implementation plan identified this as a focus area, and, therefore, even greater effort is anticipated shortly.

Research Plan Subissue: EFF2.1; EFF.5.1

APG: Computational Toxicology Program: Provide at least one computational model for assessing endocrine disruptor compounds**.**

See description under LTG 1.

What the MYP says about the EDCs research program at a glance

There are a total of 21 unique APGs identified in the EDCs MYP. The APGs for the program are arrayed across a twelve year period starting with FY01 and ending with FY12. The first three years have

only a single APG each. There are three APGs scheduled for completion in FY04, FY06, and FY07 each. At present there are 5 APGs slated for completion in FY08, 2 APGs in FY09, and one in FY12. The APMs are aligned by year and by Laboratory/Center starting in FY00 and ending in FY12. Those APMs listed in FY00-02 are ones that have been successfully completed. The majority of the APMs are aligned through FY06 with just a few scattered ones in later years. It is envisioned, as this process progresses and the MYP is updated, that the later years will depict increasing numbers of APMs as has occurred with each of the annual revisions that has taken place since FY00. The majority of the current and projected EDCs research program is concentrated in two areas: effects and risk management.

The effects related research is being conducted for both human health and wildlife and is ongoing intramurally within NHEERL and extramurally through the STAR program. The emphasis on the intramural effects program is more related to human health and for the STAR program there is a balance between human health and wildlife grants. Both the intramural and STAR programs effects-related research are addressing all three Long-Term Goals and their associated APGs. The complementary research in these programs will go a long way to helping us make a significant impact in the critical areas under which these programs are aligned. These programs have been ongoing for a number of years, and, therefore, achieved a number of Milestones in FY00 that merited inclusion when the MYP was first developed. Because the effects issues are many and are so complex, research to address a number of the LTGs will be ongoing for quite a few years, at least through FY12.

The risk management research program is an intramural program with NRMRL which has been phasing in for the last few years. One APM was achieved in FY00 and FY01 and two in FY02. After that, on an annual basis, there are increasing numbers of APMs that will be achieved across a number of APGs that address LTGs 1 and 2 and specifically areas associated with sources of exposure and managing unreasonable risks. Several sources of EDCs have been identified on which to focus the near term research: contaminated sediments, sources of combustion, CAFOs, waste water treatment plants, and drinking water plants. As research progresses toward identifying and perhaps developing methods to mitigate exposures from these sources, new sources will be identified and, thus, the program will be continually maintained through at least FY09. Among the federal agencies participating in the CENR working group, EPA stands virtually alone in the area of risk management research.

EPA must demonstrate a strong leadership role in designing and conducting relevant exposure research for the foreseeable future. EDC exposure research appears as a high priority data gap on every notable organization's list. High quality, real world exposure data and corresponding exposure factors are deemed critical for the Agency's risk assessments. Prior to FY03, NERL's EDC exposure research program focused on: 1) developing field exposure methods, 2) the collection of exposure data and critical exposure factors associated with children's exposures to EDCs, and 3) the development of multimedia, multi-pathway models to assess ecological and human exposures. Some APMs associated with this earlier exposure research were completed in FY00-02, with more being completed in FY03 and beyond. NERL, working collaboratively with the other ORD laboratories and centers, has redefined its current program and designed an integrated EDC exposure research program to efficiently and effectively employ the limited

EDC resources to address the highest priority science issues. The NERL program leverages on other ORD laboratory/center EDC research programs, planned Federal Agency-sponsored programs containing EDC research components (e.g., National Children's Study, NHANES), and on relevant exposure research activities outlined in MYPs for Safe Food, Safe Communities, Human Health Risk Assessment, and Ecosystem Protection. A strong NERL and NCER relationship will be established to successfully employ the extramural STAR grant program to address critical exposure-related data gaps that cannot be addressed solely with the intramural resources.

There is an extremely limited effort underway in the area of risk assessment guidance, guidelines, and methods development. Greater emphasis needs to be placed in this area in order to have the tools necessary to be able to integrate effects and exposure data related to human health and the environment. As our intramural and extramural programs are generating results and data start coming into the Agency from the screening and testing program, we need to be able to have methods available to integrate the findings. Further, the efforts needed in the area of EDCs are ones that will have far reaching effects beyond just EDCs in terms of how the Agency conducts risk assessments for human health and wildlife. EPA has shown leadership for almost 20 years in the development of risk assessment guidance and here they have the capability to push the science even further.

VI. GUIDANCE FOR IMPLEMENTATION OF MULTI-YEAR PLAN

Because of the breadth of uncertainties associated with the endocrine-disruption hypothesis, effective implementation of this multi-year plan requires extensive coordination and communication among the research managers in ORD, and continued involvement of an ORD Multi-Year Planning Committee, to ensure that the most relevant and defensible research projects are selected for funding. Several key components will help ensure the success of an integrated research program for endocrine disruptors that implements the multi-year plan:

Intramural Coordination:

- The individual National Laboratories and Centers, if they have not done so already, should develop Implementation Plans for addressing the research activities identified in the *Research Plan* and the multi-year plan. These Implementation Plans should be reviewed by the ORD Multi-Year Planning Committee for their ability to provide a useful and integrated research output to the Program/Regional Offices.
- For the intramural research, it is presumed that investigator-initiated responses to internal (either on a laboratory or center basis or across ORD) requests for applications (RFAs) that are derived from the *Research Plan*, the Multi-Year Plan, and individual laboratory/center Implementation Plans, will provide the basis for the coordinated ORD research effort in endocrine disruption. The process should be similar and parallel to that already being used for the last 7 years in the STAR program.
- Coordination within the intramural program is especially important for research that transcends branches, divisions, laboratories, or centers. For example, combined field and lab and effect and exposure projects should require close collaboration among nearly every component of ORD.

- Annual reports of progress and updating of the multi-year plan by each Laboratory and Center, under the auspices of the multi-year planning committee, will facilitate the exchange of information within ORD, assist in the direction of work to the highest priority areas, help fine-tune the research directions as new information from the program emerges, and importantly, communicate with EPA's Program/Regional Offices on progress in understanding the nature and extent of the EDC problem and solutions to address them.

Intramural and Extramural Coordination

- Recognizing that integration of the intramural research program with the extramural grants is crucial to effective resource utilization, intramural and extramural RFAs should be targeted to achieve both the breadth and depth of balance needed to address the problems. The multi-year plan and the *Research Plan* have identified those areas which are most amenable to being conducted either within our own laboratories/center or through the STAR program.
- From the submissions in response to intramural and extramural RFAs, projects should be selected for funding on the basis of both scientific excellence and programmatic relevancy using criteria identified in the *Research Plan*.
- Results from both the intramural and extramural program should be integrated and assimilated into a state of ORD science assessment (SOOSA), that is updated routinely.
- Interactions between the recipients of the STAR grants and the intramural investigators involved in endocrine disruptor research through such mechanisms as annual or bi-annual workshops should be encouraged, as this would help exchange information and expand collaborations.

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VIII. ACRONYMS

ACC	American Chemistry Council
APG	Annual Performance Goal
APM	Annual Performance Measure
ATSDR	Agency for Toxic Substances and Disease Registry
CAFO	Confined Animal Feeding Operation
CDC	Centers for Disease Control and Prevention
CENR	Committee on Environment and Natural Resources
CT	Computational Toxicology
DDT	Dichlorodiphenyltrichloroethane
DES	Diethylstilbestrol
DOD	Department of Defense
DOE	Department of Energy
DOI	Department of Interior
EDCs	Endocrine Disrupting Chemicals
EDSTAC	Endocrine Disruptors Screening and Testing Advisory Committee

EPA	Environmental Protection Agency
EU	European Union
FDA	Food and Drug Administration
FQPA	Food Quality Protection Act
G-8	Governments of the 8 leading nations
GEDRI	Global Endocrine Disruptors Research Inventory
GPRA	Government Performance and Results Act
IPCS	International Programme on Chemical Substances
JRC	Joint Research Centre
LTG	Long-Term Goal
MOA	Mechanism/mode of Action
MYP	Multi-Year Plan
NCEA	National Center for Environmental Assessment
NCER	National Center for Environmental Research
NCI	National Cancer Institute
NERL	National Exposure Research Laboratory
NHEERL	National Health and Environmental Effects Research Laboratory
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NOAA	National Oceanographic and Atmospheric Agency
NRC	National Research Council
NRMRL	National Risk Management Research Laboratory
NSF	National Science Foundation
NSTC	National Science and Technology Council
OECD	Organization for Economic Cooperation and Development
ORD	Office of Research and Development
OSTP	Office of Science and Technology Policy
PAH	Polyaromatic Hydrocarbon
PBTK	Physiologically Based Toxicokinetic
PCBs	Polychlorinated Biphenyls
PCDFs	Polychlorinated Dibenzofurans
PHAH	Polyhalogenated Aromatic Hydrocarbon
QSAR	Quantitative Structure Activity Relationship
RFA	Request for Applications
RM	Risk Management
RME	Risk Management Evaluation
SDWAA	Safe Drinking Water Act Amendments
SOOSA	State of ORD Science Assessment
STAR	Science to Achieve Results
S&T	Screening and Testing
TEF	Toxicity Equivalent Factor

USDA	US Department of Agriculture
WHO	World Health Organization

APPENDIX
POTENTIAL ADDITIONAL RESEARCH

In the event that additional resources become available, the EDC research program would be expanded to pursue additional lines of research or accelerate the conduct of research already captured in the 2000-2012 timeframe. This new or accelerated research addresses the 10 critical questions identified in the *Research Strategy* and falls within existing APGs aligned within LTGs 1 and 2.

In the background section different methods, tools, and approaches are identified that would move the EDCs program a lot more forward should additional resources become available. These are not prioritized here but can be, based upon the amount of additional funds that may become available and the progress made in the current program. The new or accelerated areas are aligned under the APG(s) that would most benefit from this research. In the application section that follows, a specific case study is identified where we propose application of the methods, tools, and approaches to work in an integrated cross-Laboratory/Center manner to work on a real-world situation.

BACKGROUND

APGs - Provide at least one computational model for assessing endocrine disruptor compounds; Determine degree to which effects of EDCs with defined mechanisms/modes of action can be extrapolated across classes of vertebrates

Progress in the ability to sequence the human genome has led to a rapid development of laboratory methods to profile the expression of mRNAs and proteins. cDNA microarray and proteomics technologies that assess gene expression on a genome-wide basis may provide a "global" perspective about how an organism responds to specific stressors, such as exposure to endocrine disruptors. This information can define cellular networks or response genes, identify target molecules or toxicity, provide future biomarkers and alternative test procedures, and identify individuals with increased susceptibility to endocrine disruptors. Measuring specific changes in gene expression in humans and other species that are exposed to endocrine disruptors could lead to a "signature" for a given pathway of toxicity. Comparison of effects from animal and human assays will permit a direct assessment of interspecies extrapolation. This is important because there is significant uncertainty about how to extrapolate data from many current *in vitro* assays and rodent bioassays to humans.

The overall approach of this research program will be to develop microarray technologies to assess changes in expression of genes for high priority target sites such as the estrogen or androgen receptors. This effort represents and is consistent with a part of the new Computational Toxicology research program as it relates to endocrine disruptors. Specific changes in gene expression in humans and other species exposed to endocrine disruptor and other environmental chemicals will be evaluated to identify patterns of changes for a given pathway associated with endocrine disruption. Once these patterns of change have been identified, more focused arrays will be developed to assess the potential toxicity of chemicals in a rapid,

prospective manner. This research could result in better interspecies extrapolation, greater confidence in animal models, a reduction in the number of animals needed for testing, and insights into pathways of toxicity and mechanisms of endocrine disruption. Results from these studies could also lead to the development of new tools for human exposure assessment. Using patterns of changes from genomic or proteomic studies could help identify the agent and dose to which individuals or populations have been exposed. Surveillance programs could result for humans and animals where exposure to and/or contamination by endocrine disruptors are suspected.

Collaboration between intramural and extramural research scientists will be given a high priority. Workshops involving ORD and extramural scientists will be needed to develop principles for the selection of appropriate endpoints to be included in microarrays. Basic research on microarray technology and approaches to the statistical analysis of patterns of changes observed in genomic and proteomic studies will be supported intramurally, as well as by grants through the STAR program. Workshops involving ORD scientists and regional and program office scientists will also be needed to explore approaches and principles for the use of genomic and proteomic data in a risk assessment context.

APGs - Characterize sources of exposure and environmental fates of EDCs; Evaluate exposure methods, measurement protocols, and models for the assessment of risk management efficacy on EDCs

There are limited quality data describing real world ecological or human EDC exposures and/or the key factors associated with these EDCs. All the research that has been done up to this point has been on the chemistry of selected EDCs. Biological activity has never been adequately tracked except in some very focused source-biased studies. The relationships among chemicals and mixtures and their bioavailability is a complete unknown. As a result of these shortfalls, risk assessors resort to using default assumptions and/or mathematical outputs from exposure models that have not been evaluated with real world exposure data to develop risk assessments and implement risk management strategies. Equally important, the majority of the contemporary EDC exposure research has been focused on addressing either the ecological or human exposure methodologies and science issues, with few studies looking at the integrated ecological to human EDC exposure issue. However, the real world fate and transport of EDCs through the environment ultimately impacts human exposures to EDCs. Similarly, many human activities result in increased EDC exposures to the environment.

With additional resources, NERL plans initially to conduct a workshop to identify the key EDC exposure issues (including major routes, exposure factors, exposure to dose relationships, etc.) and then develop an integrated ecological and human exposure research study design to address the most important issues. Nationally and internationally recognized EDC exposure experts will be invited to attend this workshop. ORD will take the workshop input and develop a draft integrated eco/human exposure study design and conduct a small scale exposure study to characterize the extent of EDC key factors influencing ecological and human exposures to EDCs. The initial tests of the study design will attempt to address the highest priority issues and hypotheses, based on available resources and opportunities to collaborate with

other EPA and federal agency programs. The results of this study will be used to upgrade the integrated exposure study design in preparation for pilot testing.

The results of this additional research will provide the scientific community key data characterizing the extent of EDC exposures and the relationship between ecological exposures and human exposures to EDCs.

APG - Identify key risk assessment issues and develop guidance for assessing endocrine disruptors

The MYP for EDCs must, in its final measurement, be able to provide for proper evaluation of EDC risks. Developing guidance for EDC risk assessment is identified as high priority by program and regional offices to support their risk management decisions. The goal of this project area for FY06 is development of a framework to improve integration of human and ecological information on EDCs into Agency risk assessments. This supports the ORD MYP which calls for case studies that integrate health and ecological exposures and effects, followed by a framework for risk assessment, and finally a guidance document.

Assessment research must consider the major scientific uncertainties in the potential health and environmental effects of EDC through understanding of results from multiple *in vitro* and *in vivo* assay systems, and new scientific approaches (e.g., genomics), on multiple hormone systems in multiple species. Information and results from effects, exposure, and risk management intramural and extramural programs will feed into this research area.

Current ongoing research is focused on identification of issues critical to EDC risk assessment, and on developing case studies which consider integration of human health and ecological data in hazard and risk assessment. The case study projects (FY01, 02) focus on key EDCs as examples to explore incorporation of EDC-related testing data into hazard and risk assessment. This provides background for development of an assessment framework to improve integration of human health and ecological assessment. However, current funding and staffing is inadequate to provide a concentrated focus to address the increased data and research on EDCs. This has limited activity to two case studies and basic evaluation of risk assessment decision points important to EDCs. A proposal for evaluation of biomarkers common to environmental and human species was delayed to FY04 to utilize information from grants (NCER), since there was too little funding to initiate work internally. While much of the development work for the framework will be done within ORD due to potential policy implications, funding for intra- and extramural scientific consultations and collaboration, including workshops and peer reviews, will be necessary to assure proper development and acceptance of Agency assessment approaches. Additional resources will allow development work on the framework to start earlier and improve our ability to meet APG/APM deadlines in this project area.

Successful completion of the Agency's activities under this GPRA objective will provide the Agency with a consistent approach which supports domestic and international EDC risk assessment activities and supports effective prioritization of environmental exposure determinations and risk management research and solutions.

APGs - Evaluate at least three existing risk management tools to reduce exposure to EDCs; Develop at least two newrisk management tools to reduce exposure to EDCs; Evaluate exposure methods, measurement protocols, and models for the assessment or risk management efficacy on EDCs

New risk management research will provide a greater understanding of sources of EDCs and our ability to remove EDCs from various environmental media. Specifically, new research will allow a greater understanding of wastewater treatment of EDCs, the fate of EDCs in sediments, the efficacy of conventional and innovative drinking water treatment processes to remove EDCs, and the development of tools for pollution prevention.

First, ongoing research on understanding the fate of EDCs in conventional municipal sewage treatment plants will be expanded to investigate other common sewage treatment plant designs. Specifically, the ability of septic systems and constructed wetlands to treat EDCs (e.g., alkylphenolic compounds and steroid hormones) will be studied. Approximately 30% of U.S. households use some form of on-site sewage treatment such as septic systems. Also, as urban sprawl continues, suburban communities are increasingly employing decentralized (small-community) wastewater treatment systems such as constructed wetlands. The ability of septic systems and constructed wetland to treat EDCs is virtually unknown. This work will gather information on the treatability of EDCs by these common waste treatment systems and develop new tools to enhance these treatment as needed.

Second, work will commence to evaluate the ability of conventional and innovative drinking water treatment processes to remove EDCs from source water. Certain EDCs such as alkylphenolic compounds, steroid hormones, and bisphenol A have been observed in surface water. In addition, there are preliminary observations of these compounds in finished drinking water. The ability of treatment systems to remove these compounds is virtually unknown. This work will evaluate the ability of conventional treatment processes such as filtration, coagulation and sedimentation, to remove EDCs. Conventional treatment can be amended with various innovative processes such as granular activated carbon and membrane separations. This new work will also determine the efficacy of removing EDCs with these innovative treatment systems.

Third, new work will determine if natural processes in EDC-contaminated sediments can control exposure of aquatic wildlife to EDCs. Hydrophobic EDCs that exit sewage treatment plants such as alkylphenolic compounds will partition to aquatic sediments. This new work will evaluate the natural ability of biological and chemical processes in sediments to transform EDCs into innocuous products. Sediments that cannot remove EDCs will accumulate these chemicals causing long-term exposure to aquatic wildlife. This work will generate a portion of the information needed to manage the risk of EDCs associated with sewage treatment systems by developing an understanding of the ability of natural processes to mange EDCs released into the environment.

Fourth, pollution prevention (P2) approaches will be developed in this new work. Many known or likely EDCs continue to be produced and used in industrial products. For example, alkylphenol ethoxylates

continue to be used as domestic and industrial detergent, phthalate esters continue to be used as plasticizers, and bisphenol A continues to be a building block in certain plastics. This new work will involve two components: (1) the adaptation of existing P2 software that will identify substitutes for EDCs that possess the desired chemical properties, and (2) development of an advanced quantitative structural activity relationship (QSARs) that will evaluate the endocrine activity of the proposed chemical substitute. The new work will be applied initially to searching for substitutes for phthalates that are not estrogenic.

The completion of this new work will deliver important risk management information to key environmental stakeholders. The Office of Water, state and local environmental agencies, and the public will use the results of this work to develop risk management strategies for EDCs associated with sewage treatment and drinking water sources The P2 work will provide the Agency and interested industries tools to propose or develop substitute chemicals for EDCs that are currently produced.

As noted previously, in the section that follows, a specific case study is identified where we propose application of the methods, tools, and approaches identified in the Background section to work in an integrated cross-Laboratory/Center manner on a real-world situation. Depending on the amount of additional resources that may become available, a decision will be made to either propose one or more of the areas identified above or the following integrated case study, where every ORD laboratory/center has a role on a single environmental problem.

APPLICATION: CASE STUDY-

Integrated Concentrated Animal Feeding Operations (CAFOs) Project: Associated Impacts on Human and Wildlife Populations and Risk Management Options

The Office of Water is attempting to control nutrient, sediment, and chemical run-off from concentrated animal feeding operations (CAFOs) through NPDES permits and Effluent Limitation Guidelines. CAFOs and the production of large volumes of animal waste are major environmental concerns facing every EPA Region. Stressors of increasing concern include veterinary synthetic estrogens and androgenic steroids associated with animal production as well as natural hormones. Natural estrogenic and androgenic steroids and their excretion products are found in animal urine. Studies in Europe have shown that natural estrogenic substances, such as estradiol, when released to waterways may cause adverse effects on aquatic species. Also synthetic steroids, such as the synthetic androgen trenbolone, are widely used in animal feed operations in the US. Based on studies published by European researchers, this synthetic steroid, and its metabolites, are persistent in the environment. NHEERL studies established that trenbolone is a potent *in vivo* reproductive toxicant in fathead minnows, and in vitro mammalian and fish cell line studies have also confirmed it acts as an androgen receptor agonist. Preliminary, unpublished field studies conducted by the USFWS in the mid-west suggest an association between cattle feedlots that employ trenbolone and alterations in the condition of naturally occurring fathead minnow populations

The impact of these stressors on surface waters, groundwater, sediment, aquatic ecosystems, wildlife, and humans is largely unknown. In addition, there is limited information available on the reduction in risk that will result from the changes in animal waste management described in the revisions to CAFO regulations. While other Federal Agencies are also working on this issue, the fact that this is a high profile regulatory issue for EPA dictates that EPA should be providing leadership in this area. Other Agencies with whom we are already cooperating with or planning to cooperate with on CAFOs include USDA, USGS, FDA, and CDC. The convergence of a high profile regulatory program with a multi-disciplinary scientific challenge establishes an excellent case study to demonstrate ORD's ability to integrate its capabilities across the Laboratories/ Centers and engage scientists from the program and regional offices, other Federal Agencies, and academia to work collaboratively to solve a significant Agency concern.

This proposed research program responds to a critical, emerging regulatory challenge, by: 1) establishing techniques to quantify and characterize the magnitude and extent of human and wildlife population effects and causes of impairment by multiple chemical stressors caused by CAFOs, 2) developing improved methods for integrated human and ecological risk assessments, 3) determining the efficacy of proposed CAFO waste management schemes, and 4) developing new risk management options for stressors from CAFOs. The integrated research would include:

- Combining analytical chemistry and molecular science capabilities to develop biologically-based diagnostic techniques to establish toxicity identification, evaluation protocols, isolation of natural and synthetic hormones, veterinary pharmaceutical agents, and pathogens in feedlot effluent. (NHEERL, NERL, NRMRL, NCER)
- Developing a draft integrated eco/human exposure study design and conducting exposure studies to characterize the extent of key factors influencing ecological and human exposures to nutrients, endocrine disrupting chemicals (EDCs), other environmental chemicals including veterinary pharmaceuticals, and pathogens at the localized level. Evaluating the potential for regional scale impacts with remote sensing. (NERL, NCER)
- Quantifying dose response relationships for adverse reproductive, and other toxic effects to refine health and ecological risk assessments. (NHEERL, NCEA, NCER)
- Using these data as a practical case study supporting the development of Agency risk assessment guidelines EDCs which integrate human and ecological information. (NCEA)
- Evaluating the ability of conventional and innovative wastewater treatment processes to remove CAFO stressors to groundwater and surface water in order to reduce impacts to source water and offer management options for effluent control and pollution prevention. (NRMRL)
- Sponsoring a solicitation for competitive grants with universities that would link the intramural and extramural scientists and, thus, significantly expand the scope of scientific investigations and promote partnerships with state and local agencies (e.g., through land grant universities and extension programs) charged to manage feeding operations. (NCER)

TABLE 1.

LONG TERM GOAL 1. Provide a better understanding of the science underlying the effects, exposure, assessment and management of endocrine disruptors

ANNUAL PERFORMANCE GOALS AND MEASURES		YEAR	LAB/ CENTER
APG - Characterize the effects of exposure to multiple EDCs, in various combinations such as those with similar and different mechanisms of action		**2003**	**ORD**
APM	Determination of the mechanism(s) by which developmental exposure to PCBs disrupts thyroid hormones to produce ototoxicity, characterization of the effects of exposure to mixtures of PHAHs and determination of whether non-AH receptor mechanisms underlie the neurotoxicity of some PHAHs	2001	NHEERL
APM	Report on effects of early developmental exposure to endocrine disrupting pesticides on reproductive function in adults	2002	NCER
APM	Report on lab and field analysis of mechanisms by which tributyltin, alone and in combination with 3 methylcholanthrene, causes pseudohermaphroditism in marine gastropods	2003	NCER
APM 220	Report on the effects of mixtures of dioxin-like chemicals on development in the rat	2003	NHEERL
APG - Determine the shape of the dose-response curve in a variety of species exposed to ambient levels of EDCs		**2005**	**ORD**
APM	Conduct *in vitro* studies to determine the dose and time response relationships between exposure to chlorotriazines, alterations in the CNS and changes in pituitary hormone secretion	2000	NHEERL

APM	Report on effects of pre- and peri-natal exposures to PCBs on the metabolism of estrogens and androgens and on the ability of methoxychlor to cause reproductive toxicity at environmentally relevant levels of exposure	2001	NCER
APM	Conduct *in vivo* studies to determine the dose and time response relationships between exposure to chlorotriazines, alterations in the CNS and changes in pituitary hormone secretion	2001	NHEERL
APM	Evaluation of toxicant-induced alterations in mammalian reproductive development to compare dose response relationships, critical periods of exposure, *in vivo* tissue levels of the active toxicant and *in vivo* and *in vitro* mechanisms of action	2001	NHEERL
APM	Evaluation of the effect of chlorotriazines on the ovulatory LH surge and their potential disruption of pregnancy	2001	NHEERL
APM	Determine dose-responses for glucocorticoid and thyroid hormone disruption during chemically induced cancer in rodents	2002	NHEERL
APM	Evaluate dose metrics for developmental toxicants for use in low dose extrapolations	2002	NHEERL
APM	Report on analysis of effects of low, environmentally relevant exposure to EDCs during fetal development on prostatic growth at different stages of the life cycle	2003	NCER
APM 220	Report on the effects of mixtures of dioxin-like chemicals on development in the rat	2003	NHEERL
APM 26	Report on dose-response effects of EDCs that affect thyroid homeostasis as a target	2004	NHEERL
APM 27	Report on dose-response effects of EDCs acting by androgenic or anti-androgenic activity	2004	NHEERL
APM	Announce RFA soliciting research to characterize exposures to EDCs and determine the effects of low, ambient level exposures to EDCs	2004	NCER
APM	Report on the effects of chloroatrazines and metabolites on pubertal development in rats	2005	NHEERL

APG - Identify key risk assessment issues and develop guidance for assessing endocrine disruptors		**2006**	
APM	Complete one case study resulting in integrated human health and ecological assessments for selected classes of EDCs	2001	NCEA
APM	Produce a workshop report for the EDSTAC screening process for EDCs and determine application of EDSTAC testing program for chemical hazard and risk assessment	2001	NCEA
APM	Framework for conducting human health and ecological dose-response assessments for classes of EDCs at environmentally relevant concentrations	2004	NCEA
APM	Develop an integrated health and ecological risk assessment guideline for EDCs	2006	NCEA
APG 118 - Determine critical biological factors during development resulting in toxicities later in life		**2006**	
APM	Report on effects of pre- and peri-natal exposures to PCBs on the metabolism of estrogens and androgens and on the ability of methoxychlor to cause reproductive toxicity at environmentally relevant levels of exposure	2001	NCER
APM	Report on analysis of the most sensitive developmental stages in birds to EDCs	2001	NCER
APM	Determination of the mechanism(s) by which developmental exposure to PCBs disrupts thyroid hormones to produce ototoxicity, characterization of the effects of exposure to mixtures of PHAHs and determination of whether non-AH receptor mechanisms underlie the neurotoxicity of some PHAHs	2001	NHEERL
APM	Evaluation of toxicant-induced alterations in mammalian reproductive development to compare dose response relationships, critical periods of exposure, *in vivo* tissue levels of the active toxicant and *in vivo* and *in vitro* mechanisms of action	2001	NHEERL
APM	Determine whether GABA-A receptor activation plays a role in endocrine mediated developmental neurotoxicity	2001	NHEERL

APM	Evaluation of the effects of increasing serum prolactin levels in rats prior to puberty on lateral prostate inflammation at 120 days of age	2001	NHEERL
APM	Report on analysis of the ability of phytoestrogens (at human intake levels) to alter the normal sexually dimorphic development of the brain, behavior, and neuroendocrine control of reproduction in rats	2002	NCER
APM	Report on identification of the most critical stage in the life cycle of quail to the effects of endocrine disruptors	2002	NCER
APM	Report on effects of exposure to EDCs during early critical stages of embryonic development and the appearance of prostatic abnormalities in later life	2002	NCER
APM	Report on effects of early developmental exposure to endocrine disrupting pesticides on reproductive function in adults	2002	NCER
APM	Development of a method to assess potential health risks associated with exposure to EDCs which are developmental toxicants	2002	NHEERL
APM	Evaluation of dose metrics for developmental toxicants for use in low dose extrapolation	2002	NHEERL
APM	Evaluation of the effects of atrazine on the female reproductive system following lactational exposure	2002	NHEERL
APM	Examination of the effects of developmental exposure to both synthetic thyroid inhibitors and environmental pollutants with potentially similar thyroid activity on the ontogeny of learning and memory in rodent models	2002	NHEERL
APM	Report on analysis of effects of low, environmentally relevant exposure to EDCs during fetal development on prostatic growth at different stages of the life cycle	2003	NCER
APM	Report on analysis of effects of adolescent exposure to methoxychlor in rhesus monkeys on subsequent reproductive, immunological, brain, and skeletal function during puberty	2003	NCER
APM	Report on analysis of effects of EDCs on growth factors and receptors that control growth and development of the testis	2003	NCER

APM 118	Report on methods to assess endocrine disruptors in pubertal male and female rats	2003	NHEERL
APM 220	Report on the effects of mixtures of dioxin-like chemicals on development in the rat	2003	NHEERL
APM	(Further) Examination of the effects of developmental exposure to both synthetic thyroid inhibitors and environmental pollutants with potentially similar thyroid activity on the ontogeny of learning and memory in rodent models	2003	NHEERL
APM 221	Report on altered growth patterns in reproductive tissue in animals prenatally exposed to dioxin	2003	NHEERL
APM 28	Report on dose-response effects of perinatal exposure to EDC-active pesticides and immunocompetence	2004	NHEERL
APM 29	Evaluation of the effects of atrazine on the female reproductive system following prepubertal exposure	2004	NHEERL
APG 119 - Determine degree to which effects of EDCs with defined mechanisms/modes of action can be extrapolated across classes of vertebrates		**2007**	**ORD**
APM	Report on the molecular mechanisms underlying estrogen receptor functions in ER knockout mice	2000	NCER
APM	Report on comparative analysis in mice, fish, birds, and frogs of the endocrine disrupting activities of PCBs and PAHs at the molecular level (estrogen receptor) and at the tissue and organ levels	2002	NCER
APM	Determine relevance of rodent thyroid hormone assay for other species, including amphibians, birds, and fish	2002	NHEERL
APM 222	Report on comparative developmental toxicology studies with native and non-native amphibian species exposed to EDCs with established mechanisms of action	2003	NHEERL
APM 30	Report on effects of EDCs on aromatase activity in multiple species	2004	NHEERL
APM 31	Report on molecular methods to identify androgenic and anti-androgenic effects of EDCs in multiple species	2004	NHEERL

APM 32	Report on structure activity relationships, *in vitro*, and *in vivo* models to assess reproductive effects of EDCs in small fish models	2004	NHEERL
APM	Report on aquatic models to define toxicity pathways as a basis for extrapolation across species and biological levels of organization	2006	NHEERL
APM	Report on molecular methods to characterize endocrine disrupting effects of environmental chemicals	2006	NHEERL
APG - Evaluate exposure methods, measurement protocols, and models for the assessment of risk management efficacy on EDCs		**2008**	**ORD**
APM 83	*Develop a protocol for conducting an exposure analysis for children that includes all relevant pathways (also in Safe Food and Human Health MYPs)*	*2004*	*NERL*
APM 216	*Develop a second generation aggregate exposure model (SHEDS) for pesticides that characterizes uncertainty and variability in model inputs and outputs (also in Safe Food and Human Health MYPs)*	*2004*	*NERL*
APM 127	*Characterize the ratios of different forms of organophosphates and other widely used (and growing market share), non-persistent (i.e., more generally toxic) pesticides in environmental and food samples (also in Ecosystem Protection MYP)*	*2004*	*NERL*
APM 30	*Develop a prototype source-to-exposure-to-dose modeling framework that enables the complex computation for human exposure modeling (also in Safe Food and Human Health MYPs)*	*2004*	*NERL*
APM 33	*Analysis and report on factors for children's exposure to pesticides that may lead to high-level, short-term exposure to pesticides (also in Safe Food and Human Health MYPs)*	*2004*	*NERL*
APM 37	*Initiate Follow-on children's xxposure study to characterize aggregate exposures for selected pesticides, EDCs, and persistent pollutants (also in Safe Food and Human Health MYPs)*	*2004*	*NERL*

APM 34	*Peer-reviewed design for field study to evaluate protocols for obtaining reliable data on children's exposure to pesticides, EDCs, and other persistent pollutants (also in Safe Food and Human Health MYPs)*	*2004*	*NERL*
APM 201	*Report on application of EDC detection methods to risk management strategies for aquatic ecosystems (also in Ecosystem Protection MYP)*	*2004*	*NERL*
APM 271	*Report on presence of estrogenic and androgenic substances in effluents from concentrated animal feeding operations (also in Ecosystem Protection MYP)*	*2004*	*NERL*
APM 272	Use of minnow vitellogenin gene expression methods for monitoring and detection of estrogenicity from PCB contamination in Lake Hartwell	2004	NERL
APM	SOP for a bioassay of estrogenic activity adapted to risk management applications	2004	NRMRL
APM	Report on analytic method to monitor natural and synthetic hormones associated with risk management of CAFOs	2004	NRMRL
APM	Report on analytic method to monitor natural and synthetic hormones for the characterization of wastewater treatment plants	2004	NRMRL
APM	Technical report - bioavailability of two or three selected chiral pesticides with EDC properties	2005	NERL
APM	Development and evaluation through targeted pilot studies of analytical methods for alkylphenol ethoxylates with EDC properties	2005	NERL
APM	Development and evaluation of DNA microarray methods for diagnostic characterization of select EDCs and other model environmental stressors	2005	NERL
APM	Provide OPPTS, Regions and States with evaluated method for characterizing exposure to two or more suspect EDC metals	2005	NERL

APM	Report on integrated EDC field study of EDCs from concentrated animal feeding operations - NERL molecular diagnostics and analytical chemistry - NHEERL toxicity and effects measurements - NRMRL risk management technology evaluation	2005	NERL NRMRL NHEERL
APM	*Innovative, low burden exposure research tools supporting the design and implementation of the National Children's Study (also in Human Health MYP)*	*2005*	*NERL*
APM	*Provide an updated toolbox of improved data, methods, algorithms, exposure factors, etc. for modeling young children's aggregate exposures to pesticides and other key environmental contaminants (also in Air Toxics, Safe Food, Safe Communities, and Human Health MYPs)*	*2005*	*NERL*
APM	*Report on genomic analyses of exposure of fathead minnows to binary and ternary chemical mixtures (also in Ecosystem Protection MYP)*	*2005*	*NERL*
APM	Provide NHEERL, OPPTS and the scientific community with an evaluated method for characterizing chlorotriazine exposure in tissues	2006	NERL
APM	Development and evaluation of innovative analytical and sampling method for assessing exposures to one or two EDC suspected phthalates	2006	NERL
APM	Report on development and evaluation of biological indicators of exposure of several teleosts and invertebrate organisms to model EDCs	2006	NERL
APM	SOP for a bioassay of androgenic activity adapted to risk management applications	2006	NRMRL
APM	Provide the Regions and States with evaluated exposure tools and documentation for their use in assessing the efficacy of remediation technologies for EDCs	2007	NERL
APM	Evaluated and upgraded EDC compartmental model	2007	NERL

APM	*Demonstrate the use of NERL's human exposure modeling tools and databases to characterize and assess young children's exposures to pesticides and other environmental contaminants (also in Human Health MYP).*	*2008*	*NERL*
APM	SOP for a bioassay of thyroid-endocrine activity adapted to risk management applications	2008	NRMRL
APG - Provide at least one computational model for assessing endocrine disruptor compounds		**2008**	
APM	Announce RFA for the development of HTPS for prioritizing chemicals for testing for potential endocrine disruption	2003	NCER
APM	Announce RFA for incorporation of computational methods, through the use of systems biology approaches, in hazard identification and risk assessment	2003	NCER
APM	Report on the linkage of genomics-driven exposure indicators to effects in fish exposed to androgenic compounds	2005	
APM	Report on roles of pharmacokinetic and pharmacodynamic factors in dose-response and relative potency for compounds with endocrine activity using computational methodologies	2005	
APM	Evaluate one *in vitro* technique for assessment of steroidogenesis	2005	NHEERL
APM	Publish database on binding affinities of chemicals for the estrogen receptor	2005	NHEERL
APM	Report on the use of genomic data to validate the output of PB/PK/PD models in fish	2006	
APM	Report on the use of computational techniques to evaluate endocrine disruptor effects on GnRH	2006	NHEERL
APM	Establish database for non-pesticide chemicals from industrial sources to develop and refine a model for interspecies extrapolation	2006	NHEERL
APM	Report on a high throughput zebrafish embryo gene expression system for screening EDCs	2007	NCER

APM	Report on a mechanistic approach to screening chemicals and mixtures for endocrine activity using an invertebrate model	2007	NCER
APM	Report on development and application of a bioluminescent yeast-reporter system for screening chemicals for estrogenic and androgenic effects	2007	NCER
APM	Report on developing high throughput screening approaches for prioritizing chemicals for the EDSP	2007	NCER
APM	Establish database for inorganic chemicals from industrial sources to develop and refine a model for interspecies extrapolation	2007	NHEERL
APM	Report on molecular endpoints to be used in extrapolation models of effects of industrial chemicals in fish	2008	NHEERL
APG - Identify risk management EDCs research		**2008**	**ORD**
APM	Identify RM research needs from draft Risk Management Evaluation (RME)	2000	NRMRL
APM	Complete revision of RME for first round of EDCs of concern	2001	NRMRL
APM	Revision of RME for second round of EDCs of concern	2005	NRMRL
APM	Revision of RME for third round of EDCs of concern	2008	NRMRL
APG - Evaluate at least three existing risk management tools to reduce exposure to EDCs		**2009**	**ORD**
APM	Report describing the efficacy of conventional treatment of steroid hormones and alkylphenol ethoxylates in sewage to support ORD efforts to further characterize and manage EDC risks	2003	NRMRL
APM	Report on emissions of suspected EDC compounds from combustion sources to support ORD efforts to further characterize and manage EDC risks	2003	NRMRL
APM	*Interim progress report on the treatability of selected endocrine disrupting chemicals as requested by the Office of Water (also in Drinking Water MYP)*	*2003*	*NRMRL*

APM	*Report on the reduction in suspected EDCs achievable using existing manure management practices at CAFOs (also in Water Quality MYP).*	*2004*	*NRMRL*
APM	Report on performance of sludge digestion on reducing suspected EDCs in biosolids	2005	NRMRL
APM	Report on the drinking water treatability of selected reproductive hormones	2005	NRMRL
APM	Report on the ability of natural processes to manage estrogenic alkylphenols in aquatic sediments	2005	NRMRL
APM	*Report on the reduction of EDCs achieved by current biosolids management practices for Class A and Class B materials (also in Water Quality MYP)*	*2006*	*NRMRL*
APM	Report on the fate of other EDCs in wastewater treatment plants	2007	NRMRL
APM	Report on fate of EDCs in septic systems	2007	NRMRL
APM	Report on the ability of natural processes to manage steroid hormones in aquatic sediments	2007	NRMRL
APM	*Report on drinking water treatability of selected EDCs (surfactant degradation products) (also in Drinking Water MYP)*	*2007*	*NRMRL*
APM	*Determine treatability of selected additional EDCs (also in Drinking Water MYP)*	*2009*	*NRMRL*
APG - Develop at least two new risk management tools to reduce exposure to EDCs		**2009**	**ORD**
APM	Report on optimizing wastewater treatment plant operation for removing steroid hormones and alkylphenolic EDCs	2005	NRMRL
APM	Report on a methodology to predict potential endocrine activity using shape signatures for use in pollution prevention tools	2005	NRMRL
APM	Report on the potential of biodegradation to remove hormones from groundwater associated with CAFOs	2006	NRMRL

APM	Publish a pollution prevention computational tool that suggests substitutes for EDCs	2006	NRMRL
APM	*Report on how to reduce environmental risk from synthetic and natural hormones emanating from CAFO manure management systems (also in Water Quality MYP)*	*2007*	*NRMRL*
APM	Report on optimizing septic systems to remove EDCs	2009	NRMRL
APG - Develop systems models to test and predict vulnerabilities of the neuroendocrine system to contaminant-induced effects		**2012**	**ORD**
APM 26	Report on dose-response effects of EDCs that affect thyroid homeostasis as a target	2004	NHEERL
APM	Report on at least 1 procedure for measuring transgenerational effects in invertebrates to xenobiotics	2005	NHEERL
APM	Provide report from workshop on current knowledge of testing for neuroendocrine toxicity pathways and systems biology in aquatic species	2005	NHEERL
APM	Develop at least one approach for diagnosing mode-of-action for endocrine-disrupting chemicals in an amphibian model using toxicogenomic/proteomic techniques	2006	NHEERL
APM	Develop at least 1 technique based on toxicogenomic/ proteomic approaches as the basis for extrapolating across small fish species	2007	NHEERL
APM	Report on generalized amphibian model for testing adverse developmental effects associated with multiple endocrine pathways	2008	NHEERL
APM	Report on the use of genomic approaches and computational models to test for effects of contaminants on reproductive and developmental processes in aquatic species	2009	NHEERL
APM	Report on at least 1 model to define toxicity pathways as a basis for extrapolation across vertebrate aquatic species	2010	NHEERL

APM	Report on linked systems models for predicting contaminant-induced effects in aquatic species arising from multiple, interacting endocrine pathways	2011	NHEERL

Shading denotes APG and associated APMs appear in multiple LTGs
Italics denotes APM appears in multiple MYPs

TABLE 2.

LONG TERM GOAL 2. Determine the extent of the impact of endocrine disruptors on humans, wildlife, and the environment

ANNUAL PERFORMANCE GOALS AND MEASURES		YEAR	LAB/ CENTER
APG - Develop field methods to assess environmental exposures in tissues and environmental compartments		**2002**	**ORD**
APM	Interim reports on the development of user-friendly biological measures of estrogenicity of pesticides and suspected EDCs as a tool for evaluating their presence in water	2000	NERL
APM	Journal article on describing entry of agriculture based pharmaceuticals into ecosystems	2000	NERL
APM	Interim report documenting performance of confirmatory methods for toxic metals in the fresh water and sediment analysis	2000	NERL
APM	Standard operating procedure of laboratory confirmation of trace elements in water, soil, and sediments	2000	NERL
APM	Pilot study to test power of analytical methods for measuring suspected EDCs	2001	NERL
APM	Journal article on speciation and detection of organotins from environmental media	2001	NERL
APM	Interim report on alkylphenol methodology	2001	NERL
APM	Report to Regions 3 and 5 on alkylphenol methodology	2002	NERL
APM	Report on preliminary results from EDC investigation of selected Neuse River sites	2002	NERL
APG 121 - Determine efficacy of wildlife species as sentinels		**2004**	**ORD**
APM	Report on common markers for EDC effects in wildlife and human systems	2004	NCEA

APM 34	Report on comparative growth and reproductive responses of invertebrate population to xenobiotics	2004	NHEERL
APM 47	Report on the sensitivity and reproducibility of an estrogen-responsive sheepshead minnow cDNA macroarray: field application and assessment	2004	NHEERL
APM	Report on efficacy of wildlife species (e.g., fish, reptile, avian, invertebrate species) as sensitive indicators of endocrine disrupting effects of chemicals in the environment	2004	NCER
APG 122 - Evaluate several classes of chemicals suspected of being EDCs & determine potencies in laboratory studies		**2004**	**ORD**
APM	Report on whether exposure to dietary phytoestrogens will cause delayed neuro- and reproductive toxicity	2000	NCER
APM	Report on analysis of adverse reproductive system effects in human daughters from mother's exposure to halogenated hydrocarbons (PBBs)	2001	NCER
APM	Report on analysis of effects of methoxychlor and environmental estrogen receptor in ER knockout mice	2001	NCER
APM	Determination of the mechanism(s) by which developmental exposure to PCBs disrupts thyroid hormones to produce ototoxicity, characterization of the effects of exposure to mixtures of PHAHs and determination of whether non-AH receptor mechanisms underlie the neurotoxicity of some PHAHs	2001	NHEERL
APM	Identify the etiology of metabolic quinones in mammary cancer induced by EDCs	2001	NHEERL
APM	Determine the influence of classes of EDCs on proliferation and apoptosis in human mammary cells	2001	NHEERL
APM	Conduct *in vivo* studies to determine the dose and time response relationships between exposure to chlorotriazines, alterations in the CNS and changes in pituitary hormone secretion	2001	NHEERL
APM	Evaluation of the effect of chlorotriazines on the ovulatory LH surge and their potential disruption of pregnancy	2001	NHEERL

APM	Report on analysis of the ability of phytoestrogens (at human intake levels) to alter the normal sexually dimorphic development of the brain, behavior, and neuroendocrine control of reproduction in rats	2002	NCER
APM	Report on mechanisms of halogenated aromatic hydrocarbon toxicity in birds	2002	NCER
APM	Report on analysis of the antagonisms between the protective effects of endogenous steroid, progesterone, and the endocrine disrupting effect of TCDD in the development of endometriosis	2002	NCER
APM	Report on effects of dioxins on ovarian function	2002	NCER
APM	Evaluation of the effects of atrazine on the female reproductive system following lactational exposure	2002	NHEERL
APM	Report on the effects of developmental exposure to both synthetic thyroid inhibitors and environmental pollutants with potentially similar thyroid activity on the ontogeny of learning and memory in rodent models	2002	NHEERL
APM	Report on analysis of effects of PCBs on thyroid function in birds in the lab and field	2003	NCER
APM 220	Report on the effects of mixtures of dioxin-like chemicals on development in the rat	2003	NHEERL
APM 221	Report on altered growth patterns in reproductive tissue in animals prenatally exposed to dioxin	2003	NHEERL
APM 118	Report on methods to assess endocrine disruptors in prepubertal female rats	2003	NHEERL
APM 48	Report on the effects of atrazine on the female reproductive system following prepubertal exposure	2004	NHEERL
APG 123 - Evaluate several classes of chemicals suspected of being EDCs in field studies & ascertain degree to which they adversely affect wildlife at the population level		**2004**	**ORD**
APM	Report on the effects of EDCs on one or more wildlife populations in South Florida	2001	NHEERL

APM	Determine acute and chronic effects of retinoids on amphibian development	2001	NHEERL
APM	Report on analysis of the role of EDCs as a cause of shark infertility on Florida's Gulf Coast	2002	NCER
APM	Report on analysis of the linkage between EDC exposure in alligators at the level of the individual and population	2002	NCER
APM	Report on analysis of the effects of EDC exposure in the field and laboratory on immune system and host resistance in alligators	2002	NCER
APM	Report on analysis of the nature, extent, mechanisms by which EDCs interfere with normal sexual development in fish	2002	NCER
APM	Report on comparative analysis in mice, fish, birds, and frogs of the endocrine disrupting activities of PCBs and PAHs at the molecular level (estrogen receptor) and at the tissue and organ levels	2002	NCER
APM	Report on whether environmental exposure to EDCs has caused developmental abnormalities in frogs and the mechanisms for such effects	2003	NCER
APM	Report on analysis of the effects of endosulfan and PAH photoactivation products at the molecular, cellular, organism, and population levels in 2 crustacean species	2003	NCER
APM	Report on lab and field analysis of mechanisms by which tributyltin, alone and in combination with 3 methylcholanthrene, causes pseudohermaphroditism in marine gastropods	2003	NCER
APM	Report on analysis of effects of PCBs on thyroid function in birds in the lab and field	2003	NCER
APM	Report on analysis of biomarkers of reproductive and larval functions in fish to predict effects of EDCs on croaker population dynamics	2003	NCER
APM	Report on lab and field analysis of the effect of retinoids as inducers of abnormal limb development in frogs	2003	NCER

APM 49	Report on the sensitivity and reproducibility of an estrogen-responsive sheepshead minnow cDNA macroarray: field application and assessment	2004	NHEERL
APG 118 - Determine critical biological factors during development resulting in toxicities later in life		**2006**	**ORD**
APM	Report on effects of pre- and peri-natal exposures to PCBs on the metabolism of estrogens and androgens and on the ability of methoxychlor to cause reproductive toxicity at environmentally relevant levels of exposure	2001	NCER
APM	Report on analysis of the most sensitive developmental stages in birds to EDCs	2001	NCER
APM	Determination of the mechanism(s) by which developmental exposure to PCBs disrupts thyroid hormones to produce ototoxicity, characterization of the effects of exposure to mixtures of PHAHs and determination of whether non-AH receptor mechanisms underlie the neurotoxicity of some PHAHs	2001	NHEERL
APM	Evaluation of toxicant-induced alterations in mammalian reproductive development to compare dose response relationships, critical periods of exposure, *in vivo* tissue levels of the active toxicant and *in vivo* and *in vitro* mechanisms of action	2001	NHEERL
APM	Determine whether GABA-A receptor activation plays a role in endocrine mediated developmental neurotoxicity	2001	NHEERL
APM	Evaluation of the effects of increasing serum prolactin levels in rats prior to puberty on lateral prostate inflammation at 120 days of age	2001	NHEERL
APM	Report on analysis of the ability of phytoestrogens (at human intake levels) to alter the normal sexually dimorphic development of the brain, behavior, and neuroendocrine control of reproduction in rats	2002	NCER
APM	Report on identification of the most critical stage in the life cycle of quail to the effects of endocrine disruptors	2002	NCER

APM	Report on effects of exposure to EDCs during early critical stages of embryonic development and the appearance of prostatic abnormalities in later life	2002	NCER
APM	Report on effects of early developmental exposure to endocrine disrupting pesticides on reproductive function in adults	2002	NCER
APM	Development of a method to assess potential health risks associated with exposure to EDCs which are developmental toxicants	2002	NHEERL
APM	Evaluate dose metrics for developmental toxicants for use in low dose extrapolations	2002	NHEERL
APM	Evaluation of the effects of atrazine on the female reproductive system following lactational exposure	2002	NHEERL
APM	Examination of the effects of developmental exposure to both synthetic thyroid inhibitors and environmental pollutants with potentially similar thyroid activity on the ontogeny of learning and memory in rodent models	2002	NHEERL
APM	Report on whether environmental exposure to EDCs has caused developmental abnormalities in frogs and the mechanisms for such effects	2003	NCER
APM	Report on identification of effects of EDCs on prostate gland, testis development, and spermatogenesis	2003	NCER
APM	Report on analysis of effects of low, environmentally relevant exposure to EDCs during fetal development on prostatic growth at different stages of the life cycle	2003	NCER
APM	Report on analysis of effects of adolescent exposure to methoxychlor in rhesus monkeys on subsequent reproductive, immunological, brain, and skeletal function during puberty	2003	NCER
APM	Report on analysis of effects of EDCs on growth factors and receptors that control grown and development of the testis	2003	NCER
APM 220	Report on the effects of mixtures of dioxin-like chemicals on development in the rat	2003	NHEERL

APM	(Further) Examination of the effects of developmental exposure to both synthetic thyroid inhibitors and environmental pollutants with potentially similar thyroid activity on the ontogeny of learning and memory in rodent models	2003	NHEERL
APM 221	Report on altered growth patterns in reproductive tissue in animals prenatally exposed to dioxin	2003	NHEERL
APM 225	Report on the effects of atrazine on the male and female reproductive system following developmental exposure	2003	NHEERL
APM 50	Report on critical windows of exposure for alterations in mammary gland development and lactational function	2004	NHEERL
APM 51	Report on the effects of atrazine on the female reproductive system following prepubertal exposure.	2004	NHEERL
APM	Report on the effects of atrazine to modify mammary gland morphology when delivered during critical periods of development	2006	NHEERL
APG 124- Determine extent to which exposure to EDCs contribute to onset or increase in severity of diseases		**2007**	**ORD**
APM	Characterization of environmental agents as risk factors in human prostate	2001	NCEA
APM	Determination of the mechanism(s) by which developmental exposure to PCBs disrupts thyroid hormones to produce ototoxicity, characterization of the effects of exposure to mixtures of PHAHs and determination of whether non-AH receptor mechanisms underlie the neurotoxicity of some PHAHs	2001	NHEERL
APM	Evaluation of the effects of increasing serum prolactin levels in rats prior to puberty on lateral prostate inflammation at 120 days of age	2001	NHEERL
APM	Report on mechanisms of EDCs in thyroid carcinogenesis	2002	NCER
APM	Report on analysis of the antagonisms between the protective effects of endogenous steroid, progesterone, and the endocrine disrupting effect of TCDD in the development of endometriosis	2002	NCER

APM	Report on effects of dioxins on ovarian function	2002	NCER
APM	Evaluation of the effects of atrazine on the female reproductive system following lactational exposure	2002	NHEERL
APM	Examination of the effects of developmental exposure to both synthetic thyroid inhibitors and environmental pollutants with potentially similar thyroid activity on the ontogeny of learning and memory in rodent models	2002	NHEERL
APM	Report on the magnitude and nature of thyroid alterations in relation to exposure to EDCs	2003	NCER
APM	Report on effects of DES, genistein, bisphenol A on sperm counts and quality of the relationship between these endpoints and changes in gene expression	2003	NCER
APM	Report on effects of low, environmentally relevant exposure to EDCs during fetal development on prostatic growth at different stages of the life cycle	2003	NCER
APM	Report on the effects of developmental exposure to both synthetic thyroid inhibitors and environmental pollutants with potentially similar thyroid activity on the ontogeny of learning and memory in rodent models	2003	NHEERL
APM 221	Report on altered growth patterns in reproductive tissue in animals prenatally exposed to dioxin	2003	NHEERL
APM 52	Report on the effects of atrazine on the female reproductive system following prepubertal exposure.	2004	NHEERL
APM	Report on the effects of atrazine to modify mammary gland morphology when delivered during critical periods of development	2006	NHEERL
APG - Determine whether adverse developmental/ reproductive effects are occurring in human populations		**2008**	**ORD**
APM	Announce RFA soliciting research on multi-disciplinary human studies demonstrating quantitative relationships between chemical exposures and manifestations of adverse effects on reproductive development mediated via alterations in the endocrine system	2000	NCER

APM	Report on analyses of adverse reproductive system effects in human daughters from mother's exposure to halogenated hydrocarbons (PBBs)	2001	NCER
APM	Report on epidemiology study on effects of organochlorines and PCBs exposures on endometriosis	2007	NCER
APM	Report on epidemiology study on effects of early exposures to phthalates on breast and genitalia development in males and females	2007	NCER
APM	Report on epidemiology study on effects of dioxins on in utero and childhood exposures on male reproductive development	2008	NCER
APM	Report on epidemiology study on effects of gestational and/or lactational exposure to heptachlor on reproductive and immune function	2008	NCER
APM	Report on epidemiology study on effects of PBDEs on thyroid	2008	NCER
APG - Characterize sources of exposure and environmental fates of EDCs		**2008**	**ORD**
APM 37	*Initiate follow-on children's exposure study to characterize aggregate exposures for selected pesticides, EDCs, and persistent pollutants (also in Safe Food and Human Health MYPs)*	*2002*	*NERL*
APM 34	*Peer-reviewed design for field study to evaluate protocols for obtaining reliable data on children's exposure to pesticides, EDCs, and other persistent pollutants (also in Safe Food and Human Health MYPs)*	*2002*	*NERL*
APM	Determine the extent to which combustion sources contribute to EDCs in the environment	2002	NRMRL
APM	Determine the extent to which CAFOs contribute to EDCs in the environment	2002	NRMRL
APM 30	By 2003, complete field monitoring study (CTEPP) to evaluate aggregate exposures of 260 young children in their homes and daycare centers to persistent organic pollutants	2003	NERL

APM 23	*Interim report on applicator exposures to pesticides in the Agricultural Health Study (also in Safe Communities)*	*2003*	*NERL*
APM	Submit a paper on emissions of EDC compounds from combustion sources to support ORD efforts to further characterize and manage EDC risks	2003	NRMRL
APM	Announce RFA soliciting research to characterize exposures to EDCs and determine the effects of low, ambient level exposures to EDCs	2004	NCER
APM	Determine the extent of exposure to key ecosystems to selected antibiotics derived from CAFOs in the Neuse River Basin	2004	NERL
APM 273	Vitellogenin gene expression in minnows and Pearl Dace from control and dosed lakes in Canadian Experimental Lake area	2004	NERL
APM 272	Use of minnow vitellogenin gene expression methods for monitoring and detection of estrogenicity from PCB contamination in Lake Hartwell	2004	NERL
APM 280	*Homeostasis disruption: unforeseen effects of PPCPs in the environment (also in Drinking Water MYP)*	*2004*	*NERL*
APM 218	*Analysis of aggregate exposures to young children in their homes and daycare centers to persistent organic pollutants (includes pesticides, EDCs, and other persistent organic compounds) (also in Safe Food and Human Health MYPs)*	*2004*	*NERL*
APM 229	*Analysis of children studies' results to identify key uncertainties and critical data gaps (also in Safe Food and Human Health MYPs)*	*2004*	*NERL*
APM 217	*Analysis of the farm applicator and family exposure results from the Agricultural Health Study (also in Safe Communities MYP)*	*2004*	*NERL*
APM	Report on the androgenic characteristics of products from biomass combustion	2004	NRMRL
APM	*Report on potential of swine CAFOs to contribute EDCs to groundwater (also in Water Quality MYP)*	*2004*	*NRMRL*

APM	Transfer of molecular diagnostic indicator technology to 5 EPA Regional laboratories	2005	NERL
APM	*Report on regional scale studies of molecular diagnostic indicators in fish from watersheds in the Midwestern United States (also in Ecosystem Protection MYP)*	*2005*	*NERL*
APM	Complete field measurements of aggregate exposures of infants and toddlers to pesticides, EDCs, and other environmental contaminants	2006	NERL
APM	Implementation of integrated ecological/human exposure field measurements study	2006	NERL
APM	Report on emission factors for androgenic EDCs from biomass sources	2006	NRMRL
APM	Provide ORD and OPPTS with summary workshop recommendations for the key objectives and design criteria for an integrated ecological and human exposure field study	2007	NERL
APM	*Analysis of aggregate exposures of infants and toddlers in homes to pesticides and other environmental contaminants. (also in Safe Food MYP)*	2007	NERL
APM	*Assessment of key factors influencing aggregate exposures of young children in one or two cohorts along the US/Mexico border (also in Human Health MYP)*	2008	NERL
APM	Report from NCER/NERL EDC exposure study	2008	NERL
APM	*Report on analysis of National Children's Study exposure data and relationships to health and stressor data (also in Safe Food and Human Health MYPs)*	*2008*	*NERL NCEA NHEERL*
APM	Report on estimation of overall contribution of androgenic activity to the environment by combustion sources	2008	NRMRL

Shading denotes APG and associated APMs appear in multiple LTGs
Italics denotes APM appears in multiple MYPs

TABLE 3.

LONG TERM GOAL 3. Support EPA's Screening and Testing Program

ANNUAL PERFORMANCE GOALS AND MEASURES		YEAR	LAB/ CENTER
APG - Evaluate existing testing guidelines for their adequacy to evaluate endocrine-mediate effects		**2001**	**ORD**
APM	Evaluate multi-generation reproductive test guideline for use in Tier 1 testing of potential EDCs	2001	NHEERL
APG - Develop standardized protocols for screening chemicals for their potential endocrine-mediated effects to meet FQPA requirements		**2006**	**ORD**
APM	Report on the development of an *in vitro* test system and markers of action for xenoestrogens during spermatogenesis	2000	NCER
APM	Determine the molecular basis for the anti-androgenic effects of some endocrine active environmental chemicals by examining their ability to bind AR, induce nuclear AR import and inhibit AR-mediated transactivation and subsequent AR-DNA binding	2000	NHEERL
APM	Comparison of the results of several *in vitro* estrogen agonist/antagonist assays to results obtained *in vivo* in an assay that assesses the ability of a compound to induce estrogen responses in uterus, vagina and brain.	2000	NHEERL
APM	Report on development of a biological model (fish) for viewing tissue and organ specific changes in gene expression caused by EDCs	2001	NCER
APM	Report on validation of animal model (fish) for detecting EDCs	2001	NCER
APM	Report on development of *in vitro* test system (shark testis) for effects of EDCs on spermatogenesis	2001	NCER
APM	Determine whether GABA-A receptor activation plays a role in endocrine mediated developmental neurotoxicity	2001	NHEERL

APM	Develop three of the short term mammalian *in vivo* tests recommended by the EDSTAC; the Hershberger and the male and female pubertal assays .	2001	NHEERL
APM	Report on development of an animal model (fish) for screening suspected EDCs	2002	NCER
APM	Report on development of QSAR based models for predicting *in vivo* and *in vitro* endocrine disrupting effects of synthetic chemicals	2002	NCER
APM	Develop an understanding of the relationship between molecular structure and effects on the estrogen receptor	2002	NHEERL
APM	Develop a short-term reproductive assay with the fathead minnow to address a recommendation of the EDSTAC	2002	NHEERL
APM	Develop a tail resorption assay with Xenopus to address a recommendation of the EDSTAC	2002	NHEERL
APM	Development of a biomarker that incorporates utilization of a complex developmental process (metamorphosis) critical to the completion of the life cycle of previously identified xenobiotic sensitive populations in the marine environment (crustaceans)	2002	NHEERL
APM 115	Report on the use of short-term screens for thyroid hormone disruptors	2003	NHEERL
APM 121	Report on the binding of chemicals from selected classes of environmental agents to proteins in the thyroid hormone system	2003	NHEERL
APM 224	Report on the validation of the Hershberger Assay for use by OECD	2003	NHEERL
APM 109	Report on integrated *in vitro* methods and QSAR models using 3-D molecular descriptors for chemical prioritization and ranking for EDCs	2003	NHEERL
APM 223	Report on stable cell lines expressing androgen and estrogen receptors, together with respective complex promoter luciferase reporters	2003	NHEERL

APM	Report on comparison of *in vitro* and *ex vivo* systems for identifying the effect of environmental chemicals on steroidogenesis	2005	NHEERL
APM	Report on standardization of short-term mammalian *in vivo* test recommended by EDSTAC	2005	NHEERL
APM	Report on standardization of an *in vitro* test to examine the effect of environmental chemicals on the androgen receptor using transfected cell lines	2006	NHEERL
APG - Identify key risk assessment issues and develop guidance for assessing endocrine disruptors		**2006**	
APM	Complete one case study resulting in integrated human health and ecological assessments for selected classes of EDCs	2001	NCEA
APM	Produce a workshop report for the EDSTAC screening process for EDCs and determine application of EDSTAC testing program for chemical hazard and risk assessment	2001	NCEA
APM	Framework for conducting human health and ecological dose-response assessments for classes of EDCs at environmentally relevant concentrations	2004	NCEA
APM	Develop an integrated health and ecological risk assessment guideline for EDCs	2006	NCEA
APG - Develop standardized protocols for testing chemicals for their potential endocrine-mediated effects to meet FQPA requirements		**2008**	**ORD**
APM	Report on method to assess potential health risks associated with exposure to EDCs which are developmental toxicants	2002	NHEERL
APM	Develop a short-term reproductive assay with the fathead minnow to address a recommendation of the EDSTAC	2002	NHEERL
APM	Report on tail resorption assay with Xenopus to address a recommendation of the EDSTAC	2002	NHEERL

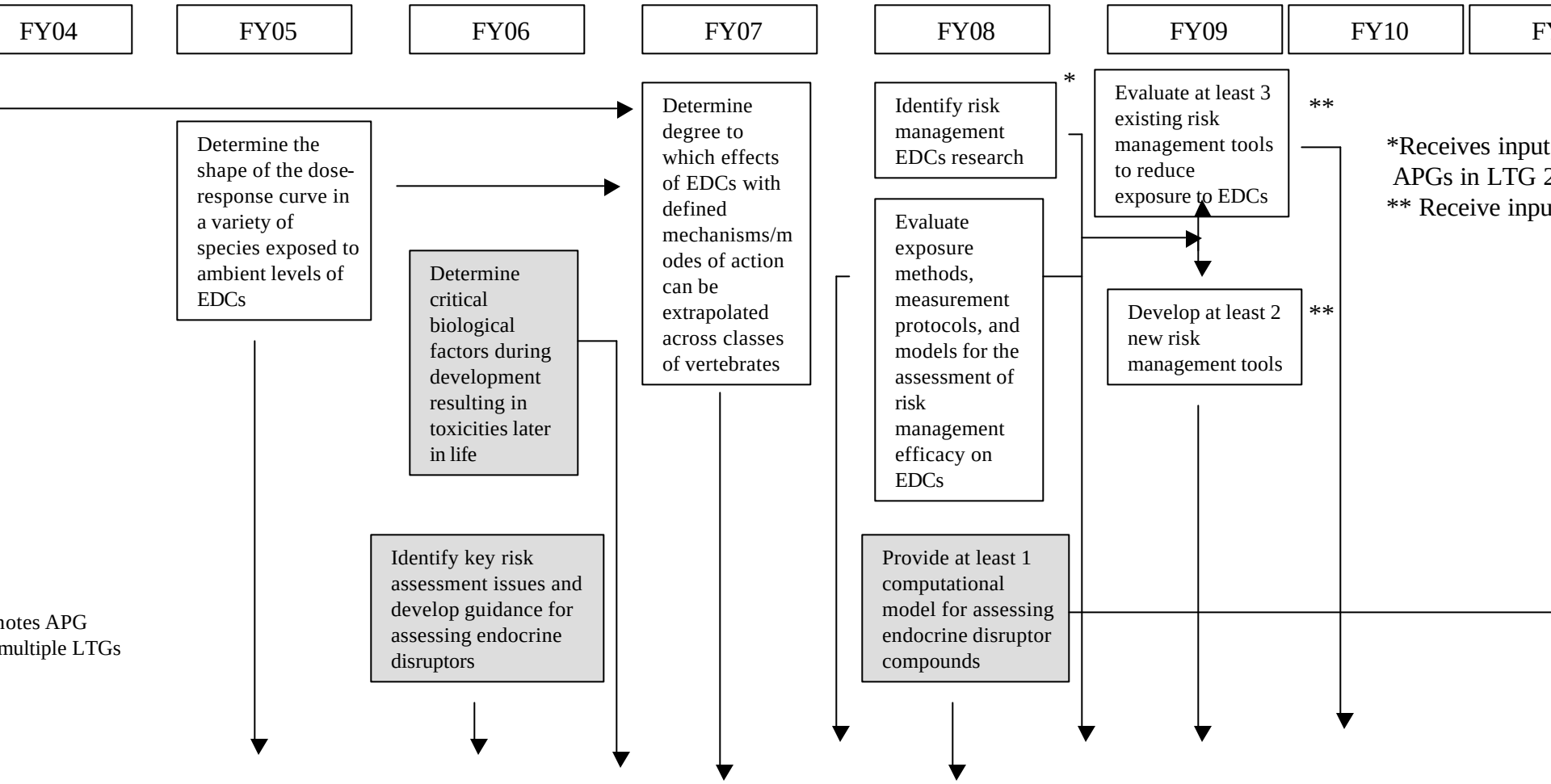
APM	Report on field validation of laboratory-based diagnostic measurements indicative of exposure to estrogenic compounds; plasma levels of vitellogenin, brain aromatase level and activity and liver induction of vitellogenin mRNA.	2002	NHEERL
APM 115	Report on the use of short-term screen for thyroid hormone disruptors	2003	NHEERL
APM	Provide a review of the one-generation study comparing two anti-androgens	2005	NHEERL
APM	Produce one standardize protocol for in utero/lactational assay and evaluate its utility using one prototypic endocrine-disrupting chemical	2007	NHEERL
APM	Report on the cumulative risk of reproductive toxicants following in utero exposure using *in vivo* testing protocols	2008	NHEERL
APG - Provide at least one computational model for assessing endocrine disruptor compounds		**2008**	
APM	Announce RFA for the development of HTPS for prioritizing chemicals for testing for potential endocrine disruption	2003	NCER
APM	Announce RFA for incorporation of computational methods, through the use of systems biology approaches, in hazard identification and risk assessment	2003	NCER
APM	Report on the linkage of genomics-driven exposure indicators to effects in fish exposed to androgenic compounds	2005	
APM	Report on roles of pharmacokinetic and pharmacodynamic factors in dose-response and relative potency for compounds with endocrine activity using computational methodologies	2005	
APM	Evaluate one *in vitro* technique for assessment of steroidogenesis	2005	NHEERL
APM	Publish database on binding affinities of chemicals for the estrogen receptor	2005	NHEERL

APM	Report on the use of computational techniques to evaluate endocrine disruptor effects on GnRH	2006	NHEERL
APM	Establish database for non-pesticide chemicals from industrial sources to develop and refine a model for interspecies extrapolation	2006	NHEERL
APM	Report on a high throughput zebrafish embryo gene expression system for screening EDCs	2007	NCER
APM	Report on a mechanistic approach to screening chemicals and mixtures for endocrine activity using an invertebrate model	2007	NCER
APM	Report on development and application of a bioluminescent yeast-reporter system for screening chemicals for estrogenic and androgenic effects	2007	NCER
APM	Report on developing high throughput screening approaches for prioritizing chemicals for the EDSP	2007	NCER
APM	Establish database for inorganic chemicals from industrial sources to develop and refine a model for interspecies extrapolation	2007	NHEERL
APM	Report on molecular endpoints to be used in extrapolation models of effects of industrial chemicals in fish	2008	NHEERL

Shading denotes APG and associated APMs appear in multiple LTGs

FIGURE 1

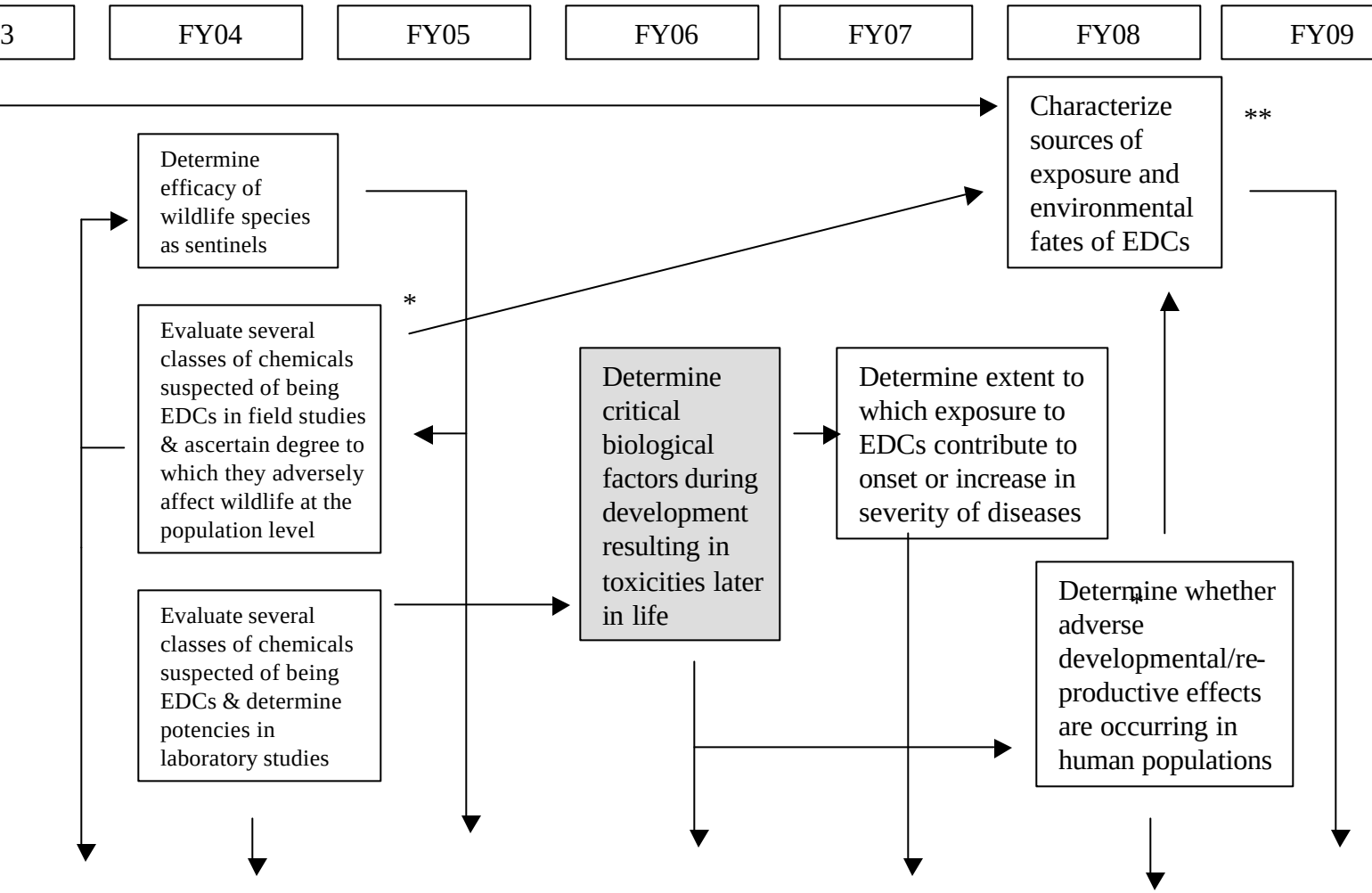
Linkage and Timeline for APGs to Meet Long Term Goal 1



a Better Understanding of Science Underlying the Effects, Exposure, Assessment, and Ma
Endocrine Disruptors

FIGURE 2

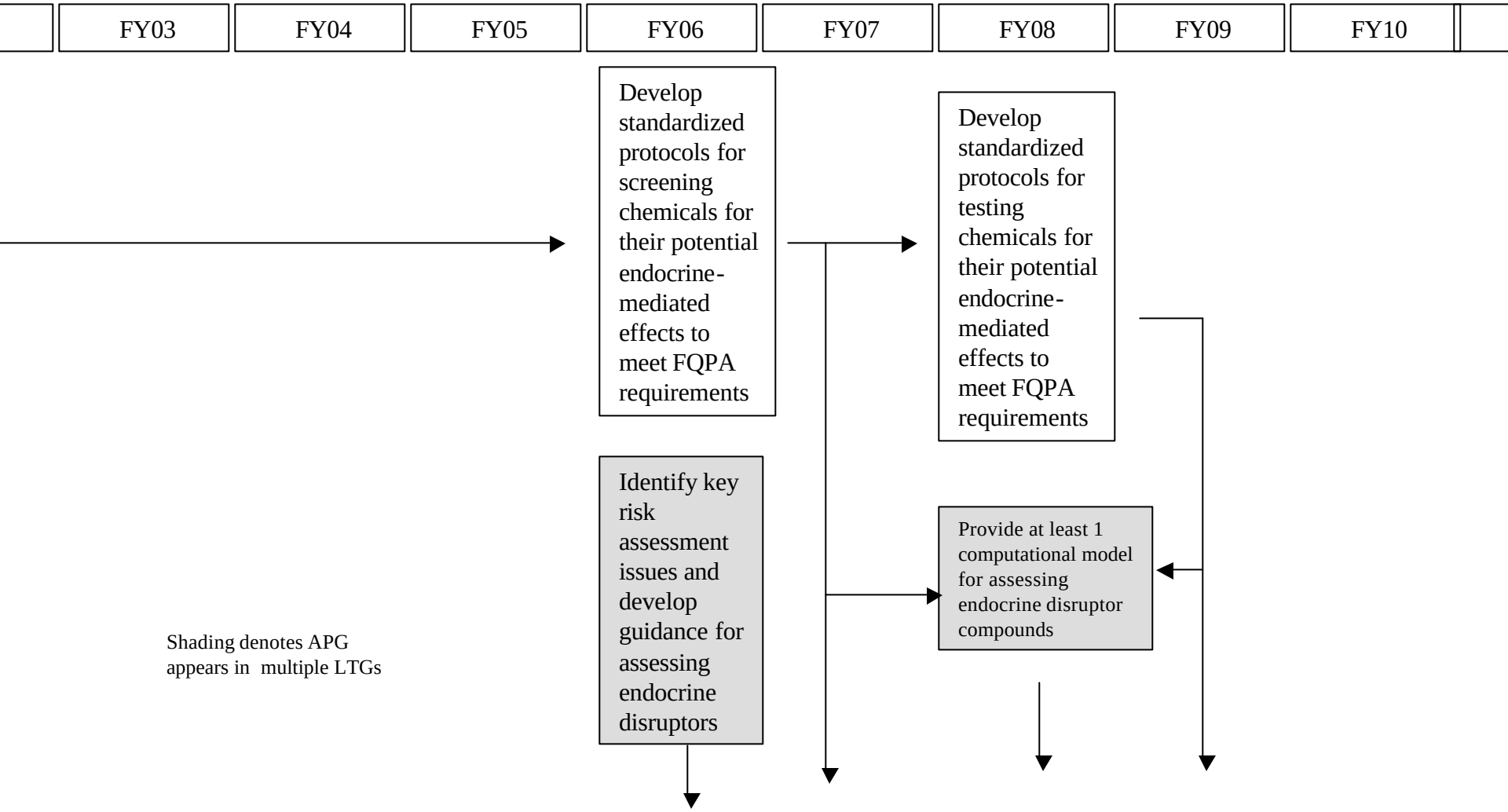
Linkage and Timeline for APGs to Meet Long Term Goal 2



e the Extent of the Impact of Endocrine Disruptors on Humans, Wildlife, and the Environ

FIGURE 3

Linkage and Timeline for APGs to Meet Long Term Goal 3



Support EPA's Screening and Testing Program

Figure 4. Endocrine Disruptors Research Program Design Logic Model

