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Research Plan for Endocrine Disruptors

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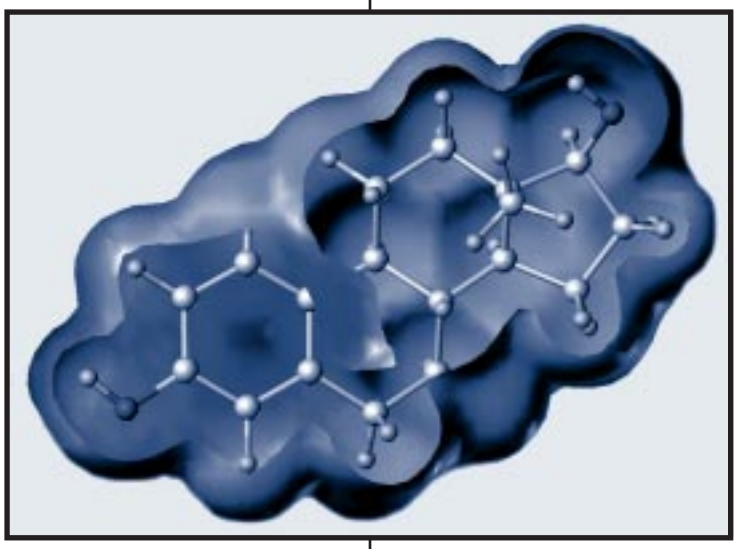

Foreword

The Strategic Research Plan for Endocrine Disruptors, one in a series of research plans produced by EPA's Office of Research and Development (ORD), identifies and describes one of EPA's high-priority research topics. This research topic was selected in accord with the ORD Strategic Plan, which identifies the following as high-priority research areas for EPA:

- broad-based fundamental research to improve human health and ecosystem risk assessment, pollution prevention, and new technologies for environmental protection; and

- research targeted at specific pollution problems in safe drinking water, high-priority air pollutants, and emerging environmental issues.

In addition, ORD has included certain other key research program areas, such as the Environmental Monitoring and Assessment Program (EMAP) and global climate change.

The Strategic Research Plan for Endocrine Disruptors is an outcome of ORD's research priority-setting process, which has employed human health and ecological health research criteria, risk management research criteria, and methods/models development criteria in order to set priorities among the many research topics identified through input from all parts of EPA and from other government and private sector organizations; the topics must also fit within EPA's mission and goals. EPA's program and regional offices—the Agency's main research clients—were consulted to ensure that the final version of this plan includes the research products they will need to fulfill their responsibilities. In addition, the Strategic Research Plan for Endocrine Disruptors was subjected to rigorous external peer review.

Strategic research plans are important tools for measuring accountability because they make clear the rationale for, and the intended products of, EPA's research. By specifying up front how EPA will manage its scientific data and information products, EPA can effectively communicate the results of its research to its clients, stakeholders, and the public. Research plans are also important budget tools, enabling EPA to clearly track progress toward achieving its research goals as required by the 1993 Government Performance and Results Act.

An implementation plan is different from a research strategy. While a research strategy provides the framework for making and explaining decisions about program purpose and direction, as well as relative priorities and research distributions, an *implementation plan* defines the research program that EPA is pursuing. The research strategy, as an overarching view of research needs and

priorities, thus provides a link between the ORD Strategic Plan and the implementation plans of ORDs Laboratories and Centers which define the research topics at the project level.

Peer review is an important component of research plan development. The peer review history for the Strategic Research Plan for Endocrine Disruptors is as follows:

Initial Internal Agency Review: February, 1996

ORD Science Council: Final Clearance, December, 1996

Lead Reviewers: Rick Linthurst, NERL
Jennette Wiltse, NCEA

Submitted for Comments
to the Endocrine Disruptor
Working Group of the
Committee on the
Environment and
Natural Resources April, 1997

External Peer Review: July 8-9, 1997; Washington, DC.

Reviewers:

William Cooper, Michigan State University
George Daston, Procter & Gamble Co.
Peter DeFur, Virginia Commonwealth University, Chair
Paul Foster, Chemical Industry Institute of Toxicology
Michael Fry, University of California, Davis
Louis Guillette, University of Florida
Holly Hattemer-Frey, SAF*Risk
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Final Acceptance by ORD: March, 1998

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US ENVIRONMENTAL PROTECTION AGENCY
RESEARCH PLAN FOR ENDOCRINE DISRUPTORS [1]
February, 1998

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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 environmental chemicals 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.

Despite these reported effects, we know little about their causes and the concentrations of EDCs that would induce effects in various populations. 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. Based upon recognition of *the potential scope of the problem*, *the possibility of serious effects on the health of populations*, and *the persistence of some endocrine-disrupting agents in the environment*, research on endocrine disruptors was identified as one of the six high-priority topics in the ORD Strategic Plan (USEPA, 1996a). If future health effects and exposure studies conclude that humans and the ecosystem are at significant risk due to exposure to EDCs, research on how best to lower or eliminate the risk will be needed. The key questions that this research plan must answer are:

The primary questions that need to be answered for endocrine disruptors

- % 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?

A time line for addressing these overarching questions is presented in Appendix I.

Given the USEPA's mandate to protect both public-health and the environment, it is in a unique position to provide leadership in this area. Therefore, in response to the growing public health concerns related to chemicals in the environment which have the potential to act as endocrine disruptors, the Office of Research and Development of the USEPA held two workshops. There, the opinions of international experts were sought to help formulate a national research plan for endocrine disrupting chemicals. The first of these was held in April 1995 in Raleigh, NC and covered both human and ecological needs from a broad-scale, risk-assessment based perspective (Kavlock et al., 1996). The second workshop, held in Duluth, MN in June 1995 built on the needs identified in the first workshop, but with a sole focus on ecological research needs (Ankley et al., 1997). Details of the deliberations and recommendations of these workshops are summarized in Section III (Research Issues) and Appendix II. This research plan 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 broad nature of the issue necessitates a coordinated effort on both the national and international level. The National Science and Technology Council (NSTC), which advises the President and his Cabinet on directions for federal research and development efforts, has established a milestone for 1995-1998 to produce a national research strategy on endocrine disrupting chemicals. This action led to formation of the Endocrine Disruptor Working Group under the Committee on the Environment and Natural Resources (CENR) of the NSTC to guide activities on a broader national scale (CENR, 1996). The USEPA chairs this coordination effort and has been instrumental in establishing a communication network on endocrine disruptors that will facilitate addressing the key research questions. The functions of the CENR workgroup are to:

- Develop a federal research framework,
- Inventory ongoing research activities in the federal government and elsewhere,
- Provide a forum for information sharing among the various national organizations,
- Outreach to non-federal organizations involved in endocrine disruptor issues, and
- Hold periodic symposia as the research emerges.

The inventory of federal research on endocrine disruption has been used to evaluate the current state of the federal effort, identify research gaps and establish priorities, and clarify governmental roles and responsibilities. To date, nearly 400 projects have been identified as being sponsored by the participating 14 agencies. The CENR framework and the inventory are available on the Internet (http://www.epa.gov/endocrine), and a summary analysis has been published (Reiter, et al, 1998). Due to the complex nature of the uncertainties posed by the endocrine disruptor hypothesis, the

overlapping concerns of federal agencies, and the resource constraints on the federal budget, close coordination and cooperation among federal agencies will be essential to the resolution of the critical research questions. For example, a number of participating agencies are currently discussing issuing a joint Request for Proposals in FY98 to address the highest priority data gaps. While the CENR will provide the umbrella for this coordination, individual agencies are responsible for development of their own independent research plans. Therefore, an important component of this present document must be to communicate with other federal organizations on USEPA's goals, priorities, and projected accomplishments.

EDCs were also identified as a high priority at the 1997 Environment Leaders' Summit of the Eight. Included among the recommended action items were: 1) the development of an international inventory of ongoing research activities, 2) the development of an international scientific assessment, 3) the development of an international research strategy after completion of the inventory and scientific assessment, and 4) support for an OECD initiative to develop a battery of screening and testing guidelines for EDCs that considers the special susceptibilities and exposures to children. In conjunction with the CENR effort, a companion effort to inventory research has been conducted in Europe (http://www.liwa.de/rneed), and efforts are currently underway under the auspices of the World Health Organization's International Programme on Chemical Safety and the Organization of Economic and Community Development to assemble international inventory and assessment of the endocrine disruptor issue. In addition, the National Research Council has also been commissioned by the USEPA's Office of Water and other federal agencies to conduct a comprehensive, critical evaluation of the scientific literature and to identify research needs. Results of this effort are expected to be available in the spring of 1998. In the interim, ORD's Risk Assessment Forum has provided an overview of the current state of knowledge of the science relative to environmental endocrine disruption in humans, laboratory testing and wildlife species (USEPA, 1996b). This document contains an extensive assessment of the principle adverse biological effects associated with exposure to endocrine-disrupting chemicals.

In developing USEPA's research plan, the committee noted that there are clearly important areas for which other federal agencies have the research lead (e.g., NCI and CDC for studies on environmental causes of breast cancer, NOAA for immunological effects in marine mammals, NSF and NIEHS for the role of hormones in the normal differentiation of the brain and reproductive track). Conversely, because of their scope and complexity, other problem areas need to be approached by multiple organizations (e.g., development of short-term screening techniques, determination of environmental contamination levels). In this plan, we first selected those areas where the USEPA should be playing at least a moderate role. Priorities were then assigned based upon an assessment of the importance of the research to the EPA program 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. It is expected that other USEPA activities (e.g., the Dioxin Reassessment and efforts to develop approaches for assessment of complex mixtures) will feed into the information base.

This document was developed to serve several purposes, including:

1. To provide a roadmap to guide the Agency's efforts on endocrine disruptor, while at the same time remaining flexible enough to adjust to recommendations evolving from the CENR and NAS efforts;

2. To establish distinctions between, and priorities for, the intramural and extramural ORD research efforts;

3. To provide a research framework for the regulatory programs;

4. To inform Agency risk assessors and risk managers of the types of data being generated for endocrine disrupting chemicals; and

4. To serve as the basis for coordination and communication of research activities with other Federal agencies and other organizations affected by this issue.

Concepts for a multi year research plan for the intramural and extramural programs priorities are presented in Section V. It is anticipated that each Laboratory and Center within ORD will develop an implementation plan for EDCs that allows the coordination and sequencing of the research elements to occur. Recognizing the dynamic nature of the research front, we emphasize that the priorities and sequencing that we propose be revisited in three to four years so the strategy can be modified accordingly.

II. REGULATORY BACKGROUND

The authorities and responsibilities of the Environmental Protection Agency are mandated primarily by thirteen major environmental statutes (CRC Report to Congress, 1995). These statutes direct the USEPA to perform a wide variety of activities with the underlying goal of protecting human health and the environment. These diverse activities include, but are not limited to: 1) identifying hazardous or toxic substances, 2) setting specific allowable levels of exposure to chemicals that are protective of human health and the environment, 3) controlling releases of chemicals into the environment, 4) responding to spills or other releases of chemicals into the environment, 5) developing a national inventory of chemical releases into the environment, 6) cleaning hazardous waste sites to levels that assure protection of human health and the environment, 7) evaluating new and existing chemicals for their ability to cause potential adverse human health and environmental effects, and to require the gathering of data on environmental exposure levels, and potential human health and ecological effects, when data are insufficient, and 8) reviewing and analyzing information the pesticide manufacturers submit in support of registration or reregistration to determine that a pesticide will not generally cause unreasonable adverse effects on the environment or to humans. Chemicals that are known or suspected of being endocrine disruptors are included in these mandated activities.

Recently, two environmental laws were enacted that specifically require the testing of pesticides and other chemicals found in or on food or in drinking water sources to determine their "estrogenic or other endocrine effects in humans." The Food Quality Protection Act of 1996 (FQPA) and the Safe Drinking Water Act Amendments of 1996 (SDWA) require the USEPA to, within two years of enactment, develop a screening program using validated test systems to determine whether substances may have an estrogenic or other endocrine effects in humans. The screening program must undergo a public comment period and peer review and be implemented within three years. The laws require that the manufacturers, registrants, or importers conduct the testing of the pesticides and other substances according to the program the USEPA develops. At joint workshops, cosponsored by USEPA, the Chemical Manufacturers Association, and the World Wildlife Fund, a number of assays potentially suitable for assessing EDCs, particularly exerting (anti-) estrogenic/androgenic effects were identified and critiqued (Gray, et al 1997; Ankley et al. 1998).

Based upon input from those workshops and others, the EDSTAC (Endocrine Disruptor Screening and Testing Advisory Committee), an advisory committee to the USEPA on implementation of the FQPA and SDWA, is assembling a battery of assays both for screening and testing potential EDCs that will be used to address the mandates of the FQPA and SDWA. In addition to in vitro gene transcription assays, proposed Tier 1 Screening Tests include mammalian assays such as the uterotrophic test for estrogen and a Hershberger type assay for androgen action, in conjunction with a short term fish reproduction test and an amphibian metamorphosis assay for thyroid-mediated processes. From an ORD research planning perspective, the forthcoming EDSTAC recommendations will be critical because several of the non-mammalian tests proposed screening and testing assays will require some level of research to bring them to the point where they could be considered standard methods.

In summary, to meet the needs of all of its mandates, the Agency, therefore, 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.

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 this reason, the Agency is embarking on initiating a major research effort on endocrine disruptors. 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. 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.

III. RESEARCH ISSUES

Answering the questions posed of the research program in endocrine disruption listed in the ***Introduction*** will entail a coordinated effort by the scientific community, for the scope is exceedingly broad and beyond the capabilities of any one research unit. One function of the CENR Working Group on Endocrine Disruptors is to assist in a partitioning of research functions among the participating agencies so that limited resources are used most effectively. Developing methods for performing hazard and risk characterization of chemicals, quantitating exposure levels and determining environmental fate of chemicals, and developing extrapolation tools have been traditional strong points of the USEPA research program. It is in these areas that we propose as our primary contributions to the overall federal effort on EDCs.

Through the conduct of the research needs workshops of 1995, the USEPA and ORD have provided national leadership in the endocrine disruptor issue through collaboratively fostering the communicative environment across government, private industry, and the public. Several general comments about future research on endocrine disrupting chemicals emanated from the discussions at the aforementioned workshops. These include:

1. The great advantage in bringing together a multi-disciplinary group of scientists representing both the human health and ecological concerns to help identify common issues;

2. Because exogenous endocrine disrupting chemicals must interact at some level with the natural receptor ligands within the body, and because the concentrations of the natural ligands are maintained within life-cycle dependent narrow limits suggest that the timing of exposure is a very significant factor in any assessment;

3. Many EDCs are persistent in the environment and bioaccumulate, and exposures are widespread throughout the entire globe;

4. The mechanistic basis of the interaction with biological systems presages the induction of subtle effects at low doses that must be interpreted as to whether the effects are adverse or not.

In general, it was felt that linking specific exposures to specific effects in the general environment would often be difficult due to the complexities of exposure, the latency of the effects, and the at times subtle nature of the outcomes. Such considerations will have significant impact on the types of research activities necessary to adequately confirm or refute the central hypothesis. Ten broad categories of research needs were identified: basic research, biomarkers, database development, exposure determination, exposure follow-up, mixtures, multi-disciplinary studies, risk assessment methods, hazard identification, and sentinel species**.** Processes that should receive particular attention include are reproduction, development, and immunocompetence. .

There is a pressing need to identify the extent of the chemical universe of concern. This clearly cannot consist of testing all chemicals in long-term chronic assays with multiple species. Tools that should be quite useful include short-term *in vitro* and *in vivo* assays as well as structure-activity relationship models, which in virtually all cases require further development and validation with multi species chronic toxicity tests. As noted in Section II, Congress has mandated

the USEPA to develop a chemical program for environmental estrogens and other endocrine disruptors as deemed necessary by August 1998. The results of screening exercises using these types of tools could be linked to key exposure data, such as production volume, persistence, etc. to help identify chemicals of greatest concern and to provide focus for a monitoring program. These types of screening tools would play significant roles in both prospective and retrospective assessments of the human health and ecological risks of EDCs. A key consideration, of course, in developing these types of methods/models is the ability to link results obtained in suborganismal systems to organismal-level effects.

To better assess the ecological risks of EDCs, work needs to be done to define linkages between potential measures of effect (usually made at the level of the individual) and assessment endpoints (which typically are at population and community levels). Similarly, linkages between these measures at different levels of biological organization need to be better defined. For example, induction of vitellogenin in male fish appears to be a very specific response to exposure to estrogen mimics, however, it is unclear what this means in terms of reproduction. The basic challenge in this research area is to identify those measures that are indicative both of exposure to EDCs and predictive of their effects in populations. Furthermore, we must develop a better definition of "normal" with respect to endocrine-regulated processes in commonly tested, or monitored, species relative to effects manifested at the population level (e.g., the degree to which circulating levels of sex steroids need to be altered before reproductive success is threatened). Steps need to be taken to adapt existing assays used for ecological risk to incorporate exposure during key developmental windows, and to ensure assessed of relevant endpoints for EDCs.

A major issue for endocrine disruption that must be addressed is the need to define what constitutes an “adverse” health effect, especially considering the multiple levels of biological observation (e.g., molecular to community level) at which effects can be observed. According to the USEPA’s interim position (Crisp et al, 1997), the Agency does not consider endocrine disruption to be an adverse endpoint *per se*, but rather to be a mode of action potentially relating to other outcomes, for example, carcinogenic, reproductive or developmental effects, routinely used in reaching regulatory decisions. The document goes on to state that “In general, due to the precise yet adaptable control mechanisms and the intertwined nature of hormonal balance, modest amounts of chemical exposure seldom compromise normal physiological functions. Fluctuations of hormone concentration and receptor activities, by design, absorb some of environmental and physiological challenges to maintain homeostasis in adults. Only when the equilibrium control mechanisms are overwhelmed do deleterious effects occur. An important question is whether homeostatic mechanisms are operative in the embryo and fetus.” Therefore, an important component of the research program must be to understand when the homeostasis border is crossed, and how this changes as a function of life stage and/or reproductive strategy. In terms of ecological risk assessment, adverse effects are most often defined in the context of decreased populations and, less frequently, changes in community structure. Metrics considered at the individual level that infer likely trends in population dynamics most commonly are, or related to, survival, growth and reproduction. Thus, chemical exposures that negatively affect these endpoints are considered adverse. Unfortunately, endpoints such as survival, growth and reproduction are fairly generic, in that they typically do not reflect specific MOAs (modes of action) in terms of impact on any particular endocrine system. Endpoints that do reflect MOA of concern generally occur at the suborganismal level, and often may not be directly translated into negative (i.e., adverse) effects at the level of the individual. Yet, changes in the status of systems at the molecular and cellular levels can be highly effective indicators, not only of MOA, but of possible adverse effects at higher levels of organization that may not be immediately manifested. Because of this, the need to

understand the effects of EDCs at multiple levels of biological organization is critical, particularly in terms of defining adverse effects as a function of a specific MOA.

Seldom, if ever, do organisms actually encounter individual endocrine disrupting chemicals in the environment, especially because of the potential for some chemicals to be persistent and to bioaccumulate. In the development of specific research activities contained in the next section, specific attention is given to the need to address the impacts of real world environmental situations in terms of simultaneous (or sequential) exposure to multiple EDCs. While this is noted in only a single issue, it should be emphasized that the concern for mixtures transcends virtually ever other activity that is contained in this research plan.

Available measures of effects, measures of exposure, and measures of organisms and ecosystem characteristics for ecological risk assessment need to be adapted to classes of organisms that have received little attention in terms of traditional toxicity test methods/approaches, such as amphibians, non-teleost fish, passerine birds, etc. Two objectives are addressed here: 1) better development of a comparative endocrinology/toxicology database and 2) better definition of baseline conditions for general processes and specific endocrine function. Without this, the usefulness of comparative endocrinology as a basis for assessing the ecological risk of EDCs is significantly decreased. To characterize the relative risks of EDCs from an ecological perspective, it is necessary that there be a high degree of consistency in data collected. This becomes critical in terms of coordinating existing monitoring programs so that: 1) biological endpoints should include effects that are indicative of the impact of EDCS on individuals and populations, and 2) chemical characterization should include those xenobiotics suspected to exert toxicity through endocrine axes. Moreover, ideally there should be overlap of measurements made across different monitoring efforts. This type of coordination is not necessarily a research issue, but is very important from the standpoint of a coherent approach to risk assessment and management decisions concerning EDCs.

If future health effects and exposure studies conclude that humans and the ecosystem are at significant risk due to exposure to EDCs, research on how best to lower or eliminate the risk will be needed. This research should be directed at managing the risks associated with high exposure pathways. First, a survey should be conducted to characterize the important types of locations or industrial processes where EDCs are released into the environment. For example, the majority of the mass of EDCs may enter the environment via pesticide use in agriculture, or via waste water effluents from certain types of chemical industries. Second, unreasonable risk must be reduced through various risk management tools, many of which must be developed or fine tuned for EDCs. For example, much of the risk may be associated with high concentrations of EDCs hazardous waste sites, such as in soils at Superfund sites, or in contaminated sediments. Risk-management research associated with this scenario should concentrate on effective means of destroying or containing EDCs at these sites. Alternatively, much of the risk associated with EDCs may be linked to exposure associated with chemical plants where the use of or production of EDCs result in exposure to workers or the neighboring ecosystem. In this case, risk management research should focus on engineered controls to minimize exposure to workers and pollution-prevention strategies to reduce the use or production of EDCs.

IV. RESEARCH APPROACH AND ACTIVITIES

Within this Chapter, specific research projects for biological effects and exposure research have been organized following the research strategy matrix developed for endocrine disruption in the ORD Strategic Plan (Appendix III). To provide a firmer basis for risk characterization, a third category, Linkage of Exposure and Biological Effects, was formulated to emphasize the critical need to integrate these main components of the research program. In many cases, the biological effects research cuts across human and ecological research problems and a coordinated, interdisciplinary approach is required. For example, EFF.1.1 (QSAR (Quantitative Structure-Activity Relationships) Models of EDC Modes of Action) is targeted at providing tools of equal utility for the prediction of both health and ecological effects, as well as the targeting of exposure assessment efforts. It is important to note that neither the Issues nor subissues are presented in priority order.

For each "Issue" or activity, a brief description, a priority (high, medium or low, plus a priority score assigned by the planning committee (see below) , and the focal area of the research (health, ecological, exposure, or some combination) is provided. To place the activities into a hypothesis-oriented context, each individual issue was evaluated according to which of the nine overarching questions stated in the Introduction it addressed. This cross walk, which is provided in Appendix IV, clearly demonstrates the areas of greatest uncertainty in our understanding of endocrine disruption, as two questions (What effects are occurring in exposed human and wildlife populations? and How and to what degree are humans and wildlife populations exposed to EDCs?) dominate in terms of the primary driving forces of the activities. The need to identify chemical classes of concern, to develop extrapolation tools, to understand the effects of multiple exposures and to understand the sources of exposure are most evident as secondary questions addressed by the issues, and illustrate the extent to which these questions transcend many of the proposed activities. A time line in which individual issues should be addressed is presented in Appendix Va-c, while the derivation of the overall priority and priority score is contained in Appendix VI. The priority score was based on the evaluation of each issue against five major ranking criteria (Programmatic Relevance, Magnitude of Biological Concern, Potential Impact of Outputs; Sequencing of the Research, and Feasibility of Technical Success) as judged on a scale of 1 (most important) to 3 (less important) by members of the planning committee. The priority score is a non-weighted sum of all ranks on all factors, and is adjusted such that the issue with the lowest score (highest overall priority) received a value of 1.

Throughout the reviews of this research plan, a number of lower priority items were eliminated, leaving a high proportion of issues ranked "high." Although these issues are all within the mission of ORD, the resources to successfully address all of them are unlikely to be available. Hence, there will be need to be selective in developing the actual implementation plans by the individual Laboratories and Centers. When doing this, it will be important to bear in mind that the most critical uncertainties lie in determining whether humans and wildlife populations are being impacted by levels of endocrine disruptors in the ambient environment, and what are the sources of those exposures. The final appendix that is presented (Appendix VII) arrays the EDC projects according to the risk assessment paradigm and is consistent with presentation under the Government Performance and Results Act (GPRA). Under GPRA, each federal agency was required to submit, by September 30, 1997, to the Office of Management and Budget and Congress a five year strategic plan. The plan was required to include:

- a comprehensive mission statement
- general goals and objectives, including outcome-related goals and objectives
- a description of how the goals and objectives are to be achieved
- a description of the program evaluations used in establishing or revising general goals and objectives.

On an annual basis, each agency is required, under GPRA to submit to OMB a performance plan covering each program activity set forth in the Agency's budget that must be consistent with the strategic plan. ORD's research on endocrine disruptors specifically falls under EPA's "Goal 8: Sound Science, Improved Understanding of Environmental Risk, and Greater Innovation to Address Environmental Problems. Objective 3: Emerging Risk Issues. Subobjective 3.2: Endocrine Disruptors."

BIOLOGICAL EFFECT STUDIES:

Research on the pathogenesis of EDC-induced adverse health effects includes studies to identify EDCs, describe dose response relationships, and evaluate the impact of EDCs on developmental, reproductive, immune, neurobehavioral and endocrine system functions in young and mature organisms. Studies that examine the latent effects of EDCs following exposure during a critical life stage should be of particular focus. Approaches for obtaining this information include studies of humans, laboratory animals, and wildlife (including invertebrate, fish, amphibian, reptile, avian, and mammalian species) exposed to suspected EDCs. The broad objectives of the research plan to evaluate the ecological risk of EDCs are twofold: 1) determine their risk relative to other stressors on populations and communities, both from a prospective and retrospective standpoint, and 2) develop and/or modify methods for testing and evaluating chemicals and environmental samples to ensure that those exerting toxicity through specific endocrine axes will be characterized. Both objectives require a reduction in uncertainty in prediction of risk across levels of biological organization, including better linkage of measurement and assessment endpoints. They also require an increased understanding of processes and species at risk, including an understanding of modes of action. General research needs and specific research approaches necessary to meet these needs are listed below. It should be noted that the specific research approaches usually address more than one of the general issues identified below, much of the necessary research can (or should be) interrelated.

EFFECTS ISSUE 1. DETERMINE THE CLASSES OF CHEMICALS THAT ACT AS EDCS AND THEIR POTENCIES.

EFF.1.1 DEVELOPMENT OF *IN VITRO*/*IN VIVO* SCREENING METHODS AND QSAR MODELS OF EDC MODES OF ACTION, FOR EXAMPLE, RECEPTOR BINDING, GENE ACTIVATION AND ENZYME INHIBITION ENCOMPASSING VERTEBRATE AND INVERTEBRATES.

Short-term *in vitro* and *in vivo* methods need to be developed to screen for EDCs with specific modes of action (MOAs), including alterations in hormone levels and induction of specific ligand inducible genes (e.g., vitellogenin). The results of these types of assays should be calibrated against effects on integrated processes (development, reproduction) at the level of the individual. Quantitative structure-activity relationship (QSARs) models need to be developed for EDCs for key events such as receptor-binding of xenobiotics, transcriptional activation, and posttranscriptional events to serve as screening tools for evaluating the chemical universe. Endocrine-mediated processes related to reproduction and development should be highlighted. In addition to being useful tools for prospective risk analyses, QSAR models can provide critical insights in retrospective evaluations of risk. For toxicants that are metabolically activated, QSAR models would allow one to identify the potentially active metabolite for *in vitro* testing.

High Priority (Adjusted Score from Appendix VI=1) , Human Health and Ecological Focus

EFFECTS ISSUE 2. EVALUATE CURRENT TESTING AND MONITORING PROCEDURES FOR ADEQUACY OF ASSESSMENT OF THE EFFECTS OF EDCS.

EFF.2.1 DEVELOPMENT, STANDARDIZATION AND UTILITY OF *IN VITRO*/*IN VIVO* TEST METHODS TO IDENTIFY ENDOCRINE DISRUPTING ACTIVITY.

Present test methods used to assess toxicity provide little information on the mode of action of a chemical or the potential to produce latent effects after developmental exposure. For human health effects, the proposed improvements to the USEPA multi generational test will provide improved EDC detection for hazard ID and dose-response, but these tests are expensive and take years to complete. However, multi generational tests are seldom used for ecological risk assessment. Hence, short-term tests are also needed for detection of EDC activity. Efforts should focus on those modes of action known to be exhibited by relevant environmental chemicals, including estrogenicity, anti-androgenicity, Ah-receptor binding, and anti-thyroidal activity. In addition to initial ligand receptor binding, endpoints should include EDC induced changes normal endocrine mediated transcriptional activation. Due to the USEPA's Congressional mandate and the direct regulatory implications of this area, research planning should be done in coordination with the USEPA regulatory program offices.

High priority (Adjusted Score from Appendix VI=13), Human and Ecological Focus,

EFFECTS ISSUE 3. DETERMINE THE SHAPES OF THE DOSE-RESPONSE CURVES FOR EDCS AT RELEVANT EXPOSURES AND THE TISSUE LEVELS ASSOCIATED WITH ADVERSE EFFECTS.

EFF.3.1 MODE-OF ACTION STUDIES FOR DEVELOPMENTAL AND REPRODUCTIVE, CENTRAL NERVOUS SYSTEM, AND NEUROENDOCRINE TOXICITY IN LABORATORY ANIMALS FOLLOWING DEVELOPMENTAL EXPOSURES.

For both between-chemical and between-species extrapolation, a more complete understanding of specific chemical MOA is required. Since many EDCs elicit toxicity through receptor-based interactions, these types of chemicals should be particularly amenable to MOA research. Other endocrine disrupting agents may act through membrane receptors, enzyme alterations, and other non-nuclear receptor based pathways. Research in this area should be tightly coupled not only with QSAR analyses, but also with comparative endocrinology and toxicology. The emphasis of this research should be on mechanisms that operate in the low end of the dose-response curve, and the development of quantitative descriptions of rate limiting steps for later incorporation into formal BBDR (Biologically Base Dose-Response) Models.

High Priority (Adjusted Score from Appendix VI=23); Human and Ecological Focus;

EFF.3.2 DEVELOPMENTAL AND ACUTE EFFECTS OF EDCS ON IMMUNE FUNCTION OF LABORATORY ANIMALS.

Numerous reports of immune alterations have been reported in EDC exposed wildlife populations and children. Studies of EDCs in animal models are needed to verify these effects under controlled conditions.

High/Medium Priority (Adjusted Score from Appendix VI=27); Human and Ecological Focus

EFF.3.3 STUDIES USING ANIMAL MODELS OF SUSPECTED EDC-INDUCED HUMAN DISEASES SUCH AS REDUCTIONS IN SPERM COUNTS, AND INCREASED INCIDENCES OF INFERTILITY, TESTICULAR CANCER, HYPOSPADIAS, ENDOMETRIOSIS, BREAST CANCER AND PROSTATE CANCER.

For several of the aforementioned conditions, adequate animal models have not been developed and validated. Validated animal models can greatly enhance the process of identifying the potential of EDCs to produce diseases in the human population. Specifically, research is needed on models of testicular cancer, endometriosis, breast cancer and benign prostatic hyperplasia and prostate cancer. Once these animal models are developed, they can be used to test hypotheses that low, environmentally relevant doses of EDCs can induce similar conditions in humans.

High priority (Adjusted Score from Appendix VI=10); Human Focus;

EFF.3.4 PHARMACOKINETIC STUDIES OF HIGHLY RELEVANT EDCS WITH PARTICULAR FOCUS ON CRITICAL PERIODS OF DEVELOPMENT OF REPRODUCTIVE, NEUROENDOCRINE AND IMMUNE SYSTEMS.

The lack of validated PK models to predict transplacental and breast milk deposition of EDCs in fetal and neonatal target organs limits our ability to determine when adverse concentrations would result as a consequence of chronic and acute maternal exposures. We anticipate that PK models for developmental EDC exposure can be readily developed and would provide extremely useful predictive information for characterizing dose-response relationships on the basis of delivered dose to the target tissue.

High Priority (Adjusted Score from Appendix VI=24); Human Focus;

EFF.3.5 DEVELOPMENT OF BIOLOGICALLY BASED DOSE-RESPONSE MODELS FOR HIGHLY RELEVANT EDCS WITH PARTICULAR FOCUS ON CRITICAL PERIODS OF DEVELOPMENT OF REPRODUCTIVE AND IMMUNE SYSTEMS AND THE

CNS.

Understanding the various steps in the pathogenesis of adverse effects is key to reducing the uncertainties in extrapolation of animal test data to humans. BBDR studies should be linked to the development of pharmacokinetic models described in EFF.3.4. Incorporating modes of action in quantitative risk models is essential to understanding the risks of low dose exposures, which should be the primary area of emphasis for this research area. Although these models are of high relevance and great potential impact, they, are also extremely complex to construct and represent relatively high risk research projects.

High/Medium Priority (Adjusted Score from Appendix VI=34); Human Focus;

EFF.3.6 STUDIES ON THE MODES OF ACTION OF EDCS ON CELLULAR, MOLECULAR, NEUROENDOCRINE CNS FUNCTION IN PUBERTAL AND ADULT LABORATORY RODENTS.

Steroid and thyroid hormones are important in the regulation of puberty in developing animals and in modulating CNS function in adults. Therefore, these processes are potentially sensitive to alteration by EDCs and research is needed to characterize the extent of the impact relative to other endpoints of known responsiveness.

Medium priority (Adjusted Score from Appendix VI=37); Human Focus;

EFFECTS ISSUE 4. DESCRIBE THE NORMAL ENDOCRINE PROFILES IN WILDLIFE SPECIES.

Little is known about normal variability in different wildlife species relative to most endocrine systems or endocrine-mediated endpoints such as temporal variations in basic hormonal profiles and developmental and fecundity rates. A recent example of how this can be a problem arose in a study in which seeming differences in plasma sex steroids in fish collected from several field locations were reported, but it was unclear whether these differences were due to site-specific (e.g., contaminant) factors, or normal temporal variations in the test species (e.g., correlated with reproductive cycles). Data of this type can be collected in routine (field) monitoring experiments, or in more focused comparative physiology/toxicology studies. In any case, because of the commonality in endocrine function across (at least vertebrate) species, comparative studies are particularly important, because they help form the technical basis for extrapolation across species. For example, if it is possible to establish that a chemical that is estrogenic in one class of vertebrates also is likely to exert estrogenic effects in other classes, this is critical information in terms of screening. In fact, this is a major (but as yet generally unproven) supposition in the design of screening assays for EDCs by the EDSTAC. Thus, it is important that the technical underpinnings of the assumption of commonality in response across species be fully assessed. Although basic endocrinology research has been, and continues to be funded to some extent by other Federal agencies (e.g., NSF), this type of research generally has not been systematic enough to serve as a basis for the type extrapolations needed by EPA to deal with EDCs. This does highlight, however, the need for continued coordination among Federal agencies with respect to

EDC-related research.

EFF.4.1 DEFINITION OF "BASELINE" ENDOCRINE STATUS IN WILDLIFE POPULATIONS AND THEIR LABORATORY SURROGATES.

At present, we are uncertain about the normal values of many EDC-influenced factors in fish and wildlife populations. These include elements such as intracellular receptor numbers, and circulating hormone concentrations, developmental rates, and reproductive capacity, and population sex rations, and age structures. This type of information is critical not only to extrapolation in prospective risk assessments, but effective monitoring in retrospective analyses.

High Priority (Adjusted Score from Appendix VI=26), Ecological Focus,

EFF.4.2 STUDIES IN COMPARATIVE ENDOCRINOLOGY AND TOXICOLOGY.

Basic endocrine system structure and function can be remarkably well conserved across phyla; however, many key, and potentially sensitive species have not been evaluated with respect to endocrine function, particularly from a toxicology perspective. Thus, baseline research on specific endocrine systems related to reproduction, development, and immunocompetence across several representative classes of animals could reduce uncertainty associated with among species extrapolations. These types of studies should specifically include those organisms which historically have received little attention in terms of environmental toxicology, and/or are experiencing declines in populations. Part of this task would be to use laboratory studies to confirm EDC-related hypotheses generated from field studies. The key for using comparative endocrinology/toxicology data to extrapolate among species will be the concurrent development of biologically based dose-response and PB-TK models; this modeling perspective is needed in recognition of the fact that it is impossible to test every permutation of chemical and species.

Medium Priority (Adjusted Score from Appendix VI=33), Ecological Focus,

EFF.4.3 STUDIES ON THE ROLE OF HORMONES IN SEXUAL DIFFERENTIATION OF NONMAMMALIAN SPECIES AND THE EFFECTS OF EDCs ON THIS PROCESS IN INVERTEBRATE, AVIAN, REPTILIAN, AMPHIBIAN AND FISH SPECIES.

Numerous alterations of reproduction have been attributed to EDC exposure during development of wildlife species. It is often impossible to determine the biological plausibility of these speculations because the hormonal regulations of sexual differentiation are not completely, or are poorly understood in nonmammalian vertebrates.

Medium Priority (Adjusted Score from Appendix VI=36); Ecological Focus;

EFFECTS ISSUE 5. EXTRAPOLATE EFFECTS AT THE INDIVIDUAL LEVEL TO POPULATIONS FOR FISH WILDLIFE SPECIES.

There is a need to identify/validate measurement endpoints that are indicative of the effects of EDCs, not only at individual and sub-organismal levels, but at the level of populations and communities. Linkages among proposed measurement endpoints are uncertain; for example, at the level of the individual, the impact of induction of vitellogenin in male fish exposed to estrogenic chemicals on reproductive success is not known. Similarly, impacts on endocrine-mediated processes at the level of the individual can be difficult to translate into population-level effects. This latter linkage also is key to defining relationships between measurement and assessment endpoints in ecological risk assessments. In this plan, we identify general criteria to consider in terms of species selection (e.g., those that have received little attention in the past, but might be experiencing population-level declines); however, these recommendations should be taken in the context of specific research issues. The clear implication is that not all wildlife species can or will be considered in terms of ecological research with EDCs; this is logistically impossible. Therefore, there needs to be an emphasis on species selection which best enables extrapolation of potential EDC effects across animal species/classes.

EFF.5.1 BIOASSAYS FOR EVALUATING INTEGRATED EFFECTS.

Many of the standard toxicity tests currently in use for regulatory activities such as product registration, monitoring environmental samples such as sediments, effluents, etc., are inadequate for detecting some of the key reproductive, developmental, and immunological effects of EDCs. Problems include use of species that are insensitive to specific EDCs, lack of exposure during critical windows of sensitivity, and failure to consider latent and/or EDC-specific effects. These tests should be modified where possible and/or new assays developed as needed. When selecting species/endpoints for assessing effects of EDCs, care should be taken to ensure that the information gathered is useful for predicting population-level effects. This effort should be coordinated with activities covered under EFF.5.2 and LNK.2.2 so that as measurement endpoints are developed to the level of the individual, they are then evaluated at the population/community levels.

High Priority (Adjusted Score from Appendix VI=26); Ecological Focus;

EFF.5.2 EVALUATION OF EFFECTS AT POPULATION AND COMMUNITY LEVELS.

To effectively utilize measurement endpoints collected at lower levels of biological organization (e.g., suborganismal, individual) in ecological risk assessments, it is necessary to translate these results into impacts at population and, if possible, community levels. Moreover, there may be measurement endpoints sensitive to the effects of EDCs both at population (e.g., sex ratios) and community (e.g., guild structure) levels. In either case, further research is needed to quantify EDC impacts at these higher levels of organization. Experimental systems that can prove particularly useful for this type of work include microcosms and mesocosms.

Although EPA no longer utilizes mesocosm data as part of the pesticide registration process, mesocosms are useful in the context of specific tests of experimental hypotheses. The use of mesocosms to test EDC effects on populations in a true environmental setting offers a powerful and cost-effective alternative to full-scale field studies.(Note that as EFF.5.1 proceeds, this would become a high priority).

High/Medium Priority (Adjusted Score from Appendix VI=22); Ecological and Exposure Focus;

EFF.5.3 DETERMINATION OF SENTINEL SPECIES

Appropriate sentinel species for monitoring need to be identified. Selection of sentinel or keystone species is highly context-specific, i.e., research planning should not be based upon selection of any particular class/species of animals, but on "problem" chemicals/sites or toxicological endpoints/issues. From that, appropriate animal models for research can be identified. Considerations for their selection should include: 1) representation of different life history strategies (both simple and complex); 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 (i.e., widespread or local) of a species. Surrogate (non-endangered, noncommercial) species for study need to be identified for which effects can be related to endangered or commercially important species.

High priority (Adjusted Score from Appendix VI=26); Ecological Focus;

EFFECTS ISSUE 6. CHARACTERIZE THE EFFECTS OF EXPOSURE TO MULTIPLE EDCS.

EFF.6.1 SYSTEMATIC STUDIES OF THE INTERACTIONS OF LOW, RELEVANT DOSAGE LEVELS OF MIXTURES OF RELEVANT EDCS.

In most cases, humans and other organisms are exposed to relatively low doses of mixtures of chemicals with EDC activity. It is unclear at the present how such mixtures will behave. While some scientists have reported that effects will typically be additive in nature, others have reported that estrogens and anti-estrogens will cancel one another out, while some other studies indicate that EDCs act synergistically. While this is the only issue devoted exclusively to the study of mixtures, the issue of multiple exposures is impacts on many of the other issues identified in the this plan as evidence by cross walk of issues and overarching questions presented in Appendix IV.

High Priority (Adjusted Score from Appendix VI=16); Human and Ecological Focus;

EXPOSURE ASSESSMENT STUDIES:

The pathways between source and exposure to EDCs are complex. Many of the suspected EDC's studied to date are organic compounds or organic forms of a few heavy metals that are persistent, can bioaccumulate, and biomagnify in the food chain. Knowledge of the nature of these factors is basic to predicting future exposures and the efficacy of exposure prevention strategies. For example, slight variations in chemical form and physicochemical characteristics (e.g., planarity, isomerization, and polarity), may manifest themselves in various ways that affect exposure (e.g., differences in transport and routes of exposure, increased or decreased bioavailability, changes in exposure pathways, potential for atmospheric and hydrological transformation, and fate).

Another major challenge is the need to understand complex exposure patterns, rather than simple net annual exposure. As discussed in the Biological Effects section, there are certain to be windows of vulnerability to exposure because of temporal and seasonal patterns of endocrine functions. For example, exposure to one EDC during an animal's mating season may have significant effects, whereas for another EDC, exposure during gestation may be more crucial. Therefore, ORD will conduct exposure research of endocrine disrupting substances within the Agency's risk assessment framework, and will explore methods and models to measure and to predict exposure to these substances.

At the outset, ORD's exposure research will emphasize three areas. The first involves better physico-chemical characterization of a few known or highly suspect EDCs to obtain a better near-term understanding of the potential effects of chemicals of current concern. The second area is developing pathway models (e.g., compartmental transport, fate, or transformation) for chemicals which are likely to be endocrine disruptors. In both of these areas, existing information in the public literature or in the USEPA data files will be evaluated to establish current capabilities, and to identify data gaps and uncertainties before new parameters and models are developed. The third area is to reduce uncertainties in the flux of EDCs in and out of sediments, a major exposure source for many bioaccumulative compounds.

EXPOSURE ISSUE 1: DEVELOP A FRAMEWORK TO CHARACTERIZE AND TO DIAGNOSE AND PREDICT ECOLOGICAL AND HUMAN EXPOSURE TO EDCs.

EXP.1.1 IDENTIFICATION AND EVALUATION OF CLASSES OF SUSPECT EDCs TO WHICH HUMANS AND ECOSYSTEMS ARE LIKELY TO BE EXPOSED IN THE ENVIRONMENT.

The physicochemical attributes of substances associated with endocrine disruption, which occur with suspect EDCs in the environment, or that have transport, transformation, and fate characteristics similar to EDCs need to be systematically characterized. Once distinguishing chemical characteristics have been identified for suspect EDCs, generic categories of attributes may be defined and used to screen new or previously unsuspected substances for EDC potential. Definition of generic categories would also facilitate the development of EDC scenarios and uncertainty distributions for subsequent exposure modeling research. Attributes categories will be updated as additional information becomes available under

Exposure Issue 3 and Effects Issue 1.

High Priority (Adjusted Score from Appendix VI=9); Exposure Focus;

EXP.1.2 DEVELOP, SELECT AND APPLY COMPARTMENTAL MODELS TO ENHANCE UNDERSTANDING OF HOW EDCs BEHAVE IN ENVIRONMENTAL MEDIA AND TO PREDICT EDC EXPOSURES.

The environmental media through which EDCs are transported can be treated as compartments in mathematical models. Research is needed to identify the major compartments through which EDCs move, change, accumulate, and reside. The models will then account for the persistence, bioaccumulation, bioconcentration, and biomagnification of chemicals within each environmental medium according to the physicochemical properties identified in EXP.1.1. Models that diagnose or predict the movement of EDCs from source to receptor will be applied, adapted, or developed to simulate EDC movement and change in the environment. Geographic scale will play a crucial role in model selection. There may be a need for predictive capability on the micro scale (e.g., occupational, residential), field scale (e.g., production plant emissions), regional scale (e.g., farm applications impacting watersheds) and global scale (e.g., long-range transport with exposure at remote sites). For human exposure, the initial focus should be on the micro-scale, whereas for ecosystems, regional models are needed.

High Priority (Adjusted Score from Appendix VI=28); Exposure Focus;

EXPOSURE ISSUE 2: PROVIDE ADEQUATE (SENSITIVE, RELIABLE, AND INEXPENSIVE) TOOLS TO ESTIMATE EXPOSURE TO EDCs.

The Science Advisory Board's 1995 report to the USEPA, *Beyond the Horizon: Using Foresight to Protect the Environmental Future* said, "EPA should attempt to identify, monitor, and analyze the most potentially serious of these unconventional stressors, and then assess their adverse effects on human health and ecological systems." A major shortcoming of analytical environmental chemistry today is the inability to monitor for non-volatile/non-extractable/thermally labile (unconventional) organic pollutants, which may often be the most prevalent types and amounts of compounds in many environmental samples. A true, rational assessment of ecological and human risk can be obtained only with the ability to characterize and monitor this problematic, unknown fraction. Very few methods address the extraction, characterization, and identification of EDCs in tissue, either plant or animal, and this may very well end up being the limitation of most of the existing methodologies. An initial subelement under this Issue will be to gain a better understanding of our ability to collect, prepare, and analyze environmental and biological samples for a few EDCs selected based upon toxicity and bioavailability to select organisms, and presence and persistence in the environment.

EXP.2.1 IMPROVED UNDERSTANDING OF TRANSPORT, TRANSFORMATION, AND FATE OF EDCs IN ENVIRONMENTAL MEDIA

Many of the suspect EDCs identified to date are low solubility, neutral organic compounds that are highly sorbed to organic carbon phases of sediments, suspended particles in the water column, airborne particulate matter and soil. While currently available predictive tools (based on hydrophobic solution theory) are reliable for estimating movement and change of some EDCs between the sediment and water column, comparable tools for estimating kinetics of sorption and desorption processes are lacking. Research is needed to develop models to predict these processes for ionizable EDCs under varying pH and ionic strength conditions. In addition to sorption kinetics, the biological relevance of EDCs should be better understood. This includes the interactions of microbial, chemical, and physical processes. The interplay of theses processes should be an overarching theme for any study of fate in the environment. Transformation processes of significant relevance to EDCs include the action of chemical and biological reductants in anaerobic and low dissolved oxygen environments, such as an assessment of the role of sulfur-based nucleophiles in reducing the sulfur in the herbicide atrazine, and the passage of EDCs among abiotic and biotic systems, such as sediment flora and gut, gill, and other benthic fish tissues.

High Priority (Adjusted Score from Appendix VI=28); Exposure and Ecological Focus;

EXP.2.2 DEVELOP MEASUREMENT METHODS FOR EDCs IN ANIMAL AND PLANT TISSUE AND ENVIRONMENTAL COMPARTMENTS

To understand the risks of EDCs, improved field methods are necessary to characterize their fate and transport. Methodologies must be developed and used to optimize monitoring and analytical throughput in all environmental media, with high sensitivity. For example, piscine populations exposed to sewage discharge plumes have shown intersexuality; however, causality has not been established. To improve weight of evidence, research is needed to improve sample extraction methods, extract preconcentration, chromatographic separation, and analyte detection.

High Priority (Adjusted Score from Appendix VI=10); Exposure and Ecological Focus;

EXP.2.3 DEVELOP EXPOSURE SCREENING TOOLS AND BIOMARKERS FOR EDCs.

EDC concentrations in human and wildlife tissues and other biological media must be compared to concentrations in the abiotic environment. Promising research has begun in the development of probes for gene expression resulting from EDC binding to hormone receptors in fish and wildlife. Exposures of organisms to EDCs can be detected with good sensitivity by probing for changes in gene expression brought on by hormone receptor binding. Biomarkers of exposure are needed to screen ecosystems for exposures, to improve exposure estimates in future epidemiological

studies, and to assist in developing and verifying human and ecosystem exposure models. These techniques should aid in identifying and characterizing sources and intensity of exposures. This screening and biomarker research will entail collaboration with the pharmacokinetic research described in the Effects Section., and the results will be incorporated into the biotic components of exposure models developed under EXP.1.2.

High Priority (Adjusted Score from Appendix VI=21); Exposure and Ecological Focus;

EXPOSURE ISSUE 3: DETERMINE THE TOTAL ECOSYSTEM AND HUMAN EXPOSURES TO EDCs OF CONCERN.

The previously described exposure research, will substantially increase our understanding of the potential risks from EDCs. It will also identify and prioritize targeted uncertainties requiring further study. For example, the compartmental modeling studies under Exposure Issue 1 may indicate that for chemicals having certain physico-chemical properties, air to water transport is the predominant factor in enhancing exposures to these compounds. If so, more intense research would be needed on atmospheric phase equilibria and deposition of these compounds. Exposure to other compounds may be more influenced by microbes in sediments, suggesting another area for more intense research, but not for others. On a broader scale, effects research may identify a high potency EDC that also potentially has a widespread exposure. This may necessitate an exposure or epidemiological study of this EDC. Gathering reliable data from the field is necessary for direct assessment of EDC exposure, for development and verification of predictive and diagnostic exposure models, and for priority setting for additional study of vulnerable or contaminated sites.

EXP.3.1 STUDY MATERNAL/INTERGENERATIONAL TRANSFER OF EDCs.

For endocrine disruptor modes-of-action, certain stages of development in humans and wildlife present windows of exposure, where the organism is particularly vulnerable to hormonal disruption. Depending upon their reproductive strategy, developing organisms may be exposed directly to EDCs, or may receive exposure via the egg yolk, or may be exposed via transplacental and lactational transfer. In most cases, there is a dearth of information regarding the magnitudes of exposure that developing invertebrates, amphibia, fish, reptiles, birds, and mammals face concerning EDCs. The uptake, storage and magnification of EDCs in the parental organisms and the amount of EDCs transferred to the embryonic and neonatal animals should be studied. Selection of animal models should be based upon reproductive or physiological characteristics, such as placental mammals, life cycle, developmental stage at hatching, and sex determination mechanisms. The results will be incorporated into the exposure model that include biotic compartments of exposure models developed under Exposure Issue.

Medium Priority (Adjusted Score from Appendix VI=35); Exposure, Human Health

and Ecological Focus;

EXP.3.2 STUDY BIOACCUMULATION OF EDCs IN FOOD WEBS.

There is a need for field studies to measure available human and wildlife tissue and other biological media for EDCs to compare concentrations in the abiotic environment to concentrations in the food chain. The use of the top carnivores and higher level species does not obviate the need for the study of bioavailability, and concentrations of EDCs in lower trophic levels. However, it provides a framework for the study of the entire ecosystem, and baseline data regarding the build up on EDCs. These considerations will be incorporated into the pilot studies described in the next section. This task can provide data on EDC levels in wildlife tissues that can serve as an ecological counterpart to the human data collected in EXP3.3.

Medium Priority (Adjusted Score from Appendix VI=34); Exposure and Ecological Focus;

EXP.3.3 POPULATION BASED DISTRIBUTIONS OF EDC EXPOSURES

There is a need to determine the distribution of exposures to endocrine disrupting chemicals in the environment to evaluate the proportion of the general population that may be at risk to adverse health effects. Consideration should be given to ensuring that existing programs such as NHANES (National Health and Nutrition Survey) include monitoring of the important classes of EDCs such as phthalates, phenols, phytoestrogens, organochlorines, and other pesticides and herbicides. The availability of such information would tell us whether the general population is exposed and whether exposure characteristics differ among subpopulations.

High Priority (Adjusted Score from Appendix VI=22), Exposure and Human Focus,

LINKING BIOLOGICAL EFFECTS, EXPOSURE AND RISK MANAGEMENT RESEARCH:

One of the potential strengths of the research program within ORD is to bridge the gaps between effects, exposure and risk management-based research through interaction of the various centers and laboratories. Since the extent of the need for risk management research is unknown at this time, the majority of this section discusses a linked effects and exposure research program.

We have attempted to develop a basis upon which to formulate an integrative effects/exposure program by crafting project areas in which both types of research must work together to accomplish the objectives. We also introduce, in a general sense, risk reduction issues. The importance of these projects are not in accordance with their position at the conclusion of the Research Issues Section, for it was felt that the groundwork on specific issues relevant to effects and exposure research had to precede this section for full comprehension of the scope of required coordinated effort. The efforts to address the effects and exposure issues presented in this research plan must be implemented comprehensively. The research results must be linked to ensure that the biological responses in human and wildlife populations can be compared to environmental concentrations and pathway estimates from exposure models and field investigations. In some instances, the scope of the research necessitates that we utilize extramural resources to obtain the expertise needed to either augment our research capabilities (thus requiring cooperative agreements) or assume primary research responsibilities (through the grants program).

Data bases that contain information about EDCs need to be identified and reviewed, and methods identified to improve coordination, reliability, and access by the scientific community. EXP.1.1 and LNK.1.1 will first prioritize potential hot spots and problem areas based upon exposure (elevated concentrations of EDCs) or effects (organisms exhibiting responses possibly related to endocrine disruption). Reliable and standardized data bases are vital in testing effects/exposure hypotheses, and in validating the compartmental, exposure, and effects models. Compartmental models and laboratory studies must be linked to field research by developing mechanism-based dose-response models. Exposure levels observed in the field will be used as a basis for identifying realistic dose ranges in laboratory experiments.

As the EDC research program matures, it is likely that risk management research will need to be added to the linked research activities. Already there is sufficient evidence to conclude that some EDCs present unacceptable risk in limited situations. Ongoing and future health effects and exposure studies may conclude there is larger scale, unacceptable risk of exposure of EDCs to humans and ecosystems. Significant research on how best reduce the risk to acceptable levels will be needed. This research should be directed at managing unacceptable risks associated with high exposure pathways. General risk management approaches that would need specific development for EDCs include (1) removal of high mass sources of EDCs in the environment, i.e., site remediation, (2) pollution prevention to minimize the use, release, or production of EDCs, and (3) engineered controls, i.e., manipulation of exposure, to reduce exposures to humans and the ecosystem to acceptable levels when source removal and pollution prevention approaches are not suitable.

LINKAGE ISSUE 1. INTEGRATE HUMAN AND ECOLOGICAL EFFECTS RESEARCH WITH EXPOSURE RESEARCH WITHIN THE RISK ASSESSMENT PARADIGM.

LNK.1.1 ESTABLISH FRAMEWORKS FOR COMPREHENSIVE EDC INVESTIGATIONS AND ASSESSMENTS

The primary goal of this effort is to identify, characterize, prioritize and assess the potential exposures and effects to selected suspect EDCs through a joint effort of NHEERL, NERL, NRMRL and NCEA. On the assessment side, a framework will be developed to integrate experimental and observational data for both human health and ecological effects in order to conduct holistic risk assessment for EDC modes-of-action. Among other issues, this effort will consider how best to incorporate modes-of-action, multiple chemical exposure, critical life stages, criteria for adversity, dose-response relationships and inter-species comparisons. Such tools needed as the knowledge base on endocrine disruptors increases over the next few years. From a review of the current state of knowledge and databases for several suspect endocrine disruptors (i.e., physicochemical data, fate-and-transport information, anticipated human and ecological effects, and exposure), an initial risk characterization of a few chemicals within a specific class will be collaboratively developed. A framework that characterizes potential exposure pathways and effects will be used to generate probability matrices that (1) identify potential routes of exposure and health outcomes and (2) array suspected endocrine disruptors against potential exposure pathways and health outcomes. Such efforts should facilitate the evaluation of causality of reported adverse health effects. This database will also provide the basis for clearly identifying major gaps in both exposure and effects relative to endocrine disruptors, establish a strong linkage between the needs to identify and characterize source distributions, provide the basis for prioritizing research efforts proposed for assessing exposures and effects identified in integrated field assessment (LNK.2.2), and provide a framework for integrated both exposure and effects results to develop appropriate risk assessment and risk management strategies.

High Priority (Adjusted Score from Appendix VI=24); Exposure, Ecological and Human Focus;

LINKAGE ISSUE 2. DETERMINE CLASSES AND CONCENTRATIONS OF EDCs ASSOCIATED WITH OBSERVATIONS OF ENDOCRINE DISRUPTION.

LNK.2.1 EVALUATION OF EXISTING DATA AND CURRENT PROGRAMS.

Efforts are needed to (1) develop a database of chemicals (and their effective concentrations) known to cause, or strongly suspected of causing, reproductive and developmental effects via an EDC related mechanism, (2) identify loading estimates for determining exposure to potential EDCs; (3) identify appropriate reference sites; and (4) factor into consideration potential sensitivities of specific populations given loading estimates, geographic distribution, and life history traits. These efforts will assist in hypothesis generation and identification of information gaps needed for

implementation of the integrated studies described in other linkage projects. There is a good deal of archived biological and environmental chemistry data that could be used to identify hot spots/problem areas and species at risk. Examples of existing monitoring programs in the U.S. that may be useful include the Environmental Monitoring and Assessment Program (EMAP) of the USEPA, the National Status and Trends Program (BEST) of the NBS, and the National Water Quality Assessment Program (NAWQA) administered by the U.S. Geological Survey. We need to improve our use and dissemination of existing exposure and effects data, as well as the use of specimen banking. Suitable historical control/reference data for assessment of effects must be identified, data must be collected with a high degree of consistency, and effects of EDCs must be explored in individual organisms as well as populations.

High Priority (Adjusted Score from Appendix VI=29); Ecological and Exposure Focus;

LNK.2.2 INTEGRATED EFFORTS ON WILDLIFE AT EDC-CONTAMINATED SITES.

Coordinated effects and exposure measurements are needed for areas suspected to be contaminated with high concentrations of EDCs. Here, biomarker researchers can test screening tools, *in situ* results can be compared to *in vivo* and *in vitro* findings, and biologically plausible hypotheses (exposure and/or effects) can be evaluated. Several specific sites will be selected based upon strong weight of evidence that populations have been affected by exposure to EDCs. This evidence can consist of ecological epidemiology, positive response or exposure screens, historical data (from LNK.1.1) suggesting that EDCs are present in environmental media, or where fate models suggest a hot spot. An ecosystem approach should be adopted and multiple phylogenetic groups and trophic levels should be studied at a given site. The site will be used to test and validate predictive, integrated models that utilize SAR, toxicokinetics, bioenergetics, environmental chemistry, and population ecology, provide a means for testing effects and exposure screening tools, and will provide multimedia sample material for analytical methods development (EXP2.2). To provide all the necessary expertise, this would have to be a carefully coordinated intramural and extramural effort, with clear need for cooperative agreements rather than grants.

High Priority (Adjusted Score from Appendix VI=14); Ecological and Exposure Focus;

LNK.2.3 EXAMINE HUMAN POPULATIONS FOLLOWING DEVELOPMENTAL EXPOSURE TO EDCs FOR ALTERATIONS IN CNS, REPRODUCTIVE OR IMMUNOLOGICAL FUNCTION.

A number of human populations have been exposed to EDCs at high to moderate dosage levels of EDCs (e.g., PCBs/PCDFs, DES) during development. These populations should be thoroughly studied for latent adverse effects to determine if observations from rodent studies (e.g., low sperm counts, infertility in male and

female offspring, shortened reproductive life span, ovarian atrophy, increases in prostatitis, etc.) with these chemicals are manifest in humans after *in utero* exposure. Thus, the DES sons should be reexamined for declines in sperm numbers and semen quality and increases in benign prostatic hyperplasia and prostate cancer, and the DES daughters should be followed for increased incidence of reproductive abnormalities and cancers as they age. Similarly, populations exposed to high levels of p,p' DDE in areas of the world where it is still in use should be examined for increased incidences of cryptorchidism, testicular cancer, and urogenital malformations, as these are induced by *in utero* exposure to antiandrogens in rodents, primates, and humans. Such studies should make every effort to link effects with exposure or exposure-related parameters. Consideration should also be given to additional studies on potent, high volume EDCs other than those discussed above.

High Priority (Adjusted Score from Appendix VI=19), Human and Exposure Focus

LNK 2.4 EPIDEMIOLOGICAL STUDIES OF HUMAN POPULATIONS EXPOSED AS ADULTS.

Both cohort-based approaches searching for adverse health outcomes in EDC exposed populations, and case-control approaches focused on specific health effects such as reductions in sperm counts or increased incidences of infertility, hypospadias, endometriosis or cancers of the breast and reproductive tract are needed to ascertain the range of possible risks resulting from EDC exposures. For example, a number of human populations (albeit mostly male), have been occupationally exposed to EDCs (e.g., DDT, DDD, DDE, TCDD, DBCP, PCBs) at moderate to high dosage levels as adults. These populations should be studied for latent adverse effects. Although adults are not typically the most sensitive human subpopulation for the effects of EDCs, these data can be compared to high dose data obtained in adult male rodent studies to determine if humans and rodents respond in a similar manner. Although obtaining accurate and relevant exposure information is likely to be difficult, case-control studies of suspected EDC induced diseases will be useful in the overall evaluation of the hypothesis that such effects are related to specific exposures.

High/Medium Priority (Adjusted Score from Appendix VI=25), Human and Exposure Focus,

LNK.2.5 STUDIES OF WILDLIFE POPULATIONS TO ESTABLISH RELATIONSHIPS BETWEEN EDCS AND IMMUNE FUNCTION.

Numerous reports of immune alterations have been reported in EDC exposed wildlife populations. These observations need to be replicated in additional populations. Results should be compared to outputs of EFF.3.2.

Medium to Low Priority (Adjusted Score from Appendix VI=41); Ecological and Exposure Focus;

LINKAGE ISSUE 3. ESTABLISH STATUS AND TRENDS OF HUMAN AND WILDLIFE ENDOCRINE DISRUPTION AND EDC EXPOSURE

To establish the scope of potential EDC-mediated effects, there is a need to systematically collect exposure and effects data from different ecosystems. It is clear that existing or proposed resources would not allow development of major new monitoring program for EDCs; however, coordination with existing programs with respect to the type of data collected as well as evaluation of existing data could prove extremely valuable. Determination of exposure levels responsible for population level effects is an important component of the research needs.

LNK.3.1 EXAMINE EXISTING HUMAN TISSUE/SERUM BANKS FOR CORRELATIONS OF EDCS AND HORMONE LEVELS. IDENTIFICATION OF EDCS THAT OCCUR AT HIGH LEVELS IN ECOSYSTEMS.

Human tissue and serum banks could be examined for concentrations of specific endocrine disrupting chemicals. For the contaminant information to be useful, some knowledge about the pharmacokinetics and metabolism would be required, as it would be possible to lead to false negative conclusions if the dynamic relationship between exposure and biological effect mediated via hormonal alterations is not understood. With respect to measurement of hormone levels, the stability of the hormone in serum and the age, sex, and health of the donor would need to be considered in interpretation of any results.

Medium to low priority (Adjusted Score from Appendix VI=53); Human Focus;

LNK.3.2 EXAMINE EXISTING CANCER AND BIRTH DEFECT REGISTRIES FOR INCIDENCES OF EDC-LIKE HEALTH EFFECTS IN HUMANS

It has been suggested that the effects of EDC chemicals manifest themselves in the human population in a predictable fashion as a direct consequence of the role of hormones in reproductive development and in the regulation of some tumor types. The existing human health information is quite weak, hence, it is difficult to determine if effects are increasing as some have claimed. Studies are needed to evaluate whether these outcomes (e.g., hypospadias, cryptorchidism, diminished semen quality, endometriosis, breast, testicular, and prostatic cancers) are increasing or decreasing over time and to identify the true incidence of these effects in the human population at the present time.

Medium Priority (Adjusted Score from Appendix VI=34), Human Focus,

LINKAGE ISSUE 4: DEVELOP RISK MANAGEMENT APPROACHES TO REDUCE OR ELIMINATE ENVIRONMENTAL EXPOSURES TO EDCs.

LNK.4.1 CHARACTERIZATION OF THE SOURCES OF EDCs IN THE ENVIRONMENT

To develop effective risk management strategies for EDCs, the major sources of EDCs entering the environment causing exposure of humans and the ecosystems must be identified. Such a survey could be conducted by collecting existing data from databases associated with the Toxic Release Inventory, hazardous waste sites, pesticide production and use, incinerator effluent compositions, etc.

Medium priority (Adjusted Score from Appendix VI=31), Risk management focus

LNK.4.2 DEVELOPMENT OF TOOLS FOR RISK MANAGEMENT OF EDCs

Based on the exposure studies and results from LNK.3.4, tools to manage the unreasonable risks associated with EDCs will need to be developed. These tools may include, for example, methods to induce biodegradation of EDCs at hazardous waste sites or in contaminated sediments, or pollution prevention strategies for chemical plants that employ or produce EDCs. These tools must significantly lower unreasonable risks associated with EDCs at an affordable cost.

Medium priority (Adjusted Score from Appendix VI=27), Risk management focus,

V. RESEARCH IMPLEMENTATION GUIDANCE

In accordance with the breadth of uncertainties associated with the endocrine-disruption hypothesis, the research topics identified in this plan are quite broad in scope and are likely to outstrip the available resources. Implementation of this plan will therefore require extensive coordination and communication among the research managers in ORD, assistance from external review panels, and continued involvement of the ORD ED Research Planning Committee, to ensure that the most relevant and defensible research projects are selected for funding. Targeting the research effort is complicated by the fact that there is a considerable existing intramural research program in addition to enhanced availability of extramural resources. Coordination within the intramural program is especially important for the Linkage Studies. These combined field and lab and effect and exposure projects will require close collaboration among nearly every component of ORD.

It is presumed that investigator-initiated responses to RFAs derived from this Research Plan will provide the basis upon which the expanded ORD research effort in endocrine disruption will be built. From these submissions, projects will be selected for funding on the basis of both scientific excellence and programmatic relevancy using criteria provided below. A similar, parallel process will be used to target the RFAs in the STAR (Science To Achieve Results) Program and to select grants for funding. Recognizing that integration of the intramural research program with the extramural grants is crucial to effective resource utilization, intramural and extramural RFAs will have to be targeted to achieve both the breadth and depth of balance needed to address the problems. For example, when designing the RFA for the intramural research program, consideration should be given to questions such as: (1) Do we have laboratories capable of undertaking the research? (2) Do we have scientists currently working in these areas? (3) What is scope of the effort needed to study the problem? And (4) Does the intramural program have the capacity to accomplish goals in a timely manner? Answering such questions will provide an important element in determining how best to focus both the intramural and the extramural RFAs. While the particular processes vary, ORD maintains a high standard of external peer review regardless of whether the intramural or extramural pathway is taken to resolve a scientific uncertainty. Intramural project proposals are subject to external scientific review and internal relevancy review at the initiation stage, as well as periodic programmatic reviews, and during the tri-annual site reviews of individual research divisions by external scientific panels. Extramural project proposals are subject to both study section review by external experts, and relevancy reviews by Agency staff prior to funding.

The scope of the endocrine disruptor problem suggests that additional oversight of the ORD effort may be required to maintain an appropriate balance between the various components of the research plan and to ensure that the major data gaps are addressed. The danger in a program developed largely through investigator-initiated activities, even within a defined topic such as endocrine disruption, is that the individual components do not complement each other sufficiently to achieve the overall goals as stated in the Introduction. To help avoid this potential problem, the individual National Laboratories and Centers are expected to develop Implementation Plans for addressing the research activities identified in this Plan. These Implementation Plans should be reviewed by the ORD Research Planning Committee for their ability to provide a useful and integrated research output to the Program Offices. Annual reports of progress and presentation of the upcoming research objectives from each Laboratory and Center 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 the USEPA's Program Offices on progress in understanding the nature and extent of the EDC problem. 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 are also encouraged, as this would help exchange information and expand collaborations.

The following decision-making criteria for use in priority setting within the endocrine disruptors research program have been developed with the above considerations in mind.

Risk-Based Planning: Research that addresses an element of the risk assessment paradigm and is designed to reduce the greatest uncertainties is of the highest priority.

Scientific Excellence: The quality of the science selected for support is of critical importance to both the regulatory application of the resulting information and the overall credibility of the Agency.

Programmatic Relevance: The degree to which a research project addresses a specific statutory requirement will be an important ranking factor.

Other Sources of Data: It is important to determine whether research that will provide equivalent or complementary information is underway or planned elsewhere. A high priority will be given to projects that leverage resources within and/or outside the Agency.

Capabilities/Capacities: The likelihood that research can be implemented within a reasonable period of time using existing facilities, expertise, and available resources will be considered when ranking competing projects. This criterion applies to work conducted intramurally as well as in situations where in-house expertise is needed to oversee the completion of work conducted through a cooperative agreement, contract or grant

Sequence of Research: The value of some research, regardless of its priority ranking on other criteria, is dependent upon the completion of other work. Research that is dependent upon completion of otherwise equally ranked work will receive a lower priority. Such time dependency requires that periodic review of progress is made in order to move to the next stage.

As noted in the Introduction, an important component of the implementation of this plan will be an in-depth review in three to four years to ensure that it remains appropriately focused and to re-adjust priorities as needed. For example, research related to risk management actions was given only a "medium" priority in this plan pending resolution of the extent the endocrine disruption problem. Such efforts are likely to grow in importance and merit a higher priority for funding. Conversely, other topics may fade in importance as the key uncertainties are addressed.

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APPENDIX I. Time Lines for Major Research Questions.

OVERARCHING QUESTION	FISCAL YEAR						
	96	97	98	99	00	01	02
What effects are occurring in exposed humans and wildlife populations?	>>>>>>>>>>>>>>>>>>>>>>>>						
What are the chemical classes of interest and their potencies?	>>>>>>>>>>>>>>>>						
What are the dose-response characteristics in the low dose region?			>>>>>>>>>>>>>>>>>>>				
Do our current testing guidelines adequately evaluate potential endocrine mediated effect?		>>>>>>>>>>>>					
What are the effects of exposure to multiple EDCs, and will a TEF approach be applicable?		>>>>>>>>>>>>>>>>>					
How, and to what degree, are humans and wildlife exposed to EDCs?			>>>>>>>>>>>				
What are the major sources and environmental fates of EDCs?		>>>>>>>>>>>>>>>>>					
How can unreasonable risks be managed?			>>>>>>>>>>>>>>>>>>				

APPENDIX II. SUMMARY DELIBERATIONS OF THE USEPA WORKSHOPS

The premise of these workshops was given that environmental endocrine disruptors (EDs, or endocrine disrupting chemicals (EDCs)) have caused a variety of adverse biological effects in wildlife species, domestic animals, and humans, there is a need to identify research that would assist the federal government in making informed public health and regulatory decisions. An "environmental endocrine disruptor" was broadly defined as "an exogenous agent that interferes with the production, release, transport, metabolism, binding, action or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes." Importantly, this definition reflects a growing awareness that the issue extends considerably beyond that of "environmental estrogens" and includes anti-androgens and agents that act on other components of the endocrine system such as the thyroid and pituitary glands.

The majority of the invited experts at the Raleigh workshop agreed that the endocrine disruptor hypothesis was of sufficient concern to warrant a concerted research effort. In particular, the study of potential effects on reproductive development at multiple phylogenetic levels was deemed the most important area in need of attention. It was repeatedly emphasized that the developing embryo, fetus, and neonate should not be viewed as small adults and that the processes of development are especially vulnerable to brief periods of endocrine disruption. However, for many of the effects reported in both wildlife and humans that have been attributed to, or associated with, endocrine disruption, exposure assessment has generally been inadequate for quantitative risk assessment. Because of this, some participants felt it was difficult to critically evaluate and establish the level of priority relative to other research topics. Still other participants reminded the workshop not to lose sight of the presence of natural occurring endocrine disruptors (e.g., phytoestrogens) as the effects of man-made chemicals are studied.

The objectives of the ecological research strategy workshop were two-fold: to identify research needs and approaches to determine the relative ecological risk of EDCs compared to other stressors on populations and communities, both from a prospective and retrospective standpoint, and to make recommendations for developing and/or modifying the requirements for testing and evaluating chemicals and environmental samples so as to ensure that those exerting toxicity through specific endocrine axes will be adequately characterized.

Several general comments pertaining to future research on endocrine disrupting chemicals emanated from the discussions. These include the recognition that there was a great advantage in bringing together a multi-disciplinary group of scientists representing both the human health and ecological health viewpoints to help identify common issues and that this interaction must be nurtured as the research agenda unfolds. The workgroup noted some key similarities and differences exist between endocrine disruptors and other chemicals which can cause adverse biological effects. Two of the key differences are: the presence of natural ligands within the body that must interact at some level with the exogenous chemical; and that the concentrations of the natural ligands within the body fluctuate during the life cycle and must be maintained within narrow limits at key times during development. This latter point makes consideration of timing of exposure a very significant factor in any assessment. While timing of exposure is important, many EDCs are persistent in the environment and bioaccumulate, and exposures are widespread throughout the entire globe. This can have important ramifications on a biological system that is geared to often cyclical homeostatic control mechanisms such as many of the hormones of the endocrine system. Lastly, the mechanistic basis of the interaction with biological systems presages the induction of subtle effects at low doses that must be

interpreted as to whether the effects are adverse or not. As the level of organization at which biological responses to endocrine disruptors are observed decreases (e.g. from physiological to cellular to molecular), the challenge to describe the effects as adverse at the level of the individual and the population increases. In this regard, endocrine disruptors are not unlike other types of chemicals for which toxicological information is amassed.

In general, it was felt that linking specific exposures to specific effects in the general environment would often be difficult due to the complexities of exposure, the latency of the effects, and the at times subtle nature of the outcomes. Therefore, to confirm the validity of the hypothesis it is likely that there will be heavy reliance on the application of epidemiological criteria for causality (strength of the association, presence of a dose-response relationship, specificity of the association, consistency across studies, biological plausibility, and coherence of the evidence). Such considerations will have significant impact on the types of research activities necessary to adequately confirm or refute the central hypothesis. Ten broad categories of research needs were identified: basic research, biomarkers, database development, exposure determination, exposure follow-up, mixtures, multi-disciplinary studies, risk assessment methods, hazard identification, and sentinel species. Several workgroups noted the complexity in identifying whether effects of xenobiotics on those systems were the result of primary or secondary aspects of endocrine disruption. Workshop participants particularly noted that identification and characterization of effects on the developing reproductive system were considered of high priority for additional research due to the high sensitivity and frequent irreversibility of effects following even brief exposures. More refined exposure assessments and research on the toxicology of mixtures were also considered to be of high importance. Special emphasis was placed on consideration of the unique challenges endocrine disruptors might pose to the risk assessment paradigm. Interestingly, the fact that there is an understanding of the mechanisms underlying endocrine disruption induced by some chemicals was seen as an advantage in that it may result in a common, biologically based, human health risk assessment process for all effects (i.e., both cancer and noncancer).

The following specific research strategies were suggested over the course of the Duluth workshop to start to address the research recommendations listed above:

1) Review and compile available data on endocrine function and endocrine cycles in species of concern (e.g., vulnerable species) to identify areas where additional research is needed.

2) Consolidate and review data from ongoing monitoring programs (e.g., Environmental Monitoring and Assessment Program, National Water Quality Assessment Program, National Status and Trends Program) to identify trends that may be associated with effects of EDCs.

3) Modify existing monitoring programs to include information relevant to EDCs such as measurement of relevant chemicals, information about sex ratios and endocrine para-meters.

4) Increase emphasis on research in comparative endocrinology/toxicology to allow extrapolation among species.

5) Conduct focused research projects at a few selected sites with known endocrine disruptor problems. Examine multiple species at several levels of organization to establish linkages between endpoints measured in the laboratory at the

suborganismal/individual level and changes in the field at higher levels of organization. Strategies and information developed from these projects could then be used to assess or predict impacts of EDCs in other areas.

Appendix III. Overview of Research Plan, Tasks and Outputs for Endocrine Disruptors

Subtopic	Strategic Focus	Tasks	Products	Uses
Biological Effects	Defining the classes of chemicals that act as EDCs and their potencies.	Develop *in vitro/in vivo* methods and structure-activity models to screen for EDC action	Methods to describe the hazard potential of EDCs and likely modes of action and potencies	Hazard characterization to support implementation of the FQPA and the SDWA
	Evaluating current testing guidelines and monitoring procedures for adequacy of assessment of EDCs	Enhance ability of existing test methods (e.g., multi generational studies in mammals and life cycle tests in fish and wildlife) to evaluate manifestations of endocrine disruption and underlying modes of action	Revised testing guidelines that are more indicative of the most sensitive life-stage, sex, and target tissue for chemicals which act through the endocrine system	To improve regulatory testing requirements and data interpretation
	Determining the shapes of dose-response curves for EDCs at relevant exposures and the tissue levels associated with adverse effects	Assess effects of EDC exposure on neuroendocrine, immunological, and reproductive function in developing and adult animals in support of pharmacokinetic and biologically based dose-response models, with emphasis on animal models of EDC-induced human diseases.	Animal models of EDC induced health effects that provide increased understanding of the types and magnitudes of risks for exposure to EDCs during various phases of the life cycles	To provide quantitative dose-response evaluation and reduced uncertainties for human health extrapolations
	Describing the normal endocrine profiles in wildlife species	Provide baseline endocrine information for wildlife populations and their laboratory surrogates, with emphasis on comparative endocrinology and developmental control of sex differentiation, especially for species with little historical attention	Databases of endocrine profiles in species from multiple phylogenetic levels and improved understanding of the role of the endocrine system in sex differentiation	To assess the impact of EDCs in wildlife populations
	Extrapolating effects at the individual level to populations for fish and wildlife	Translate results from measurement endpoints at lower levels of biological organization to impacts on populations and communities through use of microcosms and mesocosms Identify appropriate sentinel species for environmental monitoring	Models predicting population level effects from studies at lower levels of biological organization	To facilitate ecological risk assessment based on effects in individuals

Appendix III. Overview of Research Plan, Tasks and Outputs for Endocrine Disruptors

Subtopic	Strategic Focus	Tasks	Products	Uses
	Characterizing the effects of exposure to multiple EDCs	Systematically study the interactions of EDCs at low, relevant dose levels to understand potential for synergism	Assessment of the validity of the additivity principal for EDCs and predictive models for synergistic interactions	To reduce uncertainties associated with assessment of exposure to multiple EDCs
Exposure Studies	Developing a framework to characterize and to diagnose and predict ecological and human exposure to EDCs	Use physicochemical attributes to identify transport, transformation and environmental fate characteristics associated with exposure scenarios of concern to biological organisms Construct compartmental models to predict environmental behaviors	Validated models to predict and assess transport, fate and exposure to EDCs from source to receptor	To conduct preliminary environmental exposure assessments and set priorities for additional focused research.
	Providing adequate tools to estimate exposure to EDCs	Develop new methods, and refine existing ones (e.g., analytical chemistry, sample extraction, biomarkers) to acquire data for compartmental models, with emphasis on the transport and transformation in sediments and tools for assessing exposure in individuals	Field and laboratory tools to better quantitate EDCs in multi-media.	To improve characterization of exposure to EDCs.
	Determining total ecosystem and human exposures to EDCs of concern	Examine multi generational transfer of EDCs in ecosystems, including biomagnification processes important to higher vertebrates Provide information on EDC exposure distribution in the general human population.	Exposure assessments for EDCs in key wildlife species and the general human population.	To monitor the environment for signals of EDC exposure and effects.
Linkage of Effects, Exposure and Risk Management	Integrating human and ecological effects research with exposure research within the risk assessment paradigm	Construct framework to identify, characterize, prioritize and assess potential and risks to EDCs and provide database for preliminary risk characterization	Coordinated process for identifying exposure and effects of concern for additional intensive characterization of risk.	To conduct preliminary risk assessments and assist research prioritization

Appendix III. Overview of Research Plan, Tasks and Outputs for Endocrine Disruptors

Subtopic	Strategic Focus	Tasks	Products	Uses
	Determining classes and concentrations of EDCs associated with observations of endocrine disruption	Develop informational database for EDCs, including biological effects, environmental concentrations and historical trends from existing monitoring programs Conduct integrated toxicology and exposure studies in areas or human populations with suspected contamination or exposure to EDCs	Database on EDC levels in the human environment and various ecosystems associated with biological effects of concern	Centralized Information source for environmental monitoring of EDCs
	Establishing status and trends of human and wildlife endocrine disruption and EDC exposure	Examine existing monitoring efforts and exposure and effect registries for relevancy to addressing EDC uncertainties.	Consolidated databases of status and trends relevant to EDC exposures and effects.	For environmental monitoring and comparison of effects with more intensive exposures.
	Developing risk management approaches to reduce or eliminate environmental exposure to EDCs.	Identify major sources of EDCs entering the environment Develop tools for risk management such as biodegradation processes or pollution prevention strategies	Risk management tools for elimination or prevention of exposures to significant EDCs.	To develop remedial actions where adverse effects of EDCs have been documented.

EDC = Endocrine Disrupting Chemical
FQPA = Food Quality Protection Act
SDWA = Safe Drinking Water Act

APPENDIX IV. Cross Tabulation of the Nine Overarching Research Questions with the Individual Research Activities Specified 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?
ISSUE										
EFF1	Determine the classes of chemicals that act as EDCs and their potencies		TT	T	T		T	T	T	T
EFF2	Evaluate current testing and monitoring procedures for adequacy of assessment of the effects of EDCs	T	T	T	TT	T				
EFF3	Mode of action studies in laboratory animal models following developmental exposure.			TT	T		T			
	Developmental and acute effects on immune function	T	TT	T			T			
	Studies of EDC induced human effects in animal models	T	T	TT	T	T				
	Pharmacokinetic studies of highly relevant EDCs	T		T		TT	T			
	Development of BBDR models for highly relevant EDCs	T		T		TT	T			
	Mode of action studies in pubertal and adult laboratory models		T	TT		T	T			
EFF4	Definition of baseline endocrine status in wildlife populations	TT	T			T		T		T
	Studies in comparative endocrinology and toxicology	T	T			TT	T			
	Studies on the role of hormones in sexual differentiation	T	T	T	T	TT				

APPENDIX IV. Cross Tabulation of the Nine Overarching Research Questions with the Individual Research Activities Specified 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?
EFF5	Bioassays for evaluating integrated effects	T	T		TT	T		T		
	Evaluation of effects at populations and community levels	TT				T		T		T
	Determination of sentinel species	TT	T			T		T	T	T
EFF6	Studies of interactions of low, relevant dose levels of mixtures		T	T	T	T	TT			T
EXP1	Identification and evaluation of classes of suspect EDCs		T					TT	T	T
	Development and application of compartmental models					T		T	TT	T
EXP2	Abiotic Fate							TT	T	T
	Biotic Fate	T						TT	T	T
	Develop measurement methods and biomarkers for high throughput	T						TT	T	
EXP3	Study inter-generational transfer in ecosystems	T						TT	T	
	Study bioaccumulation in food webs	T					T	TT	T	
	Obtain population based distributions of EDC exposures	T		T			T	TT	T	T
LNK1	Framework for comprehensive, multi-laboratory EDC investigations	T				T	T	TT	T	T

APPENDIX IV. Cross Tabulation of the Nine Overarching Research Questions with the Individual Research Activities Specified 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?
LNK2	Evaluation of existing data and programs for EDC monitoring	T	T					TT	T	T
	Integrated studies of wildlife at contaminated sites	TT			T	T	T	T		T
	Examine human populations exposed developmentally	TT		T			T			
	Examine human populations exposed as adults	TT		T				T	T	
	Studies of wildlife populations to establish relationships between EDCs and immune function	TT	T				T	T		T
LNK3	Examine existing human tissue banks for correlations between EDCs and hormone levels.	T	T					TT		
	Examine existing cancer and birth defect registries for incidences of EDC like effects	TT						T		
LNK4	Characterization of the sources of EDCs in the environment	T						T	TT	T
	Development of risk management tools for EDCs	T					T	T	T	TT

APPENDIX V.a. TASK SUMMARY AND PROPOSED SEQUENCE FOR EFFECT STUDIES.

	FOCUS[1]			PRIORITY[2]	PROPOSED TIME FRAME[3]					
ISSUE	**HH**	**EE**	**EX**		**FY96**	**FY97**	**FY98**	**FY99**	**FY00**	**FY01**
EFF.1.1	X	X		H(1)	X	X	X	X		
EFF.2.1	X	X		H(13)	X	X	X	X		
EFF.3.1	X	X		H(23)	X	X	X	X	X	
EFF.3.2	X	X		H/M(27)				X	X	X
EFF.3.3	X			H(10)		X	X	X	X	
EFF.3.4	X			H(24)	X	X	X	X		
EFF.3.5	X			H/M(34)			X	X	X	X
EFF.3.6	X			M(37)			X	X	X	
EFF.4.1		X		H(26)	X	X	X			
EFF.4.2		X		M(33)		X	X	X		
EFF.4.3		X		H(36)		X	X	X		
EFF.5.1		X		H(26)	X	X	X			
EFF.5.2		X		H/M(22)			X	X	X	
EFF.5.3		X		H(26)		X	X	X		
EFF.6.1	X	X		H(16)		X	X	X		

[1] HH, Human Health, EE, Ecological Effect, EX, Exposure Assessment
[2] As Priority (Priority Score). Priorities H (High), M Medium, (L) Low. See Appendix VI for basis of prioritization score.
[3] Assignment based logical sequence of research, placing issues addressing the most uncertainties of most concern earlier in the implementation process.

APPENDIX V.b. TASK SUMMARY AND PROPOSED SEQUENCE FOR EXPOSURE STUDIES.

	FOCUS[1]			PRIORITY[2]	PROPOSED TIME FRAME[3]					
ISSUE	**HH**	**EE**	**EX**		**FY96**	**FY97**	**FY98**	**FY99**	**FY00**	**FY01**
EXP.1.1			X	H(9)	X	X				
EXP.1.2			X	H(28)	X	X	X	X		
EXP.2.1		X	X	H(28)		X	X	X	X	
EXP.2.2			X	H(10)			X	X	X	
EXP.2.3	X	X	X	H(21)	X	X	X	X	X	
EXP.3.1	X	X	X	M(35)		X	X	X	X	
EXP.3.2		X	X	M(34)		X	X	X	X	
EXP.3.3	X	X		H(22)		X	X	X	X	X

[1] HH, Human Health, EE, Ecological Effect, EX, Exposure Assessment
[2] As Priority (Priority Score). Priorities H (High), M Medium, (L) Low. See Appendix VI. for basis of prioritization score.
[3] Assignment based logical sequence of research, placing issues addressing the most uncertainties of most concern earlier in the implementation process.

APPENDIX V.c. TASK SUMMARY AND PROPOSED SEQUENCE FOR LINKAGE STUDIES.

	FOCUS[1]			PRIORITY[2]	PROPOSED TIME FRAME[3]					
ISSUE	**HH**	**EE**	**EX**		**FY96**	**FY97**	**FY98**	**FY99**	**FY00**	**FY01**
LNK.1.1	X	X	X	H(24)	X	X	X	X		
LNK.2.1		X	X	H(29)	X	X	X			
LNK.2.2		X	X	H(14)		X	X	X	X	
LNK.2.3	X		X	H(19)		X	X	X	X	X
LNK.2.4	X		X	H/M(25)		X	X	X	X	X
LNK.2.5		X	X	M/L(41)				X	X	X
LNK.3.1	X		X	M/L(53)			X	X	X	X
LNK.3.2	X			M/L(34)			X	X	X	
LNK.4.1				M(31)		X	X	X		
LNK.4.2				M(27)				X	X	X

[1] HH, Human Health, EE, Ecological Effect, EX, Exposure Assessment
[2] As Priority (Priority Score). Priorities H (High), M Medium, (L) Low. See Appendix VI for basis of prioritization score.
[3] Assignment based logical sequence of research, placing issues addressing the most uncertainties of most concern earlier in the implementation process.

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Issue	Short Title	Programmatic Relevance	Biological Concern	Potential Impact	Sequence	Technical Success	Total Score	Adjusted Score
EFF1.1	Chemical Classes	8	8	8	8	10	42	1
EFF2.1	Testing Procedures	8	14	14	9	9	54	13
EFF3.1	Modes of Action	16	14	9	9	16	64	23
EFF3.2	Developmental Immune Effects	15	17	15	10	11	68	27
EFF3.3	Animal Models of Diseases	9	8	9	8	17	51	10
EFF3.4	Pharmacokinetics	11	15	14	14	11	65	24
EFF3.5	BBDR Models	16	15	9	13	22	75	34
EFF3.6	Adult neuroendocrine Effects	19	20	15	11	13	78	37
EFF4.1	Endocrine Baselines	18	14	13	8	14	67	26
EFF4.2	Comparative Endocrinology	15	15	15	14	15	74	33
EFF4.3	Sexual Differentiation	20	13	13	15	16	77	36
EFF5.1	Integrated Bioassays	14	15	8	14	16	67	26
EFF5.2	Population Effects	9	9	9	15	21	63	22
EFF5.3	Sentinel Species	15	11	15	10	16	67	26
EFF6.1	Interactions	9	12	9	16	11	57	16
EXP1.1	Classes of EDCs	8	13	8	10	11	50	9
EXP1.2	Compartmental Models	15	15	13	15	11	69	28
EXP2.1	Abiotic Fate	16	22	8	11	12	69	28
EXP2.2	Biotic Fate	8	9	15	9	10	51	10
EXP2.3	High Throughput	13	15	9	9	16	62	21
EXP3.1	Intergeneratioanl Transfer	18	12	13	17	16	76	35
EXP3.2	Trophic Dynamics	17	13	14	16	15	75	34
EXP3.3	Population Distributions	9	15	8	15	16	63	22
LNK1.1	Comprehensive Framework	21	9	11	9	15	65	24
LNK2.1	Existing Monitoring	13	14	19	9	15	70	29
LNK2.2	Integrated Wildlife Studies	14	8	8	9	16	55	14

APPENDIX VI. Cumulative Priority Ranking Scores[1]								
LNK2.3	Human Development	14	9	8	9	20	60	19
LNK2.4	Human Adults	14	15	8	10	19	66	25
LNK2.5	Wildlife Immunotoxicology	16	15	15	15	21	82	41
LNK3.1	Tissue Banks	18	22	15	16	23	94	53
LNK3.2	Registries	17	10	10	15	23	75	34
LNK4.1	Sources of EDCs	8	16	9	22	17	72	31
LNK4.2	Management of EDCs	9	10	9	24	16	68	27

[1] Each member of the planning committee was asked to assign a weight of from 1 to 3 (1 being the highest) to each of five factors (Programmatic Relevance, Magnitude of Biological Concern, Potential Impact of Research, Sequence of the Research, and Technical Feasibility of the Research). The values in the columns under each of the five factors is the sum of the weights assigned by 8 individuals (thus, an issue would receive a highest possible score of 8, and the lowest a possible score of 24). The column marked “Total Score” is the sum of weights for the five individual factors, while the Adjusted Score substracts the lowest total score, and then adds one, such that the highest priority issue has a value of 1. This is the value used in the text and in Appendix Va-c.

Agency Goals/Objectives/Sub-Objectives	EFFECTS					EXPOSURE					RISK ASSESSMENT			RISK MANAGEMENT					
	Surveillance (human health/ecology)	Effects Indicators	Stressors	Mechanisms of Action	Predictive Models	Source/Exposure	Process Modeling (Physical, Chemical,	Environmental Characterization	Exposure Analysis/Assessment	Exposure Dose	Health and Ecological Risk Assessment	Risk Assessment Methods. Tools,	Risk Assessor Support (Guidance and	Source/Problem Characterization	Prevention Methods	Control Methods	Remediation/Restoration Methods	Performance/Cost Verification	Technology Transfer
8: PROVIDE SOUND SCIENCE TO IMPROVE UNDERSTANDING OF ENVIRONMENTAL RISK AND DEVELOP AND IMPLEMENT INNOVATIVE APPROACHES FOR CURRENT AND FUTURE ENVIRONMENTAL PROBLEMS																			
ORD Science Objective #3: Emerging Risk Issues: Establish capability and mechanisms within EPA to anticipate and identify environmental or other changes that may portend future risk, integrate futures planning into ongoing programs, and promote coordinated preparation for and response to change																			
ORD Science Sub-Objective #3.2: Endocrine Disruptors	MM-35 LNK. 2.2 3.1 MM-56 LNK. 2.1	MM-64 EFF. 1.1 2.1 MM-65 EFF. 5.1	MM-7 ? MM-12 EFF. 3.1 3.2 3.3 3.4 3.5 3.6 MM-30 LNK. 1.1 MM-56 LNK. 2.1	MM-24 EFF. 4.1 4.2 4.3 MM-58 EFF. 6.1 MM-64 EFF. 1.1 2.1	MM-23 EFF. 5.2 5.3		MM-66 EXP. 1.1 1.2	MM-17 EXP. 2.1 2.2 2.3 MM-45 EXP. 3.1 3.2 3.3 MM-57 LNK. 2.1	MM-8 ? MM-28 LNK. 1.1 MM-36 LNK. 2.2 3.1		MM-63 LNK. 3.3 LNK. 2.3 2.4 2.5 3.2	MM-29 LNK. 1.1	MM-55 LNK. 2.1	MM-18 LNK. 4.1 4.2					