EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20502

November 22, 1996

Dear Colleague:

I am pleased to introduce the National Science and Technology Council (NSTC) report "The Health and Ecological Effects of Endocrine Disrupting Chemicals." In response to the need to coordinate the Federal government's response to issues relating to endocrine disrupting chemicals and their potential adverse effects on human heath and wildlife, the Committee on Environment and Natural Resources formed a Work Group on Endocrine Disruptors.

This document, which is the first product of this Work Group, establishes a framework for considering the issue of endocrine disruptors. It categorizes major research activities into three groups: methods development, model development, and laboratory and field data acquisition. The next phase of the CENR effort will match these needs against current Federally funded research efforts to develop a coordinated interagency research plan.

Sincerely,

John H. Gibbons
Assistant to the President
for
Science and Technology

THE HEALTH AND ECOLOGICAL EFFECTS OF ENDOCRINE DISRUPTING CHEMICALS

A FRAMEWORK FOR PLANNING

Committee on Environment and Natural Resources
National Science and Technology Council

November 22, 1996

The purpose of this document is to provide a planning framework for Federal research related to the human health and ecological effects of endocrine disrupting chemicals. The Administration is committed to a broad range of high priority investments (including science and technology), as well as to deficit reduction, and to a smaller, more efficient Federal government. This document does not represent the final determinant in an overall Administration budget making process. The research program presented in this guide will have to compete for resources against other high priority Federal programs. If these programs compete successfully, they will be included in future Administration budgets.

About the National Science and Technology Council

President Clinton established the National Science and Technology Council (NSTC) by Executive Order on November 23, 1993. This cabinet-level council is the principal means for the President to coordinate science, space, and technology policies across the Federal Government. NSTC acts as a "virtual" agency for science and technology to coordinate the diverse parts of the Federal research and development enterprise. The NSTC is chaired by the President. Membership consists of the Vice President, Assistant to the President for Science and Technology, Cabinet Secretaries and Agency Heads with significant science and technology responsibilities, and other senior White House officials.

An important objective of the NSTC is the establishment of clear national goals for Federal science and technology investments in areas ranging from information technologies and health research, to improving transportation systems and strengthening fundamental research. The Council prepares research and development strategies that are coordinated across Federal agencies to form an investment package that is aimed at accomplishing multiple national goals.

To obtain additional information regarding the NSTC, contact the NSTC Executive Secretariat at 202-456-6100.

About the Office of Science and Technology Policy

The Office of Science and Technology Policy (OSTP) was established by the National Science and Technology Policy, Organization, and Priorities Act of 1976. OSTP's responsibilities include advising the President in policy formulation and budget development on all questions in which science and technology are important elements; articulating the President's science and technology policies and programs, and fostering strong partnerships among Federal, State, and local governments, and the scientific communities in industry and academe.

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EXECUTIVE SUMMARY

A growing body of scientific evidence has begun to suggest that a range of chemicals introduced into the environment by humans may be producing adverse health effects in humans and in wildlife species by disrupting endocrine system function. In some instances it is clear that such chemicals, referred to as endocrine disrupting chemicals (EDCs) have induced a variety of adverse health effects in humans and wildlife. While this issue has attracted considerable attention in the scientific community over the last several years, there is a great deal to be learned about the extensiveness of the chemical classes that can act as endocrine disruptors, their concentrations in the environment, and their ability to induce specific adverse health effects. To coordinate the Federal government's response to this issue, a Work Group on Endocrine Disruptors was formed under the auspices of the NSTC's Committee on Environment and Natural Resources (CENR). The objectives of the Work Group are to: (1) develop a planning framework for Federal research related to the human health and ecological effects of endocrine disrupting chemicals; (2) conduct an inventory of on-going Federal research programs; and (3) identify research gaps and develop a coordinated interagency plan to address priority research needs.

This document, which is the first product of the Work Group, reviews the current state of the science and major uncertainties related to endocrine disrupting chemicals and establishes a framework for research areas that need attention. Because of the many outstanding issues, it is difficult to assign an overall priority to the endocrine disruption issue relative to other environmental and public health concerns, such as habitat destruction, global warming, or drinking water disinfection. However, it is very clear that more research is warranted to understand the potential consequences of the issue.

This framework categorizes major research needs into three groups; methods development, model development, and laboratory and field data acquisition. Cost effective methods to identify human health and ecological hazards and to detect environmental contamination must be developed and validated. Predictive models are necessary to estimate exposure and risk from endocrine disrupting chemicals. Finally, studies must be initiated to quantify the degree of effect and magnitude of exposure for species at risk. Biological effects research is needed to: (1) characterize the effects of EDCs, singly and in combination, on the developing organism, particularly as related to the effects on the reproductive and neurological systems; (2) to assess potential carcinogenic effects; (3) to evaluate and characterize mixtures in terms of modes of action and potential for synergistic interaction; and (4) to develop tools to help translate information from basic research and molecular and cellular level effect studies into the risk assessment process.

The next phase of the CENR effort, will match these needs against current Federally funded research efforts to identify priority research areas and to develop a coordinated, interagency research plan. Ultimately, the Work Group plans to expand this assessment process to include organizations outside the Federal government that are

also conducting research on this issue.

THE HEALTH AND ECOLOGICAL EFFECTS OF ENDOCRINE DISRUPTING CHEMICALS

A FRAMEWORK FOR PLANNING

INTRODUCTION

A growing body of scientific evidence has begun to suggest that a range of chemicals introduced into the environment by humans may be producing adverse health effects in us and in wildlife species by disrupting endocrine system function (Kavlock et al, 1996; Ankley et al 1996; Sheehan, 1995; Medical Research Council, 1995, Umweltbundesamt, 1995; Danish Environmental Protection Agency, 1995; McLachlan and Korach, 1995; Colborn and Clements, 1992). These chemicals, collectively referred to as endocrine disruptors, exert their effects by mimicking or interfering with the actions of hormones. Chemicals identified as endocrine disruptors include pesticides (such as DDT and its metabolites), industrial chemicals (such as surfactants and PCBs), drugs (such as DES), and contaminants (such as dioxins).

Most of the effects ostensibly associated with exposure to endocrine disrupting chemicals (EDCs), such as reproductive dysfunction and sexual abnormalities, have been observed in wild life populations receiving relatively high levels of exposure to persistent chlorinated compounds. The extent to which these efforts are occurring is unclear. Whether similar, albeit more subtle, effects are occurring in humans or in wildlife populations at lower exposure levels is unclear. Reports of possible declines in sperm production in humans over the last four decades–as well as increases in rates of certain cancers that may have an endocrine-related basis (breast, prostate, testicular)–have led to speculation about environmentally mediated endocrine disruption. These observations, coupled with data from controlled laboratory studies on reproductive, neurologic and immunologic effects following exposure to some EDCs, have generated a climate of concern surrounding the potential consequences of exposure to endocrine disruptors. The fact that many of the same hormones and their receptors are present across species, genera, classes and even phyla suggests that effects reported in one species from exposure to endocrine disrupting chemicals could have widespread biological implications.

Federal agencies are currently funding several hundred research projects relating to endocrine disruption. There is also a considerable amount of basic research funded by the Federal government on the biochemistry of hormones and their regulation and control of physiological processes. What has been lacking is a government-wide coordinated and integrated research effort that addresses the key scientific uncertainties related to the adverse effects of endocrine disrupting chemicals. Recognizing this, the National Science and Technology Council's, Committee on Environment and Natural Resources (CENR) recommended that a Federal research strategy be developed on

endocrine disruption and established an interagency work group. [1] The objectives of the work group are to: 1) develop a planning framework for Federal research related to the human health and ecological effects of endocrine disrupting chemicals; 2) conduct an inventory of on-going Federal research programs; and 3) identify research gaps and develop a coordinated interagency plan to address priority research needs. These efforts will be completed in the in the next several months. The group also plans to work more broadly with organizations outside the Federal government that are also conducting research on this issue to coordinate efforts and to disseminate information to the scientific community and the general public.

This document, which is intended to fulfill the first objective, is based largely on the findings of two workshops held by the Environmental Protection Agency's Office of Research and Development (Kavlock et al., 1996; Ankley et al., 1996) to assess the risk of endocrine disruption on human health and the environment (see Appendix). These workshops had broad participation from other Federal agencies, industry, academia, and international representatives.

Presented below are: 1) a brief review of the current state of scientific knowledge related to the human health and ecological effects of endocrine disruption; 2) a discussion of the underlying uncertainties surrounding this issue; and 3) a description of the research areas that need attention. In conjunction with the results of the inventory of Federal endocrine disruptor research programs, this paper will provide the framework for developing a Federal research plan and coordinating additional research efforts on EDCs. This plan will be revised, as needed, as new information becomes available. One source of new information will be an upcoming National Academy of Sciences assessment. [2]

As the emerging research program identifies the actual nature and extent of the impact of endocrine disruption on human health and wildlife, it may be necessary to consider expansion to other areas, such as assessing the relevance of potential endocrine-induced changes in social behaviors, economic impacts, risk assessment, and risk management strategies to mitigate risks and prevent additional input of EDCs into the environment.

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(1) The work group is chaired by the Environmental Protection Agency, with the Department of the Interior and the National Institute of Environmental Health Sciences as co-chairs. Other agencies participating include the National Oceanic and Atmospheric Administration, the National Science Foundation, the Food and Drug Administration, the Centers for Disease Control, the Agency for Toxic Substances and Disease Registry, the National Cancer Institute, the Smithsonian Institution, the Departments of Agriculture, Defense, and Energy, and the Office of Science and Technology Policy.

(2) The National Academy of Sciences has also convened a panel to review the literature on endocrine disruptors, with a report expected to be released in mid 1997. The output from that process should allow for a re-examination and potential re-focusing of the overall Federal research strategy.

CURRENT STATE OF SCIENTIFIC KNOWLEDGE

HUMAN HEALTH AND ECOLOGICAL EFFECTS

At least four major categories of adverse biological effects may be linked to exposure to EDCs: cancer, reproductive and developmental alterations, neurological and immunological effects. Endocrine systems that may be involved include the thyroid, adrenal, pituitary, and gonadal.

Cancer: The hypothesis that endocrine disruptors can cause cancer in humans is based largely on the clear association between exposure of females *in utero* to diethylstilbestrol (DES), a potent synthetic estrogen taken by pregnant women to avoid miscarriage, and subsequent onset of reproductive organ cancers. In addition, cancer trend data for the period 1973-1991 show increases in the incidence of endocrine-mediated cancers (female breast, 24%; testicular, 41%; prostate, 126%). Some of these reported increases are probably due to changes in screening practices, as well as to changing demographics of the human population. In the case of female breast cancer, epidemiological studies have identified a variety of risk factors, including several that relate to hormonal activity. For example, elevated lifetime exposure to increased amounts of estrogens is known to increase the risk of breast cancer. Several studies have implicated synthetic estrogens as important risk factors although some controversy exists in this case. There is limited and conflicting evidence of a possible relationship between levels of pesticide residue in human adipose tissue and the risk of breast cancer. While the upward trends in cancers of the prostate and testes are intriguing, there are as yet no identified associations between tumors at these sites and environmental chemicals.

The role of hormones and hormone disruptors in tumor production in wildlife species is unclear. A high prevalence of tumors has been detected in fish from heavily polluted waters where the predominant risk factor was identified as exposure to PAHs (polycyclic aromatic hydrocarbons), and to a lesser extent, PCBs and DDT. Importantly, exposure of fish to PAHs is associated with reproductive effects that are consistent with anti-estrogenic activity. Moreover, gonadal tumors have been identified in soft-shelled clams off the coast of Maine, and in quahog clams off the eastern coast of Florida. In the former instance, the effect may have resulted from herbicides released by forestry management practices, although a mechanism for herbicide tumorigenesis is not known. Despite the lack of direct evidence for hormonally mediated tumors in wildlife, the occurrence of tumors in wildlife species inhabiting chemically contaminated environments suggests that endocrine disrupting chemicals may be involved. The absence of evidence in this area may simply reflect the absence of research to determine the role of endocrine disrupting chemicals in tumorigenesis in wildlife.

***Reproductive and Developmental Effects*:** In humans, documented cases of adverse reproductive outcome in individuals (or their offspring) exposed accidentally to high doses of endocrine disrupting chemicals have been reported. Examples include: 1) shortened penises, as well as other effects, in the offspring of women exposed to dioxin contaminated rice oil in Yucheng, China; 2) reduced sperm count, one of several toxic effects, suffered by workers exposed to high doses of Kepone at a Hopewell, Virginia pesticide factory; and 3) although direct evidence of effects of dioxin itself on human reproduction is lacking, women living near the Seveso, Italy pesticide plant, produced more female children than normal in the nine months following a 1976 explosion.

Field and laboratory studies of wildlife species that have been exposed to high levels of certain chemicals have revealed effects in offspring that appear to be the result of endocrine disruption, that include altered reproductive behaviors, reproductive impairment, feminization and demasculinization, embryonic deformities, and abnormalities of sexual development. Affected species include invertebrates, fish, reptiles, birds, and mammals. Chemicals with known or suspected endocrine disrupting properties have been detected in these animals or their environment, but a clear etiological link has yet to be established for more than a few of the observations.

Neurological Effects: Although exposure to endocrine disruptors in humans and animals has been associated with neurotoxicity (effects on behavior, learning/memory, sensory function, neuroendocrine and psychomotor development), it is uncertain whether these effects are causally related to the disruption of endocrine function. The difficulty is that there are many mechanisms potentially involved in the induction of neurotoxicity, some of which involve direct effects on the neuroendocrine control of hormone levels, and others that involve alterations in the maturation of the central nervous system in response to altered hormone levels. Regardless of the mode of action, it is important to determine if these chemicals are producing neurotoxicity in organisms at environmentally relevant dose levels. Several chemicals or chemical classes are suspected of producing neurotoxicity by an endocrine-like mechanism, including PCBs, dioxins, DDT and related chlorinated pesticides, and some metals.

Immunological Effects: Evidence for immunological effects in humans is not strong; the observation that exposure to certain endocrine disruptors (such as dioxins, PCBs, pesticides, and DES) can alter the types of lymphocytes circulating in the blood is suggestive of immunosuppression and potential disease susceptibility. It is not known whether these effects are the direct result of endocrine dysfunction.

Impaired immune function associated with exposure to PCBs and DDT has been observed in birds in the Great Lakes and marine mammals. Fish exposed to PAHs have shown evidence of immune system dysfunction. Other studies have reported evidence of immune suppression in fish and wildlife similar to findings in laboratory animals exposed to TCDD, DES, PCBs, carbamates, organochlorines, organometals and certain heavy

metals.

EXPOSURE ASSESSMENT

Even if everything were known about the biological effects of endocrine disruptors in humans and wildlife, it would still be necessary to know environmental exposure pathways before the risks could be assessed and preventive measures taken. While adequate exposure assessment for EDCs, both in the external environment as well as in the internal environment of exposed organisms, has generally been lacking, there are exceptions to this (e.g., failed natural reproduction of Lake Trout in Lake Erie exposed to chemicals such as dioxins and PCBs, altered reproductive development in the Lake Apopka alligators exposed to dicofol, cross bills and other birth defects in the cormorants in Lake Michigan exposed to PCBs and dioxins, and developmental neurological problems in humans exposed to PCB and PCDF contaminated rice oil). These have provided the most compelling reasons for believing that exposure to endocrine disruptors can have effects in populations.

The situations that have yielded the strongest links between exposure to EDCs and adverse effects have generally involved exposure conditions in excess of those present in the ambient environment. There is a fair amount of information available on the levels of some organochlorines (e.g., PCBs and DDE) in wildlife and human tissue (including breast milk), but for most EDCs there is a paucity of information on the concentrations in the environment and biological tissues. Endocrine disruptors pose several challenges to exposure assessment, in part due to the heterogenous chemical classes that have been implicated. In addition, the pathways between source and exposure are complex (e.g., although many organochlorine pesticides are no longer used in the US, there is evidence that atmospheric circulation of materials originating in countries where they are still used may be responsible for current deposition in the Great Lakes); many EDCs are persistent and accumulate in animal tissues, and there may be long latency periods between the exposure and the manifestation of the response (e.g., exposure during very brief periods during in utero development may lead to effects that are not manifest until the offspring has passed puberty). Further, heavily polluted areas may serve as redistribution sources for these compounds.

UNDERLYING UNCERTAINTIES

The consensus emerging from the scientific debate surrounding EDCs is that there are insufficient data to determine the relative ecological and human health risks associated with these environmental contaminants. This is due, in part, to the complex role of the endocrine system in regulating essential physiological and developmental processes and the difficulty in determining whether the effects are the result of primary

disturbances of endocrine function (i.e., are other systems in the body more sensitive to exposure to these chemicals and the endocrine system is affected as a consequence). In addition, chemically caused perturbations in endocrine function, whether in humans or wildlife, is inherently difficult to distinguish from other causes, such as poor nutrition, that may impair normal growth, development, and reproduction. The high variability associated with measurements of normal endocrine function may also obscure effects of EDCs. These factors complicate the identification of a mechanistic basis for biological effects observed in laboratory populations and create difficulties in establishing etiological links between exposure and reported effects in wildlife populations. Thus, it is important to determine the mechanism of action that is operative in causing the critical effect. Although many of the effects of endocrine disruptors are known to occur through interaction with receptors that then act as transcription factors, a number of non-genomic mechanisms are being identified by which EDCs can exert biological effects. Many of these pathways are poorly understood, and answering questions about the basic organization and range of sensitivity of endocrine and neuroendocrine systems may someday change the way we think about the action of EDCs. There is also considerable uncertainty regarding exposure assessment for endocrine disruptors, including knowing which chemical or chemical classes are the most important to measure, as well as the quantitative issues related to the comparative distribution of exposures in the environment and in biological tissues. Further, there are significant questions about potential synergistic interactions between endocrine disrupting compounds.

There are also extrapolation issues that must be resolved. Results from laboratory studies are often the basis for predictions of response in humans and wildlife. Estimating risk from laboratory observations usually requires extrapolation that introduces uncertainties (e.g., from high-dose effects to low-dose effects, from species to species, from controlled laboratory settings to field conditions, etc.). In the area of endocrine disruption, the most important uncertainties raised in predicting risks include: age and species variations in sensitivity; the life stages at greatest risk to adverse effects; genetic predisposition; prediction of population-level effects from studies of individuals; unidentified mechanisms of toxicity; the possibility of non-monotonic dose-response relationships; and the estimation of effect at relatively low (i.e., observed in the environment) doses.

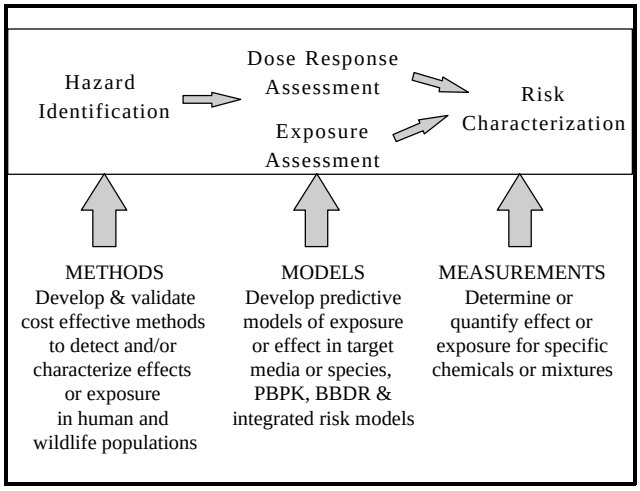
Because of these and other outstanding issues, it is difficult to assign an overall priority to this topic relative to other environmental and public health concerns, such as habitat destruction, global warming, or drinking water disinfection, but it is very clear that more research is warranted to understand the potential consequences of the issue.

RESEARCH NEEDS

To provide data relevant to the formulation of sound environmental policy, it is important to forge a research strategy based on risk-based principles and a strong basic science component. For human health effects, the principles of hazard identification, dose-response analysis, exposure assessment, and risk characterization are clearly captured in the risk assessment paradigm described by the National Academy of Sciences (NAS, 1983). For ecological effects, a similar framework for risk assessment, consisting of problem formulation, analysis (characterization of exposure and effects) and risk characterization, has been proposed (USEPA, 1992).

Three types of research activities support the risk assessment process. In the area of hazard identification, research efforts focus on the development and validation of ***methods*** that can identify the hazard and provide presumptive evidence of causality between exposure and effects. For dose-response assessment, research involves the development and validation of predictive ***models*** of dose, effect, and fate and transport that permit integration and extrapolation of data. The systematic collection of information (***measurements***) for subsequent analysis is also required to fill specific gaps in knowledge. Operationally, work in these three broad activities must proceed in an iterative fashion as methods and models are verified by measurement research and new predictions and gaps in the knowledge emerge. Testing new predictions and filling critical data gaps promote a deeper understanding of the relationship between exposure and effect.

The research needs for endocrine disrupting chemicals can be grouped into ten broad categories: hazard identification, biomarkers, risk models, basic research, mixtures, exposure determination, exposure follow-up, multidisciplinary studies, sentinel species, and database development. These categories have been further consolidated into the three over-arching types of research described above.



Methods

Methods need to be developed, validated and applied to identify and characterize hazard. Efforts include the refinement of current chemical testing protocols for assessing effects on the endocrine system and the development of sensitive and reliable tools to monitor populations for exposure and effects.

RESEARCH COMPONENTS SUPPORTING THE PRINCIPAL ELEMENTS OF RISK ASSESSMENT FOR ENDOCRINE DISRUPTORS

METHODS DEVELOPMENT
Hazard Identification
Biomarkers

PREDICTIVE MODELS
Risk Models
Basic Research on Mechanisms
Mixtures

MEASUREMENTS
Exposure Determination and Follow-up
Multidisciplinary Research
Sentinel Species

Hazard identification: Rapid, reliable, and inexpensive tests are needed to monitor and screen chemicals for endocrine disrupting potential. Screening strategies may vary based on the type of data required. For example, data could be obtained from *in vivo* assays such as those that measure androgen-sensitive male accessory sex organ weights (e.g., the epididymis) or the presence of estrogen-inducible proteins such as vitellogenin (egg yolk protein) in the blood of male fish. Data could also be acquired from *in vitro* assays of critical aspects of endocrine disruption such as competitive receptor binding and gene reporter assays for estrogens, androgens and progestins. Attention should be focused on research to develop and validate these assays, to define a testing strategy, and to identify assay limitations. To be useful, short-term screening methods must be predictive of results obtained in *in vivo* bioassays routinely employed in the contemporary hazard characterization process. These screening assays would enable us to predict responses across a variety of species. There is a need for rapid and inexpensive methods for screening to facilitate large-scale monitoring.

Some existing test guidelines that may be used for evaluating endocrine-related effects have shortcomings in that they do not: 1) encompass sufficient numbers of species, 2) include sensitive endocrine-dependent responses, and/or 3) provide a thorough evaluation of the life cycle. Limitations in test methodologies also extend to bioassays for environmental samples such as effluents, sediments and ambient water in addition to those applied to pesticides and other toxic substances. More comprehensive tests in this area are needed, including those that can identify active components in complex mixtures and potential synergistic effects. Likewise, the conventional two-year cancer bioassay is not designed to evaluate transplacental carcinogenesis. Research is needed to determine whether exposure during critical stages of rodent development adds to the risk of cancer induction by agents which act on the endocrine system.

Biomarkers: Biomarkers are biological indicators used to determine: 1) the presence of exposure to a particular chemical; 2) a response specific to exposure to a chemical or chemical class; 3) the existence of susceptible subpopulations based upon some genetic trait. Biomarkers of endocrine disruption such as vitellogenin induction in male fish from exposure to estrogenic substances, are needed as screening tools for exposure assessment, as biological indices of latent effects, and as a means to address mechanistic issues related to identifying critical steps in the process or to understand the basis for species' differences in response. Attention needs to be focused on multi-

generational studies to identify biomarkers in offspring that can be measured shortly after exposure and that are predictive of long-term effects. In the case of ecological biomarkers, field evaluations are needed to establish which early changes or endpoints in individuals are the most predictive of population-level effects. In the case of exposure biomarkers, available human and wildlife tissues need to be measured for the presence of endocrine disruptors to compare with levels in the food chain. Research may be needed to increase the sensitivity or breadth of existing analytical techniques for the multitude of media that must be sampled, as well as for some chemical classes (e.g., the semi-volatiles) which have traditionally not been evaluated in this context.

Models

Exposure to a toxic agent initiates a cascade of biological events beginning with interactions at the cellular and molecular levels and progressing to tissue injury and/or disease. Models provide a conceptual framework for explaining these events. They may be mathematically based descriptions of the key or rate limiting steps involved in the pathogenic process, or they may be biological or physiological paradigms that help identify risk factors such as age, gender, diet, disease conditions, past exposures, and genetic predisposition. In either case, models systematize the parameters that are conditional to toxicity and help quantify the relationship between dose and response. Data from such diverse disciplines as toxicokinetics, mechanistic toxicology, molecular biology, environmental chemistry, population ecology and ethology are used in models. Models are needed to predict the levels and critical timing of exposure to these substances and the latency period between exposures and effects.

Risk Models: Risk models for endocrine-mediated effects need to be developed and refined. We currently have models of hormone-receptor interactions, but these have yet to be linked to events following hormone-receptor binding that ultimately result in the biological response of concern. Preliminary efforts to develop receptor-based quantitative models for TCDD-induced health effects in humans are underway in several laboratories and may provide important pioneering examples of the strengths and limitations of this approach (although TCDD is not a hormone, its biological effects occur through activation of the *Ah* receptor which belongs to the same super family of receptors as the steroid hormone receptors). Like the basic hormone-receptor interaction models, the TCDD models are currently focused on explaining some of the early biochemical events in the overall cascade to adverse health effects. In some cases, basic research will be required to confirm or refute theoretical assumptions, to facilitate model design, and to provide realistic ranges of estimated parameter values. Development of such models requires close collaboration between biomathematicians and experimentalists.

There is a need to develop biomathematical models to: 1) improve estimates of environmental concentrations of toxicants at the target site; 2) estimate exposure; and 3) better predict environmental and human health consequences. Models of structure-activity relationships (SAR), which codify information on physicochemical parameters and

mechanisms of toxicity to predict adverse ecological or human health effects, play a significant role in hazard detection and assist in prioritizing compounds for more extensive testing. However, the limited utility to date of SAR in predicting the biological effects of estrogenic agents must be addressed by expanding the universe of chemical structures for which data are available, the biological activities for which we have data (e.g., gene activation versus ligand binding), and structural attributes that are used to correlate with biological activity. These models require further refinement, both in terms of computational chemistry and calibration to *in vivo* toxicity.

Quantitative, mechanism-based dose-response models increase confidence in risk estimates. Such models improve extrapolations between laboratory findings and effects in humans or wildlife species. Specifically, the development of physiologically based pharmacokinetic (PBPK) models is vital to securing more accurate predictions of tissue and cellular dose, especially at critical and sensitive early life stages, and to understand the role of metabolism in the activation, distribution, and elimination of endocrine disruptors. PBPK models are important because they allow extrapolation of exposure - tissue dosimetry relationships from one exposure mode to another (e.g., inhalation to oral), from one life stage to another, and from one species to another. Similarly, toxicodynamic models (often referred to as biologically based dose response models (BBDR)) are needed to describe and quantify the key steps in the cellular, tissue and organismal responses to the proximate endocrine disruptor(s). By incorporating species-specific biological determinants of toxicity, these models should improve our ability to extrapolate from high to low exposure levels, and from species to species. At the present time, PBPK models are at a fairly mature stage of development and have been used for several chemicals whereas the pace of development of BBDR models has been slower due to the complexities of identifying and quantifying the rate-limiting steps in the induction of toxicity.

In conjunction with the biological-effects models, chemical-fate and transport models will also be important in describing and predicting the movement of endocrine disrupting chemicals in the environment (e.g., air, soil, water, sediment, and biota). Such models can be useful in predicting the movement of pollutants and their breakdown products in situations ranging from field to regional, and ultimately, global scale. They must take into account the presence of especially vulnerable groups, both in terms of life stage and life style. Compartmental models for the fate, transport and distribution of endocrine disrupting chemicals will need environmental measurement data for model development, validation and routine use.

Basic research: Fundamental research on mechanisms is essential to better understand the interplay between chemicals implicated as potential EDCs in whole organisms and the endocrine system. Baseline data on endocrine regulation in immature and adult organisms is required to reduce uncertainties surrounding age-dependent responses. The timing of exposure, which exerts a strong influence on human and ecological effects, is another issue in need of consideration. Research in this area would help characterize critical windows of susceptibility to endocrine disruption. Basic research

also is required to select animal models relevant to the study of endocrine disruptors; to identify early biomarkers of effects, and to design screening assays for rate limiting events. Emphasis should be placed on identifying representative models and relevant species. For example, it has been difficult to examine the potential of chemicals to induce human testicular or prostate cancer because animal models suitable for these tumor types have generally been lacking. Similarly, it is important to understand differences in the relative rate of developmental processes across species when assessing the potential of chemicals to affect Sertoli cell proliferation (the nurse cell for spermatagonia in testes, and whose numbers limit the amount of sperm production possible) in the testes (a proposed explanation for an estrogen-mediated decline in sperm counts in humans).

There is also a need to understand the key events involved in hormone action and the linkage between these events and toxic response. Attention should be focused on cellular and molecular processes--both receptor and non-receptor mediated--of hormone activity and on the rate-limiting steps in the induction of toxicity. This line of research is complicated by the existence of indirect-acting endocrine disruptors, which cause endocrine-related toxicity at a secondary site. Mechanistic research should therefore be constructed to discriminate between effects resulting from primary and secondary disturbances of endocrine function.

Mixtures: Not much is known about the hazards of chemical mixtures, and a scientifically sound risk assessment approach is lacking. For chemical mixtures, one approach to risk assessment is the toxic equivalency factor (TEF) method, which is useful for mixtures of chemicals sharing a common mode of action, such as certain dioxins, furans and PCBs. In such cases, the toxicity of chemicals can be summed to calculate an estimate of total toxicity for the mixture. However, the principle of additivity may not be valid for all mixtures (i.e., there may be synergistic or antagonistic interactions among chemicals regardless of whether a single or multiple mechanism of action are involved in the biological response). We need to be aware that the potential for synergistic and antagonistic interactions increases as different mechanisms of action become involved following exposure to multiple chemicals. Because there are multiple mechanisms by which the endocrine system can be perturbed, diverse chemical classes implicated as endocrine disrupting chemicals, and environmental situations in which exposures to multiple chemicals is to be expected, we need to look carefully at biological interactions with EDCs. The fact that only small perturbations in endocrine status are necessary to cause adverse effects during key developmental periods suggests that large synergistic interactions are not necessary to significantly increase the risk from multiple chemical exposures. Indeed, given the number of chemicals present in most exposure situations, even simple additivity of effects may be sufficient to yield exposure levels of concern when the total exposure burden is considered. *In vitro* and *in vivo* studies of complex mixtures are needed to evaluate the validity of TEFs for endocrine disrupting chemicals and to identify and characterize departures from additivity if they are detected. Systematic testing of assumptions implicit to the TEF approach should be performed, and TEF estimates should be improved where their feasibility has been demonstrated. When

selecting chemical mixtures for study, attention must be paid to the environmental relevance of the mixture, the appropriateness of the exposure concentrations, the chemical ratios comprising the mixture, and the multiple routes of exposure that are likely to be encountered by organisms as they come in contact with EDCs.

Measurements

The extent and magnitude of exposure and effect must be documented to accurately identify and assess problems related to EDC exposures. Environmental and exposure monitoring programs provide an important means to systematically collect data and fill critical gaps in knowledge. Currently monitoring programs include the National Health and Nutritional Examination Survey (NHANES), the National Human Exposure Assessment Survey (NHEXAS), the Market Basket Survey of the US Food and Drug Administration, the Pesticide Data Program of the US Department of Agriculture, the National Contaminant Biomonitoring Program of the National Biological Service, and NOAA's Status and Trends Program and Marine Mammal Health and Stranding Response Program. However, none of these have been oriented towards chemicals and endpoints of particular concern for endocrine disruption. As information is gathered, it can be used to establish baselines and boundaries for a variety of endocrine-related parameters, such as body burdens of EDCs, endocrine function at various life stages, and the spectrum of effects observed in highly exposed or heterogeneous populations. Such measurements facilitate prospective and retrospective analyses of trends that may be associated with EDCs. Because the chemicals that we measure may change as we learn more about the chemicals of concern, these monitoring and research programs need to be structured so as to exchange information and be responsive to the changing science.

Exposure determinations/follow-up: Exposure monitoring is important to gauge the extent of EDC contamination in the environment and to determine the levels of exposure in human and wildlife populations that may be associated with adverse effects. Delineation of the distributions of exposures in the environment and in biological tissues of exposed organisms is a critical step in prioritizing the chemicals for biological effects. Monitoring programs that measure chemical contamination in the environment or in food provide the only indication of changes in levels of contamination. Therefore, the continuation of existing environmental monitoring programs, such as those mentioned above, is crucial, provided they become more oriented toward issues particular to EDCs (i.e., they include monitoring of chemicals and biological endpoints of concern for endocrine disruption). Existing exposure and effects data should be compiled and evaluated in a systematic manner to deduce local and national trends in EDCs and population level effects. It is important that the data these programs provide are analytically comparable and complementary from a risk assessment perspective.

From an ecological perspective, data that are collected to characterize the relative

risk of endocrine disrupting chemicals need to be consistent, in terms of the endpoints measured. This becomes critical for coordinating existing monitoring programs so they include the biological endpoints that are indicative of the effects of EDCs in individuals and populations. Ideally there should be an overlap of measurements across different monitoring efforts. Although coordinating efforts among monitoring programs is not necessarily a research issue, it is important from a standpoint of a coherent national assessment program. There is also a need to better understand the fate and transport of new and existing EDCs within and between environmental compartments (air, water, sediment, biota).

Population monitoring programs help identify populations at risk. Studies should be conducted to identify and evaluate highly exposed wildlife and human populations (e.g., DES- and PCB-exposed sons and daughters). For comparison, populations exposed to ambient levels of endocrine disruptors should be included, although attention must be paid to the possibility that synergistic interactions could place these populations at risk. Further, the effects of EDCs may be latent in onset, and multiple intervening risk factors and exposures may be present prior to expression of the adverse effect, regardless of whether the exposures are to background or highly elevated levels of contamination. Assessments should focus on vulnerable groups, both in terms of sensitive life stages and, in the case of humans, lifestyle. In wildlife populations, exposure analyses will require the development and validation of monitoring tools. They also will require live capture research using non-invasive sampling techniques for accessible biological fluids and tissues (e.g., blood, urine, fat and gametes) to establish appropriate baselines of endocrine normality. Collectively, this research will help provide useful information on population variations as well as regional and seasonal effects.

Multidisciplinary research: Evaluations of human health and ecological effects are most useful when information is consolidated from multiple scientific disciplines (immunotoxicology, neurotoxicology, reproductive toxicology, carcinogenicity, ethology) and from various levels of organization (molecular/mechanistic, phylogenetic, trophic). Consequently, well-planned and coordinated research on endocrine disruption is encouraged. Laboratory and field studies should be better integrated: hypotheses generated by field studies should be pursued in more controlled laboratory conditions and relationships between particular chemicals and adverse effects identified in controlled laboratory studies should be followed up in field studies where similar exposures are documented to occur. A broader suite of laboratory test endpoints should be developed to help facilitate laboratory-to-field extrapolations. Lines of communication among human health and ecological effects researchers and between laboratory based scientists and field biologists and epidemiologists should be improved.

Sentinel species: Sentinel species are those that by virtue of their unique physiology, behavior, or position in the food web are among the first to respond to environmental stressors, be they related to habitat destruction, pollutant introduction or other factors. The identification and subsequent monitoring in the environment of sentinel

species susceptible to the effects of EDCs is an important way to provide an early warning sign of EDC contamination. To develop better linkage studies between the field and the laboratory, criteria to evaluate these species should 1) be easy and inexpensive to maintain, 2) breed readily in laboratory settings, 3) have fairly ubiquitous distribution in the environment, 4) be ecologically relevant and representative of a large number of species, and 5) there should be substantial baseline information available. Also of importance are the different life histories or developmental strategies that might make some species more susceptible to EDCs than others. It is not known at this time whether diagnostic indicators of EDC effects can be developed. Past research has not been designed to demonstrate a link between community structure or ecosystem function and EDC effects on populations. There is also a need to evaluate, characterize and develop test methods for potentially sensitive, but historically neglected species in terms of potential impact of EDCs such as invertebrates, amphibians, several songbird species, cartilaginous fish and marine mammals. Some of these animals appear to be suffering regional or global decline, but we currently have no way to evaluate any link to EDC exposures.

Database development: Databases provide a systematic way to organize information for use in problem formulation and retrospective risk assessment. They are the basis by which time-related trends are identified. There may be opportunities to use existing databases--such as records of occupational or medical exposures to endocrine disruptors--to assess current or historical effects of EDCs. Other databases, such as those containing population census data or surveillance data on the occurrence of tumors in wildlife species, need to be routinely reviewed and updated. One of the largest such database, located at the Registry for Tumors in Lower Animals, serves as a diagnostic center, repository, and information clearinghouse for tumors in wild cold-blooded vertebrates and invertebrates. It could serve as a model for higher (avian and mammalian) wildlife species. Rigorous research efforts are needed to develop meaningful new databases. Specific areas where information systems are needed include: 1) a compilation of the results of chemicals in various short-term screening tests and *in vivo* bioassays to assist in the evaluation of their sensitivity, specificity and general predictiveness;
2) prospective and retrospective analysis of reproductive health trends in humans to determine whether potentially hormone related effects, such as a decline in semen quality, is a global occurrence or limited to specific geographical regions and to determine temporal and regional trends in testicular cancer and urogenital birth defects, such as hypospadias; 3) field data on hormone levels or tissue burdens of EDCs to establish baselines and to assist in the design of future experimental assessments; and 4) a global inventory of ongoing endocrine disruptor research to ensure that key uncertainties are being addressed and that redundancies are kept to a minimum.

CONCLUSIONS

The potential for disruption of endocrine function by chemical contaminants is of

sufficient concern to warrant a concerted Federal research effort. Given the widespread distribution and persistence of some EDCs in the environment and the potential for serious effects in human, fish and wildlife populations, a Federal research strategy is needed. Based upon existing knowledge of the problem, biological research is needed to: 1) characterize the effects of EDCs on organisms, particularly as related to carcinogenesis, and reproductive, neurologic and immunologic systems; and 2) evaluate and characterize mixtures in terms of modes of action and potential for synergistic action. Basic research is required to strengthen the scientific foundation for risk estimation (e.g., baseline studies on endocrine function across classes of animals could reduce the uncertainty associated with species extrapolations). Tools are needed to help translate the information from basic research and mechanism-of-action studies into predictive models for application in the risk assessment process. In the area of exposure, we need to assess the nature and extent of contamination, including integration and utilization of exposure monitoring programs. Exposure assessments must emphasize critical stages of development and consider windows of vulnerability, both temporal and seasonal. Finally, research is needed that connects exposure information with biological effects to build the causal link needed to interpret human epidemiological and ecological field studies. In general, linking specific exposures in the environment to specific adverse health effects in humans will be difficult due to the complexities of exposure, the latency of the effects, and the subtle nature of some outcome. However, the framework presented in this document will provide a foundation for developing a cohesive federal program focused on the most relevant scientific issues.

NEXT STEPS

This document, in conjunction with the inventory effort recently completed, will be used to analyze current Federal research efforts related to endocrine disruptors. Using the expertise of Federal and other scientists, research gaps will be identified, and a research plan for filling those gaps, particularly with respect to high priority areas, will be developed. The CENR plans to work with non-Federal research funding entities, such as industry groups and universities, as well as other countries, to understand the full range of research being conducted on endocrine disruptors.

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Appendix

The EPA Workshops

The Environmental Protection Agency's Office of Research and Development (ORD) conducted two workshops in response to the growing concern about the effects of endocrine disrupting chemicals on human health and the environment. The objective of the workshops was to craft a strategy for assessing the risk of endocrine disruption and to achieve consensus on research needs in the areas of human and ecological effects. The first workshop was held in April of 1995 in Raleigh, NC, and in June, 1995, a follow-up workshop designed to define more clearly the research needs for ecological effects was convened in Duluth, MN.

Over 100 invited scientific experts from Federal agencies, industry, academia, independent organizations, and public interest groups were represented. An international perspective was brought to the workshops by involving scientists and regulators from Canada, Britain, Denmark, Germany, and Sweden. Areas of expertise included risk assessment, comparative endocrinology, environmental toxicology, animal and human toxicology, field ecology, epidemiology, and exposure assessment. Also in attendance were several hundred interested observers.

Workshop participants were challenged to summarize the current state of knowledge regarding the effects of endocrine disruptors, to identify uncertainties associated with the reported effects, to describe research that would assist the federal government in making informed decisions regarding the regulatory and public health implications of exposure to EDCs, and to establish priorities for future research activities. For purposes of clarification, 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 beyond that of "environmental estrogens" to include, for example, anti-androgens and agents that act on other components of the endocrine system, such as the thyroid, adrenal and pituitary glands.

In the first workshop (Kavlock *et al.*, 1996), participants were divided into groups to discuss research needs related to the principal health effects attributed to endocrine disruptors (carcinogenesis, neurotoxicity, reproductive and developmental toxicity, and immunotoxicity) as well as research needs to improve specific components of risk assessment (hazard detection, dose-response analysis, exposure assessment, and risk characterization). The second workshop (Ankley *et al.*, 1996) emphasized the risks of EDCs to environmental health; breakout sessions addressed topics related to the integration and implementation of research, field ecology considerations, laboratory-based issues, and topical areas related to risk (assessment endpoints, measurement endpoints, and exposure assessment).

ABSTRACT

A growing body of scientific evidence has begun to suggest that a range of chemicals introduced into the environment by humans may be producing adverse health effects in humans and in wildlife species by disrupting endocrine system function. In some instances it is clear that such chemicals, referred to as endocrine disrupting chemicals (EDCs) have induced a variety of adverse health effects in humans and wildlife. While this issue has attracted considerable attention in the scientific community over the last several years, there is a great deal to be learned about the extensiveness of the chemical classes that can act as endocrine disruptors, their concentrations in the environment, and their ability to induce specific adverse health effects. To coordinate the Federal government's response to this issue, a Work Group on Endocrine Disruptors was formed under the auspices of the NSTC's Committee on Environment and Natural Resources (CENR). This document, which is the first product of the Work Group, reviews the current state of the science and major uncertainties related to endocrine disrupting chemicals and establishes a framework for research areas that need attention. This framework categorizes major research needs into three groups; methods development, model development, and laboratory and field data acquisition. The next phase of the CENR effort will match these needs against current Federally funded research efforts to identify priority research areas and to develop a coordinated, interagency research plan. Ultimately, the Work Group plans to expand this assessment process to include organizations outside the Federal government that are also conducting research on this issue.

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