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**SPECIAL REPORT ON
ENVIRONMENTAL ENDOCRINE DISRUPTION:
AN EFFECTS ASSESSMENT
AND ANALYSIS**

**Prepared for the
Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, D.C. 20460**

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LIST OF ACRONYMS/ABBREVIATIONS

alpha-noradrenergic
aryl hydrocarbon
androgen insensitivity syndrome
anti-Mullerian hormone
alkylphenol-polyethoxylates
androgen receptor
bleached Kraft mill exposure
3', 5' cyclic AMP
choline acetyl transferase
central nervous system
tetrachlorodiphenylethane
dichlorodipenyldichloroethylene
dichlorodiphenyltrichloroethane
diethylstilbestrol
dihydrotestosterone
estradiol/testosterone ratio
ethylene thiourea
follicle-stimulating hormone
gonadotropin-releasing hormone
human chorionic gonadotropin
luteinizing hormone
MAB N-hydroxy-3,2'-dimethyl-4-amino biphenyl
no observed **effects** level
polycyclic aromatic hydrocarbons
polychlorinated biphenyls
polychlorinated dibenzodioxin
propyl thi ouraci l
carcinogenic **potency** factor
reference dose
sex/steroid hormone-binding globulin
triiodothyronine
thyroxine
thyroxine-binding globulin
tributyltin
tetrachlorodibenzo-p-dioxin
2,3,7,8-tetrachlorodibenzo-furan
testosterone-estrogen-binding globulin
tetrahydrocannabinol
temperature-dependent sexual determination
thyroid-stimulating hormone
ultraviolet

PREFACE

The U.S. Environmental Protection Agency (EPA) Risk Assessment Forum was established to promote scientific consensus on risk assessment issues and to ensure that this consensus is incorporated into appropriate risk assessment guidance. To accomplish this, the Risk Assessment Forum assembles experts throughout EPA in a formal process to study and report on these issues from an Agencywide perspective. For major risk assessment activities, the Risk Assessment Forum has established Technical Panels to conduct scientific reviews and analyses. Members are appointed to assure that necessary technical expertise is available.

Recently, a number of ecologists, epidemiologists, endocrinologists, and toxicologists have drawn attention to the potential hazardous effects that estrogenlike and antiandrogenic chemicals and certain other environmental chemicals may have on human health and ecological well-being. A hypothesis has been proposed that certain chemicals may disrupt the endocrine system. These chemicals have been called "endocrine disruptors" because they are thought to mimic natural hormones, inhibit the action of hormones, or alter the normal regulatory function of the immune, nervous, and endocrine systems. Possible human health endpoints affected by these agents include breast cancer and endometriosis in women, testicular and prostate cancers in men, abnormal sexual development, reduced male fertility, alteration in pituitary and thyroid gland function, immune suppression, and neurobehavioral effects.

In addition to potential human health effects, reports have accumulated that many chemicals that enter the environment can disrupt normal endocrine function in a variety of aquatic life and wildlife. Some of the deleterious effects observed in animals have been attributed to some persistent organic chemicals such as polychlorinated biphenyls, DDT (dichlorodiphenyl-dimethoxyethane), dioxin, and some pesticides. Adverse effects include abnormal thyroid function and development in fish and birds; decreased fertility in shellfish, fish, birds, and mammals; reduced hatching success in fish, birds, and reptiles; demasculinization and feminization of fish, birds, and mammals; defeminization and masculinization of gastropods, fish, and birds; reduced offspring survival; and alteration of immune and behavioral function in birds and mammals. It has been proposed that the above adverse effects may be due to an endocrine disrupting mechanism.

The EPA has followed closely the recent reports dealing with the potential effects of environmental endocrine disruptors on human health and ecological well-being. EPA's Science Advisory Board requested that the Risk Assessment Forum prepare a Technical Panel report that provide an overview of the current state of the science relative to endocrine disruption. It was decided that this report serve as an interim assessment to inform Agency risk assessors of the

for findings and uncertainties and to serve as a basis for a Science Policy Council position statement.

Science Policy Council's Interim Position

The EPA is aware of and concerned about information indicating the possibility of adverse effects on human health and the environment associated with exposure to endocrine disruptors. At the present time, however, there is little knowledge of or agreement on the extent of the problem. Based on the current state of the science, the Agency does not consider endocrine disruption to be an adverse endpoint *per se*, but rather to be a mode or mechanism of action essentially leading to other outcomes, for example, carcinogenic, reproductive or developmental effects, routinely considered in reaching regulatory decisions. Evidence of endocrine disruption can influence priority setting for further testing and the assessment of the results of this testing could lead to regulatory action if adverse effects are shown to occur. This position could change as additional data become available on the mechanisms and role of endocrine disruptors.

The Agency thinks that identification of environmental agents that cause adverse effects as a result of endocrine disruption, as well as enhancement of our understanding of how these agents exert their effects, will improve the EPA's ability to reduce or prevent risks, particularly to children and vulnerable ecosystems. These considerations become increasingly important as we expand our risk assessment activities to incorporate a wider range of susceptible populations, multiple pathways of exposure, and mixtures of chemical substances.

Further research and testing are needed to address existing gaps in knowledge concerning consequences of endocrine disruption. Such knowledge will reduce uncertainties in the assessment of hazard, exposure, and risk. The Agency is working with other federal agencies, as well as academic, international, and industry groups to expand the body of defensible and credible information and data on this issue. Several major activities are underway that address these needs. Some of these are listed below.

Examples of activities:

1. EPA is co-sponsoring the detailed review and interpretation of the existing literature on endocrine disruption currently underway at the National Academy of Sciences' National Research Council. This study is expected to be completed later this year;
2. EPA has developed and is implementing a multi-year endocrine disruptors research strategy;
3. EPA chairs the Workgroup convened by the President's Office of Science and Technology Policy tasked to document and then coordinate research on endocrine disruptors

the federal government. Also, this activity serves as the basis for pursuing coordination of
on an international level;

Under the mandates of the Food Quality Protection Act (FQPA) of 1996 and the 1996
amendments to the Safe Drinking Water Act (SDWA), EPA has established an advisory
committee to assist in developing a screening and testing strategy for evaluating chemicals for
potential to cause effects via endocrine disruption. The FQPA requires that the strategy be
developed and peer reviewed within two years, implemented during the third year, and that a
report be submitted to the Congress by the end of the fourth year.

EPA continues to stay abreast of scientific developments and will take regulatory action
where sound scientific information and prudent public policy dictate. We are currently
committed to pursuing domestic and international opportunities for exposure/risk reduction
of endocrine disruptors.

1. EXECUTIVE SUMMARY

SCOPE OF DOCUMENT AND AREAS CONSIDERED

This document provides an overview of the current state of the science relative to environmental endocrine disruption in humans, laboratory testing, and wildlife species. It is intended to serve as an *interim assessment and analysis of the environmental endocrine disruption hypothesis* until a more extensive exploration of environmental endocrine disruption is completed by the National Academy of Sciences (NAS). The present document is *not* intended to address all of the endocrine glands that might be disrupted by environmental insult. Furthermore, the document does not address high occupational or accidental human exposures. Rather, this document focuses on those reports of adverse human and ecological effects where a common theme of endocrine system disruption by environmental agents has been hypothesized or demonstrated.

An environmental endocrine disruptor is defined as an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior. Background information is presented on the field of endocrinology, the nature of hormones, and potential sites for endocrine disruption, with specific examples of chemicals affecting these sites. An attempt is made to present objectively the issue of endocrine disruption, consider working hypotheses, offer opposing viewpoints, analyze the available information, and provide a reasonable assessment of the problem. Emphasis is placed on disruption of central nervous system-pituitary integration of hormonal and sexual behavioral activity, female and male reproductive system development and function, and thyroid function. In addition, the potential role of environmental endocrine disruption in the induction of breast, testicular, and prostate cancers, as well as endometriosis, is evaluated. The interrelationship of the endocrine and immune system is documented. Finally, some data gaps in our understanding of the environmental endocrine disruption issue are identified and a few future research needs are recommended. A research strategy dealing with this issue is being developed within EPA.

With respect to endocrine-related ecological effects, specific examples in the peer-reviewed literature are presented and discussed. For each topic area, data gaps and areas of uncertainty are discussed, conclusions are drawn, and general research needs are suggested.