Chapter 1: Executive Summary

1.1 Purpose and Scope of Document

The last two decades have witnessed growing scientific concerns and public debate over the potential adverse effects that may result from exposure to a group of chemicals that have the potential to alter the normal functioning of the endocrine system in wildlife and humans. Concerns regarding exposure to these EDCs are due primarily to 1) adverse effects observed in certain wildlife, fish, and ecosystems; 2) the increased incidence of certain endocrine-related human diseases; and 3) endocrine disruption resulting from exposure to certain environmental chemicals observed in laboratory experimental animals. These concerns have stimulated many national governments, international organizations, scientific societies, the chemical industry, and public interest groups to establish research programs, organize conferences and workshops, and form expert groups and committees to address and evaluate EDC-related issues. Many of the proceedings of these workshops and/or committees have been published (see Table 2.1) and served as background material for this publication.

However, in the light of continuing uncertainties and highly publicized concerns, the International Programme on Chemical Safety was requested to provide an objective, global assessment of the current state-of-the-science relative to environmental endocrine disruption in humans, experimental studies, and wildlife species. This assessment builds on existing reviews and documents but is not intended to 1) cover all of the endocrine systems that may be disrupted by environmental exposures, 2) assess available test methodologies for detecting EDCs, or 3) address risk assessment and risk management issues. Rather, it focuses on the global peer-reviewed scientific literature where the associations between environmental exposures and adverse outcomes have been demonstrated or hypothesized to occur via mechanisms of endocrine disruption. Endocrine disruption is not considered a toxicological end point per se but a functional change that may lead to adverse effects. For the purposes of this document, a slight modification of the Weybridge (1996) definition was used and endocrine disruptors are defined in a generic sense as follows:

> An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.
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> A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations.

List of Abbreviations

DDE Dichlorodiphenyl dichloroethylene
DDT Dichlorodiphenyl trichloroethane
EDCs Endocrine-disrupting chemicals
GLEMEDS Great Lakes embryo mortality, edema, and deformity syndrome
PCBs Polychlorinated biphenyls
TBT Tributyl tin

Concerns regarding EDCs have generated a vast number of divergent research studies conducted under various conditions and examining various outcomes. It is extremely rare that a single study could provide all the necessary relevant information to link a particular exposure scenario to a particular health outcome in wildlife or humans. Therefore, it is essential to evaluate the entire body of relevant knowledge. A unique feature of this assessment document for evaluating diverse data sets is that it provides a framework and utilizes objective criteria for assessing causality between exposures to EDCs and selected outcomes (see Chapter 7).

Chapter 2 summarizes critical generic issues (e.g., exposure–outcome associations, dose–response relationships, role of natural hormones and phytoestrogens, etc.), several of which are particularly relevant to EDCs.

Chapter 3 provides background information on the endocrine system, the role of hormones, and potential mechanisms of endocrine disruption along with specific chemical examples of multiple modes of action. The emphasis is on the vertebrate endocrine system and on the hypothalamic-pituitary-gonad, hypothalamic-pituitary-adrenal, and hypothalamic-pituitary-thyroid axes.

Potential adverse outcomes in both wildlife (Chapter 4) and humans (Chapter 5) have focused mainly on reproductive and sexual development and function; altered immune, nervous system, and thyroid function; and hormone-related cancers. Selected data sets illustrating exposure to certain EDCs in different parts of the world are discussed in Chapter 6, along with a discussion of exposure issues particularly relevant to EDCs.

As mentioned, Chapter 7 describes a framework for evaluating the collective information from diverse data sets in a structured manner to provide objective assessments of the state-of-the-science of determining causality between exposures to EDCs and selected outcomes. Chapter 8 summarizes the conclusions and lists some general research recommendations.

1.2 Endocrine Mechanisms of Action

Research has clearly shown that EDCs can act at multiple sites via multiple mechanisms of action. Receptor-mediated mechanisms have received the most attention, but other mechanisms (e.g., hormone synthesis, transport, and metabolism) have been shown to be equally important. For most associations reported between exposure to EDCs and a variety of biologic outcomes, the mechanism(s) of action are poorly understood. This makes it difficult to distinguish between direct and indirect effects and primary versus secondary effects of exposure to EDCs. It also indicates that considerable caution is necessary in extrapolating from *in vitro* data to *in vivo* effects, in predicting effects from limited *in vivo* data, and in extrapolating from experimental data to the human situation. A collective weight of evidence is essential in determining under what conditions observed effects resulting from exposure to EDCs occur via endocrine-mediated mechanisms. This document outlines a number of criteria that can be used as a basis for attribution of an effect to an endocrine-mediated mechanism (see section 3.16).

Despite an overall lack of knowledge of mechanisms of action of EDCs, there are several examples where the mechanism of action is clearly related to direct perturbations of endocrine function and ultimately to adverse *in vivo* effects (see section 3.12). These examples also illustrate the following important issues:

- Exposure to EDCs during the period when "programming" of the endocrine system is in progress may result in a permanent change of function or sensitivity to stimulatory/inhibitory signals.
- Exposure in adulthood may be compensated for by normal homeostatic mechanisms and may therefore not result in any significant or detectable effects.
- Exposure to the same level of an endocrine signal during different life history stages or during different seasons may produce different effects.
- Because of cross talk between different components of the endocrine systems, effects may occur unpredictably in endocrine target tissues other than the system predicted to be affected.

Considerable data are available on the early molecular events involved in hormone response, but there is little knowledge of the relationship between these molecular events and the potential for adverse health outcomes. Until such data become available, it will remain difficult and controversial to attribute adverse effects due to endocrine-mediated pathways.

1.3 Dose–Response Relationships

The issue of dose–response relationships is perhaps the most controversial issue regarding EDCs. One of the reasons is that EDCs often act by mimicking or antagonizing the actions of naturally occurring hormones. These hormones (often more potent than exogenous EDCs) are present at physiologically functional concentrations, so the dose–response considerations for EDCs are often different than for other environmental chemicals, which are not acting directly on the endocrine system. Reports of low-dose effects of EDCs are highly controversial and the subject of intense research. Dose–response relationships are likely to vary for different chemicals and endocrine mechanisms. Timing of exposure is absolutely critical to the understanding of dose–response relationships for EDCs. This is true for both wildlife and humans and for cancer as well as for developmental, reproductive, immunological, and neurological effects. Numerous examples exist in the literature where age at exposure is a known risk factor.

1.4 Effects in Wildlife

Several field and laboratory studies have shown that exposure to certain EDCs has contributed to adverse effects in some wildlife species and populations. These effects vary from subtle changes in the physiology and sexual behavior of species to permanently altered sexual differentiation. Most of the data come from Europe and North America. Aquatic species (at the top of the food chain) are most affected, but effects have also been observed in terrestrial species. Some adverse effects observed in certain species are likely to be endocrine mediated, but in most cases, the causal link between exposure and endocrine disruption is unclear. Examples include the following:

Mammals: Exposure to organochlorines (PCBs, DDE) has been shown to adversely impact the reproductive and immune function in Baltic seals, resulting in marked population declines. These seals exhibit a compromised endocrine system, but precise mechanisms of action remain unclear.

Birds: Eggshell thinning and altered gonadal development have been observed in birds of prey exposed to DDT, resulting in severe population declines. A syndrome of embryonic abnormalities (known as GLEMEDS) has been observed in fish-eating birds and can be directly related to PCB exposure, but the precise linkage to endocrine function is uncertain.

Reptiles: A presumed pesticide spill in Lake Apopka (Florida, USA) provides a well-publicized example of potential EDC effects on population decline in alligators. A variety of gonadal and developmental abnormalities were observed that have been attributed to high levels of various organochlorine contaminants that disrupt endocrine homeostasis. Several hypotheses have been proposed to explain the contaminant-induced endocrine disruption, but the precise cause(s) is not known.

Amphibians: Population declines in amphibians has been observed in both pristine and polluted habitats worldwide. Currently, the data are insufficient to implicate EDCs as causative agents.

Fish: There is extensive evidence that chemical constituents present in pulp and paper mill effluents and sewage treatment effluents can affect reproductive endocrine function and contribute to alteration in reproductive development. A variety of mechanisms (e.g., hormone–receptor interactions, interference with sex steroid biosynthesis, altered pituitary function) are involved, but precise modes of action or the causative chemicals are still poorly understood.

Invertebrates: Exposure of marine gastropods to TBT (a biocide used in antifouling paints) provides the clearest example in invertebrates of an endocrine-mediated adverse effect caused by exposure to an environmental contaminant. Masculinization of marine gastropods exposed to TBT has resulted in worldwide declines of gastropods. The endocrine mechanism probably involves elevated androgen levels possibly through altered aromatase activity.

Studies in wildlife have been proposed as "sentinels" of human exposure to EDCs. However, given the diversity of wildlife, caution must be taken in extrapolating the responses to EDCs, as research has focused primarily on only a few species of wildlife. Also, potential effects of EDCs on wildlife tend to focus on the individual, whereas ecological risk assessments focus on populations and communities. The significance of disturbances in reproductive output and viability of offspring on populations is difficult to quantify. Overall, the current scientific knowledge provides evidence that certain effects observed in wildlife can be attributed to chemicals that function as EDCs. However, in most cases, the evidence of a causal link is weak, and most effects have been observed in areas where chemical contamination is high.

1.5 Human Health Effects

Analysis of the human data by itself, while generating concerns, has so far failed to provide firm evidence of direct causal associations between low-level (i.e., levels measured in the general population) exposure to chemicals with EDCs and adverse health outcomes. It is difficult to compare and integrate results from diverse human studies, because data are often collected at different time periods, using different experimental designs and under different exposure conditions. Often exposure data are completely lacking. Of particular concern is the lack of exposure data during critical periods of development that influence later functioning in adult life. Furthermore, the concentrations and potencies of endogenous hormones and phytoestrogens are generally higher than those of exogenous chemicals. Despite these difficulties, exposure to EDCs has been suggested to play a role in adverse health outcomes, and concerns remain. The following examples illustrate these concerns:

Reproductive Effects: A number of studies report a decline (since the 1930s) in human sperm quality in several countries. There clearly are important variations in sperm count, both within and between countries, but there are no firm data that directly addressed

the possible cause and effect relationship between declining sperm quality and exposure to EDCs. Studies to date have been retrospective. Several meta-analyses of existing studies reached different conclusions, and the issue remains controversial. Even if there has been deterioration in semen quality, this would not necessarily be due to endocrine disruption.

Available human and experimental animal studies demonstrate that high-level exposure to certain environmental chemicals can impair fertility and increase the rate of spontaneous abortion, but the relationship to endocrine disruption remains speculative.

Declining sex ratios (fewer males) have been recorded in a number of regions and countries, and there is evidence that unidentified external influences are associated with such changes, but the mechanism(s) is unknown.

Temporal increases in the frequency of development abnormalities of the male reproductive tract, particularly cryptorchidism and hypospadias, have been reported, but the role of exposure to EDCs is unclear. Experimental data show that a number of chemicals can disrupt development of the male reproductive tract via endocrine mechanisms.

Endometriosis: Exposure to certain EDCs has been reported to be associated with endometriosis, but the studies remain equivocal.

Precocious Puberty: Concerns have been raised about the influence of EDCs on the timing of puberty, but the possible mechanisms of action and role of other factors such as nutrition need to be clarified.

Neural Function: Data from human and experimental animal studies clearly indicate that exposure (particularly prenatal exposure) to certain EDCs (e.g., PCBs) can have adverse effects on neurological development, neuroendocrine function, and behavior. Some of these effects appear to result from altered thyroid or neurotransmitter function, but in most instances endocrine mechanisms have not been demonstrated. Similar effects can also result from exposure to chemicals that induce developmental neurotoxicity but have no known endocrine action.

Immune Function: Exposure to environmental chemicals, including certain EDCs, has been shown to alter immune function in humans and animals. However, it is not clear whether such impaired function is due to endocrine-mediated mechanisms.

Cancer: Temporal increases in the incidence of certain cancers listed below in hormonally sensitive tissues in many parts of the industrialized world are often cited as evidence that widespread exposure of the general population to EDCs has had adverse impacts on human health. These increases cannot be adequately explained by improved diagnostic techniques, and it has been argued that these trends coincide roughly with the increased use and release of industrial chemicals into the environment.

Breast Cancer: Numerous human epidemiological studies and experimental laboratory studies have been conducted to determine whether environmental EDCs may contribute to an increased risk of breast cancer, but the current scientific evidence does not support a direct association between exposure to environmental EDCs and increased risk of breast cancer. However, studies published to date have measured EDC exposure levels in adult women; data on exposures during critical periods of development are lacking. Adult women currently at risk for breast cancer may have been exposed to exogenous EDCs *in utero* or during infancy, childhood, and adolescence in the mid-twentieth century when contaminant levels of organochlorines were higher.

Endometrial Cancer: Limited available data do not support a causative role for EDCs in endometrial cancer.

Testicular Cancer: Temporal increases in the incidence of testicular cancer have been reported in certain countries, but rates vary considerably among countries. The risk started rising around 1910 in Nordic countries, and somewhat earlier in England and Wales, and therefore cannot be attributed solely to chemicals introduced in the mid or late twentieth century. Some evidence suggests that the incidence of cryptorchidism and hypospadias may show similar geographic variations to the incidence of testicular cancer and that these conditions may be developmentally linked. However, EDC exposure data for critical periods are lacking.

Prostate Cancer: Exposure to certain pesticides and organochlorines has been linked to increases in the incidence of prostate cancer in a few limited studies, but most studies have found no association, and the mechanism is unknown.

Thyroid Cancer: A direct association between exposure to EDCs and thyroid cancer has not been demonstrated.

Overall, the biological plausibility of possible damage to certain human functions (particularly reproductive and developing systems) from exposure to EDCs seems strong when viewed against the background of known influences of endogenous and exogenous hormones on many of these processes. Furthermore, the evidence of adverse outcomes in wildlife and laboratory animals exposed to EDCs substantiates human concerns. The changes in human health trends in some areas (for some outcomes) are also sufficient to warrant concern and make this area a high research priority, but non-EDC mechanisms also need to be explored.

1.6 Exposure

Often the weakest link in determining whether observed adverse effects in humans and/or wildlife are linked to EDCs is the absence of adequate exposure data. Often data are limited to accidentally highly exposed groups. Most exposure information has focused on the presence of persistent organic pollutants in Europe and North America. Data on the magnitude and trends of global human or wildlife exposure are limited. Potential sources of exposure are through contaminated food, contaminated groundwater, combustion sources, and contaminants in consumer products. Information on exposure during critical development periods is generally lacking. The exposure data sets that exist are primarily for various environmental media (air, food, water) rather than the most relevant internal exposure (blood, tissue). Limited exceptions are human breast milk and adipose tissue samples. Worldwide, despite large expenditures of money, time, and effort, comparable data sets for assessing exposures to EDCs for humans or wildlife are not available. Such information is essential to adequately evaluate exposure–response relationships in field and epidemiology studies and to use these relationships to produce credible risk assessments.

1.7 Causal Criteria and Weight of Evidence for Effects Resulting from Exposure to EDCs

Chapter 7 outlines a structured format [based on modifications of criteria proposed by Bradford-Hill (1965), Fox et al. (1991), and Ankley et al. (1997)] for assessing postulated relationships between altered health outcomes and exposure to EDCs. Examples (see Tables 7.1 and 7.2) were selected to illustrate the broad range of data (or lack thereof) available for determining the overall strength of the evidence for causal associations for a particular outcome and exposure of concern. These examples illustrate that for many hypotheses there are insufficient data to reach any definitive conclusions. However, in some examples there is sufficient evidence for endocrine-mediated effects to warrant concerns.