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The Impact of Endocrine Disruption: A Consensus Statement on the State of the Science

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In 2002, the joint International Programme on Chemical Safety (IPCS) of the World Health Organization (WHO), the United Nations Environment Programme (UNEP), and the International Labour Organisation (ILO) published a report titled *Global Assessment of the State-of-the-Science of Endocrine Disruptors* (http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/). Since 2002, intense scientific work has improved our understanding of the impacts of endocrine-disrupting chemicals (EDCs) on human and wildlife health, such that in 2012, the UNEP and WHO, in collaboration with international experts, have produced an updated document on EDCs, *State of the Science of Endocrine Disrupting Chemicals - 2012* (<http://www.who.int/ceh/publications/endocrine/en/index.html>) that includes scientific information on human and wildlife impacts and lists key concerns for decision makers and others concerned about the future of human and wildlife health.

The basis for these key concerns is described in the *State of the Science of Endocrine Disrupting Chemicals - 2012* (<http://www.who.int/ceh/publications/endocrine/en/index.html>) and includes extensive references to the science behind the concerns. A shorter summary, primarily for decision makers, elaborates on the key concerns listed below and also on suggested considerations related to EDCs (*State of the Science of Endocrine Disrupting Chemicals - 2012: Summary for Decision-Makers*; <http://www.who.int/ceh/publications/endocrine/en/index.html>).

The key concerns noted in the *State of the Science of Endocrine Disrupting Chemicals - 2012* (<http://www.who.int/ceh/publications/endocrine/en/index.html>) are as follows:

- Human and wildlife health depends on the ability to reproduce and develop normally. This is not possible without a healthy endocrine system.
- Three strands of evidence fuel concerns over endocrine disruptors:
 - The high incidence and the increasing trends of many endocrine-related disorders in humans;
 - Observations of endocrine-related effects in wildlife populations;
 - The identification of chemicals with endocrine disrupting properties linked to disease outcomes in laboratory studies.

- Many endocrine-related diseases and disorders are on the rise.
 - Large proportions (up to 40%) of young men in some countries have low semen quality, which reduces their ability to father children.
 - The incidence of genital malformations, such as non-descending testes (cryptorchidisms) and penile malformations (hypospadias), in baby boys has increased over time or levelled off at unfavourably high rates.
 - The incidence of adverse pregnancy outcomes, such as preterm birth and low birth weight, has increased in many countries.
 - Neurobehavioural disorders associated with thyroid disruption affect a high proportion of children in some countries and have increased over past decades.
 - Global rates of endocrine-related cancers (breast, endometrial, ovarian, prostate, testicular and thyroid) have been increasing over the past 40–50 years.
 - There is a trend towards earlier onset of breast development in young girls in all countries where this has been studied. This is a risk factor for breast cancer.
 - The prevalence of obesity and type 2 diabetes has dramatically increased worldwide over the last 40 years. WHO estimates that 1.5 billion adults worldwide are overweight or obese and that the number with type 2 diabetes increased from 153 million to 347 million between 1980 and 2008.
- Close to 800 chemicals are known or suspected to be capable of interfering with hormone receptors, hormone synthesis or hormone conversion. However, only a small fraction of these chemicals have been investigated in tests capable of identifying overt endocrine effects in intact organisms.
 - The vast majority of chemicals in current commercial use have not been tested at all.
 - This lack of data introduces significant uncertainties about the true extent of risks from chemicals that potentially could disrupt the endocrine system.
- Human and wildlife populations all over the world are exposed to EDCs.
 - There is global transport of many known and potential EDCs through natural processes as well as through commerce, leading to worldwide exposure.
 - Unlike 10 years ago, we now know that humans and wildlife are exposed to far more EDCs than just those that are POPs [persistent organic pollutants].
 - Levels of some newer POPs in humans and wildlife are still increasing, and there is also exposure to less persistent and less bioaccumulative, but ubiquitous, chemicals.

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- New sources of human exposure to EDCs and potential EDCs, in addition to food and drinking-water, have been identified.
 - Children can have higher exposures to chemicals compared with adults—for example, through their hand-to-mouth activity and higher metabolic rate.
 - The speed with which the increases in disease incidence have occurred in recent decades rules out genetic factors as the sole plausible explanation. Environmental and other non-genetic factors, including nutrition, age of mother, viral diseases and chemical exposures, are also at play, but are difficult to identify. Despite these difficulties, some associations have become apparent:
 - Non-descended testes in young boys are linked with exposure to diethylstilbestrol (DES) and polybrominated diphenyl ethers (PBDEs) and with occupational pesticide exposure during pregnancy. Recent evidence also shows links with the painkiller paracetamol. However, there is little to suggest that polychlorinated biphenyls (PCBs) or dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyltrichloroethane (DDT) are associated with cryptorchidism.
 - High exposures to polychlorinated dioxins and certain PCBs (in women who lack some detoxifying enzymes) are risk factors in breast cancer. Although exposure to natural and synthetic estrogens is associated with breast cancer, similar evidence linking estrogenic environmental chemicals with the disease is not available.
 - Prostate cancer risks are related to occupational exposures to pesticides (of an unidentified nature), to some PCBs and to arsenic. Cadmium exposure has been linked with prostate cancer in some, but not all, epidemiological studies, although the associations are weak.
 - Developmental neurotoxicity with negative impacts on brain development is linked with PCBs. Attention deficit/hyperactivity disorder (ADHD) is overrepresented in populations with elevated exposure to organophosphate pesticides. Other chemicals have not been investigated.
 - An excess risk of thyroid cancer was observed among pesticide applicators and their wives, although the nature of the pesticides involved was not defined.
 - Significant knowledge gaps exist as to associations between exposures to EDCs and other endocrine diseases, as follows:
 - There is very little epidemiological evidence to link EDC exposure with adverse pregnancy outcomes, early onset of breast development, obesity or diabetes.
 - There is almost no information about associations between EDC exposure and endometrial or ovarian cancer.
 - High accidental exposures to PCBs during fetal development or to dioxins in childhood increase the risk of reduced semen quality in adulthood. With the exception of these studies, there are no data sets that include information about fetal EDC exposures and adult measures of semen quality.
 - No studies exist that explore the potential link between fetal exposure to EDCs and the risk of testicular cancer occurring 20–40 years later.
 - Numerous laboratory studies support the idea that chemical exposures contribute to endocrine disorders in humans and wildlife. The most sensitive window of exposure to EDCs is during critical periods of development, such as during fetal development and puberty.
 - Developmental exposures can cause changes that, while not evident as birth defects, can induce permanent changes that lead to increased incidence of diseases throughout life.
 - These insights from endocrine disruptor research in animals have an impact on current practice in toxicological testing and screening. Instead of solely studying effects of exposures in adulthood, the effects of exposures during sensitive windows in fetal development, perinatal life, childhood and puberty require careful scrutiny.
 - Worldwide, there has been a failure to adequately address the underlying environmental causes of trends in endocrine diseases and disorders.
 - Health-care systems do not have mechanisms in place to address the contribution of environmental risk factors to endocrine disorders. The benefits that can be reaped by adopting primary preventive measures for dealing with these diseases and disorders have remained largely unrealized.
 - Wildlife populations have been affected by endocrine disruption, with negative impacts on growth and reproduction. These effects are widespread and have been due primarily to POPs. Bans of these chemicals have reduced exposure and led to recovery of some populations.
 - It is therefore plausible that additional EDCs, which have been increasing in the environment and are of recent concern, are contributing to current population declines in wildlife species. Wildlife populations that are also challenged by other environmental stressors are particularly vulnerable to EDC exposures.
 - Internationally agreed and validated test methods for the identification of endocrine disruptors capture only a limited range of the known spectrum of endocrine disrupting effects. This increases the likelihood that harmful effects in humans and wildlife are being overlooked.
 - For many endocrine disrupting effects, agreed and validated test methods do not exist, although scientific tools and laboratory methods are available.
 - For a large range of human health effects, such as female reproductive disorders and hormonal cancers, there are no viable laboratory models. This seriously hampers progress in understanding the full scale of risks.
 - Disease risk due to EDCs may be significantly underestimated.
 - A focus on linking one EDC to one disease severely underestimates the disease risk from mixtures of EDCs. We know that humans and wildlife are simultaneously exposed to many EDCs; thus, the measurement of the linkage between exposure to mixtures of EDCs and disease or dysfunction is more physiologically relevant. In addition, it is likely that exposure to a single EDC may cause disease syndromes or multiple diseases, an area that has not been adequately studied.
 - An important focus should be on reducing exposures by a variety of mechanisms. Government actions to reduce exposures, while limited, have proven to be effective in specific cases (e.g. bans and restrictions on lead, chlorpyrifos, tributyltin, PCBs and some other POPs). This has contributed to decreases in the frequency of disorders in humans and wildlife.
 - Despite substantial advances in our understanding of EDCs, uncertainties and knowledge gaps still exist that are too important to ignore. These knowledge gaps hamper progress towards better protection of the public and wildlife. An integrated, coordinated international effort is needed to define the role of EDCs in current declines in human and wildlife health and in wildlife populations.
- With the present state of the science of EDCs, we are now poised to have an important impact on disease prevention. The increase in noncommunicable diseases in humans and wildlife over the past 40 years indicates an important role of the environment in disease etiology. EDCs are an important component of the environmental influences on disease, along with nutrition and other factors. Thus, reducing exposures to EDCs could have an important impact on actual disease prevention. Prevention of disease is always better than intervening after the disease occurs, both in terms of cost and human suffering: The benefits of early action outweigh the costs.
- To take advantage of our current knowledge to improve human and wildlife health by preventing environmentally induced diseases, we propose the following ideas for consideration (*State of the Science of Endocrine Disrupting Chemicals - 2012: Summary for Decision-Makers*; <http://www.who.int/ceh/publications/endocrine/en/index.html>):
- Strengthening knowledge of EDCs:** It is critical to move beyond the piecemeal, one chemical at a time, one disease at a time, one dose approach currently used by scientists studying animal models, humans or wildlife. Understanding the effects of the mixtures of chemicals to which humans and wildlife are exposed is increasingly important. Assessment of EDC action by scientists needs to take into account the characteristics of the endocrine system that are being disrupted, including tissue specificity and sensitive windows of exposure across the lifespan. While there are different perspectives on the importance of low-dose effects and non-monotonic dose–response curves for EDCs, this issue is important in determining whether current testing protocols are sufficient to identify EDCs. Interdisciplinary efforts that

combine knowledge from wildlife, experimental animal and human studies are needed to provide a more holistic approach for identifying the chemicals that are responsible for the increased incidence of endocrine-related disease and dysfunction. The known EDCs may not be representative of the full range of relevant molecular structures and properties due to a far too narrow focus on halogenated chemicals for many exposure assessments and testing for endocrine disrupting effects. Thus, research is needed to identify other possible EDCs. Endocrine disruption is no longer limited to estrogenic, androgenic and thyroid pathways. Chemicals also interfere with metabolism, fat storage, bone development and the immune system, and this suggests that all endocrine systems can and will be affected by EDCs. Together, these new insights stress a critical need to acquire a better understanding of the endocrine system to determine how EDCs affect normal endocrine function, how windows of exposure may affect disease incidence (particularly for childhood respiratory diseases) and how these effects may be passed on to generations to come.

Furthermore, new approaches are needed to examine the effects of mixtures of endocrine disruptors on disease susceptibility and etiology, as examination of one endocrine disruptor at a time is likely to underestimate the combined risk from simultaneous exposure to multiple endocrine disruptors. Assessment of human health effects due to EDCs needs to include the effects of exposure to chemical mixtures on a single disease as well as the effects of exposure to a single chemical on multiple diseases. Since human studies, while important, cannot show cause and effect, it is critical to develop cause and effect data in animals to support the studies on humans.

Improved testing for EDCs: Validated screening and testing systems have been developed by a number of governments, and it requires considerable time and effort to ensure that these systems function properly. These systems include both *in vitro* and *in vivo* endpoints and various species, including fish, amphibians and mammals. New approaches are also being explored whereby large batteries of high-throughput *in vitro* tests are being investigated for their ability to predict toxicity, the results of which may be used in hazard identification and potentially risk assessment. These new approaches are important as one considers the number of chemicals for which there is no information, and these high-throughput assays may provide important, albeit incomplete, information. An additional challenge to moving forward is that EDC research over the past decade has revealed the complex interactions of some chemicals with endocrine systems, which may escape detection in current validated test systems. Finally, it will be important to develop weight-of-evidence approaches that allow effective consideration of research from all levels—from *in vitro* mechanistic data to human epidemiological data.

Reducing exposures and thereby vulnerability to disease: It is imperative that we know the nature of EDCs to which humans and wildlife are exposed, together with information about their concentrations in blood, placenta, amniotic fluid and other tissues, across lifespans, sexes, ethnicities (or species of wildlife) and regions. Many information gaps currently exist with regard to what is found in human and wildlife tissues, more so for developing countries and countries with economies in transition and for chemicals that are less bioaccumulative in the body. Long-term records to help us understand changes in exposures exist only for POPs and only for a few countries.

In addition, there is a need to continue expanding the list of chemicals currently examined to include those contained in materials and goods as well as chemical by-products; it is impossible to assess exposure without knowing the chemicals to target. The comprehensive measurement of all exposure events during a lifetime is needed, as opposed to biomonitoring at specific time points, and this requires longitudinal sampling, particularly during critical life stages, such as fetal development, early childhood and the reproductive years.

Wildlife and humans are exposed to a wide variety of EDCs that differ greatly in their physical and chemical properties. Further, these compounds are generally present at trace concentrations and in complex matrices requiring highly selective and sensitive analytical methods for their measurement. The wide range of different compound classes requires a variety of analytical approaches and techniques, making it challenging to understand all of the different chemicals in the environment and in human and wildlife tissues. There is a growing need to develop new analytical techniques and approaches to prioritize the assessment of EDCs. There is global transport of EDCs through natural processes (ocean and air currents) as well as commerce, leading to worldwide exposures. New sources of exposure to EDCs, in addition to food, have been identified and include indoor environments and electronics recycling and dumpsites (of particular concern in developing countries and countries with economies in transition). The sources and routes of exposure to EDCs need to be further investigated.

Identifying endocrine active chemicals: Identifying chemicals with endocrine disrupting potential among all of the chemicals used and released worldwide is a major challenge, and it is likely that we are currently assessing only the “tip of the iceberg”. It is possible to trace high production volume chemicals, but that is not the case for the numerous additives and process chemicals. Adding greatly to the complexity, and to the number of chemicals in our environment, are the unknown or unintended by-products that are formed during chemical manufacturing, during combustion processes and via environmental transformations. While the active ingredients in pharmaceuticals and pesticides have to be documented on the final product, this is not the case for chemicals in articles, materials and goods. Personal hygiene products and cosmetics require declarations of the ingredients, and the number of chemicals applied in this sphere of uses counts in the thousands. Many sources of EDCs are not known because of a lack of chemical constituent declarations in products, materials and goods. We need to know where the exposures are coming from.

Creating supportive environments for scientific advances, innovation and disease prevention: Exposure to EDCs and their effects on human and wildlife health are a global problem that will require global solutions. More programs are needed that foster collaboration and data sharing among scientists and between governmental agencies and countries. To protect human health from the combined effects of exposures to EDCs, poor nutrition and poor living conditions, there is a need to develop programs and collaborations among developed and developing countries and those in economic transition. There is also a need to stimulate new adaptive approaches that break down institutional and traditional scientific barriers and stimulate interdisciplinary and multidisciplinary team science.

Methods for evaluating evidence: There is currently no widely agreed system for evaluating the strength of evidence of associations between exposures to chemicals (including EDCs) and adverse health outcomes. A transparent methodology is also missing. The need for developing better approaches for evaluating the strength of evidence, together with improved methods of risk assessment, is widely recognized. Methods for synthesizing the science into evidence-based decisions have been developed and validated in clinical arenas. However, due to differences between environmental and clinical health sciences, the evidence base and decision context of these methods are not applicable to exposures to environmental contaminants, including EDCs. To meet this challenge, it will be necessary to exploit new methodological approaches. It is essential to evaluate associations between EDC exposures and health outcomes by further developing methods for which proof of concept is currently under development.