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Identification of risks from exposure to ENDOCRINE-DISRUPTING CHEMICALS at the country level

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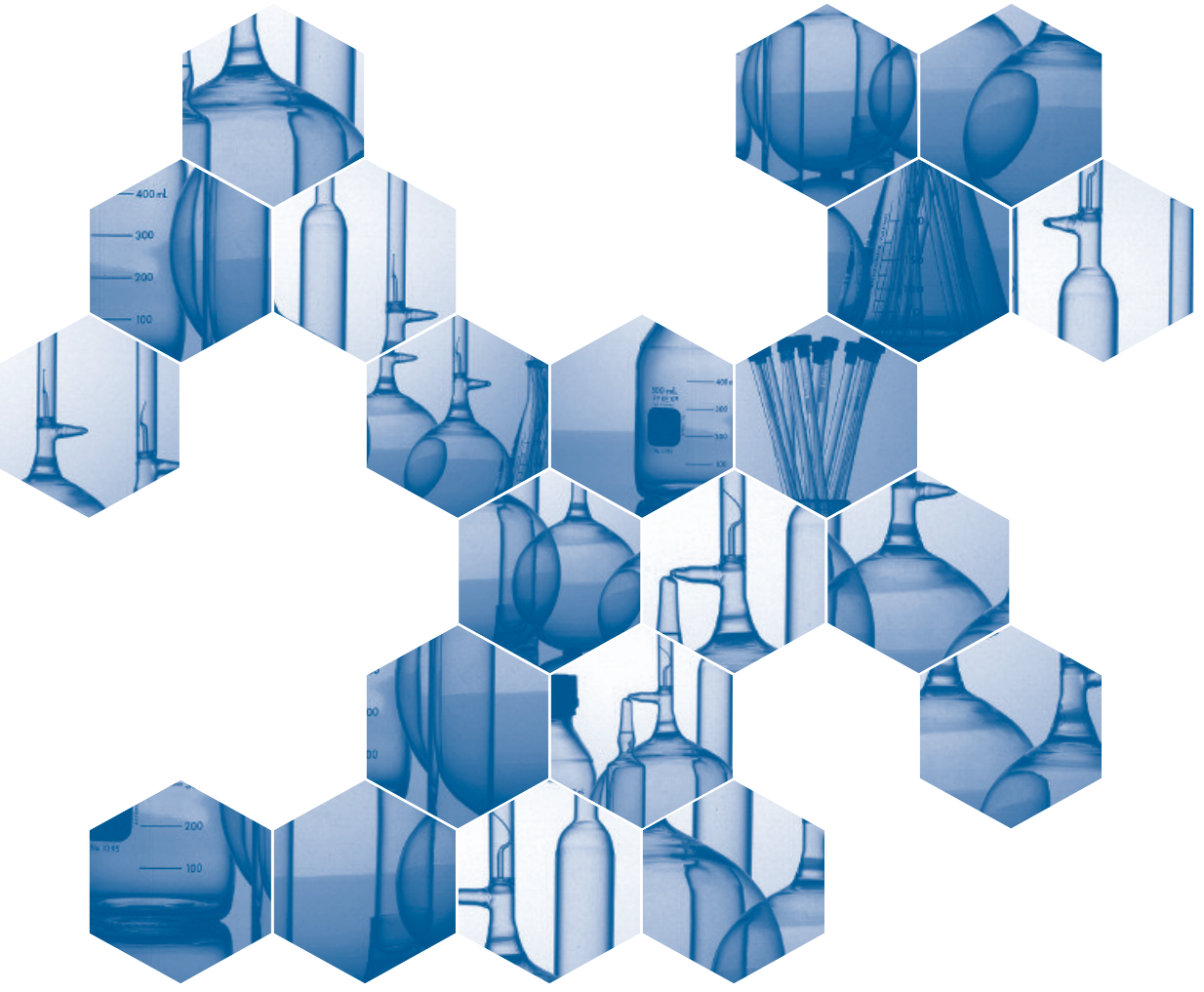

Identification of risks from exposure to ENDOCRINE-DISRUPTING CHEMICALS at the country level

Abstract

This document provides information on activities being carried out in the area of endocrine-disrupting chemicals (EDCs) in selected countries, including epidemiological studies on exposure to and the effects of EDCs. It also outlines action needed in the future to prevent the negative impact of EDCs on human health in accordance with the Parma Declaration on Environment and Health (2010) and resolution III/2/F on endocrine-disrupting chemicals of the Strategic Approach to International Chemicals Management (SAICM).

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Contents

Abbreviations iv
Acronyms iv

1. Introduction 1

2. Programmes and activities on endocrine disruptors in selected countries 2
- 2.1 Denmark 2
- 2.2 France 2
- 2.3 Japan 2
- 2.4 Republic of Korea 3
- 2.5 United States of America 3

3. Proposed action to address EDC-related issues at the country level 4
- 3.1 Identification of institutions 4
- 3.2 Coordination of EDC-related activities at the country level 4
- 3.3 Development of national policy on EDCs: identifying priorities 4
- 3.4 Participation in information-exchange networks 5
- 3.5 Awareness raising 5

4. Overview of epidemiological studies on exposure to and effects of EDCs 6
- 4.1 Human health 6
  - 4.1.1 Reproductive health 6
  - 4.1.2 Thyroid effects 8
  - 4.1.3 Neurodevelopment in children 9
  - 4.1.4 Hormone-related cancers 10
  - 4.1.5 Effects on the metabolic system 10
- 4.2 Vulnerable population groups 11
  - 4.2.1 Fetal development 11
  - 4.2.2 Puberty 11

5. Future needs 14

6. Discussion 15

7. Conclusions 17

8. References 18

Abbreviations

ADHD	attention deficit hyperactivity disorder
BBP	benzylbutyl phthalate
DBP	dibutyl phthalate
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
DEHP	di(2-ethylhexyl) phthalate
DEP	diethyl phthalate
DES	diethylstilbestrol
DMP	dimethyl phthalate
DOP	dioctyl phthalate
EDC	endocrine-disrupting chemical
HRT	hormone replacement therapy
IUGR	intrauterine growth restriction
LH	luteinizing hormone
NCD	noncommunicable diseases
NGO	nongovernmental organization
PBBs	polybrominated biphenyls
PBDE	polybrominated diphenyl ether
PCBs	polychlorinated biphenyls
PCOS	polycystic ovary syndrome
POPs	persistent organic pollutants
T3	triiodothyronine
T4	thyroxine
TDS	testicular dysgenesis syndrome
TGC	testicular germ cell cancer
TSH	thyroid stimulating hormone
UV	ultraviolet

Acronyms

BCERC	Breast Cancer and Environment Research Center
EDRP	Endocrine Disruptor Research Program
EDSP	Endocrine Disruptor Screening Program
EDSTAC	Endocrine Disruptor Screening and Testing Advisory Committee
EPA	Environmental Protection Agency
FFDCA	Federal Food, Drug and Cosmetic Act
GLOBOCAN	Cancer incidence and mortality worldwide
IARC	International Agency for Research on Cancer
ICCM3	Third session of the International Conference on Chemicals Management
IFCS	Intergovernmental Forum on Chemical Safety
ILO	International Labour Organization
IOMC	Inter-Organization Programme for the Sound Management of Chemicals
IPCS	International Programme on Chemical Safety
NEHAP 2	The second French national environment and health action plan
NHANES	National Health and Nutrition Examination Survey
OECD	Organisation for Economic Co-operation and Development
PNRPE	French national research programme for endocrine disruptors
PROS	Pediatric Research in Office Settings
PST	Occupational Health Plan 2010–2014
SAICM	Strategic Approach to International Chemicals Management
SPEED'98	Strategic Programs on Environmental Endocrine Disruptors '98
UNEP	United Nations Environment Programme
USA	United States of America

1. Introduction

At its second session in 1997, the Intergovernmental Forum on Chemical Safety (IFCS) agreed on the need for an in-depth investigation into the human, environmental and ecotoxicological aspects of endocrine-disrupting substances and requested the Inter-Organization Programme for the Sound Management of Chemicals (IOMC)[1] to address this topic. Following this recommendation, the International Programme on Chemical Safety (IPCS),[2] published the document, *Global assessment of the state-of-the-science of endocrine disruptors* (IPCS, 2002), which concluded that there was ample evidence of endocrine disruption from wildlife and animal studies, but that there was limited knowledge about the association between human disorders and exposure to endocrine disruptors.

Over the last decade, scientific understanding of the relationship between environment and health has advanced rapidly, and there is now stronger evidence that the trends of many endocrine-related disorders in humans are increasing. We now know that there are particularly vulnerable periods during fetal and postnatal life, when endocrine-disrupting chemicals (EDCs), either alone or in mixtures, have a strong and often irreversible effect on the developing organs, whereas the same exposures in adults may have a lesser or no effect. There is an accumulation of data suggesting that many adult diseases are of fetal origin but the causes remain unexplained (UNEP/WHO, 2013).

Resolution III/2/F on endocrine-disrupting chemicals and the Global Plan of Action of the Strategic Approach to International Chemicals Management (SAICM) propose that stakeholders address EDC-related issues in certain work areas in connection, for example, with:

- developing action plans to address priority concerns related to specific vulnerable groups;
- prioritizing the assessment of or studies on groups of chemicals that pose an unreasonable risk to human health and the environment and might include chemicals adversely affecting the endocrine system;
- filling the gaps in scientific knowledge about, for example, endocrine disruptors; and
- harmonizing the principles and methods of risk assessment (e.g. in vulnerable groups) with specific toxicological endpoints (e.g. endocrine disruption and ecotoxicology) and new tools.

SAICM recognizes the need to improve risk-reduction measures to prevent the adverse effects of chemicals on the health of vulnerable groups, such as children, pregnant women, fertile populations, the elderly, the poor, and workers, as well as on susceptible environments. It exemplifies the minimization of chemical exposure before conception and through gestation, infancy, childhood and adolescence as a measure of safeguarding the health of women and children.

At its third session, held in Nairobi, Kenya, in September 2012, the International Conference on Chemicals Management agreed to consider EDCs as an emerging policy issue of SAICM.

Recent scientific reviews and reports published by the Endocrine Society (Diamanti-Kandarakis et al., 2009), the European Commission (Kortenkamp et al., 2011) and the European Environment Agency (2012) illustrate the scientific interest in, and complexity of, this issue. These documents concluded that there is emerging evidence of adverse reproductive outcomes (infertility, cancers, malformation) from exposure to EDCs. There is also mounting evidence of the effects of these chemicals on thyroid function, brain function, metabolism (obesity), and insulin and glucose homeostasis.

Taking these developments into account, UNEP and WHO, in collaboration with a working group of international experts, reviewed and updated the information contained in the *Global assessment of the state-of-the-science of endocrine disruptors* (IPCS, 2002), which resulted in the publication of *State of the science of endocrine disrupting chemicals – 2012* (UNEP/WHO, 2013).

[1] The following nine organizations participate in IOMC: the United Nations Food and Agriculture Organization (FAO); the United Nations Development Programme (UNDP); the United Nations Environment Programme (UNEP); the United Nations Industrial Development Organization (UNIDO); the United Nations Institute for Training and Research (UNITAR); the International Labour Organization (ILO); the Organisation for Economic Co-operation and Development (OECD); the World Bank; and WHO.

[2] The International Programme on Chemical Safety (IPCS), established in 1980, is a joint venture of UNEP, ILO and WHO.

2. Programmes and activities on endocrine disruptors in selected countries

2.1 Denmark

Since 1995, Denmark has launched several governmental programmes on EDCs. These have resulted in the publication of reports summarizing current knowledge about male reproductive disorders and the environmental endocrine-disrupting effects caused by chemicals. Research programmes in the area of endocrine disruptors have also been supported. A national strategy for EDC-related work was presented in 2002. The Centre for Endocrine Disruptors was established in 2008 and is funded by the Danish Government (OECD, 2010).

The Danish Food Directorate, the Danish Environmental Protection Agency (Danish EPA)[3] and the National Board of Health have published an information booklet entitled *Food for thought – facts about endocrine disrupting substances*, describing the possible effects of EDCs on health and illustrating how and where one can be exposed to them. The booklet has a special focus on pregnant women and parents of small children and is intended for all Danish consumers.

The Ministry of the Environment conducted a campaign to raise public awareness about endocrine disruptors and their effects on the unborn child after combined exposures to these substances. The campaign involved the networking of midwives, doctors and nurses in distributing the material, which was also used in dialogue with pregnant and nursing women.

The Danish EPA carried out a survey between July 2011 and March 2012 on the exposure of pregnant consumers to suspected endocrine disruptors (Danish EPA, 2012a) and issued an information booklet entitled, *Expecting a baby? Advice about chemicals and pregnancy* (Danish EPA, 2012b).

2.2 France

The French national research programme for endocrine disruptors (PNRPE) was launched in 2004.[4] Its aim is to respond to public authorities on EDC-related issues and support fundamental and applied multidisciplinary research on screening methodologies, biomarkers, mechanisms of action, the biokinetics of endocrine disruptors in the organism and their fate in the environment, hazard-identification and risk-assessment methodologies, monitoring and related socioeconomic aspects.

France has two other major governmental programmes aimed at assessing the impact of several factors (including endocrine disruptors) on the general population and on workers, namely, *The second French national environment and health action plan (NEHAP 2)* (Ministry of Ecology, Energy, Sustainable Development and the Sea, 2010) and the *Occupational health plan 2010–2014 (PST)* (Ministry of Labour, Employment, Vocational Training and Social Dialogue, 2010). The latter is dedicated to workers and aims to improve professional risk prevention.

2.3 Japan

In Japan, three ministries have programmes dealing with EDCs: the Ministry of Health, Labour and Welfare, the Ministry of Economy, Trade and Industry and the Ministry of the Environment.

The Ministry of Health, Labour and Welfare has established the Advisory Committee on Health Influence of Endocrine Disrupting Chemicals, the functions of which are to evaluate the risk of endocrine

[3] Danish EPA website: http://www.mst.dk/English/Chemicals/endocrine_disruptors/, accessed 3 February 2014.
[4] Information (in French) on PNRPE: http://www.pnrpe.fr/, accessed 3 February 2014.

disruptors on human health, the need to take prompt action to protect human health and the necessity for risk communication with the general public. The Committee has developed a framework for testing possible EDCs. Screening tests have been carried out on a number of chemicals and a priority list has been compiled for future definitive testing based on their results.

The Ministry of Economy, Trade and Industry has established an advisory body, the Endocrine Disruptive Effect Subcommittee. It has also funded studies to assess the hazards of 15 potential EDCs and is involved in the OECD Test Guidelines Programme.

The Ministry of the Environment established Strategic Programs on Environmental Endocrine Disruptors '98 (SPEED '98) (Japan Environment Agency, 1998) in 1998 and the ExTEND 2005 programme in 2005. The latter involves basic research on the mechanisms of endocrine disruption, environmental monitoring (the observation of wildlife and measurement of environmental concentrations and exposure levels), the development of test methods, hazard and risk assessment, risk management, the promotion of information sharing and risk communication, and the organization of annual international symposia.

2.4 Republic of Korea

In 1999, the relevant ministries of the Republic of Korea established a mid- and long-term research plan for endocrine disruptors. The research projects conducted under this plan dealt mainly with the environmental monitoring of endocrine disruptors and the assessment of their ecological effect. In accordance with the subsequent five-year research plan (2007–2011), the results were reviewed and a plan prepared for the safety management of endocrine disrupters in each relevant ministry.

The Ministry of the Environment of the Republic of Korea has established a public website containing basic information about EDCs.[5]

2.5 United States of America

The United States Environmental Protection Agency (EPA) developed the Endocrine Disruptor Screening Program (EDSP) in response to the statutory mandate included in the Federal Food, Drug and Cosmetic Act (FFDCA), namely to "…develop a screening program…to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effects as the Administrator may designate".

Also in response to this mandate, in 1996, the United States EPA chartered the federal Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) to address endocrine disruption. The Committee made several key recommendations, namely to:

- address the potential effects of chemical exposure on both humans and the environment;
- examine the effects of EDCs on estrogen, androgen and thyroid hormone-related processes;
- include pesticide and non-pesticide chemicals, contaminants and (after evaluating single chemicals) mixtures in the investigation;
- develop a two-tiered screening and testing strategy (now known EDSP).

The United States EPA's Office of Research and Development also developed the Multi-year Plan for Endocrine Disruptors to identify science-specific questions, which will be addressed by the Endocrine Disruptor Research Program (EDRP) over the next 5–10 years. The plan is updated every few years to take into account the current state of the science relating to EDCs, and any updates in EDRP's strategic direction.

[5] Ministry of Environment of the Republic of Korea website: http://eng.me.go.kr/eng/web/index.do?menuId=165&findDepth=1 , accessed 24 January 2014.

3. Proposed action to address EDC-related issues at the country level

3.1 Identification of institutions

As the above examples of country programmes and activities on endocrine disruptors demonstrate, action to address EDC issues depends on the country's infrastructure, its capacity for dealing with these issues and its awareness about them. While some countries establish new programmes, structures and agencies for this purpose, some use already existing structures with an added focus on EDCs.

For countries (especially developing countries) with limited capacity and no EDC programmes, the logical approach would be to build on existing programmes rather than establish new ones. For example, an already existing national programme on sound chemical management could be used as a platform and a specialized committee on EDCs could be established under its umbrella. Consideration should be given to the best use of the institutions available in the country, such as departments of toxicology and children's environmental health units, and/or to strengthening them to serve the purpose.

3.2 Coordination of EDC-related activities at the country level

EDCs comprise a diverse field, involving public health, environmental protection, economics, industry, agriculture, worker protection, and water and waste management, which means that a wide range of governmental ministries and agencies have related responsibilities.

The effective coordination of the whole range of those responsible for EDC-related issues allows all those involved to familiarize themselves with each other's activities, priorities and positions in this area. Moreover, it implies that this information could be used to improve the quality of EDC-related strategic decision-making.

One of the institutions involved should take the lead in strengthening cooperation among the stakeholders engaged in risk management, such as those dealing with the safety of food and drinking water, air quality, and the safe use of chemicals. The same or a different institution could take the lead with respect to international cooperation and information sharing.

3.3 Development of national policy on EDCs: identifying priorities

A national platform or similar mechanism for chemicals management could host the development of national policy on EDCs. The multisectoral nature of that body would facilitate the coordination of ongoing activities and, as diverse interests would be represented, ensure that all existing priorities were taken into account.

A national plan could include identification of the situation in the country pertaining to EDCs, including – but not limited to – information on environmental pollution caused by endocrine disruptors and their sources, and ongoing surveillance of the possible adverse effects of chemical exposure on human health. A priority list of EDCs could be derived from this situation analysis. Countries with limited capacity could consider using lists of potential EDCs compiled in other countries and/or by regional bodies, such as the European Commission, to evaluate their own situations with respect to the chemicals included in these lists.

Data collection and knowledge building are important elements of a strategic plan.

3.4 Participation in information-exchange networks

The exchange of information and networking at the international level are essential and of special benefit to scientists and policy-makers in developing countries and countries with economies in transition, leading to a greater understanding of EDC-related issues. However, more effort to this end is needed at the international level. The third session of the International Conference on Chemicals Management (ICCM3), Nairobi, Kenya, 17–21 September 2012, encouraged the organizations participating in IOMC to "raise awareness and facilitate science-based information exchange, dissemination and networking…" (SAICM, 2012).

3.5 Awareness raising

Although numerous chemicals have already been identified as potential EDCs, and some developed countries and international organizations started work to address them already in the mid-1990s, there is still a need to raise awareness in developing countries and countries with economies in transition about the effects of exposure to EDCs.

At the international level, in 2012, a resolution was adopted by ICCM3 on including EDCs in SAICM as an emerging issue. In addition, the Conference ascertained "that information dissemination and awareness-raising on endocrine-disrupting chemicals are particularly relevant and that improving the availability of and access to information on such chemicals is a priority" (SAICM, 2012).

Another decision of the Conference was "to implement cooperative actions on endocrine-disrupting chemicals with the overall objective of increasing awareness and understanding among policymakers and other stakeholders".

At the General Assembly of the United Nations High-level Meeting on the Prevention and Control of Non-Communicable Diseases, New York, 19–20 September 2011, strategies were promoted for the control of noncommunicable diseases (NCDs) with a focus on poor diet, physical inactivity, tobacco use and alcohol consumption. Scientific knowledge on early exposure to environmental chemicals and the development of NCDs in adulthood is increasing, and early-life interventions, including the prevention of toxic exposures, are an important component of NCD prevention (Balbus et al., 2013, Barouki et al., 2012).

At the national level, awareness-raising activities on EDCs should address all stakeholders, including policy-makers, civil society, the scientific community, public-interest nongovernmental organizations (NGOs), workers, trade unions, different levels of health personnel (doctors, nurses), and the public, especially pregnant women.

Exposure to EDCs that occurs during the vulnerable periods of human and wildlife development – from fertilization through fetal development and through nursing of young offspring – raises particular concern. It is very important to raise public awareness about endocrine disruptors and the effects of exposure to them on the unborn child. Priority should be given to the preparation and dissemination, through health personnel, of informative, capacity-building material addressing pregnant and nursing women.

4. Overview of epidemiological studies on exposure to and effects of EDCs

The following overview is based mainly on information contained in two recent publications: *State of the science of endocrine disrupting chemicals – 2012* (UNEP/WHO, 2013); and *Possible developmental early effects of endocrine disrupters on child health* (WHO, 2012).

4.1 Human health

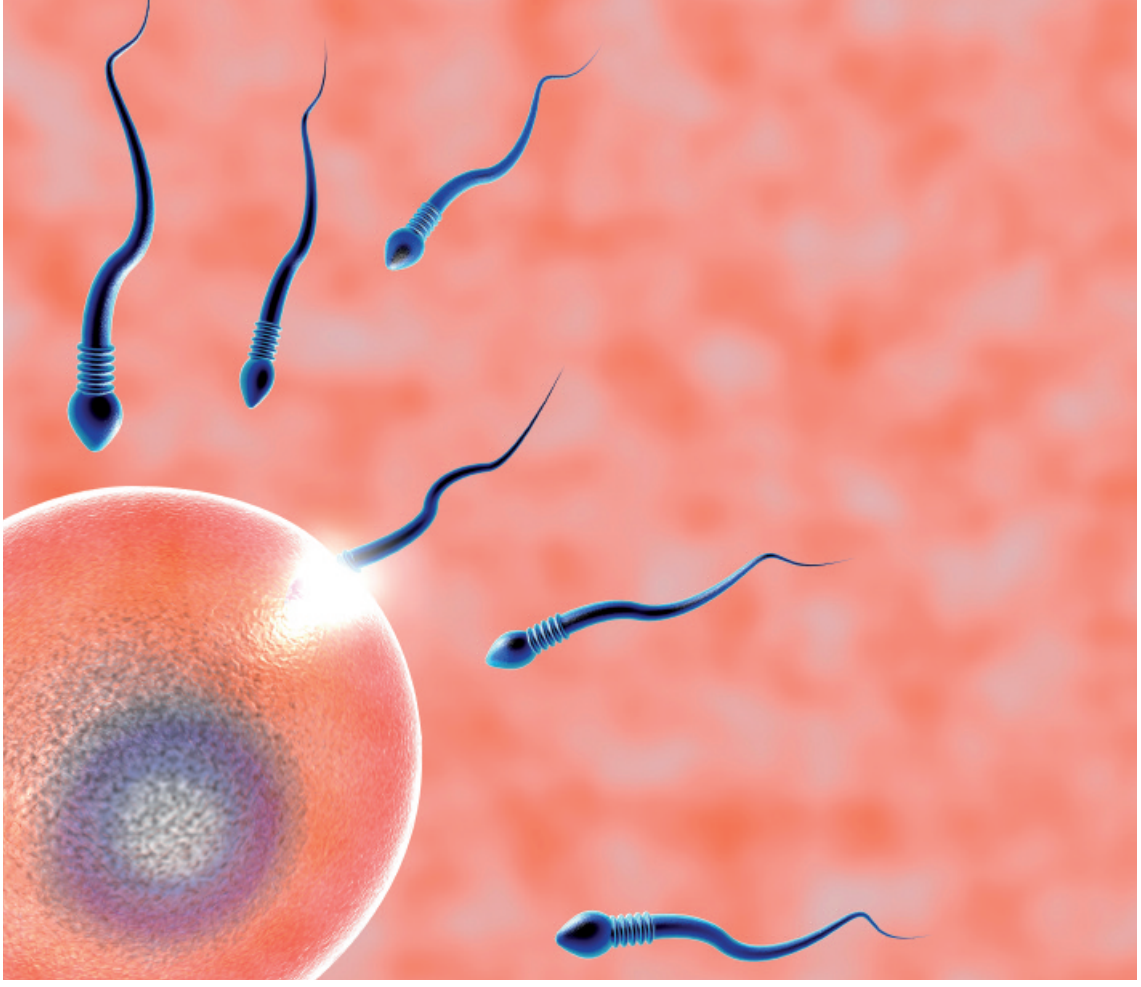
4.1.1 Reproductive health

The effects of endocrine disruptors observed in the human reproductive system are shown in Table 1 (WHO, 2012).

Table 1. Effects of endocrine disruptors observed in the human reproductive system

Contaminant	Sex	Observation	References
Diethylstilbestrol (DES)	Male	Increased risk of hypospadias	Brouwers et al., 2006; Klip et al., 2002
		Tendency towards smaller testes	Bibbo et al., 1977; Gill et al., 1977, Ross et al., 1983
		Increased prevalence of cryptorchidism	Palmer et al., 2009
		Capsular induration of testis	Bibbo et al., 1977; Gill et al., 1977
		Severe sperm abnormalities	Bibbo et al., 1977; Gill et al., 1977
		Epididymal cysts	Bibbo et al., 1977; Gill et al., 1977; Palmer et al., 2009
		Infection/inflammation of testis	Palmer et al., 2009
	Female	Increased risk of breast cancer	Palmer et al., 2006
		Vaginal adenosis	Bibbo et al., 1977; Sherman et al., 1974
		Oligomenorrhea	Bibbo et al., 1977
		Increased risk of clear cell adenocarcinoma of the vagina and cervix	Herbst et al., 1971; Herbst et al., 1979; Verloop et al., 2010
		Increased frequency of preterm delivery, first-trimester spontaneous abortion, second-trimester pregnancy loss and ectopic pregnancy	Kaufman et al., 2000
Phthalate esters (BBP, DBP, DEHP, DEP, DMP, DOP)	Male	Associated with anogenital index	Swan et al., 2005
		Positive correlation with increased serum LH/testosterone ratio	Main et al., 2006
Flame retardants (polybrominated diphenyl ethers)	Male	Associated with cryptorchidism	Main et al., 2007
Phytoestrogens	Male	Associated with hypospadias	North et al., 2000
Dioxins	Female	Increased probability of female births	Mocarelli et al., 1996; Mocarelli et al., 2000
Polychlorinated biphenyls (PCBs)	Male	Higher percentage of oligospermia, abnormal morphology and reduced sperm capacity of binding and penetration to hamster oocyte	Hsu et al., 2003

Note: BBP = benzylbutyl phthalate; DBP = dibutyl phthalate; DEHP = di(2-ethylhexyl) phthalate; DEP = diethyl phthalate; DMP = dimethyl phthalate; DOP = dioctyl phthalate.
Source: WHO, 2012.



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4.1.1.1 Male reproductive health

Male reproductive health has been a major focus of research on EDCs since the early 1990s when evidence of adverse secular trends in sperm counts as a result of exposure to EDCs first came to light. It is suspected that exposure during the early stages of life causes, at least partially, hypospadias, congenital cryptorchidism, poor semen quality, testicular dysgenesis syndrome and testicular germ cell cancer (TGC) (UNEP/WHO, 2013).

Hypospadias and cryptorchidism can be induced in experimental animals by exposing them to several endocrine disruptors that are either antiandrogenic or estrogenic (Toppari, 2008). Examples of these antiandrogens are the fungicides, vinclozolin and procymidone, and dichlorodiphenyldichloroethylene (DDE), the persistent congener of estrogenic dichlorodiphenyltrichloroethane (DDT), that act as androgen receptor antagonists (Gray et al., 2006), and phthalate esters, dibutyl phthalate and diethyl hexyl phthalate that disturb androgen biosynthesis (Mylchreest et al., 2002; Fisher et al., 2003).

TGC is often found in association with hypospadias, cryptorchidism and poor semen quality, suggesting that they are risk factors for one another and that they could be related components of a single underlying condition, namely testicular dysgenesis syndrome (TDS), which originates during fetal life as a result of exposure to contaminants (Skakkebæk, Rajpert-De Meyts & Main, 2001; UNEP/WHO, 2013).

Increases in the incidence of TGC (Huyghe, Matsuda & Thonneau, 2003; Richiardi et al., 2004), cryptorchidism (Toppari et al., 2010) and hypospadias (Källen et al., 1986; Paulozzi, 1999; Toppari, Kaleva & Virtanen 2001; Nassar, Bower & Barker, 2007; Lund et al., 2009) and widespread poor semen quality (Bonde et al., 1998; Guzick et al., 2001; Skakkebæk, 2010) are most likely due to environmental factors (UNEP/WHO, 2013). Exposures that interfere with the developing testis, including androgen action and/or production during fetal life, are likely to be crucial in the pathogenesis of TDS disorders (Skakkebæk, Rajpert-De Meyts & Main 2001; Sharpe & Skakkebaek, 2008). Other causes of poor semen quality are also known, such as genetic defects in sex chromosomes (Krausz, 2011; UNEP/WHO, 2013).

4.1.1.2 Female reproductive health

Given that endogenous estrogens participate in the development and functioning of the female reproductive system, it is biologically plausible that exposure to EDCs influences female reproductive health.

Currently available data relevant to human populations from all countries in which studies have taken place show that today millions of women are affected by the reproductive disorders, polycystic ovary syndrome (PCOS), uterine fibroids, and endometriosis.

These three disorders cause infertility or subfertility. Genetic and environmental factors (including diet, age, exercise habits, sexually transmitted diseases, and access to good health-care services) play a role in a woman's overall reproductive health and, thus, could contribute to these disorders. As an example of the influence of environmental factors, changes in nutrition and general health are widely recognized as underlying reasons for the advancement of the menarche over the last 200 years from an average age of approximately 17 years to 13 years (Aksglæde et al., 2008; 2009; Parent et al., 2003).

Exposure to EDCs during pregnancy can lead to reproductive health problems in female offspring as their eggs are exposed while they are developing and, as eggs are for a lifetime, even the effects of in-utero exposures are transmitted (UNEP/WHO, 2013).

Associations between prenatal exposure to EDCs and other chemicals, and a number of adverse pregnancy outcomes, including miscarriage, preeclampsia (characterized by hypertension during pregnancy), intrauterine growth restriction (IUGR), poor weight gain during fetal development, and preterm delivery, have been reported (Stillerman et al., 2008; Slama & Cordier, 2010). Prenatal exposure to lead and glycol ethers has been shown to entail an increased risk of miscarriage (Slama & Cordier, 2010).

4.1.2 Thyroid effects

During the past several decades, there has been an increasing incidence of human thyroid diseases and disorders (e.g. congenital and adult hypothyroidisms, Hashimoto's thyroiditis, Graves' disease) in many parts of the world, such that the burden of thyroid disease counts approximately two billion people

worldwide (UNEP/WHO, 2013). Thyroid diseases and disorders represent a particularly high and increasing disease burden in children and adolescents in several of the countries in which they have been studied (McGrogan et al., 2008).

It is well established that thyroid hormones are of special importance in the development of the brain, which, in utero, is dependent upon normal levels of thyroid hormones. La Franchi has already described small modifications in thyroid serum levels during pregnancy or at birth in association with cognitive deficits (La Franchi, 2010; WHO, 2012).

Experimental studies have shown that numerous chemicals can interfere with thyroid function. The list of environmental chemicals – mostly man-made – that can cause a reduction in levels of thyroid hormone circulating in experimental animals is very long (Howdeshell, 2002; Brucker-Davis, 1998; UNEP/WHO, 2013).

Several groups of chemicals, e.g. dioxin-like compounds and certain flame retardants, have a high degree of structural similarity with the thyroid hormones, T3 and T4, thus competing with the hormones for the thyroid hormone (TH) receptor and transport proteins (WHO, 2012).

There is now reasonably firm evidence that PCBs and several other common contaminants have a thyroid-disrupting effect. These include brominated flame retardants, phthalates, bisphenol A and perfluorinated chemicals. In all cases, chemical exposure has been associated with serum thyroid hormone levels (UNEP/WHO, 2013)

A number of studies have concluded that there is an association between PCB exposure and measures of thyroid function, and support the hypothesis that PCBs can reduce circulating levels of thyroid hormone (Abdelouahab et al., 2008; Hagmar et al., 2001a; 2001b; Persky et al., 2001; Schell et al., 2008; Turyk, Anderson & Persky, 2007).

The results of some studies indicate that PCB body burden suppresses serum T4, while others indicate serum T3. In some cases, the findings are in men, in other cases in women. Overall, there is not a uniform picture.

In studies of pregnant women, PCB body burden is positively associated with serum thyroid-stimulating hormone (TSH) (Chevrier et al., 2007; Takser et al., 2005). Studies of newborns also indicate that PCB body burden suppresses thyroid function (Chevrier et al., 2007; Herbstman et al., 2008). However, a number of studies report no association between PCB body burden and measures of thyroid function (e.g., Dallaire et al., 2008; Dallaire et al., 2009; Longnecker et al., 2000).

Boas, Feldt-Rasmussen and Main (2011) reviewed the literature linking a variety of chemical exposures to thyroid function in humans. These include polybrominated disphenyl ether (PBDE), pesticides, perfluorinated chemicals, phthalates, bisphenol A, UV filters and perchlorate. With the possible exception of perchlorate, the relationship between these chemicals and thyroid function has not been studied as extensively as their relationship with PCBs.

4.1.3 Neurodevelopment in children

Currently, there is considerable concern about the potential relationship between the increasing prevalence of neurodevelopmental disorders and the exponential increase in exposure to pollutants over the past several decades (Landrigan & Goldman, 2011a; 2011b; Weiss & Landrigan, 2000). Since the 1970s, there have been dramatic increases in the prevalence of previously rare neurodevelopmental disorders, such as autism, attention deficit hyperactivity disorder (ADHD) and autistic disorder, learning disabilities and childhood and adult depressive disorders. Whereas, for example, the prevalence of autism in children was estimated to be 4–5 in 10 000 in the 1970s, current literature describes 1–110 children as being affected by this disorder today (Wing et al., 1976; Rice, 2007; UNEP/WHO, 2013).

ADHD is over-represented in populations with elevated exposure to organophosphate pesticides. Other chemicals have not been investigated (UNEP/WHO, 2013).

Although there have been earlier observations that environmental factors could affect brain development and neurobehaviour (Cranefield & Federn, 1963), our knowledge of the relationship between neurodevelopmental disorders and chemical exposure has since advanced. It is now clear that children – especially during fetal development – are sensitive to the neurotoxic effects of lead and mercury, even at low levels (e.g. Needleman, 2009). According to current research, there seems to be no level below which exposure to lead does not harm the developing central nervous system (WHO, 2010a). There is, furthermore, growing evidence that PCBs affect neurodevelopment negatively (WHO, 2010b). In-utero exposure to mercury is known to cause, among others, mental retardation, congenital malformations, loss of vision and hearing, language disorders and developmental delays (WHO, 2010c).

4.1.4 Hormone-related cancers

The role of steroidal hormones in various cancers has been a topic of intensive research since the early 1940s. Although this work has established the biological plausibility of a strong involvement of endogenous estrogens and androgens in the disease processes, the possible contribution of foreign chemicals has only fairly recently received attention.

During the last ten years, new evidence has emerged, which shows that exposure to pharmaceutical steroidal estrogens, including the synthetic estrogen, DES, and steroids used in hormone replacement therapy (HRT), increases the risk of breast cancer. The Million Women Study (United Kingdom) found that all forms of HRT, including estrogen-only and estrogen-progesterone types, increased this risk (Banks et al., 2003).

The involvement of in-utero exposure to DES in vaginal cancers and breast cancer has heightened the concern that a multitude of other hormonally active chemicals in everyday use are causing these diseases.

The breast is particularly vulnerable to cancer-causing influences during development in the womb and during puberty (Soto et al., 2008). Women whose mothers used DES during pregnancy to avoid the risk of miscarriage have a high risk for breast cancer (Palmer et al., 2006). Studies involving laboratory animals also suggest that exposure to xenoestrogens during development can alter the development of the mammary tissue with the possible consequence of breast cancer (Munoz-de-Toro et al., 2005; Maffini et al., 2006; Murray et al., 2007).

With respect to breast, endometrial, ovarian and prostate cancers, the role of endogenous and therapeutic estrogens is well documented, which makes it biologically plausible that xenoestrogens might also contribute to the risk of developing these diseases. However, chemicals shown to be associated with breast cancer (dioxins, PCBs and solvents) or prostate cancer (unspecified agricultural pesticides, PCBs, cadmium and arsenic) either do not have strong estrogenic potential or are unspecified. The possibility of EDC involvement in ovarian and endometrial cancers has received little attention.

4.1.5 Effects on the metabolic system

The endocrine system is involved in the control of metabolism, giving rise to the possibility that EDCs may influence metabolic function. Interest has been shown in the possibility that chemicals may interfere in the programming of, for example, glucose homeostasis during development and, thereby, play a role in the association of conditions, such as diabetes and obesity and also cardiovascular disease and hypertension (Kortenkamp et al., 2011). As an example, certain EDCs have been described as affecting the function of beta cells in the pancreas, which are responsible for insulin production and, therefore, crucial for glucose homeostasis (e.g. Cooper et al., 2009).

4.1.5.1 Obesity

The prevalence of obesity is rising dramatically in both wealthy and poor countries, and paediatric obesity has tripled over the last five decades (Diamanti-Kandarakis et al., 2009). Although obesity is

probably caused by a combination of genetic and environmental factors, the genetic contribution is substantial (Chen, Brown & Russo, 2009). Environmental risk factors for obesity include a "westernized" diet, characterized by a high caloric intake and a lack of exercise, indicating a sedentary lifestyle (Diamanti-Kandarakis et al., 2009; Kortenkamp et al., 2011).

There is evidence that the risk of becoming obese may begin during pregnancy and early childhood and that rapid weight gain in the first few months of life is an associated factor (Ong et al., 2000; McAllister et al., 2009).

4.1.5.2 Type-2 diabetes

Obesity is also correlated with type-2 diabetes, and exposure to chemicals that have been shown to cause obesity in animal models also results in altered glucose tolerance and reduced insulin resistance (UNEP/WHO, 2013).

As regards humans, there is growing epidemiological evidence that exposure to EDCs in adulthood may contribute to the development of type-2 diabetes. Studies report an increased risk of type-2 diabetes after exposure to persistent organic pollutants (POPs) (including PCBs, DDE, dioxin, organochlorine pesticides, and hexachlorobenzene), arsenic and some flame retardants (e.g. Neel & Sargis, 2011; Everett, Frithsen & Player, 2011; Reilly et al., 2011; IPCS, 2011).

4.2 Vulnerable population groups

The most sensitive windows of exposure to EDCs are found during critical periods of development, such as fetal development, early life and puberty.

4.2.1 Fetal development

Exposure to EDCs during the early, vulnerable periods of human and wildlife development – from fertilization through fetal development and the nursing of offspring – gives particular rise for concern. When chemicals with endocrine-disrupting activity are present during development, they will affect the programming of cell and tissue development and, thus, their effects are expected to be permanent. When the same endocrine disruptor is present later – in childhood or adulthood – the effects will be different and could be transient.

Exposure to harmful substances may affect the development of functional body systems and, as a result, have a lifetime effect on an individual's health (WHO, 2006). Periods of increased vulnerability range from preconception to the final stages of adolescence (WHO, 2006).

Exposure during fetal development can cause changes that, while not evident as birth defects (the newborn may look healthy), can induce permanent changes that lead to an increased risk for disease incidence throughout life.

The breast is particularly vulnerable to cancer-causing influences during the periods when the duct structures grow; two especially sensitive periods are: (1) during development in the womb when breast tissue is formed (Soto et al. 2008); and (2) during puberty when the first significant growth phase of the ductal system takes place.

4.2.2 Puberty

Age at menarche has been approximately 13 years for several decades, whereas 200 years ago, it was 17 years (Aksglæde et al., 2008; 2009). This decline may have been brought about by improved nutrition and better health and living conditions (Parent et al., 2003). However, there now seems to be a new downward trend; breast development is appearing much earlier than two years before menarche, which has been the case until now. This is demonstrated by studies conducted in the USA (Paediatric Research in Office Settings (PROS), National Health and Nutrition Examination Survey (NHANES III), and Breast Cancer and Environment Research Program (BCERC)) and Europe (UNEP/WHO, 2013; WHO, 2012).

A summary of the epidemiological studies carried out to investigate the role of endocrine disruptors in causing early puberty are summarized in Table 2.

The significance of chemical exposure before or during puberty was demonstrated in the results of a study on the possible association between breast cancer and exposure to DDT at a young age. It was found that, in women born after 1931, high levels of p,p'–DDT were associated with a five-fold increase in the risk for breast cancer (Cohn et al. 2007). When DDT came into widespread use, these women were all under 14 years of age, and when the use of DDT in USA peaked, most of them were still under 20.

There is evidence that exposure to lead is associated with a slight delay in the onset of puberty whereas none of the other exposure studies so far show any clear association with the timing of puberty apart from polybrominated biphenyls that were linked to an early age at menarche and to pubic-hair development.

Taking all the evidence into consideration, while it is biologically plausible that exposure to endocrine disruptors could contribute to changes in the timing of pubertal development, there is an absence of demonstrated epidemiological associations, which warrants further investigation. One of the difficulties in this connection is the complexity of relating this endpoint with exposures that may have occurred at different times during development and for different durations of time. Exposures to mixtures have not been considered. Many other factors (such as nutrition) are known to influence the timing of puberty and they may vary from individual to individual and from population to population.

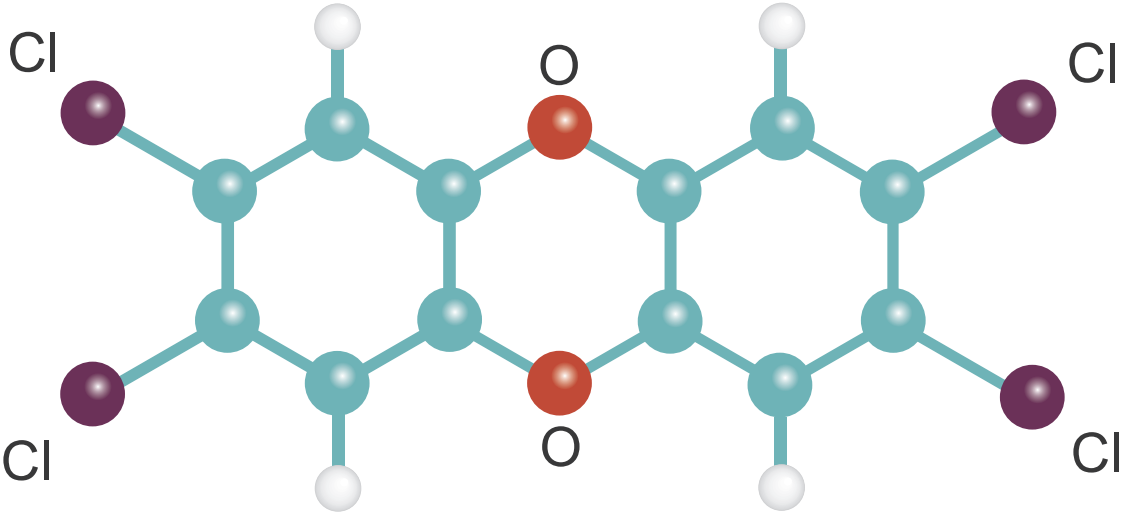

Table 2. Overview of epidemiological studies investigating the effects of EDCs on onset of human puberty

Contaminant	Sex	Observation	References
Chlorinated pesticides (DDT and DDE)	Male	No association with pubertal development	Gladen et al., 2000
	Female	Younger age at menarche	Vasiliu et al., 2004
		Precocious puberty	Krstevska-Konstantinova et al., 2001
		No association with breast or pubic-hair development	Wolff et al., 2008
		No association with pubertal development	Gladen et al., 2000
Dioxins	Male	No association with sexual maturation	Den Hond et al., 2002
	Female	Later onset of breast development	Leijs et al., 2008
		No association with the onset of menarche	Warner et al., 2004
		Lower stage of breast development	Den Hond et al., 2002
Polychlorinated biphenyls (PCBs)	Female	Slowed breast development	Staessen et al., 2001
		No association with menarche or pubertal development	Den Hond et al., 2002; Vasiliu et al., 2004
		No association with breast or pubic-hair development	Wolff et al., 2008
		No association with pubertal development	Gladen et al., 2000
	Male	Late first ejaculation	Leijs et al., 2008
		Reduced penile length	Guo et al., 2004
		Slowed genital development	Den Hond et al., 2002; Staessen et al. 2001
		No association with pubertal development	Mol et al., 2002
		No association with pubertal development	Gladen et al., 2000
Polybrominated biphenyls (PBBs)	Female	Earlier age at menarche and pubic-hair development	Blanck et al., 2000
Bisphenol-A	Female	No association with breast or pubic-hair development	Wolff et al., 2008
Lead	Female	Delayed breast and pubic-hair development	Selevan et al., 2003
		Delayed menarche and pubic-hair development	Wu et al., 2003
		Inversely associated with inhibin B levels	Gollenberg et al., 2010
		Delayed breast development, pubic-hair growth and age of reaching menarche	Naicker et al., 2010
	Male	Delayed onset of puberty on the basis of testicular volume of > 3 ml, genitalia staging and pubic-hair staging	Williams et al., 2010
Cadmium	Female	High levels of both cadmium and lead inversely associated with inhibin B levels	Gollenberg et al., 2010

Source: WHO, 2012.

5. Future needs

The problem of exposure to EDCs and their negative effects on, and potential cause of disease in, humans and wildlife is global and requires global solutions. More programmes are needed that foster collaboration and data-sharing among scientists, among governmental agencies and among countries.

To protect human health from the problems resulting from the combined effects of exposure to EDCs, poor nutrition and poor living conditions, there is a need to develop programmes to this end and encourage collaboration between developed and developing countries.

The recently published UNEP/WHO (2013) report, *State of the science of endocrine disrupting chemicals – 2012*, identified the future needs as follows.

(a) Strengthening knowledge of EDCs.
(b) Improved testing for EDCs.
(c) Reducing exposures and thereby vulnerability to disease.
(d) Identifying endocrine active chemicals.
(e) Creating enabling environments for scientific advances, innovation and disease prevention.
(f) Methods of evaluating evidence.

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6. Discussion

The identification of 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. Adding greatly to the complexity of the issue, and to the number of chemicals in our environment, are the unknown or unintended byproducts that are formed during chemical manufacturing and combustion processes and via environmental transformations. In addition, many EDC sources are unknown because a large number of products, materials and goods, as well as waste products and e-waste, lack declarations indicating their chemical constituents (UNEP/WHO, 2013).

EDCs are found in a multitude of applications, including pesticides, pharmaceuticals, flame retardants, plastic additives and more. These chemicals can be found as residues or contaminants in food and other products and may be released from the products that contain them.

While most of the developed countries initiated programmes and activities in the mid-1990s, and OECD member countries cooperate through the OECD Conceptual Framework for the Testing and Assessment of Endocrine Disrupting Chemicals, there is still a need to develop new methods of testing and analysis for many other areas of the endocrine system. There are also gaps in the knowledge about exposure to and the effects of EDCs. Most of the studies to this end are conducted in developed countries.

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 on humans and wildlife are being overlooked. For many endocrine-disrupting effects, agreed and validated test methods do not exist. For a large range of the effects on human health, such as female reproductive disorders and hormonal cancers, there are no viable laboratory models. This seriously hampers progress in understanding the full scale of the risks (UNEP/WHO, 2013).

Most studies on endocrine disruptors have focused predominantly on chemicals that interact with estrogen, androgen and thyroid hormone systems. A growing number of studies, however, indicate that environmental chemicals can interfere with other endocrine systems (Casals-Casas & Desvergne, 2011).

In almost all developing countries and countries with economies in transition no activities or programmes on endocrine disruptors exist, and there is an increasing need to promote an awareness and understanding among policy-makers and stakeholders of the significance of exposure to these chemicals. The inclusion of EDCs among the policy issues managed within the SAICM policy framework is very timely and provides an opportunity for fostering cooperation among developed and developing countries.

There is increasing credible evidence that human and wildlife health is currently being adversely affected by exposure to a large-scale mixture of man-made chemicals. The incidence of developmental, neurobehavioural, reproductive and other health outcomes is increasing in human populations across the globe and many of these have been found to be associated with exposure to individual, man-made chemicals. These findings are paralleled, in some cases, in findings relating to wildlife and laboratory animals. Thus, there is a growing concern that chemicals are causing adverse health effects in both human and wildlife populations by interfering with their endocrine systems.

Increases in disease incidence rule out genetic factors as the sole plausible explanation for their occurrence. Environmental and other non-genetic factors, such as nutrition, the age of the mother, viral diseases and exposure to chemicals, also contribute but are difficult to identify. As an example, breast cancer is the most common malignancy in females and an estimated 1.4 million new cases are diagnosed yearly (Ferlay et al., 2010). Breast cancer shows a wide variation in geographical incidence, suggesting that environmental factors play a role in the etiology. Risk factors for breast cancer include early age at menarche, late age at first birth, nulliparity, socioeconomic status, primary family history of breast cancer, exposure to ionizing radiation, a high-fat diet, adult weight gain and high levels of alcohol

consumption (Madigan et al.,1995). Genetics explain only a small fraction of breast cancers (Kortenkamp et al., 2011)

Endocrine disruptors can interact throughout life with the same pathways as hormones. When chemicals with endocrine-disrupting activity are present during development, they will affect the programming of cell and tissue development and, therefore, their effects can be expected to be permanent. When the same endocrine disruptor is present later in life – in childhood or adulthood – the effects will be different and could be transient. Variations in sensitivity to, and the effects of, endocrine disruptors over the lifespan have several important implications. When studies are designed to link chemical exposures in humans to specific outcomes, it is important to measure the exposures at the developmental time-point that is appropriate for the specific outcome measured; of course, in some case the outcome may not become visible before adulthood. This may be more difficult to do in the case of chemicals that do not remain in the body (e.g. many pesticides) than in the case of those that do (e.g. flame retardants, POPs).

7. Conclusions

The problem of exposure to EDCs and their negative effects on, and potential to cause disease in, humans and wildlife is global and requires global solutions. More programmes are needed that foster collaboration and data-sharing among scientists, among governmental agencies and among countries.

Awareness raising and capacity building among health professionals are important to facilitate the collection of information on the assessment and evidence of effects and the implementation of protective measures.

To protect humans from health problems and disorders resulting from the combined effects of exposure to EDCs, poor nutrition and poor living conditions, there is a need to develop programmes to this end and encourage collaboration between developed and developing countries.

There is a need for international mechanisms of providing up-to-date information and expert scientific advice to relevant stakeholders for the purpose of identifying or recommending potential measures to reduce exposure to or the effects of EDCs, particularly in vulnerable populations.

International support is needed in connection with building national capacities, particularly in developing countries and countries with economies in transition, with the aim of generating sound, evidence-based information and assessing EDC-related issues to support decision-making, including the prioritization of action to reduce risks.

In developing countries and countries with economies in transition there has not been much focus on studying EDC-related problems and they are rarely addressed. The capacity for assessing and managing risks from EDCs needs to be improved, particularly in developing countries.

Worldwide, there has been a failure to adequately address the underlying environmental causes of the increasing trends in endocrine diseases and disorders. Health-care systems do not have mechanisms in place to address the contribution of environmental risk factors to these trends. The benefits that can be gained by adopting primary preventive measures for dealing with them have largely remained unrealized (UNEP/WHO, 2013).

An increasing number of scientific studies suggest that EDCs, particularly in combination, play a role in the development of chronic diseases (including hormone-related cancers, obesity, diabetes and cardiovascular disease) and reproductive problems; further research is needed to obtain a better understanding of these associations.

The risk of health impacts from exposure to hormone disruptors is especially high during early development when multiple developing tissues may be affected. An endocrine disease or disorder induced during early development might only become apparent decades later, and exposure to one chemical could lead to multiple health risks not only in the exposed individual but also in subsequent generations.

The most sensitive windows of exposure to EDCs are found during critical periods of development, such as those of fetal development and puberty. This is when the ability of endocrine disruptors to alter the normal hormonal control of development is perhaps the most significant consequence of exposure because the developmental effects will occur at lower doses than are required for effects in adults (Alonso-Magdalena et al., 2010). In addition, the effects of exposure to endocrine disruptors during development will remain throughout life since the programming of cell differentiation and tissue development will be affected, resulting in tissue that has a different predisposition for disease in adulthood from that of non-exposed tissue.

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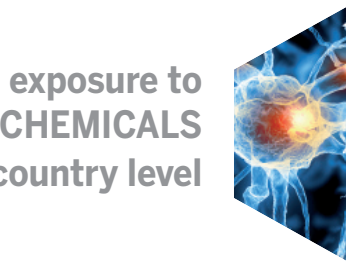

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