ENDOCRINE DISRUPTING CHEMICALS AND WOMEN’S REPRODUCTIVE HEALTH

FACTSHEET
ENDOCRINE DISRUPTING CHEMICALS (EDCs) AND WOMEN’S REPRODUCTIVE HEALTH

This factsheet was written by FREIA and the Health and Environment Alliance (HEAL), and is endorsed by the International Federation of Gynecology and Obstetrics (FIGO) and the International Federation of Fertility Societies (IFFS).

Email: info@freiaproject.eu
Web: www.freiaproject.eu
Twitter: @freiaprojectEU

©FREIA
February 2020

FREIA logo and icons are designed by NOBLE.STUDIO

A glossary of some of the terms used in this factsheet can be found on page 12
ACKNOWLEDGEMENTS

The FREIA project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No. 825100 (FREIA). This output reflects the views only of the author(s) and the European Union cannot be held responsible for any use which may be make of the information contained therein.

TACKLING THE ISSUES OF EDCs

FREIA aims to share our scientific findings to promote a sustainable society and improve the health of women

ADVANCE EDC TESTING FOR MORE PROTECTIVE CHEMICALS REGULATION

BETTER INFORMATION ABOUT EDCs FOR HEALTHIER LIFESTYLE CHOICES

Find out more at www.freiaproject.eu
It is beyond a doubt that endocrine disrupting chemicals (EDCs) impact the health of humans, animals and the environment globally. Surprisingly, we still don’t know exactly how EDCs can harm female reproductive health. This is one of the reasons that we currently have no good test methods and regulatory procedures to address this.

The European Commission has funded eight research projects to improve test methods for EDC identification. One of these projects is called FREIA: “Female Reproductive toxicity of Endocrine disrupting chemicals (EDCs): a human evidence-based screening and Identification Approach”, after the Nordic goddess of fertility.

This factsheet gives an overview of what is currently known about EDCs and their impact on women’s reproductive health. It also highlights the challenges to adequately regulate EDCs in European chemical regulations and how FREIA aims to improve this.
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Why focus on women’s reproductive health</td>
<td>1</td>
</tr>
<tr>
<td>Endocrine disrupting chemicals (EDCs)</td>
<td>2</td>
</tr>
<tr>
<td>Examples of known and suspected EDCs and where to find them</td>
<td>3</td>
</tr>
<tr>
<td>Women’s reproductive health challenges</td>
<td>4</td>
</tr>
<tr>
<td>Why endocrine disrupting chemicals matter</td>
<td>5</td>
</tr>
<tr>
<td>The timing makes the poison</td>
<td>6</td>
</tr>
<tr>
<td>Testing and regulating EDCs in Europe</td>
<td>8</td>
</tr>
<tr>
<td>Caring and sharing for a sustainable future</td>
<td>9</td>
</tr>
<tr>
<td>FREIA goals and partners</td>
<td>10</td>
</tr>
<tr>
<td>Glossary</td>
<td>12</td>
</tr>
<tr>
<td>Sources</td>
<td>13</td>
</tr>
</tbody>
</table>
WHY FOCUS ON WOMEN’S REPRODUCTIVE HEALTH

Good reproductive health is important for the well-being of women and, if they wish to conceive, for the well-being of their children and future generations. The number of women with reproductive health problems is increasing globally.

A woman’s reproductive health is already largely established early in her life, during embryonic and fetal development in the womb. It matures during puberty and hormones play a crucial role at every step of development. Hormones are also critical for maintaining reproductive health in the reproductive years and beyond. It is clear that a woman’s reproductive health is sensitive to chemicals that disturb hormonal processes, at all phases of her life.

We are all exposed to a cocktail of different chemicals in our everyday lives, including chemicals that can disturb hormonal processes. These chemicals are known as hormone or endocrine disrupting chemicals (EDCs).

A clear example how disruption of hormones can affect women’s reproductive health is the ‘DES disaster’, where overt reproductive effects have been described in women and their children, after taking the synthetic estrogen diethylstilbestrol (DES) as a drug during pregnancy\(^\text{ii}\). The negative effects of this drug are still apparent even three generations down the line.

Today, we still have huge gaps in understanding how endocrine disrupting chemicals (EDCs) can affect women’s reproductive health. This makes it difficult to identify, regulate and take protective measures against chemicals that can disturb hormonal processes.
ENDOCRINE DISRUPTING CHEMICALS (EDCs)

Hormone – or endocrine – disrupting chemicals (EDCs) are often human-made chemicals that interfere with the production, transport, excretion and/or function of hormones.

Together with the neurological and immune systems, the hormone or endocrine system is one of our three main communication systems within the body. Hormones are produced in glands and tissues, secreted into the blood and transported to distant target organs to regulate biological processes.

When normal hormonal signaling is disturbed by EDCs, this may lead to adverse health effects. Scientific evidence shows that exposure to EDCs can have profound effects on a woman’s reproductive health.

Exposure to endocrine disrupting chemicals happens daily indoors and outdoors, at home, in the office, at school or at daycare facilities. EDCs can be found in many products that we use on a daily basis, from household and personal care products to plastic food packages. Some pesticides used for agricultural purposes or at home are also EDCs.

We are exposed via the air, dust, food and water or via our skin. EDCs can be transferred from the pregnant woman to the developing fetus or child through the placenta and breast milk.
 EXAMPLES OF KNOWN AND SUSPECTED ENDOCRINE DISRUPTING CHEMICALS AND WHERE TO FIND THEM

Plastic food packages may contain **BISPHENOL A (BPA)** or **PHTHALATES** such as DEHP, which have been identified as substances of very high concern by European regulators for their endocrine disrupting properties. BPA is used in the production of hard plastics or to prevent corrosion of tin cans, whereas phthalates are used as plastic softeners.

Fruits and vegetables may contain residues of **PESTICIDES**, which have been documented for their effects on the endocrine systems, such as chlorpyrifos, prochloraz and ketoconazole.

Water- and stain repellent coatings used in many consumer products such as non-stick cookware, raincoats, carpets and furniture contain **PERFLUORINATED CHEMICALS (PFAS)** with endocrine activity, such as PFOS and PFOA.

**ANTI-MICROBIAL CHEMICALS** used in personal care products may be endocrine disruptors, such as triclosan and triclocarban. Other examples are **PHTHALATES** (DEHP, DMP, DEP and DBP) or **PARABENS**, which are commonly used in cosmetics for example to make nail polish less brittle, hairspray flexible or as solvents in perfumes.
In every stage of a woman’s life, hormones play important roles in development, maturation and normal functioning of her reproductive system. Disruption of hormonal balance is often the cause of reproductive health issues in women.

Known factors that can affect reproductive health are obesity, smoking, age at first menstruation, age at menopause, age at first childbirth, duration of breastfeeding. Besides these known factors, exposure to EDCs has also been associated with several health conditions. These include problems during pregnancy and/or at birth, early puberty, menstrual irregularities, polycystic ovary syndrome (PCOS), endometriosis, breast cancer, or early menopause (premature ovarian insufficiency or failure).vi

**WOMEN’S REPRODUCTIVE HEALTH CHALLENGES**

In Europe alone, the burden of diseases as a consequence of exposure to endocrine disrupting chemicals (EDCs) is estimated to cost at least 163 billion euros every year. This is around 325 euros for each European citizen, every year.vii

Part of these costs is related to women’s reproductive health issues, such as uterine fibroids (163 million) and endometriosis (1.25 billion).viii

**THE PRICE WE ALL PAY**

It is difficult to give a cost estimate for female infertility due to EDC exposure, because the reason for not becoming pregnant is often unexplained and may be caused by female factors, male factors or a combination of both. It is clear though, that the demand for assisted reproductive techniques (ART) such as in vitro fertilization (IVF) has risen over the last 40 years. The contribution of EDCs to the cost associated with ART is estimated at 4.7 billion euros.vii
**WHY ENDOCRINE DISRUPTING CHEMICALS MATTER**

**EDCs are everywhere** in our environment. This means that women can be exposed for example via food, water, personal care products, furniture and pharmaceutical drugs. Healthy lifestyle choices can lower one’s exposure, but mainly ambitious public policies are needed to regulate EDCs better.

EDC effects are largely overlooked in current chemical regulations. This is partly due to the lack of adequate test methods.

EDCs can have effects at very low doses that are usually considered “safe” for consumers according to traditional risk assessment methods.

There are life stages in which women are extra sensitive for hormone disruption, e.g. in the womb, as newborns, as adolescent undergoing puberty, as a pregnant woman. Exposure to EDCs during these susceptible periods in her life may cause irreversible damage to a woman’s health.

Effects of EDCs may not be so apparent at first sight. Effects from exposure in the womb might only become visible later in life, for instance fertility problems. EDCs may also affect multiple generations, as is seen for diethylstilbestrol (DES).
Numerous concerns about reproductive effects in humans and wildlife originate from findings linking exposure to endocrine disrupting chemicals (EDCs) in the womb to declining sperm counts and increasing prevalence of undescended testes, testicular cancer and urinary duct malformation in males.

The effects that EDCs may have on female reproduction have been overlooked for many years. This is thought-provoking considering that the finite reserve of eggs is clearly a significantly more limiting factor in human reproduction than the production of sperm.

In the transition from (unborn) girl to an adult woman, many hormonal processes are activated or reactivated, leading to several phases in life during which she is sensitive to EDC exposure.

Depending on the life-stage at which EDC exposure occurs, different effects may arise due to differences in basic follicle biology in the embryo, fetus, young girl, adolescent and adult woman. The effects of EDC exposure during early life may be activated or become worse due to additional EDC exposure throughout a woman’s life.

The increasing understanding of EDCs has changed the ways of viewing toxic actions. Traditionally, toxicology has primarily focused on the chemical: “the dose makes the poison”. It is now clear that the state (or life-stage) of the targeted organism is also critical. Better implementing “timing” into toxicological and regulatory sciences is a great challenge, but will certainly lead to more protective chemical regulations in the EU and beyond.

**THE TIMING MAKES THE POISON**

**STAGES OF OOCYTE DEVELOPMENT: EXPOSURE TO EDCs AT DIFFERENT LIFE STAGES LEADS TO DIFFERENT EFFECTS**

![Diagram showing stages of oocyte development and effects of EDC exposure](image)

- **±300.000 follicles with oocytes**
- **±400 ovulations**
- **Before birth**
- **Infancy and childhood**
- **Each month from puberty to menopause**

**Effect of EDC**

- Fewer oocytes
- Early or delayed puberty, irregular menstrual cycle
- Early menopause, infertility

The increasing understanding of EDCs has changed the ways of viewing toxic actions. Traditionally, toxicology has primarily focused on the chemical: “the dose makes the poison”. It is now clear that the state (or life-stage) of the targeted organism is also critical. Better implementing “timing” into toxicological and regulatory sciences is a great challenge, but will certainly lead to more protective chemical regulations in the EU and beyond.
During a woman’s reproductive years (between 15 and 49 years of age), outside of pregnancy and breastfeeding, typically only a single oocyte completes the maturation process every month until menopause marks the end of the ability to conceive a child. Approximately 400 follicles will eventually mature to the ovulatory stage during a woman’s life. To maintain the periodical maturation of oocytes and have a regular menstrual cycle, the right amount of hormones need to be produced by the ovaries at the right time. Some EDCs are known to affect the production of hormones, but it is yet to be determined how the production of hormones in the ovary is affected. Whether EDCs can affect growth, maturation and accelerated loss of follicles has not yet been thoroughly addressed.

After decades of clinical use, it was discovered that DES causes cancer of the female reproductive tract, impaired fertility, endometriosis and earlier menopause in the daughters born from women taking these drugs during pregnancy. This shows that female reproductive disorders in adulthood can originate from hormonal changes during development. At birth, a baby girl has approximately three hundred thousand primordial follicles containing immature eggs or oocytes. While we have some information from animal studies, the effects of EDCs on ovarian development in the human fetus, and the number and quality of oocytes are still unknown.

In girls, puberty begins typically between the ages of 10 and 14 with activation of hormonal signaling. After that, ovarian follicles are periodically recruited to restart growth and mature. Both hormonal signaling and pubertal onset are susceptible to disturbances resulting from EDC exposure, such as phthalates and bisphenol A. For example, the role of EDCs in early breast development in girls has increasingly been discussed over the last decade. Clearly, EDCs can affect processes that mark the beginning of puberty. Yet, the exact processes that trigger effects on puberty still need to be clarified.
European law requires chemicals to go through a safety evaluation before being allowed on the market. The type of information that needs to be provided by industry to the regulators depends on the type of chemical to be evaluated, e.g. a pesticide, biocide or industrial chemical.

Regulators assess the endocrine disrupting properties of a chemical mostly based on data from standard test protocols that are agreed upon by the Organisation for Economic Co-operation and Development (OECD). Unfortunately, currently available protocols are not well-suited to pick up effects of EDCs on important health effects, including effects on female reproductive health. This is especially the case for effects as a result of early life exposure, in the womb, during infancy and puberty, when a woman’s body is still under development.

The process to identify an EDC differs between chemical regulations. Specific identification criteria for EDCs only exist for pesticides and biocides. In the REACH regulation, endocrine disrupting properties of industrial chemicals are assessed case by case and is based on existing scientific evidence and expert opinion. Other regulations addressing the safety of chemicals in everyday products, such as cosmetics, toys or food contact materials, currently do not have specific identification processes for EDCs.

The lack of coherent identification processes for EDCs across chemical regulations have increasingly come under the spotlight of European policy debates. This has led the European Commission to commit to updating its strategy on endocrine disruptors; the previous one dates back to 1999. Upon taking office in late 2019, the European Commission President as well as Environment and Health Commissioners have committed to making endocrine disruptors a high priority during their mandate.

"Europe needs to move towards a zero-pollution ambition. I will put forward a cross-cutting strategy to protect citizens’ health from environmental degradation and pollution, addressing air and water quality, hazardous chemicals, industrial emissions, pesticides and endocrine disrupters."

Ursula van der Leyen, 2019, President of the European Commission
Exposure to endocrine disrupting chemicals (EDCs) can lead to seriously debilitating health problems and diseases. This means that properly addressing EDCs – in chemical regulations, science, education and health care – can also help to prevent diseases and stimulate a healthy and sustainable society.

Sharing scientific findings is instrumental for informing society about the potential health risks of EDCs. Here, medical and reproductive health communities play important roles in translating science into practical advice for female patients.

It is especially important to train and educate younger generations about the potential health risks of chemical exposures and the positive health effects life-style choices can have.

The youth of today are our future politicians, healthcare professionals, scientists, chemical producers and may also become parents. Engaging today’s youth generation in the environmental health debate will ensure a healthier society for generations to come.

“Dramatic increases in exposure to toxic chemicals in the last four decades is threatening human reproduction and health”

*International Federation of Gynecology and Obstetrics (FIGO)*
The FREIA project is dedicated to safeguarding women’s reproductive health against endocrine disrupting chemicals. To achieve this goal, we will...

...gain new understandings and insights into adverse effects of endocrine disruption on women’s health.

...develop new test methods and improve existing ones to detect EDCs that are toxic to women’s reproduction in order to support protective chemical regulation.

...promote sustainable options for a healthy society and improve the health of women worldwide.
The FREIA consortium consists of eleven partners with outstanding scientific and regulatory expertise on endocrine disruption in relation to women’s reproductive health, early life development, epidemiology, endocrinology and toxicology.

We work closely with seven other EU-funded projects in a cluster called EURION: European Cluster to Improve Identification of Endocrine Disruptors. These projects develop test methods to identify EDCs that cause thyroid hormone disruption, developmental neurotoxic effects, and metabolic diseases. For more information, visit: www.eurion-cluster.eu

The Health and Environment Alliance (HEAL) is our strong collaborator for policy and advocacy actions as well as dissemination and communication on health protection.

We have established partnerships with the International Federation of Gynecologists and Obstetrics (FIGO) and the International Federation of Fertility Societies (IFFS), both major actors in advocating and communicating actions to promote women’s health and a healthy society.
Breast cancer: The lifetime risk is about 1 in 8 women. Genetics, smoking, age at first menstruation and onset of menopause, age at first child, duration of breastfeeding are known to affect a woman’s chance of developing breast cancer. EDCs linked to breast cancer include DES, BPA, early life exposure to DDT and dioxins.

Endocrine disrupting chemical (EDC): “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, its progeny, or (sub) populations”, according to the 2002 definition of the World Health Organization.

Endometriosis is a condition in which the tissue that normally lines the inside of the uterus, also grows outside the uterus, often in the pelvic area, ovaries and Fallopian tubes. Endometriosis is a painful condition which increases the risk for infertility. It affects 10-15% of women in reproductive age. Endometriosis is linked to DES, phthalates and persistent organic pollutants such as anti-malaria compound DDT.

Hormones are chemical messengers in our body. Some hormones stimulate the release of hormones in other glands, such as GnRH (gonadotropin releasing hormone). Others stimulate the production of hormones, such as FSH (follicle stimulating hormone), LH (luteinizing hormone) and TSH (thyroid stimulating hormone). Some hormones have direct effects on a target cell, such as thyroid hormones T3 (triiodothyronine) and T4 (thyroxine), estrogens (e.g. estradiol), androgens (e.g. testosterone) and progestogens (e.g. progesterone).

Infertility is the inability to conceive a child. About 1 in 6-8 couples have troubles getting pregnant or staying pregnant. There are many causes for infertility and involve female (20-30%), male (20-30%) factors, both male and female or unexplained factors (40%). Female infertility may have a plethora of underlying causes, including endometriosis, disorders related to ovary dysfunction such as PCOS, but also factors like infections and lifestyle. Fertility issues are linked to DES, BPA and phthalates.

Irregular menstrual cycles may in itself occur during puberty, particularly at the start of puberty as it may take one or two years for menstrual cycles to become regular. When three or more periods are missed, this is referred to as amenorrhea. This may occur as a result of natural causes (for example pregnancy), but also as a side effect of medication such as antidepressants, or hormonal disbalance.

Polycystic ovary syndrome (PCOS) is a hormonal condition. Women with PCOS produce more male hormones than normal. Symptoms include abnormal menstrual cycles and excess hair growth. PCOS is the most common cause of infertility in women. PCOS is linked to BPA.

Premature ovarian insufficiency or failure (POI). Women have POI when the ovaries have a reduced estrogen production or release fewer eggs before the age of 40. The result of POI is infertility. Women may also experience symptoms similar to menopause, as a result of low estrogen levels. Contrary to menopause though, women may still occasionally or irregularly have a period and become pregnant.

An oocyte is an immature egg. Oocytes are enclosed by specialized cells, together called the follicle. A woman is born with all the follicles she will ever have. Typically, every month one oocyte will become a mature egg. During this process, the follicle enlarges and becomes filled with follicular fluid. Once matured, the oocyte or egg will be released from the ovarium (ovulation) and is ready to be fertilized by sperm.

Ovarian cysts are fluid-filled sacs in or on the ovary. Most cysts are harmless and will disappear without treatment. Some ovarian cysts may develop as a result of endometriosis or PCOS and cause serious symptoms, such as pelvic pain and bloating.

Reproductive health is “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and to its functions and processes”, according to the United Nations'.
Sources


iii. See for instance:


v. Figure from: Andrea C. Gore, PhD, David Crews, PhD, Loretta L. Doan, PhD, Michele LaMerrill, PhD, MPH, Heather Pati, PhD, and Ami Zota, ScD, MS. Introduction to Endocrine Disrupting Chemicals (EDCs). A guide for public interest organizations and policy-makers. December 2014. The Endocrine Society and International Pollutants Elimination Network (IPEN). https://ipen.org/documents/introduction-endocrine-disrupting-chemicals-edcs


xiii. Conclusions of the workshop organized by the European Commission on “Setting priorities for further development of test methods and testing approached for endocrine disruptors” (Paris, 31 May – 2 June, 2017), with experts from academia and regulatory authorities.


SAFEGUARDING WOMEN’S REPRODUCTIVE HEALTH AGAINST ENDOCRINE DISRUPTORS

Find out more at www.freiaproject.eu

The FREIA project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No. 825100 (FREIA). This output reflects the views only of the author(s) and the European Union cannot be held responsible for any use which may be make of the information contained therein.