Page intentionally left blank
ENDOCRINE DISRUPTING CHEMICALS (EDCs) AND WOMEN’S REPRODUCTIVE HEALTH
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 authors and the European Union cannot be held responsible for any errors which might be made in the information contained therein.

TACKLIN THE MAITERS O EDCs

FREIA aims tae whack oor scientific finnins tae gie a heeze tae a sustainable society an improve the hail o weemen

ADVANCE EDC TESTING FUR MAIR PROTECTIVE CHEMICALS REGULATION

BETTER INFORMATION ABOOT EDCs FUR HEALTHIER LIFESTYLE CHOICES

Find oot mair aat www.freiaproject.eu
It is ayont aa doot aat endocrine kerfufflin chemicals (EDCs) impact the hail o humans knowt an the environment ower the warld. O a winner we still dinna ken exactly fit EDCs can herm female reproductive hail This is een o the rizzons aat we currently hiv nae guid test wyes an regulatory procedures tae address this.

The European Commission his fundit eicht research projecks tae improve test methods fer EDC identification. Een o these projects is caad FREIA Female Reproductive toxicity o Endocrine kerfufflin chemicals EDCs a human evidence based screenin an Identification Approach aifter the Nordic goddess o fertility.

This factsheet gives an owersicht o fit is currently kent eenoo EDCs an their impack on weemen s reproductive hail. It highlights the challenges o adequately regulate EDCs in European chemical regulations an fit FREIA aims tae dee tae mak this better.
FIT WYE FOCUS ON WEEMEN’S REPRODUCTIVE HAIL?

Gweed reproductive hail is important fer the weelbein o weemen an, gin they wish tae conceive, fer the weel bein o their geets an future generations. The nummer o weemen wi reproductive hail problems is increasin world-wide.

A wifie’s reproductive hail is already gey near establishet early in her lyffe durin embryonic an fetal development in the wyme. It matures durin puberty an hormones play a crucial role aat ilkae step o development. Hormones are gey critical in maintainin reproductive hail in the reproductive years an ayont. It is clear aat a wifie’s reproductive hail is sensitive tae chemicals aat kerfuffle hormonal processes aat aa phases o her lyffe.

We are aa exposed tae a heeze o different chemicals in oor iveryday lives including those aat can disturb hormonal processes Than chemicals are kent as hormone or endocrine disrupting chemicals (EDCs).

A clear example o fit disruption o hormones can dee tae weemen’s reproductive hail is the DES mishanter, far overt reproductive effects hiv been described in weemen an their geets aifter takkin the synthetic estrogen diethylstilbestrol, DES, as a drug durin pregnancy. The contermashious effects o this drug are still apparent even three generations doon the line.

Eenoo, we still hiv muckle gaps in unnerstaunin fit wey endocrine kerfufflin chemicals, EDCs, can affeck weemen’s reproductive hail. This maks it deefficult tae identifee, regulate, an take protective measures agin chemicals aat can kerfuffle hormonal processes.
ENDOCRINE KERFUFFLIN CHEMICALS (EDCs)

Hormone or endocrine disrupting chemicals, EDCs, are affen man vrucht chemicals aat ficher wi the production, transport, excretion, an/or function o hormones.

Thegither wi the neurological an immune systems, the hormone or endocrine system is een o oor three main communication systems within the body. Hormones are makkit in glands an tissues, secreted inta the bleed, an taen tae hyne aff target organs tae regulate biological processes.

Fin normal hormonal signaling is kerfuffled bi EDCs, this micht lead tae adverse hail effects Scientific evidence shows aat exposure tae EDCs can hiv profun effecks on a wifie’s reproductive hail.

Exposure tae endocrine kerfufflin chemicals happens daily, inbye an ootbye, at hame, in the office, at skail or at daycare airts. EDCs can be funn in mony products aat we eese ilkie day fae hoosehold an personal care producks tae plastic maet packages. A when pesticides used fer agricultural eese or aat hame are EDCs tee.

We are exposit via the air styoo, maet, an satty bree or via oor skin. EDCs can be transferrit fae the pregnant wifie tae the growin fetus or bairn ben the placenta an breist milk.
EXAMPLES O KENT AN JALOUSED ENDOCRINE KERFUFLIN CHEMICALS AN FAR TAE FINN THEM

Plastic maet packages micht contain **BISPHENOL A (BPA)**, or **PHTHALATES** sic as DEHP, whilk hiv bin identifeed as substances o gye heich consarn bi European regulators fer their endocrine kerfufflin properties. BPA is eesit in the makkinn o hard-vrocht plastics or tae haud aff corrosion o tin cans, whereas phthalates are eesit as plastic saffeners.

Fruits an veggies micht contain residues o **PESTICIDES**, whilk hiv been documented fer their effects on the endocrine systems, sic as chlorpyrifos, prochloraz, an ketoconazole.

Satty bree an blad repellent coatings used in mony consumer products, sic as non-stick cookware, raincoats, carpets an furniture, contain **PERFLUORINATED CHEMICALS (PFAS)**, sic as PFOS an PFOA, whilk ficher wi endocrine activity.

**ANTI-MICROBIAL CHEMICALS**, sic as triclosan an triclocarban, eesit in personal care products, micht be endocrine kerfufflers as weel. Ither examples are **PHTHALATES**, DEHP DMP DEP an DBP, or **PARABENS**, whilk are commonly eesit in fit mak nail blaik less brittle, hairspray raxxy, or as solvents in perfumes.
WEEMEN’S REPRODUCTIVE HAIL CHALLENGES

In ilkae stage o a wifie’s lyffe, hormones play important roles in development maturation an normal functionin o her reproductive system. Kerfufflin o hormonal balance is affen the cause o reproductive hail issues in weemen.

Kent factors that can affeck reproductive hail are bein creashie, smoking, age at first menstruation, age at menopause, age at first childbirth, an duration o breistfeeding/ Apairt frae thon weel-kent factors exposure tae EDCs has likewyse bin associatit wi puckles o hail conditions. These include problems durin pregnancy as odrapit early puberty menstrual irregularities, polycystic ovary syndrome (PCOS), endometriosis, breist cancer, or early menopause, premature ovarian insufficiency or failure.

It is hard tae gie a cost estimate fur female infertility due tae EDC exposure kis the rizzen eur nae becoming pregnant is affen unexplainit an mey be causit bi female factors, male factors or a mellin o baith. It is clear, though, aat the demand fer assistit reproductive techniques (ART), sic as in vitro fertilization (IVF), has risen ower the hinmaist 40 year. The contribution o EDCs tae the cost associatit wi ART is estimated at 4.7 billion euros.
EDCs are awaye in oor environment. This means aat weemen can be exposed, fer example via maet, satty bree, personal care producks, furniture an pharmaceutical drugs. Healthy lifestyle choices can lower oor exposure, bit maistly ambitious public policies are nott tae regulate EDCs better.

EDC effecks are largely overluikit in chemical regulations eenoo. This is paitly due tae the faut o adequate test wyes.

EDCs can hiv effects aat gye laich doses aat are usually thocht safe fer consumers accordin tae traditional weys o jelousin risk.

There are lyffe stages in whilk weemen are gey sensitive fur hormone disruption, e.g. in the wyme, as newborns, as haufins unnergaun puberty, as pregnant wifies. Exposure tae EDCs during these susceptible periods in her lyffe micht cause irreversible damage tae a wifie’s hail.

Effecks o EDCs micht nae be sae apparent at first sicht. Effecks fae exposure in the wyme might anely becam veesible later in lyffe, fer instance fertility problems. EDCs micht affeck multiple generations, tee, as is seen wi diethylstilbestrol (DES).
Mony consarns aboot reproductive effecks in humans an wildlife stert fae findins linkin exposure tae endocrine kerfufflin chemicals (EDCs) in the wyme, tae dwinin sperm coonts an growin prevalence o undescended steens, an testicular cancer, an urinary duct malformation in chielsix.

The effecks aat EDCs micht hae on female reproduction hiv been miskent fer mony years. This is thocht steerin, conseederin at the finite reserve o aiggs is clearly a significantly mair leemitin factor in human reproduction nor the makkin o sperm.

In the cheengin fae unborn quine tae an adult wifie, mony hormonal processes are activatit or reactivatit leading tae a puckle phases in lyffe during whilk she is sensitive tae EDC exposure.

Depending on the lyffe stage aat whilk EDC exposure occurs, different effecks micht arise due tae differences in basic follicle biology in the embryo fetus young quine, hauflin, an adult wifie. The effecks o EDC exposure durin early lyffe micht be activated or become wur daw tae additional EDC exposure aa benc a wifie’s lyffe.

The growin unnerstaunin o EDCs has cheengit the weys we view toxic actions. Traditionally, toxicology has primarily focusit on the chemical - the dose maks the pyson. It is noo clear at the state or lyffe stage o the targeted organism is also critical. Takkin tent o timin in the toxicological an regulatory sciences is a great challenge, bit it’ll o a certainly lead tae mair protective chemical regulations in the EU an ayont.

THE TIMIN MAKES THE PYSON

STAGES O OOCYTE DEVELOPMENT EXPOSURE TAE EDCS AT DIFFERENT LYFFE STAGES LEADS TAE DIFFERENT EFFECKS

- BEFORE BIRTH
- INFANCY and BAIRNHOOD
- ILK MONTH FAE PUBERTY TAE MENOPAUSE

±300,000 FOLLICLES WITH OOCYTES

±400 OVULATIONS

- FYOWER OOCYTES
- EARLY or DELAYED PUBERTY, IRREGULAR MENSTRUAL CYCLE
- EARLY MENOPAUSE, INFERTILITY
During a wife’s reproductive years, atween 15 an 49 years o age, ootbye o pregnancy an breastfeeding, in the ordnar wye, anely a single oocyte completes the maturation process ilkae month, until menopause marks the eyn o the ability tae faa wi a bairn. About 400 follicles’ll eventually mature tae the ovulatory stage durin a wife’s lyffe. Tae maintain the periodical maturation o oocytes an hiv a regular menstrual cycle, the richt sup o hormones need tae be vrocht bi the ovaries aat the richt time. Some EDCs are kent tae affect the makkin o hormones, bit it is yet tae be kent fit wey inbye the ovary. Whither EDCs can affeck growth, maturation, an acceleratit loss o follicles has nae yet been thoroughly seen till.

In quines, puberty sterts maist times atween the ages o 10 an 14, wi activation o hormonal signaling. Aifter at, ovarian follicles are whyley recruitit tae restert growth an mature. Baire hormonal signaling an pubertal onset are susceptible tae disturbances resultin fae EDC exposure, sic as phthalates an bisphenol A. Fer example the role o EDCs in early breist development in quines his increasinly been spukken aboot ower the hinmaist decade. Clearly, EDCs can affeck processes at merk the stert o puberty. Yet the exact processes at trigger effecks on puberty still need tae be clarifeet.

Aifter decades o clinical eese, it wis fun oot at DES causes cancer o the female reproductive tract, spyles fertility, endometriosis, an earlier menopause in the dochters born fae weemen takkin these drugs durin pregnancy. This shows at female reproductive disorders in adulthood can stert fae hormonal chynges durin development. A bairn-quine hai aboot three hunner thoosand primordial follicles containing immature aiggs or oocytes. Fyles we hiv some information fae animal studies, the effects o EDCs on ovarian development in the human fetus, an the number an quality o oocytes, are still unkent.
European law requires chemicals to undergo a safety evaluation before being allowed on the market. The type of information that needs to be given 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 disruptor properties of a chemical mostly found in data from standard test protocols that are agreed upon by the Organisation for Economic Co-operation and Development (OECD). However, currently available protocols are not well suited to detect 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 childhood 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 rax regulation, endocrine disruptor properties of industrial chemicals are assessed case by case, often based on existing scientific evidence or expert opinion. Other regulations addressing the safety of chemicals in ordinary products, such as cosmetics, toys, or material contact materials currently do not have specific identification processes for EDCs.

The lack of coherent identification processes for EDCs across chemical regulations has 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 the first quarter of 2019, the European Commission President as well as Environment and Health Commissioners committed to making endocrine disruptors a high priority during their mandate.

"Europe needs to flip to a zero pollution ambition, I’ll pit for it a cross-cutting strategy to protect citizens’ health from environmental degradation and pollution, addressing air, a healthy breathing quality, hazardous chemicals, industrial emissions, pesticides, and endocrine disruptors."

Ursula van der Leyen, 2019, President of the European Commission
CARIN AND SHARING FER A SUSTAINABLE FUTURE

Exposure tae endocrine disruptin chemicals (EDCs) can lead tae seriously kerufflin hail problems an diseases. This means at properly addressin EDCs in chemical regulations, science, education, an hail care can also help tae prevent diseases an stimulate a healthy an sustainable society.

Sharing scientific findins is instrumental fer informing society aboot the potential hail risks o EDCs. Here, medical an reproductive hail communities play important roles in translatin science intae practical advice fer female patients.

It is maist important tae train an educate younger fowk aboot the science ahin potential hail risks o chemical exposures an the positive hail effects lyffe style choices can hiv.

The youth o the day are oor future politicians, healthcare professionals, Scientists, chemical producers, an micht become aul fowk on the wa tee. Engaging the day’s youth fowk in the environmental hail debate will makk sicca o a healthier society fer generations tae come.

“Byordnar increases in exposure tae toxic chemicals in the hinmaist fower decades is threatenin human reproduction an hail”

International Federation of Gynecology and Obstetrics (FIGO)
The FREIA prottick is gaan ower tae safeguairdin weemen’s reproductive hail agwen endocrine kerfufflin chemicals tae achieve this goal we ah’ll...

...bigg spleet new unnerstaunin an insichts intae coorse effecks o endocrine disruption on weemen’s health.

...makk spleet new test wyes an improve existin eens tae deteck EDCs aat are toxic tae weemen’s reproduction in order tae support protective chemical regulation.

...gie a heeze tae sustainable options fer a healthy society an improve the hail o weemen worldwide.
The FREIA consortium consists of eleven partners with outstanding scientific and regulatory expertise on endocrine kerfufflin in relation to women’s reproductive health, early life development, epidemiology, endocrinology and toxicology.

We darg closely with seven other EU funded projects in a boorach caad EURION (European Cluster to Improve Identification of Endocrine Kerfufflers). These project develop test methods to identify EDCs at cause thyroid hormone disruption, developmental neurotoxic effects, and metabolic diseases. For more information visit: www.eurion-cluster.eu

The hail an Environment Alliance HEAL is our strang fier fur policy and advocacy actions as weel as dissemination an communication on hail protection.

We hiv established partnerships wi the International Federation of Gynecologists an Obstetrics (FIGO) an the International Federation of Fertility Societies (IFFS), baith major actors in advocatin an communicatin actions tae promote weemen’s hail an a healthy society tee.
**GLOSSARY**

**Breast cancer** lifetime risk is about 1 in 8 women. Genetics, rikkin age at first menstruation and onset of menopause, age at first childbirth, and 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 subpopulations 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 chronic condition that 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 compounds 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), sex hormones (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 having trouble getting pregnant or experiencing prolonged pregnancy are many causes for infertility. An 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, or other factors like infections and lifestyle. Fertility issues are linked to DES, BPA, and phthalates.

**Irregular menstrual cycles** may occur during puberty, particularly at the onset of puberty, as it may take one to two years for menstrual cycles to become regular. If more than three or four periods are missed, this is referred to as amenorrhea. This may occur as a result of natural causes (e.g., pregnancy) or as a side effect of medication such as antidepressants or hormonal imbalance.

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

**Premature ovarian insufficiency or failure (POI).** Women with POI in 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 an become pregnant.

An **oocyte** is an immature egg. Oocytes are enclosed by specialized cells that form the follicle. A woman is born with all the follicles she will ever have. Typically, each month, one oocyte will become a mature egg. During this process, the follicle enlarges and becomes full of follicular fluid. Once mature, the oocyte or egg will be released from the ovary (ovulation) and is ripe to be fertilized by sperm.

**Ovarian cysts** are fluid-filled sacs in or on the ovary. Most cysts are harmless and will disappear on their own. Some ovarian cysts may develop as a result of endometriosis or PCOS and can cause serious symptoms such as pelvic pain or infertility. Ovarian cysts may develop as a result of endometriosis or PCOS and can cause serious symptoms such as pelvic pain, or infertility.

**Reproductive health** is "a state of complete physical, mental, and social well-being in all areas of life, not merely the absence of disease or infirmity. In all matters relating to the reproductive system an tae its functions an processes according to the United Nations'.

**Uterine fibroids** occur in 25-50% of women. Uterine fibroids are muscle cells and tissues that grow in an area of the uterus and can cause pelvic pain or infertility. They are linked to DES, BPA, and organochlorine pesticides such as DDT and dieldrin.


iii. See for instance:


v. Figure from: Andrea C. Gore, PhD, David Crews, PhD, Loretta L. Doan, PhD, Michele La Merrill, PhD, MPH, Heather Patiasul, 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.


SAFEGUARDIN
WEEMEN’S REPRODUCTIVE HAIL
AGAIN
ENDOCRINE KERFUFFLERS

Find oot mair aat www.freiaproject.eu

The FREIA prottick has received funding fae the European Union’s Horizon 2020 research an innovation programme under grant agreement nae 825100 FREIA. This output reflects the views anely o the author s an the European Union cannot be held responsible fur ony eese whilk mye be mak o the information contained therein.