

## International Research and Research Training Centre in Endocrine Disruption of Male Reproduction and Child Health



### Introduktion

Det nyoprettede internationale center EDMaRC med base i København blev oprettet i maj 2014. Centret danner ramme om forskning og undervisning i hormonforstyrrelser, herunder pigers tidligere pubertet, mænds ringe sædkvalitet og en høj forekomst af testikelkræft. Disse tendenser gør sig gældende i både Danmark og udlandet, og ifølge WHO/UNEP og det Europæiske Forskningsråd er der behov for en koordineret indsats på området. EDMaRC imødekommer netop dette ønske og er i færd med at skabe et samlet forsknings- og uddannelsesmiljø, der ventes at få stor international gennemslagskraft og fremhæver den danske førerposition på området.

EDMaRC er etableret på Rigshospitalets Afdeling for Vækst og Reproduktion i tæt samarbejde med Københavns Universitet. Afdeling for Vækst og Reproduktion har gennem en årrække været en international spydspids på området og stedet tiltrækker forskere fra hele verden. En række internationale forskere har peget på, at Afdeling for Vækst og Reproduktion er det oplagte centrum for dette internationale initiativ.

Nedenfor er resumé af powerpoint præsentationen, som vil blive vist ved mødet.

### Hvad får Danmark ud af EDMaRC?

#### **Ny viden om årsager til hormonforstyrrelser**

- Betydningen af miljøfaktorer og livsstil
- Samspil mellem kemikalier i miljøet, livsstil, genetik og reproduktiv sundhed
- Afdækning af mørketal - frivillig vs. ufrivillig barnløshed
- Årsager til ufrivillig barnløshed
- Årsager til pubertetsforstyrrelser og følgerne af disse

#### **Bedre vidensgrundlag for forebyggelse og regulering**

- Bedre information til befolkningen
- Mere vidensbaseret regulering og beslutningsproces
- Reducerede udgifter til hormonrelaterede sygdomme inkl. barnløshed for fremtidige generationer
- Sundere miljø

#### **Styrkelse af internationalt samarbejde**

- Fastholder Danmarks førende position på området
- Øget know-how til Danmark - udviklingsmuligheder
- Øgede muligheder for at hente internationale forskningsmidler hjem til Danmark

## Hvorfor er der brug for EDMaRC?

### Stigende forekomst af sygdomme relateret til hormonforstyrrelser

- Ufrugtbarhed meget udbredt
- Testikelkræft stigende (toppen af isbjerget)
- Dårlig sædkvalitet meget udbredt
- Misdannelser af kønsorganer stigende
- For tidlig pubertet (piger) stigende

### WHO, UNEP, NIH USA og det Europæiske Forskningsråd fokuserer på problemstillingen

Bilag nr. 1 – Link til WHO rapporten

Bilag nr.2 – Link til Europæiske Forskningsråd artikel

### Store personlige og samfundsmæssige omkostninger

Bilag nr.3 – Link til rapport sponsoreret af Nordisk Ministerråd: The Cost of Inaction: 592 mio Euro / år Mandlig reproduktion; Skandinavien: Nordisk Ministerråd

Bilag nr. 4 – Link til videnskabelig artikel sponsoreret af Endocrine Society (Den internationale forening for eksperter i hormonsygdomme): 4 mia Euro / år Fertilitet; Europa : Endocrine Society

## Hvorfor EDMaRC på Rigshospitalet?

### Danmark har en unik international position

Gruppen bag EDMaRC:

- Er pionerer inden for hormonforstyrrelser hos mennesker
  - 1991: WHO workshop arrangeret af forskerteam på Rigshospitalet satte fokus på miljøets påvirkning af human reproduktion: "Impact on the Environment on Reproductive Health"
  - 1995: Forskergruppen stod bag MST rapport om mandlig reproduktion og miljøkemikalier
  - Siden 2000: vært for 7 internationale konferencer om hormonforstyrrende stoffer
- Unikt tværfagligt forskningsteam i hormonsygdomme
- Mangeårig kliniske ekspertise med hormonsygdomme
- Højt citerede forskere inden for reproduktion

### Internationale organisationer bruger ofte EDMaRC eksperter:

- WHO
- EU kommissionen
- EU parlamentet
- NIH USA
- Nordiske forskningsråd
- EFSA

## Hvad bidrager EDMaRC med?

### Internationale forskningsprojekter

- Harvard University, Boston (USA)
- National Institutes of Health, Washington (USA)
- University of Cambridge (UK)
- Mount Sinai Hospital, NY (USA)
- University of Western Australia, Perth (AUS)
- University of Santiago (Chile)
- University of Turku (FIN)

### Uddannelse af ny generation af topforskere

- Internationalt miljø med gæsteforskere til DK
- Internationale kurser af høj kvalitet
- 8-10 Ph.D'er (3 årige) i løbet af de fire år

### Eksempel på planlagt forskningsprojekt:

EDMaRC-1: stor undersøgelse af ufrugtbarhed, barnløshed og baggrunden for de lave fødselstal i DK

#### Formål:

Kortlægge planlagte og ikke-planlagte graviditeter samt hyppighed af frivillig og ufrivillig barnløshed og udforske årsager til ufrivillig barnløshed (mandlige og kvindelige faktorer) inkl. hormonforstyrrelser og andre sygdomme, miljøkemikalier inkl. hormonforstyrrende stoffer, andre årsager inkl. livsstil, stress, medicin, genetiske og epigenetiske faktorer.

#### Metode – tre-trins raket:

Befolkningsundersøgelse (800.000 deltagere):

- spørgeskema og registerstudie

Befolkningsundersøgelse (10.000 deltagere):

- spørgeskema og registerstudie
- urinprøver til bl.a. måling af miljøkemikalier

Ventetid-til-graviditet undersøgelse (1.000 deltagere, fulgt 12 mdr.):

- Spørgeskema/dagbog (til mand og kvinde)
- Klinisk undersøgelse
- Sædanalyser
- Blod - hormoner, genetiske undersøgelser, kemikalier
- Urin - tidlige aborter, kemikalier

Bilag nr.1 :

WHO rapport – State of the Science of Endocrine Disrupting Chemicals 2012:

[http://apps.who.int/iris/bitstream/10665/78102/1/WHO\\_HSE\\_PHE\\_IHE\\_2013.1\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/78102/1/WHO_HSE_PHE_IHE_2013.1_eng.pdf?ua=1)



## Bilag nr.2:

European Science Foundation – Male Reproductive Health, Science Policy Briefing, September 2010:  
[http://www.esf.org/fileadmin/Public\\_documents/Publications/SPB40\\_MaleReproductiveHealth.pdf](http://www.esf.org/fileadmin/Public_documents/Publications/SPB40_MaleReproductiveHealth.pdf)



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40

## Male Reproductive Health

Its impacts in relation to general wellbeing and low European fertility rates

### Contents

1 • Foreword  
1 • Introduction  
2 • Issues and challenges

7 • Conclusions  
8 • Recommendations for a common research strategy

9 • References  
12 • Expert Group  
12 • Acknowledgement

### Foreword

Research in the area of male reproductive health has in the past focused mainly on birth control and family planning in non-developing countries, contraception, and sexually transmitted diseases such as HIV. Only little attention has been paid to male reproductive health disorders that lead to impaired fertility resulting in lower birth rates especially in industrialised countries. There is therefore an urgent need for better understanding the status of male reproductive health, especially in Europe and in industrialised countries where lifestyle and environmental factors may have a negative impact.

This Science Policy Briefing is the first to highlight this important issue which could have a dramatic impact on future birth rates and demographic changes in industrialised countries. It summarises the various exogenous and endogenous factors which can have an impact on male reproductive health and provides policy advice to national and European funding institutions.

The report was developed by a group of leading European experts. The issue was first raised by Professor Niels E. Skakkebaek during a mini symposium organised at the European Medical Research Councils (EMRC) plenary meeting in Strasbourg in April 2009. A first strategic meeting was held in Copenhagen on 20 May 2009 and the report was then written and finalised by the high level expert group present at this meeting.

This paper aims to increase awareness about the major consequences that reduced male reproductive health can have. It also provides advice on where and how to strengthen research in this area. Male reproductive health has been a low priority for funding agencies in European countries over the last 25 years. This has led to a lack of continuity in funding and a large translational gap between basic scientists and clinicians working with European patients.

The main policy recommendations are as follows:

- Increase awareness of male reproductive health issues
- Strengthen interdisciplinary, translational research in the area of male reproductive health issues
- Implement long-term, epidemiological studies aimed at better understanding the causes and effects of male reproductive disorders
- Target research efforts at preventing/minimising the occurrence of disorders rather than developing drug treatments.

Recommended funding instruments are transdisciplinary research networks which should be implemented at the European and international level to strengthen this highly important research area for the benefit of society.

We would like to thank the members of the high level expert group for their excellent work.

**Professor Marja Makarow**, ESF Chief Executive  
**Professor Liselotte Højgaard**, EMRC Chair

### Introduction

In most European countries fertility rates have declined drastically to below replacement level – the level at which the rate of new births can replace a population (1,2). This decline is primarily due to changes in social and economic conditions, such as wider use of contraception and more women seeking careers and postponing childbirth (1). However, declining fertility rates may also partly result from a decreased ability to conceive. In Europe there is a growing demand for use of assisted reproduction techniques (ART; 3,4), and a growing body of evidence points towards adverse trends in male reproductive health, including reduced semen quality, increased incidence of testicular cancer and increased or an already high incidence of congenital reproductive malformations (cryptorchidism and hypospadias; 5). It is to be expected that poor semen quality in young men, when combined with the high prevalence of increased age at attempting for pregnancy in women (when fertility is already declining), will lead to increased fertility problems in couples and its attendant socio-economic impacts.

Other than cancers, reproductive problems in men are generally not life-threatening, but in the last five years there has been a growing recognition that male reproductive function and risk of cardiometabolic disorders, including abdominal obesity, type 2 diabetes and hypertension are interlinked, as late-onset hypogonadism (low/subnormal testosterone levels) in men is an important determinant and/or consequence of these disorders (6,7). Moreover, the (normal) age-related decline in testosterone levels in men (8) clearly predisposes to such disorders with broad effects on wellbeing and mortality (7,9). Estimates of the incidence of hypogonadism vary from ~10% (10) to nearer 40% in men >45 years (11). The European-wide increase in the proportion of the male population that are of older age

[www.esf.org](http://www.esf.org)



## Bilag nr.4:

JCEM videnskabelig artikel: Male Reproductive Disorders, Diseases, and Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union:

<http://press.endocrine.org/doi/10.1210/jc.2014-4325>

ORIGINAL ARTICLE

# Male Reproductive Disorders, Diseases, and Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union

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**Introduction:** Increasing evidence suggests that endocrine-disrupting chemicals (EDCs) contribute to male reproductive diseases and disorders.

**Purpose:** To estimate the incidence/prevalence of selected male reproductive disorders/diseases and associated economic costs that can be reasonably attributed to specific EDC exposures in the European Union (EU).

**Methods:** An expert panel evaluated evidence for probability of causation using the Intergovernmental Panel on Climate Change weight-of-evidence characterization. Exposure-response relationships and reference levels were evaluated, and biomarker data were organized from carefully identified studies from the peer-reviewed literature to represent European exposure and approximate burden of disease as it occurred in 2010. The cost-of-illness estimation utilized multiple peer-reviewed sources.

**Results:** The expert panel identified low epidemiological and strong toxicological evidence for male infertility attributable to phthalate exposure, with a 40–69% probability of causing 618 000 additional assisted reproductive technology procedures, costing €4.71 billion annually. Low epidemiological and strong toxicological evidence was also identified for cryptorchidism due to prenatal polybrominated diphenyl ether exposure, resulting in a 40–69% probability that 4615 cases result, at a cost of €130 million (sensitivity analysis, €117–130 million). A much more modest (0–19%) probability of causation in testicular cancer by polybrominated diphenyl ethers was identified due to very low epidemiological and weak toxicological evidence, with 6830 potential cases annually and costs of €848 million annually (sensitivity analysis, €313–848 million). The panel assigned 40–69% probability of lower T concentrations in 55- to 64-year-old men due to phthalate exposure, with 24 800 associated deaths annually and lost economic productivity of €7.96 billion.

**Conclusions:** EDCs may contribute substantially to male reproductive disorders and diseases, with nearly €15 billion annual associated costs in the EU. These estimates represent only a few EDCs for which there were sufficient epidemiological studies and those with the highest probability of causation. These public health costs should be considered as the EU contemplates regulatory action on EDCs. (*J Clin Endocrinol Metab* 100: 1267–1277, 2015)