

CEFIC Long-range Research Initiative Request for Proposals (RfP)

Title and Code Number

Are changes in human reproduction a major factor in explaining the increases in 14 diseases and health parameters thought to be related to the endocrine system? – **LRI EMSG60**

Background

Currently there is great controversy about the causes of rising trends of a number of diseases and health parameters (*see below for list*) in human populations that are thought to be endocrine related. Toxicological and environmental epidemiologic research into the causes of these endocrine related diseases have mainly focussed on exposure to chemicals with postulated endocrine disruptive properties (i.e. endocrine disruptors). However, there are many epidemiology studies in the open scientific literature reporting on other causes for these diseases, mainly centring around human reproduction.

Indeed, over the last six or seven decades, family composition has dramatically changed from an average of 4 children per family to below 2. In Western societies, it has become custom to postpone pregnancy to later in life. Postnatal mortality has dropped and artificial reproductive treatments, such as in-vitro fertilization, have been introduced. These factors have significant effects on the health status of the next generation at birth and later in life.

The overall aim of this project is to systematically overview the available literature on the effect of changes in human reproduction on the incidence of several diseases and health parameters. However, before embarking on an extensive literature review it is important to establish whether the incidences of these diseases and health parameters have increased or whether the reported increases are artefactual. We hypothesize that the increased incidence in these diseases, if real, can at least partly be explained by changes in human reproduction.

Objectives

The project's objectives are to review the scientific literature (e.g. PubMed, Medline, Google Scholar) in a systematic manner on:

1. Whether the reported increases in these 14 diseases and health parameters in our Western society are real or caused by artefacts, for example as a result of changes in diagnostic criteria, improved reporting/registration and/or improved patient awareness.
2. Whether the increased incidences of these 14 diseases and health parameters are attributable to changes in human reproduction.

Scope

Objective 1: Critically review the literature on the incidence of 14 diseases and health parameters

The 2012 WHO/UNEP report¹ on endocrine disruption postulates that the incidence of a number of diseases and health parameters has increased over time (*see list below*). Before going into extensive debates about the causes of these increases it is important to assess whether these increases are real or a result of artefacts, such as improved reporting, improved patient awareness, changed diagnostic criteria and improved detection. If there is scientific debate about whether increases in disease incidences are real or artefact, this is commonly reflected in the open scientific literature. There is for example a considerable debate in the medical literature whether the rising trend in reported prostate cancer is due to PSA screening or whether it is real. It is expected from the project team that they will critically review the open medical literature on these debates (if they exist) and to what extent a consensus has been reached.

Objective 2: Explore potential associations between increasing incidences of these diseases/health parameters and changes in human reproduction

There is also considerable debate about the causes of the rising trends of these 14 diseases and health parameters. The seminal 2012 WHO/UNEP report¹ on endocrine disruption postulated that the increases in 14 diseases and health parameters are caused by exposure to chemicals with endocrine disruptors.

These 14 diseases and health parameters are:

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| 1. Semen quality | 8. Breast cancer |
| 2. Hypospadias | 9. Testicular cancer |
| 3. Cryptorchidism | 10. Prostate cancer |
| 4. Preterm birth | 11. Early breast development |
| 5. Low birth weight | 12. Polycystic ovarian syndrome (PCOS) |
| 6. Neurobehavioral disorders like autism and ADHD | 13. Obesity |
| 7. Endometrial cancer | 14. Diabetes |

Although the report mentions some other potential causal factors, it does not expand on these.

Over the past seventy years there have been profound changes in human reproduction. In Western societies, couples have postponed pregnancy and are having fewer children than before. The average female fertility rate in Europe has dropped from 4 in 1950 to around 1.8 in 2010, indicating that families have become much smaller. This has resulted in shifts in the percentage of children being first-born and an increasing parental age at first pregnancy. In the Netherlands for example, the percentage of first-born children has increased from 27% in 1950 to 45% in 2015 and the percentage of children that are first-borns with a mother older than 35 from 1.7% to 6.9%. (Statistics Netherlands). First-born boys have a threefold higher risk of testicular cancer as compared to fourth-born boys.² In 1950, 31% of boys were fourth born or more as compared to 5% in 2015, in the

Netherlands. Similarly, the prevalence of hypospadias has been reported to be over 8 times higher in first-born boys with a mother aged 35 or older as compared to multiparous boys with a mother aged less than 30.³ By simply combining these risks related to birth order and maternal age, using readily available demographic data an increase in testicular cancer of 26% and an increase of 34% in hypospadias prevalence can be explained.⁴

Furthermore, since family size today is rather a result of family planning, including IVF and not so much of fertility or subfertility, the percentage of children born to sub-fertile couples has doubled from 5% to approximately 10%.⁴ Children born to sub-fertile couples are at an increased risk of being preterm or having a low birth weight, with all the consequences later in life, including cryptorchidism⁵ and metabolic diseases.⁶

It is expected from the project team to explore potential associations between rising incidences of the 14 mentioned diseases/health parameters and such changes in human reproduction.

For several of the 14 mentioned diseases and health parameters, other factors that have changed over time will also have played a significant role: increased food intake, a more sedentary lifestyle and obesity and diabetes, factors that also are relevant to fertility and human reproduction. The latter factors should be included in the project, but the emphasis is expected to be on the impact of changes in human reproduction.

The methodology foreseen for this project is that of systematic review and meta-analysis of scientific literature databases such as Medline to:

1. Assess whether the increases in the 14 diseases and health parameters over time are verified or artefactual
2. If these increases are verified, whether they can be associated to changes in human reproduction, by combining the risk described in the literature with readily available demographic data

The project proposal must include a description of the methodology that will be applied and should be based on the PRISMA guideline for Systematic Reviews (<http://www.prisma-statement.org>). In addition, the project proposal, once accepted by Cefic LRI, must be pre-registered for example at the US government clinical trials register (<https://clinicaltrials.gov/>) or at the PROSPERO systematic reviews depository, prior to the start of the literature searches. If preregistration triggers any relevant comments, these must be shared with the Cefic LRI monitoring team and, if deemed an improvement, should be taken up.

Deliverables

The final report shall contain an executive summary (2 pages max), a main part (max. 50 pages) and a detailed bibliography. It is expected that the findings will be developed into at least one open-access peer reviewed publication, following poster(s) and presentation(s) at suitable scientific conference(s) and including holding a workshop.

Cost and Timing

Start in 2020, duration two years in the form of a post-doc project

Budget in the order of € 250.000

Partnering/Co-funding

Applicants should provide an indication of additional partners and funding opportunities that can be appropriately leveraged as part of their proposal. Partners can include, but are not limited to industry, government/regulatory organizations, research institutes, etc. Statements from potential partners should be included in the proposal package. Given the scope of the project it is recommended to include gynaecological or endocrinological expertise alongside experience in the conduct of systematic literature reviews.

Fit with LRI objectives/Possible regulatory and policy impact involvements/Dissemination

Applicants should provide information on the fit of their proposal with LRI objectives and an indication on how and where they could play a role in the regulatory and policy areas. Dissemination plans should also be included.

References

- ¹Bergman A. State of the Science of Endocrine Disrupting Chemicals. New York: WHO/UNEP; 2012.
- ²Prenner A, Hsieh CC, Engholm G, Trichopoulos D, Jensen OM. Birth order and risk of testicular cancer. *Cancer Causes Control* 1992;3:265-72.
- ³Carmichael SL, Shaw GM, Laurent C, Olney RS, Lammer EJ, National Birth Defects Prevention S. Maternal reproductive and demographic characteristics as risk factors for hypospadias. *Paediatr Perinat Epidemiol* 2007;21:210-8.
- ⁴Swaen GMH, Boffetta P, Zeegers M. Impact of changes in human reproduction on the incidence of endocrine-related diseases. *Crit Rev Toxicol* 2018;48:789-95.
- ⁵Virtanen HE, Toppari J. Epidemiology and pathogenesis of cryptorchidism. *Hum Reprod Update* 2008;14:49-58.
- ⁶Huang YT, Lin HY, Wang CH, Su BH, Lin CC. Association of preterm birth and small for gestational age with metabolic outcomes in children and adolescents: A population-based cohort study from Taiwan. *Pediatr Neonatol* 2018;59:147-53.

DEADLINE FOR SUBMISSIONS: September 1st, 2019

Please see www.cefic-lri.org/funding-opportunities/apply-for-a-grant/ for general LRI objectives information, project proposal form and further guidance for grant applications.