

Project Final Summary

NOT CONFIDENTIAL		
Title of the project Increasing incidence of human male reproductive health disorders in relation to environmental effects on growth- and sex steroid-induced alterations in programmed development		
Acronym of the project Envir. Reprod. Health		
Type of contract	shared-cost RTD action	Total project cost (€ 5.689.074
Contract number	Duration	EU contribution
QLK4-CT-1999-01422	66 Months	€ 2.685.895
Commencement date 1. February 2000		Period covered by the final report 1 February 2000 - 31 July 2005
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Key words reproductive health, developmental genes, environment, endocrine disruptors		
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Summary

The general objective of the project was to establish the status of infant and adult reproductive health in Europe, to identify potential environmental causes and to evaluate non-invasive methods for detection of environmental exposure. The proposal had both short- and longer-term goals, both of which address the following two questions. First, via which pathway(s) could changes in lifestyle/environmental exposures over the past half-century have induced changes in the male foetus/neonate, which result in increased likelihood of reproductive disorders? Second, if disruption of the androgen:oestrogen balance within the foetus is the underlying cause for these disorders (no other satisfactory mechanism has yet been proposed), how does this occur and how can this be detected, given the inaccessibility of the human foetus and the absence of data regarding the relative levels of androgens and oestrogens within its developing reproductive system? In seeking answers to these questions, we extended the clinical studies and statistical evaluation established via earlier EU-funding. Moreover, we utilise differences in incidence of reproductive disorders between participating EU countries and experimental animal models to investigate the mechanisms behind these disorders.

The project has resulted in a large number of scientific publications (see reference list below) and more than 15 Ph.Ds. Birth cohort and case-control studies on congenital malformations of the male reproductive organs have been carried out in Denmark, Finland, France, UK, and Spain. A total of 1458 Finnish, 1064 Danish, 1442 French, and 702 Spanish newborn boys have been examined. The British birth cohort study is still ongoing, and by the beginning of year 2005 >1000 pregnant mothers were recruited and approximately 350 boys examined at birth. The Danish, Finnish and Spanish studies are completed and the data have entered in a central database containing extensive information on medical, anthropometrical, biochemical, and lifestyle data. The French and British data are entered into separate local databases. The evaluation of the data is still ongoing. Accurate data on the incidence of cryptorchidism and hypospadias in Denmark and Finland have been published showing that the prevalence of malformations is significantly higher in Denmark than in Finland. Hormone levels at three months of age are also different between Denmark and Finland, because inhibin B concentrations of Finnish boys are higher. A manuscript on these findings has been drafted. Cryptorchid boys show signs of mild primary gonadal failure, as their gonadotropin values are higher than those of healthy boys. Data on prevalence rates are also available from the Spanish and French studies and seem to be intermediate of the Danish and Finnish prevalences. Chemical analyses of placenta and breast milk collected from cases and controls have been initiated. Genetic studies have been carried out in a number of cases with cryptorchidism or hypospadias for polymorphic polynucleotide (CAG)_n repeat length of the exon 1 in the androgen receptor (AR) gene and LH variant gene. All cases studied so far have had normal CAG repeat length in their androgen receptor gene. A manuscript of the prevalence of the LH variant gene in boys with cryptorchidism has been published.

The European studies on reproductive health of partners to pregnant women have verified a geographical variation in semen quality within Europe. The data collected on semen quality, medical history, lifestyle factors etc. in the partners to pregnant women studies are currently being evaluated in order to identify determinants of fertility and semen quality. An increase in sperm abnormalities was related to medical treatment of the study subjects mother's during her pregnancy, higher birth-weight and previous treatment for cryptorchidism. Several sperm defects were related to stress, weekly working hour, occupational posture and metal welding, suggesting directions for further exposure studies.

Studies on reproductive health of young men from the general population have been completed in Denmark, Finland, Scotland, Spain, Estonia, Latvia and Lithuania. In total information on the reproductive health of more than 6800 young men from these countries have been compiled in a central database. In Denmark and Finland longitudinal data from a subgroup of young men from

the general population are also available. (In Denmark the study is extended with new cohorts each year funded by local grants.) The first papers on semen quality in young men from different regions of Europe have been published described the observation of large geographical differences. Further evaluation of data is currently carried out in order to identify determinants of male reproductive health. A paper on the effect of maternal smoking has been published showing that male reproductive health is adversely affected by maternal smoking during pregnancy.

Genetic studies on men with symptoms of TDS (infertility or testicular cancer) have been carried out for polymorphic polynucleotide (CAG)_n repeat length of the exon 1 in the androgen receptor (AR) gene and micro Y deletions in order to identify genetic causes of TDS. No differences in the distribution of (CAG)_n between patients with testicular cancer and normal controls was found. In contrast, Y chromosome microdeletions in the AZF region have been confirmed as a frequent genetic factor responsible for male infertility.

Clinical studies on men with symptoms of TDS have confirmed that more than one symptom of TDS is frequently present in infertile men or testicular cancer patients. Thus, a higher frequency of histological signs of TDS (undifferentiated tubules, microliths and carcinoma in situ, CIS) has been found in contra-lateral biopsies of patients with unilateral testicular tumours.

A series of *in utero* and neonatal exposures to endocrine disrupting chemicals have been performed in rat. These studies have shown that doses of diethylstilboestrol (DES), which induced major reproductive tract abnormalities did so not because of its intrinsic oestrogen activity alone, but because they resulted in a major distortion of the normal androgen-oestrogen balance. Contrary to expectations, these studies have also established that the neonatal male rat is remarkably insensitive to disturbance by oestrogen treatment. Instead focus has changed to possible effects on endogenous hormone production. Thus, effects on the StAR (steroidogenic acute regulatory) protein level following exposure to endocrine disrupters have been investigated. It has also been shown that alkylphenols may alter androgenic status in developing foetuses.

A panel of sensitive bioassays for androgenic, estrogenic, anti-androgenic and anti-thyroid activity has been developed and evaluated. Data on total androgenic and estrogenic bioactivity in children have been published. A range of chemicals of potential relevance as endocrine disruptors has been tested in the *in vitro* assay established to assess anti-androgenic effects. A notable and novel finding was the observation that zearalanol, used extensively in the USA as a growth promoter in cattle, in addition to its known estrogenic effect also is a potent anti-androgen.

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