DEER
Developmental effects of environment on reproduction

It is becoming increasingly clear that the commonest disorders of male reproductive health in newborn (cryptorchidism, hypospadias) and young adult (low sperm counts, testis germ cell cancer) human males may be caused by adverse events in fetal life. These reproductive disorders are thought to comprise a testicular dysgenesis syndrome (TDS), which arises because of a cascade of changes triggered by maldevelopment and malfunction of the fetal testis. The incidence of TDS disorders appears to be increasing in Europe.

Several pieces of evidence suggest that common environmental chemicals, probably acting together in mixtures or in combination with other factors (genetic, lifestyle) could contribute causally to TDS. However, there are numerous obstacles to proving this scientifically, such as the long latency (up to 40 years) between cause (in fetal life) and health consequence.

How will DEER address these problems?

DEER will take advantage of existing human birth cohorts with their associated chemical exposure analyses. Established animal and in vitro models will be used to improve our understanding of fetal testis development and function and its relationship to male reproductive development. More specifically:

- Longitudinal follow-up of established birth cohorts as they approach and enter puberty will allow us to relate early occurrence of TDS disorders.
- Effects of earlier maternal chemical exposures (in pregnancy) as well as current lifestyle and exposures will be scrutinised in cohorts of young men and related to their reproductive health.
- Associations between exposures, lifestyle, and health outcomes observed in the human studies will be explored mechanistically in animal and in vitro models.
- Metabolomics and associated chemical mixtures analysis will provide new insights into real-life human exposures and interaction with the endocrine systems.
- Systems biology and bioinformatic analytical approaches will be used for assessing exposure-outcome associations based on a real-life exposure scenario.

NECTAR – www.nectarcluster.eu

Coordination: Professor Andreas Kortenkamp, The School of Pharmacy, University of London, London (UK), andreas.kortenkamp@pharmacy.ac.uk
Dr Erika Rosivatz, The School of Pharmacy, University of London, London (UK), erika.rosivatz@pharmacy.ac.uk

CONTAMED – www.contamed.eu

Coordination: Professor Andreas Kortenkamp, The School of Pharmacy, University of London, London (UK), andreas.kortenkamp@pharmacy.ac.uk
Partners: Dr Ulla Hass, National Food Institute, Technical University of Denmark, Copenhagen (Denmark). Dr Elizabeth Hill, University of Sussex, School of Life Sciences, Famer, Brightton (UK). Prof Nicolas Olea, University of Granada, Centre for Biomedical Research, Granada (Spain). Dr Alex Burdorf, University Medical Centre Rotterdam, Rotterdam (The Netherlands).
Prof Walter Lichtensteiger and Dr Margret Schlumpf, GREENTox, Zurich (Switzerland). Prof Michael Faust, F+R Environmental Consulting, Bremen (Germany). Dr Susan Ring, University of Bristol, Dept of Social Medicine, Bristol (UK).

REEF – www.abdn.ac.uk/reef/

Coordination: Professor Paul Fowler, University of Aberdeen, Aberdeen (UK), p.a.fowler@abdn.ac.uk
Partners: Dr Stewart Rhind, Macaulay Institute, Aberdeen, (UK). Prof Bernd Fischer, Martin Luther University, Halle-Wittenberg, (Germany). Drs Richard Lea and Kevin Sinclair, University of Nottingham, Sutton Bonnington (UK). Dr Caterine Cotinet, INRA, Jouy-en-Josas (France). Dr Paola Pasur, University of Milan, Milan (Italy).

DEER – www.eu-deer.net

Coordination: Professor Jorma Toppari, University of Turku, Turku (Finland), jortop@utu.fi
Partners: Dr Anders Juel, Copenhagen University Hospital, Copenhagen (Denmark). Prof Richard Sharpe, Queen’s Medical Research Institute, Edinburgh (UK). Prof Manuel Tena-Sempere, University of Cordoba, Cordoba (Spain). Prof Bernard Jégou, University of Rennes 1, Rennes (France).
Dr Nina Atanassova, Bulgarian Academy of Sciences, Sofia (Bulgaria). Prof Søren Brunak, Technical University of Denmark, Copenhagen (Denmark). Prof Bruno Le Bizec, l’École Nationale Vétérinaire de Nantes, Nantes (France). Prof Shanna Swan, University of Rochester, Rochester (USA).

European Commission, Directorate General Research

Contact: Dr Tuomo Karjalainen, European Commission, Research Directorate-General, Directorate I (Environment) Unit I.S. (Climate Change and Environmental Risks), B-1049 Brussels (Belgium). tuomo.karjalainen@ec.europa.eu
NECTAR is a cluster of EU-funded projects set up to investigate the potential impact of chemicals and pollutants on male and female reproductive health. NECTAR was launched on May 1st 2008 and joins together the REEF, DEER and CONTAMED projects.

The three projects examine what are known as endocrine disruptors – chemicals that interfere with normal hormone function. These include both natural and man made substances – such as compounds used in plastics and pesticides, together with heavy metals – to which European citizens are exposed every day and which can mimic or interfere with our hormones. NECTAR will promote interaction and cooperation between REEF, DEER and CONTAMED.

CONTAMED

Contaminant mixtures and human reproductive health – novel strategies for health impact and risk assessment of endocrine disrupters

Of considerable concern in Europe is a decline in male semen quality and an associated decrease in fertility. There have also been reports of increased incidence of physical defects of male reproductive organs in newborns.

Environmental chemicals may contribute to disruption of signalling pathways in the fetus and thereby be involved in the causation of these disorders. At present, individual substances cannot be shown to contribute to adverse effects at relevant exposure levels, however, people are typically exposed to multiple chemicals simultaneously and there are indications that combinations of chemicals may play a cumulative role. However, more information is needed to substantiate these findings.

How will CONTAMED address these problems?
The CONTAMED partnership believes that the issue of environmental factors and their possible role in the deterioration of human reproductive health in Europe cannot be resolved without considering combined exposures. CONTAMED will analyse human tissue specimens from existing mother-child cohorts, conduct experimental studies in animals and laboratory assays, and will use cutting-edge chemical analytical techniques. The project’s aims are:

• To investigate the effects of simultaneous exposure to endocrine disrupting chemicals (EDCs) in fetal life on male reproductive health.

• To develop biomarkers for assessment of total internal load of EDCs in mother-child cohorts from Europe.

• To study the possible role of EDC mixtures in producing prolonged and delayed adverse reproductive effects.

• To screen for previously unrecognised EDCs in human tissues.

• To provide the knowledge necessary to set the scene for environmentally relevant human health exposure studies.

• To contribute to improvements in regulatory chemical safety assessment in Europe.

REEF

Reproductive effects of environmental chemicals in females

There is a large body of evidence that when a developing foetus is exposed to environmental chemicals (ECs), its future reproductive potential may well be reduced. These ECs include endocrine disrupting compounds (EDCs), and their adverse effects are seen in wildlife, domestic species and humans. Currently scientists think that such exposure to ECs is part of the mechanism increasing the rates of reproductive defects and infertility in males and females.

Studies on plasticisers, phthalates, and many other chemicals show that the female reproductive tract is sensitive to damaging effects of these ECs. The sheep, exposed to sewage sludge treated pastures, provides a model of real-life exposure to a broad range of environmental ECs. Sheep are long-lived and have many reproductive similarities with humans. Therefore REEF will utilise this model in order to clarify links between exposure of the female during fetal development, her reproductive capacity as an adult and the extent to which damage is passed on to her own young.

How will REEF address these problems?
REEF will analyse tissues from sheep and mouse models of exposure to real-life complex mixtures of ECs and then directly relate the outcomes to the human fetal ovary. The project’s aims are:

• To examine the effects of sewage sludge exposure during specific periods of foetal ovarian development in the sheep.

• To investigate the effects of environmental concentrations of DEHP and PCBs on female reproductive development in the sheep and mouse.

• To determine the trans-generational effects of DEHP and PCB exposure on second generation sheep and mouse ovaries.

• To study the effects of DEHP and PCBs on cultured human and sheep foetal ovaries.

• To integrate human and animal models.