The COMPRENDO Project:

Comparative research on endocrine disrupters - phylogenetic approach and common principles focusing on androgenic/ antiandrogenic compounds

The special issue of endocrine active chemicals (EACs) and their potential to cause serious health problems in humans and wildlife species at extremely low doses makes it questionable whether drinking water and food are still without impact on normal development, sexual differentiation and also whether they allow normal reproduction and ageing of individuals without avoidable health effects. Identification of chemicals as EACs would make it necessary to take restrictive measures to avoid further harm to humans and wildlife.

Objectives

COMPRENDO, as an interdisciplinary, integrated approach addressed endocrine disruption in human and wildlife species by focusing on androgenic/ antiandrogenic compounds (AACs).

The overall goal of COMPRENDO was to improve the understanding of the effects of EACs on aquatic wildlife and humans. This was meant to help to improve environmental quality standards and also the public health in Europe.

To this end the key objectives were to:

- Characterise the human and environmental exposure to AACs;
- Determine the impacts of environmentally relevant doses/concentrations of AACs on a wide range of human-relevant models and aquatic test species;
- Develop new biological effect measures and species-specific critical endpoints, including a molecular screen for genomic effects of AACs;
- Identify common principles of AAC action in different species and to develop new animal models for extrapolation to human health;
- Develop laboratory cultures for suitable aquatic invertebrates and to establish their baseline endocrinology;
- Characterise the risk originating from AACs in humans and wildlife.

Key findings and conclusions

- The investigations on food contamination with pesticides, organochlorines and organotin compounds of the participating European countries revealed that in none of these cases an exceedance of ADI (Acceptable Daily Intake) values was observed taking into consideration national eating and consumer habits. However, the latter refer to single substance intake, whereas foods contain a complex mixture of chemical residues. Therefore these data do not allow to finally decide on which impacts even low AAC contaminations may have on the individual health of consumers. Furthermore, current safety regulations for consumer health protection do not consider endocrine effects;
- No significant correlation between sex steroid concentration and the chemical residues in blood of the donors was found. However, this does not necessarily mean that there is no correlation but that, for example, we did not focus on the relevant endpoints/parameters;
- Cytotoxicity assessments resulted in low dose effects with stimulation effects compared to the controls. Cytotoxic effects were only observed at very high concentrations for some of the androgenic compounds;
- Anabolic effects manifesting themselves as disproportionate cell growth of oestrogen receptor (ER)/androgen receptor (AR)-positive (MCF7, LNCap-FGC) human breast and prostate cancer cell lines when exposed to low doses of AACs were observed. If present *in vivo*, it cannot be excluded that this may also affect tissue homeostasis;
- Androgen mimicking substances, such as organotins and some pesticides, resulted in the induction of virilisation, a reduced reproductive performance, an accelerated sexual maturity, reduced larval development, reduced skeletal density, misaligned sex ratios, changes in sex steroid titres and enzyme activities and various effects on reproductive organs under histopathological investigation. Feminisation effects, reduced egg diameters and the lack of spermatids and spermatophores have been observed for anti-androgen exposure. The observed effect concentrations were in the range of environmentally relevant concentrations and partially resulted in new PNEC (Predicted No Effect concentration)-values for risk assessment.

Relevance and contribution to EU policy

The consortium was able to propose two new test species to the OECD, regarding the development of guidelines for chemical testing. COMPRENDO provided important contributions to the exploration of functionality of the steroidogenesis in the animal kingdom. The results will therefore facilitate the current efforts for new approaches toward the improvement of environmental and human risk assessment for EACs – on a national and an international scale. In summary, it can be stated that the observed effects of chemical exposure in vertebrates and invertebrates suppose the existence of highly conserved configured pathways in the endocrine system throughout the animal kingdom. Especially in view of the planned EU-wide ban of vertebrate animal testing in the cosmetics industry in 2009 and a general ban in 2013, invertebrate test species may present a reasonable alternative.

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