Endocrine Disruptors – The Veterinary Aspects

DESCRIPTION ENDocrine DISRUPTING CHEmicals (EDCs)

Chemicals are all around us and are part of our everyday lives. However, some chemicals can have harmful effects on the endocrine system of both humans and animals. EDCs (also referred as endocrine modulators, environmental hormones, and endocrine active compounds) are chemicals that produce adverse developmental, reproductive, neurological, metabolic, behavioural and immune effects by interfering with the natural hormone systems.

WHO/IPCS (2002) defines endocrine disrupting chemicals (EDCs) as ‘an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations.’

Identification of EDCs requires evidence that direct perturbation of the endocrine system leads to adverse effects in vivo. There are four concerns with endocrine disruption: (1) low dose matters; (2) wide range of health effects; (3) persistence of biological effects; and (4) ubiquitous exposure. EDCs in the environment have been associated with abnormal thyroid function in birds and fish, decreased fertility in birds, fish, shellfish and mammals, decreased hatching success in fish, birds and turtles, de-masculinisation and defeminisation of fish and birds and alterations in the immune function of birds and mammals (Colborn et al., 1993). Another major concern in humans is the disruption of
thyroid hormone signalling by ECDs, which may alter the process of neural differentiation, which is potentially linked to cognitive deficits. The neurological development of mammals is largely dependent on normal thyroid hormone homeostasis, and it is likely to be particularly sensitive to disruption of the thyroid axis (Jugan et al., 2010). The health effects can be felt long after exposure has stopped and these chemicals may pose a risk for the next generation.

EDCs alter hormonal function by:
(1) Mimic or partly mimic naturally occurring hormones in the body of the animal like oestrogens, androgens, and thyroid hormones, potentially producing overstimulation;
(2) Bind to a receptor within a cell and block the endogenous hormone from binding (such as anti-oestrogens and anti-androgens); and
(3) Interfere or block the way natural hormones or their receptors are made or controlled by altering their metabolism in the liver (NIH, 2010).

EDCs involve a wide variety of chemical classes. They are often commonly dispersed in the environment and therefore can be found in virtually all regions of the world.

Examples of these chemicals are: natural and synthetic hormones, plant constituents, pesticides, compounds used in the plastics industry (e.g., bisphenol A), in medical equipment and in consumer products (e.g. phthalates) and other industrial by-products and pollutants (WHO/IPCS, 2002).

The issue of dose-response relationships is the most controversial regarding EDCs; these substances often act by mimicking or antagonizing the actions of naturally occurring hormones and natural hormones (often more potent than exogenous EDCs) present at functional physiologically concentrations. Thus, the dose-response considerations for EDCs are often different than for other environmental chemicals, which are not acting directly on the endocrine system (WHO, 2010; Schug et al., 2016).

General Concern

There is a growing concern in the EU and worldwide about the negative impacts possibly caused by EDCs on the environment, on human health and on (wildlife) animal health (Rahman Kabir et al., 2015; Giulivo et al., 2016). Although there is limited evidence to prove that low-dose exposures are causing adverse health effects in humans, there is a large body of research in experimental animals and wildlife suggesting that endocrine disruptors may cause:
(1) Reductions in male fertility and declines in the numbers of males born;
(2) Abnormalities in male reproductive organs;
(3) Female reproductive health issues, including fertility problems, early puberty, and early reproductive senescence;
(4) Increases in mammary, ovarian, and prostate cancers; and
(5) Increases in immune and autoimmune diseases, and some neurodegenerative diseases (NIH, 2010).

A high incidence and an increasing trend have been noticed in many endocrine-related disorders in humans (Giulivo et al., 2015). Genetic factors as the sole plausible explanation can be ruled out by the speed of increase in disease incidence. Several factors can be of influence, which make them difficult to identify. Nevertheless in some studies associations have become apparent. For example, undescended testicles in young boys have been linked with exposure to diethylstilbestrol (DES) and polybrominated diphenyl ethers (PBDEs). High exposure to polychlorinated biphenyls (PBCs) has been associated with
breast cancer, prostate cancer and developmental neurotoxicity with negative impacts on brain development. The most sensitive period of exposure to EDCs is during the critical period of development (Bergman et al., 2013).

There are still many uncertainties and data gaps about the knowledge of EDCs (Schug et al., 2016). There is a great lack of studies, which clearly address exposure-outcome relationships of EDCs on wildlife and human health. Especially the EDCs with long-term effects are more difficult to detect. Another major issue in evaluating the impact of EDCs on human, animals and the environment is whether the literature represents nature. Twelve persistent organic pollutants (POPs) are singled out for elimination and/or reduction in a legally binding treaty and several processes are ongoing to add additional chemicals to the list (WHO/IPCS, 2002). On May 22, 2001, the USA and 119 other nations signed an international treaty in Stockholm (known also as "Stockholm Convention") to phase out use and production of 12 POPs worldwide (aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, HCB, mirex, toxaphene, PCBs, PCDDs and PCDFs). They also established a procedure to add other chemicals to the list of banned pollutants.

Veterinary Concern

Wildlife health depends on the ability to reproduce and develop normally. This is not possible without a healthy endocrine system. Humans, domestic animals and wildlife animals are simultaneously exposed to many EDCs. Endocrine systems are very similar across vertebrate species and the endocrine system-related effects are not necessarily species dependent. The animal susceptibility is also dependent on the stage of development of target tissues (i.e. foetal and post-natal exposures more exaggerated that adulthood) (Bernhoft, 2006). In animals, adverse consequences, - such as subfertility, premature reproductive senescence, and cancer-, are linked to early exposure, although they may not be apparent until much later in life (Newbold et al., 2006).

The disease risk may be significantly underestimated according to “State of the Science of Endocrine Disrupting Chemicals-2012” prepared by a collaboration between WHO and UNEP (Bergman et al., 2013). From animal studies, researchers have learned much about the mechanisms through which EDCs influence the endocrine system and alter hormonal functions (Kiyama et al., 2015).

Animal Exposure

Domestic animals are mainly dietary exposed to EDCs. Wildlife are mostly exposed through polluted rain water, well water, lakes, oceans, freshwater, marine and terrestrial food (Colborn et al., 1993; Bernhoft, 2006).

Sort of EDC’s:

EDCs can be either synthetic (xenoestrogens) or naturally occurring compounds and act via various modes of actions (Kiyama and Wada-Kiyama, 2015). They can modulate nuclear steroid hormone receptors, and/or enzymes that are involved in steroid hormone synthesis.

- **Synthetic endocrine disrupting compounds** (xenoestrogens)
  Important synthetic endocrine disrupting contaminants are the POPs. Fish-eating animals such as wild minks, otters, some seal and whale species, polar bears and sea birds, are mostly exposed to POPs. Recently sprayed grass may contain endocrine disrupting pesticides and could harm domesticated grass-eating animals (Bernhoft, 2006).
Carnivorous pet animals may be exposed to various amounts of POPs and other synthetic endocrine disruptors depending on the type of feeding stuff and the owners’ lifestyle.

- **Natural endocrine disrupting compounds (phytoestrogens)**
  Substances exhibiting estrogenic activity (i.e., phytoestrogens) are widely distributed in the plant kingdom. Grass-eating animals are exposed to phytoestrogens particularly sheep and cattle may be affected. The estrogenic principles of plants have been, in most cases, chemically identified as isoflavones, which occur naturally in the form of glucosides. All grass-eating animals (cattle, sheep and horses) are exposed to plant and fungus derived oestrogens (*Fusarium* spp molds), respectively phytoestrogens, such as genistein, and mycoestrogens, such as zearalenone, produced by *Fusarium graminearum*. Isoflavones have been isolated from soybean (i.e. genistein and daidzin). Biochanin A, another isoflavone derivative has been isolated from Bengal gram (*Cicer arietinum*) and red clover (*Trifolium pratense* L.). Coumestrol, a coumarin derivative, was isolated from alfalfa (*Medicago sativa*). Estrogenism due to zearalenone was clinically recognised as vulvovaginitis in pre-pubertal gilts fed with moldy corn (maize), and zearalenone is occasionally reported as a disease-causing agent in sporadic outbreaks in dairy cattle, sheep, chickens, and turkeys.

Pigs may be affected by intake of amounts of soybeans and are sensitive to the mycoestrogen zearalenone. Disturbed thyroid function may occur in pigs and ruminants fed with goitrogenic glucosinolates present in plants of *Brassica* family. Those are common fodder plants and vegetables such as rape, cabbage and broccoli. Wild ruminants are also exposed, but the variation in diet composition and a possibly degree of adaptation could be the explanation for the lack of effects in these animals (Bernhoft, 2006).

**European and International Initiatives**

To improve the environment and health of people within the European Union, the Commission adopted the ‘Community strategy for endocrine disruptors’ (EC, 1999). This community strategy focusses on short, medium and long-term actions. The short-term actions involve the setting up of information to use as a background for the medium and long-term actions.

The short term actions are:
(1) to set up a “priority list” of substances for further evaluation of their role in endocrine disruptions;
(2) Monitoring levels of suspect chemicals in food and the environment;
(3) Identification of vulnerable groups of people who need to be given special consideration (e.g. children);
(4) Establishment of an international network to enable information exchange and coordination of research and testing; and
(5) Communication with the public and continuing consultation with stakeholders.

The medium-term actions focus on the practical and experimental activities allowing for suspected chemicals to be tested in a speedy and accurate way. To ensure this, the Commission works closely with the World Health Organisation (WHO) through the International Programme for Chemical Safety (IPCS) in addition to overseas governments, departments and agencies to fund programmes for Research and Development.

The long-term actions relate to updating, amending or adapting the legislative instruments that protect the health of humans and wildlife in the EU. This includes the Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals
(REACH) (EC, 2006). EDCs not addressed in this specific legislation will be dealt with under environmental legislative instruments.

The Commission finalised the study ‘Information Exchange and International Coordination on Endocrine Disruptors’ with the aim to access the global initiatives on Endocrine Disruptors, concerning regulatory, testing and research activities and make recommendations on ways to improve coordination and the sharing of the workload (EC (1999)).

**EDC’s and hormones used in the veterinary profession**

EDC is a general term for all substances that are able to interfere with the endocrine system. Hormones used in meat industry are of major concern due to their ability to interfere with the human endocrine system.


Therapeutic hormones used in the veterinary medicine have also the ability to interfere with the endocrine system and thus have potential endocrine disrupting activity (EC, 1999). The largest share is needed in the farm industry. These are hormones, such as oxytocin, progesterone, prostaglandin and gonadotropin releasing hormone (GRH).

Several hormones used in small animals include synthetic progestins, such as medroxyprogesterone and megestrol acetates, GRH, human chrorionic gonadotropin (hCG), cloprostenol (a synthetic F-class prostaglandin), proligestone (a synthetic steroidal progesterone) and aglepristone (an antiprogestosterone). Directive 2008/97/EC amending the Directive 96/22/EC does not relate to companion animals.

As indicated previously, a priority list is made by the EU, to map suspected chemicals for further evaluation. **The priority list of EDCs by the EU mainly involves environmental polluting chemicals, and does not include therapeutic hormones.**

**Conclusions and recommendations.**

The EU has introduced specific legislative obligations aimed at phasing out endocrine disrupting chemicals in water, industrial chemicals, plant protection products and biocides.

Given the complexity of the endocrine system, chemicals can cause effects by a wide variety of both direct and indirect mechanisms. Domestic and non-domestic animals can be exposed to very low levels of EDCs present in the environment, making it difficult to assess the exposure effects on the animal to multiple endocrine disruptors simultaneously.

The effects of EDCs is related to dose and to duration of exposure. EDCs can have effects at low doses that are not predicted by effects at higher doses. The affinity of an endocrine active substance toward a specific receptor and its internal concentration are in orders of magnitude lower compared with physiological concentrations of respective hormones.

Carnivorous pet animals may be exposed to various amounts of POPs and other synthetic endocrine disruptors depending on the type of feeding stuff and the owners’ lifestyle.
Domestic grass-eating animals are exposed to plant protection products, phytoestrogenic and mycoestrogenic compounds, that are potentially potent estrogenic compounds.

Veterinary medicine is a complex matter because of multiplicity of animal species as well as breed, age, sex and (patho)physiological status concerned. In veterinary medicine prevention measures and intervention strategies have to be developed to reduce any adverse effects produced by EDCs at long term.

As veterinarians, we should be well informed and aware of the effects of exposure of animals to all suspected EDCs.

References


