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# FVE Use of hormones in Veterinary Medicine

# REFLECTION PAPER


## *ABSTRACT*

Hormones are used by veterinary practitioners all around the world and on various clinical indications. In the EU, the exogenous hormone therapy can be divided in hormones for therapeutic use or for other uses, such as to regulate or control reproduction (e.g. cats and dogs to supress oestrus and cattle to improve reproduction). The use of hormones as growth enhancers in livestock (i.e. increased body weight, and rates and efficiency of live weight gain) is forbidden in Europe due to health concerns. The exogenous hormone therapy for large and small animals is considered safe for public health. Moreover, there is a specific legislation banning the use of growth-promoting in Europe. Besides health issues, there is also an increasing societal demand on food and animal welfare. According to the EU legislation, animals have an intrinsic value which must be respected and they should be treated as sentient creates. Finally, is highlighted that there are feed additives that are not anabolic or classical growth promoter agents such as digestibility enhancers and gut flora stabilizers among others, that are alternatives in improving or ameliorate animal; this feed additives are not anabolic or classical growth promoters agents.


## *General information*

The peptide hormones of the anterior pituitary are critical for the regulation of growth, reproduction, and metabolism. Their secretion is not only controlled by stimulatory and inhibitory peptides of hypothalamic origin, but also is influenced by hormones of the peripheral endocrine glands, by disease, and buy many drugs. The interrelationship between the pituitary and its target tissues represent elegant examples of feedback regulation. These interactions have been exploited for many years in the diagnosis and treatment of clinical disorders in endocrinology.

For a fundamental organic physiological maintenance, the endocrine system uses chemicals to exert specific biochemical effects on target cells at distant sites. These chemicals are synthetized by specialized cells of the endocrine organs or glands and are secreted into the blood stream for endocrine signalling. Chemicals with these physiological signalling compounds are called hormones (Higgins et al., 2013). With the development of modern techniques for peptide synthesis and production of recombinant macromolecules, the peptide and protein hormones of the pituitary and hypothalamus have themselves emerged as therapeutic tools.

Hormones are widely used by veterinary practitioners all around the world and on various indications. The use of hormones can be divided in therapeutic use or other in which

hormones are used to interfere with the physiological functions of normal animals (i.e., regulate reproduction or the enhance production).

*Hormones for therapeutic use*

In companion animals, a small percentage is used as replacement therapy in animals with endocrine dysfunction. Examples are as follows: thyrotropin (thyroid-stimulating hormone) that increases iodine uptake by the thyroid gland, and increases the production and secretion of thyroid hormones; is used for temporary supportive therapy in hypothyroidism in dogs.

A more significant part is the use of corticosteroids for example dermatological preparations of systemic anti-inflammatory agents in these animals to treat many immune and nonimmune conditions (allergic and nonspecific eczemas). But the greatest share is represented by the application of corticotrophin commonly called ACTH (adrenocorticotropic hormone); ACTH stimulates the adrenal cortex to stimulate the production and release of glucocorticoids (primary cortisol in mammals and corticosterone in bird). In veterinary medicine, ACTH is used in dogs, cats, and beef or dairy cattle for stimulation of the adrenal cortex and as a therapeutic agent in primary bovine ketosis.

Hormonal therapy for neoplasia in veterinary medicine commonly involves the use of glucocorticoids. Prednisone and prednisolone are used to treat lymphoreticular neoplasms in combination with other chemotherapeutic agents. Dexamethasone, prednisone and prednisolone are particularly used in treatment of leukaemias and lymphomas of central nervous system. Other steroid hormones utilized in veterinary cancer therapy include estrogenic treatment of prostatic hyperplasia, perianal glandular neoplasms, and palliation of advanced prostatic carcinoma. Progestins are used to oppose growth stimulatory effects of hormone in endometrial, prostatic, breast, renal cell, and ovarian carcinomas. Synthetic progestins as megestrol can be used in dogs (male) in the benign prostatic hypertrophy.

*Hormones for other use*

Other indications to use the hormones are to regulate reproduction or the enhance animal production. The breeding of domestic animals is controlled by owners, but it also influenced by feeding and husbandry conditions in general. This may lead to reproductive dysfunction as a clinical problem encountered by the owner and not by the animal.

Other drug acting on the reproductive system are oxytocin (hypothalamic hormone used for induction or enhancement of uterine contractions at parturition, postpartum retained placenta and metritis, uterine involution after manual correction of prolapsed uterus in dogs, and to promote milk let-down, and to treat agalactia, as complemental treatment of mastitis and agalactia), progesterone, prostaglandin $F_{2\alpha}$ and other prostaglandin analogues. Prostaglandin $F_{2\alpha}$ is used primarily to treat luteal function, it is applied in the induction or synchronization of estrus in polyestrous species, treatment of pymetra en dogs, cats, and cattle (Higgins et al., 2013); and induction of abortion in luteal-dependent species (e.g., goats, dogs and cats). Gonadotropin releasing hormone (GnRH) (hypothalamic hormone used to treat ovarian cysts and other reproductive disorders in a variety of species; superovulation in cattle with follicle-stimulating hormone (FSH) and induction of ovulation in mares with human chorionic gonadotrophin (hCG)). Bromocryptine and carbegoline (dopaminergic agents that caused decreased serum prolactin concentrations) is also used for inducing synchronizing estrus in dogs and as abortifacient in dogs or cats.

***General use of Hormones in Veterinary Medicine in EU***

*Companion Animals*

The use of endocrine-interfering drugs in normal healthy cats and dogs to supress estrus, is very common in the EU. For example, a female cat and dog often put in a permanent hormonal anoestrus. The GnRH agonist deslorelin acetate (implant of slow release) is used to castrated male dogs. It stops the production of sex hormones (testosterone and estrogen). Deslorelin is also used to treat benign prostate hyperplasia in dogs.

*Food Producing Animals*

Progesterone hormone is widely used for estrus synchronisation in cattle to reduce the need for continuous observation of estrus signs and increase the efficiency in production in normal animals. Not only the increase of efficiency, but also the production itself can be assisted by the use of hormones. Additionaly these are also called growth-promoting agents, naturally occurring and synthetic anabolic steroids. These hormones are only used in animals for regulation of meat animal growth. To prevent misuse, the use of growth hormones has been forbidden within Directive 96/22/EC (EC, 1996)**.** This group of hormones involve steroids (oestradiol, testosterone, progesterone), synthetic steroids (trenbolone acetate, melengestrol acetate) and synthetic nonsteroidal estrogens (diethylstilbestrol, hexestrol, dienestrol, stanozolol, zeranol), thyreostatics (e.g., thiouracil), beta-agonists (e.g., clenbuterol), and others (EC, 2001). The Council Directive 96/22/EC (EC, 1996) prohibits the use of certain substances for specific purposes in food producing animals and was amended by Directive 2008/97/EC that stated Member states shall prohibit the placing on the market of the substances listed in Annex II (thyrostatic substances; stilbenes, stilbene derivatives, their salts and esters, and oestradiol 17β and its ester-like derivatives) for administering to any animals, the meat and products of which are intended for human consumption. However, prohibited substances like clenbuterol ($\beta_2$-agonist) could be used as exception to induce tocolysis in cows when calving as well as to treat respiratory problems, navicular disease and laminitis and to induce tocolysis in *equidae* (EC, 2008). The anabolic activity of a number of hormones has been recognized for many years; these hormones and their derivatives increase protein synthesis particularly in skeletal muscle and therefore produce increases in bodyweight and are administered as an ear implant, either as a compressed tablets or a silastic rubber implant.

An exception to this use is for therapeutic purpose. To enhance the restricted use of hormones, all hormones are legally categorised as 'Prescription Only Medicines' (POM) within Directive 2001/82/EC by the European Union (EC, 2001). Nowadays, hormones used by veterinary practitioners in the farm industry in the EU occur naturally in animals and are permitted for zootechnical and therapeutic treatment.

***General use of Hormones in Veterinary Medicine outside EU***

*Companion Animals*

Progestogens are used to supress estrus in bitch. In the United States there is a shift in the use of hormones when comparing to the European Union. Only megestrol acetate as a progestin is approved for estrus control in bitches. And it is not registered for cats. This is due to the dose-dependent undesirable effects of progestin's that may occur at therapeutic doses (Nelson, 2014). In cats, has been used for many dermatologic and behavioural-related conditions. In the dog, GnRH is used for stimulating testosterone production in diagnosis of cryptorchidism.

*Food Producing Animals*

Hormones in the meat industry are commonly used. The exogenous hormone therapy can be used in a range of treatment, to regulate or control reproduction. The control may take the form of suppression or induction and synchronization of reproductive activity, so the same hormone may be used for both purposes (e.g, progestegens to supress estrus in the mare, to induce any synchronize estrus for managed mating programs in mare and sow).

The zootechnical feed additives have been introduced to replace anabolic and classical growth promoting agents. The zootechnical feed additives is defined as any additive used to affect favourably the performance of animals in good health or used to affect favourably the environment, and includes the following functional groups: (1) digestibility enhancers (2) gut flora stabilizers: microorganisms or other chemically defined substances; (3) substances which favourably affect the environment; and (4) other zootechnical additives (EC, 2003).

While in Europe using hormones for growth-promotion is banned, this is not the case in all parts of the world yet. In Europe, this was done due to the potential danger to public health because the meat and other edible parts of animals treated with them may contain trace quantities (called "residues") of the substances or of their metabolites. The growth promoters hormones are administered as an ear implant (i.e., compressed tablets or a silicone rubber implant). Many studies conducted on risk assessment of natural steroid hormones have presented negligible impacts on human health when they are used under good veterinary practices.

***Human Health Concerns***

Emerging concerns in public health related to hormonal active substances regards especially the hormones mentioned by the Directive 96/23/EC: Oestradiol-17β, progesterone, testosterone, zeranol, trenbolone and melengestrol has been deeply described. Emerging issues concerning public health related to the activity of these growth-promoting hormones include neurobiological, developmental, reproductive and immunological effect, as well as immunotoxicity, genotoxicity and carcinogenicity. A risk of consumer has been identified for the six hormones by excess intake of hormone residues and their metabolites.

Oestradiol-17β is considered to be a complete carcinogen by a substantial body of recent evidence as it exerts both tumour-initiating and tumour-promoting effects (EC, 2015). But the data concerning the daily intake of this hormone by meat consumption are insufficient to form the basis of a sound quantitative risk assessment to human health[8]. Unfortunately, there is a lack of understanding of critical developmental periods in the human life as well as uncertainties in the estimates of endogenous hormone production rates and metabolic clearance capacity. Therefore, no threshold values can be stablished for any of the six substances (EC, 2015).There is evidence to the suggestions of receptor-mediated increased proliferation in epithelial cells as the mode of action of hormonal carcinogens in humans. Endogenous as well as exogenous susceptibility factors appear to play a role as modulators, but the magnitude by which humans vary in their susceptibility to hormone-related cancer remains yet to be determined (CVMP, 2004).

Many studies conducted on risk assessment of natural steroid hormones have presented negligible impacts on human health when they are used under good veterinary practices (Jeong et al, 2010). To guarantee the safety of food, the European Council published Directive 96/22/EC (EC, 1996) and 96/23/EC (EC, 1996a) which constitute the present legal framework for controlling residues in foods of animal origin. The last report on the

results from the monitoring of veterinary medicinal product residues was conducted in 2013. Of the total targeted samples, 1,299 samples (0.31 %) out of the 419,528 target samples were non-compliant. Out of that non-compliant samples were reported for stilbenes and derivatives in bovines and pigs (both 0.01 %). For antithyroid agent, there were 0.77 % non-compliant samples, all for thiouracil, most likely due to feeding diets rich in cruciferous plants. In the group of steroids, non-compliant samples (all for anabolic steroids) were found in bovines (0.04 %), pigs (0.18 %), sheep and goats (0.35 %) and horses (1.73 %). The relatively high percentage of non-compliant results in pigs was most likely the endogenous production. In the group of resorcyclic acid lactones (RALs), 0.14 % of the samples were non-compliant for zearalanone and derivatives (EFSA, 2016). For beta-agonists (these compounds are not hormones), there were 0.05 % non-compliant samples. Clenbuterol, with the exception of specific veterinary therapeutic indications is forbidden in the EU, but outside of the EU are used other beta-agonist, with a different pharmacological and safety profile such as ractopamine, and zilpaterol hydrochloride.

***Animal Health, Welfare and Integrity Concerns***

*Companion Animals*

As mentioned before, the US does not approve medroxyprogesterone acetate (MPA) (synthetic progestin) for estrus suppression in cats and dogs in contrast to the EU. Side effects as cystic endometrial hyperplasia, mammary hyperplasia and increased incidence of mammary tumours, have been associated with the use of progestins (Nelson, 2014). But the Committee for medicinal products for veterinary use (CVMP) of EMA investigated this issue and concluded that the long-term use of depot medroxyprogesterone acetate does not increase the overall risk on breast, cervical, ovarian or liver cancer (EMEA, 2009).

*Food Producing Animals*

Side effects concerning hormone treatment for growth stimulation generally concern the use of oestrogens in steers. Feminization and raised tail-heads were describes as early as 1958. Bulling has also occurred with increased frequency, although in most animals it is limited to the first few days after implantation (Velle, 1981).

Another hormone which was a matter of discussion was the Bovine somatotropin (bST) with anabolic and growth-promoting effects mediated through insulin-like growth factor-I (IGF-I). bST is forbidden in 2000 for use in the EU and is used to increase milk yield. bST administration causes substantially and very significant poorer welfare because of increased foot disorders, mastitis, reproductive disorders and other production related diseases which leads to unnecessary pain, suffering and distress (Higgins et al., 2013). Outside of the EU bST, four analogues of bST (somagrebove, sometribove, somavubove and somidobove) and somatotropins bovine recombinant, are used to increase milk production.

The current discussion regarding hormones used by veterinary practitioners in the farm industry, mainly regards the risk in public health. But there is also an increasing societal demand on food and animal welfare. The basic factors such as a sufficient amount of good quality spermatozoa at the appropriate time and way and at the correct place have been recognized for a long time and are still valid. But the way in which cattle is kept has changed considerably over time and fertility seems to decline every year. Final fertility status of cattle is a result of interactions of a range of factors. These involve environmental conditions such as season, herd size, age composition, to pure managerial factors like breeding policy, nutrition, estrus detection etcetera. Whether or not a farmer can cope with these factors is very important for the efficiency of breeding (Opsomer et al., 2006). To prevent the dependence on reproduction hormones, many alternatives are

still open for increasing productivity in meat and milk production. For example: breeding programmes, regulation of rumen fermentation and disease control (Nelson, 2014). To determine whether an animal has a negative welfare due to the use of reproductive hormones is clearly a characteristic of an individual and is concerned with the effects of all aspects of its environment (SCAHAW, 1999). But the use of these hormones should not be the solution for other welfare problems which negatively influence fertility. Beside health and welfare issues, according to the Directive 2010/63/EU on the protection of animals used for scientific purposes (EU, 2010), animals have an intrinsic value which must be respected and they should be treated as sentient creates. This results in the responsibility of people to ensure the welfare and health of animals (Singer, 1999). By using hormones as a solution for the decline in fertility, we ignore other factors which could involve this decline and thereby we could negatively influence animal health and welfare. And the structural use of reproduction hormones could be interpreted as instrumalism and results in a lack of respect to the intrinsic value of the animal. Another ethical issue regards the protection of the integrity of the animal. The structural use of hormones enables the animal to not independently maintain itself (Rutgers and Heeger, 1999).

**Conclusions and recommendations**

The presence of unauthorised substances and residues of veterinary drugs in food may pose a risk factor for public health. In the EU, a group of hormones such as natural and synthetic steroids, and nonsteroidal estrogens, thyreostatics, certain $\beta_2$-agonists, and somatothropin have been prohibited due to end-point of health public concerns.

It is well known that hormones serve different function at different ages, having important physiological roles and many sites of action and effects in the body tissues and organs, at very low doses have a high biological activity. The untoward effects appeared after administration of hormones are well known.

Hormones are used by veterinary practitioners, as therapeutic agents on different clinical indications, both in food producing animals and companion animals. Some steroid hormones are nowadays utilised in veterinary cancer therapy, being under regulatory registration tracking; the exceptional off-label/extra-label use of authorized medicines ("cascade system") must be the last-resort when therapeutically justified.

A critical factor in the hormone treatment of all food-producing animals is the mandatory withdrawal period, designed to ensure that no significant drug residue is present in the animal at slaughter time. The dose regimen (dose administered, interval and duration of treatment) should be respected.

The use of hormones must comply by responsible use guidelines or recommendations. Responsible use is an integral part of the professional code of conduct.

FVE strongly rejects all illegal use of hormones.

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