Introduction

Endocrine disruption has emerged as a prominent policy and scientific issue since the report on chemically induced alterations in sexual development presented in 1992 by Clement and Colborn (Colborn and Clement 1992). For instance, the search term ‘endocrine disrupt*’ in the database ‘Web of Science’ had 324 hits in 1999 and increased to 6856 hits in 2014. Initially, an endocrine disruptor was regarded as a chemical compound able to bind to nuclear hormone receptors, in particular oestrogen receptors, and thereby act as an agonist or antagonist of the endocrine system. However, following more research in the field, it became evident that exogenous compounds could affect the endocrine system at several points along endocrine pathways, for example steroid biosynthesis and metabolism (Sanderson 2006; Tabb and Blumberg 2006; Diamanti-Kandarakis et al. 2009). The current international definition of an endocrine disruptors is thus: ‘An endocrine disruptor is 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) population’ (Damstra et al. 2002). Yet, this definition is under reconsideration and might become more inclusive and be more based on endocrinological concepts than toxicological concepts, emphasizing the differences in effects effect at different life-stages (Zoeller et al. 2012).

Reports on the adverse effects on reproduction in different species have been presented in several reviews, for example effects on spermatogenesis (Veeramachaneni et al. 2008; Yeung et al. 2011) and cryptorchidism (Virtanen and Adamsson 2012), altered time of onset of puberty (Magnusson and Ljungvall 2013), and disturbed sexual behaviour (Frye et al. 2012). Notably, endocrine disruptors mostly cause adverse and irreversible effects during development in utero and post-natally. In contrast, effects in the adult are mostly reversible when the exposure to the disruptor ceases (McLachlan et al. 2012).

The scientific and public concern that many environmental pollutants could be endocrine disruptors in humans as well as in wildlife has contributed to a rapid expansion of scientific literature in the field and there are several recent reviews on the subject (Hotchkiss et al. 2008; Diamanti-Kandarakis et al. 2009; Hamlin and Guillette 2010; Sharpe 2010; Fowler et al. 2012; Bergman et al. 2013). Examples of chemicals of concern are polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethylenes (DDTs), polybrominated diphenylethers (PBDEs), perfluorooalkyl acids, bisphenol A (BPA) and phthalates (such as di(2-ethylhexyl) phthalate, DEHP). However, there are also non-anthropogenic phytooestrogens that may act as endocrine disruptors with clinical impact (Jefferson et al. 2012).

The objective of the current review was to give a brief overview of the literature on how livestock may contribute to the spreading of endocrine disruptors in the environment, on the extent that domestic animals, or cells from domestic animals, have been used to study metabolism and effects of endocrine disruptors and, finally, on the exposure of domestic animals to endocrine disruptors. With that background, we then focus on the known and potential clinical impact of anthropogenic and natural endocrine disruptors on domestic animal reproduction.

Research on endocrine disruptors and reproduction in domestic animals

Domestic animals relate to endocrine disruptors in many ways. One is the controversial use of synthetic steroid hormones as growth promoters in beef cattle in certain countries. It has been a shown that the soil and run-off from large feedlots contain large amounts of bioactive steroids that may affect wildlife and the environment around these cattle feeding operations (Bartelt-Hunt et al. 2012). However, even from live-
stock operations not using these kinds of growth promoters, there is leakage into the environment of endocrine active substances (endogenous) that may affect the wild fauna (Bartelt-Hunt et al. 2012; Cavallin et al. 2014). Also, pig manure may contain endocrine disrupting compounds in amounts that might be an environmental concern (Combaltbert et al. 2012). A cautious conclusion from this literature is that manure from livestock operations – both those using as well as those not using endocrine growth promoters – may spread endocrine disruptors into the environment. Yet, more research is needed in this area before firm conclusions can be made.

There is also an increasing amount of literature from experimental studies in which domestic animals have been used to investigate endocrine disruption – for recent reviews, see Magnusson and Dencker (2010), Magnusson (2012) and Evans et al. (2014). These studies have been performed in both sexes and in various species such as goat (Oskam et al. 2005), sheep (Krogeneaes et al. 2014; Corbel et al. 2015) and pig (Ljungvall et al. 2008; Gralén et al. 2012), looking at mechanisms of action as well as effects. It can be concluded from these studies that some effects are similar across species – including the well-studied laboratory species – whereas some are different. The latter might be due to differences in uptake of the endocrine disrupters from the intestines, differences in the metabolism of the endocrine disrupters, differences in the endocrine signalling and endocrine enzymes in the exposed species, etc. Extrapolation of these findings from such controlled experimental studies to a clinical situation must, however, be made with care. In the clinic or real life, the animal is often exposed to a mixture of compounds and the dose of the individual chemical is frequently lower than in the experimental situation.

The well-advanced reproductive biotechnology techniques for domestic animals have allowed the use of bovine and porcine in vitro maturation/fertilization models for studying endocrine disruptors, as recently reviewed by Santos et al. (2014) and previously by others (Brevini et al. 2005; Magnusson 2005). Cells or systems used are for instance oocytes (Grossman et al. 2012), co-culture of theca and granulosa cells (Gregoraszczuk et al. 2008a,b), Leydig cells (Castellanos et al. 2013), sperm (Mohamed et al. 2011; Lukac et al. 2013) and testicular interstitial cells (Pathirana et al. 2011). These studies provide important insights into the mechanism of action for several endocrine disruptors under strict controlled conditions on cells vital for reproductive success. These studies also indicate risks of effects from the examined compounds on the reproductive system in real life. However, often it is not possible to include the toxicokinetics and metabolic aspects of the compounds in these studies, which is why their clinical relevance is sometimes questioned.

Finally, there is a group of reports where concentrations of known endocrine disrupters seen in studies with laboratory rodents have been compared with those recorded in various tissues of domestic animals. In some cases, the health and performance of the animal itself has been the concern, as with dairy cows (Petro et al. 2010) and sheep (Rhind et al. 2011); sometimes the focus has been on food safety aspects such as in pork and beef (Glynn et al. 2009) or milk (Desiato et al. 2014); and occasionally, the animal has been used as a sentinel for chemical exposure such as in pet cats and dogs (Ali et al. 2013).

Endocrine disruption and reproduction in farm animals – clinical observations

Endocrine disruption is typically seen in species that are higher in the trophic ladder, as several of the anthropogenic compounds of concern are biomagnified in the food chain. In contrast, herbivorous domestic ruminants, being lower in the trophic ladder, are less likely to be exposed to high concentrations of anthropogenic endocrine disrupting substances. However, it has been suggested that animals grazing in areas near incineration plants might be exposed to high amounts of environmental pollutants with endocrine disrupting properties (Ingelido et al. 2009). In countries practicing the spreading of sewage sludge on pastures, concentrations of endocrine disrupting chemicals were analysed in cattle and sheep and regarded to be too low to impair reproductive performance (Petro et al. 2010; Rhind et al. 2010). Similarly, in a large survey in Sweden in the pig, which is often fed processed food and thereby at risk of eating chemical pollutants that have been biomagnified, the burden of organochlorine contaminants at slaughter was found to be close to the detection limit of the analytical methods used (Glynn et al. 2009).

One of the few reports in farm animals indicating endocrine disruption caused by environmental pollutants is regarding heifers that were drinking water in direct contact with a sewerage overflow. These animals showed increased age at first calving (Meijer et al. 1999). The reproduction of farmed animals that are higher up in the food chain, such as the American mink, could potentially be affected by diets high in fish from polluted waters. Indeed, organochlorines in polluted fish have been seen to cause decreased litter size and increased offspring mortality in mink (Aulerich and Ringer 1977; Bursian et al. 2013).

Although the evidence of endocrine disruption caused by environmental pollutants is weak, reports are more prominent when it comes to phytooestrogens. Perhaps the most classical is the so-called sweet clover disease, caused by formononetin and genistein that bind to the oestrogen receptors and modulate oestrogen enzymes resulting in prolapsed uterus and embryonic death in sheep (Cox 1978; Beck et al. 2005). Another well-known example is pigs suffering from various signs of hyperoestrogenism, such as vaginal prolapse, abortions and stillbirths, because of the phytooestrogen zearalenone (ZEA) produced by Fusarium fungi which contaminate cereals (reviewed by Fink-Gremmels and Malekinjad

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Endocrine disruptors and dogs and cats

In comparison with the large number of studies regarding endocrine disruptors and the reproductive health of humans and wildlife, published studies on cats and dogs are very few. Pet animals share the home environment of the owners and may, therefore, be exposed to similar levels of endocrine disruptors. Because of this, dogs have been proposed as sentinels for human exposure to pollutants (Bukowski and Wartenberg 1997; Van der Schalie et al. 1999; Backer et al. 2001; Schmidt 2009). Similarly, cats have been suggested as sentinels for exposure to house dust (Mensching et al. 2012). In addition, dogs and cats may suffer from similar diseases as humans. For instance, mammary adenocarcinoma is comparable in dogs and humans, and associations with elevated concentrations of certain PCB congeners have been found in both species (Sévère et al. 2015).

In addition to the environmental exposure (indoor and outdoor) that dogs and cats share with their human companions, pet food is a route of exposure. For example, PBDEs have been found in both pet food and serum of dogs and cats (Dye et al. 2007; Venier and Hites 2011). Pet food has been found to contain phytooestrogens at levels that may have biological effects (Court and Freeman 2002; Cerundolo et al. 2004). Dog and cat food has also been found to contain BPA (Kang and Kondo 2002) as well as mycotoxins (Leung et al. 2006). Experimental studies showed that zearalenone (ZEA) affects the reproductive organs of bitches (Gajecka 2013), but very few studies have examined adverse effects of BPA or other plasticizers (such as phthalates) in dogs. Dog toys have been found to contain both BPA and phthalates and, therefore, could represent another route of exposure (Wooten and Smith 2013; Nohrborg 2015).

Concluding remarks

Several solid experimental evidences, both in vivo and in vitro, demonstrate clinical effects and explain mechanisms of action of man-made endocrine disruptors on farm animal reproduction. In real life, under non-experimental conditions, there is, however, little, if any, evidence that man-made endocrine disruptors are a clinical concern for reproduction in domestic animals. In contrast, phytooestrogens are a well-known clinical issue that might become more prevalent following the climate change. Finally, it is also clear that cats and dogs are exposed to a variety of chemicals that may affect the reproductive system, which may call for words of caution.

Author Contributions

UM structured the study, reviewed the literature and wrote the manuscript. SP reviewed the literature and wrote the manuscript.

Conflict of Interest

None of the authors have any conflict of interest to declare.

References

Ali N, Malik RN, Mehdi T, Eqani SAMAS, Javeed A, Neels H, Covaci A, 2013: Organohalogenated contaminants (OHCs) in the serum and hair of pet cats and dogs: biosentinels of indoor pollution. Sci Total Environ 449, 29–36.

Aulerich RJ, Ringor RK, 1977: Current status of PCB toxicity to man, and effect on their reproduction. Arch Environ Contam Toxicol 6, 279–292.

Backer LC, Grindem CB, Corbett WT, Collins L, Hunter JL, 2001: Pet dogs as sentinels for environmental contamination. Sci Total Environ 274, 161–169.

Barrett-Hunt SL, Snow DD, Kranz WL, Mader TL, Shapiro CA, Donk S, Shelton DP, Tarkelson DD, Zhang TC, 2012: Effect of growth promotants on the occurrence of endogenous and synthetic steroid hormones on feedlot soils and in runoff from beef cattle feeding operations. Environ Sci Technol 46, 1352–1360.

Beck V, Rohr U, Jungbauer A, 2005: Phytooestrogens derived from red clover: an alternative to estrogen replacement therapy? J Steroid Biochem Mol Biol 94, 499–518.

Bergman A, Heindel JJ, Jobling S, Kidd KA, Zoeller RT, Jobling SK, 2013: State of the Science of Endocrine Disrupting Chemicals 2012: An Assessment of the State of the Science of Endocrine Disrupter Preparations Based by a Group of Experts for the United Nations Environment Programme and World Health Organization. World Health Organization, Geneva.

Brevini TA, Cillo F, Antonini S, Gandolfi F, 2005: Effects of endocrine disrupters on the oocytes and embryos of farm animals. Reprod Domest Anim 40, 291–299.

Bukowski JA, Wartenberg D, 1997: An alternative approach for investigating the carcinogenicity of indoor air pollution: pets as sentinels of environmental cancer risk. Environ Health Perspect 105, 1312–1319.

Bursian SJ, Kern J, Remington RE, Link JE, Fitzgerald SD, 2013: Dietary exposure of mink (Mustela vison) to fish from the upper Hudson River, New York, USA: effects on reproduction and offspring growth and mortality. Environ Toxicol Chem 32, 780–793.

Castellanos CG, Sorvik IB, Tannum MB, Verhaegen S, Brandt I, Ropstad E, 2013: Differential effects of the persistent DDT metabolite methyldichloro-DDE in non-stimulated and LH-stimulated neonatal porcine Leydig cells. Toxicol Appl Pharmacol 267, 247–255.

Cavallin JE, Durham EJ, Evans N, Jensen KM, Kahl MD, Kolpin DW, Kołodziej EP, Foreman WT, LaLone CA, Makynen EA, 2014: Integrated assessment of runoff.
from livestock farming operations: analytical chemistry, in vitro bioassays, and in vivo fish exposures. Environ Toxicol Chem 33, 1849–1857.

Cerbelot R, Court MH, Hao Q, Michel KE, 2004: Identification and concentration of phytotoxins in commercial dog foods. Am J Vet Res 65, 592–596.

Colborn T, Clement C, 1992: Chemically-induced alterations in sexual and functional development: the wildlife-human connection. In: Mehlen MA, (ed). Advances in Modern Environmental Toxicology 21, Princeton Scientific Publishing Co., Inc. Princeton:

Combaltbert S, Bellet V, Bernet N, Colborn T, Court MH, Hao Q, Michel KE, 1992: Chemically-induced alterations in sexual and functional development: the wildlife-human connection. In: Mehlen MA, (ed). Advances in Modern Environmental Toxicology 21, Princeton Scientific Publishing Co., Inc. Princeton:

Corbel T, Perdu E, Gayrard V, Puel S, Cox R, 1978: Plant Estrogens Affecting human and wildlife health: where we are today and where we need to go. Toxicol Sci 105, 235–259.

Ingeleido AM, Abballe A, di Domenico A, Fochi I, Iacovella N, Saragosa A, Spagnolesi M, Valentinii S, De Felice E, 2009: Levels and profiles of polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and polychlorinated biphenyls in feeds and milk from farms in the vicinity of incineration plants in Tuscany, Italy. Arch Environ Contam Toxicol 57, 397–404.

Jefferson WN, Patisaul HB, Williams C, 2012: Reproductive consequences of developmental phytostrogen exposure. Reproduction 143, 247–60.

Kang J-H, Kondo F, 2002: Determination of bisphenol A in canned pet foods. Res Vet Sci 73, 177–182.

Krogenaes AK, Rogstad E, Gutleb AC, Hardnes N, Berg V, Dahl E, Fowler PA, 2014: In utero exposure to environmentally relevant concentrations of PCB 153 and PCB 118 disrupts fetal testis development in sheep. J Toxicol Environ Health A 77, 628–649.

Leung MCK, Díaz-Llano G, Smith TK, 2006: Mycotoxins in Pet Food: a Review. Reprod Toxicol 21, 56–66.

Ljungvall K, Veeramachaneni DNR, Hout M, Hulsen F, Magnusson U, 2008: Morphology and morphometry of the reproductive organs in prepubertal and postpubertal male pigs exposed to di(2-ethylhexyl) phthalate before puberty: precocious development of bulbourethral glands. Theriogenology 70, 984–991.

Lukac N, Lukacova J, Pinto B, Kruzicka Z, Twrda E, Massanyi P, 2013: The effect of nonylphenol on the motility and viability of bovine spermatozoa in vitro. J Environ Sci Health A Tox Hazard Subst Environ Eng 48, 973–979.

Magnusson U, 2005: Can farm animals help to study endocrine disruption? Domest Anim Endocrinol 29, 430–435.

Magnusson U, 2012: Environmental endocrine disruptors in farm animal reproduction: research and reality. Reprod Domest Anim 47, 333–337.

Magnusson U, Dencker L, 2010: Toxicogenomics of reproductive endocrine disruption. In: Jiang Z, Ott TL (ed.). Reproductive Genomics in Domestic Animals. Wiley-Blackwell, Hoboken, pp. 397–412.

Magnusson U, Ljungvall K, 2013: Environmental pollutants and dysregulation of male puberty-a comparison among species. Reprod Toxicol 44, 23–32.

McLachlan JA, Tilghman SL, Burow ME, Bratton MR, 2012: Environmental signaling and reproduction: a comparative biological and chemical perspective. Mol Cell Endocrinol 354, 60–62.

Meijer GAL, de Bree J, Wagenaar JA, Spoelstra SF, 1999: Sewerage overflows put production and fertility of dairy cows at risk. J Environ Qual 28, 1381–1383.
Mensching DA, Slater M, Scott JW, Ferguson DC, Beasley VR, 2012: The feline thyroid gland: a model for endocrine disruption by polychlorinated diphenyl ethers (PBDEs)? J Toxicol Environ Health, A 75, 201–212.
Mohamed E-SA, Park Y-J, Song W-H, Shin D-H, You Y-A, Ryu B-Y, Pang M-G, 2011: Xenosterogenic compounds promote capacitation and an acrosome reaction in porcine sperm. Theriogenology 75, 1161–1169.
Nohrborg S, 2015: Reproductive parameters in porcine sperm. Theriogenology 83, 297–304.
Oskam IC, Lyche JL, Krogenæs A, Thomsen DC, Beasley VR, 2012: The feline reproductive system and related hormones of young male goats. Reproduction 143, 731–742.
Pathirana I, Kawate N, Tsuji M, Takahashi M, Hatoya S, Inaba T, Tamada H, 2011: In vitro effects of estradiol-17β, monobutyl phthalate and mono-(2-ethylhexyl) phthalate on the secretion of testosterone and insulin-like peptide 3 by interstitial cells of scrotal and retained testes in dogs. Theriogenology 76, 1227–1233.
Petroleum, Covaci A, Leroy JL, Durtu AC, De Coen W, Bols PE, 2010: Occurrence of endocrine disrupting compounds in tissues and body fluids of Belgian dairy cows and its implications for the use of the cow as a model to study endocrine disruption. Sci Total Environ 408, 5423–5428.
Rhind S, Evans N, Bellingham M, Sharpe R, Cotinot C, Mandon-Pepin B, Loub B, Sinclair K, Lea R, Pocar P, 2010: Effects of environmental pollutants on the reproduction of domestic animals. Animal Reprod Sci 115, 1227–1239.
Rhind S, Kyle C, Mackie C, Yates K, Duff E, 2011: Geographic variation in tissue accumulation of endocrine disrupting compounds (EDCs) in grazing sheep. Environ Pollut 159, 416–422.
Sanderson JT, 2006: The steroid hormone biosynthesis pathway as a target for endocrine-disrupting chemicals. Toxicol Sci 94, 3–21.
Santos RR, Schoevers EJ, Roel BA, 2014: Usefulness of bovine and porcine IVM/IVF models for reproductive toxicology. Reprod Biol Endocrinol 12, 117.
Schmidt PL, 2009: Companion animals as sentinels for public health. Vet Clin N Am Small Anim Pract 39, 241–250.
Sève S, Marchand P, Guiffard I, Morio F, Venisseau A, Veyrand B, Le Bizec B, Antignac J-P, Abadie J, 2015: Pollutants in pet dogs: a model for environmental links to breast cancer. Springerplus 4, 27.
Sharpe RM, 2010: Environmental/lifestyle effects on spermatogenesis. Phil Trans R Soc B 365, 1697–1712.
Tabb MM, Blumberg B, 2006: New modes of action for endocrine-disrupting chemicals. Mol Endocrinol 20, 475–482.
Van Der Fels-Klerx HJ, Klemsdal S, Hietanen V, Lindblad M, Ioannou-Kakouri E, Van Asselt ED, 2012: Mycotoxin contamination of cereal grain commodities in relation to climate in North West Europe. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 29, 1581–1592.
Van der Schalie WH, Gardner HS Jr, Bantle JA, De Rosa CT, Finch RA, Reif JS, Reuter RH, Bucker LC, Burger J, Folmar LC, 1999: Animals as sentinel animals of human health hazards of environmental chemicals. Environ Health Perspect 107, 309.
Veermani DR, 2008: Impact of environmental pollutants on the male: effects on germ cell differentiation. Anim Reprod Sci 105, 144–157.
Venier M, Hites RA, 2011: Flame retardants in the serum of pet dogs and in their food. Environ Sci Technol 45, 4602–4608.
Virtanen HE, Adamsson A, 2012: Cryptorchidism and endocrine disrupting chemicals. Mol Cell Endocrinol 355, 208–220.
Wooten KJ, Smith PN, 2013: Canine toys and training devices as sources of exposure to phthalates and bisphenol A: quantitation of chemicals in leachate and in vitro screening for endocrine activity. Chemosphere 93, 2245–2253.
Yeung BH, Wan HT, Law YW, Wong CK, 2011: Endocrine disrupting chemicals: multiple effects on testicular signaling and spermatogenesis. Spermatogenesis 1, 231–239.
Zinedine A, Soriano JM, Molto JC, Manes J, 2007: Review on the toxicity, occurrence, metabolism, detoxification, regulations and intake of zearealenone: an oestrogenic mycotoxin. Food Chem Toxicol 45, 1–18.
Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebæk NE, Soto AM, Woodruff TJ, Vom Saal FS, 2012: Endocrine-disrupting chemicals and public health protection: a statement of principles from the Endocrine Society. Endocrinology 153, 4097–4110.

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