Journal of Environmental Management 301 (2022) 113708

Contents lists available at ScienceDirect

Journal of Environmental Management

journal homepage: www.elsevier.com/locate/jenvman

Ecological and human health risks of manure-borne steroid estrogens: A 20-year global synthesis study

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ARTICLE INFO

Keywords:
17β-estradiol equivalent
Low dose
Endocrine disruptors
Predicted environmental concentration
Feedlot effluent

ABSTRACT

Estrone (E1), 17α-estradiol (17α-E2), 17β-estradiol (17β-E2), and estriol (E3) are persistent in livestock manure and present serious pollution concerns because they can trigger endocrine disruption at part-per-trillion levels. This study conducted a global analysis of estrogen occurrence in manure using all literature data over the past 20 years. Besides, predicted environmental concentration (PEC) in soil and water was estimated using fate models, and risk/harm quotient (RQ/HQ) methods were applied to screen risks on children as well as on sensitive aquatic and soil species. The estradiol equivalent values ranged from 6.6 to 4.78×10^4 ng/g and 12.4 to 9.46×10^4 ng/L in the solid and liquid fraction. The estrogenic potency ranking in both fractions were 17β-E2> E1>17α-E2>E3. RQs of measured environmental concentration in the liquid fraction pose medium (E3) to high risk (E1, 17α-E2 & 17β-E2) to fish but are lower than risks posed by xenoestrogens. However, the RQ of PECs on both soil organisms and aquatic species were insignificant (RQ $<$ 0.01), and HQs of contaminated water and soil ingestion were within acceptable limits. Nevertheless, meticulous toxicity studies are still required to confirm (or deny) the findings because endocrine disruption potency from mixtures of these classes of compounds cannot be ignored.

1. Introduction

Steroid estrogens (SEs) are potent endocrine-disrupting chemicals (EDCs), even at 2 ng/L (Caldwell et al., 2012; da Cunha et al., 2016; Kolodziej et al., 2004). Estrone (E1), 17α-estradiol (17α-E2), 17β-estradiol (17β-E2), and estriol (E3) are regularly detected manure-borne SEs in soil and aquatic ecosystems (Gross-Sorokin et al., 2006; Hirano et al., 2004; Hutchinson et al., 1999; Jobling et al., 1998; van Aerle et al., 2001). Steroid estrogens can reach drinking water sources, provoking harmful human health effects (Barceló and Petrović, 2008; Bergman et al., 2012; Lamb et al., 2014). They also contribute to endocrine disruption activity in aquatic ecosystems (Arcand-Hoy and Benson, 1998; Kidd et al., 2014), such as the occurrence of intersex fish (Arlos et al., 2018; Harries et al., 1996; Jobling et al, 1998, 2006; Lee Pow et al., 2017; Lei et al., 2020; Schultz et al., 2013). Their primary introduction pathways into the environment include leakage from feedlots and animal facilities (L. Zhao et al., 2010), biosolid fertilizers (Gray et al., 2017), discharge of effluents (Snow et al., 2009), manure-fertilizer application (Ying et al., 2002), wastewater treatment plant (WWTPs) effluents (Välitalo et al., 2016) and runoff from agro-ecosystems (Gray et al., 2017; Tran et al., 2018).

Natural SEs present the greatest endocrine disruption potency (Combalbert and Hernandez-Raquet, 2010) and have the highest binding affinity to nuclear estrogen receptors (ER), surpassing other xenoestrogens except pharmaceuticals designed with endocrine-mediated mechanisms, e.g., 17α-ethinylestradiol (EE2) used for reproductive control (Pillon et al., 2005; Tapiero et al., 2002). For example, the cell line invitro test produced EEQ values of 17.6, 0.66, 0.32, and 246 for E3, bisphenol A (BPA), nonylphenol (NP), and EE2, respectively (Balaguer et al., 1999; Pillon et al., 2005).

Approximately 90% of estrogens in the environment come from animal manure and effluents, which are rarely treated (He et al., 2019). Zhang et al. (2014) reported that China's livestock excretes 2.05 million kg/yr. SEs annually. The European Union (EU) and the United States (USA), livestock SEs loads are 33,000 kg/yr, and 49,000 kg/yr, respectively (Lange et al., 2002). Despite these confirmations-no global manure-borne SEs monitoring has been presented, limiting our

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https://doi.org/10.1016/j.jenvman.2021.113708
Received 14 May 2021; Received in revised form 17 August 2021; Accepted 6 September 2021

Abbreviations

17α-E2	17α-estradiol
17β-E2	17β-estradiol
BPA	Bisphenol A
E1	Estrone
E3	Estriol
EDCs	Endocrine-disrupting chemicals
EE2	17α-ethinylestradiol
EEQ	17β-E2 Equivalent
EU	European Union
FAO	Food and Agricultural Organization of the United Nations
HQ	Health Quotient
MEC	Measured Environmental Concentration
NP	Nonylphenol
PNEC	Predicted Environmental Concentration
RQ	Risk Quotient
SEs	STPs Steroid estrogens Sewage Treatment Plants
TGD	Technical Guidance Document
US EPA	United States Environmental Protection Agency
WHO	World Health Organization
WWTPs	Wastewater Treatment Plants

understanding of their risks on environmental matrices and organisms. Risk assessment of SEs challenges conventional toxicology concepts, especially the common perception that dose is directly related to toxicity (Testai et al., 2013; Vandenberg et al., 2013; Welshons et al., 2003). Effect probability cannot predict the effects at low doses (Kortenkamp, 2007; Zoeller and Vandenberg, 2015). Conversely, ubiquitous SEs have received little pollution control attention. In contrast, highly monitored and regulated EDCs such as BPA and NP have lower estrogenic potency (Myers et al., 2009).

The adverse environmental effects of SEs have considerably raised scientific concerns over the past 30 years (Adeel et al., 2017a; Hotchkiss et al., 2008; Kolpin et al., 2002), necessitating inclusion in the regulatory lists of the European Commission (2003) and US Environmental Protection Agency (USEPA) (2016). To ensure environmental protection, the EU Technical Guidance Document (EU TGD) has specified fate models for estimating predicted environmental concentration (PEC) in environmental matrices based on the measured environmental concentration (MEC) of discharge or in applied manure (European Commission, 2003). The associated ecological and human health risks are then characterized through standard deterministic procedures (Caldwell et al., 2012; European Commission, 2003; Wang et al., 2019), which compares the concentrations (MEC & PEC) and the worst-case predicted no-effect concentration (PNEC) derived from standard toxicity assays (European Commission, 2003).

Most global studies on SEs pollution have focused on risk assessment in sediments, surface waters, and WWTPs. For example, Du et al. (2020) analyzed the occurrence and risks of SEs in WWTPs and surface water, Tran et al. (2018) summarized the occurrence and environmental fate of E1, 17α-E2, 17β-E2, E3 and EE2 in WWTPs and Adeel et al. (2017a) studied selected occurrence and risks of E1, 17α-E2, 17β-E2, E3 and EE2 in soil, animal manure and water bodies close to WWTPs and Sewage Treatment Plants (STPs). However, the occurrence and risks of SEs in manure and feedlot effluents were relatively less observed. Manure-borne estrogens studies have focused on national and regional cases (Combalbert and Hernandez-Raquet, 2010; Xu et al., 2018; Z. Zhao et al., 2010). Under this context, we applied EU and USEPA fate models to elucidate the risks of SEs on sensitive organisms and human health based on MECs data from the literature.

To date, no study has used the global MECs of manure-borne SEs to assess the ecological and human health risks in manure, surface water and manure-amended soil. This study's synthesis approach involved aggregating MECs reported in publications from January 2000 to December 2020 and categorized them into liquid and solid fraction concentrations. Then the global burden of manure-borne SEs was mapped, and their risks to vadose zone soil organisms and human ingestion of soil after manure application were estimated. Assessments of associated ecological and human health risks were performed in aquatic ecosystems and drinking water. Finally, the risks of the SEs were compared to those posed by xenoestrogens (NP, BPA, atrazine, and glyphosate).

2. Materials and methods

2.1. Data collection

We retrieved SEs concentration data from livestock manure reported in gray literature and scientific journals from Google Scholar (Google Inc., Mountain View, CA, USA), Web of Science (Thompson Reuters, New York, NY, USA), and international Dissertation and Thesis repository (ProQuest). Included studies had reported monitoring data. The expanded search terms were: (1) (manure or droppings or dung) and (steroid hormones or steroid estrogens); (steroid hormones or steroid estrogens in manure or droppings or dung); (steroid hormones or steroid estrogens concentration in manure or droppings or dung); (2) (manure slurry or manure sludge) and (steroid hormones or steroid estrogens); (steroid hormones or steroid estrogens in manure slurry/sludge or droppings slurry/sludge or dung slurry/sludge); (steroid hormones or steroid estrogens concentration in manure slurry/sludge or droppings slurry/sludge or dung slurry/sludge).

The data obtained were further refined using the following criteria; (1) if the location had SE data for several years, the selection criteria included the most recent monitoring data; (2) in cases of multiple data values, we used median values and (3) the chosen studies should contain the individual SE concentration in the manure or slurry. The inclusion and exclusion criteria is highlighted (Fig. S1). In total, 55 articles on SEs were selected; 32 reported concentration in solid fraction and 38 reported concentration in the liquid fraction (Tables S1 and S2). This study has also included data on concentrations of xenoestrogens (NP, BPA, atrazine and glyphosate) commonly observed in surface waters adjacent to agroecosystems. Overall, 72 articles published within the same period mentioned above were selected (18 for each xenoestrogen) (Table S4).

2.2. Ecological risk modeling

2.2.1. Risk quotient

According to the TGD, risk quotients (RQ) have been widely applied for risk characterization and quantitative environmental risk assessments. Therefore, ecotoxicological risks were evaluated in the aquatic and terrestrial ecosystems using RQ methods (Fig. 1) (European Commission, 2003). The RQ of each SE in soil and surface water was assessed based on the ratio of MEC to the PNEC below which no adverse effects are to happen (Eqn. (1)).

$$RQ = \frac{MEC}{PNEC} \quad (1)$$

where MEC is the monitored concentration of pollutants in (ng/g or ng/L) and PNEC is the predicted no-effect concentration. According to standard environmental risk ranking criteria, ecological risks have four levels: insignificant risk (<0.01); low risk (0.01 = RQs<0.1); medium risks (0.1 = RQ < 1), and high risk (RQs≥1). The screening-level analysis applies RQ values; therefore, values > 1 only indicate the need for additional research, not necessarily showing likely adverse ecological impacts.

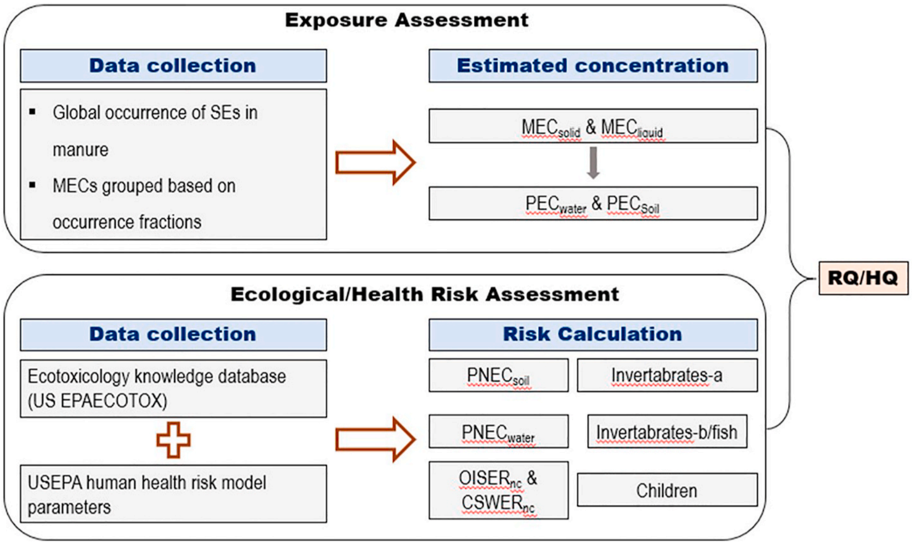

Fig. 1. Framework applied for manure-borne steroid estrogen risk assessment. MEC_{solid} and MEC_{liquid} represent the reported concentration in solid and liquid fraction manure, and $PNEC_{water}$ and $PNEC_{solid}$ represent the estimated environmental concentration in surface water and manure amended soils, respectively. RQ of invertebrate-a is the ecotoxicity to soil invertebrates; RQ of invertebrate-b and fish is the ecotoxicity to aquatic species, and HQ to children is a hazard to human health via soil ingestion and drinking water.

2.2.2. Estrogenic activity analysis

Based on the reported SE concentration in environmental matrices, the 17β-E2 equivalent (EEQ) calculation applied Eqn. (2).

$$\text{EEQs} = \sum_{i=1}^{n} (\text{EEF}i \times \text{MEC}i) \tag{2}$$

EEQs in ng/L or ng/g is the concentration of β-E2 equivalency. EEF*i* is the 17β-E2 factor of estrogen *i* MEC*i* (ng/L or ng/g), the measured environmental concentration of estrogen *i* and n = 3. According to literature results, the EEQ values for 17β-E2, E1, 17α-E2, and E3 are 1, 0.33, 0.125, and 0.033, respectively (He et al., 2015).

2.2.3. Predicted concentration in surface water and soil

The PECs in surface waters and soils were estimated according to TGD's model Eqns. (3) and (4) (European Commission, 2003). In the case of surface water concentrations, the distance from the point of contaminated water discharge to the point with complete mixing do vary with locations, climate, seasons, and geographical condition. However, a fixed dilution factor was applied and calculated according to Eqns. (3) and (4) for PEC water and soil, respectively.

$$\text{PECwater} = \frac{\text{MECeffluent}}{(1 + \text{Kpsusp} \times \text{SUSPwater} \times 10^6) \quad \text{DILUTION}} \tag{3}$$

$$\text{PECsoil} = \frac{\text{MEC} \times \text{APPLmanure}}{\text{DEPTHsoil} \times \text{RHOsoil}} \tag{4}$$

where Kp_{susp} represents the soil-water partitioning coefficient of suspended matter (0.1 L/kg), $SUSP_{water}$ is suspended matter concentration in the surface water (15 mg/L), and DILUTION is the dilution factor (10). $APPL_{manure}$ is the manure application rate (0.5 kg/m^2 for agricultural soils); $DEPTH_{soil}$ is the mixing depth of soil (0.20 m for farm soils), and RHO_{soil} is the bulk density of wet soil (1700 kg/m^3) for agricultural soil (European Commission, 2003; Stasinakis et al., 2013).

2.3. Toxicity to aquatic organisms

The endpoints used to assess aquatic ecotoxicology included; reproduction impacts, internal vitellogenin formation, and hermaphroditism. This study focused on selecting fish and crustaceans as the target ecological receptors because they are sensitive to aquatic contaminants and are widely applied in lifecycle studies (Table S1). The reproductive effects of fish represent the most significant biologically sensitive endpoint for short and long-duration studies, and crustaceans represent widespread aquatic invertebrates (Andersen et al., 2001). The current study used PNEC of SEs derived using the species sensitivity distribution (SSD) based on chronic fish toxicity assessments. The $PNEC_{water}$ values adopted for aquatic risks to fish were 6, 16, 2, and 60 ng/L for E1, 17α-E2, 17β-E2, and E3, respectively (Caldwell et al., 2012). The PNECwater for the crustaceans was inferred using the assessment factor method based on the US EPA's recommended toxicity assessment values (Eqn. (5)).

$$\text{PNECwater} = \frac{L(E)50 \ or \ NOEC}{\text{AF}} \tag{5}$$

where L(E)50 is the half lethal concentration (ng/L), NOEC is the no observed effect concentration (ng/L), and AF is the assessment factor. Chronic toxicity data can better represent an organism's exposure to continuous environmental contaminants; hence, the chronic data (NOEC) were obtained from the EPAECOTOX database and Song et al. (2018).

2.4. Toxicity to soil organisms

The $PNEC_{soil}$ values were estimated from $PNEC_{water}$ because of the literature's limited toxicological data of natural SEs on terrestrial compartments. The $PNEC_{soil}$ values from the literature were calculated by applying the equilibrium partition approach (Eqn. (6)).

$$\text{PNEC}_{soil} = \text{PNEC}_{water} \times \text{K}_d \tag{6}$$

where K_d is the soil-water partition coefficient, which considers both adsorption and absorption of contaminants on soil's particles, and K_d values from the literature were used to determine the $PNEC_{soil}$ of soil invertebrates (Nie et al., 2014). The PNEC values applied in assessing risks of manure application on agricultural soil invertebrates were; 0.99 ng/g (*S. purpuratus),* 7.92 ng/g (*S. purpuratus),* 2.51 ng/g (*T. battagliai*), and 711 ng/g (*S. purpuratus*) for 17β-E2, 17α-E2, E1 and E3*,* respectively (Martín et al., 2012).

2.5. Human health risks

The World Health Organization (WHO) and USEPA have not provided carcinogenic risk evaluation parameters and potency factors for assessing human health risks from exposure to SEs. Therefore, this study evaluated the non-carcinogenic risks of total EEQs in manure and slurry. Children were selected as the risk receptors because they are sensitive to non-carcinogenic effects compared to adults (Song et al., 2018). The liquid fraction concentrations can reach surface water sources used for potable water; therefore, oral drinking was the considered pathway. The dose of each exposure pathway was calculated using Eqns. (7) and (8) (US EPA, 2009):

$$OISER_{nc} = \frac{OISE_{nc} \times ED_c \times EF_c \times ABS_o}{BW_c \times AT_{nc}} \times 10\hat{6} \tag{7}$$

$$CSWER_{nc} = \frac{WCR_c \times ED_c \times EF_c}{BW_c \times AT_{nc}} \times 10\hat{6} \tag{8}$$

$OISER_{nc}$ oral intake of soil exposure ($kg.kg^{-1}.d^{-1}$); $OISE_{nc}$ oral soil intake amount for children (200 mg d^{-1}); ED_c is the duration of exposure (6 years); EF_c is the exposure frequency (350 days); ABS_o is the oral intake absorption efficiency factor (1); BW_c is the bodyweight of children (15.9 kg); AT_{nc} is the average time of non-carcinogenic effect (2190 days); $CSWER_{nc}$ is the exposure dose through drinking of the affected surface water ($L.kg^{-1}.d^{-1}$), and WCR_c is the daily drinking water quantity of children (0.87 L d^{-1}).

The dose threshold effect expresses the non-carcinogenic effects of SEs based on the HQ method (Fig. 1). An HQ value < 1 indicates no harmful effects on human health, and HQs with values > 1 were linked to unacceptable levels of non-carcinogenic risks. Eqns. (9) and (10) show the formulae of estimating HQs of soil and water, respectively (US EPA, 2009):

$$HQsoil = \frac{OISERnc \times Csur}{RfDo \times SAF} \tag{9}$$

$$HQsw = \frac{CSWERnc \times Csw}{RfDo \times WAF} \tag{10}$$

HQ_{soil} is the risk associated with the pathway of oral intake of soil, and HQ_{sw} is the risk quotient under the path of drinking surface water. C_{sur} is the pollutant concentration in the topsoil in (PEC $mg.kg^{-1}$); C_{sw} is the pollutant concentration in surface water sources; SAF is the reference dose distribution coefficient exposed to soil; RfDo is the oral ingestion reference dose (5.0-E5 $mg.kg^{-1}.d^{-1}$); SAF is the reference dose distribution coefficient exposed to soil (0.2), and WAF represents the reference dose distribution exposure to surface water (0.2). All parameter values were from USEPA.

3. Results and discussion

3.1. Spatial livestock and steroid estrogen distribution

3.1.1. Contamination hotspots of manure-borne SEs

Global risk assessment of manure-borne SEs hinges on the access to excretion data from the livestock population and their sub-national spatial distributions. However, potential pollution hotspots remain primarily unreported. Thus, the global abundance of livestock species and distribution can be used to quantify manure production. For this purpose, the Food and Agricultural Organization's (FAO) latest global livestock distribution maps (areal weighting) were used to highlight the potential nation-level manure production (Gilbert et al., 2018). The areal weight model spreads the individual species evenly on a census polygon, and the density in each pixel represents the average population per km^2 of suitable land. The national livestock dataset was generated using Random Forests, a machine learning technique that disaggregates livestock data and provides accurate gap filling (Nicolas et al., 2016).

Fig. 2 highlight the potential SEs contamination from livestock in all regions. For example, cattle are the most populous animal species with high numbers of $>$50 heads per km^2 in India, Brazil, Europe, Central America, East, West, and South Africa, but disproportionately small numbers in Russia, North Canada, Western Australia, and North Africa. The largest proportion of chicken ($>$250 per km^2) was in China, Southern Europe, Mexico, India, the Middle East, and West Africa. However, pigs had the lowest global footprint, with China and Western Europe having the highest population ($>$250 pigs per km^2). High goat populations were in Brazil, Southeast Asia, central, west, and East Africa. Ducks' population was high (250–1000 per Km^2) in Bangladesh, China, Egypt, France, Nigeria, and Southeast Asia.

Powers et al. (2019) reported that manure-rich agricultural land was most abundant in Europe, Brazil, China, South East Asia, and India, with small patches occurring in Central USA, East and Central Africa, and Central America. Moreover, the study observed that manure-rich cultivated areas ($>$90th percentile and $>$90% cropland) accounted for 3.2%

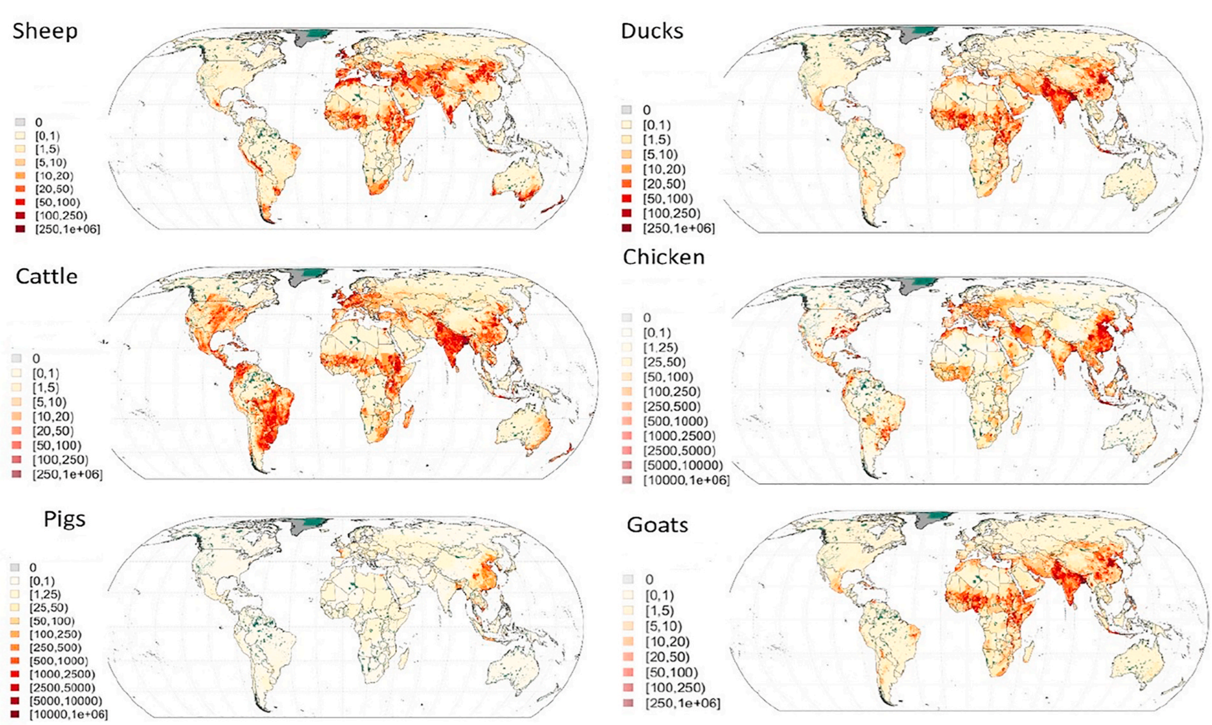

Fig. 2. Global livestock occurrence and distribution map in Gilbert et al. (2018).

of the global manure-fertilizer application and were abundant in China and India. Lower manure production (<75 percentile) was in Indonesia, western Russia, China's interior, and west Africa. These findings are congruent with global spatial livestock distribution statistics. Notably, global animal densities have increased consistently over the past 20–40 years and are expected to continue growing, raising the potential SEs excretion in manure. The phenomenon could be attributed to the rising human population that requires higher meat, poultry, and dairy for consumption (Acosta and De los Santos-Montero, 2019; Herrero and Thornton, 2010; Metson et al., 2016, 2014).

3.1.2. Spatial distribution of reported steroid estrogen

Figs. 3 and 4 illustrate the spatial distributions of SEs (percentage concentrations of all detected SEs per location) in solid and liquid manure matrices, respectively. Most of the studies were from North America (55.71%) and Asia (24.29%) (Fig. S2). It is, however, essential to note that the manure monitoring studies are pretty erratic, with most publications in 2010 (11.59%) followed by 2007 and 2009, both at 10.14%. Fig. S3 illustrates the publication patterns, and most studies were between 2007 and 2012, with a tapering off from 2015, indicating that SEs have not been receiving monitoring impetus despite the associated increasing scientific attention (Adeel et al., 2017a; Hotchkiss et al., 2008; Kolpin et al., 2002). On the contrary, studies of SEs in surface water, WWTPs, and biosolids within the same period have been described to be at a sustainable research phase because the number of studies is progressive, with an annual range of 24–28 articles per year between 2015 and 2020 (Du et al., 2020).

MECs in the liquid and solid fraction had majority entries of 17β-E2 followed by E1. These can be attributed to their ubiquity and an emphasis on monitoring the two SEs because of their adverse environmental and human health risks, such as reproductive defects in aquatic and terrestrial organisms and human beings (Caldwell et al., 2010; US EPA, 2011). Notably, monitoring and reporting SEs is not a universal phenomenon; nevertheless, limited data does not mean that the locations experience a low SEs pollution burden. The global livestock population data highlighted potential hotspots in all regions, but the spatial distribution of occurrence data varies substantially with glaring data gaps in the literature. For example, areas known to be practicing intensive animal operations such as Australia, South Africa, Europe, and Asia may be contributing significant estrogen loads to the environment. Similar scarce data from these locations have been reported by studies focusing on global estrogen pollution in surface waters (Adeel et al., 2017a; Du et al., 2020). Generally, manure-borne estrogens' spatial distribution highlights the differences in livestock farming practices, environmental characteristics, legislative frameworks, research directions, and farm waste management.

Similarly, there is a global shift in diet and consumption preferences towards livestock products, increasing the production of SEs. The world population and income have been rising over the last few decades and are expected to demand higher livestock products. For example, the bulk of the world population is in Asia's developing countries, with their meat consumption growing at 4% and dairy products at 2–3% per annum (FAO, 2006; Prakash and Stigler, 2012). Aggregate SEs pollution is shaped by these trends, not only through an increase in livestock production *per se* but also by linking to artificial estrogen released in manure that may eventually reach water sources and terrestrial habitats.

Notably, livestock production covers the most considerable agricultural land use globally; hence, the projected global population growth that needs more livestock and their products will have negative environmental implications linked to manure-borne estrogen pollution (Dangal et al., 2017). Moreover, the spatial distribution of MEC may be attributed to the high number of studies in some regions (Figs. 3 and 4) but does not correlate with the global SE contamination hotspots (Fig. 2), showing a significant gap of knowledge in such regions. The variations may also provide information on hormones as growth promoters in animal production (Fekadu et al., 2019; Xu et al., 2018).

3.2. Steroid estrogen concentration in global manure

The concentrations of SEs in the liquid and solid fraction of manure are shown in Tables S2 and S3. 17β-E2 and E1 were the most frequently detected estrogens in the solid fraction of manure. The concentrations of E1, 17α-E2, 17β-E2, and E 3 in the solid fraction ranged from 7.3 to 99,667 (median 183.2 ng/g), 2.9 to 33,333 (median 93 ng/g), 0.54 to 1500 (median 104.4 ng/g) and 9.88 to 9733 (median 86 ng/g), respectively. Based on the ranking of median total EEQs, 17β-E2 had the highest percent EEQ of 58.22%, followed by E1 (33.71%), 17α-E2 (6.48%), and E3 (1.59%).

The liquid fraction SEs concentration in E1, 17α-E2, 17β-E2, and E3 were 15.6–25,395 (median 618.31 ng/L), 10.2 to 3000 (median 965 ng/L), 2.5 to 72,000 (median 250 ng/L), and 10.3 to 6298 (median 430 ng/L), respectively. The EEQs concentration in the liquid fraction was dominated by 17β-E2 (42.46%) followed by E1 (34.64%), 17α-E2 (20.49%), and E3 (2.41%). Fig. 5 illustrates the log concentration of the individual SEs in liquid and solid fractions. Overall, the estrogenic potency in both manure fractions was in the order of 17β-E2> E1>17α-E2>E3.

The highest total SE concentration in solid and liquid fractions was from North Dakota (1.33 × 10^5 ng/g) and North Carolina (2.65 × 10^5 ng/L), respectively (Tables S1 and S2). The European data had no wide variability among the nations. For example, in Spain, France, Denmark, and The Netherlands, 17β-E2 concentrations in the solid-fraction ranged

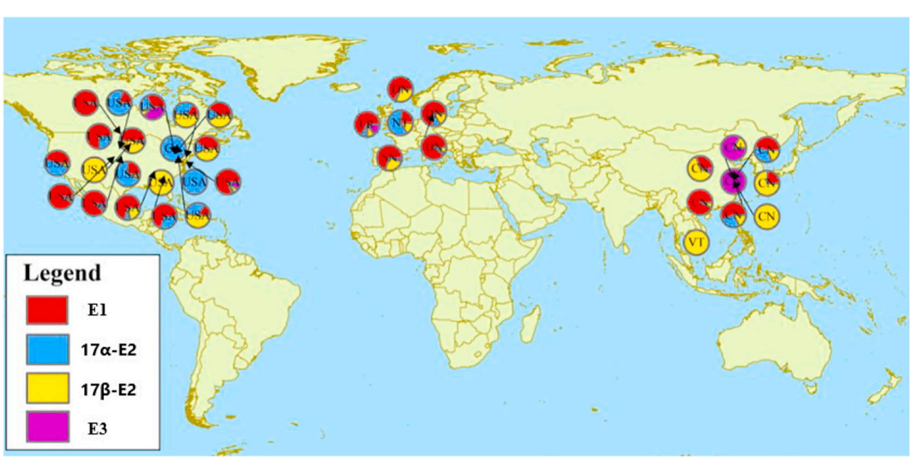

Fig. 3. Global distribution of steroid estrogens in solid-fraction manure. Pie chart comprises of individual steroid estrogen as a proportion of total at each site. The country abbreviations are DN-Denmark, FR-France, NT-Netherlands, SN-Spain, CN-China, VT-Vietnam, CAN-Canada, and the USA-United States of America.

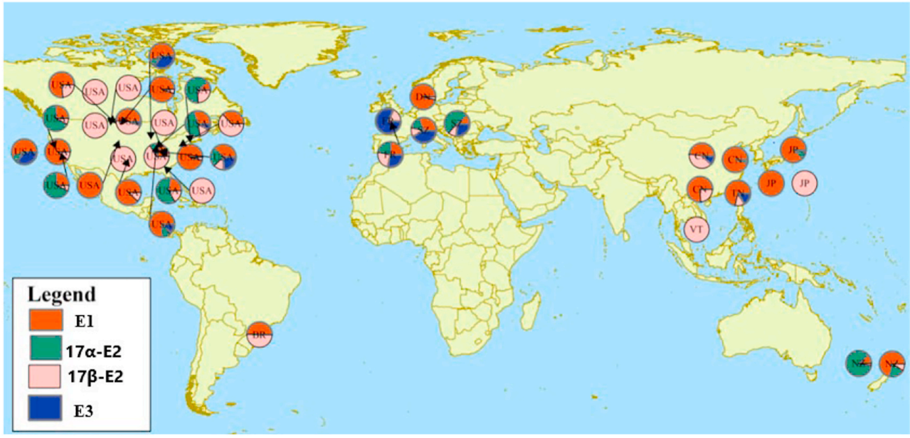

Fig. 4. Global distribution of steroid estrogens in liquid-fraction manure. Pie chart comprises of individual natural estrogen as a proportion of total at each site. The country abbreviations are DN-Denmark, SZ-Switzerland, FR-France, CN-China, JP-Japan, VT-Vietnam, NZ-New Zealand, TN-Taiwan, BR-Brazil, and the USA-United States of America.

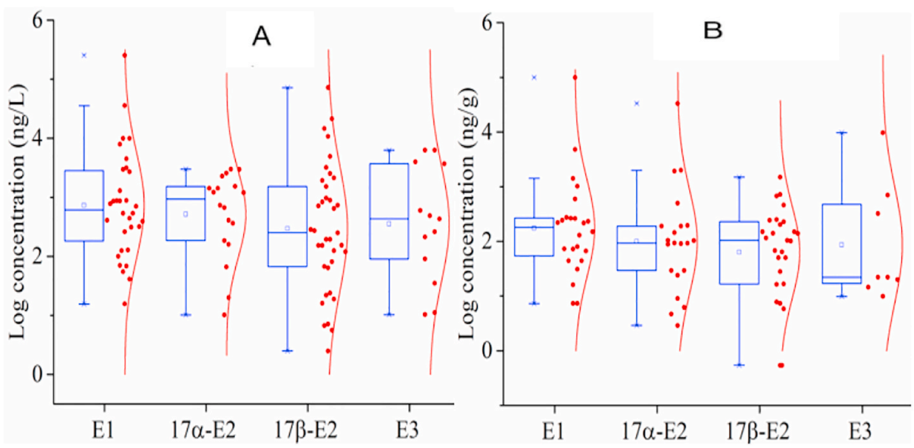

Fig. 5. Log concentration of estrogens in liquid-fraction (A) and solid-fraction (B) manure.

from 50 ng/g to 202.3 ng/g. Similarly, studies on SEs in the European water bodies also reported no wide variability across the Czech Republic, Italy, France, Luxemburg, Germany, and Spain (Fekadu et al., 2019). On the contrary, there were large variations in MECs of 17β-E2 in the USA and China with range values of 1500 ng/g and 700 ng/g, respectively. The concentrations of 17β-E2 in the solid fraction of manure in Europe are about 9.8 and 4.6 times lower than those reported in the USA and China. Similarly, significant MEC variations were reported in the liquid fraction, and the 17β-E2 concentrations ranged from 5.6 ng/L to 7.2×10^4 ng/L, which were higher levels than the data reported in the other regions.

The lowest total MECs in the solid and liquid fraction was reported in Mekong Delta, Vietnam, and Miyazaki, Japan. The latter data were measured after manure digestion in a biogas plant, and the system had removed 80% of the 17β-E2 from the digestion liquid, whereas the former was measured in fresh cow feces (Tables S2 and S3). Notably, in the Mekong Delta, animal excrements are disposed directly into surface water, with only a few pretreatment cases using vermicomposting systems or biogas plants, potentially polluting surface water in the region (Gudda et al., 2020; Le et al., 2013).

Furthermore, the total number of estrogen entries in the studies varied probably because of differences in sample source and study contexts. In general, SEs' concentration in solid-fraction manure was higher than those in liquid fractions. The SEs tend to accumulate in the solid fraction because of their low volatility and high hydrophobic nature; hence they may probably be absent in the liquid fraction in some cases (Paterakis et al., 2012). Moreover, estrogens have a log K_{ow} value $\geq$ 3, indicating that they can potentially undergo sorption into solid-fraction manure, sediments, and soil compartments, posing additional risks (Matthiessen et al, 1998, 2006). These findings demonstrate the importance of monitoring manure's estrogen concentration as they can undergo desorption after farm application, posing environmental pollution risks.

Estrogen concentration varied substantially. The variations are attributable to animal types, manure characteristics, reproductive cycles, and the livestock's biological characteristics (Leet et al., 2012; Raman et al, 2001, 2004). For example, cows excrete 256–7300 μg/cow/day, and pregnant cows excrete 11,300–31,464 μg/cow/day. Pregnant pigs' manure has an estrogen load of 16–80 μg/pig/day and 700–1700 μg/pig/day in urine, whereas cycling pig's urine has 64–100 μg/pig/day. Dairy manure has 39 ng/g E1, and 18.4 n/g 17β-E2 and slurry has 1.5 μg/L 17β-E2 and 4.5 μg/L E1 (Johnson et al., 2006; Raman et al., 2004). Pig slurry has 2 μg/L 17β-E2 and 6–14 μg/L E1, while farrowing sows slurry has 4 μg/L 17β-E2 and 6 μg/L E1 (Raman et al., 2004). Broilers excrete 27.5 μg/L 17β-E2 (Finlay-Moore et al., 2000) and 14–65 μg/L combined 17β-E2 and E1 (Shore et al., 1993), while layers litter has 31 ng/g 17β-E2 (Hanselman et al., 2003). Pregnant livestock contributes a higher SE load.

However, developing patterns to explain the variations locally and globally is technical because they were collected under different experimental setups and study contexts. Most studies reported 17β-E2 and E1 as the key contributors of estrogen loads in manure. Similarly, studies of estrogens in surface water adjacent to farms, tile-drained ecosystems, and waste treatment effluents have documented related observations (Atkinson et al., 2012; Damkjaer et al., 2018; Gall et al., 2014; Raman et al., 2004).

The range of MECs was above those reported in WWTPs influent and effluent in Europe (Tiedeken et al., 2017), Asia, Europe, North America, and Africa (Barbosa et al., 2016), Asia, America, Europe, and Oceania (Ghirardini et al., 2020). And higher than concentrations in solid matrices, i.e., soil and sediment in Africa (Madikizela et al., 2020), biosolid and sludge in Latin America (Reichert et al., 2019), and in global sludge, manure, and sediment (aus der Beek et al., 2016). However, some of these studies included EE2, 17 α-Estradiol-3-sulfate, 17 β-E2-3S, 17β -Estradiol-3-sulfate; 17 β -E2-17S, 17 β -E2-17G, etc. These observed lower concentrations in non-manure matrices show that livestock wastes require concerted monitoring and treatment before discharge into the environment.

Comparison of PECs with estrogen concentration in WWTPs effluents show that the median levels are lower than those reported in Finland, France, Netherlands, USA, Spain, Australia, Japan, France, Portugal, Canada, and Greece (Välitalo et al., 2016). The maximum concentrations were within the ranges reported in Korea (Sim et al., 2011b), North America (de Mes et al., 2005; Kolpin et al., 2002), and Europe (de Mes et al., 2005; Ribeiro et al., 2009). but lower than levels in Canada (Atkinson et al., 2012), Brazil (Pessoa et al., 2014), China (Ben et al., 2018; Lei et al., 2020), South Africa (Kibambe et al., 2020), Tanzania (Damkjaer et al., 2018), and Argentina (Valdés et al., 2015). Effluent sample concentrations vary with locations, and several cases were on a similar level to PECs. The results indicate a need to monitor and advance the feedlot effluent treatment process, especially for large-scale feedlots with significant waste loading.

3.3. Ecological risks of steroid estrogens

3.3.1. Aquatic risk assessment

RQs of slurry-contaminated surface water were used to assess risks to invertebrates and fish in aquatic ecosystems by applying various PNECs (Table 2). The RQs calculations were based on MECs (Table S3) and PECs (Table 1), and the RQ values were used to develop a risk characterization matrix (Fig. 6). Aquatic risks of the MECs were high, with 33.33% exhibiting RQs>1. All the 17β-E2 and E1 RQs on fish were >1, thus categorized as posing high risks. The median and maximum MECs of 17α-E2 had RQ values > 1, posing high risks to fish. Notably, only 6.25% of the median MECs had RQs >1 across all the aquatic test species, indicating low risks. Conversely, 62.5% of the RQs of the maximum MECs, which represent the worst-case scenario, were >1, exhibiting a compulsive estrogenic risk potency. RQs in surface water was relatively low. Correspondingly, only fish exposed to the maximum 17β-E2 and E1 faced high risks, and 75% of the test species experienced insignificant risks. Generally, SEs contaminated effluents pose higher risks to fish.

As illustrated in Fig. 6, risks to invertebrates were low for the median PEC in surface water. However, all the invertebrates experience low to high risks from exposure to medium effluent concentrations except exposure to E3 and shrimps exposed to 17β-E2. Notably, maximum MECs pose a high risk to all the invertebrates. Likewise, none of the MECs presented insignificant risks to fish, confirming these contaminants' ecological significance. The toxicity results are based on widely used species in North America, Asia, and Europe, representing fish and invertebrates found in natural waters in those regions, and the data are based on multigenerational risk assessment of sensitive species; hence the $PNEC_{water}$ applied is protective (Caldwell et al., 2012).

Comparatively, Table S4 summarizes the concentration of pesticides (atrazine and glyphosate) and industrial chemicals (BPA and NP) in surface waters. Fig. 7 illustrates the log concentration of the SEs in effluents discussed so far compared to the four xenoestrogens' surface water concentrations. The RQ values of atrazine, glyphosate, NP and BPA were 0.01–160 (median 0.59), 0.004–84 (median 0.43), 0.04–939 (median 1.19) and 0.05–133 (median 2.04), respectively. BPA and nonylphenol pose high risks (RQ > 1), whereas atrazine and glyphosate pose medium risks (0.1 < RQ < 1) to the test species. In this situation, xenoestrogens' ecological risks on aquatic species are higher than those from SEs in surface waters but within the same range as risks posed by feedlot effluents. In general, the maximum RQs of xenoestrogens were more than 1000-fold; hence their contamination risks are more serious.

Ninety-eight percent of estrogens' EEQs in effluents are way above the PNEC of 2 ng/L protective to fish (Caldwell et al., 2012). There is a high likelihood that EEQs in receiving aquatic ecosystems may exceed the safety threshold, thereby posing risks to aquatic life (Gadd et al., 2010). Particularly, 17β-E2 and E1 pose significant risks to aquatic organisms, and there is a need for concerted attention on their monitoring and removal in effluents. Also, decomposition and manure holding can degrade SEs because of their short half-lives (Combalbert and Hernandez-Raquet, 2010; Li et al., 2018; Mirzaei et al., 2019; Raman et al., 2001; Song et al., 2018; Villemur et al., 2013). Unfortunately, few policy regulations and national environmental protection bodies focus on this group of estrogens, emphasizing regulation of synthetic estrogens (EE2), which are more persistent (Capolupo et al., 2018; Hannah et al., 2009; Zhang et al., 2007). Manure-borne SEs are ubiquitous in environmental matrices at parts-per-billion levels, and consequently, their known detrimental effects on biota at trace exposure levels warrant global pollution control attention.

Table 1
Measured and predicted concentration of estrogens and estradiol equivalents in manure.

Estrogen	Solid fraction concentration (ng/g)							
	MEC		EEQ		PEC		EEQ	
	median	Max	median	max	median	max	median	Max
E1	150	99,667	49.5	32890.11	0.27	146.61	0.09 (34.62)	48.38 (84.6)
17α-E2	92.85	33,333	11.61	4166.63	0.14	49.03	0.02 (7.69)	6.13 (10.72)
17β-E2	104.4	1500	104.4	1500	0.15	2.21	0.15 (57.69)	2.21 (3.86)
E3	22	9733	0.73	321.19	0.13	14.32	0.004 (1.54)	0.47 (0.82)
Total	369.25	144,233	166.24	38877.93	0.69	212.17	0.26	57.19
Liquid fraction concentration (ng/L)								
E1	618.35	253,951	204.05	83803.83	0.03	13.83	0.009 (17.65)	4.15 (25.89)
17α-E2	965	3000	120.63	375	0.02	0.06	0.0025 (4.90)	0.01 (0.06)
17β-E2	250	72,000	250	72,000	0.04	11.88	0.04 (78.43)	11.88 (74.11)
E3	430	6298	14.19	207.83	0.001	0.03	0.00003 (0.06)	0.0001 (0.0006)
Total	2263.35	335,249	588.87	156386.7	0.091	25.8	0.051	16.03

MEC: measured environmental concentration in manure; PEC; predicted environmental concentration in manure amended soil (solid-fraction) and surface water (liquid fraction); EEQ*;* 17β-E2 equivalent concentration. Data of median and maximum concentrations and values in bracket are the percentage EEQ contribution of individual estrogens in final environmental matrices.

Table 2
Data on chronic toxicity of 17β-E2 on target aquatic organisms.

Estrogen	Organism	Subphylum	Test	$PNEC_{water}$ (ng/L)	$PNEC_{soil}$ (ng/g)	Reference
17β-E2	Water flea	Crustacean	NOEC:6 days	1000	N.A.	Song et al. (2018)
	Calanoid copepod		NOEC:30 days	600	N.A	
	Shrimp		NOEC:3 days	1000	N.A	
	Pacific purple sea Urchin	Crustacean	EC_{50}	N.A	0.99	Martín et al. (2012)
	Fish	Fish	NOEC	2	N.A	Caldwell et al. (2012)
17α-E2	Fish	Fish	NOEC	16	N.A	Caldwell et al. (2012)
	Pacific purple sea Urchin	Crustacean	EC_{50}	N.A	7.92	Estimated in this study
E1	Pacific purple sea Urchin	Crustacean	LC_{50}:10 days	N.A	711	Martín et al. (2012)
	Fish	Fish	NOEC	6	N.A	Caldwell et al. (2012)
E3	Harpacticoida	Crustacean	EC_{50}	N.A	2.51	Martín et al. (2012)
	Fish	Fish	NOEC	60	N.A	Caldwell et al. (2012)
GP	Fish	Fish	NOEC	196,000	N.A	
AT	Fish	Fish	NOEC:100 days	10,000	N.A	
	Aquatic invertebrates	Crustacean	NOEC:100 days	10,000	N.A	
BPA	Aquatic species		NOEC	60	N.A	
NP	Aquatic species		NOEC	330	N.A	

EC50: Effective Concentration; LC50: Lethal Concentration; LOEC: Lowest Observed Effect Concentration; NOEC: No Observed Effect Concentration.

Fig. 6. The potential risks to aquatic organisms exposed to steroid estrogens from the liquid-fraction of manure. The risk quotient (RQ) is based on the measured environmental concentrations and predicted environmental concentrations in surface waters (minimum, median, and maximum) against the lowest predicted no effect concentration values of select steroid estrogen on target organisms. Risk categories applied were; insignificant risk (<0.01); low risk (0.01≤ RQs<0.1); medium risks (0.1 = RQ < 1), and high risk (RQs≥1).

3.3.2. Risks to vadose zone microbial communities

The calculated RQs of soil on the test species were <1, indicating insignificant ecological risk of SEs introduced through manure application. The highest RQ values correspond to maximum PECs on Pacific purple sea urchin; 17β-E2 (2.2) and E1 (19.3). Generally, the soil biota's ecological risks were not severe because the RQs did not exceed the risk threshold of the terrestrial invertebrates. The RQ of soil organisms was lower than those of aquatic organisms. Notably, the maximum PEC posed high risks to the test species, except for those exposed to E3. Similar observations were reported by Song et al. (2018) on ecological risk assessment of microbes exposed to livestock and poultry manure.

According to Zhou et al. (2020), the manure fertilizer application can introduce other micropollutants such as antibiotics and artificial hormones in farm soils. Several studies have reported the occurrence of free estrogens in the runoff after dairy manure application (Dyer et al., 2001), in streams close to grazing fields (Matthiessen et al., 2006), and in groundwater close to manure holding structures (Arnon et al., 2008; Song et al., 2018). Therefore, future risk assessments should include assays on the toxicities of SE mixtures with other micropollutants such as xenoestrogens and antibiotics to elucidate synergistic or antagonistic outcomes.

Immunocytochemistry and in-situ hybridization studies on the expression of alpha and beta receptors (ERα and ERβ) in *Podarcis sicula* during its annual breeding season showed that it's *Cauda* and *efferent ductules* expressed ERα and ERβ throughout the year on exposure to estrogens (Verderame et al., 2012). Verderame and Scudiero (2018) also reported that amphibians, fish, reptiles, and birds showed widespread ER in ducts and testicular cells. The two studies affirm that environmental estrogens may exert phylogenetically conserved consequences, but their physiological effects impact male reproductive processes. Finally, there has been little clarity on the relationship between structures and activities of ERα and ERβ ligands in steroid hormones. However, recent findings show that trace level compounds with similar structures to estrogens can activate ERα and ERβ receptors (Berggren et al., 2015; Leung et al., 2016; Maggiora, 2006; Tan et al., 2020). Molecular dynamic simulations and molecular docking predicted agonistic, antagonistic, or the mixed action of trace level EDCs; thus, confirming that estrogens pose risks at environmentally relevant levels (Tan et al., 2020).

3.4. Human health risks

The HQs of SEs through drinking surface water exposure were all <1. And the total median HQs of exposure to surface water and soil was <1. The median integrated exposure of the two pathways was 0.0002, also <1. These values indicate very low non-carcinogenic risks to human health and are within acceptable levels. Notably, the risks of oral uptake of soil through ingestion were higher with HQs >1 for the maximum PEC_{soil} of E1, 17α-E2, and 17β-E2. The HQs of maximum concentration of E1 in soil were higher than that of 17β-E2 by a magnitude of 22. Generally, the non-carcinogenic risks of surface water were within acceptable levels and did not pose health risks to children.

The non-carcinogenic health risks of surface water contaminated by effluents showed low risks. Based on the PECs in surface water, the

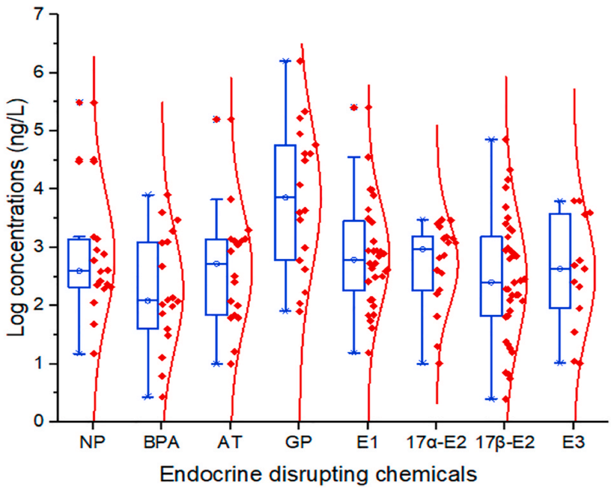

Fig. 7. Log concentration of estrogens in liquid fraction & select endocrine-disrupting chemicals in surface waters. Box-and-whisker plot showing estrogens and four xenoestrogens in surface water. The horizontal line in the box represents the median value, "□" represents the mean value and the lower and upper edges of the box represent the 25th and 75th percentiles, respectively. The whiskers extending from the top and bottom sides of the box represent the highest and lowest values. "◆" are the outlier values. NP; Nonylphenol, BPA; Bisphenol A; AT; Atrazine; GP; Glyphosate, E1; Estrone, 17α-E2; 17α-estradiol, 17β-E2; 17β-estradiol and E3; Estriol.

contamination levels fall within safe limits for children. However, the risks of soil ingestion are higher but present lower public health hazards because children's oral intake of agricultural soil is less likely to occur. Non-carcinogenic harm of estrogens in soil and effluents contaminated drinking water should not be assumed as falling within acceptable levels because of estrogen disruption potency at trace concentrations.

The current model used to assess human health risks is uncertain because it is based on PECs, PNECs, and cumulative assessment of individual estrogens without factoring EDCs mixtures in environmental matrices and other synergistic substances. The analysis also utilized chronic health impacts without considering the potential for acute toxicity associated with periodic peak concentrations. Numerous environmental estrogen risk assessments focus on the relationship with breast cancer (Ibarluzea et al., 2004; Moos et al., 2009; Treviño et al., 2015) and monitoring concentrations in drinking water and evaluating their threshold against ADIs or dietary intakes (Caldwell et al., 2010; Fan et al., 2013; Nie et al., 2014). Overall, most global studies showed that the estrogen concentration in drinking water is within acceptable risk levels. Similarly, this study predicted that surface water concentrations were below 10 ng/L, which does not surpass the USEPA, WHO, and EU limits (European Commission, 2003; Kuster et al., 2008). Admittedly, exposure to estrogen at negligible or low-risk levels can interfere with hormone signaling leading to endocrine system disruption through nuclear receptors. Numerous studies have reported that estrogen in drinking water can affect reproductive development (Birnbaum, 2010), contribute to menopause, lead to sperm count decline and males' feminization (Hopkinson et al., 1977; Li et al., 2013; Ström et al., 2004; Sumpter and Jobling, 2013). Nevertheless, despite estrogens' global footprint in water, environmental authorities and water resource managers rarely include estrogens and other EDCs from livestock farms in routine screening programs (Gee et al., 2015; Sim et al., 2011a; Wee and Aris, 2019). Similar findings have been reported in surface waters and soils contaminated by pharmaceuticals (Cha and Carlson, 2018; Drewes and Shore, 2001; Ramírez-Morales et al., 2021; Sim et al., 2011a; Wohde et al., 2016) and antibiotic resistance genes (Chen et al., 2015; Dungan et al., 2018; Heuer et al., 2011; Joy et al., 2014; Soni et al., 2015; Sui et al., 2012; Wen et al., 2019; Zhang et al., 2013). These observations highlight the prevailing risks and knowledge gaps on trace-level estrogens' potential human health risks from feedlot effluents into drinking water sources.

4. Implications and future perspectives

The presence of estrogens in livestock manure and their discharge or leakages into environmental matrices represent ubiquitous and persistent contamination globally. However, most studies have focused on the occurrence and risks of SEs in WWTPs and surface water (Adeel et al., 2017b; Du et al., 2020), whereas limited research is on animal husbandry sources (He et al., 2015). The global footprint of livestock and potential estrogen hotspots of SE contamination in most regions is a key concern because of associated endocrine disruption impacts. Although SEs have low environmental persistence, their ubiquitous state, pseudo-persistence, and estrogenic potency at trace concentrations necessitate holistic monitoring, control, and regulatory frameworks to protect organisms and human health.

Occurrence, fate, hazards, and mixture exposure assessment of manure-borne SEs need to be improved before the global ecological and human health risks can be assessed and mapped. Therefore, routine monitoring studies and regulatory limits of SE levels in manure and effluents are necessary, emphasizing toxicological tests and human health risk assessments. Future studies should also monitor SEs excretion by more miniature studied livestock such as goats, sheep, buffaloes, and horses. Their population has been increasing in recent decades and has footprints in most regions (Gilbert et al., 2018). Also, SEs are excreted in free and conjugated forms (Palme et al., 1996), but the latter have been rarely investigated; hence associated risks require quantification and inclusion in monitoring and risk assessment studies. Experiments of SEs risks to soil-dwelling species are necessary to identify hazards on terrestrial species based on manure application frequency and seasonality. Moreover, estrogens may have synergistic, antagonistic, agonist, or mixture outcomes determined by action with other xenoestrogen and contaminants; hence such action requires further investigation (Archer et al., 2020; Chen et al., 2007; Frische et al., 2009). Nonetheless, manure treatment and recognizing the need to monitor and remediate SEs in livestock effluents will reduce associated ecological and human health risks.

5. Conclusions

The study highlighted the global livestock footprint, manure-borne SEs concentration, predicted concentration in manure amended soils, and effluent contaminated surface water. Most of the data were from studies in the USA and China, with no available literature data from the Middle East and Africa. The total EEQs in the solid and liquid fractions of manure were predominated by 17β-E2, contributing 58.22% and 42.46%, respectively, and were ranked in the following order: 17β-E2>E1>17α-E2>E3. There were compulsive risks to fish from MECs in the liquid fractions. The RQ values of PECs are <1 for terrestrial organisms exposed to manure amended soils and aquatic organisms in contaminated surface water, indicating the low ecological concern, however, the maximum PEC of 17β-E2 and E1 representing the worst-case scenario, posed high risks to fish. Xenoestrogens (atrazine, glyphosate, NP and BPA) pose comparatively higher ecological risks on aquatic species than SEs in surface waters but within the same range as risks posed by feedlot effluents. Notably, maximum concentrations exhibited plausible risks to organisms and human health. Therefore, monitoring and controlling feedlot wastewater and manure disposal discharge is essential in reducing estrogens' potential risk in surface water and manure-amended soils. Given the limited monitoring data on manure-borne estrogens in literature, more studies are necessary to assess livestock's contribution to the burden of environmental estrogens. These results suggest that manure-borne estrogens' ecological and human health impact should not be ignored, and fate after manure application or effluent discharge into surface water requires further investigations. Finally, rigorous manure-borne estrogen monitoring and manure treatment are necessary to control SEs pollution and endocrine disruption risks.

Credit author statement

Fredrick Owino Gudda: Conceptualization, Methodology, Data curation and writing. Mohamed Ateia: Writing and Supervision. Michael Gatheru Waigi: Writing – review & editing. Jian Wang: Review & Visualization. Yanzheng Gao: Funding acquisition, review and Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the National Nature Science Foundation of China (41877125), National Science Fund for Distinguished Young Scholars (41925029), and M.A. is grateful for financial support by the Collaborative Water-Energy Research Center (CoWERC), supported by the Binational Industrial Research and Development Foundation under Energy Center grant EC-15.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jenvman.2021.113708.

Data availability

The data supporting the findings of this study are available within the article and in the supplementary files.

Box-and-whisker plots illustrating estrogens in manure. The horizontal line in the box represents the median value, and the lower and upper edges of the box represent the 25th and 75th percentiles, respectively. The whiskers extending from the top and bottom sides of the box represent the highest and lowest values. "*" is the outlier values, and "●" are the individual measured environmental concentrations. The distribution curve shows the scattering of all data points representing the concentrations.

References

Acosta, A., De los Santos-Montero, L.A., 2019. What is driving livestock total factor productivity change? A persistent and transient efficiency analysis. Glob. Food Sec. https://doi.org/10.1016/j.gfs.2019.06.001.

Adeel, M., Song, X., Wang, Y., Francis, D., Yang, Y., 2017a. Environmental impact of estrogens on human, animal and plant life: a critical review. Environ. Int. 99, 107–119. https://doi.org/10.1016/j.envint.2016.12.010.

Adeel, M., Song, X., Wang, Y., Francis, D., Yang, Y., 2017b. Environmental impact of estrogens on human, animal and plant life: a critical review. Environ. Int. 99, 107–119. https://doi.org/10.1016/j.envint.2016.12.010.

Andersen, H.R., Wollenberger, L., Halling-Sørensen, B., Kusk, K.O., 2001. Development of copepod nauplii to copepodites - a parameter for chronic toxicity including endocrine disruption. Environ. Toxicol. Chem. https://doi.org/10.1002/etc.5620201222.

Arcand-Hoy, L.D., Benson, W.H., 1998. FISH reproduction: an ecologically relevant indicator OF endocrine disruption. Environ. Toxicol. Chem. 17, 49. https://doi.org/10.1897/1551-5028(1998)017<0049:FRAERI>2.3.CO;2.

Archer, E., Wolfaardt, G.M., van Wyk, J.H., van Blerk, N., 2020. Investigating (anti) estrogenic activities within South African wastewater and receiving surface waters: implication for reliable monitoring. Environ. Pollut. https://doi.org/10.1016/j.envpol.2020.114424.

Arlos, M.J., Parker, W.J., Bicudo, J.R., Law, P., Hicks, K.A., Fuzzen, M.L.M., Andrews, S. A., Servos, M.R., 2018. Modeling the exposure of wild fish to endocrine active chemicals: potential linkages of total estrogenicity to field-observed intersex. Water Res. 139, 187–197. https://doi.org/10.1016/j.watres.2018.04.005.

Arnon, S., Dahan, O., Elhanany, S., Cohen, K., Pankratov, I., Gross, A., Ronen, Z., Baram, S., Shore, L.S., 2008. Transport of testosterone and estrogen from dairy-farm waste lagoons to groundwater. Environ. Sci. Technol. https://doi.org/10.1021/es800784m.

Atkinson, S.K., Marlatt, V.L., Kimpe, L.E., Lean, D.R.S., Trudeau, V.L., Blais, J.M., 2012. The occurrence of steroidal estrogens in south-eastern Ontario wastewater treatment plants. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv.2012.04.069.

aus der Beek, T., Weber, F.-A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., Küster, A., 2016. Pharmaceuticals in the environment-Global occurrences and perspectives. Environ. Toxicol. Chem. 35, 823–835. https://doi.org/10.1002/etc.3339.

Balaguer, P., François, F., Comunale, F., Fenet, H., Boussioux, A.M., Pons, M., Nicolas, J. C., Casellas, C., 1999. Reporter cell lines to study the estrogenic effects of xenoestrogens. In: Science of the Total Environment. https://doi.org/10.1016/S0048-9697(99)00178-3.

Barbosa, M.O., Moreira, N.F.F., Ribeiro, A.R., Pereira, M.F.R., Silva, A.M.T., 2016. Occurrence and removal of organic micropollutants: an overview of the watch list of EU Decision 2015/495. Water Res. 94, 257–279. https://doi.org/10.1016/j.watres.2016.02.047.

Barceló, D., Petrović, M., 2008. Emerging Contaminants from Industrial and Municipal Waste: Occurrence, Analysis and Effects. Springer.

Ben, W., Zhu, B., Yuan, X., Zhang, Y., Yang, M., Qiang, Z., 2018. Occurrence, removal and risk of organic micropollutants in wastewater treatment plants across China: comparison of wastewater treatment processes. Water Res. 130, 38–46. https://doi.org/10.1016/j.watres.2017.11.057.

Berggren, E., Amcoff, P., Benigni, R., Blackburn, K., Carney, E., Cronin, M., Deluyker, H., Gautier, F., Judson, R.S., Kass, G.E.N., Keller, D., Knight, D., Lilienblum, W., Mahony, C., Rusyn, I., Schultz, T., Schwarz, M., Schüürmann, G., White, A., Burton, J., Lostia, A.M., Munn, S., Worth, A., 2015. Chemical safety assessment using read-across: assessing the use of novel testing methods to strengthen the evidence base for decision making. Environ. Health Perspect. https://doi.org/10.1289/ehp.1409342.

Bergman, Å., Heindel, J., Jobling, S., Kidd, K., Zoeller, R.T., 2012. State-of-the-science of Endocrine Disrupting Chemicals. Toxicol. Lett. https://doi.org/10.1016/j.toxlet.2012.03.020, 2012.

Birnbaum, L.S., 2010. Endocrine Disrupting Chemicals in Drinking Water: Risks to Human Health and the Environment, pp. 1–177.

Caldwell, D.J., Mastrocco, F., Nowak, E., Johnston, J., Yekel, H., Pfeiffer, D., Hoyt, M., DuPlessie, B.M., Anderson, P.D., 2010. An assessment of potential exposure and risk from estrogens in drinking water. Environ. Health Perspect. 118, 338–344. https://doi.org/10.1289/ehp.0900654.

Caldwell, D.J., Mastrocco, F., Anderson, P.D., Länge, R., Sumpter, J.P., 2012. Predicted-no-effect concentrations for the steroid estrogens estrone, 17β-estradiol, estriol, and 17α-ethinylestradiol. Environ. Toxicol. Chem. 31, 1396–1406. https://doi.org/10.1002/etc.1825.

Capolupo, M., Díaz-Garduño, B., Martín-Díaz, M.L., 2018. The impact of propranolol, 17α-ethinylestradiol, and gemfibrozil on early life stages of marine organisms: effects and risk assessment. Environ. Sci. Pollut. Res. https://doi.org/10.1007/s11356-018-3185-6.

Cha, J., Carlson, K.H., 2018. Occurrence of β-lactam and polyether ionophore antibiotics in lagoon water and animal manure. Sci. Total Environ. 640–641, 1346–1353. https://doi.org/10.1016/j.scitotenv.2018.05.391.

Chen, P.J., Rosenfeldt, E.J., Kullman, S.W., Hinton, D.E., Linden, K.G., 2007. Biological assessments of a mixture of endocrine disruptors at environmentally relevant concentrations in water following UV/H2O2 oxidation. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv.2006.12.051.

Chen, B., Hao, L., Guo, X., Wang, N., Ye, B., 2015. Prevalence of antibiotic resistance genes of wastewater and surface water in livestock farms of Jiangsu Province, China. Environ. Sci. Pollut. Res. https://doi.org/10.1007/s11356-015-4636-y.

Combalbert, S., Hernandez-Raquet, G., 2010. Occurrence, fate, and biodegradation of estrogens in sewage and manure. Appl. Microbiol. Biotechnol. https://doi.org/10.1007/s00253-010-2547-x.

da Cunha, D., da Silva, S., Bila, D., da Mota Oliveira, J., de Novaes Sarcinelli, P., Larentis, A., 2016. Regulation of the synthetic estrogen 17α-ethinylestradiol in water bodies in Europe, the United States, and Brazil Regulamentação do estrogênio sintético 17α-etinilestradiol em matrizes aquáticas. Cad. Saúde Pública.

Damkjaer, K., Weisser, J.J., Msigala, S.C., Mdegela, R., Styrishave, B., 2018. Occurrence, removal and risk assessment of steroid hormones in two wastewater stabilization pond systems in Morogoro, Tanzania. Chemosphere 212, 1142–1154. https://doi.org/10.1016/j.chemosphere.2018.08.053.

Dangal, S.R.S., Tian, H., Zhang, B., Pan, S., Lu, C., Yang, J., 2017. Methane emission from global livestock sector during 1890–2014: magnitude, trends and spatiotemporal patterns. Global Change Biol. https://doi.org/10.1111/gcb.13709.

de Mes, T., Zeeman, G., Lettinga, G., 2005. Occurrence and fate of estrone, 17β-estradiol and 17α-ethynylestradiol in STPs for domestic wastewater. Rev. Environ. Sci. Bio/Technology 4, 275–311. https://doi.org/10.1007/s11157-005-3216-x.

Drewes, J.E., Shore, L.S., 2001. Concerns about pharmaceuticals in water reuse, groundwater recharge, and animal waste. ACS Symp. Ser. https://doi.org/10.1021/bk-2001-0791.ch012.

Du, B., Fan, G., Yu, W., Yang, S., Zhou, J., Luo, J., 2020. Occurrence and risk assessment of steroid estrogens in environmental water samples: a five-year worldwide perspective. Environ. Pollut. 267, 115405. https://doi.org/10.1016/j.envpol.2020.115405.

Dungan, R.S., McKinney, C.W., Leytem, A.B., 2018. Tracking antibiotic resistance genes in soil irrigated with dairy wastewater. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv.2018.04.020.

Dyer, a R., Raman, D.R., Mullen, M.D., Burns, R.T., Moody, L.B., Layton, A.C., Sayler, G. S., 2001. Determination of 17β-Estradiol Concentrations in Runoff from Plots Receiving Dairy Manure. Asae.

European Commission, 2003. Technical guidance document on risk assessment Part III in support of commission directive 93/67/EEC on risk assessment for new notified substances. Eur. Comm. Jt. Res. Cent. 337 https://doi.org/10.1002/mp.12308.

Fan, Z., Hu, J., An, W., Yang, M., 2013. Detection and occurrence of chlorinated byproducts of bisphenol a, nonylphenol, and estrogens in drinking water of China: comparison to the parent compounds. Environ. Sci. Technol. https://doi.org/10.1021/es401504a.

FAO, 2006. World Agriculture: towards 2030/2050 Prospects for Food, Nutrition, Agriculture and Major Commodity Groups. Fao 78.

Fekadu, S., Alemayehu, E., Dewil, R., Van der Bruggen, B., 2019. Pharmaceuticals in freshwater aquatic environments: a comparison of the African and European challenge. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv.2018.11.072.

Finlay-Moore, O., Hartel, P.G., Cabrera, M.L., 2000. 17β-Estradiol and testosterone in soil and runoff from grasslands amended with broiler litter. J. Environ. Qual. 29, 1604–1611. https://doi.org/10.2134/jeq2000.00472425002900050030x.

Frische, T., Faust, M., Meyer, W., Backhaus, T., 2009. Toxic masking and synergistic modulation of the estrogenic activity of chemical mixtures in a yeast estrogen screen (YES). Environ. Sci. Pollut. Res. https://doi.org/10.1007/s11356-009-0184-7.

Gadd, J.B., Tremblay, L.A., Northcott, G.L., 2010. Steroid estrogens, conjugated estrogens and estrogenic activity in farm dairy shed effluents. Environ. Pollut. https://doi.org/10.1016/j.envpol.2009.10.015.

Gall, H.E., Sassman, S.A., Jenkinson, B., Lee, L.S., Jafvert, C.T., 2014. Hormone loads exported by a tile-drained agroecosystem receiving animal wastes. Hydrol. Process. 28, 1318–1328. https://doi.org/10.1002/hyp.9664.

Gee, R.H., Rockett, L.S., Rumsby, P.C., 2015. Considerations of endocrine disrupters in drinking water. Endocrine Disruption and Human Health. https://doi.org/10.1016/B978-0-12-801139-3.00018-1.

Ghirardini, A., Grillini, V., Verlicchi, P., 2020. A review of the occurrence of selected micropollutants and microorganisms in different raw and treated manure – environmental risk due to antibiotics after application to soil. Sci. Total Environ. 707, 136118. https://doi.org/10.1016/j.scitotenv.2019.136118.

Gilbert, M., Nicolas, G., Cinardi, G., Van Boeckel, T.P., Vanwambeke, S.O., Wint, G.R.W., Robinson, T.P., 2018. Global distribution data for cattle, buffaloes, horses, sheep, goats, pigs, chickens and ducks in 2010. Sci. Data 5, 180227. https://doi.org/10.1038/sdata.2018.227.

Gray, J.L., Borch, T., Furlong, E.T., Davis, J.G., Yager, T.J., Yang, Y.-Y., Kolpin, D.W., 2017. Rainfall-runoff of anthropogenic waste indicators from agricultural fields applied with municipal biosolids. Sci. Total Environ. 580, 83–89. https://doi.org/10.1016/j.scitotenv.2016.03.033.

Gross-Sorokin, M.Y., Roast, S.D., Brighty, G.C., 2006. Assessment of feminization of male fish in English rivers by the environment agency of England and Wales. Environ. https://doi.org/10.1289/ehp.8068. Health Perspect.

Gudda, F.O., Waigi, M.G., Odinga, E.S., Yang, B., Carter, L., Gao, Y., 2020. Antibiotic-contaminated wastewater irrigated vegetables pose resistance selection risks to the gut microbiome. Environ. Pollut. https://doi.org/10.1016/j.envpol.2020.114752.

Hannah, R., D'Aco, V.J., Anderson, P.D., Buzby, M.E., Caldwell, D.J., Cunningham, V.L., Ericson, J.F., Johnson, A.C., Parke, N.J., Samuelian, J.H., Sumpter, J.P., 2009. Exposure assessment of 17α-ethinylestradiol in surface waters of the United States and Europe. Environ. Toxicol. Chem. https://doi.org/10.1897/08-622.1.

Hanselman, T.A., Graetz, D.A., Wilkie, A.C., 2003. Manure-borne estrogens as potential environmental contaminants: a review. Environ. Sci. Technol. 37, 5471–5478. https://doi.org/10.1021/es034410+.

Harries, J.E., Sheahan, D.A., Jobling, S., Matthiessen, P., Neall, P., Routledge, E.J., Rycroft, R., Sumpter, J.P., Tylor, T., 1996. A survey of estrogenic activity in United Kingdom inland waters. Environ. Toxicol. Chem. 15 https://doi.org/10.1897/1551-5028(1996)015<1993:ASOEAI>2.3.CO;2, 1993.

He, D., Ye, X., Xiao, Y., Zhao, N., Long, J., Zhang, P., Fan, Y., Ding, S., Jin, X., Tian, C., Xu, S., Ying, C., 2015. Dietary exposure to endocrine disrupting chemicals in metropolitan population from China: a risk assessment based on probabilistic approach. Chemosphere 139, 2–8. https://doi.org/10.1016/j.chemosphere.2015.05.036.

He, Y., Wang, T., Sun, F., Wang, L., Ji, R., 2019. Effects of veterinary antibiotics on the fate and persistence of 17β-estradiol in swine manure. J. Hazard Mater. 375, 198–205. https://doi.org/10.1016/j.jhazmat.2019.04.080.

Herrero, M., Thornton, P.K., 2010. Mixed crop livestock systems in the developing world: present and future. Adv. Anim. Biosci. 1, 481–482. https://doi.org/10.1017/S2040470010001019.

Heuer, H., Schmitt, H., Smalla, K., 2011. Antibiotic resistance gene spread due to manure application on agricultural fields. Curr. Opin. Microbiol. 14, 236–243. https://doi.org/10.1016/j.mib.2011.04.009.

Hirano, M., Ishibashi, H., Matsumura, N., Nagao, Y., Watanabe, N., Watanabe, A., Onikura, N., Kishi, K., Arizono, K., 2004. Acute toxicity responses of two Crustaceans, americamysis bahia and Daphnia magna, to endocrine disrupters. J. Health Sci. 50, 97–100. https://doi.org/10.1248/jhs.50.97.

Hopkinson, C.R.N., Mauss, J., Schenck, B., Fritze, E., Hirschhäuser, C., 1977. Some interrelationships between plasma levels of LH, FSH, oestradiol 17β, androgens and semen analysis data in male infertility patients. Andrologia. https://doi.org/10.1111/j.1439-0272.1977.tb01291.x.

Hotchkiss, A.K., Rider, C.V., Blystone, C.R., Wilson, V.S., Hartig, P.C., Ankley, G.T., Foster, P.M., Gray, C.L., Gray, L.E., 2008. Fifteen years after "wingspread" - environmental endocrine disrupters and human and wildlife health: where we are today and where we need to go. Toxicol. Sci. https://doi.org/10.1093/toxsci/kfn030.

Hutchinson, T.H., Pounds, N.A., Hampel, M., Williams, T.D., 1999. Impact of natural and synthetic steroids on the survival, development and reproduction of marine copepods (Tisbe battagliai). Sci. Total Environ. 233, 167–179. https://doi.org/10.1016/S0048-9697(99)00223-5.

Ibarluzea, J.M., Fernández, M.F., Santa-Marina, L., Olea-Serrano, M.F., Rivas, A.M., Aurrekoetxea, J.J., Expósito, J., Lorenzo, M., Torné, P., Villalobos, M., Pedraza, V., Sasco, A.J., Olea, N., 2004. Breast cancer risk and the combined effect of environmental estrogens. Cancer Causes Control. https://doi.org/10.1023/B:CACO.0000036167.51236.86.

Jobling, S., Nolan, M., Tyler, C.R., Brighty, G., Sumpter, J.P., 1998. Widespread sexual disruption in wild fish. Environ. Sci. Technol. 32, 2498–2506. https://doi.org/10.1021/es9710870.

Jobling, S., Williams, R., Johnson, A., Taylor, A., Gross-Sorokin, M., Nolan, M., Tyler, C. R., van Aerle, R., Santos, E., Brighty, G., 2006. Predicted exposures to steroid estrogens in U.K. Rivers correlate with widespread sexual disruption in wild fish populations. Environ. Health Perspect. 114, 32–39. https://doi.org/10.1289/ehp.8050.

Johnson, A.C., Williams, R.J., Matthiessen, P., 2006. The potential steroid hormone contribution of farm animals to freshwaters, the United Kingdom as a case study. Sci. Total Environ. 362, 166–178. https://doi.org/10.1016/j.scitotenv.2005.06.014.

Joy, S.R., Li, X., Snow, D.D., Gilley, J.E., Woodbury, B., Bartelt-Hunt, S.L., 2014. Fate of antimicrobials and antimicrobial resistance genes in simulated swine manure storage. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv.2014.02.027.

Kibambe, M.G., Momba, M.N.B., Daso, A.P., Van Zijl, M.C., Coetzee, M.A.A., 2020. Efficiency of selected wastewater treatment processes in removing estrogen compounds and reducing estrogenic activity using the T47D-KBLUC reporter gene assay. J. Environ. Manag. 260, 110135. https://doi.org/10.1016/j.jenvman.2020.110135.

Kidd, K.A., Paterson, M.J., Rennie, M.D., Podemski, C.L., Findlay, D.L., Blanchfield, P.J., Liber, K., 2014. Direct and indirect responses of a freshwater food web to a potent synthetic oestrogen. Philos. Trans. R. Soc. B Biol. Sci. 369, 20130578. https://doi.org/10.1098/rstb.2013.0578.

Kolodziej, E.P., Harter, T., Sedlak, D.L., 2004. Dairy wastewater, aquaculture, and spawning fish as sources of steroid hormones in the aquatic environment. Environ. Sci. Technol. https://doi.org/10.1021/es049585d.

Kolpin, D.W., Furlong, E.T., Meyer, M.T., Thurman, E.M., Zaugg, S.D., Barber, L.B., Buxton, H.T., 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. Streams, 1999−2000: a national reconnaissance. Environ. Sci. Technol. 36, 1202–1211. https://doi.org/10.1021/es011055j.

Kortenkamp, A., 2007. Ten years of mixing cocktails: a review of combination effects of endocrine-disrupting chemicals. Environ. Health Perspect. 115, 98–105. https://doi.org/10.1289/ehp.9357.

Kuster, M., López de Alda, M.J., Hernando, M.D., Petrovic, M., Martín-Alonso, J., Barceló, D., 2008. Analysis and occurrence of pharmaceuticals, estrogens, progestogens and polar pesticides in sewage treatment plant effluents, river water and drinking water in the Llobregat river basin (Barcelona, Spain). J. Hydrol. https://doi.org/10.1016/j.jhydrol.2008.05.030.

Lamb, J.C., Boffetta, P., Foster, W.G., Goodman, J.E., Hentz, K.L., Rhomberg, L.R., Staveley, J., Swaen, G., Van Der Kraak, G., Williams, A.L., 2014. Critical comments on the WHO-unep state of the science of endocrine disrupting chemicals - 2012. Regul. Toxicol. Pharmacol. https://doi.org/10.1016/j.yrtph.2014.02.002.

Lange, I.G., Daxenberger, A., Schiffer, B., Witters, H., Ibarreta, D., Meyer, H.H.D., 2002. Sex hormones originating from different livestock production systems: fate and potential disrupting activity in the environment. Anal. Chim. Acta 473, 27–37. https://doi.org/10.1016/S0003-2670(02)00748-1.

Le, T.A.H., Clemens, J., Nguyen, T.H., 2013. Performance of different composting techniques in reducing oestrogens content in manure from livestock in a Vietnamese setting. Environ. Monit. Assess. 185, 415–423. https://doi.org/10.1007/s10661-012-2563-7.

Lee Pow, C.S.D., Law, J. Mac, Kwak, T.J., Cope, W.G., Rice, J.A., Kullman, S.W., Aday, D. D., 2017. Endocrine active contaminants in aquatic systems and intersex in common sport fishes. Environ. Toxicol. Chem. 36, 959–968. https://doi.org/10.1002/etc.3607.

Leet, J.K., Lee, L.S., Gall, H.E., Goforth, R.R., Sassman, S., Gordon, D.A., Lazorchak, J.M., Smith, M.E., Jafvert, C.T., Sepúlveda, M.S., 2012. Assessing impacts of land-applied manure from concentrated animal feeding operations on fish populations and communities. Environ. Sci. Technol. 46, 13440–13447. https://doi.org/10.1021/es302599t.

Lei, K., Lin, C.-Y., Zhu, Y., Chen, W., Pan, H.-Y., Sun, Z., Sweetman, A., Zhang, Q., He, M.-C., 2020. Estrogens in municipal wastewater and receiving waters in the Beijing-Tianjin-Hebei region, China: occurrence and risk assessment of mixtures. J. Hazard Mater. 389, 121891. https://doi.org/10.1016/j.jhazmat.2019.121891.

Leung, M.C.K., Phuong, J., Baker, N.C., Sipes, N.S., Klinefelter, G.R., Martin, M.T., McLaurin, K.W., Woodrow Setzer, R., Darney, S.P., Judson, R.S., Knudsen, T.B., 2016. Systems toxicology of male reproductive development: profiling 774 chemicals for molecular targets and adverse outcomes. Environ. Health Perspect. https://doi.org/10.1289/ehp.1510385.

Li, W., Notani, D., Ma, Q., Tanasa, B., Nunez, E., Chen, A.Y., Merkurjev, D., Zhang, J., Ohgi, K., Song, X., Oh, S., Kim, H.S., Glass, C.K., Rosenfeld, M.G., 2013. Functional roles of enhancer RNAs for oestrogen-dependent transcriptional activation. Nature. https://doi.org/10.1038/nature12210.

Li, M., Zhao, X., Zhang, X., Wu, D., Leng, S., 2018. Biodegradation of 17β-estradiol by bacterial co-culture isolated from manure. Sci. Rep. https://doi.org/10.1038/s41598-018-22169-0.

Madikizela, L.M., Ncube, S., Chimuka, L., 2020. Analysis, occurrence and removal of pharmaceuticals in African water resources: a current status. J. Environ. Manag. 253, 109741. https://doi.org/10.1016/j.jenvman.2019.109741.

Maggiora, G.M., 2006. On outliers and activity cliffs - why QSAR often disappoints. J. Chem. Inf. Model. https://doi.org/10.1021/ci060117s.

Martín, J., Camacho-mu, D., Santos, J.L., Aparicio, I., Alonso, E., 2012. Occurrence of Pharmaceutical Compounds in Wastewater and Sludge from Wastewater Treatment Plants : Removal and Ecotoxicological Impact of Wastewater Discharges and Sludge Disposal, vol. 240, pp. 40–47. https://doi.org/10.1016/j.jhazmat.2012.04.068.

Matthiessen, P., Bifield, S., Jarrett, F., Kirby, M.F., Law, R.J., McMinn, W.R., Sheahan, D. A., Thain, J.E., Whale, G.F., 1998. An assessment of sediment toxicity in the River Tyne Estuary, UK by means of bioassays. Mar. Environ. Res. https://doi.org/10.1016/S0141-1136(96)00098-0.

Matthiessen, P., Arnold, D., Johnson, A.C., Pepper, T.J., Pottinger, T.G., Pulman, K.G.T., 2006. Contamination of headwater streams in the United Kingdom by oestrogenic hormones from livestock farms. Sci. Total Environ. 367, 616–630. https://doi.org/10.1016/j.scitotenv.2006.02.007.

Metson, G.S., Smith, V.H., Cordell, D.J., Vaccari, D.A., Elser, J.J., Bennett, E.M., 2014. Phosphorus is a key component of the resource demands for meat, eggs, and dairy production in the United States. Proc. Natl. Acad. Sci. Unit. States Am. 111, E4906–E4907. https://doi.org/10.1073/pnas.1417759111.

Metson, G.S., MacDonald, G.K., Haberman, D., Nesme, T., Bennett, E.M., 2016. Feeding the corn belt: opportunities for phosphorus recycling in U.S. Agriculture. Sci. Total Environ. 542, 1117–1126. https://doi.org/10.1016/j.scitotenv.2015.08.047.

Mirzaei, R., Mesdaghinia, A., Hoseini, S.S., Yunesian, M., 2019. Antibiotics in urban wastewater and rivers of Tehran, Iran: consumption, mass load, occurrence, and ecological risk. Chemosphere 221, 55–66. https://doi.org/10.1016/j.chemosphere.2018.12.187.

Moos, W.H., Dykens, J.A., Nohynek, D., Rubinchik, E., Howell, N., 2009. Review of the effects of 17α-estradiol in humans: a less feminizing estrogen with neuroprotective potential. Drug Dev. Res. https://doi.org/10.1002/ddr.20284.

Myers, J.P., Zoeller, R.T., vom Saal, F.S., 2009. A clash of old and new scientific concepts in toxicity, with important implications for public health. Environ. Health Perspect. 117, 1652–1655. https://doi.org/10.1289/ehp.0900887.

Nicolas, G., Robinson, T.P., Wint, G.R.W., Conchedda, G., Cinardi, G., Gilbert, M., 2016. Using Random Forest to improve the downscaling of global livestock census data. PloS One. https://doi.org/10.1371/journal.pone.0150424.

Nie, M., Yang, Y., Liu, M., Yan, C., Shi, H., Dong, W., Zhou, J.L., 2014. Environmental estrogens in a drinking water reservoir area in Shanghai: occurrence, colloidal contribution and risk assessment. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv.2013.12.010.

Palme, R., Fischer, P., Schildorfer, H., Ismail, M.N., 1996. Excretion of infused 14C-steroid hormones via faeces and urine in domestic livestock. Anim. Reprod. Sci. https://doi.org/10.1016/0378-4320(95)01458-6.

Paterakis, N., Chiu, T.Y., Koh, Y.K.K., Lester, J.N., McAdam, E.J., Scrimshaw, M.D., Soares, A., Cartmell, E., 2012. The effectiveness of anaerobic digestion in removing estrogens and nonylphenol ethoxylates. J. Hazard Mater. https://doi.org/10.1016/j.jhazmat.2011.10.075.

Pessoa, G.P., de Souza, N.C., Vidal, C.B., Alves, J.A.C., Firmino, P.I.M., Nascimento, R.F., dos Santos, A.B., 2014. Occurrence and removal of estrogens in Brazilian wastewater treatment plants. Sci. Total Environ. 490, 288–295. https://doi.org/10.1016/j.scitotenv.2014.05.008.

Pillon, A., Servant, N., Vignon, F., Balaguer, P., Nicolas, J.C., 2005. In vivo bioluminescence imaging to evaluate estrogenic activities of endocrine disrupters. Anal. Biochem. https://doi.org/10.1016/j.ab.2005.02.032.

Powers, S.M., Chowdhury, R.B., MacDonald, G.K., Metson, G.S., Beusen, A.H.W., Bouwman, A.F., Hampton, S.E., Mayer, B.K., McCrackin, M.L., Vaccari, D.A., 2019. Global opportunities to increase agricultural independence through phosphorus recycling. Earth's Future 7, 370–383. https://doi.org/10.1029/2018EF001097.

Prakash, A., Stigler, M., 2012. Food and Agriculture Organisation statistical year book 2012 world food and agriculture. FAO Stat. year B 198–213.

Raman, D.R., Layton, A.C., Moody, L.B., Easter, J.P., Sayler, G.S., Burns, R.T., Mullen, M. D., 2001. Degradation of estrogens in dairy waste solids: effects of acidification and temperature. Trans. Am. Soc. Agric. Eng. https://doi.org/10.13031/2013.7027.

Raman, D.R., Williams, E.L., Layton, A.C., Burns, R.T., Easter, J.P., Daugherty, A.S., Mullen, M.D., Sayler, G.S., 2004. Estrogen content of dairy and swine wastes. Environ. Sci. Technol. 38, 3567–3573. https://doi.org/10.1021/es0353208.

Ramírez-Morales, D., Masís-Mora, M., Beita-Sandí, W., Montiel-Mora, J.R., Fernández-Fernández, E., Méndez-Rivera, M., Arias-Mora, V., Leiva-Salas, A., Brenes-Alfaro, L., Rodríguez-Rodríguez, C.E., 2021. Pharmaceuticals in farms and surrounding surface water bodies: hazard and ecotoxicity in a swine production area in Costa Rica. Chemosphere 129574. https://doi.org/10.1016/j.chemosphere.2021.129574.

Reichert, G., Hilgert, S., Fuchs, S., Azevedo, J.C.R., 2019. Emerging contaminants and antibiotic resistance in the different environmental matrices of Latin America. Environ. Pollut. 255, 113140. https://doi.org/10.1016/j.envpol.2019.113140.

Ribeiro, C., Tiritan, M.E., Rocha, E., Rocha, M.J., 2009. Seasonal and spatial distribution of several endocrine-disrupting compounds in the douro river estuary, Portugal. Arch. Environ. Contam. Toxicol. 56, 1–11. https://doi.org/10.1007/s00244-008-9158-x.

Schultz, M.M., Minarik, T.A., Martinovic-Weigelt, D., Curran, E.M., Bartell, S.E., Schoenfuss, H.L., 2013. Environmental estrogens in an urban aquatic ecosystem: II. Biological effects. Environ. Int. 61, 138–149. https://doi.org/10.1016/j.envint.2013.08.006.

Shore, L.S., Harel-Markowitz, E., Gurevich, M., Shemesh, M., 1993. Factors affecting the concentration of testosterone in poultry litter. J. Environ. Sci. Heal. . Part A Environ. Sci. Eng. Toxicol. 28, 1737–1749. https://doi.org/10.1080/10934529309375974.

Sim, W.-J., Lee, J.-W., Lee, E.-S., Shin, S.-K., Hwang, S.-R., Oh, J.-E., 2011a. Occurrence and distribution of pharmaceuticals in wastewater from households, livestock farms, hospitals and pharmaceutical manufactures. Chemosphere 82, 179–186. https://doi.org/10.1016/j.chemosphere.2010.10.026.

Sim, W.-J., Lee, J.-W., Shin, S.-K., Song, K.-B., Oh, J.-E., 2011b. Assessment of fates of estrogens in wastewater and sludge from various types of wastewater treatment plants. Chemosphere 82, 1448–1453. https://doi.org/10.1016/j.chemosphere.2010.11.045.

Snow, D.D., Bartelt-Hunt, S.L., Devivo, S., Saunders, S., Cassada, D.A., 2009. Detection, occurrence, and fate of emerging contaminants in agricultural environments. Water Environ. Res. https://doi.org/10.2175/106143009x461573.

Song, X., Wen, Y., Wang, Y., Adeel, M., Yang, Y., 2018. Environmental risk assessment of the emerging EDCs contaminants from rural soil and aqueous sources: analytical and modelling approaches. Chemosphere 198, 546–555. https://doi.org/10.1016/j.chemosphere.2018.01.060.

Soni, B., Bartelt-Hunt, S.L., Snow, D.D., Gilley, J.E., Woodbury, B.L., Marx, D.B., Li, X., 2015. Narrow grass hedges reduce tylosin and associated antimicrobial resistance genes in agricultural runoff. J. Environ. Qual. https://doi.org/10.2134/jeq2014.09.0389.

Stasinakis, A.S., Thomaidis, N.S., Arvaniti, O.S., Asimakopoulos, A.G., Samaras, V.G., Ajibola, A., Mamais, D., Lekkas, T.D., 2013. Contribution of primary and secondary treatment on the removal of benzothiazoles, benzotriazoles, endocrine disruptors, pharmaceuticals and perfluorinated compounds in a sewage treatment plant. Sci. Total Environ. 463–464, 1067–1075. https://doi.org/10.1016/j.scitotenv.2013.06.087.

Ström, A., Hartman, J., Foster, J.S., Kietz, S., Wimalasena, J., Gustafsson, J.Å., 2004. Estrogen receptor β inhibits 17β-estradiol-stimulated proliferation of the breast cancer cell line T47D. Proc. Natl. Acad. Sci. U. S. A. https://doi.org/10.1073/pnas.0308319100.

Sui, Q., Wang, B., Zhao, W., Huang, J., Yu, G., Deng, S., Qiu, Z., Lu, S., 2012. Identification of priority pharmaceuticals in the water environment of China. Chemosphere 89, 280–286. https://doi.org/10.1016/j.chemosphere.2012.04.037.

Sumpter, J.P., Jobling, S., 2013. The occurrence, causes, and consequences of estrogens in the aquatic environment. Environ. Toxicol. Chem. https://doi.org/10.1002/etc.2084.

Tan, H., Wang, X., Hong, H., Benfenati, E., Giesy, J.P., Gini, G.C., Kusko, R., Zhang, X., Yu, H., Shi, W., 2020. Structures of endocrine-disrupting chemicals determine binding to and activation of the estrogen receptor α and androgen receptor. Environ. Sci. Technol. acs.est., 0c02639 https://doi.org/10.1021/acs.est.0c02639.

Tapiero, H., Nguyen Ba, G., Tew, K.D., 2002. Estrogens and Environmental Estrogens. Biomed. Pharmacother. https://doi.org/10.1016/S0753-3322(01)00155-X.

Testai, E., Galli, C.L., Dekant, W., Marinovich, M., Piersma, A.H., Sharpe, R.M., 2013. A plea for risk assessment of endocrine disrupting chemicals. Toxicology. https://doi.org/10.1016/j.tox.2013.07.018.

Tiedeken, E.J., Tahar, A., McHugh, B., Rowan, N.J., 2017. Monitoring, sources, receptors, and control measures for three European Union watch list substances of emerging concern in receiving waters – a 20 year systematic review. Sci. Total Environ. 574, 1140–1163. https://doi.org/10.1016/j.scitotenv.2016.09.084.

Tran, N.H., Reinhard, M., Gin, K.Y.-H., 2018. Occurrence and fate of emerging contaminants in municipal wastewater treatment plants from different geographical regions-a review. Water Res. 133, 182–207. https://doi.org/10.1016/j.watres.2017.12.029.

Treviño, L.S., Wang, Q., Walker, C.L., 2015. Hypothesis: activation of rapid signaling by environmental estrogens and epigenetic reprogramming in breast cancer. Reprod. Toxicol. https://doi.org/10.1016/j.reprotox.2014.12.014.

US EPA, 2009. Risk assessment guidance for superfund volume I: human health evaluation manual (Part F, supplemental guidance for inhalation risk assessment). Off. Superfund Remediat. Technol. Innov. Environ. Prot. Agency I, 1–68.

US EPA, 2011. Exposure Factors Handbook: 2011 Edition. U.S. Environ. Prot. Agency EPA/600/R-, 1–1466 https://doi.org/EPA/600/R-090/052F.

Valdés, M.E., Marino, D.J., Wunderlin, D.A. lbert, Somoza, G.M. anue, Ronco, A.E. stel, Carriquiriborde, P., 2015. Screening concentration of E1, E2 and EE2 in sewage effluents and surface waters of the "Pampas" region and the "Río de la Plata" estuary (Argentina). Bull. Environ. Contam. Toxicol. 94, 29–33. https://doi.org/10.1007/s00128-014-1417-0.

Välitalo, P., Perkola, N., Seiler, T.-B., Sillanpää, M., Kuckelkorn, J., Mikola, A., Hollert, H., Schultz, E., 2016. Estrogenic activity in Finnish municipal wastewater effluents. Water Res. 88, 740–749. https://doi.org/10.1016/j.watres.2015.10.056.

van Aerle, R., Nolan, M., Jobling, S., Christiansen, L.B., Sumpter, J.P., Tyler, C.R., 2001. Sexual disruption in a second species of wild cyprinid fish (the gudgeon, Gobio gobio) in United Kingdom freshwaters. Environ. Toxicol. Chem. https://doi.org/10.1002/etc.5620201225.

Vandenberg, L.N., Colborn, T., Hayes, T.B., Heindel, J.J., Jacobs, D.R., Lee, D.H., Myers, J.P., Shioda, T., Soto, A.M., vom Saal, F.S., Welshons, W.V., Zoeller, R.T., 2013. Regulatory decisions on endocrine disrupting chemicals should be based on the principles of endocrinology. Reprod. Toxicol. https://doi.org/10.1016/j.reprotox.2013.02.002.

Verderame, M., Scudiero, R., 2018. A comparative review on estrogen receptors in the reproductive male tract of non mammalian vertebrates. Steroids. https://doi.org/10.1016/j.steroids.2018.04.00.

Verderame, M., Angelini, F., Limatola, E., 2012. Expression of estrogen receptor alpha switches off secretory activity in the epididymal channel of the lizard Podarcis sicula. Mol. Reprod. Dev. https://doi.org/10.1002/mrd.22005.

Villemur, R., Cunha dos Santos, S.C., Ouellette, J., Juteau, P., Lépine, F., Déziel, E., 2013. Biodegradation of endocrine disruptors in solid-liquid two-phase partitioning systems by enrichment cultures. Appl. Environ. Microbiol. https://doi.org/10.1128/AEM.01239-13.

Wang, J., Odinga, E.S., Zhang, W., Zhou, X., Yang, B., Waigi, M.G., Gao, Y., 2019. Polyaromatic hydrocarbons in biochars and human health risks of food crops grown in biochar-amended soils: a synthesis study. Environ. Int. 130, 104899. https://doi.org/10.1016/j.envint.2019.06.009.

Wee, S.Y., Aris, A.Z., 2019. Occurrence and Public-Perceived Risk of Endocrine Disrupting Compounds in Drinking Water. Npj Clean Water. https://doi.org/10.1038/s41545-018-0029-3.

Welshons, W.V., Thayer, K.A., Judy, B.M., Taylor, J.A., Curran, E.M., vom Saal, F.S., 2003. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. Environ. Health Perspect. https://doi.org/10.1289/ehp.5494.

Wen, X., Mi, J., Wang, Y., Ma, B., Zou, Y., Liao, X., Liang, J.B., Wu, Y., 2019. Occurrence and contamination profiles of antibiotic resistance genes from swine manure to receiving environments in Guangdong Province southern China. Ecotoxicol. Environ. Saf. https://doi.org/10.1016/j.ecoenv.2019.02.023.

Wohde, M., Berkner, S., Junker, T., Konradi, S., Schwarz, L., Düring, R.A., 2016. Occurrence and transformation of veterinary pharmaceuticals and biocides in manure: a literature review. Environ. Sci. Eur. https://doi.org/10.1186/s12302-016-0091-8.

Xu, P., Zhou, X., Xu, D., Xiang, Y., Ling, W., Chen, M., 2018. Contamination and risk assessment of estrogens in livestock manure: a case study in Jiangsu province, China. Int. J. Environ. Res. Publ. Health 15, 125. https://doi.org/10.3390/ijerph15010125.

Ying, G.G., Kookana, R.S., Ru, Y.J., 2002. Occurrence and fate of hormone steroids in the environment. Environ. Int. https://doi.org/10.1016/S0160-4120(02)00075-2.

Zhang, H., Cui, D., Wang, B., Han, Y.H., Balimane, P., Yang, Z., Sinz, M., Rodrigues, A.D., 2007. Pharmacokinetic drug interactions involving 17α-ethinylestradiol: a new look at an old drug. Clin. Pharmacokinet. https://doi.org/10.2165/00003088-200746020-00003.

Zhang, Y., Zhang, C., Parker, D.B., Snow, D.D., Zhou, Z., Li, X., 2013. Occurrence of antimicrobials and antimicrobial resistance genes in beef cattle storage ponds and swine treatment lagoons. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv.2013.06.016.

Zhang, Q., Zhao, J.-L., Ying, G.-G., Liu, Y.-S., Pan, C.-G., 2014. Emission estimation and multimedia fate modeling of seven steroids at the river basin scale in China. Environ. Sci. Technol. 48, 7982–7992. https://doi.org/10.1021/es501226h.

Zhao, L., Dong, Y.H., Wang, H., 2010. Residues of veterinary antibiotics in manures from feedlot livestock in eight provinces of China. Sci. Total Environ. 408, 1069–1075. https://doi.org/10.1016/j.scitotenv.2009.11.014.

Zhao, Z., Knowlton, K.F., Love, N.G., Ogejo, J.A., 2010. Estrogen removal from. DAIRY MANURE BY PILOT-SCALE TREATMENT REACTORS 53, 1295–1301.

Zhou, X., Wang, J., Lu, C., Liao, Q., Gudda, F.O., Ling, W., 2020. Antibiotics in animal manure and manure-based fertilizers: occurrence and ecological risk assessment. Chemosphere 255, 127006. https://doi.org/10.1016/j.chemosphere.2020.127006.

Zoeller, R.T., Vandenberg, L.N., 2015. Assessing dose–response relationships for endocrine disrupting chemicals (EDCs): a focus on non-monotonicity. Environ. Heal. 14, 42. https://doi.org/10.1186/s12940-015-0029-4.