

Review

An Overview of the Glucocorticoids' Pathways in the Environment and Their Removal Using Conventional Wastewater Treatment Systems

Munshi Md. Shafwat Yazdan ^{1,*}, Md Tanvir Ahad ^{2,*}, Zayed Mallick ³, Synthia Parveen Mallick ⁴, Ishrat Jahan ⁵ and Mozammel Mazumder ⁶

¹ Civil and Environmental Engineering, Idaho State University, Pocatello, ID 83209, USA

² School of Aerospace and Mechanical Engineering, University of Oklahoma, Norman, OK 73019, USA

³ Environmental Science and Management, North South University, Dhaka 1230, Bangladesh; Zayed.mallick@northsouth.edu

⁴ Civil, Construction and Environmental Engineering, Marquette University, Milwaukee, WI 53233, USA; synthiaparveen.mallick@marquette.edu

⁵ Computer Science Engineering, East West University, Dhaka 1212, Bangladesh; arnajahan00@gmail.com

⁶ School of Chemical and Biomolecular Engineering, University of Notre Dame, Notre Dame, ID 46556, USA; mmazumde@nd.edu

* Correspondence: yazdmuns@isu.edu (M.M.S.Y.); Md.Tanvir.Ahad-1@ou.edu (M.T.A.)



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Abstract: Numerous micropollutants, especially endocrine-disrupting compounds (EDCs), can pollute natural aquatic environments causing great concern for human and ecosystem health. While most of the conversation revolves around estrogen and androgen, glucocorticoids (GCs) are also prevalent in natural waters. Despite the fact that GCs play a crucial role in both inflammatory and immunologic development activities, they are also detected in natural waters and considered as one of the EDCs. Although many researchers have mentioned the adverse effect of GCs on aquatic organisms, a complete management technology to remove these pollutants from surface and coastal waters is yet to be established. In the current study, six glucocorticoids (prednisone, prednisolone, cortisone, cortisol, dexamethasone, and 6R-methylprednisolone) have been selected according to their higher detection frequency in environmental waters. The concentration of selected GCs ranged from 0.05 ng/L to 433 ng/L and their removal efficiency ranged from 10% to 99% depending on the water source and associated removal technologies. Although advanced technologies are available for achieving successful removal of GCs, associated operational and economic considerations make implementation of these processes unsustainable. Further studies are necessary to resolve the entry routes of GCs compounds into the surface water or drinking water permanently as well as employ sustainable detection and removal technologies.

Keywords: endocrine disrupting compounds; hormones; glucocorticoids; environmental and health impact; wastewater treatment plant; micropollutants

1. Introduction

In the past few decades, thousands of endocrine-disrupting compounds (EDCs) entered into the water cycle through different ways [1–4]. According to EPA, endocrine-disrupting chemicals (EDCs), which can be both natural and synthetic substances in our environment, are typically pharmaceutical and personal care products (PPCPs) and foods that interfere with hormone biosynthesis and metabolism resulting in a deviation from normal homeostatic control or reproduction [5]. Humans and animals are exposed primarily through ingestion of contaminated foods (e.g., fish, meat, and dairy products) [6]. Incidentally, steroid and hormone mimics have also been addressed among chemicals (natural or synthetic) used for preparing and preserving foods [7,8]. Processed and packaged foods (Finnish foods mostly meat and fish, tinned food, infant formula etc.) can accumulate the

traces of EDCs that leaching out of materials used in assembling, processing, transporting, and storage [9–11].

Discharge of hospital waste, household sewage, agricultural and industrial waste, husbandry waste, and usually inadequate removal in many wastewaters treatment plants (WWTPs) are the most common sources for EDC's hazardous presence in the environment [12–20]. It is worthwhile to note that primary and secondary treatments target organic matter, carbon, nutrients removal which are generally 10^6 times higher in concentration in a typical wastewater compared to GCs. Therefore, GCs would be outcompeted by carbon or nutrients in primary and secondary treatments and employment of tertiary treatment for removal of GCs would be more effective. Several studies have reported and mentioned that chronic exposure to these chemicals or compounds can cause exotic and unanticipated side effects [4,12–15]. Despite being warned of in the past few years, EDCs still were not considered as a priority pollutant that would require mandatory removal from wastewater. Currently adopted treatment processes in WWTPs unfortunately are generally not successful in eliminating EDCs completely [2,3]. Moreover, identification of these compounds is challenging in a conventional WWTP as they are present at a very low concentration, typically at the range of ng/L [16]. Researchers have introduced new analytical techniques for EDCs detection. As a result, recently published works focused on detection of EDCs in natural waters, and a lot of evidence and examples suggest that the impact of EDCs on aquatic wildlife and human is very concerning [12,16–18]. There has been a shift towards more awareness regarding the presence of EDCs in the environmental waters and their associated impacts [19]. Moreover, steroid hormones have also attracted increased concerns, such as EDCs [14,16]. Although estrogen and androgen have occupied most of the debate, glucocorticoid (GCs) have become a major concern due to their detection in the environment [1,21,22]. It is reported that the amount of excretion masses of natural and synthetic GCs is quite a bit higher than estrogen and androgen [23,24]. Considering the usage of GCs to be of both synthetic and natural sources, the existence and fate of these compounds in the environment requires greater consideration.

Natural GCs, such as cortisol, cortisone and other metabolites are linked with the control of energy supply, suppress the responses to inflammation and infection in vertebrates [25]. On the other hand, synthetic GCs (prednisone, prednisolone, dexamethasone, and 6R-methylprednisolone) have been used greatly in human and muscle size in animals [26]. GCs can be classified into five groups on the basis of their structure: hydrocortisone, acetoneide, betamethasone, halogenated and prodrug esters [27–29]. Therefore, a large volume of GCs (both natural and synthetic) may be released into surface water through the effluent of sewage treatment plants (STPs) or runoff and become a major potential warning for the aquatic environments [30].

Livestock manure carries several organic contaminants; mostly steroids such as GCs, and their fates in the course of composting are still undetermined. For an example, the amount of synthetic glucocorticoid prednisolone detected in feces ranged from (3.0 to 32.0 ng/g), in flush water (88.6 to 1390 ng/L), and suspended particles (8.0 to 42.6 ng/g) respectively [31,32]. On the other hand, detection amount of dexamethasone in the flush water and suspended particles was about 260 ± 27.9 ng/L and 35.0 ± 5.1 ng/g, respectively [33].

The principal use of GCs is for inflammation treatment of asthma, skin issue and joint pain problems [24,34–36]. GCs are also being used in significant amounts in many personal care products, like creams and lotions for face and body skin related issues [37–42]. Hence, a significant amount of natural and synthetic GCs may be drained into nearby surface water and finally infiltrate into ground water [30]. As a result of inadequate removal from WWTPs, GC activity has been demonstrated in 27% of surface water samples ($n = 115$) collected in more than 14 states in the US, more than 10 countries in Europe, and many riverine areas of China, Japan, Australia, etc. [40,43–45].

GC compounds can severely damage the reproduction of both domestic and wild animals, leading to sexual abnormalities, intersex development, reduced sperm counts, decreased fertility rate, and hormone-dependent cancer in humans [20,22,24,34,40]. There is a growing concern that aquatic organisms are in great danger due to the abundance of GCs in the environment. In this study, we have investigated the pathways for GCs'

introduction into environmental waters and consequences of along with the removal of GCs in conventional wastewater treatment processes. This review included literature published from different scientific databases and publishers including Google Scholar, ScienceDirect, Elsevier, Springer, Scopus, NCBI, and NIH. The search item included: glucocorticoids (GCs), hormone (GCs) removal, micro pollutant removal, removal of GCs from wastewater, steroidal hormones, and removal efficiency of GCs as the search keywords.

2. Properties of Frequently Found Glucocorticoids in Water

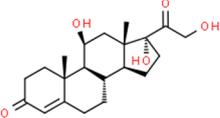
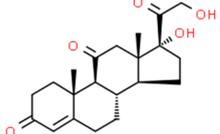
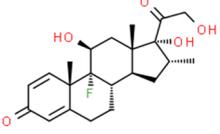
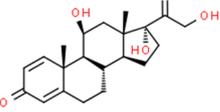
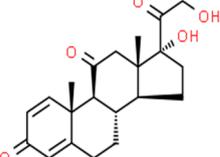
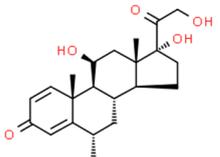
Some natural and synthetic GCs from different sources of waste disrupt the normal activities of the endocrine glands [25,45–49]. Some of these GCs adversely affect the growth and production of fish and plants [4,22,45,49]. GCs are categorized into five structural groups: acetonide, hydrocortisone, betamethasone, halogenated and labile pro-drug esters [28–30,50]. Natural and synthetic glucocorticoids hormones: betamethasone, betamethasone D5, budesonide, clobetasol, clobetasol propionate, clobetasol propionate, corticosterone, cortisone, cyproterone acetate, desonide, dexamethasone, dexamethasone-21-acetate, DMS, flumetasone, fluorometholone, fluticasone propionate, halometasone, hydrocortisone (cortisol), hydroxycortisol, medroxyprogesterone, megestrol, megestrol acetate, methylprednisolone, 6 α -mifepristone, prednisolone, prednisone, prednisone, triamcinolone acetonide, triamcinolone acetonide and many more [51–65]. Among them, six of the most frequently found GCs in water—cortisol, cortisone, dexamethasone, prednisolone, prednisone, and 6 α -methylprednisolone—were considered in this review [36].

The human body employs natural GCs as a vital part of the feedback mechanism to reduce inflammation [66,67]. Synthetic glucocorticoids, sometime known as exogenous GCs are used to treat different diseases caused by an overactive immune system [66–71]. Common diseases like asthma, allergies, both human and animal autoimmune diseases as well as sepsis are some of the examples of conditions caused by an overactive immune system [21,72–77]. In typical wastewater, these compounds are present at a lower concentration (ng/L) which is generally 10^6 times lower than carbon or nutrients content of wastewater. The degradation of micropollutant can be classified into four categories, e.g., easily degradable, moderately degradable, poorly and very poorly degradable. Removal of these GCs compounds in wastewater treatment plants (WWTPs) has been extensively studied and the scientists has considered biological treatment technology as critical to micropollutant removal [78]. Biological wastewater treatments have to consider some factors regarding micropollutant removal, such as solid retention time (SRT) [79,80] pH, hydraulic retention time (HRT) [81], nitrification [82,83] redox conditions [84,85], suspended/attached growth [86], and heterotrophic activity [87]. Although the main driving factor for the permanently biological micropollutant removal at WWTPs is still unknown [88]. The reason behind this issue can be some critical parameters being unknown or the degradation of different micropollutants having different structures in mixed micropollutant groups. Hence, due to competition between the targeted compounds, a conventional WWTP generally cannot remove micropollutants effectively which eventually poses a threat to aquatic beings once they are released into the receiving waterbodies with the treated wastewater effluent [89–91].

GCs have a tetra cyclic structure: three cyclohexane rings as well as cyclopentane rings [92,93]. Although natural and synthetic GCS have different cyclic networks, they have some common ring networks all around their physical properties (Table 1) [94]. To predict their occurrence and fate into the natural and engineered scientific environment, physical and chemical characteristics of GCs compounds need to be considered. GCs do not dissolve well in water [89]. Octanol–water partition coefficient (K_{ow}) is a partition coefficient defined as a ratio of dissolving a chemical compound in octanol phase and concentration in water of aqueous phase at a specific temperature mostly under the equilibrium conditions [95–99]. K_{ow} value represents the absorption and dissolution of any compounds [76,77,100]. Although dispersion of GCs between aqueous solution and natural surroundings is always relative in nature, octanol-water partition coefficient is a good

choice for solubility characterization [95,96]. From Table 1, the log of K_{ow} for frequently found GCs compounds is in the range of 1.4–3.5 [89,91,94,101]. Although comparing with some of the estrogens (e.g., 17 α -ethinylestradiol (3.67–4.15) [102,103], 17 β -estradiol (3.94–4.01) [102,103], estrone (2.45–3.43) [102,103], estriol (2.55–2.81) [102,103], the K_{ow} values of GCs are moderately low. This range means that, GCs compounds hydrophilicity is moderate, and they tend to be predominantly distributed which means they tend to adsorb onto solid surface in the solid waste environments [95,98]. A considerable number of total GCs released by humans and animals are in the form of conjugated metabolites in their urine [98]. Although the polar conjugates are inactive biologically, their solubility is higher compared to those not conjugated [101].

Table 1. Properties of six frequently found glucocorticoids (GCs) in water.

Compounds	CAS	Molecular Weight (g/mole)	log K_{ow}	Formula	Structure
Cortisol	152-58-9	362.5	3.5	$C_{21}H_{30}O_5$	
Cortisone	53-06-5	360.4	1.5	$C_{21}H_{28}O_5$	
Dexamethasone	50-02-2	392.5	1.8	$C_{22}H_{29}FO_5$	
Prednisolone	53-03-2	360.5	1.6	$C_{21}H_{28}O_5$	
Prednisone	50-24-8	358.4	1.4	$C_{21}H_{28}O_5$	
6 α -methylprednisolone	83-43-2	374.5	2.0	$C_{22}H_{30}O_5$	

3. Glucocorticoids' Sources and Pathways in Environment

There are two major ways for GCs to get into the environment. It can enter natural environment firstly, through point sources (for an example, WWTPs) and secondly, non-point sources (such as agricultural runoff) [104–107]. Glucocorticoids are generally used in veterinary medicine to recover or reconstruct muscle strength as well as muscle growth and development in animals [95]. As a result, a huge portion of glucocorticoids, excreted mainly by mammals' urine, is considered to be discharged into the aquatic environment. These compounds are released into the environment through STPs effluent, seasonal wet runoff, and thus contribute as potential pollutants in the environment [96]. A mixture of GCs has been detected in drinking water which were then tracked back to the source

river water used as the influent for the drinking water treatment process [106]. Presence of GCs was detected in both the influent and effluent (ending in the water supply systems and tap water) of the drinking water processes in those cases [107]. Table 2 shows all the targeted GCs found in wastewater in different countries which eventually end up in natural waterbodies due to lack of effective treatment of GCs in wastewater. As stated above, not only human, but also animal, wastes are the primary sources of GCs in aquatic environments. Both treated solid and liquid wastes are recognized as potential pathways for these compounds to make their way into the environment [108–112]. Figure 1 shows the contamination of the different parts of the environment due to the GCs.

Table 2. Environmental and health impact of glucocorticoids.

Compounds	Effluent Concentration (ng/L)	Toxicity and Impacts	Sources	References
Prednisolone or beclomethasone	0.7–1.7	Studies showed a significant increase of plasma glucose levels in fathead minnow; also number of leukocytes in the peripheral blood was decreased and fold changed in the transcripts of more genes.	Europe: United Kingdom, The Netherlands, Spain, Switzerland, Hungary, Wastewater in France, Hospital Wastewater in Netherlands, Surface water in Spain, (Czech and Slovak republics Sewage and River water)	[13,113–115]
Cortisol	100–145	It was reported that cortisol suppress immune function in fish. The exposure of zebrafish to cortisol (145 ng/L) could cause the accelerated hatching, increased significant level of heart rate, deteriorate the muscle contractions, and genetic expression changes.	Asia: Japan (Ehime Prefecture), China (Sewage Treatment Plants (STPs) and Receiving River Waters Beijing), India, Malaysia,	[21,55,77,115–117]
Dexamethasone (Betamethasone)	>0.1–1.7	Dexamethasone or betamethasone affected adversely on the reproduction, growth, and development in fathead minnow (<i>Pimephales promelas</i>); this could affect the development, reproduction, growth and mRNA expression of amphibians and fish.	Oceania: Australia (River water and municipal sewage)	[20,26,118–122]
Prendnisone	0.2–100	Several stuies have showed that the presense of prendnisone made increase of se rum free amino acid levels significantly in common carp (<i>Cyprinus carpio</i>), morphological changes with swimming behavior, and adverse effects on physiology of zebrafish at the exposure concentration of 100 ng/L.	New Zealand: New Zealand (municipal sewage)	[23,42,123,124]

Table 2. Cont.

Compounds	Effluent Concentration (ng/L)	Toxicity and Impacts	Sources	References
Cortisone	1.3–433	It has been reported that unlike cortisol, unexpected exposure (91 ng/L) could cause the accelerated hatching, increased significant level of heart rate, deteriorate the muscle contractions, and genetic expression changes in Zebra fish	North America: USA, Drinking water in Canada, Mexico.	[58,116,120,124,125]
6 α -methylprednisolone	60–91	Serum free amino acid levels was increased in common carp (<i>Cyprinus carpio</i>) due to 6 α -methylprednisolone.	South America: Wastewater in Uruguay and Brazil, shallow lakes system Argentina	[113,115,123,124]

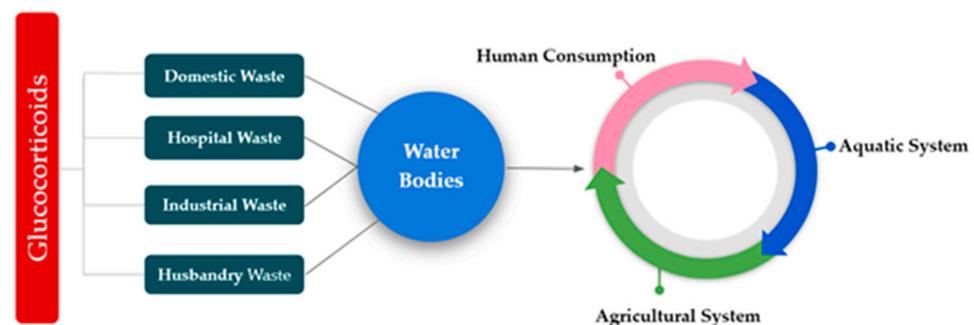


Figure 1. Fate of glucocorticoids (GCs) in different sectors of the environment.

4. Adverse Effects of Glucocorticoids' in Natural Environment

The adverse effects GCs' due to the discharge of effluents from WWTPs to the aquatic environments are affected by several factors including effluent volume, the concentration of the targeted compounds in wastewater, the water flow rate of the receiving river, meteorological or climate conditions, and probably some other factors that affect dissipation through dilution and/or degradation. Table 2 summarizes all the findings collected from the respective articles. Some of the studies reported detection of GCs in environmental samples and showed adverse effects on fishes even at a lower concentration (in the range of ng/L) [116,118–120,126].

Exposure to cortisol (concentration range of 100–145 ng/L) and clobetasol propionate (concentration range of 60–91 ng/L) could damage the immune system of zebrafish severely [119,120]. Increased heart rate, contractions of muscle degradation, acceleration of hatching, and changes in generic expressions are some of the major incidents reported due to cortisol and clobetasol propionate exposure [116]. As genes encode proteins, so do proteins control cell function [127]. In consequence, the thousands of genes asserted in a singular cell determine the exact activity or capability of that cell [128]. A glucocorticoid receptor works as a hormone-dependent major component that controls the expression of glucocorticoid-responsive genes [129–131]. Prednisolone exposure up to 100 ng/L concentration can lead to shifts in the morphology, swimming nature and physiology of zebrafish [126]. Dexamethasone exposure might negatively affect the reproductivity, muscle growth and cause deviation in mRNA expression of amphibians and fish [118,121,126].

A recently published study showed that the individual exposure of zebrafish to cortisone at a concentration of 0.7–1 μ g/L, 6 α -methylprednisolone at a concentration of 0.5–1 μ g/L and clobetasol propionate at about 60–91 ng/L resulted in transcriptional and physiological effects [132]. All the six GCs showed adverse effects including increased heart

rate and, in some extent, fold changes in the transcripts of genes. Prednisolone metabolite was reported to show some activities of mineralocorticoid and influences sedative, anticonvulsant and anxiolytic effects in fishes [133,134]. Rainbow darter (*Etheostoma caeruleum*) was also reported to be impacted by GCs near in Grand River Canada [132]. Presence of GCs in the water changed the diversity as well as the structure of the gut content microbiome of the rainbow fish [132,135].

On the other hand, halogen atoms (Cl, F) presence in some GCs can make their activity very strong in contrast to their natural counterparts and make them more recalcitrant in WWTPs and other water treatment plants [136–140]. Some studies mentioned low sperm count in men, sexual health deterioration, and breast cancer in women due to the exposure to GCs [36,141–144]. Additionally, some natural and synthetic GCs that were not emphasized in this study could also affect aquatic environments negatively [144]. Fundamental understanding of environmental and health impacts of GCs on humans and animals are challenging as the process involves long-term studies investigating side effects long-term after the exposure, and variable age and time of exposure [113,145,146].

5. Glucocorticoids Compounds Removal Methods Efficiency

Despite the fact that the existing wastewater treatment plants are designed for the removal of nutrients, partial removal of GCs has been detected in different cases [124]. Nonetheless, large differences in the efficiency of GC removal have been varied. The removal efficiency varies between 10 to 98% in different countries based on location and concentrations [147]. Different removing technologies accentuate on the relevance of geographical location parameters [148]. For the last two decades, advancement in technical analysis has empowered scientists to rethink about the occurrence and fate of natural and synthetic GCs in wastewater treatment plants even in ng/L level [108,147]. Removal efficiency of treatment plants regarding the six major GCs are listed in Table 3. The conventional treatment plants have three major facilities, namely as preliminary, primary, and secondary. Tertiary treatment is needed while discharging the effluent to the ground water or surface waters. Possible removal methods of GCs from treatment units include volatilization, photocatalysis, biological degradation, nanotechnology, chlorination, adsorption, Fe (VI) treatment as a tertiary treatment technology [117,149–157]. Table 3 shows the effect of each reported method in various studies.

Table 3. Engineering processes and their efficiency for Glucocorticoid's removal.

Process	Removal Efficiency	References
Adsorption with nano particles, e.g., Fe (VI) nanoparticle adsorption	Highly Effective (80–99%)	[95]
Adsorption with activated carbon	Highly Effective (98%)	[150–152]
Sorption	Effective (98%)	[108,117]
Photocatalysis ($\mu\text{g}/\text{liter}$ levels)	Effective (>95%)	[158–162]
Chlorination	Activated sludge systems combined with chlorination in tertiary treatment has been effective (95%)	[108]
Combination of reverse osmosis and micro-filtration	Depends on the concentration of GCs. (56–90%)	[163]
Advanced oxidation processes (Ozone, UV/H ₂ O ₂ , photo-Fenton processes)	Highly Effective (<90%)	[151]
Combination of ozonation and granular activated carbon (GAC)	Moderately Effective (70–85%)	[151,163]
Ultrafiltration	Not Effective (~8%) but for hydrophobic membranes (such as Cortisone) its efficiency goes beyond 80%	[154]
Activated sludge systems with UV disinfection	Not Effective (49%)	[163]
Combination of membrane filtration, ultra-filtration	Depends on the filtration type, size, and effluent concentration	[95]
Attached growth process	Varies between compounds, Moderately Effective	[135,150]
Microfiltration membranes	Not Effective (<18% unless combines with activated carbon or ultrafiltration)	[153,154,164]
Coagulation and flocculation	Not Effective (<10%)	[108,117,145,149,165]

6. Conclusions

Water quality issues have garnered a significant attention worldwide. Over the years, the challenge is to conserve aquatic ecosystems, to secure quality of aquatic lives and to minimize negative impacts on human health. Conventional WWTPs generally cannot remove GCs effectively, affecting the receiving environment and human health negatively eventually. Therefore, potentially unsafe GCs may enter the surface waters and sometime in ground water. As a result, a majority number of GCs compounds remain a problem within the existing legal norms. Among all the treatment processes, absorption with activated carbon, other absorbents or nanoparticles, oxidation methods relative to other technologies show greater efficiency in GCs removal. Although filtration alone cannot effectively remove GCs, combination of filtration with other technologies can remove GCs efficiently [151–154]. Across many countries, wastewater effluent is considered as one of the major sources of GCs in aquatic environments. However, surface runoff, as well as livestock sewage, are also significant sources of these compounds. Removal technologies and their efficiency varies according to the wastewater composition and treatment infrastructures. This leads to differences in degree of accuracy in implementation of removal technologies for GCs removal. Consequently, there is an inconsistency in inspecting GC's fate and occurrences in different types and stages of wastewater treatment processes, especially quantification

of very low concentrations of GCs in stabilized sludge. There are some operational factors such as temperature, pH, solubility, and many other engineering parameters that are still not analyzed well for GCs characterization and removal purposes. Based on the investigations of the secondary data in this study, it can be concluded that more scientific case-study-based research should be conducted to determine GCs compounds fate and transport in water resources, their selection and detection techniques, along with the best management practices and the most economically feasible removal technologies.

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