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Are synthetic glucocorticoids in the aquatic environment a risk to fish?

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ABSTRACT

The glucocorticosteroid, or glucocorticoid (GC), system is largely conserved across vertebrates and plays a central role in numerous vital physiological processes including bone development, immunomodulation, and modification of glucose metabolism and the induction of stress-related behaviours. As a result of their wide-ranging actions, synthetic GCs are widely prescribed for numerous human and veterinary therapeutic purposes and consequently have been detected extensively within the aquatic environment. Synthetic GCs designed for humans are pharmacologically active in non-mammalian vertebrates, including fish, however they are generally detected in surface waters at low (ng/L) concentrations. In this review, we assess the potential environmental risk of synthetic GCs to fish by comparing available experimental data and effect levels in fish with those in mammals. We found the majority of compounds were predicted to have insignificant risk to fish, however some compounds were predicted to be of moderate and high risk to fish, although the dataset of compounds used for this analysis was small. Given the common mode of action and high level of inter-species target conservation exhibited amongst the GCs, we also give due consideration to the potential for mixture effects, which may be particularly significant when considering the potential for environmental impact from this class of pharmaceuticals. Finally, we also provide recommendations for further research to more fully understand the potential environmental impact of this relatively understudied group of commonly prescribed human and veterinary drugs.

1. Introduction

Glucocorticosteroids, or glucocorticoids (GCs) have been used for more than 70 years to treat a wide variety of diseases, including rheumatoid arthritis, asthma and Crohn's disease (Barnes, 1998; David et al., 1970; Franchimont, 2004). The human therapeutic use of GCs is primarily associated with their anti-inflammatory properties (Mah et al., 2004). GCs are also used as veterinary medicines to treat similar disorders in pets and livestock (Ferguson et al., 2013). Both naturally occurring GCs (e.g. cortisol and cortisone), and synthetic GCs (e.g. hydrocortisone, dexamethasone, and prednisolone) act primarily through the glucocorticoid receptor (GR), in turn inducing transactivation or transrepression of specific genes, however, they can also act through non-genomic pathways through the direct binding of a ligand to the GR. With a growing and ageing human population, our reliance on GCs, as for many other pharmaceuticals, is increasing and this, in turn, is increasing the potential for measurable environmental impacts.

In this review, we describe which GCs are found in the environment, the bioavailability of both natural and synthetic GCs, and how they are metabolised in fish. We then compare the GC physiology of mammals (including humans) and fish, to assess for their commonalities and differences that may confer species-specific (in)sensitivity. With an emphasis on environmentally-relevant concentrations, we then compare the effects reported in fish versus established therapeutic and adverse effects in mammals. Finally, we attempt to assess the potential risks of GC drugs to fish in the natural environment (accepting the data limitations on environmental concentrations for some GCs), highlight gaps in our understanding and identify research priorities to help ensure the protection of fish and fish populations from these relatively poorly understood but frequently detected pharmaceutical environmental contaminants.

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Table 1
Maximum measured concentrations of glucocorticoids from environmental samples.

Compound	Influent (ng/L)	Effluent (ng/L)	Surface Water (ng/L)	Location	Reference
α-Cortolone triacetate	–	–	0.95	China	Shen et al., 2020
6α-Methylprednisolone	393	6	4	Czech Republic and Switzerland	Macikova et al., 2014
	<20	ND	–	Spain	Herrero et al., 2012
	2	<0.02	0.08	China	Chang et al., 2007
	1420[+]	–	–	Switzerland	Kovalova et al., 2012
	8	1	5	Switzerland	Ammann et al., 2014
	–	1.53	–	USA	Jia et al., 2016
	–	–	0.41	China	Chang et al., 2009
	–	3.4	–	Japan	Nakayama et al., 2016
	~8200[+]	–	–	France	Bailly et al., 2013
	–	–	12	China	Shen et al., 2020
	0.2	0.03	–	China	Fan et al., 2011
11-Oxo fluticasone propionate	–	–	0.93	China	Shen et al., 2020
Beclomethasone	–	–	1.7	China	Shen et al., 2020
Beclomethasone 17-propionate	–	–	0.82	China	Shen et al., 2020
Beclomethasone dipropionate	–	BDL	–	Sweden	Grabic et al., 2012
	20	BDL	BDL	Sweden	Fick et al., 2011
	–	ND	–	Japan	Nakayama et al., 2016
Betamethasone	<20	<10	–	Spain	Herrero et al., 2012
	343	–	–	Portugal	Salgado et al., 2011
	–	0.66	–	USA	Jia et al., 2016
	–	–	7.2	China	Shen et al., 2020
	15	7	–	France	Piram et al., 2008
Betamethasone 17-valerate	8.6	1.3	–	Japan	Kitaichi et al., 2010
	–	4.7	–	Japan	Isobe et al., 2015
	–	7.6	–	Japan	Nakayama et al., 2016
	–	14*	–	Japan	Suzuki et al., 2015
Betamethasone 21-acetate	–	–	39	China	Shen et al., 2020
Betamethasone dipropionate	ND	ND	–	Japan	Kitaichi et al., 2010
Budesonide	7	5	4	Czech Republic and Switzerland	Macikova et al., 2014
	ND	3	–	France	Piram et al., 2008
	420	610	–	Greece	Kosma et al., 2014
	–	96	–	Sweden	Grabic et al., 2012
	1	<1	4	Switzerland	Ammann et al., 2014
	–	0.36	–	USA	Jia et al., 2016
	–	–	48	China	Shen et al., 2020
	12,302	–	–	Portugal	Salgado et al., 2011
Clobetasol	4	<1	<1	Switzerland	Ammann et al., 2014
	–	–	0.61	China	Shen et al., 2020
Clobetasol butyrate	–	ND	–	Japan	Nakayama et al., 2016
Clobetasol propionate	7	1	1	Czech Republic and Switzerland	Macikova et al., 2014
	–	3	–	Japan	Isobe et al., 2015
	7	<1	<1	Switzerland	Ammann et al., 2014
	–	2.35	–	USA	Jia et al., 2016
	–	4.9	–	Japan	Nakayama et al., 2016
	–	–	7.3	China	Shen et al., 2020
	–	78*	–	Japan	Suzuki et al., 2015
Cloticasone propionate	–	–	0.78	China	Shen et al., 2020
Corticosterone	–	–	ND	Switzerland	Zhang and Fent, 2018
	21	5	6	Switzerland	Ammann et al., 2014
	21	5	6	Czech Republic and Switzerland	Macikova et al., 2014
	1	0.13	–	China	Fan et al., 2011
Cortisol acetate	–	–	30	China	Shen et al., 2020
Cortisol/Hydrocortisone	270	<10	–	Spain	Herrero et al., 2012
	120	1.9	3.4	China	Chang et al., 2007
	301	ND	–	Netherlands	Schriks et al., 2010
	53	63	–	France	Piram et al., 2008
	28.8	ND	–	China	Liu et al., 2011
	–	–	2.67	Hungary	Tölgyesi et al., 2010
	370	38	–	USA	Trenholm et al., 2008
	–	–	20	China	Chang et al., 2009
	–	0.12*	–	Japan	Suzuki et al., 2015
	22.1	0.13	–	China	Fan et al., 2011
	–	1.3	–	Japan	Isobe et al., 2015
	160	26	10	Switzerland	Ammann et al., 2014
	–	1.57	–	USA	Jia et al., 2016
	–	6.6	–	Japan	Nakayama et al., 2016
	130	–	–	China	Liu et al., 2012
	–	–	11	China	Shen et al., 2020
	–	–	7	USA	Anumol et al., 2013
Cortisone	285	ND	–	Spain	Herrero et al., 2012
	86	0.58	4.2	China	Chang et al., 2007
	472	ND	–	Netherlands	Schriks et al., 2010
	174	229	–	France	Piram et al., 2008

(*continued on next page*)

Table 1 (*continued*)

Compound	Influent (ng/L)	Effluent (ng/L)	Surface Water (ng/L)	Location	Reference
	45.8	ND	–	China	Liu et al., 2011
	–	–	28	China	Chang et al., 2009
	–	0.51	–	USA	Jia et al., 2016
	–	–	433	China	Shen et al., 2020
	15.6	0.24	–	China	Fan et al., 2011
Cortisone acetate	–	–	0.49	China	Shen et al., 2020
Dexamethasone	<20	<10	–	Spain	Herrero et al., 2012
	3.4	0.09	0.31	China	Chang et al., 2007
	90	ND	–	Netherlands	Schriks et al., 2010
	15	7	–	France	Piram et al., 2008
	22.6	ND	–	China	Liu et al., 2011
	–	–	<0.07	Hungary	Tölgyesi et al., 2010
	147[+]	ND	–	Switzerland	Kovalova et al., 2012
	BDL	BDL	–	Portugal	Santos et al., 2013
	ND	ND	ND	Spain	Gros et al., 2012
	–	ND	ND	Poland and Czech Republic	Baranowska and Kowalski, 2012
	–	–	8	China	Chang et al., 2009
	–	1.3*	–	Japan	Suzuki et al., 2015
	0.81	0.03	–	China	Fan et al., 2011
	–	0.16	–	USA	Jia et al., 2016
	–	1.7	–	Japan	Nakayama et al., 2016
	–	–	12	China	Shen et al., 2020
	–	–	<1	USA	Anumol et al., 2013
Dexamethasone 21-acetate	–	–	50	China	Shen et al., 2020
Dexamethasone and Betamethasone	9.4	ND	–	Japan	Kitaichi et al., 2010
	106	16	13	Switzerland	Ammann et al., 2014
	1720	15	15	Czech Republic and Switzerland	Macikova et al., 2014
	15	7	–	France	Piram et al., 2008
	–	1.3	–	Japan	Isobe et al., 2015
Difluprednate	–	ND	–	Japan	Nakayama et al., 2016
Fludrocortisone acetate	82	–	14	Switzerland	Ammann et al., 2014
	–	–	ND	Switzerland	Zhang and Fent, 2018
Flumetasone	6	5	2	Czech Republic and Switzerland	Macikova et al., 2014
	6	3	2	Switzerland	Ammann et al., 2014
	–	–	1.43	Hungary	Tölgyesi et al., 2010
Flumethasone acetate	–	–	1.7	China	Shen et al., 2020
Flunisolide	–	–	0.99	China	Shen et al., 2020
	7	5	–	France	Piram et al., 2008
Fluocinolone acetonide	0.3	11	–	France	Piram et al., 2008
	–	3.69	–	USA	Jia et al., 2016
	–	–	0.79	China	Shen et al., 2020
	ND	ND	–	Japan	Kitaichi et al., 2010
Fluocinonide	ND	–	–	USA	Nagarnaik et al., 2010
	–	0.27	–	USA	Jia et al., 2016
Fluorometholone	3	<1	1	Czech Republic and Switzerland	Macikova et al., 2014
	3	<1	<1	Switzerland	Ammann et al., 2014
Fluticasone propionate	5	<1	<1	Czech Republic and Switzerland	Macikova et al., 2014
	7809	–	–	Portugal	Salgado et al., 2011
	–	1.43	–	USA	Jia et al., 2016
	–	–	0.67	China	Shen et al., 2020
	4	<1	<1	Switzerland	Ammann et al. 2014
Hydrocortisone acetate	3.8	ND	–	Japan	Kitaichi et al., 2010
Hydrocortisone and Cortisone	939	29	10	Czech Republic and Switzerland	Macikova et al., 2014
Prednisolone	33	ND	–	Spain	Herrero et al., 2012
	7.5	0.72	0.64	China	Chang et al., 2007
	1918	ND	–	Netherlands	Schriks et al., 2010
	–	–	0.58	Hungary	Tölgyesi et al., 2010
	ND	ND	–	Spain	Huerta-Fontela et al., 2010
	–	ND	ND	Poland and Czech Republic	Baranowska and Kowalski, 2012
	–	1.7	–	Japan	Nakayama et al., 2016
	1.7	0.07	–	China	Fan et al., 2011
	1221	<5	12	Switzerland	Ammann et al., 2014
	–	0.34	–	USA	Jia et al., 2016
	–	1.6	–	Japan	Isobe et al., 2015
	17	–	ND	Japan	Kitaichi et al., 2010
	–	–	1.8	China	Chang et al., 2009
	–	–	94	China	Shen et al., 2020
	~7800[+]	–	–	France	Bailly et al., 2013
	–	0.34*	–	Japan	Suzuki et al., 2015
Prednisolone acetate	ND	ND	–	Japan	Kitaichi et al., 2010
Prednisolone and Prednisone	336	<5	12	Switzerland	Ammann et al., 2014
	1221	24	13	Czech Republic and Switzerland	Macikova et al., 2014
Prednisone	45	<10	–	Spain	Herrero et al., 2012
	8.4	0.18	0.86	China	Chang et al., 2007
	545	ND	–	Netherlands	Schriks et al., 2010
	ND	ND	–	Spain	Huerta-Fontela et al., 2010

(*continued on next page*)

Table 1 (*continued*)

Compound	Influent (ng/L)	Effluent (ng/L)	Surface Water (ng/L)	Location	Reference
	–	–	2.4	China	Chang et al., 2009
	0.57	0.06	–	China	Fan et al., 2011
	8.5	ND	–	China	Liu et al., 2011
	–	–	1.3	China	Shen et al., 2020
	–	–	<25	USA	Anumol et al., 2013
Rimexolone	–	–	47	China	Shen et al., 2020
Triamcinolone	–	–	<0.5	Hungary	Tölgyesi et al., 2010
	–	–	22	China	Shen et al., 2020
	31	30	–	France	Piram et al., 2008
Triamcinolone acetonide	14	5	1	Czech Republic and Switzerland	Macikova et al., 2014
	<50	<20	–	Spain	Herrero et al., 2012
	41	14	–	Netherlands	Schriks et al., 2010
	40	3	–	France	Piram et al., 2008
	–	–	<0.63	Hungary	Tölgyesi et al., 2010
	ND	ND	–	Japan	Kitaichi et al., 2010
	6	1	<1	Switzerland	Ammann et al., 2014
	–	14	–	USA	Jia et al., 2016
	–	–	14	China	Shen et al., 2020
	–	–	<7	USA	Anumol et al., 2013
Triamcinolone diacetate	–	–	9	China	Shen et al., 2020
Total Glucocorticoids	–	–	43*	USA	Conley et al., 2017
	–	–	2.34*	USA	Stavreva et al., 2021
	–	–	100*	USA	Cavallin et al., 2021
	42	0.7	–	China	Fan et al., 2011
	3423	96	57	Czech Republic and Switzerland	Macikova et al., 2014
	–	534.1*	85.8*	Switzerland	Sonavane et al., 2018
	243*	38*	1.3*	Netherlands	van der Linden et al., 2008
	ND*	ND*	–	Tunisia	Mnif et al., 2010
	BDL*	BDL*	–	Netherlands	Brand et al., 2013
	–	–	2.7*	Netherlands	Schriks et al., 2013
	85*	70*	–	Australia	Bain et al., 2014

ND = Not detected
BDL = Below detection limit
"+" = Average concentration
* = Theoretical dexamethasone equivalent.

2. GCs in the aquatic environment

Synthetic GCs principally enter the aquatic environment via the excretion of the compound and/or its metabolites from patients, and to a lesser degree from use in livestock and aquaculture (Liu et al., 2015). The highest reported concentrations of GCs have been measured in untreated hospital wastewaters in Switzerland, where a total GC burden was measured at 3423 ng/L, comprising 1720 ng/L betamethasone/dexamethasone and 1221 ng/L prednisolone/prednisone (Macikova et al., 2014). Wastewater treatment plants (WWTPs), however, have generally been shown to effectively remove GCs from influent, with removal rates ranging between 50 and 100% (Chang et al., 2007; Fan et al., 2011; Macikova et al., 2014). Consequently, GCs, if detected, are usually found in effluents in the low ng/L range, and further dilution and degradation in surface waters mean that measured environmental concentrations are typically in the low ng/L to high pg/L range (see Table 1). Although there is wide variability in levels reflecting these processes at play (as well as differences in detection sensitivity) an attempt to model the environmental concentrations of synthetic GCs in the River Thames, UK, has suggested that in the best case scenario (lowest excretion, and highest removal), a mean concentration of up to 30 ng/L of total GCs might be expected in surface waters, with a worst-case scenario predicting concentrations up to 850 ng/L in polluted "hot spots" (Kugathas et al., 2012).

3. Uptake and metabolism of GCs in fish

Understanding the bioavailability of synthetic GCs and their metabolism is key for considering their potential for inducing health effects in fish. It has been suggested that uptake of synthetic GCs from the environment is most likely to occur via direct exchange across the gills, due to the continuous mass exchange of materials across them (Randall et al., 1998). However, differences in the physicochemical properties of each drug, will have a major bearing on this. A drug with a higher LogD_{ow} value, for example, will have a higher affinity for lipids than water, therefore increasing the rate of passive diffusion of the drug into gills from the water. Physiochemical properties and structure of a selection of synthetic GCs are shown in Supplementary Tables 1 and 2. Uptake of synthetic GCs via food ingestion is believed to play only a minor part role in their bioavailability for fish.

Relatively little is known about the pharmacokinetics of GCs in fish compared with mammals. A study by Margiotta-Casaluci et al. 2016 on beclomethasone dipropionate (BDP) reported that in fathead minnows exposed to an environmentally relevant concentration of BDP (10 ng/L for 21 days), the average plasma concentration of the drug was within the range of Human Therapeutic Plasma Concentrations (H_TPC) with C_{max} values between 0.8 and 1.4 ng/mL. Furthermore, these authors reported biological effects at those plasma concentrations, with a reduction in lymphocytes and increased expression of secondary sexual characteristics. The effect concentrations of different synthetic GC compounds, however, have been reported to be very different in fish. To illustrate this, Lalone et al. 2012 reported GR gene expression changes in the fathead minnow for exposure to 50 μg dexamethasone/L, whereas, in contrast, Margiotta-Casaluci et al. 2016 found comparable changes at 0.1 μg/L for BDP. Critically, the advent of new synthetic GCs has also led to an increase in drug potency, for example, fluticasone furoate has around 250 times higher relative GR binding affinity compared to prednisolone (Daley-Yates, 2015). Equally, an increased potency of a drug often means the reduction in a given dose and in turn the likelihood for a reduction in their environmental concentration. Therefore, gaining a better understanding of the potential environmental effects of these drugs is arguably more important than ever.

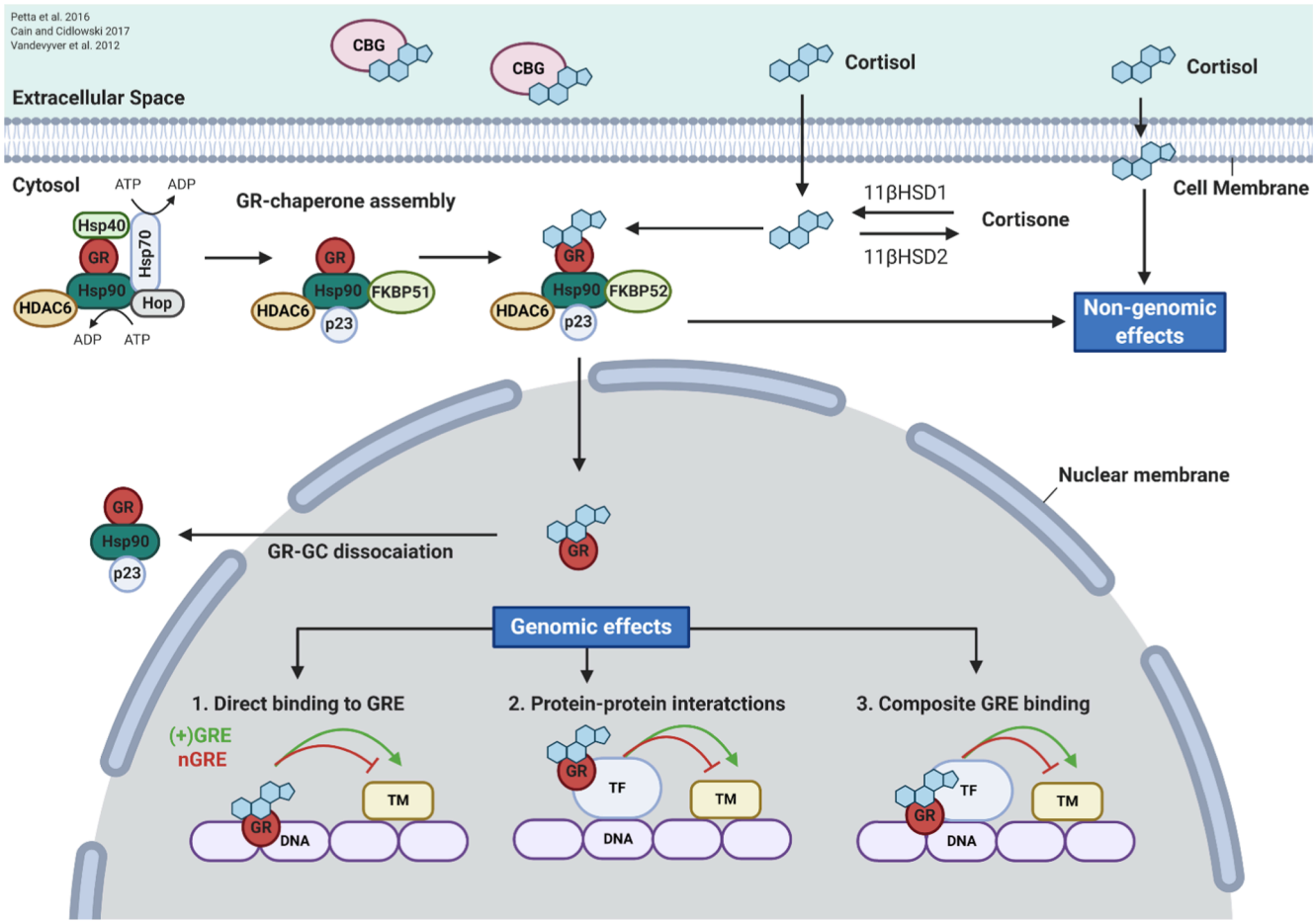

Fig. 1. Schematic of the mechanisms of action of glucocorticoids (based on Cain and Cidlowski 2017). Created with BioRender.com.

Little is known also about GC metabolism in fish. In humans, cortisol and cortisone are predominantly metabolised in the liver by the 11β hydroxysteroid dehydrogenases (11β-HSDs), with 11β-HSD2 converting active cortisol in inactive cortisone (Arlt and Stewart, 2005). Synthetic GC metabolism in humans, however, is tissue-specific. For example, in the placenta, 11β-HSD2 can metabolise a variety of synthetic GCs including beclomethasone, prednisolone, dexamethasone, and betamethasone, but not budesonide or fluticasone (Murphy et al., 2007). Furthermore, prednisone is converted to the active metabolite prednisolone via 11β-HSD1 in osteoblasts (Cooper et al., 2003).

In humans, synthetic GCs have an elimination half-life ranging from 1 to 5 h, although the biological half-life can be up to days in length. This is true for dexamethasone, where its biological effects on anti-inflammatory activity are known to continue for between 36 and 72 h after dosing (Becker, 2013). Of the few studies undertaken in fish, in fathead minnow, BDP has been shown to be rapidly metabolised to beclomethasone 17-monopropionate, and subsequently into free beclomethasone (Margiotta-Casaluci et al., 2016). As such its metabolic pathway and products are similar to those in humans. In mammals, excretion of GCs occurs through the kidneys, hepatobiliary system and the lungs, the latter of which is especially important for inhaled GCs used as asthma medication (Pleuvry, 2005), but again the routes and rates of excretion of any GC is yet to be determined in any fish species.

4. GC system in mammals (humans)

In mammals, endogenous GCs (eGCs) (cortisol and corticosterone) have widespread functions within the body and their production and secretion are controlled by the hypothalamic-pituitaryadrenal (HPA) axis. eGCs are produced from cholesterol in the mitochondria (Cain and Cidlowski, 2017) and in the cascade of their production, neural, cytokine and endocrine signals are received in the hypothalamus, stimulating the release of corticotropin-releasing hormone (CRH) which further stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH) (Webster et al., 2002). ACTH is then transported via the blood to the adrenal cortex where stimulation of the *zona reticularis* and *zona fasciculata* produces cortisol and corticosterone, which, in turn, are secreted into the circulatory system (Cain and Cidlowski, 2016; Everly and Lating, 2013; Quax et al., 2013). Excess cortisol levels negatively feedback to the hypothalamus resulting in a reduction in the production of CRH and ACTH (Cain and Cidlowski, 2016). In human plasma approximately 80–90% of cortisol is bound to cortisol binding globulin (CBG), 5–15% bound to serum albumin, and 3–10% of the cortisol unbound (Cain and Cidlowski, 2016; Laue and Cutler, 1997). Free cortisol is more readily able to diffuse across the plasma membranes and interact with cytosolic receptors, activating GR signalling, and therefore CBG-binding can regulate the activity of GCs (Desantis et al., 2013). The cell may also regulate the number of active GCs via 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes that catalyse the conversion of cortisol to cortisone, and vice versa (Seckl and Walker, 2001). 11β-HSD1 converts GCs from inactive to active forms, while 11β-HSD2 catalyses the conversion of cortisol into cortisone which reduces the activity of GCs in the cell.

GCs act principally through the GR, which acts as a ligand-activated transcription factor. In the absence of the ligand, the GR, located in the cytoplasm, forms a protein complex with heat shock proteins, immunophilins (FK506 family) and other molecular chaperones (Schaaf et al., 2009; Schäcke et al., 2002). As the ligand binds, the receptor

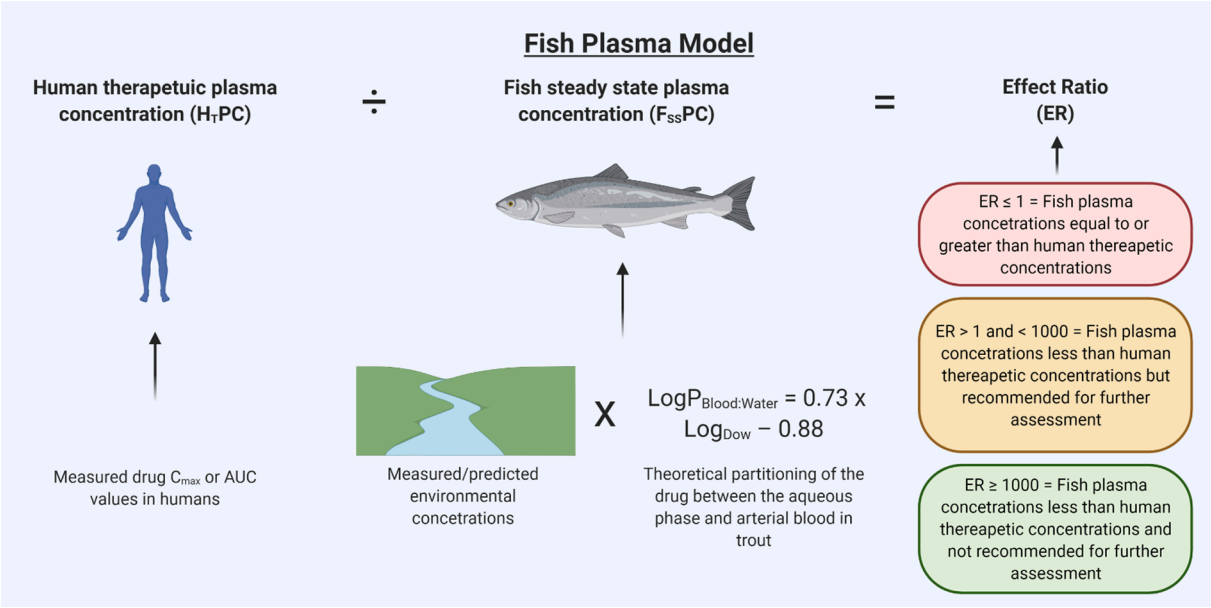

Fig. 2. Illustration of how the calculations were performed to produce the fish plasma model data and a description of the outcome of the effect ratio result. Calculations taken from Huggett et al., 2003 and Fitzsimmons et al., 2001. Created with BioRender.com.

translocates to the nucleus where it affects gene regulation in three ways (Cain and Cidlowski, 2017). Firstly, the GR/ligand complex can directly bind to GC response elements (GREs) or to negative GREs on DNA. Secondly, the GR can bind to a transcription factor, thus interacting indirectly with DNA. Finally, composite binding of the GR to DNA containing GRE's as well as proteins including transcription factors can occur (Cain and Cidlowski, 2017). Positive and negative gene regulation can occur through any of these mechanisms via transactivation or transrepression of the target gene. These processes are summarised in Fig. 1. GCs can also act through non-genomic pathways, which represent more rapid response pathways independent of gene transcription. Non-genomic activation occurs through GRs in cell plasma membranes which are associated with G protein-dependent signalling cascades and downstream kinases (Tasker et al., 2006). A review by Das et al. 2018 suggests that there are four main mechanisms: activation of GR on the plasma membrane; activation of an unknown novel receptor; changes to the lipid bilayer through intercalation of cortisol molecules; and through the opening of Ca^{2+} channels increasing intracellular Ca^{2+}.

Several different receptor isoforms of the GR are produced via alternative splicing. A total of five splice variants are now thought to occur which include GRα (the classical GR invoking the mechanism as described above), GRβ, GRγ, GR-A and GR-P (Cain and Cidlowski, 2016). GRβ is thought to be a dominant-negative inhibitor of GRα and does not bind GC agonists (Bamberger et al., 1995; Oakley et al., 1996). GRγ appears to be able to increase the range of genes capable of being regulated by GC action due to its altered DNA-binding domain (DBD) (Cain and Cidlowski, 2016), while GR-P can increase the activity of GRα (Lange et al., 2010). Little research has been done on the biological modes of action of GR-A. As GRs are located in almost all cells in the body, GCs can act on most organ systems, including the nervous, immune, cardiovascular, respiratory, reproductive, musculoskeletal and integumentary systems (Thau et al., 2021).

5. GC system in fish

In fish as in mammals, cortisol is the main eGC, however, cortisol is produced in the interrenal gland, a structure analogous to the adrenal glands of mammals but embedded in the kidney (Schoonheim et al., 2010). Consequently, in fish, the axis controlling the GC system is referred to as the hypothalamic-pituitary interrenal (HPI) axis.

The GR is well conserved across jawed vertebrates (Thornton, 2001; Bridgham et al., 2006), The majority of teleost species, however, possess two GRs, named GR1 and GR2 (Bury, 2017; Stolte et al., 2006), which are the result of a genome duplication event approximately 350–400 million years ago after the split from the tetrapods (Volff, 2005). In the cichlid Burton's mouthbrooder *Astatotilapia burtoni* and rainbow trout *Oncorhynchus mykiss* (Bury et al., 2003; Greenwood et al., 2003) both GRs have been shown to bind GCs. Contrasting with these species, zebrafish (*Danio rerio*) have lost the *gr1* gene (Schaaf et al., 2008) and possess two different isoforms for the *gr2* gene, named zGRα and zGRβ. These zebrafish isoforms function similarly to humans, with zGRβ acting as an inhibitor of zGRα (Schaaf et al., 2008). Other fish, including the Japanese flounder (*Paralichthys olivaceus*), have been shown to have a single GR but with no evidence of differing isoforms (Stolte et al., 2006; Takeo et al., 1996), meaning that zebrafish are the only fish species that have been shown to have this "human-like" activity (Bury, 2017). Furthermore, zebrafish and human GRα show a high level of conservation. The DNA binding domain of the GR protein has a 98.4% similarity (amino acids) and the ligand-binding domain has 86.5% similarity (Schaaf et al., 2009) thus increasing the likelihood of biological effects in certain non-target species such as fish within an environmental context. Although no specific CBG has been identified in fish, there have been similar molecules detected that perform a similar function in reducing the bioavailability of cortisol (Baker, 2003; Idler and Freeman, 1968; Sadoul and Geffroy, 2019). The maximum corticosteroid-binding capacity can vary greatly between fish species (e.g. 2.73 ng/ml in Atlantic cod (*Gadus morhua*), to 513 ng/ml in South American Lungfish (*Lepidosiren paradoxa*), however the binding affinity of GCs to these molecules is low and the proportion of free cortisol higher compared to other vertebrates (Desantis et al., 2013). The major organ targets of eGCs in fish are the liver, gills and the intestine, which play fundamental roles in the regulation of energy metabolism and mineral balance within the body (Wendelaar Bonga, 1997).

6. Potential effects of synthetic GCs in fish; an interspecies comparison with known effects in mammals

Few data are available outlining the effects of synthetic GCs in fish, particularly at environmentally-relevant concentrations. Despite this and given the high level of conservation of the HPA/HPI system between

mammals and fish, conservation of pharmacological activity in at least some cases is also likely. Here we compare the main actions of GCs in mammals with potential effects in fish given the level of conservation of these systems across species and in turn make inferences about the likelihood of such effects in fish within an environmental context. We have included data from studies conducted on fish that have used concentrations in excess of levels currently detected in the environment, as these studies help to illustrate the potential for pharmacological activity in fish as a non-target species (i.e. the physiologically responsive 'machinery' are present and functional). Furthermore, as there are virtually no data available concerning the tissue levels of glucocorticoids in fish, the potential remains for their accumulation at target sites at levels considerably higher than those currently reported in surface waters for chronic exposures. We have sought to highlight where studies covered in this review have direct relevance to current environmental scenarios and those that are included based more on helping to build mechanistic understandings.

6.1. Glucose metabolism

For a full review on the regulation of glucose homeostasis by GCs in mammals and fish see Kuo et al. 2015 and Polakof et al., 2012. One of the main effects of GCs is to release energy substrates including glucose and amino/fatty acids into the circulation to supply the body with the energy requirements needed during periods of stress and high energetic demand (Barton et al., 1987; Geer et al., 2015). To do so GCs break down muscle proteins, fat cells and stimulate gluconeogenesis in the liver (Mommsen et al., 1999; Vijayan et al., 1994). As insulin counters these processes, GCs also can reduce the effects of insulin on the body and as a consequence, cells in the body can become more resistant to insulin after chronic exposure to GCs (Andrews and Walker, 1999). In fish, however, insulin alone has been shown to inadequately control levels of glucose, possibly suggesting reduced control of glycaemia compared to mammals (Mazur et al., 1992), and therefore the effects of GCs on this process are unknown. GCs can also reduce glucose utilisation by cells and therefore increase circulating levels of glucose (Geer et al., 2015).

Chronic exposure of GCs in mammals leads to altered states of energy substrates throughout the whole body and may result in hyperglycaemia, hyperinsulinemia, hypertriglyceridemia, weight gain and increasing deposition of adipose tissue in the trunk (Geer et al., 2015; Zakrzewska et al., 1999). Interestingly, the effects of GCs can also cause foetal reprogramming in rats by altering PEPCK expression, which catalyses a rate-limiting step in gluconeogenesis, and results in hyperglycaemia in the adult offspring (Nyirenda et al., 2001). This suggests that if these drugs reached such levels in the environment, there is the potential for trans-generational effects on energy balance systems.

Given that the effects of GCs on glucose control are one of the prominent effects in mammalian systems, the majority of published studies in fish have focussed on this. Findings in fish include enhanced gluconeogenesis and amino acid catabolism, and a reduced capacity to utilise glucose leading to increased hyperglycaemia at concentrations from 0.042 μg/L (Carney Almroth et al., 2015; Kugathas et al., 2013; Kugathas and Sumpter, 2011; Laiz-Carrión et al., 2002; Margiotta-Casaluci et al., 2016; Wilson et al., 2016; Zhao et al., 2016) and effects on genes relating to glucose metabolism at concentrations from 0.07 μg/L (Carney Almroth et al., 2015; Kugathas et al., 2013; Margiotta-Casaluci et al., 2016; Willi et al., 2019a, 2019b, 2018; Wilson et al., 2016; Zhao et al., 2016).

6.2. Immunosuppression

In mammals, GCs are immunosuppressive due to their therapeutic anti-inflammatory properties. A review by Cain and Cidlowski, 2017 summarises the extensive research focussed on the three-phase process of GC-induced immunosuppression in mammals. Initially, signalling pathways are inhibited by GC action and cause a reduction of pro-inflammatory cytokines and eicosanoids by macrophages resulting in a reduction in the detection of harmful agents as well as reducing blood flow locally. Next, GCs suppress the movement of leukocytes from capillaries into the tissue, downregulate the production of chemokines and chemoattractants and reduce the expression of adhesion molecules in the leukocytes. Finally, GCs increase the phagocytic action of apoptotic cells and debris in monocytes and macrophages enabling greater sensitization of the cells to other pro-resolving factors. It is also suggested that GCs may be important for the transition from inflammation to healing (Sharif et al., 2015; Wicke et al., 2000) and they have also been shown to have effects on T- and B-cells (Coutinho and Chapman, 2011; Cain and Cidlowski, 2017).

Studies on the immune effects of GCs in fish suggest similarities with those seen in mammals described above. For example, exposure to fathead minnow of 0.01 μg/L BDP, over 21 days, resulted in a 64% reduction in the lymphocyte population, while exposures to 1 μg/L BDP and prednisolone resulted in a reduction of blood leucocytes by 18% and 13%, respectively, suggesting effects a low concentrations can result in adverse effects in fish (Kugathas and Sumpter, 2011; Margiotta-Casaluci et al., 2016). Other synthetic derivatives, such as prednisolone (9011 μg/L) (Geurtzen et al., 2017), dexamethasone (392,464 μg/L) (Sharif et al., 2015) and beclomethasone (13,026 μg/L) (Chatzopoulou et al., 2016; Xie et al., 2021), have also been shown induce very similar effects in zebrafish models, with reductions in the numbers of immune cells during development, maintenance and regeneration of bones, or following wound induction (Sharif et al., 2015). These latter exposure scenarios, however, are orders of magnitude higher than those that bear any environmental relevance for fish. This immunoinhibitory effect in fish is also extended to altered immune-related gene expression. For example, zebrafish embryos have also shown significant alterations to *fkbp5*, *irg1l*, *socs3* and *gilz* for exposures to corticosterone, clobetasol propionate, fluticasone propionate and triamcinolone acetonide at concentrations of ~1 μg/L and fludrocortisone acetate at 0.68 μg/L (Willi et al., 2019a, 2019b, 2018; Zhao et al., 2016). Exposure of zebrafish to supra environmental concentrations of beclomethasone have been reported to both stimulate the classic pro-inflammatory gene, *tnfa*, plus seven genes related to phagocytosis (13,026 μg/L; Xie et al., 2021) but equally have no effect on the migration of macrophages (up to 13,026 μg/L; Chatzopoulou et al., 2016). In mammals, sex-related differences are reported for GCs with males more likely to be affected by their anti-inflammatory actions but whether this is the case in fish is not known (Duma et al., 2010).

6.3. Cardiovascular system

The mammalian GR (and mineralocorticoid receptor (MR)) is highly expressed in blood vessels and myocardium reflecting a key role of GCs in cardiovascular system function (Walker, 2007). Furthermore, the use of GCs to treat patients has also been identified as an increased risk factor for heart failure (Souverein et al., 2004; Wei et al., 2004), myocardial infarction and strokes (Huang et al., 2013). Indeed, GC action on the cardiovascular system can be seen in the vascular smooth muscle, endothelial cells, myocardium and macrophages affecting vascular development, remodelling, tone and inflammation (Walker, 2007).

Despite this clear role in mammalian cardiovascular physiological function, few studies have looked at the effects of GCs on the cardiovascular system in fish and for these studies, there have been some contradictory results also. For example in zebrafish embryos, GC exposure has been reported to result in an increased heart rate at very low concentrations (ranging from 0.081 μg/L to 2.07 μg/L (Willi et al., 2019a, 2019b, 2018; Zhao et al., 2016) and this has also been shown for the F1 embryos of adult zebrafish treated with fludrocortisone at 0.006 μg/L (for 21 days; Zhao et al., 2016)). In the case of the latter study where F1 embryos only were exposed to fludrocortisone the effective concentration for reducing the heart rate was 0.081 μg/L (Zhao et al.,

2016). In contrast, with these studies, microinjection of 32 pg/nL cortisol into one-cell zebrafish embryos increased heart deformities including pericardial oedema, malformed chambers and resulted in a lower resting heartbeat rate in larvae post-hatch (Nesan and Vijayan, 2012). Exposed fish also had reduced cardiac performance when exposed to a secondary stressor. Differences between these two sets of findings in zebrafish may be due to the differences in GC delivery method, drug concentration or some other factor(s) such as animal strain, condition or specific developmental stage. Clobetasol propionate (10 μg/L) has also been shown to effect the blood coagulation cascade, by altering the expression of blood coagulation related genes, *f7*, *f9b*, *fga*, and *serpinc* (Schmid and Fent, 2020).

6.4. Muscle atrophy

The effects of GCs on muscle have been well documented with GC treated patients commonly exhibiting reductions in both muscle strength and muscle mass. Atrophy occurs as GCs stimulate muscle protein catabolism and decrease protein synthesis via the ubiquitin-proteasome system, apoptosis, the IGF1-Akt-mTOR signalling pathway, autophagy lysosome system and myostatin stimulation (Braun and Marks, 2015; Torres-Velarde et al., 2018; Valenzuela et al., 2018). Collectively, this results in reductions in amino acid transport, IGF-1, inhibition of stimulatory insulin, and amino acid action and down-regulation of myogenin (Pereira and Freire de Carvalho, 2011; Schakman et al., 2008). Fast-twitch skeletal muscle seems to be more affected by GCs than slow-twitch and cardiac muscle, which may be due to a reduced expression of the GR in slow-twitch and cardiac muscle cells (Braun and Marks, 2015).

Again, few studies have researched the effects of GCs on muscle atrophy in fish. However, a study on salmonid fish (Galt et al., 2016) has shown that the expression of *myostatin* and *HSP90* were significantly altered in the muscle of Chinook salmon (*Oncorhynchus tshawytscha*), cutthroat trout (*Oncorhynchus clarkia*), brook trout (*Salvelinus fontinalis*) and Atlantic salmon (*Salmo salar*) 48 h after they were intraperitoneally injected with cortisol (50 μg/g body weight). All 3 species had increased glucose and cortisol levels, as predicted, however, only Chinook salmon and cutthroat trout had increased *myostatin* expression in muscle suggesting a species-specific response. In another study on rose snapper (*Lutjanus guttatus*) muscle cells, dexamethasone exposure (19.6 μg/L) resulted in increased *myostatin-1* and *foxo3b* expression suggesting an increase in genes associated with atrophy of muscle tissue (Torres-Velarde et al., 2018). Contrasting with this, in an exposure of juvenile rainbow trout to cortisol (intraperitoneal injection of 2 μL/g body weight) no changes were seen in the expression of *myostatin-1a* and *-1b* in either red or white muscle tissue (Galt et al., 2014). *In vitro* experiments with primary trout myoblasts by the same authors, however, suggested a dose-dependent increase in *myostatin-1b* expression after exposure to cortisol (although the vehicle control also showed an increase) (Galt et al., 2014). Collectively, these findings indicate possible inter-species differences in the regulation of these genes following GC exposure, perhaps due to functional divergence of *myostatin* gene function (Galt et al., 2014). Studies in zebrafish embryos have shown dose-dependent reductions in spontaneous muscle contractions after exposure to cortisol (1.345 μg/L), clobetasol propionate (9.38 μg/L), fluticasone propionate (0.977 μg/L), triamcinolone acetonide (120 μg/L), corticosterone (1.06 μg/L), betamethasone (0.11 μg/L), flumethasone (19.4 μg/L) and fludrocortisone acetate (0.683 μg/L) (Willi et al., 2019a, 2019b, 2018; Zhao et al., 2016). This could have a significant bearing on the fitness of certain species in their ability to swim, hunt and avoid predation etc.

6.5. Embryonic development

In normal mammalian development, eGCs are found at low concentrations in the developing embryos and derive from maternal transfer during embryogenesis. In the foetus, 11βHSD2 maintains cortisol concentrations (Fowden and Forhead, 2004) and as it develops, GCs are produced. Studies in humans suggest that increased levels of GCs can cause a reduction in birth weight (Seckl, 2001) and have effects on the development of the gut, heart, kidneys, lungs and pancreas. In zebrafish (Nesan and Vijayan, 2013), studies have shown that GC exposure accelerates hatching at 72 hpf at concentrations low as 0.09 μg/L (corticosterone) (Willi et al., 2019a, 2019b, 2018; Zhao et al., 2016). Despite this, the use of GC therapy in pregnant women is widespread (Kemp et al., 2016), and reported side effects include reduced foetal brain growth (Huang et al., 1999) and on GC programming. In zebrafish, this can result in effects throughout the subsequent life of an individual, notably on the cardiovascular system, brain function, stress response and glucose metabolism (Nesan and Vijayan, 2013).

GCs appear essential for normal zebrafish embryonic growth and function, with the loss of the GR protein resulting in malformations, reduced growth and increased mortality in embryos (Nesan et al., 2012). A detailed review on currently known pathways and genes affected by GCs during development in zebrafish is provided in Nesan and Vijayan 2013, and include: matrix metalloproteinases (Hillegass et al., 2008, 2007) required for somitogenesis and craniofacial development; bone morphogenetic protein developmental signalling factors (Nesan et al., 2012); and genes responsible for myogenesis (Nesan et al., 2012), osmoregulation (Hwang, 1993), cardiogenesis (Nesan and Vijayan, 2012) and cardiac performance (Nesan and Vijayan, 2012). Therefore, alteration in the levels of circulating GC in developing embryos could lead to a variety of developmental abnormalities. A study exploring gene expression profiles in developing zebrafish embryos found seven genes down regulated after exposure to dexamethasone, prednisolone and triamcinolone at concentrations as low as 0.018–0.0197 μg/L, however morphological changes were not seen below exposure concentrations of 18–19.7 μg/L in transgenic lines (Chen et al., 2017). Zebrafish larvae treated with cortisol at a high dosing (≥72 μg/L) had increased circulating cortisol levels and GC signalling, with genes linked to the immune and defence responses upregulated, but only at the very high exposure of 362 μg/L. Fish exposed to 362 μg cortisol/L that were raised to adulthood still had increased basal cortisol levels and altered expression of genes associated with the defence response and its regulation (Hartig et al., 2016). Adults also suffered from impaired tailfin regeneration and altered expression and regulation of pro-inflammatory genes. This suggests that GC exposure during early life stages can have significant implications for animal health in later life stages, however, again the very high exposure levels for these effects bear no environmental relevance.

6.6. Bone formation and development

In mammals, GCs have major effects on bone formation, growth and function, which can result in glucocorticoid-induced osteoporosis (GIOP) in patients undergoing GC therapy. Most importantly, GCs cause reductions in the number of osteoblasts and impairment of their function, which in turn inhibit bone formation (Delany et al., 1994; Payer et al., 2010). GCs also trigger osteoclastogenesis resulting in increased bone resorption and increased expression of collagenase 3, an enzyme involved in the breakdown of the extracellular matrix.

Similarly, in fish, zebrafish larvae (15 dpf) treated with prednisolone (at 9011 μg/L) had a reduced bone mass and *mmp9* and *mmp13* (genes associated with the breakdown of the extracellular matrix) were upregulated, whilst *entpd5a* (bone mineralization), *acp5a* (bone resorption and ossification) and *sost* (bone formation) (He et al., 2018) were downregulated. Other studies using 8–10 dpf zebrafish larvae have shown that prednisolone (9011 μg/L) also affects genes associated with the focal adhesion signalling pathway, downregulating *itga10* and *itgbl1*, suggesting effects on the extracellular matrix, as occurs in mammals (Huo et al., 2018). As bone and scales have very similar structures, zebrafish scales have been used to non-invasively study GIOP (Chaichit et al., 2021; Pasqualetti et al., 2015, 2012). These studies have shown

that zebrafish exposed to dexamethasone (intraperitoneal injection of 30 μg per g fish body weight and 9811 μg/L) exhibited smaller regenerating scales with less circularity, as well as reductions in scale expression of *mmp2*, *mmp9*, *rankl* (osteoclast differentiation and activation) and *ctsk* (bone remodelling and resorption) (Chaichit et al., 2021; Saito et al., 2020). As well as effects on bone, prednisolone has been shown to damage the cartilage of zebrafish larvae (9011 μg/L) as well as reducing the expression of collagen-encoding genes through GR transcriptional inhibition (1802 μg/L) (*col1a1a*, *col2a1a*, *col9a3*, *col10a1a*, *col11a1a*, and *col11a2*) (Jiang et al., 2021).

GCs also reduce bone regenerative capabilities in fish (Ando et al., 2017; Bohns et al., 2021). In larval and adult zebrafish, exposed to 9011 and 18,022 μg/L, respectively, there were reductions in the numbers, activity and differentiation of osteoblasts and osteoclasts during growth, maintenance and regeneration of bones, as well as reductions in mineralised and calcified areas in larvae (Geurtzen et al., 2017). Similarly, after the amputation of the caudal fin, exposed adult fish had significantly reduced tail fin regeneration capability (Geurtzen et al., 2017). Exposure to budesonide (4305 μg/L) also provided evidence that synthetic GCs greatly reduce the regenerative capabilities of bone in zebrafish (Oppedal and Goldsmith, 2010). In contrast, however, Sharif et al. 2015 showed that exposure of 1dpf zebrafish embryos to dexamethasone treatment (392,464 μg/L for 6 h) resulted in a significant delay to wound healing at later life stages, with most of this effect seen during the beginning of the wound healing process (up to 5 h). Geurtzen et al. 2017 and Azetsu et al. 2019 suggested that this is a result of reduced effective recruitment of osteoclasts to the site of injury. Similar research by De Vrieze et al, 2014 using zebrafish scale regeneration studies supports this (9011 μg/L prednisolone), albeit here the hypothesis was that this was due to an increase in osteoclast activity and matrix resorption. Therefore, although the exact mechanisms are still debated, defects in osteoclasts function seem to be the primary mechanism(s) for GC effects on bone and scale development in fish. However, again these studies on GC effects on bone development and formation in fish have all been carried out at very high concentrations that bear no environmental relevance.

6.7. Behaviour

GC programming can have major effects on the function of the HPA axis in mammals, whether through exposure to exogenous GCs or an increase in endogenous cortisol levels. Such effects can ultimately alter brain development and function throughout life suggested to include reducing exploratory behaviour or increasing the chance of attention deficit-hyperactivity disorder and depression (Kapoor et al., 2008; Lupien et al., 2009; Welberg et al., 2001). A review of GC programming on HPA axis function by Kapoor et al. 2008 summarises the evidence of the effects GCs can have on neuro-behavioural development and function in mammals.

A few studies only have investigated the effects of GC exposure on fish behaviour. They include studies in smallmouth bass (*Micropterus dolomieu*) (Algera et al., 2017) and largemouth bass (*Micropterus salmoides*) (Redfern et al., 2017) where inducing elevated plasma cortisol (via intraperitoneal injection of hydrocortisone hemisuccinate at between 25 and 525 μg per g fish body weight) to levels that occur circulating in the plasma following exposure to ecologically-relevant stressors, such as catch-and-release angling and confinement, resulted in reductions in boldness, aggression, and exploratory behaviours. In another study exposing zebrafish larvae (120hpf) to dexamethasone (1.4 μg/L), cortisol (362 μg/L), prednisone (358 μg/L) and prednisolone (360 μg/L) for 48 h showed similar outcomes, with small reductions in locomotor activity (Zhao et al., 2017). A study by Zhao et al. 2016 showed that exposure of zebrafish embryos to fludrocortisone acetate resulted in a significant increase in locomotor activity at 0.081 μg/L. In the larval offspring of adult fish exposed to fludrocortisone acetate (for 21-days), the effect levels were even lower at 0.042 μg/L. This indicates the potential for maternal effects of GC exposure on behaviour in the next generation, including for environmentally relevant exposures.

GCs can also increase appetite, which is a common side effect in human patients after GC therapy (Berthon et al., 2014). This effect also occurs in other mammals, for example, an *ad-lib* feeding challenge in F2 generation ewes injected with dexamethasone resulted in 10% higher food consumption and a 20% increase in weight compared with controls (Long et al., 2013), indicating also GC exposure can affect appetite programming over generations. There is evidence also to support a similar effect in fish. For example, in goldfish (*Carassius auratus*) exposure to cortisol at 50 μg/g via the food resulted in a stimulated appetite, although this effect was not seen at a treatment level of 500 μg/g (Bernier et al., 2004). The mechanism behind this effect on appetite may link to the neuropeptide Y (NPY); and this is supported in studies on both fish and rats (Beck, 2006).

GCs may also affect reproductive behaviours. For example, in the plainfin midshipman (*Porichthys notatus*) differences in GR and MR expression occur in the central nervous system and liver, and plasma cortisol levels, in “singing” males (which build and guard nests while courting females, with a humming sound) compared with “sneaker” males (that steal into the nest of “singing” males to fertilise eggs deposited there) (Arterbery et al., 2010), however, little research on this subject has been done using synthetic compounds.

6.8. Reproductive development and function

In humans, excessive levels of GCs can affect sexual characteristics, for example, women with Cushing’s syndrome exhibit hyperandrogenic features such as hirsutism, acne or male-pattern alopecia and menstrual irregularity (Kaltsas et al., 2000). Many fish species show hermaphroditism and/or sex change during their lives and it has been suggested that cortisol may be central to this process via mediating a switching in the production of oestrogens to androgens (Goikoetxea et al., 2017). In support of this, cortisol (0.8 mg/g food) treated larval pejerrey (*Odontesthes bonariensis*) show increased 11-KT and testosterone, as well as upregulation of *amh* and downregulation of *cyp19a1a,* which are indicators of masculinisation (Hattori et al., 2009). Similarly, exposure of pejerrey to dexamethasone (0.4 mg/g food) and cortisol (0.8 mg/g food) at 24 °C, which is considered to be a gender-neutral temperature for this species (pejerrey shows temperature-dependent sex determination) resulted in significantly more males (Hattori et al., 2009). It is not known, however, whether these effects are controlled through the GR or the androgen receptor (AR), as it has been shown that some GCs can alter AR transcription and AR levels (Burnstein et al., 1995; Lempiäinen et al., 2017), although this is dependent on the drugs’ specificity for the AR. Examples include exposure of fathead minnows (for 21 days) to beclomethasone dipropionate (1 μg/L) where females developed male secondary sexual characteristics (increased number of tubercles and black dorsal fins, a reduction in ovipositor length, and reduced blood vitellogenin) (Kugathas et al. 2013), and exposure (1000 μg/g food) of the three-spot wrasse (*Halichoeres trimaculatus*) (Nozu and Nakamura, 2015), western mosquitofish (*Gambusia affinis*, 500 μg/L) (Knapp et al., 2011) and black sea bass (*Centropristis striata*, 300 μg/g food) (Miller et al., 2019) to cortisol, resulted in females developing spermatogenic germ cells. Importantly, a GC response element is present in the fish *cyp19a1a* gene (which converts androgen to oestrogen) providing a possible mechanism behind the reductions in oestradiol levels in these studies (Miller et al., 2019). Collectively these effects are suggested to occur via cross-talk between the AR and GCs, through the down-regulation of aromatase expression by *cyp19a1a* reducing levels of oestrogens, and/or through upregulation of *amh* promoting masculinisation (Goikoetxea et al., 2017). Exposure to the synthetic GC beclomethasone dipropionate has also been shown to inhibit egg production in a dose-dependent manner in fathead minnow with an EC_{50} value of 596 ng/L (Thrupp et al., 2018). Several studies, for example, have shown decreased plasma vitellogenin levels (the main yolk protein

Table 2
Summary table of lowest observable effect data for glucocorticoid-induced effects in fish models.

Endpoint	Effect	Compound	Concentration (μg/L)	Exposure	Species	Reference
Cardiovascular system	Increased heart rate	Fludrocortisone acetate	0.006	21 days	Zebrafish (F1 generation)	Zhao et al. 2016
Immunosuppression	Reduction in lymphocytes	Beclomethasone dipropionate	0.01	21 days	Fathead Minnow (Adult)	Margiotta-Casaluci et al. 2016
Glucose metabolism	Increase in plasma glucose	Fludrocortisone acetate	0.042	21 days	Zebrafish (Adult)	Zhao et al. 2016
Behaviour	Increased swimming activity	Fludrocortisone acetate	0.042	21 days	Zebrafish (F1 generation)	Zhao et al. 2016
Development	Accelerated hatching	Corticosterone	0.09	72 hpf	Zebrafish (Embryos)	Willi et al. 2019b
Muscle atrophy	Reduction in spontaneous muscle contractions	Betamethasone	0.11	24 hpf	Zebrafish (Embryos)	Willi et al. 2019b
Osteoporosis	Increased craniofacial measurements	Prednisolone	1	4 dpf	Zebrafish (Embryos)	McNeil et al. 2016
Masculinisation	Females develop male secondary sexual characteristics	Beclomethasone dipropionate	1	21 days	Fathead Minnow (Adult)	Kugathas et al. 2013
Osmoregulation	Alterations in Na + K + -ATPase activity	Dexamethasone	39	2 h	European eel (Adult gill)	Marsigliante et al. 2000
Reproduction	Reduction in eggs spawned per female	Dexamethasone	500	21 days	Fathead Minnow (Adult)	LaLone et al. 2012

precursor in fish) in fish treated with GCs (Berg et al., 2004; Carragher et al., 1989; Kugathas et al., 2013). In female fish, cortisol may also stimulate the onset of puberty by increasing gonadotropins in the pituitary, at the start of oogenesis (Milla et al., 2009). A study using a zebrafish glucocorticoid mutant also showed that female mutants had reduced fertility due to impairments of the kisspeptin-gonadotropin-releasing hormone system, changes in the signalling of oocyte maturation and ovulation, reduced ovulation and alterations to the molecular structure of the follicles (Maradonna et al., 2020).

GCs can also affect reproductive development in male fish (reviewed by Milla et al. 2009). In the Japanese eel (*Anguilla japonica*), moderate concentrations of GCs in spermatogonia have been reported to enhance spermatogonial proliferation induced by 11-KT (Ozaki et al., 2006). Most studies, however, suggest that GCs have a detrimental impact on the male reproductive cycle in fish. For example, increased cortisol has been shown to reduce testicular development, decrease gonad growth and delay spermatogenesis in rainbow trout and common carp (Campbell et al., 1992; Consten et al., 2002).

6.9. Osmoregulation

In fish, cortisol may act both as a GC and mineralocorticoid; neither 11-deoxycorticosterone (DOC) or aldosterone (both mineralocorticoids) have effects on ion regulation in fish (McCormick et al., 2008) and as such cortisol is especially important for saltwater adaptation. Cortisol has been referred to as the "seawater adapting" hormone working in conjunction with the growth hormone and IGF-1 axis. The gill surface is the major diffusion/transport tissue involved in maintaining osmoregulatory balance and multiple reviews have covered the function of cortisol on this tissue (Kwong et al., 2016; McCormick, 2001, 1995). Cortisol treatment (50 μg/g injection) has been shown to increase Na^+K^+-ATPase activity (McCormick et al., 2008), Ca^{2+} uptake through upregulation of epithelial calcium channels gene expression (20 mg/L) (Lin et al., 2016), Na^+ uptake (at 181 μg/L) (Kumai et al., 2012) and regulating the secretion of hydrogen through H^+-ATPase-rich ionocytes (at 20 mg/L) (Lin et al., 2015). The mechanism for the effect of cortisol in saltwater tolerance is known to occur predominantly by increasing the expression of the saltwater Na^+/K^+-ATPase (NKAα1b) isoform in gill (Bernier et al., 2009; McCormick, 2001), and modifying water and ion uptake in the intestine (Veillette et al., 1995). In freshwater fish, cortisol and prolactin act together to minimise the loss of sodium and chloride ions, as well as stimulating the freshwater Na^+/K^+-ATPase (NKAα1a) isoform which in turn increases sodium re-uptake across various osmoregulatory surfaces (Bernier et al., 2009; Tokarz et al., 2015).

In the European eel (*Anguilla anguilla*), exposure to dexamethasone (39 μg/L) results in increases in Na^+K^+-ATPase activity in ionocytes of both saltwater and freshwater adapted animals, while activity in pavement cells decreased in freshwater adapted animals but increased in saltwater-adapted animals (Marsigliante et al., 2000). A similar effect was seen in gilthead seabream *Sparus aurata* whereby cortisol (400 mg/kg food) and dexamethasone (300 mg/kg food) fed animals had reduced Na^+K^+-ATPase and H^+-ATPase gill activity, which resulted in increased plasma ammonia (both treatments) and increased plasma osmolality (dexamethasone) (Jerez-Cepa et al., 2019). Acid-base regulation by ionocytes in the gills are understood to be controlled by the sodium/hydrogen exchanger and cortisol exposure (25 mg/L) has also been shown to increase acid secretion in 7 dpf medaka larvae through the upregulation of *nhe3* and *rhcg1* (acid-secretion-related transporters) by glucocorticoid receptor 2 (Lin et al., 2021). Given the fundamental importance of osmoregulation in fish physiological function and survival, and especially given the likely effects of climate change on aquatic environment ion balances, further research focusing on exposure to synthetic GC at environmental levels in relation to osmoregulatory function would seem to be of particular future importance.

A summary of the potential effects GCs on fish is given in Table 2 detailing the lowest observable effects data currently in the literature for each given endpoint discussed above. The values given are as they have been reported in the available literature and without any systematic evaluation of their comparative merits. As such, the use of quality assessment criteria such as the Criteria for Reporting and Evaluating ecotoxicity Data (CRED; Moermond et al., 2016) may aid in the judgment of whether or not environmental concentrations of glucocorticoids are likely to be adversely affecting fish.

7. Does the evidence suggest GCs are a risk to fish in the environment?

Given the conservation of the HPI/HPA axis and function of GCs between mammals and fish, the likelihood of biological effects after GC exposure in fish is high, although whether this is likely to occur at concentrations found in the environment is less clear. The majority of studies on GCs in fish have focused on the role of eGCs and the stress response, however, as outlined above, there are some studies in which the pharmacological and toxicological effects of synthetic GCs in fish have been demonstrated, albeit in some cases the results are contradictory. It is also the case that many of these exposures have been conducted at concentrations orders of magnitude higher than have been detected in surface waters.

Table 3
Calculated worst-case scenario parameters and outputs for the "Fish Plasma Model" for a range of synthetic GCs. See Fig. 2 for details on calculations and descriptive outcomes of effect ratios (Al-Habet and Rogers (1989), Brogden and Wagstaff (1997), Daley-Yates et al. (2001), Derendorf et al. (1995), Dilger et al. (2009), Harrison and Tattersfield (2003), He et al. (2011), Hochhaus et al. (1990), Loew et al. (1986), Nolting et al. (2001), Polito et al. (2016), Sagcal-Gironella et al. (2011), Toothaker et al. (1982), Varoni et al. (2012)).

Compound	logD_{ow} (pH 7.4)[a]	$LogP_{Blood;Water}$	Maximum environmental concentrations (ng/L)	Minimum H_TPC (ng/L)	Predicted F_{SS}PC (ng/L)	Effect ratio
Rimexolone	3.8	78.34	47 (Shen et al., 2020)	150 (Brogden and Wagstaff, 1997)	3682.1	0.041
Fluticasone propionate	3.71	67.19	<1 (Ammann et al., 2014; Macikova et al., 2014)	130 (Harrison and Tattersfield, 2003)	<67.2	>1.93
Beclomethasone 17-propionate	3.46	44.24	0.82 (Shen et al., 2020)	66.8 (Daley-Yates et al., 2001)	36.28	1.84
Clobetasol propionate	3.36	37.39	7.3 (Shen et al., 2020)	120 (Varoni et al., 2012)	272.97	0.44
Budesonide	3.02	21.07	48 (Shen et al., 2020)	180 (Dilger et al., 2009)	1,011.36	0.18
Clobetasol	2.74	13.19	<1 (Ammann et al., 2014)	120 (Varoni et al., 2012)	<13.19	>9.10
Triamcinolone acetonide	2.57	9.91	14 (Shen et al., 2020)	2,000 (Derendorf et al., 1995)	138.75	14.42
Flunisolide	2.54	9.42	0.99 (Shen et al., 2020)	1,060 (Nolting et al., 2001)	9.33	114
Fludrocortisone acetate	2.24	5.69	14 (Ammann et al., 2014)	190 (Polito et al., 2016)	79.67	2.38
Triamcinolone diacetate	2.15	4.89	9 (Shen et al., 2020)	69,840 (Hochhaus et al., 1990)	44.03	1,586
6α-Methylprednisolone	1.97	3.61	12 (Shen et al., 2020)	207,000 (Al-Habet and Rogers, 1989)	43.38	4,772
Dexamethasone	1.92	3.32	12 (Shen et al., 2020)	7,900 (Loew et al., 1986)	26.59	297
Betamethasone	1.92	3.32	7.2 (Shen et al., 2020)	14,500 (He et al., 2011)	23.93	606
Cortisol / Hydrocortisone	1.66	2.15	20 (Chang et al., 2009)	199,000 (Toothaker et al., 1982)	42.94	4,635
Prednisolone	1.66	2.14	94 (Shen et al., 2020)	301,000 (Sagcal-Gironella et al., 2011)	201.16	1,496
Triamcinolone	0.92	0.62	22 (Shen et al., 2020)	2,000 (Derendorf et al., 1995)	13.62	146.9

[a]Taken from ACD/Labs.

Many of the underlying mechanisms of GC action in mammals, let alone fish, are not fully understood, and improving our knowledge of these mechanisms is crucial to better understand the potential impact of GCs in non-target species groups. Of those studies in which effects have been demonstrated in fish, the data suggest that these are highly dependent on the life stage exposed and duration of exposure and concentration of the drug used. Despite this, some general themes emerge. Overall, consistent effects have been shown on the genes regulating glucose, immune function and developmental processes and at low ng/L concentrations, that are comparable with those concentrations measured in the aquatic environment. Despite this, the vast majority of physiochemical, physiological or behavioural effects are seen at, and above, 1 μg/L, and these concentrations are highly unlikely to be achieved in most environments or the bodies of animals therein. There are, however, some exceptions. Plasma glucose concentrations, immune cell numbers, behaviour and heart rate effects have all been observed in fish at water concentrations of $\leq$ 1 μg/L and this, therefore, suggests that certain biological effects are possible in wild fish populations exposed to

synthetic GC drugs. The lowest observable effects for the majority of endpoints were observed in exposure studies extending to 21 days, which suggests that exposure period is important for these compounds, with longer exposures resulting in effects at significantly lower concentrations than shorter exposures. Therefore, understanding the fluctuations in concentrations of these compounds and the spatiotemporal distribution and life histories of species in the aquatic environment is critical in understanding the risks to different species. Consequently, more chronic exposure studies are warranted in fish that mimic real-world exposure scenarios over full life cycles and across multiple generations in compounds deemed to be of higher risk, given the available information, to robustly assess the true risk of synthetic GCs to populations of fish. Indeed, it has been suggested that transgenerational effects of GCs are possible via alterations to the epigenome (via modification of DNA methylation, histone acetylation and microRNA expression) which can all be induced by prenatal exposure to these drugs (Moisiadis and Matthews, 2014). Whether such effects result in adverse consequences in these animals remains to be demonstrated and, in common with other biologically active compounds found in the environment, this is a much-needed area for future research. Using the data from such studies, simple quantitative *in silico* approaches, such as a comparison of predicted environmental concentration/no effect concentrations ratios (PEC:PNEC), or the use of the fish plasma model of Huggett et al. 2003 can be used to support the assessment of potential environmental risk. Application of the latter approach, which uses to $LogD_{ow}$, human therapeutic concentrations and measured environmental concentrations to estimated risk has been applied to various synthetic GCs and the results of this analysis are shown in (Table 3). We emphasise that in these assessments the model is highly conservative, taking the lowest reported therapeutic concentrations and the highest reported environmental measurements to predict an effect ratio. The simple model outputs suggest that three GCs (rimexolone, clobetasol propionate and budesonide), have the potential to induce biological effects in fish at concentrations that have been reported present in the environment. We do though point out that the paucity of the environmental measurements for these synthetic GCs are limiting in the resulting risk projections for our analyses. Indeed, we highlight that more environmental measurements of GCs in surface waters are vital to provide high confidence in the level of exposure likely to be encountered in natural waters and better understand the risks of this class of pharmaceutical to fish.

The issue of mixture-mediated effects for synthetic GCs is an important one given that all GCs share a common pharmacological and strongly conserved mechanism of action. In this respect, an additive effect has been reported for exposure of zebrafish embryos to a mixture of clobetasol propionate and cortisol, on heart rate and spontaneous muscle contraction (Willi et al. 2018). Similarly, exposure to the synthetic steroids EE2, trenbolone, beclomethasone dipropionate, desogestrel and levonorgestrel, has been shown to have additive suppressive effects on egg production in the fathead minnow (Thrupp et al., 2018). Similar effects in fathead minnows were found for an exposure to a mixture of beclomethasone dipropionate and trenbolone (Thrupp et al., 2018). Future research needs to assess the interactive effects of environmentally relevant mixtures of GCs, and combinations with other potent synthetic steroids, to better assess likely risks to organisms in the aquatic environment.

In conclusion, GCs have widespread effects in vertebrates, including fish, and affect many key processes in the body including glucose metabolism, immune function and various developmental processes. GCs are present in some surface waters at levels shown to cause biological effects in fish and given their widespread use is on the rise, levels in the environment are likely to increase. Using the fish plasma model, over half of GC compounds were predicted to have insignificant risk to fish (56%), however some were predicted to be of moderate (25%) and potentially high (19%) risk to fish, although the dataset of compounds used for this analysis was small. It is hoped that this review will encourage, and support continued and directed research into the effects of this relatively unstudied group of potent steroid drugs in fish at environmental concentrations and in mixtures (and other wildlife species) as well as *in situ* field studies to ensure better understanding of potential risks of GCs in the natural environment.

Author contributions

The manuscript was written through contributions from all authors and all authors have given approval to the final version.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Charles Hamilton was in receipt of a scholarship (awarded to Prof. Charles Tyler, Dr Matthew Winter and Dr Luigi Margiotta-Casaluci) co-funded by AstraZeneca. Dr Stewart Owen is an employee of AstraZeneca, a biopharmaceutical company with an interest in the discovery, development and commercialisation of prescription medicine including glucocorticoids.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107163.

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