Exploring biological read across of endocrine-mediated effects between birds and other vertebrates

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Introduction

Regulation (EC) No. 1107/2009 states that for approval, pesticide active substances require a consideration of endocrine disrupting (ED) properties that may cause adverse effects on non-target organisms, with the relevant guidance being EFSA/ECHA (2018). A battery of test methods is available in mammals, fish and amphibians (OECD, 2018) which focus on the modalities of Estrogen, Androgen, Thyroid, and Steroidogenesis. However, for bird species only 2 in-vivo test guidelines are available for use in the ED assessment of chemicals, and these have limitations: the one generation avian reproduction study (OECD 206), which includes only apical endpoints (EFSA/ECHA, 2018) and the US EPA avian 2 generation toxicity test in Japanese quail ('ATGT'; US EPA TG OCSPP 890.2100/740-C-15-003), which is not currently validated by the OECD. In order to determine if the available suite of ED studies in other vertebrates would capture substances with ED concerns for birds, the observed effects on birds and other vertebrates were considered via a review of published *in vivo* case studies with known EDs. Here, 4 examples from this review are presented, representing the key EATS modalities.

E — Methoxychlor

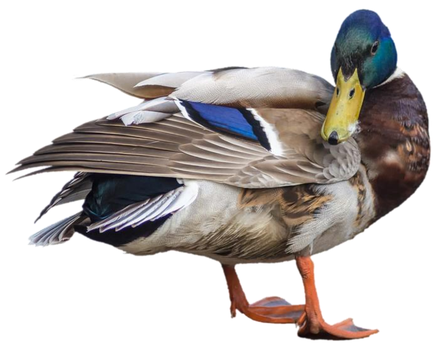
Estrogenic

Birds	Other Vertebrates
Feminised male sexual behaviour, plasma estradiol ↓, androgens ↓	Mammal: male sexual interest ↓, male testosterone levels ↓, body weight ↓, number of foetuses ↓, foetus weight ↓
	Fish: male testosterone levels ↓, female 17β-estradiol ↓, female gonad histopathology, female gonadosomatic index (GSI) ↓, fecundity/fertility effects
	Amphibian: male testis weight ↓, male sperm count ↓, female ovary size ↓, female gonad histopathology

A — Vinclozolin

Anti-Androgen

Birds	Other Vertebrates
Male spermatogenesis ↓, male reproductive performance ↓, Avian 2-gen: some effects on estradiol, testosterone, thyroid	Mammals: male seminal vesicle ↓, urogenital malformations, disrupted sexual differentiation
	Fish: male VTG ↑, male 17β-estradiol ↑, male testosterone ↓, male GSI ↑, female 17β-estradiol ↓, female GSI ↑, female gonad histopathology, fecundity/fertility ↓



- The endocrine system structure and function are highly conserved between birds and other vertebrate taxa, especially mammals
- Some differences exist e.g., calcium mobilization and sexual development
- However, an assessment using several case-studies suggests that there is a good basis for biological read across between birds and other vertebrates
- ED concerns in birds are considered likely to be captured by tests with other vertebrates
- This provides a basis for further investigation into potential endocrine similarities between birds and other vertebrates

T — Mancozeb

Thyroid inhibitor

Birds	Other Vertebrates
Thyroid histopathology, thyroid weight ↑, thyroid volume ↑, plasma T4 ↓, changes in plasma T3/TSH. Delay in singing, delay pairing, delay secondary sexual characteristics	Mammal: thyroid tumors, thyroid histopathology, plasma T4 ↓
	Amphibian: thyroid histopathology, delayed development

S — Fadrozole

Steroidogenesis

Birds	Other Vertebrates
Bird song ↓, aromatase activity ↓, steroidogenesis ↓, estrogenic action ↓	Fish: Brain aromatase ↓, female plasma β estradiol ↓, female VTG ↓, male testosterone ↑, fecundity ↓, male/female gonad histopathology
	Amphibians: masculinization
	Mammals: estrogen synthesis ↓

References

Alward et al. (2016) DOI: 10.1038/srep32344; Ankley et al. (2002) DOI: 10.1093/toxsci/67.1.121; Ankley & Jensen (2014) DOI: 10.1002/etc.2708; ECHA/EFSA (2018); Eroschenko et al. (2002) DOI: 10.1016/s0892-0362(01)00194-5; European Food Safety Authority (2019); Fort et al. (2004) DOI: 10.1093/toxsci/kfh230; Gladue & Clemens (1980) DOI: 10.1210/endo-106-6-1917; Gray et al. (1994) DOI: 10.1006/taap.1994.1227; Grisham et al. (2007) DOI: 10.1016/j.neulet.2007.03.002; McArdle et al. (2020) DOI: 10.1002/etc.4682; McGary et al. (2001) DOI: 10.1897/1551-5028(2001)020<2487:iovorb>2.0.co;2; Niemann et al. (2004) DOI: 10.1007/s00244-003-2285-5; OECD (2018); Olmstead et al. (2009) DOI: 10.1002/etc.4163; Ottinger et al. (2005) DOI: 10.1016/j.brainresbull.2004.11.019; Ottinger & Rochester (2013); Pandey et al. (2017) DOI: 10.1016/j.physbeh.2017.01.030; Pandey & Mohanty (2015) DOI: 10.1016/j.chemosphere.2014.11.061; Steel et al. (1987) DOI: 10.1016/0039-128x(83)90068-5; US EPA TG OCSPP 890.2100/740-C-15-003 (2015).

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