Development and evaluation of adverse outcome pathways predicting adverse effects of conazole fungicides on avian species

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Conazoles are a class of fungicides commonly used in agriculture and as pharmaceuticals to prevent the spread of fungus through inhibition of cytochrome P450 14α-demethylase (CYP51). However these fungicides are known to act promiscuously on other cytochrome P450 enzymes (CYPs), including those involved in steriodogenesis, leading to adverse reproductive effects in fish. Key events in the adverse outcome pathway (AOP) describing the effects of steriodogenesis-inhibiting conazoles on fish include depressed steroid synthesis, decreased vitellogenin production, impaired oocyte growth and maturation, and ultimately reductions in spawning and cumulative fecundity. As oviparous species, egg formation in birds involves tightly regulated steriodogenesis and vitellogenesis, making these species potentially susceptible to analogous effects associated with conazole exposure. Further, birds have been shown to experience dysregulation of non-steroidogenic CYPs upon exposure to various fungicides. Utilizing mammalian-oriented ToxCast data for 16 conazoles sorted by potency and positive hit rate in the screening assays, we identified additional molecular targets impacted by exposure to conozoles, including hepatic CYPs (multiple CYP2 and CYP3 isoforms) and PXR. Upon conducting several protein alignments comparing mammalian CYP2 or CYP3 isoforms to available aves protein sequences we identified CYP 2C45 and CYP 2H2 as potential analogous targets for the action of conazoles in bird species (e.g., great cormorant, zebra finch, chicken, and wild turkey). Among these, CYP2C45 is thought to be involved in the biotransformation of steroids in birds, suggesting it may be another important target to consider relative to reproductive and endocrine effects. By leveraging the defined AOP for the effects of conazole fungicides on fish, US EPA's ToxCast data to identify molecular targets subject to perturbation by conazoles, and analyses of CYP enzyme similarity among taxa we have begun to delineate a number of hypothesized AOPs relevant to the effects of conazoles on birds.