

Science for Environment Policy

Anti-diabetic drug causes intersex in male fish

Intersex fish, in which male reproductive tissues become 'feminised', are increasingly being identified. This effect has traditionally been attributed to birth-control medications. This study exposed fish to a widely prescribed anti-diabetic, metformin. Male fish developed female sexual characteristics and reproductive rate decreased, which suggests that metformin may be a non-traditional endocrine-disrupting compound.

Intersex fish have been identified in watersheds downstream of wastewater treatment plants (WWTPs) across the world. [Endocrine disrupting compounds](#) (EDCs) introduced into the [aquatic environment](#) by human activity have been named as the most likely cause. Endocrine disruption is often attributed to the presence of hormones, such as oestrogens found in the contraceptive pill. However, new research suggests that EDCs could act via pathways separate to the archetypal hormone receptor pathways. This is a possibility worth exploring, as many non-hormone pharmaceuticals are found in effluent, and often at much higher concentrations than oestrogens.

Among these, the anti-diabetic drug metformin is one of the most abundant. Although metformin does not share the hormone-like structure of conventional EDCs, fish exposed to metformin for short periods of time have shown signs of endocrine disruption, such as the expression of an egg-yolk protein normally only found in females.

To investigate the effect of long-term exposure, the authors of this study exposed fathead minnows (*Pimephales promelas*) to metformin from the fry stage (30 days post-hatch) to adulthood (around 1 year). They then assessed gonad morphology, secondary sex characteristics, growth and reproduction.

Fathead minnow fry were divided into tanks dosed with metformin at similar concentrations to those measured in WWTP effluent in Wisconsin, USA, which were also similar to those of European effluents. Control tanks were also established. After 320 days of group exposure, adult male-female pairs were separated to assess reproductive success under metformin exposure.

At the end of exposure, the fish were weighed, measured and photographed. The secondary sex characteristics (features that appear at sexual maturity and distinguish between genders) of male minnows were scored on a scale of 0–9. Male testes were assessed under a microscope, receiving a score for intersexuality on a scale of 0–7.

Exposed male minnows displayed significant intersexuality. 84% of metformin-treated males were intersex compared to just 13% of the controls, and histological analysis of their tissues generated an average score of 3.8 (meaning egg cells occurred frequently throughout testicular tissue) compared to 0.2 for the control. Some sections taken from the exposed fish were entirely made up of female (egg) cells.

Treatment with metformin also led to significant reductions in weight and body size, and the number and size of clutches of eggs was significantly lower in metformin-exposed pairs. Surprisingly however, males with an intersex score as high as six (meaning over half of the testis was comprised of ova) had high secondary sex scores, displaying the usual male features. Furthermore, they were still able to produce eggs. This suggests metformin does not cause endocrine disruption via changes to the synthesis of hormones and may instead act via insulin signalling.

This study, the first to investigate the endocrine disrupting effects of full life cycle exposure to metformin in fish, shows that metformin leads to the development of intersex in males, reduces the size of male fish, and reduces reproductive rate.

The authors also highlight the importance of broadening investigations beyond traditional hormone receptor and response assays. They say metformin would likely not be detected by existing EDC assays and call for [screening methods](#) that consider non-traditional endocrine disrupting pathways.



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