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The Effect of Environmental Concentrations of Metformin on Growth, Development, Sex Differentiation, and Nitrogen Metabolism of Developing Zebrafish (*Danio rerio*)

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Abstract

Metformin is the most widely prescribed anti-hyperglycemic medication and has been categorized as an emerging contaminant in aquatic ecosystems owing to its ubiquitous environmental occurrence. Metformin in the concentrations range of 10-50 µg/L has been reported from natural water bodies worldwide. The exact effects of pharmaceutics contaminant, metformin on aquatic ecosystem health remain poorly known. Studies have acclaimed metformin-mediated reproductive health effects in aquatic fauna, suggesting non-classical pathways of endocrine disruption. However, the growth-related and physiological effects of metformin on aquatic organisms remain poorly known. This study was carried out to investigate the effects of long-term exposure to environmentally relevant concentrations of metformin on growth, development, and physiology of juvenile zebrafish (*Danio rerio*). Zebrafish of 25 dpf (days post-fertilization) were acclimatized for 5 days, exposed to environmental doses of metformin (10 µg/L, 50 µg/L), and controlled for 60 days in triplicate treatments. Increments in body length and weight, specific growth rate, body mass index, condition factor, sex ratio, and nitrogen excretion were investigated. The condition factor was used to determine the general well-being of fish. According to the results, length gain of fish was not significantly different between treatments and control ($p>0.05$). However, weight gain, specific growth rate, and body mass index were significantly low in zebrafish under 50 µg/L of metformin treatment, when compared with fish in control and 10 µg/L of metformin treatments ($p<0.05$). Significantly low condition factors were observed under both metformin concentrations, indicating the poor well-being of fish under metformin exposure ($p<0.05$). Ammonia excretion rate of zebrafish was significantly low in 50 µg/L of metformin treatment than 10 µg/L of metformin and control, indicating disturbed nitrogen metabolism ($p<0.05$). Significantly high female-biased sex ratios were observed under both metformin concentrations in 90 days old zebrafish. However, control treatment had male: female sex ratio of 1:1 ($p<0.05$). Based on the findings it can be concluded that, long-term exposure to environmentally relevant concentrations of metformin could lead to detrimental effects on the growth, sex differentiation and physiology of developing zebrafish. These findings highlight the adverse impacts of pharmaceutical pollution on aquatic ecosystems.

***Keywords**:* Metformin, Growth, Sex ratio, Zebrafish, Endocrine disruption