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Exposure to environmentally relevant concentrations of acetaminophen increases the vitellogenin expression in juvenile *Danio rerio* (zebrafish)

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Non-Steroidal Anti Inflammatory Drug acetaminophen has become the most common pharmaceutical pollutant in aquatic ecosystems. Recently a non-classical pathway of endocrine disruption is suggested with acetaminophen. Early life stages account for a significant level of hormone-regulated development therefore, it is important to assess whether early life exposure to acetaminophen could result in endocrine disruption in aquatic organisms. Vitellogenin (Vtg) is an egg precursor protein produced in response to estrogen and serves as a reliable molecular marker to assess the xenoestrogen-induced endocrine disruption. Therefore, this study was carried out to investigate the effects of long-term juvenile exposure to environmentally relevant concentrations of acetaminophen on vitellogenin expression in model organism, zebrafish (*Danio rerio*). Zebrafish of 25 days post fertilization were maintained under environmentally relevant acetaminophen concentrations of 10 µg/L, and 75 µg/L, and in control tanks for 60 days in triplicate with 18 fish in each tank. Vtg-1, the most predominant type of Vtg mRNA produced in zebrafish liver was analyzed using qRT-PCR with β-actin as the housekeeping gene. Furthermore, hepatic vitellogenin expression has been observed with hematoxylin and eosin staining of zebrafish hepatic sections. According to the results, acetaminophen-exposed zebrafish showed higher Vtg-1 gene expression than the fish of control treatment. 10 µg/L acetaminophen showed the highest Vtg-1 expression followed by 75 µg/L of acetaminophen in fish. Hematoxylin and eosin staining of the liver of male zebrafish from control treatments appeared eosinophilic indicating the absence of Vtg while hepatocytes of control female fish were more basophilic indicating Vtg expression. However, under 10 µg/L of acetaminophen exposure, male and female fish hepatocytes appeared more basophilic than the control treatment indicating acetaminophen-induced Vtg secretion. However, 10 µg/L concentration shows a higher basophilic nature compared to 75 µg/L, especially in female fish. The lowered Vtg expression in 75 µg/L can be due to the increased hepatotoxicity caused by the higher doses of acetaminophen which overrides the physiological activity in acetaminophen-treated fish, dilated capillaries were observed compared to fish in the control treatment. It has been demonstrated that estrogenic xenobiotics stimulate the synthesis of Vtg by acting on the liver's estrogen receptors. Increased Vtg -1 mRNA in low acetaminophen concentration as shown in qRT-PCR and liver histopathology postulate an “estrogen-like activity of acetaminophen”. The results indicate that acetaminophen has the potential to increase vitellogenin expression in zebrafish even under environmentally relevant low concentrations indicating an endocrine disruption effect during juvenile exposure.

Keywords: Acetaminophen, Endocrine disruption, Vitellogenin, Juvenile zebrafish, environmentally relevant doses

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