Multistage Neuroendocrine and Metabolic Disruption Induced by Diisopentyl Phthalate in Zebrafish: Evidence from Embryonic, Larval, and Adult Exposure Models

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INTRODUCTION: Diisopentyl phthalate (DiPP), a plasticizer widely used in consumer goods, has been increasingly detected in environmental samples and human biological matrices, including pregnant women in Brazil. This finding raises concerns about potential endocrine-disrupting effects during critical developmental periods. Despite its recognized bioaccumulation potential and persistence, little is known about its multistage impacts across vertebrate life cycles. The detection of DiPP metabolites in maternal samples highlights the urgent need to evaluate its toxicological effects, particularly regarding developmental, neuroendocrine, and reproductive health risks. **OBJECTIVE:** This study aimed to investigate acute and chronic DiPP toxicity across three key life stages, embryos, larvae, and adults, of zebrafish (*Danio rerio*), integrating behavioral, molecular, metabolic, and reproductive endpoints. **MATERIALS AND METHODS:** Zebrafish embryos and larvae were acutely exposed to DiPP (12.5–1000 µg/L) and evaluated for morphological changes, neurobehavioral parameters (activity/inactivity index, tail coiling, swimming behavior), acetylcholinesterase activity, oxidative stress biomarkers, energy metabolism, and gene expression (neurodevelopment, neurotransmission, endocrine disruption). Adult females were chronically exposed (30 days) to environmentally relevant concentrations (31.25, 62.5, and 125 µg/L), followed by behavioral assays (anxiety-like and social behavior), ovarian histology, vitellogenin quantification (ELISA), metabolic gene analysis (*pparα, pparγ, g6pca1/2*), and assessment of oxidative stress markers in brain and liver. **RESULTS AND CONCLUSION:** Acute DiPP exposure in embryos and larvae induced hypoactivity, impaired neuromuscular development, morphological malformations (spinal curvature, edema), reduced acetylcholinesterase activity, altered energy allocation, and increased oxidative stress, with significant modulation of neurodevelopmental (*neurog1, sox2, pax6a*) and estrogen-related (*vtg1, esr1, cyp19a1b*) genes. Behavioral endpoints were highly sensitive, revealing early neurotoxicity. In adults, chronic exposure triggered strong anxiogenic behavior and social withdrawal, associated with dopaminergic and serotonergic pathway disruption. Reproductive toxicity was evidenced by accelerated folliculogenesis, increased ovarian maturation, upregulation of kiss1 and vitellogenin, and reduced estrogen receptor expression. Metabolic disruption was confirmed by altered lipid and glucose metabolism genes and oxidative stress imbalance between brain and liver tissues. Overall, DiPP induces integrated neuroendocrine and metabolic toxicity from early development through adulthood in zebrafish, emphasizing the urgent need for regulatory action to address human and environmental health risks.

Endocrine disruption; Behavioral toxicity; Oxidative stress; Reproductive impairment; Environmental contaminant.

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