

# Developmental pyrethroid exposure disrupts molecular pathways for circadian rhythms and MAP kinase in mouse brain.

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**Introduction:** Neurodevelopmental disorders (NDDs) are a category of pervasive disorders of the developing nervous system with few or no recognized biomarkers. A significant portion of the risk for NDDs, including attention deficit hyperactivity disorder (ADHD), is contributed by the environment, and exposure to pyrethroid pesticides during pregnancy has been identified as a potential risk factor for NDD in the unborn child. We recently showed that low-dose developmental exposure to the pyrethroid pesticide deltamethrin in mice causes male-biased changes to ADHD- and NDD-relevant behaviors as well as the striatal dopamine system.

**Objective:** Here, we used an integrated multiomics approach to determine the broadest possible set of biological changes in the mouse brain caused by developmental pyrethroid exposure (DPE).

**Methods:** Using a litter-based, split-sample design, we exposed mouse dams during pregnancy and lactation to deltamethrin (3 mg/kg or vehicle every 3 days) at a concentration well below the EPA-determined benchmark dose used for regulatory guidance. We raised male offspring to adulthood, euthanized them, and pulverized and divided whole brain samples for split-sample transcriptomics, kinomics and multiomics integration.

**Results:** Transcriptome analysis revealed alterations to multiple canonical clock genes, and kinome analysis revealed changes in the activity of multiple kinases involved in synaptic plasticity. Multiomics integration revealed a dysregulated protein-protein interaction network containing primary clusters for mitogen-activated protein (MAP) kinase cascades, regulation of apoptosis, and synaptic function.

**Conclusion:** These results demonstrate that DPE causes a multi-modal biophenotype in the brain relevant to ADHD and identifies new potential mechanisms of action.