High-content screening in zebrafish embryos identifies abamectin as a potent neurotoxicant

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ABSTRACT

During development, the nervous system is a sensitive target for chemical exposure in both humans and animal models, and early life-stage exposures can lead to long-term effects on motor activity, sensory function, and cognition. Currently, there are minimal to no developmental neurotoxicity (DNT) data available for thousands of chemicals used in commerce, and it is impractical to screen these chemicals in rodent models using the existing DNT test guideline, as this test is costly, time- and animal-intensive, and low-throughput. Therefore, there is a recognized need to use alternative non-mammalian models to support screening and prioritization of chemicals for DNT testing, as well as hypothesis-driven studies that may help uncover mechanisms of DNT for pesticides and understudied high-production volume chemicals in commerce. Using zebrafish as an animal model, the objectives of this dissertation were to: 1) develop a high-content screening (HCS) assay for rapid and cost-effective identification of potential developmental neurotoxicants during zebrafish embryogenesis, and 2) begin investigating the mechanism of action of abamectin – an insecticide identified as a positive hit in our HCS assay – within zebrafish embryos. Data presented within Chapter 2 suggests that, compared to existing zebrafish-based assays, our HCS assay provides a simpler, streamlined discovery platform for identifying and prioritizing potential developmental neurotoxicants with: 1) increased sample sizes; (2) broad concentration–response format; (3) short assay duration (~22 h total); and (4) minimal technical grade test material...
needed for screening. Data presented within Chapter 3 suggests that 1) abamectin induces rapid and reversible hypoactivity within early zebrafish embryos, 2) abamectin-induced hypoactivity is blocked by pretreatment with γ-aminobutyric acid (GABA) antagonists, and 3) zebrafish and mammalian ionotropic GABA receptor subunits are homologous – suggesting that these findings may have relevance to rodent models and humans. Overall, our findings suggest that zebrafish-based behavioral assays can be used within a tiered regulatory toxicity testing framework to help screen and prioritize chemicals for DNT testing in rodent models and develop hypothesis-driven studies in zebrafish embryos. Therefore, our HCS assay, in combination with follow-up studies, provides a rapid, cost-effective method for identifying and characterizing potential developmental neurotoxicants, helping to fill the current DNT data gap.