

Use of Zebrafish Data in DART Health Hazard Assessment

Introduction

Marlissa Campbell, Ph.D.

Developmental and Reproductive Toxicant
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Use of zebrafish data in recent OEHHA hazard identification documents (HIDs)

- “Evidence on the Developmental Toxicity of Cannabis (Marijuana) Smoke and Δ^9 -THC” OEHHA 2019
- “Evidence on the Male Reproductive Toxicity of Perfluorononanoic Acid (PFNA) and Its Salts and Perfluorodecanoic Acid (PFDA) and Its Salts” OEHHA 2021



“Evidence on the Developmental Toxicity of Cannabis (Marijuana) Smoke and Δ^9 -THC” OEHHA 2019

Neurodevelopmental effects observed in zebrafish included

- Δ^9 -THC exposure altered motor responses to visual stimuli
- Δ^9 -THC exposure altered motor responses to sound stimuli

Mechanistic data on the endocannabinoid system in zebrafish

- Widespread expression of an endocannabinoid receptor (CB1R) in specific regions of the CNS in zebrafish larvae by 48 hours post fertilization (hpf)
- Δ^9 -THC during gastrulation (~6 hpf) caused effects consistent with altered calcium ion homeostasis during neurodevelopment

Zebrafish compared to rodent test species

- Findings in zebrafish supported effects seen in mammalian models



“Evidence on the Male Reproductive Toxicity of Perfluorononanoic Acid (PFNA) and Its Salts...” OEHHA 2021

PFNA exposure of zebrafish

- Reduced egg production and hatching
- Increased serum testosterone and estradiol
- Altered gonadal expression of genes related to the hypothalamic-pituitary-gonadal (HPG) axis
- Increased transthyretin transcription

Zebrafish results for PFNA compared to rodent test species

- Inconsistencies could be related to species differences, or to other aspects of experimental procedure (dose, timing, etc.)



“Evidence on the Male Reproductive Toxicity of...
Perfluorodecanoic Acid (PFDA) and Its Salts” OEHHA 2021

PFDA exposure of zebrafish

- Changes in plasma hormone ratios (e.g., estradiol to testosterone)
- Dose-dependent increase in gonadal expression of the steroidogenic enzyme, aromatase
- Increased expression of the vitellogenin 1 gene in the livers of male zebrafish, suggesting estrogenic effects

Zebrafish results for PFDA compared to rodent test species

- Zebrafish data are consistent with other evidence suggesting involvement of effects on the hypothalamic-pituitary-gonadal (HPG) axis in PFDA-mediated male reproductive toxicity



Potential increase in use of zebrafish for evaluating toxicity

US EPA 2019 Memorandum

- Reduce requests for and funding of mammalian studies by 30% by 2025
- After 2035, mammalian studies to require case-by-case approval
- Aquatic animals not protected as “live vertebrates” prior to hatching (~72 hours post-fertilization for zebrafish)

EU Policies and Proposals

- Animal testing for cosmetic products prohibited since 2013
- Planning for EU-wide action and timelines phasing out use of animals in research and testing
- Zebrafish larvae not protected as animals prior to 120 hours post-fertilization



General introduction to today's presentations

1. Comparative reproductive and developmental biology of zebrafish
2. Zebrafish as a model for large scale screening for potential DART hazard and risk
3. Zebrafish as an experimental model for investigating development at the cellular level
4. Zebrafish as an experimental model for investigating development at the molecular level

