

**Abstract Title:**

An evaluation of the chronic effects of Endocrine Disrupting Chemical 4-tert-octylphenol using Japanese Medaka in a Multigenerational Test.

**Authors:**

M. Dybvig<sup>3</sup>, R. Johnson<sup>1</sup>, K. Flynn<sup>1</sup>, D. Hammermeister<sup>1</sup>, D. Lothenbach<sup>1</sup>, F. Whiteman<sup>1</sup>, M. Haasch<sup>2</sup>, J. Nagel<sup>3</sup>, W. Backe<sup>3</sup>, M. Sykes<sup>3</sup>, M. Mereness<sup>3</sup>, H. Waterhouse<sup>3</sup>, and C. Blanksma<sup>3</sup>

<sup>1</sup>, U.S. EPA, NHEERL, Mid-Continent Ecology Division, Duluth, MN; <sup>2</sup>, National Research Council, Research Associate; <sup>3</sup>, Student Services Contractor.

The US EPA seeks to assess the potential effects of chemicals on populations of fish. For many of these chemicals there is little information regarding their potential to produce effects on reproduction and reproductive development through two full generations. To facilitate and improve this process, predictive tools are being developed to prioritize chemicals for testing. One such approach is the medaka multigeneration test (MMT). The MMT allows evaluation of both structural and activational endocrine pathways within and across generations. The test consists of continuously exposing three generations of fish to a chemical starting with young adults of the first generation. Endpoints measured are liver vitellogenin mRNA levels, sexual phenotypic markers such as anal fin papillae, and gonadal sex, and histopathology evaluation of kidney, liver and gonad. All of these endpoints are evaluated in the context of the genetic sex of the individual, based on the presence or absence of the medaka male-sex determining gene DMY. Non-reproductive toxicity evaluation is also measured using standard toxicity endpoints such as embryo hatch, growth, and survival. The most likely mode of action for 4-tert-octylphenol is a pathway related to binding and activating the estrogen receptor. The results of the MMT for 4-tert-octylphenol indicate that the F0 generation is at least 2 times less sensitive than the F1 and F2 generations. Developmental endpoints appear to be 2 to 8 times more sensitive than activational endpoints.

**Keywords:** Medaka, 4-tert-octylphenol, Endocrine Disruption Chemical, Multigenerational Medaka Test.

Melissa Dybvig  
Mid-Continent Ecology Division (MED)  
Environmental Protection Agency  
6201 Congdon Blvd.  
Duluth, MN 55804  
218-529-5242  
218-529-5000  
[m.dybvig@hotmail.com](mailto:m.dybvig@hotmail.com)

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