

EPA Risk-e-Learning webinar  
"Ecological Risk: New Tools and Approaches"

Seminar title: "PAH and PCB Toxicity and Adaptation - Lessons Learned from Chronically Exposed Wild Populations"

## **Mechanisms of PAH Developmental Toxicity and Evolved Resistance: The Elizabeth River Story**

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### **References cited and other key papers on PAH synergy and resistance adaptations in *Fundulus heteroclitus* in the Elizabeth River, VA.**

- Armknrecht, S.L., S.L. Kaattari, and P.A. Van Veld (1998). An elevated glutathione S-transferase in creosote-resistant mummichog (*Fundulus heteroclitus*). *Aquat Toxicol* **41**, 1-16.
- Bacanskas, L.R., J. Whitaker, and R.T. Di Giulio. (2004). Oxidative stress in two populations of killifish (*Fundulus heteroclitus*) with differing contaminant exposure histories. *Mar Environ Res* **58**, 597-601.
- Billiard, S.M., A.R. Timme-Laragy, D.M. Wassenberg, C. Cockman, and R.T. Di Giulio. (2006). The role of the aryl hydrocarbon receptor pathway in mediating synergistic developmental toxicity of polycyclic aromatic hydrocarbons to zebrafish. *Toxicol Sci* **92**, 26-536.
- Billiard, S.M., J.N. Meyer, D.M. Wassenberg, P.V. Hodson, and R.T. Di Giulio. (2008). Nonadditive effects of PAHs on early vertebrate development: mechanisms and implications for risk assessment. *Toxicol Sci* **105**, 5-23.
- Clark, B.W., C.W. Matson, D. Jung, and R.T. Di Giulio. (2010). AHR2 mediates cardiac teratogenesis of polycyclic aromatic hydrocarbons and PCB-126 in Atlantic killifish (*Fundulus heteroclitus*). *Aquat Toxicol* **99**, 232-240.
- Cooper, P.S., W.K. Vogelbein, and P.A. Van Veld. (1999). Altered expression of the xenobiotic transporter P-glycoprotein in liver and liver tumours of mummichog (*Fundulus heteroclitus*) from a creosote-contaminated environment. *Biomarkers* **4**, 48-58.
- Faisal, M., B.A. Weeks, W.K. Vogelbein, and R.J. Huggett. (1991). Evidence of aberration of the natural cytotoxic-cell activity in *Fundulus heteroclitus* (Pisces, Cyprinodontidae) from the Elizabeth River, Virginia. *Vet Immunol Immunopathol* **29**, 339-351.
- Frederick, L.A., P.A. Van Veld, and C.D. Rice CD. (2007). Bioindicators of immune function in creosote-adapted estuarine killifish, *Fundulus heteroclitus*. *J Toxicol Environl Health* **70(A)**, 1433-1442.
- Gaworecki, K.M., C.D. Rice, and P. van den Hurk (2004). Induction of phenol-type sulfotransferase and glucuronosyltransferase in channel catfish and mummichog. *Mar Environ Res* **58**, 525-528.

- Jung, D., Y. Cho, Y., L. B. Collins, J.A. Swenberg, and R.T. Di Giulio. (2009). Effects of benzo[a]pyrene on mitochondrial and nuclear DNA damage in Atlantic killifish (*Fundulus heteroclitus*) from a creosote-contaminated and reference site. *Aquat Toxicol* **95**, 44-51.
- Jung, D., Y. Cho, J.N. Meyer, and R.T. Di Giulio. (2009). The long amplicon quantitative PCR for DNA damage assay as a sensitive method of assessing DNA damage in the environmental model, Atlantic killifish (*Fundulus heteroclitus*). *Comp Biochem Physiol* **149(C)**,182-186.
- Jung, D., and R.T. Di Giulio. (2010). Identification of mitochondrial cytochrome P450 induced in response to polycyclic aromatic hydrocarbons in the Atlantic killifish (*Fundulus heteroclitus*). *Comp Biochem Physiol* **151(C)**,107-112.
- Matson, C.W., B.W. Clark, M.J. Jenny, C.R. Fleming, M.E. Hahn, and R.T. Di Giulio. (2008). Development of the morpholino gene knockdown technique in *Fundulus heteroclitus*: a tool for studying molecular mechanisms in an established environmental model. *Aquat Toxicol* **87**:289-295.
- Meyer, J.N., and R.T. Di Giulio. (2002). Patterns of heritability of decreased EROD activity and resistance to PCB 126-induced teratogenesis in laboratory-reared offspring of killifish (*Fundulus heteroclitus*) from a creosote-contaminated site in the Elizabeth River, VA, USA. *Mar Environ Res* **54**, 621-626.
- Meyer, J.N., D.E. Nacci, and R.T. Di Giulio. (2002). Cytochrome P4501A (CYP1A) in killifish (*Fundulus heteroclitus*): Heritability of altered expression and relationship to survival in contaminated sediments. *Toxicol Sci* **68**, 69-81.
- Meyer, J.N., and R.T. Di Giulio. (2003). Heritable adaptation and fitness costs in killifish (*Fundulus heteroclitus*) inhabiting a polluted estuary. *Ecol Appl* **13**,490-503.
- Meyer, J.N., J.D. Smith, G.W. Winston and R.T. Di Giulio. (2003). Antioxidant defenses in killifish (*Fundulus heteroclitus*) exposed to contaminated sediments and model prooxidants: short-term and heritable responses. *Aquat Toxicol* **65**, 377-395.
- Meyer, J.N., Wassenberg, D.M., S.I. Karchner, M.E. Hahn and R.T. Di Giulio. (2003). Expression and inducibility of aryl hydrocarbon receptor pathway genes in wild-caught killifish (*Fundulus heteroclitus*) with different contaminant-exposure histories. *Environ Toxicol Chem* **22**, 2337-2343.
- Meyer, J.N., D.C. Volz, J.H. Freedman, and R.T. Di Giulio. (2005). Differential display of hepatic mRNA from killifish (*Fundulus heteroclitus*) inhabiting a Superfund estuary. *Aquat Toxicol* **73**, 327-341.
- Mulvey, M., M.C. Newman, W. Vogelbein, and M.A. Unger. (2002). Genetic structure of *Fundulus heteroclitus* from PAH-contaminated and neighboring sites in the Elizabeth and York Rivers. *Aquat Toxicol* **61**, 195-209.
- Mulvey, M., M.C. Newman, W.K. Vogelbein, M.A. Unger and D.R. Ownby. (2003). Genetic structure and mtDNA diversity of *Fundulus heteroclitus* populations from polycyclic aromatic hydrocarbon-contaminated sites. *Environ Toxicol Chem* **22**, 671-677.

- Nacci, D.E., and T.R. Gleason, and W.R. Munns. (2002). Evolutionary and ecological effects of multi-generational exposures to anthropogenic stressors. *Hum Ecol Risk Assess* **8**, 91-97.
- Nacci, D. L. Coiro, D.M. Wassenberg, and R.T. Di Giulio. (2005). A non-destructive technique to measure cytochrome P4501A enzyme activity in living embryos of the estuarine fish *Fundulus heteroclitus*. Pp. 209-226 in: Ostrander, G.K., *Techniques in Aquatic Toxicology*, Vol. 2. CRC Press, Boca Raton, FL.
- Ownby, D.R., M.C. Newman, M. Mulvey, and W.K. Vogelbein, M.A. Unger, and L.F. Arzayus. (2002). Fish (*Fundulus heteroclitus*) populations with different exposure histories differ in tolerance of creosote-contaminated sediments. *Environ Toxicol Chem* **21**, 1897-1902.
- Timme-Laragy, A.R., C.J. Cockman, C.W. Matson, and R.T. Di Giulio. (2007). Synergistic induction of AHR regulated genes in developmental toxicity from two model PAHs in zebrafish. *Aquat Toxicol* **85**, 241-250.
- Timme-Laragy, A.R., L.A. Van Tiem, and R.T. Di Giulio. (2009). Antioxidant responses and NRF2 in synergistic developmental toxicity of PAHs in zebrafish. *Toxicol Sci* **109**, 217-227.
- Van Veld, P. A., Ko, U., Vogelbein, W. K., and Westbrook, D. J. (1991). Glutathione S-transferase in intestine, liver and hepatic lesions of mummichog (*Fundulus heteroclitus*) from a creosote-contaminated environment. *Fish Physiol Biochem* **9**, 69–376.
- Van Veld, P. A., Vogelbein, W. K., Smolowitz, R., Woodin, B. R., and Stegeman, J. J. (1992). Cytochrome P-450IA1 in hepatic lesions of a teleost fish (*Fundulus heteroclitus*) collected from a polycyclic aromatic hydrocarbon contaminated site. *Carcinogenesis*, **13**, 505–507.
- Van Veld, P.A., and D.J. Westbrook. (1995). Evidence for depression of cytochrome P4501A in a population of chemically resistant mummichog (*Fundulus heteroclitus*). *Environ Sci* **3**, 221-234.
- Van Veld, P.A., and D.E. Nacci. (2008). Toxicity resistance. Pp. 597-641 in Di Giulio, R.T., and D.E. Hinton. *The Toxicology of Fishes*. CRC Press, Boca Raton, FL.
- Vogelbein, W.K., J.W. Fournie, P.A. Vanveld and R.J. Huggett. (1990). Hepatic neoplasms in the mummichog *Fundulus-Heteroclitus* from a creosote-contaminated site. *Cancer Res* **50**, 5978-5986.
- Wassenberg, D., E. Swails, and R. Di Giulio. (2002). Effects of combined exposures to benzo[a]pyrene and 3,3',4,4',5-pentachlorobiphenyl on *Fundulus heteroclitus*. *Mar Environ Res* **54**, 279-283.
- Wassenberg, D.M. and R.T. Di Giulio. (2004). Synergistic embryotoxicity of polycyclic aromatic hydrocarbon aryl hydrocarbon receptor Agonists with cytochrome P4501A inhibitors in *Fundulus heteroclitus*. *Environ Health Perspect* **112**, 1658-1664.
- Wassenberg, D.M. and R.T. Di Giulio. (2004). Teratogenesis in *Fundulus heteroclitus* embryos exposed to a creosote-contaminated sediment extract and CYP1A inhibitors. *Mar Environ Res* **58**, 163-168.

- Wassenberg, D., A. Nerlinger, L. Battle, and R. Di Giulio. (2005). Effects of the PAH-heterocycles, carbazole and dibenzothiophene, on *in vivo* and *in vitro* CYP1A activity and PAH-derived embryotoxicity. *Environ Toxicol Chem* **24**, 2526-2532.
- Wills, L.P., S. Zhu, K.L. Willett, and R.T. Di Giulio. (2009). Effect of the CYP1A inhibitor fluoranthene on the biotransformation of benzo[a]pyrene in two populations of *Fundulus heteroclitus* with different exposure histories. *Aquat Toxicol* **92**,195-201.
- Wills, L.P., C.W. Matson, C.D. Landon, and R.T. Di Giulio. (2010). Characterization of the recalcitrant CYP1 phenotype found in Atlantic killifish (*Fundulus heteroclitus*) inhabiting a Superfund site on the Elizabeth River, VA. *Aquat Toxicol* **99**, 33-41.
- Wills, L.P., D. Jung, K. Koerhn, S. Zhu, K.L. Willett, D.E. Hinton, and R.T. Di Giulio. Comparative chronic liver toxicity of benzo[a]pyrene in two populations of the Atlantic killifish (*Fundulus heteroclitus*) with different exposure histories. *Environmental Health Perspectives* (in press), on-line: doi:10.1289/ehp.0901799.