

Hello, this is Rebecca Wilson, and I'd like to welcome you to the National Institute of Environmental Health Sciences Superfund Research Program monthly Research Brief podcast.

This month, I'm bringing you some really exciting findings from the New York University School of Medicine and Woods Hole Oceanographic Institution. This work was featured in the Feb. 17th edition of *Science* magazine, a *Science* podcast, and National Public Radio's All Things Considered.

The research brief, number 195, was released on March 2, 2011, and was written by SRP contractor Maureen Avakian in conjunction with SRP-supported researchers Drs. Isaac Wirgin from New York University School of Medicine and Mark Hahn from Woods Hole Oceanographic Institution.

For over a decade, Superfund Research Program-funded researchers at New York University School of Medicine, Woods Hole Oceanographic Institution, and Duke University have been investigating the unusual resistance of some fish populations to environmental contamination. Specifically, they have focused on populations living in areas polluted with high levels of polychlorinated biphenyls (PCBs), dioxins, furans, and polycyclic aromatic hydrocarbons (PAHs).

The toxicities of these contaminants are known to be mediated by the aryl hydrocarbon receptor (AHR) pathway:

1. In the cytoplasm of the cell, the contaminant (a ligand) binds to the AHR ligand binding domain.
2. The AHR-contaminant complex is transported into the nucleus of the cell and binds with the responsive elements of genes, including cytochrome P450 1A (CYP1A).
3. The activation of the AHR pathway leads to induction of cytochrome P450 1A and most of the toxic effects of these compounds.

SRP grantees Isaac Wirgin and Mark Hahn collaborated in a series of studies to understand how Atlantic tomcod populations in the Hudson River not only survive in the polluted ecosystem, but also thrive. Tomcod from the Hudson River estuary contain some of the highest levels of PCBs and dioxins ever detected. However, Hudson River tomcod are 100-fold less sensitive to early life-stage toxicities and cytochrome P450 1A induction by PCBs and dioxins in all tissues and life stages, than tomcod from cleaner ecosystems.

Wirgin and Hahn focused on AHR2, the more functionally active AHR in fish. They began by comparing full-length AHR2 cDNA sequences from tomcod from the Hudson River and two reference locations (one near and one distant). They identified five polymorphisms and conducted additional studies on two of them -- one single nucleotide polymorphism (SNP) and a six-nucleotide deletion that results in a two amino acid deletion downstream of the AHR2 ligand binding domain. They screened for the SNP and the nucleotide deletion (referred to as the AHR2-1 allele) in tomcod from seven Atlantic coast estuaries located between the Hudson and St. Lawrence Rivers and found a remarkable distribution pattern. The AHR2-1 allele was found

in only the four southernmost populations and was found in 99% of the Hudson River tomcod, 95% of which were homozygous for the allele.

The researchers conducted *in vitro* tests to evaluate the dioxin-binding abilities of AHR2-1 and AHR2-2 (without the six-nucleotide deletion and single SNP). They found that the binding affinity of AHR2-1 for the dioxin is at least five times lower than that of AHR2-2, which would result in much larger differences *in vivo* sensitivity to contaminants. In further functional studies, they showed that the AHR2-1 protein was significantly less effective in driving reporter gene expression in PCB- and dioxin-treated AHR-deficient cells and that this difference was due to the six-nucleotide deletion.

Wirgin and Hahn suggest that the two amino acid deletion near the AHR2 ligand binding domain alters the conformation of AHR2-1 and reduces its ability to bind with PCBs and dioxins compared to the AHR2-2 protein.

While this change in the AHR2 receptor results in increased resistance to PCB toxicity, it also has potential negative implications for the tomcod and the ecosystem. The genetic changes could make the population more sensitive to other environmental stressors. The AHR is also a factor in normal development. Because Hudson River tomcod accumulate high levels of PCBs and are a major food source for striped bass and other fish, higher than normal levels of PCBs are entering the food chain, continuing to accumulate, and potentially reaching human food sources.

The presence of AHR2-1 at low frequencies in tomcod from the estuaries near the mouth of the Hudson River suggests that AHR2-1 allele was present at low frequency in the Hudson River prior to anthropogenic contamination of the ecosystem. In the ~60 years since significant releases of PCBs and dioxins began, the Hudson River tomcod may have experienced rapid evolutionary change, resulting in a population in which the AHR2-1 allele is overwhelmingly dominant.

This research is the first demonstration of a mechanism of resistance to toxicants in any vertebrate population. Drs. Wirgin and Hahn have shown that resistance can be due to one structural change in the coding region of a single gene and that evolutionary change in anthropogenically challenged natural populations can be rapid.

According to Dr. Wirgin, "This research could not have been attempted without the multidisciplinary focus of our funding vehicle, the Superfund Research Program."

If you'd like to learn more about this research, visit the Superfund Research Program website at www.niehs.nih.gov/srp. From there, click on "Who We Fund" and follow the links to the Boston University research summary. If you have any questions or comments about this month's podcast, or if you have ideas for future podcasts, contact Maureen Avakian at avakian@niehs.nih.gov.