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

This month, we're discussing a novel method that identifies a potential key pathway in arsenic-induced birth defects.

The Research Brief, Number 221, was released on May 1, 2013, and was written by SRP contractor Sara Mishamandani in conjunction with SRP-supported researcher Rebecca Fry.

Blocking the glucocorticoid receptor (or GR) pathway in a chick embryo model prevents structural birth defects induced by arsenic, according to a 2013 NIEHS-funded study at the University of North Carolina at Chapel Hill Superfund Research Program. The laboratory study was performed after computationally predicting the association between the GR pathway and metal-induced birth defects with a novel approach to identify targeted biological pathways.

An estimated 120,000 infants are born with congenital malformations each year in the United States. Of these, 60-70% are caused by unknown environmental and/or genetic causes. This study focused on ways to identify biological pathways relevant to birth defects to associate environmental contaminants with human development and disease.

Researchers led by Rebecca Fry, Ph.D., selected seven metals that are known or suspected developmental toxicants and commonly found in food, drinking water, air, and/or consumer products. The scientists identified genes associated with the metals and with developmental defects using a toxicogenomics database. They then used systems level analyses to overlay the genes onto known molecular networks to represent potential metal-mediated biological pathways.

The scientists pinpointed the GR pathway as being significantly associated with development and with exposure to arsenic, cadmium, mercury, and selenium. The GR regulates genes controlling development, metabolism, and immune response. Because the pathway was altered by toxic metals and is associated with development, the researchers hypothesized that this pathway mediated metal-induced birth defects.

The research team tested these predictions in the laboratory. They used chick embryos, a model to assess developmental toxicity, to evaluate the effects of developmental exposure to arsenic.

They observed structural defects in embryos treated with levels as low as 7.5 parts per billion (ppb), which is within the 10 ppb U.S. Environmental Protection Agency maximum allowable level of arsenic in U.S. public drinking water.

When the team chemically blocked the GR, chick embryos did not develop structural defects when exposed to arsenic. Although the GR has been studied in relationship to metal exposures, there has been little attention to its role in birth defects. To the researcher's knowledge, this is the

first study to examine the blocking of the GR as a means for prevention of metal-induced birth defects.

The researchers anticipate that the novel systems-biology based computational strategy can be employed to predict other biological pathways that mediate environmentally-induced birth defects. The method is cost-effective and can be used on a wide range of contaminants, generating information that may be useful in the prevention and treatment of metal-induced birth defects.

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 University of North Carolina 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.

Join us next month as we discuss more exciting research and technology developments from the Superfund Research Program.