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 how a commonly manufactured nanomaterial induces neurovascular toxicity.

The Research Brief, Number 220, was released on April 3, 2013, and was written by SRP contractor Sara Mishamandani in conjunction with SRP-supported researchers Lei Chen and Michal Toborek.

Nanoalumina, a widely manufactured nanomaterial, can accumulate in brain cells, inducing nerve and blood vessel damage and protein degradation in the brain, according to a 2012 NIEHS-funded study from the University of Kentucky Superfund Research Program. The study also suggests that exposure to nanoalumina disrupts the blood-brain barrier and may worsen the outcomes of neurological disorders such as stroke.

Many engineered nanomaterials (or ENMs) have been developed in recent years for industrial applications, consumer products, and medical fields. Nanoalumina is one of the most abundantly manufactured ENMs. Nanoalumina is used as an additive in surface coatings and ceramics, in filtration membranes for water purification, and in devices for drug delivery, among other applications.

Lei Chen, M.D., Ph.D., with University of Kentucky Superfund Research Program investigator Michal Toborek, M.D., Ph.D., exposed both human and mouse brain cells to nanoalumina. They found that exposure to nanoalumina disrupted mitochondrial function and increased autophagy of brain endothelial cells. Autophagy, a highly conserved pathway of protein degradation involved in various cellular functions and cell death, is normally a cellular rescue mechanism to maintain balance within cells. However, over activated autophagy may lead to excessive protein degradation and cell death. Researchers observed increased autophagy of brain endothelial cells from nanoalumina in the central nervous system and revealed that autophagy is an important mechanism involved in neurovascular toxicity (or damage of nerves and blood vessels in the brain).

Researchers also observed a decrease in mitochondrial function in the brain cortex of exposed mice, with a dramatic decrease in levels of adenosine triphosphate (or ATP). ATP transports chemical energy in the cells for metabolism and is produced in the mitochondria.

Exposure to nanoalumina also decreased the expression of the proteins occludin and claudin-5, which are involved in maintaining the integrity of the blood-brain barrier. Normal function of the blood-brain barrier, which is responsible for the exchange of nutrients and metabolites between the blood and the brain, is critical for central nervous system (or CNS) stability. Persistent accumulation of nanoalumina in the CNS may increase the likelihood of the development of

acute and/or chronic neurological disorders. In the study, researchers indicated that exposure to nanoalumina may worsen the outcome of stroke, a neurovascular disorder.

Although nanoalumina was highly toxic to cells and the brains of mice, nanocarbon, an ENM of similar size tested at the same concentrations, had a much less toxic effect. These results demonstrate that the chemical and physical properties as well as size of nanoparticles may influence biological activity and toxicity. The researchers stress the need to investigate the toxicity of ENMs individually, not as a particle size group, to establish appropriate recommendations for risk assessment.

Chen is now at Mount Sinai School of Medicine in New York. Toborek is currently at the University of Miami's Miller School of Medicine.

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 Kentucky 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.