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 the mapping of protein targets of environmental chemicals using chemoproteomic platforms.

The Research Brief, Number 253, was released on January 6, 2016, and was written by SRP contractor Sara Mishamandani in conjunction with SRP-supported researcher Daniel Nomura.

Using a platform to map the reactivity of environmental chemicals across the proteome may uncover new ways environmental chemicals interact in humans, according to a study from the University of California, Berkeley Superfund Research Program Center. Researchers use reactivity-based strategies that mine for distinct sets of proteins throughout the proteome that may be particularly sensitive to environmental chemicals.

This method uses probes to scan for targets of reactive environmental chemicals and comprehensively map the proteome in biological systems. By mapping the reactivity of the amino acid cysteine, they are able to show that certain environmental chemicals, including monomethylarsonous acid, a metabolite of arsenic, and pesticides such as chlorothalonil, show common reactivity with a set of previously unrecognized protein targets that play key roles in metabolism.

A large number of pharmaceuticals, metabolites, and environmental chemicals act through mechanisms that target proteins. However, their specific interactions with the proteome still remain poorly understood for most of these reactive chemicals. Chemoproteomic technologies enable the assessment of proteome-wide interactions of these irreversible agents directly in complex biological systems.

According to the researchers, understanding the direct chemical-protein interactions of environmental chemicals may inform how molecules interact in the body and how they can be linked to chemical toxicity, providing a direct approach to identifying environmental drivers of disease.

The researchers focused on environmental electrophiles, chemicals that seek out electron-rich sites, which can covalently react to certain regions on proteins, potentially leading to protein dysfunction and consequent adverse health effects. They exposed mice to environmental electrophiles, including the fungicide chlorothalonil, the arsenic metabolite monomethylarsonous acid, and the broad-spectrum insecticide chloropicrin. They then used a protein-profiling approach based on stable isotope labeling of amino acids in which they treated the proteomes of mice with probes that react to cysteine, an amino acid. From the labelled probes, the researchers could identify hyper-reactive cysteines, so they were able to directly map the highly reactive areas of the proteome, or the protein "hot spots."

In the past, the toxicological mechanisms underlying many reactive electrophiles have been thought to occur through indiscriminate covalent modifications on proteins or DNA leading to mutations or non-specific toxicities. This work and other recent studies, however, show that electrophiles preferentially and selectively react with certain sites on specific protein targets.

In mouse liver proteome, researchers found that chlorothalonil, monomethylarsonous acid, and chloropicrin commonly inhibit several metabolic enzymes involved in fatty acid metabolism and energetic enzymes. These protein hotspots were particularly sensitive to environmental electrophiles and showed common reactivity and inhibitory activity in response to different chemicals. The fungicide chlorothalonil specifically inhibited several metabolic enzymes involved in fatty acid metabolism and energetics, leading to dysregulated lipid metabolism in mice.

Although we are exposed to a large array of chemicals, we have little to no understanding of their interactions with reactive proteome hotspots and the resulting effects on protein function, downstream biochemistry, or ensuing pathological consequences. Most current methods provide indirect mechanisms underlying chemical toxicology or only screen for chemical interactions against a small number of known toxicological targets. This method directly maps the proteome-wide interactions of chemicals in complex biological systems.

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 California, Berkeley 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.