

# New Techniques Using Protein Adducts as Exposure Biomarkers

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## ABSTRACT

Genotoxic carcinogens initiate cancer through covalent modification of DNA. Electrophilic compounds that form adducts with DNA have been observed to share similar reaction kinetics with blood proteins. Since proteins are much more abundant than DNA in blood, and are not repaired, protein adducts can serve as biomarkers of carcinogen dose. Stable protein adducts accumulate over the life span of the protein providing a means to measure exposure to short-lived electrophiles over a relatively wide exposure window.

Despite their utility as biomarkers of carcinogen dose, protein adducts have rarely been used in either epidemiology or to identify initiators of human cancers. This is because without substantial adduct enrichment, typical concentrations of protein adducts are too low, compared to the unadducted proteins, to permit widespread discovery of new carcinogens. In addition, use of state-of-the-art mass spectrometry platforms to identify unknown protein adducts or to profile adducts with links to human cancers have been largely underutilized. Finally, once candidate carcinogens are identified, it is difficult and expensive to obtain venous blood samples for protein adduct assays when conducting large epidemiology studies.

To address these challenges, this project focuses on a method to enrich cysteinyl protein adducts of human serum albumin. Enriched protein adducts are then profiled using Fourier-Transform/Ion Cyclotron Resonance (FT/ICR) mass spectrometry to generate high resolution adduct profiles as molecular signatures of carcinogen dose. Finally, a method is developed to measure protein adducts in single drops of dried blood. Measurement of protein adducts in dried blood spots (DBS) will extend their utility to epidemiology studies and, in addition, will permit assessment of prenatal exposures to chemical toxicants via use of newborn DBS.

