

The Agency for Toxic Substances and Disease Registry & The National Center for Environmental Health
Invite you to
Superfund Basic Research Program Seminar & Networking Opportunity

**Biomarkers of Exposure
&
Paraoxonases as Biomarkers of Susceptibility to Environmentally-
Induced Diseases**

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**Wednesday
October 15
10 - 11:30 am
Building 106 Rooms 1A/1B
The Centers for Disease Control & Prevention
Chamblee Campus**

The human PON1 Q192R polymorphism affects the catalytic efficiency of hydrolysis of organophosphorus (OP) insecticides and nerve agents. A recently developed assay protocol reveals an individual's PON1 status (Q192R polymorphism and plasma levels) without the use of highly toxic OP substrates. The new PON1 status protocol has been calibrated to allow calculation of physiologically relevant rates of an individual's OP detoxication potential. It is also superior to Single Nucleotide Polymorphism (SNP) analysis for examining risk of exposure or disease in epidemiological studies. Experiments with a genetically modified mouse model system have shown that this polymorphism is physiologically relevant in determining sensitivity to exposures to diazinon/diazoxon and chlorpyrifos/chlorpyrifos oxon, but not to parathion/paraoxon or nerve agents. Expression of native and variant recombinant human PON1s in an E. coli system has provided a system for producing rHuPON1 variants with increased catalytic efficiency of OP hydrolysis. Injection of the rHuPON1K192 variant into PON1 null mice has demonstrated the therapeutic potential of engineered rHuPON1. When injected, it was non-toxic, persisted beyond 48 hours in plasma and protected against DZO exposures up to 3-times the median lethal dose.

A second component of the research involves identifying and characterizing biomarkers of exposure using mass spectrometry (MS). The aim of this effort is to carry out MS quantification of modified biomarker proteins using ¹⁵N-labeled biomarker proteins expressed in E. coli as internal standards.