



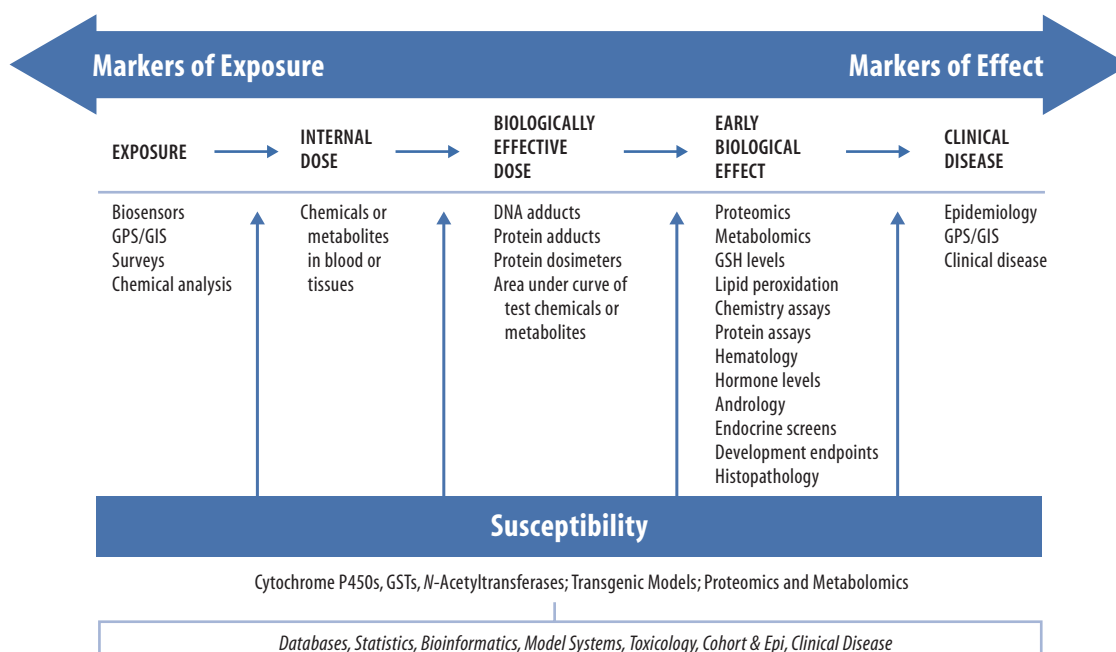
Research Services in Biomarkers

Understanding how drugs, chemicals, or environmental stressors influence the onset, progression, or resolution of disease greatly relies on having an integrated understanding of exposure, dose, and response.

For decades scientists at RTI International have been studying the influence of drugs, chemicals, and stressors on specific genes or proteins and metabolic processes.

RTI offers services in developing biomarkers for preclinical and clinical applications, as well as for utilization in epidemiological studies to understand gene-environment interactions.

RTI's wide range of services in biomarker discovery enable the design and execution of studies that utilize traditional phenotypic anchors for the development of early and more predictive markers to stage the onset and recovery from disease.



Adapted from NRC 1989; Fennell 1996; Sumner, 2005

Biomarkers

Chemical and Drug Metabolism

RTI scientists are experienced in the elucidation of drug and chemical metabolism in animal models and in field or clinical studies conducted under IRB approval. Conventional methods used by RTI scientists to establish biomarkers for exposure include administering the test chemical or vehicle control to animals, collecting tissues and biological fluids, and analyzing the test material or a compound derived from the test material spectroscopically. RTI holds licenses and certification for the synthesis and use of radiolabeled material. Many of our sponsored

studies involve the administration of a carbon-14 labeled xenobiotic with subsequent chromatographic isolation of the metabolites using radioactivity detection and characterization through synthetic standards and MS and NMR technologies. RTI also has two senior scientists with over 15 years of experience using carbon-13 labels and NMR for developing exposure biomarkers and for conducting cross-species comparisons. These techniques enable investigators to determine new metabolites, elucidate new pathways of formation, and establish qualitative and quantitative species differences in metabolism that were unresolved using conventional methods.

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Research Services in Biomarkers *(continued)*

Adducts to Proteins and DNA

RTI scientists have also developed biomarkers for exposure and markers for the measurement of internal dose, based on the measurement of DNA or protein adducts. The development of DNA adduct markers typically begins with the *in vitro* reaction of the test chemical—or its reactive metabolite—with individual nucleosides for chromatographic isolation and MS- and NMR-based identification of reaction products. Once adducts are defined based on *in vitro* experiments, sensitive MS-MS methods are developed and tissues from chemical- or drug-exposed animals are analyzed. Adducts to proteins can be used as markers of exposure and also to develop an understanding of internal dose from exposure. RTI investigators have extensive experience with measuring hemoglobin adducts from reactive chemicals and their metabolites and are experienced in the development of albumin-based adducts. Measurements have been conducted in blood collected from exposed rodents and in humans exposed to chemical agents. The use of species extrapolation models enables the estimation of human exposure.

Markers of Biological Effect

Markers of biological effect are generally established by analysis of tissues and biological fluids from animals administered no-effect levels and low-to-high-dose-effect levels of a chemical. The marker being developed as a biomarker of effect is evaluated, for example, in target and non-target tissue or in sensitive and non-sensitive species; the study design being dependent upon the chemical selected. Markers of biological effect can include biomarkers of exposure, as discussed above, that are examined as a function of no-effect and effect levels, time-to-response, or between sensitive and non-sensitive species. It is the demonstration of correlation of the level of a marker with the onset of a disease state that provides an indicator of effect.

RTI scientists provide services in the development of effect markers that include applications in proteomics and metabolomics, as well as the measurement of more traditional phenotypic anchors such as those obtained from clinical chemistry, hematology, urinalysis, and andrology assessment, and measurement of specific markers of oxidative stress, endocrine disruption, and development and reproductive toxicity.

Markers of Susceptibility

A susceptibility marker is an indicator of the ability of a specific individual or a specific classification of organism to respond in a sensitive manner to an environmental or drug influence. RTI capabilities in the generation of proteomics and metabolomics data contribute to the development of markers of susceptibility. RTI scientists have also been involved in understanding the influence of specific isozymes in mode-of-action through use of transgenic animal models and can work with clients to acquire or develop specific sensitive and non-sensitive animal models for developing susceptibility markers for specific chemicals.

Newer technologies and capabilities include the measurement of total or specific cytochrome P450s in hepatocytes, or microsomal fractions with assessment of: CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, and 4A9/11, as well as their rat homologues.

For more information about RTI's research services in biomarkers, visit www.rti.org or contact

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