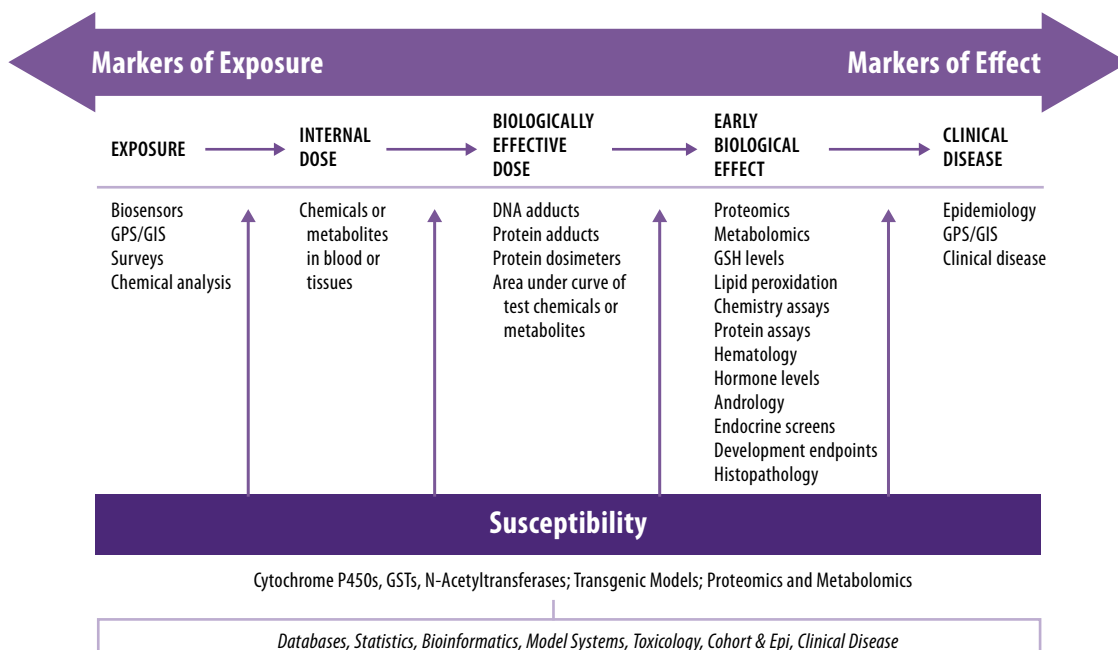


Biomarkers Research at RTI International

Understanding how drugs, chemicals, or environmental stressors influence the onset, progression, or resolution of disease greatly relies on 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 use in epidemiological studies to understand gene-environment interactions.



Adapted from NRC 1989; Fennell 1996; Sumner, 2005

RTI's researchers have a wide range of experience in biomarker discovery and can assist with the design and execution of studies that use traditional phenotypic anchors for the development of early and more predictive markers to stage the onset and recovery from disease.

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 Institutional

Review Board approval. Conventional methods 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 compounds derived from the test material, using spectroscopic methods. RTI holds licenses and certification for the synthesis and use of radio-labeled material. Many of our studies involve the administration of a carbon-14 labeled xenobiotic with subsequent chromatographic metabolite isolation using radioactivity detection and

characterization through synthetic standards and mass spectrometry (MS) and nuclear magnetic resonance (NMR) technologies. Our senior scientists have decades of experience using carbon-13 labels and NMR to develop exposure biomarkers and to conduct cross-species comparisons. These techniques enable investigators to determine new metabolites, elucidate new pathways, and establish qualitative and quantitative species differences in metabolism.

Adducts to Proteins and DNA

Our researchers 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 for developing an understanding of internal dose from exposure. RTI investigators have extensive experience measuring hemoglobin adducts from reactive chemicals and their metabolites and are highly skilled 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 on 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. Demonstrating the correlation of the level of a marker with the onset of a disease state provides an indicator of effect.

RTI provides 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, as well as 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 classification of organism to respond in a sensitive manner to an environmental or drug influence. RTI's capabilities in the generation of proteomics and metabolomics data contribute to the development of markers of susceptibility. Our researchers have also been involved in understanding the influence of specific isozymes in mode of action through use of transgenic animal models, and we 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.

More Information

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