STAR Biomarkers Research

Basic Sciences, Validation, and Application

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Healthy Communities and Ecosystems

Introduction

Every day EPA makes public health decisions to manage and reduce environmental risks based on the available science. The Agency has also launched an effort to develop public health outcomes or "indicators" that can be used to assess the effectiveness and impact of risk-based regulatory decisions. In order to reduce the uncertainties in traditional risk assessment protocols and to advance the most relevant, reliable indicators, the National Center for Environmental Research (NCER), through its ***Science to Achieve Results*** (STAR) grant program, has developed a multi-year, multi-disciplinary biological markers research portfolio.

Why biomarkers are important

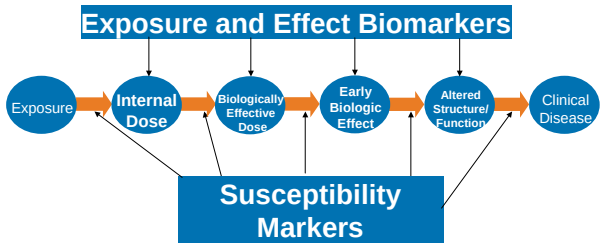
- Provide quantitative information about *exposure*, *early biologic effect* and *individual susceptibility*
- Fill in important gaps in the exposure-to-disease continuum
- Increase our understanding of chemical transport and transformation in the body
- Highlight interactions at the cellular and molecular levels that lead to toxic endpoints

One of the goals of biomarkers research is the development and validation of tools that can be utilized in a real world setting. It is useful to envision biomarkers research as a three step process:

1) Basic Sciences ; 2) Validation; 3) Application

Through numerous Request for Applications representing a wide variety of subject areas, NCER has funded important work that represents all three research categories.

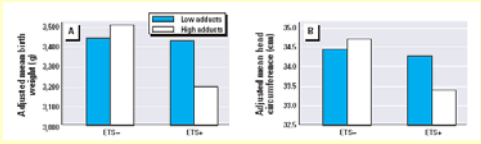
Figure illustrating exposure-dose-effect continuum with opportunities for biomarker development at various points.



Adapted from National Research Council, Biologic Markers in Reproductive Toxicology. Washington: National Academy Press, 1989

STAR Basic Sciences Research

- Identification of a genetic susceptibility factor in mice that will likely lead to identification of equivalent gene in humans - *Miller, Wake Forest University*
- Investigation of a potential suite of biomarkers to predict future asthmatics who may have been exposed to tobacco smoke in utero or during early childhood - *Klonoff-Cohen, University of California, San Diego*
- Investigation of effects of mixtures of bromoform, chloroform and PCE on perturbations of p53 expression and protein synthesis during different developmental stages – *Reinisch, Marine Biological Lab*

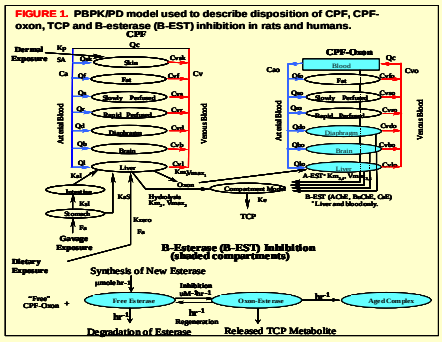


Bar graph showing interaction effect of BAP-DNA and ETS on A) birth weight and B) head circumference Perera *et al*, 2004

Exposure Assessment	Biomarkers of Exposure Effect/Susceptibility	Outcomes
PAH, $PM_{2.5}$, DEP Pesticides ETS	PAH-DNA Adducts Pesticides Cotinine, 4-ABP-Hb	Growth & Neurodevelopment
Allergens	Immune changes (lymphocyte prolif., IgE, cytokines)	Persistent Wheeze / Asthma
Metals	Lead, mercury	
Susceptibility Factors		
Nutritional deficits	Vitamins A,C,E	(Cancer Risk)
Genetic polymorphisms		
Social stressors		

Biomonitoring scheme for STAR-funded longitudinal cohort study at Columbia Center for Children's Environmental Health, Perera et al, 2004

FIGURE 1. PBPK/PD model used to describe disposition of CPF, CPF-oxon, TCP and B-esterase (B-EST) inhibition in rats and humans.



STAR Research Applies Biomarkers

- Application of urinary biomarkers to assess exposure to organophosphate pesticides - *Eskenazi, University of California, Berkeley*
- Application of various biomarkers to assess exposure, susceptibility and risk from several environmental toxicants - *Perera, Columbia University*
- Application of biomarkers of susceptibility, exposure and effect in Azerbaijan and Chinese populations with high rates of neural tube defects – *Donnelly, Texas A& M University*
- Potential application of STAR-funded biomarkers research to national-scale studies such as the National Children's Study

STAR Validation Research

- Validation of meconium as a biomarker of cumulative prenatal exposure to pesticides - *Whyatt, Columbia University*
- Validation of saliva as a biomarker of exposure to pesticides with simultaneous development and validation of a physiologically-based pharmacokinetic model - *Timchalk, Battelle Pacific Northwest Division*
- Validation of meconium as a biomarker of fetal exposure to heavy metals and pesticides - *Ostrea, Wayne State University*
- Evaluation of biomarkers of effect and susceptibility for studying cancer risk in pediatric populations
- Validation of biomarkers of chromium exposure and effect in Chinese occupational population- *Qu, New York University*
- PBPK model to evaluate age and gender dependent differences in detoxifying enzymes for biomarkers of susceptibility and effect- *Olson, State University of New York at Buffalo*

Important Biomarker Issues

Biomarkers hold much promise for improving environmental health science and human health risk assessment. However, there are important issues that surround the development, validation, and application of these tools.

- Treatment of values that fall below the analytical detection level
- Continuity of databases to facilitate meta-analysis
- Development of biorepositories for future research
- Ethical issues – biomarker interpretation; communication to study participants; susceptibility markers and social stigma and employability
- Intra- and inter-individual variability

References

National Research Council, *Biologic Markers in Reproductive Toxicology*, National Academy Press, 1989.

Perera, Frederica P., Rauh, Virginia, Whyatt, Robin M., Tsai, Wei-Yann, Bernert, John T., Tu, Yi-Hsuan, Andrews, Howard, Ramirez, Judyth, Qu, Lirong, Tang, Deliang; *Molecular Evidence of an Interaction Between Prenatal Environmental Exposures and Birth Outcomes in a Multiethnic Population*, Environmental Health Perspectives April 2004 112(5):626-630.

Timchalk C, Nolan RJ, Mendrala AL, Dittenber DA, Brzak KA, Mattsson JL; *A physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model for the organophosphate insecticide chlorpyrifos in rats and humans*, Toxicol Sci 2002 March 66(1):34-53.

Basic Sciences Research

Basic sciences research first identifies measurable properties that have potential to serve as biomarkers. Once exposed, a continuum of biological events occurs, beginning with exposure and ending with health effect. Events and parameters along the continuum can potentially be observed and quantified as biomarkers. Identification of biomarkers often begins with basic toxicology research, such as an animal study that investigates one or more of the stages along the exposure-dose-effect continuum or that aims to better understand disease susceptibility.

Important Considerations for Basic Sciences Research

- What is the distribution of the marker in human populations?
- If the marker was identified in an animal model, is there an equivalent marker in humans?
- Do analytical methods exist for quantifying the marker?
- Are there any technological considerations?

Validation

Validation of the biomarker is extremely important if it will be used in an epidemiological study or in a clinical setting. Without proper validation, the meaning of the biomarker is ambiguous and essentially useless. Validation characterizes the relationship between the marker and a stage or stages of the exposure-to-disease continuum. For example, validation of an exposure biomarker should establish the relationship between the marker and the environmental exposure in question, while a biomarker of effect should be clearly linked to a health endpoint.

Important Considerations for Validation Research

- What is the positive predictive value of the marker?
- What are the sensitivity and specificity of the marker?
- What type of validation study is most appropriate for the marker (i.e., longitudinal cohort study, case-control study)?

Application

Once developed and validated, the marker can then be applied in epidemiological studies to characterize exposure, dose, or early health effects. Historically, one of the weak points of epidemiological studies has been the struggle to adequately characterize exposure. Some methods traditionally used are retrospective questionnaires, environmental sampling (air, dust, etc.), and duplicate diet samples.

How biomarkers can improve environmental health science

- Provide quantitative measures of exposure and dose
- Identify the beginnings of the disease process, allowing for intervention strategies and/or early treatment
- Identify populations who are at higher risk of disease, allowing for intervention strategies