Interpreting Environmental Exposure Linkage to Internal Dose and Preclinical Effect Using a Biometric Systems Approach

Presenters: JD Pleil and JE Gallagher

Contributing Organizations: ORD: NERL, NHEERL

LTG 2 Poster 09

Science Questions

•Can we develop specific, reliable biomarkers to enable us to understand and quantify the population burden of disease, susceptibility, and health effects attributable to environmental exposures?
•How can environmental and biomarker measurements be linked in a conceptual model of exposure, dose, and susceptibility for identifying the toxicological pathways from stressor source to adverse health effect?
•Can blood gene expression profiles be used to assess target (lung) effects and identify key biological pathways to elucidate mechanism of action?
•Can additional predictive power be gained with computational toxicology approaches that combine biomarkers of exposure and effect with clinical indicators of disease?

Research Goals

Human exposures to environmental chemical stressors are comprised of many compounds; exposures are typically at low concentrations, of varying time profiles, and affected by individual human activities. As such, the linkages from exposure through adverse effect are difficult to assess. The overall goal of this work is to strengthen our understanding of how environmental exposures interact with human biology and to use the outcomes to develop, apply, and evaluate strategies to protect public health.

Goal 1: Develop new sampling and analysis methods to make measurements of biomarker compounds in biological fluids to retrospectively identify and quantify internal dose, and to prospectively demonstrate early biological effects.

Goal 2: Implement biomarker techniques in controlled studies to provide real measurement data for developing new hypotheses/studies, identifying toxicological pathways, and informing models.

Goal 3: Integrate biomarker and environmental measurements into population based studies to assess public health risks.

Findings and Conclusions

Biomarker measurements confirm that an exposure has occurred, reflect aggregate (multi-route) exposure, confirm internal dose, and indicate toxicological pathway.

Metabolites of exogenous chemicals demonstrate biological damping and are useful for estimating previous mean exposures.

Classical pharmacokinetic models can be developed from controlled chamber experiments and generalized to complex exposure scenarios or to cross-sectional (spot measures) studies.

Breath biomarkers have an important role in environmental health science as non-invasive surrogates for biological compounds in blood and lavage fluid samples.

Biomarkers of exposure and of effect can be integrated into assessments of the genetic components of a disease and reflect patterns in expression of specific genes.

Systems biology approach is demonstrated with three examples:

1. Conceptual construct of complexity for linking exposure to effect
2. Human subjects research using controlled exposures to diesel exhaust to link exposure to uptake and early response
3. Observational study for deducing mechanistic precursors linking genotype, phenotype, and asthma outcome.

Methods/Approach

1. Biomarkers are the link between exposure and effect

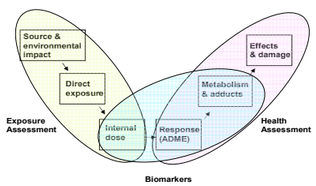
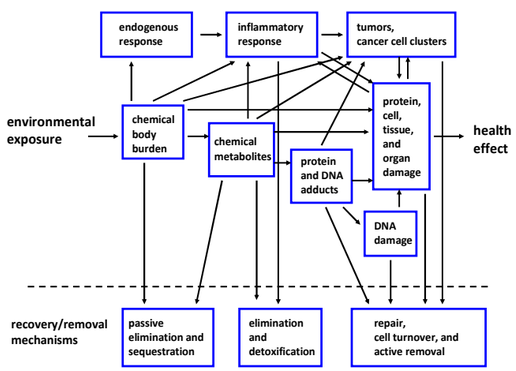
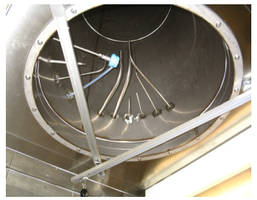


Diagram of path from source of contamination to human exposure and then to health effect. The left and right ovals represent exposure and health assessment disciplines, respectively; the center overlap area (biomarkers) represents the linkage between them.

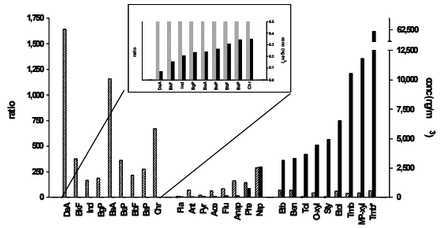


Conceptual model of the internal progression from exposure to health outcome. The interconnected boxes comprise the concept of systems biology; the arrows indicate relative rates. Biomarkers are measured to populate the boxes with real data to assess exposure, recovery, and effects.

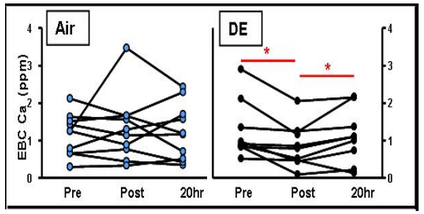
2. Measurement of Exposure and Biomarkers in Diesel Exhaust (DE) Study



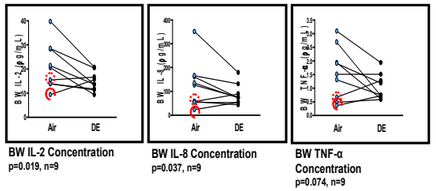
Human subjects chamber studies performed at EPA's Human Studies Facility in Chapel Hill, NC: Employs scripted behavior, controlled exposures, and pre/post- bio-fluids collection



Air concentrations and exposure ratios for polycyclic aromatic hydrocarbons (PAHs) in DE; naphthalene and phenanthrene are identified as candidate biomarkers

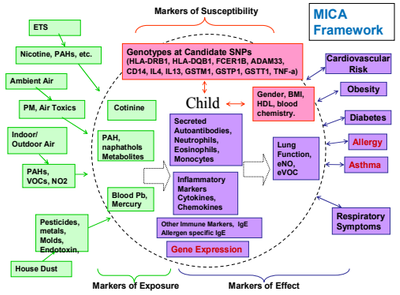


Exhaled breath (EBC) biomarker: Calcium concentration decreases significantly after 2 hr DE exposure at 100 μg/m³

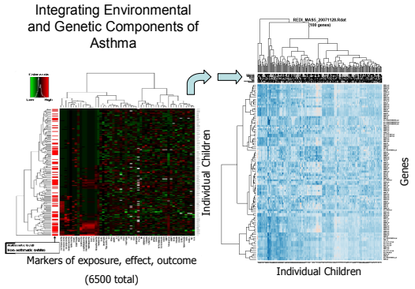


TH1 Cytokine response in upper bronchial wash fluid: All 6 detected (IL-1β, IL-2, IL-8, IL-12, TNF-α, IFNγ) with significant decreases in IL-2,IL-8, and TNF-α; (two of ten subjects are consistent outliers for all species)

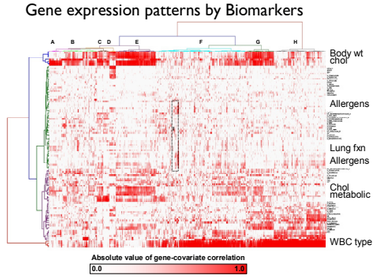
3. Mechanistic Indicators of Childhood Asthma



Integrating Environmental and Genetic Components of Asthma



Gene expression patterns by Biomarkers



Observational study interprets complex patterns of environmental conditions, genotype and phenotype to advance our current understanding of various risk factors and triggers of childhood asthma.

Impact and Outcomes

Demonstrated systems biology aspect of the "exposure to effect" pathway to identify data gaps and quantify inter-individual variance to provide estimates of susceptibility in populations.
• Demonstrated the valuable role of controlled exposure chamber studies in assessing specific uptake and elimination parameters for single and multiple chemicals.
• Demonstrated the usefulness of breath as a biological medium as a surrogate for invasive sampling using blood and bronchial lavage fluid.
• Demonstrated subtle changes in endogenous response biomarkers as indicators of cumulative exposures
• Demonstrated linkage of environmental triggers to outcomes of childhood asthma based on mechanistic indicators and genetic components.

Future Directions

Big Picture:
• Interpret existing biomarker data to fill gaps in understanding relationships between exposure and effect.
• Develop new, more detailed biomarker data for different cumulative exposures to develop the toxicological pathway in the continuum of biological responses expressed as the result of system interaction with environmental factors.

Short Term Research Plans:
•Perform direct comparisons among blood, breath, and urine sampling in large populations; relate to bronchial lavage fluid measurements and establish "normal" statistical distributions.
• Interpret NHANES data of spot measures of biomarkers in light of knowledge and parameters gleaned from repeat measures in chamber and panel studies.
• Continue to improve analytical methodology for biological media; especially for exhaled breath condensate and human plasma.
• Implement protein adduct capability in blood samples.
• Continue work with markers of inflammation, and other pre-clinical biomarkers of effect.

Researchers Involved

Contributors: M. Madden, S. Edwards, L. Neas, and A. Ghio (NHEERL); H. Hubbard, M. Morgan, and J. Sobus (NERL); E. Hubal and D. Reif (NCCT); T. Risby (Johns Hopkins); S. Rappaport (UC Berkeley); and D. Kim (Syngenta)

Cumulative Risk

This poster does not necessarily reflect EPA policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.