Household Air Pollution: Biomarkers of Exposure and Predictors of Respiratory Disease

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INDOOR AIR POLLUTION

WORKSHOP

MAY 9-11, 2011 • ARLINGTON, VA
IOM Report 2010: Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease
Biomarker Definitions

• “A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” (NIH biomarkers definitions WG, 2001)

• “Any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease” (WHO and IPCS, 2001).

• Quantifiable signs of health and disease
Biomarkers vs Clinical Endpoints

• Clinical endpoints are variables that reflect or characterize how a subject “feels, functions or survives”. Often, clinical endpoints are the primary, and to some, only relevant endpoints of clinical or biomedical research. (NIH biomarkers definitions WG, 2001)

• Biomarkers may not correlate with clinical endpoints

• Value of biomarkers as surrogate endpoints
  • But requires biomarker to be “clinically relevant” and “valid” as effective and useful to reflect endpoints

• Caveat: It is hard to find biomarkers that truly predict clinical outcomes; approved biomarkers are always “provisional” as surrogate endpoints (FDA)
Respiratory Health Effects Contributing to HAP Global Burden of Disease

- Acute health effects
  - Low birth weight
  - Perinatal morbidity/mortality (pneumonia/sepsis or surfactant deficiency? Probable impact on lung growth)
  - Acute lower respiratory tract infections (#1 cause of “under 5” mortality)*
  - Otitis media
  - Tuberculosis

- Chronic health effects
  - Asthma
  - COPD*
  - Lung cancer*

*major contributors to mortality ~ 2 million deaths per year
Effective Biomarkers of HAP
(Rylance et al. AJP: Lung, 2013)

1) Improve epidemiological accuracy in association studies with health effects
2) Reduce cost and complexity of monitoring interventions
3) Provide data for education of the public and policy makers about risk
4) Inform clinicians and public health community about human HAP exposures that are not well characterized
Standard Clinical Biomarkers of Respiratory Diseases

- Pulmonary function testing (TLC, VC, FEV₁, DLco, ABGs, CO-Hgb, bronchial hyper-responsiveness, exercise testing)
- Chest radiography, e.g., CXR, CT, MRI etc.
- Blood tests, e.g., LDH, ACE, CC16, etc.
- Fraction of exhaled nitric oxide (FeNO)
### Characteristics of Ideal HAP Biomarkers

<table>
<thead>
<tr>
<th>Issue</th>
<th>Requirement</th>
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<tbody>
<tr>
<td><strong>Field readiness</strong></td>
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<tr>
<td>Rural population</td>
<td>Stable to temperature, storage, and transport conditions</td>
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<td>Lack of cold storage</td>
<td>Single point of care test is ideal(37), such as those sought in the Gates’ Foundation “Grand Challenges in Global Health”</td>
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<td>Limited laboratory equipment</td>
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<td><strong>Marker of exposure</strong></td>
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<td>Time lag from exposure to outcome</td>
<td>Chronic complications, such as COPD result from long exposures. Measuring exposure rather than health outcome is more immediately relevant for monitoring and intervention purposes</td>
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<td><strong>Heterogeneity of effect by age</strong></td>
<td>Children most susceptible to infection, and adults to chronic respiratory complications. Biomarker of exposure more likely to be widely relevant</td>
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<td>Rapid fluctuations in exposure levels</td>
<td>Reflect cumulative exposure over days rather than hours</td>
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<td><strong>Validity/applicability</strong></td>
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<td>External validity: consistency with current measurements</td>
<td>Strong correlation between currently used metrics of exposure to ensure continuity within research and intervention programmes. Correlation with disease risk or outcome is ideal, but of secondary importance</td>
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<td>Specificity</td>
<td>Discriminate from other particulate exposures (e.g., tobacco, traffic pollution)</td>
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<td>Sensitivity</td>
<td>Be sensitive to multiple fuel sources (e.g., wood, charcoal, dung, paraffin)</td>
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<td>Pretest likelihood of outcome unknown</td>
<td>Interpretable independent of background data. Unlike clinical biomarkers, there is no known “pretest probability”</td>
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<td>Use in diverse populations</td>
<td>Consistent throughout the population at risk. Heterogeneity of response due to genetic polymorphisms [e.g., in metabolic pathways can be a problem (44)]</td>
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<td>Investigation</td>
<td>Physiological Relevance</td>
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<td>Exhaled CO/transcutaneous COHb: field test in HAP</td>
<td>High CO might explain atherosclerosis and foetal effects (through left shift in O$_2$ dissociation curve and myoglobin binding)</td>
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<td>Methoxyphenols, levoglucosan: field test and controlled use in HAP</td>
<td>Unmetabolized urinary product should reflect exposure — physiological determinants of this correlation are not well understood</td>
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<td>1-OHP: field tests for discrimination of pyrene metabolite levels at low concentration</td>
<td>Polyaromatic hydrocarbons known to be carcinogenic</td>
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<td>DNA methylation: case control or cohort studies of effect of HAP</td>
<td>Unknown relevance of CYP enzyme polymorphisms in terms of biomarker</td>
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<td>Generation of robust animal models for HAP, especially chronic exposures</td>
<td>Epigenetic effects may explain long term effects (e.g., ischaemic heart disease) Known effects of methylation on promoters of genes for inflammatory pathways (e.g., iNOS)</td>
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<td>Malondialdehyde, 8-isoprostanate, 8-oxo-7,8-dihydro-2'-deoxyguanosine: investigation of urinary and plasma performance in controlled and field tests</td>
<td>Chronic exposure effects are likely to be different than experimental acute exposures due to physiological responses (e.g., antioxidant upregulation, negative and positive feedback within signalling pathways)</td>
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<td>HAP products are known to cause oxidative stress including lipid peroxidation and DNA strand breaks. Measurement within organisms is complicated by buffering and repair mechanisms.</td>
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Biomarkers to Monitor HAP

Biomarker should quantitatively reflect exposure susceptibility or effect (disease)

Desirable characteristics:

◦ Simple
◦ Inexpensive
◦ POC
◦ Reproducible
Use of Rad-57 to Measure Carboxyhemoglobin

Pulse oximeter
Simple
Noninvasive
Reproducible?

• Mixed reviews
Human Urinary Mutagenicity after Wood Smoke Exposure (Mutagenesis 29 367, 2014)
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Poor Airway Function in Infants Predicts Poor Lung Function as Adults
Next steps: Can we learn from others who have promoted use of biomarkers in other fields?

- Biomarkers of nutrition for development (BOND)
- Use of government related foundations
- FDA public private partnerships or consortia
BOND WEBSITE:
HTTP://WWW.NICHD.NIH.GOV/GLOBAL_NUTRITION/PROGRAMS/BOND/PAGES/INDEX.ASPX
AN APPROACH TO ADDRESSING THE ROLE OF NUTRITION IN GLOBAL MCH

**Research Track**
Fund research grants utilizing established NIH mechanisms, procedures and policies

**Translational Track**
Partner with domestic and international authoritative agencies to translate evidence into practice and policy

**GOAL**
- Improve the health of mother’s and children
Next steps: Can we learn from others who have promoted use of biomarkers in other fields?

- Biomarkers of nutrition for development (BOND)
- Use of government related foundations, e.g., FNIH
- FDA public private partnerships or consortia
The Biomarkers Consortium is a public-private biomedical research partnership managed by the Foundation for the National Institutes of Health that endeavors to discover, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics.

The consortium is helping create a new era of personalized medicine, with more highly predictive markers that have an impact during a patient's illness or lifespan. Our goal is to combine the forces of the public and private sectors to accelerate the development of biomarker-based technologies, medicines, and therapies for the prevention, early detection, diagnosis, and treatment of disease.
Next steps: Can we learn from others who have promoted use of biomarkers in other fields?

- Biomarkers of nutrition for development (BOND)
- Use of government related foundations, e.g., FNIH
- FDA public private partnerships or consortia, e.g., COPD Biomarker Qualification Consortium