biomarkers appear to be more robust measures of exposure than external analytical measurements of single compounds. *(Abstract does not necessarily reflect the policy of the U.S. EPA.)*

Genetic Changes as Biomarkers of Mouse Lung Adenocarcinoma: Comparison to Human

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The incidence of adenocarcinoma of the lung is increasing in the United States, however, the difficulties in obtaining lung cancer families and representative samples of early to late stages of the disease have lead to the intense study of mouse models for lung cancer. We used Spectral Karyotyping (SKY), mapping with fluorescently labeled genomic clones (FISH), comparative genomic hybridization (CGH) arrays, gene expression arrays, Western immunoblot and real time polymerase chain reaction (PCR) to analyze 15 early passage mouse lung adenocarcinoma cell strains and nine pairs of high-invasive and low-invasive mouse lung adenocarcinoma tumor cell strain pairs to detect genetic biomarkers associated with mouse lung adenocarcinoma phenotype and tumor invasion. The duplication of chromosomes 1 and 15 and deletion of chromosome 8 were significantly associated with a high-invasive phenotype. The amplification of chromosome 1 at band C4 and E1/2- H1 were the most significant chromosomal changes in the high-invasive cell strains. Mapping with FISH and CGH array further narrowed the minimum region of duplication of chromosome 1 to 40 centimorgans (cM) and 71-82 cM. Within these minimal regions of chromosome 1 duplication, analysis of gene expression arrays and confirmation by real time PCR demonstrated increased expression of COX-2, Translin (TB-RBP), DYRK3, NUCKS and Tubulin-α4 genes in the high-invasive cell strains. Elevated expression and copy number of these genes, which are involved in inflammation, cell movement, proliferation, inhibition of apoptosis, mitotic spindle integrity and telomere elongation, were associated with an invasive phenotype and are potential genetic biomarkers of lung carcinogenesis. The amplified regions of chromosome 1 contain mouse lung suscpetibility loci. The homologous linkage groups on human chromosomes 1q32-41 and 2q are likewise altered in invasive human lung cancer. Increased copy number and expression of genes on mouse chromosome 1 may play a functional role in lung cancer development and may aid in identifying unique lung cancer biomarkers as well as susceptibility genes in mouse and human. *(The findings and conclusions in this report have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.)*

Proteomic and Metabolomic Biomarkers

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There has been an increased appreciation that chemical agents may produce biological responses in protein expression patterns (proteomic responses) or alterations in sensitive metabolic pathways (metabolomic responses) at even low dose levels over the last 20 years. This understanding coupled with the marked improvements in analytical methodologies such as 2-D gel electrophoresis, MALDI-TOF and SELDI-TOF technologies capable of identifying specific protein patterns related to exposure to chemicals either alone or as mixtures has greatly increased the capability of toxicologists to detect and interpret early cellular responses to chemical agents. Similar advances in analytical technologies such as HPLC, GC-MS, MALDI-TOF and SELDI-TOF have permitted early detection of changes in a number of essential metabolic pathways following chemical exposures by measurement of alterations in metabolic products from those pathways. These approaches are increasingly regarded as useful

also been on extended leave to work on drinking water related projects in Somalia and Thailand.

Mr. Regli is currently responsible for providing policy guidance, and technical oversite for drinking water regulations pertinent to controlling pathogenic organisms, disinfection byproducts, and emerging contaminants. He is also involved with developing measures for U.S. EPA program effectiveness in reducing waterborne disease on a national level.

Rice, Glenn E., M.S.

In March of 1990, Mr. Glenn Rice was appointed to the position of Environmental Health Scientist with the U.S. EPA, Office of Research and Development's National Center for Environmental Assessment (NCEA). He is a member of the chemical mixtures risk assessment team in NCEA. His research interest is human health risk assessment methods. For NCEA, he served as a member of the Cancer Risk Assessment Verification Endeavor (CRAVE Work Group). He has lead both a multimedia exposure assessment team in NCEA and a comparative risk assessment project team. He also served as acting science advisor for the NCEA-Cincinnati Division. He is one of the primary authors of the EPA's Mercury Study Report to Congress and EPA's Chemical Mixtures Guidance. Mr. Rice has served as the Chapter President of the Ohio Chapter for the Society of Risk Analysis. He holds a Master's in Microbiology from Miami University, as well as degrees in Biology and Chemistry from Thomas More College. Mr. Rice is currently a doctoral candidate at the Harvard School of Public Health and is a member of SRA.

Rieth, Susan, M.P.H.

Ms. Susan Rieth is a toxicologist with the U.S. EPA's Office of Research and Development, National Center for Environmental Assessment (NCEA), Integrated Risk Information System (IRIS) Program. Her primary responsibility is the development of health assessments for inclusion in the IRIS database. She served as the chair of a pilot project to explore implementation of recommendations of a Risk Assessment Forum panel for improving RfD and RfC development. Prior to joining EPA, she worked as a consultant in the area of human health risk assessment. Ms. Rieth received a B.A. degree in biology from Wellesley College and a M.P.H. degree from the University of Michigan.

Sargent, Linda M., Ph.D.

Dr. Linda Sargent, Ph.D., is currently a Research Toxicologist at Centers for Disease Control—National Institute for Occupational Safety and Health (CDC/NIOSH), Toxicology and Molecular Biology Branch, Morgantown, WV. Prior to moving to NIOSH, she held research fellowship positions at the National Cancer Institute, Bethesda, MD, McArdle Laboratory, University of Wisconsin, Madison, and the Chemical Industry Institute for Toxicological Research, Research Triangle Park, NC. Her areas of research expertise and interests are occupational and environmental carcinogenesis, genomic fingerprints of occupational carcinogens and genetic biomarkers of cancer in animal models as compared to human. She has won several awards including Young Investigator awards from the Society of Toxicology and the American Association for Cancer Research for her research in the field of carcinogenesis and environmental mixture exposure. She has adjunct appointments in the Genetics Department at West Virginia University and the Pathology Department at the University of Pittsburgh and is an external reviewer for the Toxicology Department at the University of Iowa. She has several publications in peer-reviewed journals including *Cancer Research*, *Carcinogenesis*, *Mutation Research*, *American Journal of Pathology*, *Cancer Biology* and *Therapy and Genes Chromosomes and Cancer.*

Savage, Russell E., Jr., Ph.D.

Dr. Savage hails from Ohio, where he received a B.A. (Chemistry, 1971) and M.T.S.C. (Technical and Scientific Communication, 2001) from Miami University, and the Ph.D. in Pharmacology from The Ohio State University College of Medicine (1976). Recently he was awarded the Certificate in Medical Writing from the University of Chicago. He has held academic positions with the Ohio University College of Osteopathic Medicine and the University of Cincinnati and The Ohio State University Colleges of Medicine. He has also held positions in the U.S. EPA, the Department of the Army, Department of Defense and his current position with the National Institutes for Occupational Safety and Health.

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U.S. EPA, Office of Research and Development, National Center for Environmental Assessment

and

Laurie E. Roszell, Ph.D., D.A.B.T.
U.S. Army Center for Health Promotion and Preventive Medicine

Conference Coordinator:
Patricia A. Daunt
U.S. EPA, Office of Research and Development, National Center for Environmental Assessment

Meeting Manager:
Amanda S. Madeline
Professional and Scientific Associates

11:15 a.m. **Predictive vs. Protective Aspects of AEGLs**
Tobin, Paul S., Ph.D., *U.S. EPA, Office of Pollution Prevention and Toxics*

3C. Biomarkers of Exposure and Effects

Co-Chairs:
Keshava, Nagu, Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
Fowler, Bruce A., Ph.D., Fellow A.T.S., *Agency for Toxic Substances and Disease Registry, Senior Biomedical Research Service*

Identification of new biomarkers is rapidly increasing with the availability of advanced and sensitive techniques. With the continuing advances in genomics, proteomics and other computational technologies, an improvement in designing future biomarker studies is expected, which will facilitate the identification of risk to human population. For example, ProteinChip technology coupled with surface-enhanced laser desorption/ionization time-of-flight mass spectrometry facilitates protein profiling of complex biological mixtures. These biomarkers of exposure, effect and susceptibility are effectively being used in providing new insights into the progression of a disease. In this session, a series of presentations include identification of biomarkers using new tools/technology.

8:00 a.m. **Introduction: Use of Biomarkers in Risk Assessment – a Brief Overview**
Keshava, Nagu, Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

8:15 a.m. **Chromosomal Alterations as Biomarkers of Cancer and Hereditable Risks in Human Populations**
Eastmond, David A., Ph.D., *University of California, Environmental Toxicology and Department of Cell Biology*

8:45 a.m. **Urinary Mutagenicity: A Biomarker of Genotoxic Exposures via Air, Water, and Diet**
DeMarini, David M., Ph.D., *U.S. EPA, Office of Research and Development, National Health Environmental and Effects Research Laboratory*

9:15 a.m. **Genetic Changes as Biomarkers of Mouse Lung Adenocarcinoma: Comparison to Human**
Sargent, Linda M., Ph.D., *National Institute for Occupational Safety and Health*

9:45 a.m. **Break**

10:15 a.m. **Proteomic and Metabolomic Biomarker**
Fowler, Bruce A., Ph.D., Fellow A.T.S., *Agency for Toxic Substances and Disease Registry, Senior Biomedical Research Service*

10:45 a.m. **Biomarker-Based OELs and Risk Assessments**
Savage, Russell E., Jr., Ph.D., *National Institute for Occupational Safety and Health*

11:15 a.m. **Integrative Bioinformatics – An FDA Experience**
Tong, Weida, Ph.D., *Food and Drug Administration, National Center for Toxicological Research*

11:45 a.m. – 1:00 p.m. **Lunch**