EPA Office of Pesticide Programs' Stakeholder Workshop on 21st Century Toxicology and Exposure Science October 2011 Workshop on Diagnostic Tools and Biomarkers in Pesticide Medical Management, Exposure, Surveillance, and Epidemiologic Research: State-of-the-Science, Challenges, and Opportunities

Overview: On October 11, 2011, the Office of Pesticide Programs (OPP) hosted a day long public workshop in Arlington, Virginia to discuss the challenges and opportunities regarding the status and development of diagnostic tools and biomarkers for medical management, surveillance, and epidemiologic research. Diagnostic tools and biomarkers are valuable in public health practice and are envisioned to play an important role in the model for 21st century toxicology and exposure science. This public workshop provided an opportunity for stakeholders to provide input into OPP's 21st Century strategic direction.

Since the publication of the 2007 National Research Council (NRC) of the National Academy of Sciences (NAS) report on Toxicology Testing in the 21st Century there has been a great deal of focus within the scientific community to develop and evaluate new technologies in molecular, *in vitro*, and computational sciences to supplement or replace more traditional methods of toxicity testing and risk assessment. Over the next several years, we in EPA's Pesticide Program will be evaluating and transitioning these new technologies to improve and transform our approach to pesticide risk assessment and risk management in a manner that allows us to evaluate the safety of chemicals with increasing efficiency and effectiveness while using fewer resources and experimental animals.

The Pesticide Program Dialogue Committee (PPDC) workgroup on "Integrated Testing Strategies/21st Century Toxicology" was established in 2008 to inform and engage stakeholders early in OPP's efforts to implement the NRC recommendations. The key objective of this workgroup is to advise the Pesticide Program on communication and transition issues as we move forward. The planning of this workshop was a direct outcome of the PPDC workgroup. (Also visit: Pesticide Program Dialogue Committee 21st Century Toxicology/New Integrated Testing Strategies Workgroup).

The workshop objectives included:

(1) To discuss the value of diagnostic tools and biomarkers in medical management, surveillance and epidemiologic research;

(2) To understand the state-of-the-science on analytical tools and methods, and;

(3) To explore challenges, opportunities, and policy approaches to advance the development of diagnostic tools and biomarkers in order to help realize the new model of 21st century toxicology and exposure science.

Setting the Stage:

The meeting opened with a presentation by Steven Bradbury, PhD, Director, Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention, USEPA discussing the status and need for advancing diagnostic tools for biomarkers, and advancing the NRC vision.

Dr. Bradbury discussed the rapid rate at which the science is progressing, and consequently how much more complex the questions regarding these topics are becoming. He outlined the three important applications of science for the safety of pesticides: (1) medical surveillance (2) biomonitoring, and (3) exposure. He stressed the importance of EPA working with other Federal Agencies and the scientific community to consider how to advance diagnostic tools and biomarkers.

The meeting next moved on to a series of presentations broken down into several general categories.

1. **Critical Scientific Issues for Tool Development and Interpretation of Monitoring Results**

Pharmacokinetic Considerations - Lesa L. Aylward, PhD, Principal, Summit Toxicology, LLP, stated that the objective of biomonitoring is to improve exposure measurement and characterization. Dr. Aylward outlined the potential limitations of spot sampling and the importance of understanding the representativeness of biomarkers for an individual's exposure over a biologically relevant time frame. Dr. Aylward also indicated that utilization of biomonitoring data in exposure assessment requires understanding of inter- and intra-individual variation. She concluded her presentation by emphasizing that designing studies and interpreting biomonitoring data requires understanding both pharmacokinetics and exposure patterns.

Evaluating Exposure - Dana Barr, PhD, Emory University, explained that exposure science is critical to risk assessment and risk mitigation and understanding the window of exposure is very important. It is critical to consider pharmacokinetics, the physical chemical properties of a chemical, matrices, intra- and inter-person variability, exposure scenarios, routes of exposure and relevant co-exposures (mixture issue). She concluded that there is a need to develop more pesticide-specific biomarkers, but that it may be six to ten years before these could be broadly incorporated with existing systems.

2. **Tools for Diagnosis and Biomarkers of Pesticide Exposure: The Need and Role**

Diagnostic Tools in Identification and Management of Pesticide Overexposure - James R. Roberts, MD, MPH, Associate Professor of Pediatrics, Medical University of South Carolina, opened by providing data that pesticides are among the least of all pediatric environmental health subjects that faculty feel comfortable teaching, and that only a few hours of education is provided in medical school on the health effects of various pesticides. Having a way of testing

would likely increase a physician's ability to consider and diagnose pesticide poisonings. Thus providing rapidly available diagnostic testing should be a part of registration process.

Biomarkers in Surveillance and Epidemiologic Research: Applications in Surveillance and Epidemiologic Research - Lynn Goldman, MD, Dean, School of Public Health, George Washington University, presented data gathered in the Tracking Health Related to Environmental Exposures (THREE) study in Baltimore, designed to investigate prenatal exposure to environmental chemicals and how this may affect newborn growth and development. The study examined the following biomarkers: traditional compounds such as Organochlorines, PCBs, metals, and emerging biomarkers such as flame retardants (PBDE, etc), perfluorinated compounds, cytokines, thyroid hormones, lipids and epigenetic markers.

Biomarkers in Surveillance and Epidemiologic Research: Applications for Environmental Justice; Research on Vulnerable Populations - Asa Bradman, PhD, Associate Director, Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), University of California, Berkeley, presented pesticide exposure information on pregnant women and children that have participated in CHAMACOS research and discussed the challenges of using biomarkers to assess exposure and evaluate risk. His presentation underscored that while we do have urinary metabolites for many non-persistent pesticides, there are important scientific issues that need to be considered when evaluating exposure. One important issue is that good pesticide-specific biomarkers are not available for many pesticides. Given that good biomarkers are not available for most pesticides of public health concern, the regulatory and academic communities need to step up and develop laboratory tests and biomarkers for specific pesticides.

Case Study - Washington State Cholinesterase Monitoring - Matthew C. Keifer, MD, MPH, Dean Emanuel Endowed Chair, National Farm Medicine Center, Marshfield Clinic Research Foundation, and Co Director, Upper Midwest Agricultural Health and Safety Center, presented a case study on cholinesterase, a non-specific biomarker/diagnostic tool that can help evaluate if individuals may be overexposed to pesticide and identify where worker protection is inadequate. The case study showed that monitoring programs can help motivate change to different products and better worker safety practices.

3. Biomonitoring: The State of the Art

Medical Diagnostic Tools - Presenter*:* Dean Jones, PhD, Professor, Emory University, outlined that high-performance metabolic profiling can be cost effective for personalized medicine and provides an opportunity to multiplex pesticide surveillance. He stipulated that with appropriate development, biomonitoring could become a component of personalized medicine. However, targeted analysis of everything is impractical, unaffordable, and unwarranted.

Tools of Surveillance and Epidemiologic Research - Michael Alavanja, PhD, National Institutes of Health / National Cancer Institute, Senior Investigator, discussed the background and design of the Agricultural Health Study (AHS), cancer epidemiology, and biomarker studies, and the exposure assessment in the AHS. He outlined the following as potential areas of future work:

measure monoclonal B-cell lymphocytosis, oxidative stress, epigenetic changes, markers of immune perturbation, and chromosomal aberrations.

Promising Analytical Tools - David Balshaw, PhD, National Institutes of Health / National Institute of Environmental Health Sciences (NIEHS), reported that NIEHS has successfully developed promising tools for measuring individual factors in the external environment, but that they are not yet validated or integrated. We still have not bridged the gap between external exposure and biological response. There is a need to understand the mechanistic underpinnings of gene-environment interactions. Dr. Balshaw outlined the following future activities: validation and field testing of prototype tools and candidate markers, integration of tools for multi-component analysis of exposure, and the development of technologies for biomonitoring.

Panel Discussions on Advancing Diagnostic Tools and Biomarkers: Challenges, Opportunities, and Next Steps for Solutions. Panel Discussion Facilitated by Bill Jordan, Senior Policy Advisor, Office of Pesticide Programs, USEPA

Each panelist provide a brief statement on their perspective at the beginning of the panel discussion.

Amy K. Liebman, MPA, Director of Environmental and Occupational Health, Migrant Clinicians Network, expressed that clinicians do not have proper laboratory tests to help diagnose pesticide poisonings, which are important to manage cases and help the workers/farmers with compensation process for work-related illness. The EPA should require registrants to develop diagnostic tools for pesticides.

Carol J. Burns, PhD, MPH, The Dow Chemical Company, asserted that most pesticides have analytical methods, and that we need to determine how to transfer the analytical methods from industry to regulatory agencies and clinicians. Dr. Burns asked if we can learn from drug labeling (i.e., preclude vulnerable populations, pregnant women), and stressed the importance of biomarkers to validate exposure questions.

Marylou Verder-Carlos, PhD, DVM, MPVM Assistant Director, Department of Pesticide Regulation Sacramento, California is in California working on the Maternal and Child exposure study (should be completed by June 2012) and the Fire Fighter exposure study. The University of California is currently using a badge for workers to wear after entering fields to detect chemical exposure.

Matthew C. Keifer, MD, MPH, Dean Emanuel Endowed Chair, National Farm Medicine Center, Marshfield Clinic Research Foundation, and Co Director, Upper Midwest Agricultural health and Safety Center, maintained that EPA should help clinicians by giving them tools to test pesticide poisonings.

Erik R. Janus, Technical & Regulatory Analyst, Steptoe & Johnson LLP, stated the need to use what we have and make more information available from registrants (risk characterization, pharmacokinetics etc.) and the need to validate biomonitoring tools.

Suzanne C. Fitzpatrick, PhD, DABT, Senior Science Advisor, Office of the Commissioner, Office of FDA Chief Scientist, USFDA, discussed the FDA's biomarkers efforts, and that "biomarker qualification" is a complex process that requires significant resources.

Key Topics from the Discussion:

- Clinicians need quick and cheap methods and physicians need more education. Diagnosing unknown exposures is not unique to pesticides.
- Education and training are key to preventing pesticide exposure.
- The variety of promising methods discussed should be considered to determine what technology may be available now for evaluating pesticide exposure and what technology should be a priority for future development.
- Stakeholders recommend that the PPDC create a workgroup to develop a list of pesticide chemicals and diagnostic tools for future research.

Next Steps

- PPDC workgroup will draft recommendations and give them to EPA
- Produce workshop report; possibly a journal article

Contact: For more information about the PPDC workgroup on 21st Century Toxicology/New Integrated Testing Strategies, contact Jennifer McLain (mclain.jennifer@epa.gov) or visit http://www.epa.gov/pesticides/ppdc/testing/index.html.