HESI Biological Significance of DNA Adducts
Project Committee

Presenter:
Gary Williams, M.D.
(New York Medical College)

Chair:
Lynn H. Pottenger, Ph.D., DABT
(The Dow Chemical Company)

Vice-Chair:
Robert J. Mauthe, Ph.D.
(Pfizer, Inc.)

Staff:
James Kim, Ph.D., DABT

January 2009 HESI Annual Meeting
2008 DNA Adducts Project Committee: Participation

**INDUSTRY**
- AstraZeneca AB
- The Dow Chemical Company
- DuPont Haskell Global Centers for Health and Environmental Sciences
- ExxonMobil Biomedical Sciences, Inc.
- L'Oreal
- LyondellBasell Industries
- Pfizer, Inc.
- The Procter & Gamble Company
- Rohm and Haas Company
- Shell International BV

**GOVERNMENT & ACADEMIC**
- French Atomic Energy Commission
- New York Medical College
- Open University
- University of Leicester
- University of North Carolina
- U.S. Environmental Protection Agency
- National Health and Environmental Effects Lab
- National Center for Environmental Assessment
- Office of Water
- U.S. Food and Drug Administration
- National Center for Toxicological Research
- Center for Drug Evaluation and Research
- U.S. National Institute of Environmental Health Sciences

**OTHERS**
- Dan Casciano (Casciano & Associates)
- Errol Zeiger (Errol Zeiger Consulting)
DNA Adducts Project Committee:
Mission

- Bring basic science and scientific consensus to issues regarding the biological significance of low levels of DNA adducts

- Provide a unique public forum to discuss these issues and their implications for risk assessment.

- Develop a consensus-based, science-driven framework for the application of DNA adduct data to the cancer risk assessment process.
DNA Adducts Project Committee: Objectives

- Sponsor workshops and symposia to augment public discussion on the current state-of-the-science of DNA adduct detection, measurement, and interpretation

- Engage a broad-based, multi-national group to work on the development of a framework approach for the application of DNA adduct data to risk assessment
DNA Adducts Project Committee: 2008 Accomplishments

Manuscripts

Creating context for the use of DNA adduct data in cancer risk assessment: I. Data organization

- Annie Jarabek (USEPA)
- Lynn Pottenger (Dow Chemical)
- Larry Andrews (Rohm & Haas)
- Daniel Casciano (Consultant)
- Michelle Embry (HESI)
- James Kim (HESI)
- Julian Preston (USEPA)
- Vijay Reddy (Merck)
- Rita Schoeny (USEPA)
- David Shuker (Open University)
- Julie Skare (Procter & Gamble)
- James Swenberg (University of North Carolina)
- Gary Williams (New York Medical College)
- Errol Zeiger (Consultant)
Conclusion

DNA adduct data by themselves are informative but not sufficient for assigning a MOA for tumor development

- Some DNA adducts may represent a key event in the carcinogenic MOA

- Not all DNA adducts result in mutation and not all mutations are in critical genes for carcinogenesis
DNA Adducts Project Committee: 2008 Accomplishments

Manuscripts

Creating context for the use of DNA adduct data in cancer risk assessment: II. Overview of methods of identification and quantitation of DNA damage

- Matthew Himmelstein (DuPont, USA)
- Peter J. Boogaard (Shell, NL)
- Jean Cadet (CEA/Grenoble, FR)
- Peter B. Farmer (University of Leicester, UK)
- James H. Kim (HESI, USA)
- Elizabeth A. Martin (AstraZeneca, UK)
- David E.G. Shuker (The Open University, UK)
- Ravi Persaud (L’Oreal, USA)
Conclusions

- Enhancements in specificity, sensitivity, method validation, and bridging between in vitro and in vivo studies are needed to advance the use of DNA adduct data in quantitative risk assessment.

- Framework can be used to improve interpretation of existing data and help plan future work
  - *e.g.*, case study for specific chemical data
DNA Adducts Project Committee: Moving Forward – Case Studies

Draft Conclusions: General Principles (subset)

• DNA is not pristine.
• Structural identification & characterization of DNA adducts is necessary for their use in MOA assessment.
• To establish a DNA-reactive MOA, it is necessary to demonstrate DNA adducts in the target tissues for carcinogenicity.
• DNA adducts may lead to mutations, but are not equivalent to mutations.
• For DNA adducts to lead to mutations, erroneous cellular DNA synthesis is required.
• DNA adducts are biomarkers of exposure; a subset might also be key events, but they are not biomarkers of effect and cannot be used to predict cancer risk.
DNA Adducts Project Committee: Activities

2008:
- Submitted the Risk Assessment & the DNA Adduct Measurements manuscripts to Critical Review in Toxicology for publication.

2009 Plan:
- Complete the first Case Studies Manuscript on Aflatoxin B1, Tamoxifen, and Vinyl Chloride.
- Conduct additional case studies on compounds relevant to current DNA adduct issues in cancer risk assessment.
- SOT 2009 Platform Presentation
- EMS 2009 Workshop

2010+ Plan:
- Additional manuscripts...
- Outreach plans: Poster(s), Workshops, Symposia at relevant professional society mtgs, e.g., SOT, EMS, European EMS, SRA...