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

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2008 DNA Adducts Project Committee: Participation

H E S I

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

OTHERS

Dan Casciano (Casciano & Associates)
Errol Zeiger (Errol Zeiger Consulting)

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

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)

DNA Adducts Project Committee: "Risk Assessment Manuscript"

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 (AstraZenaca, UK)
- David E.G. Shuker (The Open University, UK)
- Ravi Persaud (L'Oreal, USA)

DNA Adducts Project Committee: "Measurement Manuscript"

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

H E S I

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…