

METHODOLOGIES FOR INTERMITTENT AND SHORT-TERM EXPOSURE TO CARCINOGENS SUBCOMMITTEE

Mission

The mission of the MISTEC Subcommittee is to develop methodologies for establishing appropriate dose-metrics to assess carcinogenic risk in humans for short-term or intermittent exposures based on current understanding of the carcinogenic process, and using data from experimental studies in animals, observational studies in humans, and mechanistic studies. Identify data gaps and propose relevant research.

2010 Participants

Eli Lilly and Company
ExxonMobil Biomedical Sciences, Inc.
Imperial College London
Johnson & Johnson Pharmaceuticals
Kraft Foods
Kirkland Consulting
Michigan State University
National Institute for Public Health and the
Environment (RIVM)
National Institutes of Health
National Institute of Environmental Health
Sciences
New York Medical College
The Procter & Gamble Company
Unilever
University of Arizona
US Environmental Protection Agency
National Center for Computational Toxicology
National Health and Environmental Effects
Research Laboratory
Office of Water
US Food and Drug Administration
Center for Drug Evaluation and Research
Center for Food Safety and Applied Nutrition
World Health Organization

Committee Publication

Felter, SP, Conolly, RB, Bercu, JP, Bolger, PM, Boobis, AR, Bos, PMJ, Carthew, P, Doerrler, NG, Goodman, JI, Harrouk, WA, Kirkland, DJ, Lau, SS, Llewellyn, GC, Preston, RJ, Schoeny, R, Schnatter, AR, Tritscher, A, van Velsen, F, Williams, GM. 2011. A proposed framework for assessing risk from less-than-lifetime exposures to carcinogens. *Crit Rev Toxicol.* 41, 507-544.

METHODOLOGIES FOR INTERMITTENT AND SHORT-TERM EXPOSURE TO CARCINOGENS SUBCOMMITTEE

MISSION

The mission of the Subcommittee on Methodologies for Intermittent and Short-Term Exposures to Carcinogens (MISTEC) is to develop methodologies for establishing appropriate dose metrics to assess the potential carcinogenic risk to humans after short-term or intermittent exposures to chemicals. These methods will be based on current understanding of the carcinogenic process, and use data from experimental studies in animals, observational studies in humans, in silico data, and mechanistic studies. Data gaps will be identified and relevant research will be proposed.

2009 ACTIVITIES AND ACCOMPLISHMENTS

The MISTEC Subcommittee conducted a multi-sector workshop in December 2009 in Washington, DC, on a proposed framework for estimating potential human cancer risk from intermittent and/or short-term exposures. The workshop was among the first coordinated efforts to examine and explore risk assessment approaches for less-than-lifetime exposures. Approximately 50 invited scientists from Europe and the United States participated in the event, representing a diverse spectrum of affiliations and expertise.

The goal of the workshop was to develop a framework for new approaches for assessing risks from short-term/intermittent exposures to potential human carcinogens that can be supported with existing data/knowledge. To achieve this goal, invited participants were asked to review key literature in advance of the workshop to establish a common understanding of and familiarity with the issue and its background. Qualitative and quantitative approaches to assessing risk from lifetime exposure to carcinogenic agents were discussed at the workshop, followed by an overview of the available literature on assessing risk from short-term and/or intermittent exposure to carcinogens. A large portion of the workshop was devoted to small breakout group discussions. Data and research needs were explored.

Sponsors of the workshop included the following organizations: Eli Lilly and Company, ExxonMobil Biomedical Sciences Inc., Georgia Pacific LLC, ILSI Europe, the ILSI North America Task Force on Food and Chemical Safety, Johnson & Johnson Pharmaceuticals, the NIH National Institute of Environmental Health Sciences, the Procter & Gamble Company, the Society of Toxicology (SOT) Food Safety Specialty Section, the SOT Regulatory and Safety Evaluation Specialty Section, the SOT Risk Assessment Specialty Section, Unilever, US EPA National Center for Computational Toxicology, US EPA National Health and Environmental Effects Research Laboratory, and the US FDA Center for Food Safety and Applied Nutrition.

FUTURE ACTIVITIES

To communicate the outcome of the December 2009 workshop, the organizing committee will develop a manuscript for publication in a scientific, peer-reviewed journal. The paper will include a proposed framework for estimating potential human cancer risk from intermittent and/or short-term exposures on the basis of the rich discussions that took place at the workshop.



HESI

2009 PARTICIPATION

ACADEMIA

Imperial College London (United Kingdom)
Michigan State University
New York Medical College
University of Arizona

GOVERNMENT

National Institute for Public Health and the Environment (RIVM, The Netherlands)
National Institutes of Health
National Institute of Environmental Health Sciences
US Environmental Protection Agency
National Center for Computational Toxicology
National Health and Environmental Effects Research Laboratory
Office of Water

US Food and Drug Administration
Center for Drug Evaluation and Research
Center for Food Safety and Applied Nutrition
World Health Organization

INDUSTRY

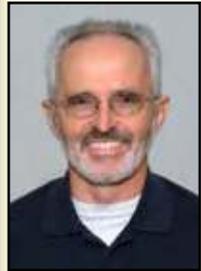
Eli Lilly and Company
ExxonMobil Biomedical Sciences Inc.
Johnson & Johnson Pharmaceuticals
Kraft Foods
The Procter & Gamble Company
Unilever

OTHER

Kirkland Consulting



Co-Chair:
Susan P. Felter, PhD
The Procter & Gamble Company



Co-Chair:
Rory B. Conolly, ScD, DABT
US Environmental Protection Agency
National Health and Environmental Effects Research Laboratory

HESI Scientific Program

Manager: Nancy G. Doerrer, MS
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Peter M.J. Bos, MSc
Centre for Substances and Integrated Risk Assessment
National Institute for Public Health and the Environment (RIVM)
Bilthoven, The Netherlands

“Short-term or intermittent exposures to relatively high concentrations or doses of carcinogens are a regular cause of concern within several risk assessment frameworks. At present, no adequate tools or strategies addressing the risks involved in these exposure situations are available, and the HESI MISTEC Subcommittee faces an intriguing challenge to develop guidance. The December 2009 workshop, bringing together experts from a great variety of disciplines and organizations, provided a good opportunity to develop a framework for estimating potential human cancer risk for less-than-lifetime exposures. Because exposure to carcinogenic substances often is of great personal and social relevance, this framework will be of significant value for national and international authorities and institutes involved in risk assessment and risk management.”



R. Julian Preston, PhD
Associate Director for Health
National Health and Environmental Effects Research Laboratory
US Environmental Protection Agency
Research Triangle Park, North Carolina

“In the past many years, considerable attention in the cancer risk assessment arena has been paid to lifetime exposures. In many situations, this is appropriate. However, a number of scenarios require that less-than-lifetime exposures be considered, namely intermittent and short-term exposures. Such considerations require that a different approach be developed for estimating the risk. The MISTEC Subcommittee established by HESI was charged with considering the manifestations of these less-than-lifetime exposures. At a December 2009 workshop to develop a framework for estimating potential human cancer risk from intermittent and/or short-term exposures, the subcommittee provided a critical forum for discussion and next steps. The development of this framework will be extremely valuable for the US EPA in the context of its Framework for Carcinogen Risk Assessment when a range of exposure scenarios are considered. This is exactly the type of effort that HESI can lead by having the ability to bring the needed experts together for extended discussions.”

Committee Presentations and Data Resources

January 20, 2009: HESI MISTEC Subcommittee Presentation.

"Methodology for Intermittent / Short-term Exposure to Carcinogens." Presented at the 2009 HESI Annual Meeting. Tucson, Arizona. Presentation by Dr. Gary Williams, New York Medical College.



H E S I

HESI

Emerging Issues Subcommittee

Methodology for Intermittent and Short-Term Exposure to Carcinogens (MISTEC)

Gary Williams

(New York Medical College)

Steering Team Scientific Advisor

HESI Emerging Issues Meeting

January 20, 2009

Tucson, Arizona



H E S I

Mission Statement

Develop methodology for establishing appropriate dose metrics to assess the potential carcinogenic risk to humans following short-term or intermittent exposures to chemicals based on current understanding of the carcinogenic process, and using data from experimental studies in animals, observational studies in humans, *in silico* data and mechanistic studies. Data gaps will be identified and relevant research proposed.



H E S I.

History

- Topic selected by EISC in January 2008
- Subcommittee kick-off meeting October 2008



2008 SUBCOMMITTEE PARTICIPATION

H E S I

LEADERSHIP

Susan P. Felter, PhD

(Procter & Gamble Company)

Gary M. Williams, MD, DABT

(New York Medical College)

INDUSTRY

Dow Chemical Company

Johnson & Johnson

Pharmaceuticals

PUBLIC

Imperial College London

Michigan State University

National Institute for Public Health and the
Environment (RIVM)

University of Arizona

US Environmental Protection Agency

National Center for Computational
Toxicology

Office of Water

US Food and Drug Administration

Center for Drug Evaluation and Research



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Objectives

- Obtain and critically evaluate available literature on the topic of assessing risk from short-term and/ or intermittent exposure to carcinogens.
- Define the scope of this project in terms of known modes of action for carcinogens (particularly for those MOAs associated with a threshold versus those that are not).



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Objectives (cont'd)

- Define “short-term” and “intermittent” exposure, particularly as distinguished from “chronic, lifetime” exposure for the purposes of quantitative cancer risk assessment. Determine whether various exposure durations can be represented by “tiers.”
 - Determine if these definitions should be modified based on type of chemical (e.g., long half-life vs. short half-life), life stage at time of exposure, or other criteria.



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Objectives (cont'd)

- Based on the scope of the project, develop recommendations for a quantitative approach (including the most appropriate dose-metric) to assessing risk. Principles of this approach include:
 - Transparency, consistency, pragmatism and health-protection.
 - Consider all possible approaches (e.g., linear low-dose extrapolation, margin-of-exposure approach, potency considerations, etc).



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Objectives (cont'd)

- Identify research that can be conducted using existing/ emerging technologies that might help fill data gaps associated with or improve our understanding of questions of exposure duration (i.e., modeling approaches, dose-surrogates, and biomarkers).



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Approach and Timeline

- Following a teleconference, the Steering Team held its first meeting on October 10, 2008.
- The draft mission statement and subcommittee objectives were developed and are under review.
- Additional subcommittee participants will be invited on an as-needed basis.
- All interested parties will be invited to attend a formal workshop in June 2009 (tentative).



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Next Steps

- Finalize the mission statement and objectives via email and conference calls by February 2009.
- Begin to draft methodology for workshop.
- Next face-to-face meeting will be held March 5-6, 2009 in Washington, D.C.



H E S I

MISTEC Timeline

TIMELINE

January 2008	January 2008 HESI Annual Meeting Presentation
Summer 2008	Build Steering Team
September 10, 2008	Hold introductory Steering Team conference call
October 2008	Steering Team meeting at HESI offices
November 2008 – February 2009	Follow-up conference calls to prepare for full Subcommittee meeting
March 5-6, 2009	Subcommittee meeting at HESI offices
March – May 2009	Prepare for 1st workshop
June 2009	Hold 1st workshop to review the ‘state of the science’
July 2009	Review and discuss workshop outcome and results
August 2009	Begin drafting white paper scope and outline
August – September 2009	Draft 1st drafts of white paper sections
October – November 2009	Prepare white paper for HESI peer review
December 2009 – January 2010	White paper HESI peer review
February – April 2010	White paper publication

December 1-3, 2009: HESI Workshop to Develop a Framework for Estimating Potential Human Cancer Risk from Intermittent and/or Short-Term Exposures, Washington, DC.