

## **CANCER HAZARD IDENTIFICATION STRATEGIES PROJECT COMMITTEE**

### **Mission**

The mission of the HESI Cancer Hazard Identification Strategies (CHIS) Project Committee was to consider new strategies that can offer an improvement in the process of identifying potential human carcinogens using a comprehensive data-based approach, taking into account dose-response and mode of action in the test system.

### **2007 Participants**

Amgen, Inc.  
AstraZeneca AB  
BASF Corporation  
Boehringer Ingelheim GmbH  
European Food Safety Authority  
Georgetown University Medical Center  
GlaxoSmithKline  
Imperial College London (UK)  
Indiana University School of Medicine  
International Agency for Research on Cancer (IARC)  
L'Oréal  
Michigan State University  
National Institute for Public Health and the  
Environment (RIVM, The Netherlands)  
NIEHS National Toxicology Program  
sanofi-aventis  
Schering-Plough Research Institute  
Syngenta Ltd.  
Technical University of Munich (Germany)  
University of Nebraska Medical Center  
University of North Carolina, Chapel Hill  
US Environmental Protection Agency  
National Health and Environmental Effects Research Laboratory  
Office of Pesticide Programs  
US Food and Drug Administration  
Center for Drug Evaluation and Research

### **Committee Publications**

Boobis A, Cohen S, Doerrner N, Galloway S, Haley P, Hard G, Hess F, MacDonald J, Thibault S, Wolf D, Wright J. 2009. A data-based assessment of alternative strategies for identification of potential human cancer hazards. *Toxicol Pathol.* 37, 714-732.



## ILSI Health and Environmental Sciences Institute

### CANCER HAZARD IDENTIFICATION STRATEGIES (CHIS) PROJECT COMMITTEE

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#### MISSION

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The mission of the HESI Cancer Hazard Identification Strategies (CHIS) Project Committee is to consider new strategies that can offer an improvement in the process of identifying potential human carcinogens using a comprehensive data-based approach, taking into account dose-response and mode of action in the test system.

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#### BACKGROUND

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After several decades, the two-year rodent cancer bioassay remains the primary testing strategy for in-life detection of compounds that pose a potential cancer hazard. Yet experimental evidence shows that cancer is often secondary to some other biological effect. The key events leading to cancer usually occur well before tumorigenesis and at lower doses than those producing tumors. Therefore, ensuring protection against the precursor lesion would provide adequate protection against carcinogenicity. The CHIS Project Committee proposes to develop strategies to detect precursor lesions, key events, and mode of action to improve the current testing approach for identifying potential human cancer hazards.

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#### OBJECTIVES

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The CHIS Project Committee has three general objectives:

- Provide a forum for government, academia, and industry to consider alternative approaches to identification of potential human cancer hazards. The focus of these discussions will be on the scientific validity of alternative strategies for identifying potential human carcinogens based on a comprehensive evaluation of available data.
- Evaluate the value and robustness of alternative approaches based on a sound assessment of available data.
- Propose additional experimental approaches for assessing the validity of alternative approaches.

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#### ACTIVITIES AND ACCOMPLISHMENTS

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The CHIS Project Committee was established by HESI as a subcommittee through the emerging issues process in January 2004. In 2006, the HESI Board of Trustees voted unanimously to elevate the group from subcommittee to Project Committee status.

The CHIS Project Committee initiated a pilot project in 2005, and completed the project in 2006. The Project Committee hypothesized that, for non-genotoxic chemicals, the signals of importance for human cancer hazard identification can be detected in shorter-term studies, rather than routinely relying on data from two-year rodent cancer bioassays. A retrospective analysis of 16 chemicals for which short- and long-term data are available was conducted. Data were obtained from the National Toxicology Program (NTP) database. The 16 chemicals were selected because they showed positive results (tumors) in two-year rodent cancer bioassays in liver, lung, kidney, or urinary bladder. Teams of pathologists reviewed 13-week data and data from mutagenicity assays for the 16 chemicals, with the objective of identifying early signals of carcinogenic potential. Peer reviewers checked recorded data. Results and conclusions are as follows:

- Cellular changes indicative of a tumorigenic endpoint can be identified for some, but not all, of the chemicals producing tumors in two-year studies after 13 weeks of chemical administration. Thirteen-week studies utilizing conventional endpoints are not adequate to identify all chemicals that will eventually produce tumors in rodents after two years.
- Additional endpoints are needed to identify some signals not detected with routine evaluation.
- Detection of “critical” endpoints in 13-week studies may identify chemicals not tumorigenic after two years (false positives).

In 2007, the Project Committee extended the pilot project to explore the incidence of false positives. Using the early signals defined in the pilot exercise, participants

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examined compounds in the NTP database that did not produce an increase in tumor incidence in liver, lung, and kidney (2000-2005).

Currently, the Project Committee is preparing a manuscript for journal submission which will address each target organ system examined in the CHIS pilot project. The manuscript will include the anatomic, histologic, and pathologic criteria used in the 13-week study for each system to predict tumorigenicity. Limitations of the pilot project will be discussed. The manuscript will also include discussion sections on proposals for additional and/or improved endpoints for inclusion in the 13-week study for each target organ system.

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### OUTREACH

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The CHIS Project Committee has engaged in various forms of outreach to explore views and perspectives on strategies for identifying human cancer hazards:

- June 2007: Continuing Education Course at the 26<sup>th</sup> Annual Symposium of the Society of Toxicologic Pathology, Puerto Rico.
- July 2006: Presentation at the 2006 Summer Toxicology Forum, Aspen, CO.
- June 2006: Presentation at the Japanese Chemical Evaluation and Research Institute (CERI), Tokyo, Japan.
- April 2006: Poster at the FDA Science Forum, Washington, DC.
- March 2006: Poster at the 45<sup>th</sup> Annual Meeting of the Society of Toxicology, San Diego, CA.
- March 2006: Drug Information Association meeting, Paris, France.

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### FUTURE ACTIVITIES

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The CHIS Project Committee will officially “sunset” in 2008 after publication of the manuscript on the pilot project in a scientific, peer-reviewed journal.

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### LEADERSHIP AND INFORMATION

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Co-Chair ..... Dr. James S. MacDonald  
(Schering-Plough Research Institute)  
Co-Chair ..... Prof. Alan R. Boobis  
(Imperial College London)  
HESI Staff ..... Nancy G. Doerrer, MS  
Ms. Cyndi Nobles

For more information, contact:  
Nancy G. Doerrer, MS  
at 202-659-3306 or [ndoerrer@hesiglobal.org](mailto:ndoerrer@hesiglobal.org).

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### PROJECT COMMITTEE PARTICIPATION

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Amgen Inc.  
AstraZeneca Pharmaceuticals  
BASF Corporation  
Boehringer Ingelheim Pharmaceuticals  
GlaxoSmithKline  
L’Oreal  
Novartis Pharmaceuticals Corporation  
sanofi-aventis  
Schering-Plough Research Institute  
Syngenta Ltd.

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### PUBLIC PARTICIPATION

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European Food Safety Authority  
Georgetown University Medical Center  
Imperial College London  
Indiana University School of Medicine  
International Agency for Research on Cancer  
Michigan State University  
National Institute for Public Health and Environment  
(RIVM, The Netherlands)  
NIEHS National Toxicology Program  
Technical University of Munich  
University of Nebraska Medical Center  
University of North Carolina, Chapel Hill  
US Environmental Protection Agency  
(National Health and Environmental Effects  
Research Laboratory)  
(Office of Pesticide Programs)  
US Food and Drug Administration  
(Center for Drug Evaluation and Research)

## **Committee Presentation and Data Resources**

July 19, 2007: HESI Cancer Hazard Identification Strategies (CHIS) Project Committee Presentation. "Overview of Status of Program and Recommendation for Action." Presented at the 2007 HESI Mid-Year Meeting. Montreal, Canada.



## HESI Cancer Hazard Identification Strategies (CHIS) Project Committee

*Overview of Status of Program and  
Recommendation for Action*

*PSSC Review  
July 19, 2007*

Co-Chairs:

**James S. MacDonald, PhD**  
(Schering-Plough Research Institute)

**Prof. Alan R. Boobis**  
(Imperial College London)

Staff:

**Nancy G. Doerrer, MS**



## CHIS PROJECT COMMITTEE: Mission

Consider new strategies that can offer an improvement to the process of identifying potential human carcinogens using a comprehensive data-based approach, taking into account dose-response and mode of action in the test system.



## 2007 CHIS PROJECT COMMITTEE: Participation

**PUBLIC (European)**

Imperial College London  
International Agency for Research on  
Cancer  
National Institute for Public Health  
and the Environment (RIVM)  
Technical University of Munich  
European Food Safety Authority

**INDUSTRY**

Amgen  
AstraZeneca Pharmaceuticals  
BASF Corporation  
Boehringer-Ingelheim Pharma.  
GlaxoSmithKline  
L'Oreal  
Novartis  
sanofi-aventis  
Schering-Plough Research Institute  
Syngenta CTL

**PUBLIC (US)**

Georgetown University Medical Center  
Indiana University School of Medicine  
Michigan State University  
NIEHS National Toxicology Program  
Stratoxon LLC  
University of Nebraska Medical Center  
University of North Carolina, Chapel Hill  
US Environmental Protection Agency  
National Health and Environmental  
Effects Research Laboratory  
Office of Pesticide Programs  
US Food and Drug Administration  
Center for Drug Evaluation and Research



## Key Dates

- Proposal was presented to membership in January 2004
- First meeting of subcommittee June 7, 2004
- Elevation to Project Committee status in January 2006
- Pilot project initiated in 2005



## CHIS PILOT PROJECT

### Hypothesis:

For non-genotoxic chemicals, the signals of importance for human cancer hazard identification can be detected in shorter-term studies, rather than routinely relying on data from two-year rodent bioassays.



## CHIS PROJECT COMMITTEE: Objectives

- Test the hypothesis that cancer hazard is identifiable from key precursor events in subchronic studies.
- If not, is this limited to certain target organs or chemical classes?
- Would it be possible to add additional endpoints to subchronic studies to improve cancer hazard identification?
- What existing and new information on precursor events would be of value in the assessment of a tumor response to a chemical (i.e., in a bioassay)?

**THE OVERALL OBJECTIVE IS TO DETERMINE IF A CONSTELLATION OF SIGNALS FROM SHORT-TERM STUDIES CAN BE DEFINED THAT RELIABLY PREDICTS HUMAN CANCER HAZARDS.**



## CHIS PILOT PROJECT: Description

- Utilized National Toxicology Program (NTP) database
- Identified 16 chemicals shown to be positive in bioassays from 2000 – 2005 (liver, lung, kidney, urinary bladder)
- Created a defined query tool with input from expert pathologists to ensure consistency of key terminology
- Searched database for 90-day studies for agreed upon endpoints and terms
  - pathologists peer-reviewed these data prior to analysis
- Considered other broad endpoints in addition to target organ histology
  - evidence of immunosuppression (histology of lymphoid tissues, bone marrow, WBC/differential count)
  - evidence of genetic toxicity



## CHIS PILOT PROJECT: NTP Chemicals (2000 – 2005) with Rodent Tumors in Liver, Lung, Kidney, or Urinary Bladder

- |                                     |                                       |
|-------------------------------------|---------------------------------------|
| • Urethane                          | • Propylene glycol mono-t-butyl ether |
| • Riddelliine                       | • 2-Methylimidazole                   |
| • Vanadium pentoxide                | • Decalin                             |
| • Triethanolamine                   | • Oxymetholone                        |
| • o-Nitrotoluene                    | • Methyl eugenol                      |
| • Anthraquinone                     | • Gallium arsenide                    |
| • Elmiron (Na pentosan-polysulfate) | • Fumonisin B1                        |
| • Indium phosphide                  |                                       |
| • Benzophenone                      |                                       |



## CHIS PILOT PROJECT: Characteristics of Selected Chemicals

H E S I

- Chemicals showed clear evidence or some evidence of carcinogenic activity in at least one cell of the NTP bioassay (MR, FR, MM, FM)
  - 13 positive in liver (1 hemangiosarcoma)
  - 5 positive in kidney
  - 7 positive in lung
  - 1 positive in urinary bladder
- 4 chemicals were clearly positive in genetic toxicity studies
  - additional 3 showed equivocal activity needing further evaluation



## CHIS PILOT PROJECT: High-level Summary of Findings

H E S I

TISSUE	CORRECT PREDICTION	PREDICTORS
Liver – rat	5/6 (wt only) 6/6 combined	weight, hypertrophy, necrosis, vacuolation / degeneration
Liver – mouse	6/8 (wt only) 7/8 combined	weight, hypertrophy, cellular foci
Kidney	4/5 (5/5 with Ames)	weight, necrosis / apoptosis, hyperplasia
Lung	4/7	inflammation, hyperplasia
Urinary Bladder	0/1	n/a



## CHIS PILOT PROJECT: Interim Conclusions

H E S I

- Cellular changes indicative of a tumorigenic endpoint can be identified for some, but not all, of the chemicals producing tumors in 2-year studies after 13 weeks of chemical administration
- 13-week studies utilizing conventional endpoints are not adequate to identify all chemicals that will eventually produce tumors in rodents after 2 years
  - additional endpoints are needed to identify some signals not detected with routine evaluation
  - detection of “critical” endpoints in 13-week studies may identify chemicals not tumorigenic after 2 years (false positives)



## CHIS CONCLUSIONS ARE SIMILAR TO THOSE OF OTHERS EXPLORING THIS AREA.

H E S I

- Elcombe et al. (Syngenta) - NTP database prospective study
  - Elcombe et al. (2002). *Environ Health Perspect.* 110: 363-375.
- Allen et al. (NTP) - NTP database retrospective study on liver
  - Allen et al. (2004). *Toxicol Pathol.* 32: 393-401.
- Pritchard et al. (NTP) – genetically modified mice
  - Pritchard et al. (2003). *Environ Health Perspect.* 111: 444-454.
- Cohen (Univ. of Nebraska) – decision tree approach
  - Cohen (2004). *Toxicol Sci.* 80: 225-229.
- Jacobs (FDA) - Retrospective assessment of FDA database
  - Jacobs (2005). *Toxicol Sci.* 88: 18-23.



H E S T

## CHIS PROJECT COMMITTEE: Outreach 2006-2007

- March 2006 poster at the 45th Annual Meeting of the **Society of Toxicology**, San Diego, CA
- March 2006 **Drug Information Association** meeting, Paris, France
- April 2006 poster at the **FDA Science Forum**, Washington, DC
- June 2006 presentation at the **Japanese Chemical Evaluation and Research Institute (CERI)**, Tokyo, Japan
- July 2006 presentation at the 2006 Summer **Toxicology Forum**, Aspen, CO
- June 2007 presentation at **Society of Toxicologic Pathology** Continuing Education Symposium, Puerto Rico



H E S T

## CHIS PROJECT COMMITTEE: Next Steps

- **Better define incidence of false positive rate.**
  - Use endpoints defined in pilot project on remainder of NTP database (compounds that did not produce an increase in tumor incidence).
    - liver, lung, kidney
  - Outcome to be included in manuscript in preparation.
- **Explore hypothesis using known human carcinogens and assumed human non-carcinogens.**
  - Continue using NTP database.
  - Outcome to be included in manuscript in preparation.
- **Test hypothesis with pharmaceutical database.**
  - Explore 90-day data vs. six-month/one-year rodent studies.
  - Will be conducted outside CHIS project dependent on completion of ongoing exercise within PhRMA.



H E S T

## CHIS PILOT PROJECT: Deliverable

- Preparation of a manuscript for submission to a peer-reviewed scientific journal in 2007.
  - Address each target organ system examined in the CHIS pilot project.
  - Include the gross or histologic criteria used in the 13-week study for each system to predict tumorigenicity.
  - Describe limitations of the pilot project.
  - Include proposals for additional and/or improved endpoints for inclusion in the 13-week study for each target organ system.



H E S T

## CHIS PROJECT COMMITTEE: Recommendation to PSSC

*It is recommended that the CHIS Project Committee sunset at the end of 2007 when the manuscript currently under development is submitted for publication.*

- No new proposals for new directions obtained from current membership.
  - No new leadership identified.
- Expectation that concept can return for action as a new proposal through emerging issues process.