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 dentifying 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
Novartis Pharmaceuticals Corporation
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, Doerrer 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.

Fact Sheet

ILSI Health and Environmental Sciences Institute

CANCER HAZARD IDENTIFICATION STRATEGIES (CHIS) PROJECT COMMITTEE

MISSION

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.

BACKGROUND

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.

OBJECTIVES

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.

ACTIVITIES AND ACCOMPLISHMENTS

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

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.

OUTREACH

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 26th 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 45th Annual Meeting of the Society of Toxicology, San Diego, CA.
- March 2006: Drug Information Association meeting, Paris, France.

FUTURE ACTIVITIES

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

LEADERSHIP AND INFORMATION

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

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PROJECT COMMITTEE PARTICIPATION

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

PUBLIC PARTICIPATION

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

CHIS PILOT PROJECT: Characteristics of Selected Chemicals

- 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

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

- 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.

- 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.

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

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.

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.

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.