HESI INTEGRATION OF BIOMONITORING EXPOSURE DATA INTO THE RISK ASSESSMENT PROCESS TECHNICAL COMMITTEE

Mission
The mission of the Technical Committee on Integration of Biomonitoring Exposure Data into the Risk Assessment Process was twofold: 1) to delineate the appropriate scientific use(s) of biomonitoring tools and/or biomonitoring data needed to characterize exposure to chemicals, and 2) to explore mechanisms for integrating biomonitoring data and toxicology data into a robust risk assessment process.

2010-2011 Participating Organizations
Agency for Toxic Substances and Disease Registry
BASF Corporation
Bayer CropScience
Centers for Disease Control National Center for Environmental Health
Emory University
ExxonMobil Biomedical Sciences, Inc.
Forschungsinstitut für Arbeitsmedizin der Deutschen Gesetzlichen Unfallversicherung
Mississippi State University
Procter & Gamble Company
Shell Health
The Dow Chemical Company
University of Leicester
US Environmental Protection Agency
US Food and Drug Administration

Committee Publications:
Albertini, R., et al., The use of biomonitoring data in exposure and human health risk assessments. Environ Health Perspect, 2006. 114(11): p. 1755-62.

Barr, D.B. and J. Angerer, Potential uses of biomonitoring data: a case study using the organophosphorus pesticides chlorpyrifos and malathion. Environ Health Perspect, 2006. 114(11): p. 1763-9.

Birnbaum, L.S. and E.A. Cohen Hubal, Polybrominated diphenyl ethers: a case study for using biomonitoring data to address risk assessment questions. Environ Health Perspect, 2006. 114(11): p. 1770-5.

Butenhoff, J.L., G.W. Olsen, and A. Pfahles-Hutchens, The applicability of biomonitoring data for perfluorooctanesulfonate to the environmental public health continuum. Environ Health Perspect, 2006. 114(11): p. 1776-82.

Calafat, A.M. and R.H. McKee, Integrating biomonitoring exposure data into the risk assessment process: phthalates [diethyl phthalate and di(2-ethylhexyl) phthalate] as a case study. Environ Health Perspect, 2006. 114(11): p. 1783-9.

Doerrer, N., Integration of biomonitoring exposure data into the risk assessment process. December 4, 2004.

Doerrer, N., and Holsapple, MP., Integration of biomonitoring exposure data into the risk assessment process. Risk Policy Report, December 4, 2004. 11(12): p. 33-35.

Doerrer, N.G., Integration of human biomonitoring exposure data into risk assessment: HESI initiatives and perspectives. Int J Hyg Environ Health, 2007. 210(3-4): p. 247-51.

Robison, S.H. and D.B. Barr, Use of biomonitoring data to evaluate methyl eugenol exposure. Environ Health Perspect, 2006. 114(11): p. 1797-801.

Biomarker Framework Tool with example

The Biomonitoring Technical Committee Biomarker of Exposure Interpretive Framework Work Group's objective is to develop a practical method for determining the appropriateness of a biomarker for a specific question of exposure. The Work Group's efforts focus on development of a weight-of evidence framework that evaluates biomarkers through the use of interpretive criteria. This tool is provided in the file for download below. Background information and guidelines are included within the document.

The Work Group applied a benzene example to the weight-of-evidence calculator. This example and the outcome are provided in the document below. This file can also be used to input new information. The user should first clear the example by using the "Clear" option at the top of the Evaluation page. View example here.

HESI Technical Committee Fact Sheet

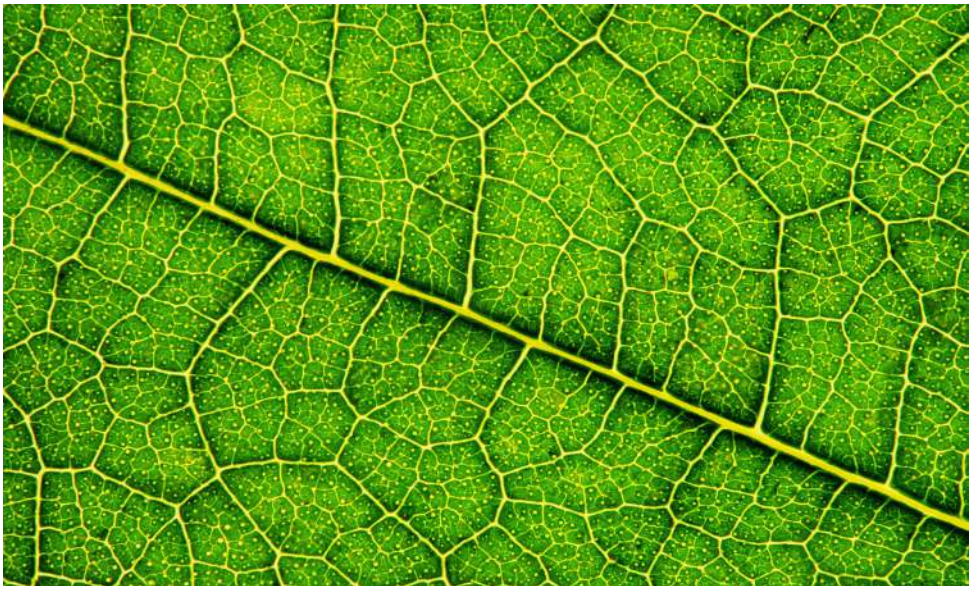
Integration of Biomonitoring Exposure Data into the Risk Assessment Process

2010-2011 Activities and Accomplishments

Co-Chair
Dr. Peter Boogaard
Shell Health

Co-Chair
Dr. Steven Robison
Procter & Gamble Company

HESI Manager:
Dr. Raegan B. O'Lone



This scientific program is committed to:

- Delineating the appropriate scientific use(s) of biomonitoring tools and/or biomonitoring data needed to characterize exposure to chemicals, and
- Exploring mechanisms for integrating biomonitoring data and toxicology data into a robust risk assessment process

Areas of scientific focus

- Generic Criteria. Aiming to formulate criteria for the use and interpretation of biomonitoring exposure data by comparing biological monitoring methodologies in occupational and environmental settings, and
- Strawman Interpretive Framework. Working to develop a practical method for determining the appropriateness of a biomarker for specific exposures through the use of interpretive criteria.

Key accomplishments:

- Development of a Weight of Evidence Calculator for assessment of the appropriateness of a biomarker for specific questions of exposure. This framework has been described in a publication and is publicly available for use by the scientific community on the HESI website.
- The Committee earlier developed generic criteria for biomonitoring. The Committee has further explored application of these criteria via a benzene case study that is anticipated for publication later this year.

What is the Committee's focus for May 2011 - April 2012

The Biomonitoring Committee is working toward completion of the benzene case study for publication in a peer reviewed journal in 2011, after which the Committee will sunset.

Recent publications

Zelenka MP, Barr DB, Nicolich MJ, Lewis RJ, Bird MG, Letinksi DJ, Metcalf SW, O'Lone RB.. A weight of evidence approach for selecting exposure biomarkers for biomonitoring. Biomarkers 2011;16(1):65-73.

2010 - 2011 Participating organizations:

- Agency for Toxic Substances and Disease Registry
- BASF Corporation
- Bayer CropScience
- Centers for Disease Control National Center for Environmental Health
- Emory University
- ExxonMobil Biomedical Sciences, Inc.
- Forschungsinstitut für Arbeitsmedizin der Deutschen Gesetzlichen Unfallversicherung
- Mississippi State University
- Procter & Gamble Company
- Shell International B.V.
- The Dow Chemical Company
- University of Leicester
- US Environmental Protection Agency
- US Food and Drug Administration

For more information, contact the committee manager
Dr. Raegan B. O'Lone, rolone@hesiglobal.org

Committee Presentations and Data Resources

January 19, 2009: HESI Biomonitoring Committee Presentation.
"Integration of Biomonitoring Exposure Data into the Risk Assessment Process." Presented at the 2009 HESI Annual Meeting. Tucson, Arizona. Presentation by Dr. Christina Cowan, The Procter & Gamble Company.

TECHNICAL COMMITTEE ON INTEGRATION OF BIOMONITORING EXPOSURE DATA INTO THE RISK ASSESSMENT PROCESS

HESI Assembly of Members Session

January 19, 2009

BIOMONITORING TECHNICAL COMMITTEE: Leadership

Co-Chairs:

Dr. Steven H. Robison
(The Procter & Gamble Company)

Dr. Peter Boogaard
(Shell Health)

Dr. Christina Cowan-Ellsberry
(presenting)

BIOMONITORING TECHNICAL COMMITTEE

2008 Industry Members

- Arkema, Inc.
- BASF Corporation
- Bayer CropScience
- Biogen Idec MA Inc.
- The Dow Chemical Company
- E.I. DuPont de Nemours & Co.
- ExxonMobil Biomedical Sciences, Inc.
- The Procter & Gamble Company
- Shell Health

Public Participation

- Agency for Toxic Substances and Disease Registry
- CDC National Center for Environmental Health
- Institute of Occupational, Social and Environmental Medicine, University of Erlangen (Berlin)
- Johns Hopkins University Bloomberg School of Public Health
- Mississippi State University
- Ohio State University School of Public Health
- University of Leicester
- University of Vermont College of Medicine
- University of Washington
- US Environmental Protection Agency
- US Food and Drug Administration

BIOMONITORING TECHNICAL COMMITTEE

Mission Statement

- To delineate the appropriate scientific use(s) of biomonitoring tools and/or biomonitoring data needed to characterize exposure to chemicals

- To explore mechanisms for integrating biomonitoring data and toxicology data into a robust risk assessment process.

Biomonitoring Projects - Completed

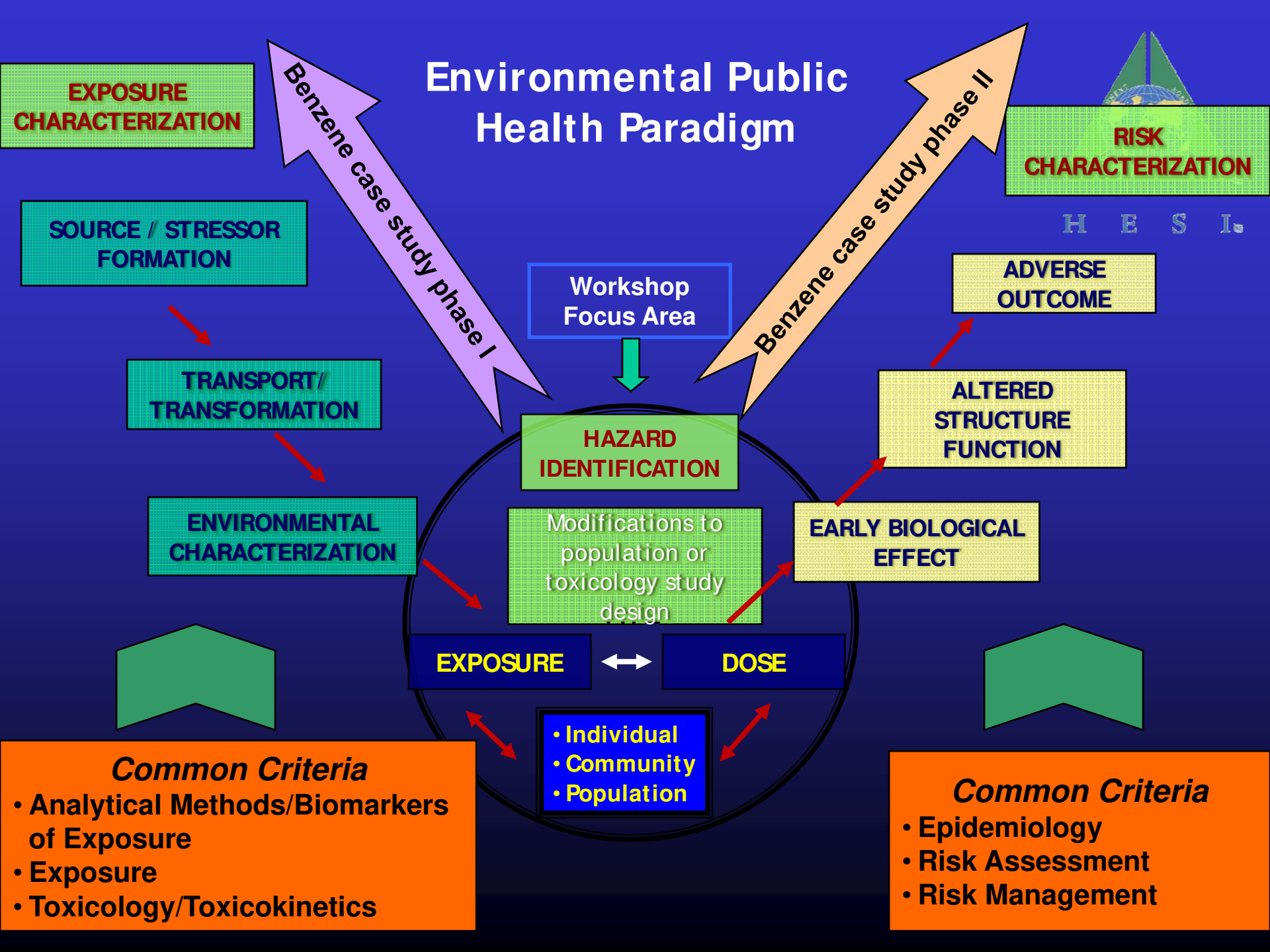
- International Biomonitoring Workshop (2004)
- Outlined "common criteria" for biomonitoring
- Presented HESI biomonitoring work to NAS Biomonitoring Committee
- Scientific Session at the 2006 HESI Annual Meeting
- Publication of the *Environmental Health Perspectives* mini-monograph
- Publication of Forum paper in *Toxicological Sciences*

Biomonitoring: Common Criteria

- Analytical Methods for Biomarkers of Exposure
- Toxicology/Toxicokinetics
- Exposure
- Epidemiology
- Risk Assessment
- Risk Management

2008: Two Work Groups

- Generic Criteria
  - **Mission: to formulate criteria for the use and interpretation of biomonitoring exposure data by comparing biological monitoring methodologies in occupational and environmental settings**
- Strawman Interpretive Framework
  - **Mission: to develop a practical method for determining the appropriateness of a biomarker for specific exposures through the use of interpretive criteria**


Environmental Public Health Paradigm
EXPOSURE CHARACTERIZATION
SOURCE / STRESSOR FORMATION
TRANSPORT/ TRANSFORMATION
ENVIRONMENTAL CHARACTERIZATION
Benzene case study phase I
Workshop Focus Area
HAZARD IDENTIFICATION
Modifications to population or toxicology study design
EXPOSURE
DOSE
• Individual
• Community
• Population
Benzene case study phase II
RISK CHARACTERIZATION
ADVERSE OUTCOME
ALTERED STRUCTURE FUNCTION
EARLY BIOLOGICAL EFFECT
Common Criteria
• Analytical Methods/Biomarkers of Exposure
• Exposure
• Toxicology/Toxicokinetics
Common Criteria
• Epidemiology
• Risk Assessment
• Risk Management

Generic Criteria Work Group:

Benzene Case Study

Objective: Determine the relationship between benzene exposure and risk

- Develop an understanding of sources of benzene exposure
- Develop an understanding of background sources of benzene metabolites and "typical" ranges
- Develop an understanding of formation and distribution of benzene metabolites in the body
- Integrate CDC/NHANES biomonitoring data on benzene into the case-study
- Develop perspective on biomonitoring data for occupational versus general population exposure
- Develop PBPK models to help put biomonitoring data for benzene into a risk-based context
- Integrate epidemiology data

Generic Criteria Work Group: 2009

Benzene Case Study

- The final work product of the Work Group will be one or more manuscripts submitted to peer-reviewed scientific journals
  - Manuscript is near completion and anticipated for submission in the first half of 2009

- Continue biomonitoring outreach efforts by presenting work at Society meetings and other venues

Status of SIF Work Group Activities

- **Completed**
  - Organized smaller working group
  - Agreed upon appropriate framework to fulfill Work Group mission
  - Identified and defined key interpretive criteria
  - Developed prototype tool for evaluating biomarkers of exposure for specific biomonitoring questions
  - Developed beta tool, called *Biomonitoring Weight of Evidence Calculator*, for evaluating biomarkers of exposure for specific exposure questions.
  - Conducted 2 independent tests for a benzene example
  - Conducted second case study

SIF Work Group Activities 2009

- **Ongoing**
  - Additional case studies with other examples in progress
  - Manuscript is in preparation; anticipated for submission by the close of 2009

- Future
  - Convert framework format from Excel to visual program
  - Make the framework program publicly available (website)

BIOMONITORING TECHNICAL COMMITTEE
2008 & 2009 Planned Outreach

H E S I

2008

- Joint Annual Conference of the International Society for Epidemiology/ International Society of Exposure Analysis, Pasadena, CA, October 2008 (poster)
- Society for Risk Analysis Annual Meeting, Boston, MA, December 2008 (presentation within platform session)

2009

- Plan to submit an abstract for the Annual Conference for the International Society of Exposure Science (ISES), Minneapolis, MN, November 2009

Biomonitoring Technical Committee Future Projects

❖ **Generic Criteria Work Group**

- ❑ Preparation of a second case study: parabens (part of the CDC-NHANES biomonitoring program)
  - o Will allow comparison of benzene case study to a compounds with a different primary route of exposure
  - o Expected Outcome: a manuscript to be submitted to the peer-reviewed literature

❖ **New project proposals solicited from the Committee**

- ❑ A request for proposals was issued in November 2008
  - o Proposals will be reviewed by the Committee for prioritization in January 2009

For more information:

Peter Boogaard: peter.boogaard@shell.com

Steven Robison: robison.sh@pg.com

January 22, 2008: HESI Biomonitoring Committee Presentation.
"Technical Committee on the Integration of Biomonitoring Exposure Data into the Risk Assessment Process." Presented at the 2008 HESI Annual Meeting. San Juan, Puerto Rico.
Presentation by Dr. Steven H. Robison, The Procter & Gamble Company.

TECHNICAL COMMITTEE ON INTEGRATION OF BIOMONITORING EXPOSURE DATA INTO THE RISK ASSESSMENT PROCESS

Presented by:

Steven H. Robison, Ph.D.

(Co-Chair, Biomonitoring Technical Committee)

January 22, 2008

BIOMONITORING TECHNICAL COMMITTEE: Leadership

H E S I

Co-Chairs:

Dr. Michael G. Bird (outgoing)
(ExxonMobil Biomedical Sciences, Inc.)

Dr. Steven H. Robison
(The Procter & Gamble Company)

Dr. Peter Boogaard (new)
(Shell Health)

BIOMONITORING TECHNICAL COMMITTEE: 2007 Industry Members

3M Corporation
Arkema, Inc.
BASF Corporation
Bayer CropScience
Biogen Idec MA Inc.
The Dow Chemical Company
Dow Corning
E.I. DuPont de Nemours & Co.
ExxonMobil Biomedical Sciences, Inc.
The Procter & Gamble Company
Shell Health

BIOMONITORING TECHNICAL COMMITTEE: 2007 Public Participation

- Agency for Toxic Substances and Disease Registry
- CDC National Center for Environmental Health
- Institute of Occupational, Social and Environmental Medicine, University of Erlangen (Berlin)
- Johns Hopkins University Bloomberg School of Public Health
- Mississippi State University
- Ohio State University School of Public Health
- University of Leicester
- University of Vermont College of Medicine
- University of Washington
- US Environmental Protection Agency
  - National Center for Computational Toxicology
  - National Exposure Research Laboratory
  - National Health and Environmental Effects Research Laboratory
  - Office of Prevention, Pesticides and Toxic Substances
- US Food and Drug Administration
  - Center for Food Safety and Applied Nutrition

BIOMONITORING TECHNICAL COMMITTEE

Mission Statement

- to delineate the appropriate scientific use(s) of biomonitoring tools and/or biomonitoring data needed to characterize exposure to chemicals

- to explore mechanisms for integrating biomonitoring data and toxicology data into a robust risk assessment process.

Biomonitoring Projects - Completed

- International Biomonitoring Workshop
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- Scientific session at the 2006 HESI Annual Meeting
- Publication of a mini-monograph in *Environmental Health Perspectives*
- Publication of Forum paper in *Toxicological Sciences*

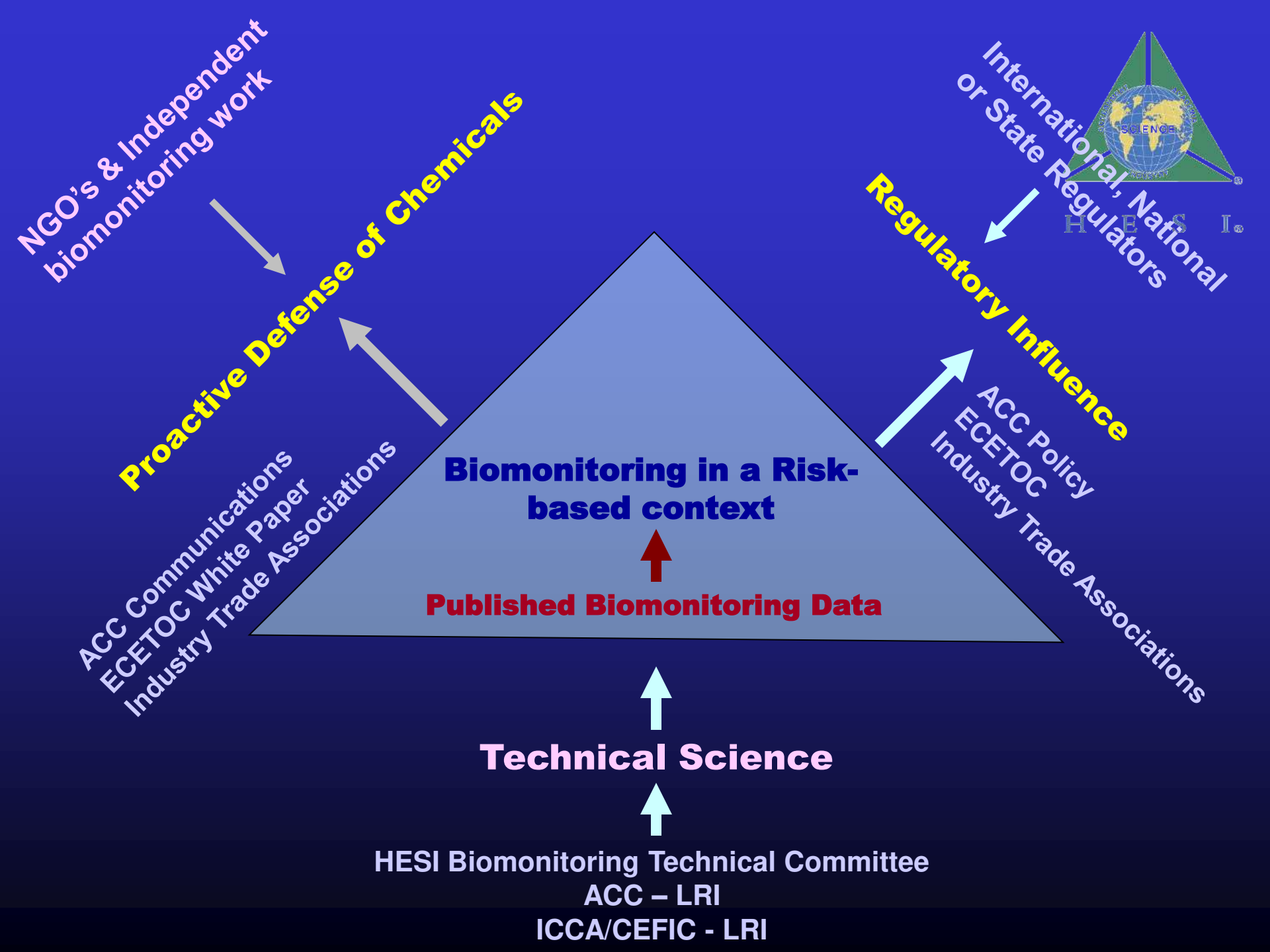
Biomonitoring Projects – Ongoing

Case Study:

- Developing an understanding of sources of benzene exposure
- Developing an understanding of background sources of benzene metabolites and “typical” ranges
- Developing an understanding of formation and distribution of benzene metabolites in the body

Biomonitoring Projects Proposed for 2008-2009

- Integrate CDC/NHANES biomonitoring data on benzene into the case-study
- Develop perspective on biomonitoring data for occupational versus general population exposure
- Develop PBPK models to help put biomonitoring data for benzene into a risk-based context
- Continue biomonitoring outreach efforts by presenting work at Society meetings and other venues


NGO's & Independent biomonitoring work
Proactive Defense of Chemicals
International, National or State Regulators
Regulatory Influence
ACC Communications
ECETOC White Paper
Industry Trade Associations
Biomonitoring in a Risk-based context
Published Biomonitoring Data
ACC Policy
ECETOC
Industry Trade Associations
Technical Science
HESI Biomonitoring Technical Committee
ACC – LRI
ICCA/CEFIC - LRI

Biomonitoring Technical Committee Completed Projects

Completed Projects

2004 International Biomonitoring Workshop

HESI, EPA, CDC, the Agency for Toxic Substances and Disease Registry (ATSDR), the International Council of Chemical Associations (ICCA), the European Chemical Industry Council (CEFIC), and the American Chemistry Council (ACC) were co-sponsors.

Workshop explored the processes and information needed for placing biomonitoring data into risk-context.

Special emphasis on integrating biomarker measurements of exposure, internal dose, and potential health outcome.

Scientists from US government agencies, international groups, academia, and industry recommended criteria for applying biomonitoring data.

Completed Projects

Publication of Workshop Proceedings

Seven manuscripts authored by participants in the Biomonitoring Technical Committee were published as a mini-monograph in *Environmental Health Perspectives* (Volume 114, pp. 1755-1801).

Papers are based on the technical discussions, research proposals, and conclusions of the September 2004 International Biomonitoring Workshop.

The manuscripts address criteria for the use of biomonitoring data in exposure and risk assessment, as well as case study analyses.

Completed Projects

H E S I

Scientific Session at 2006 HESI Annual Meeting

Biomonitoring Technical Committee hosted a Scientific Session on "Integration of Biomonitoring Exposure Data into the Risk Assessment Process."

Summary of this session was published in *Toxicological Sciences* as a Forum article in mid-2006.

The paper briefly describes speaker perspectives on diverse, and sometimes overlapping, uses of biomonitoring data, including evaluation of exposure trends, identification of susceptible populations, detection of emerging chemical risks, the conduct of epidemiology studies, and evaluation of risk reduction strategies.

Completed Projects

Interactions with the National Research Council

Based on the success of and technical guidance resulting from the 2004 International Biomonitoring Workshop, the National Academies of Sciences/National Research Council Committee on Human Biomonitoring for Environmental Chemicals consulted with the HESI Biomonitoring Technical Committee via invitations to speak at NRC meetings.

The work of the HESI Biomonitoring Technical Committee is cited in the NRC Committee's final report titled *Human Biomonitoring for Environmental Chemicals* (2006).

BIOMONITORING TECHNICAL COMMITTEE 2004-2007 Outreach

2004:

- International Biomonitoring Workshop, Research Triangle Park, NC, September 2004 (workshop organized and supported by HESI).

2005:

- 42nd Congress of the European Societies of Toxicology (EUROTOX), Krakow, Poland, September 2005 (poster)
- 31st Annual Summer Toxicology Forum, Aspen, CO, July 2005 (session)
- US Environmental Protection Agency Science Forum, Washington, DC, May 2005 (poster)
- 44th Annual Meeting of the Society of Toxicology, New Orleans, LA, March 2005 (poster)
- Meetings of the NAS/NRC Committee on Human Biomonitoring for Environmental Toxicants, Washington, DC, March 2005 (presentation)
- ICCA Biomonitoring meeting, Paris, France, June 2005 (presentation)
- US Congressional Staffers Briefing (presentation)

BIOMONITORING TECHNICAL COMMITTEE 2004-2007 Outreach

H E S I

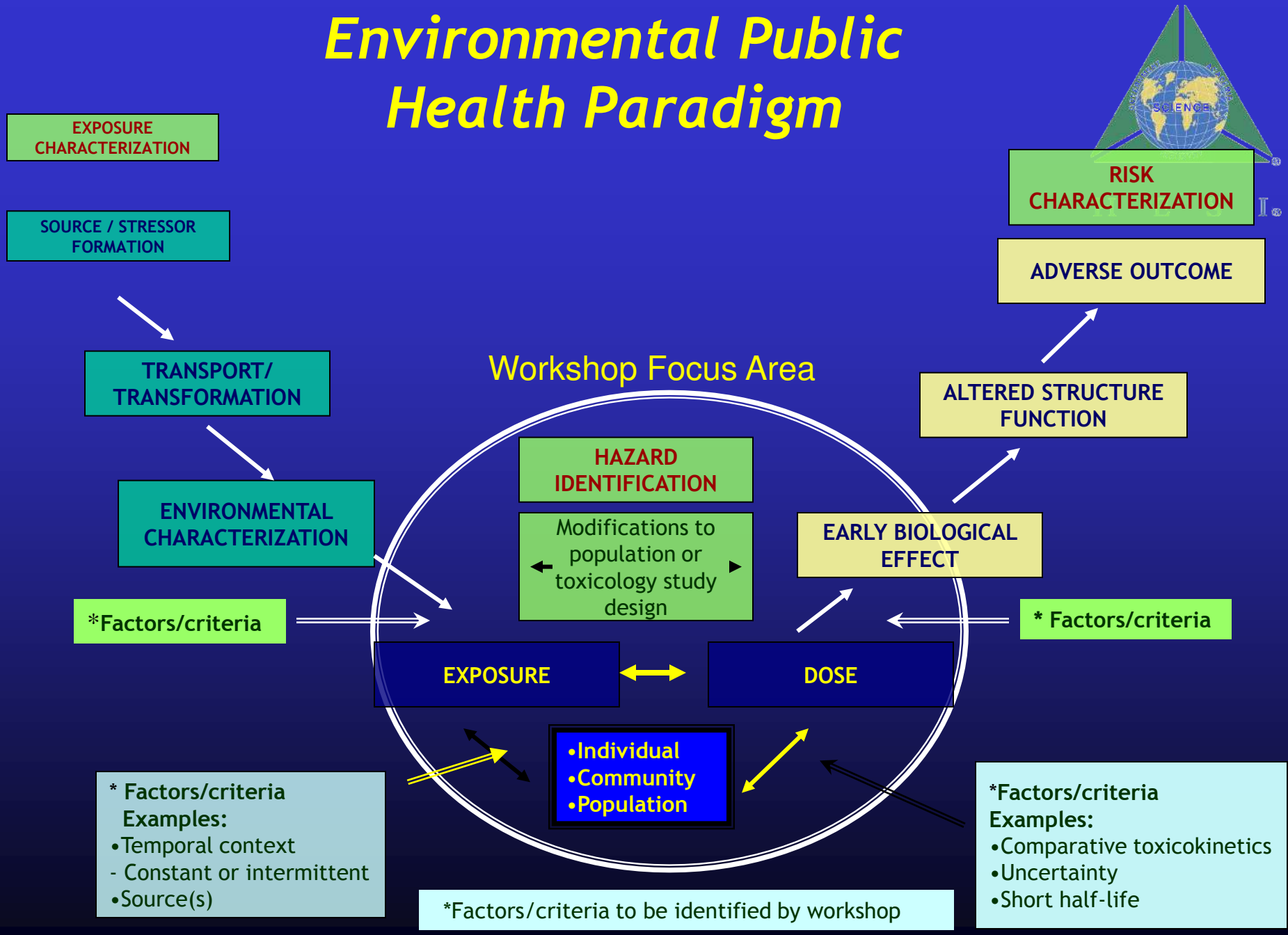
2006

- Air & Waste Management Association's Conference on Chemicals, Health, and the Environment, Ottawa, Ontario, Canada, November 2006 (presentation)
- American College of Toxicology Annual Meeting, Palm Springs, CA, November 2006 (presentation)
- ICCA Biomonitoring meeting, Minneapolis, MN, June 2006 (presentation)

2007

- 17th Annual Conference of the International Society of Exposure Analysis (ISEA), Durham, NC, October 2007 (poster)
- 44th Congress of the European Societies of Toxicology (EUROTOX), Amsterdam, The Netherlands, October 2007 (poster)
- 46th Annual Meeting of the Society of Toxicology, Charlotte, NC, March 2007 (poster)

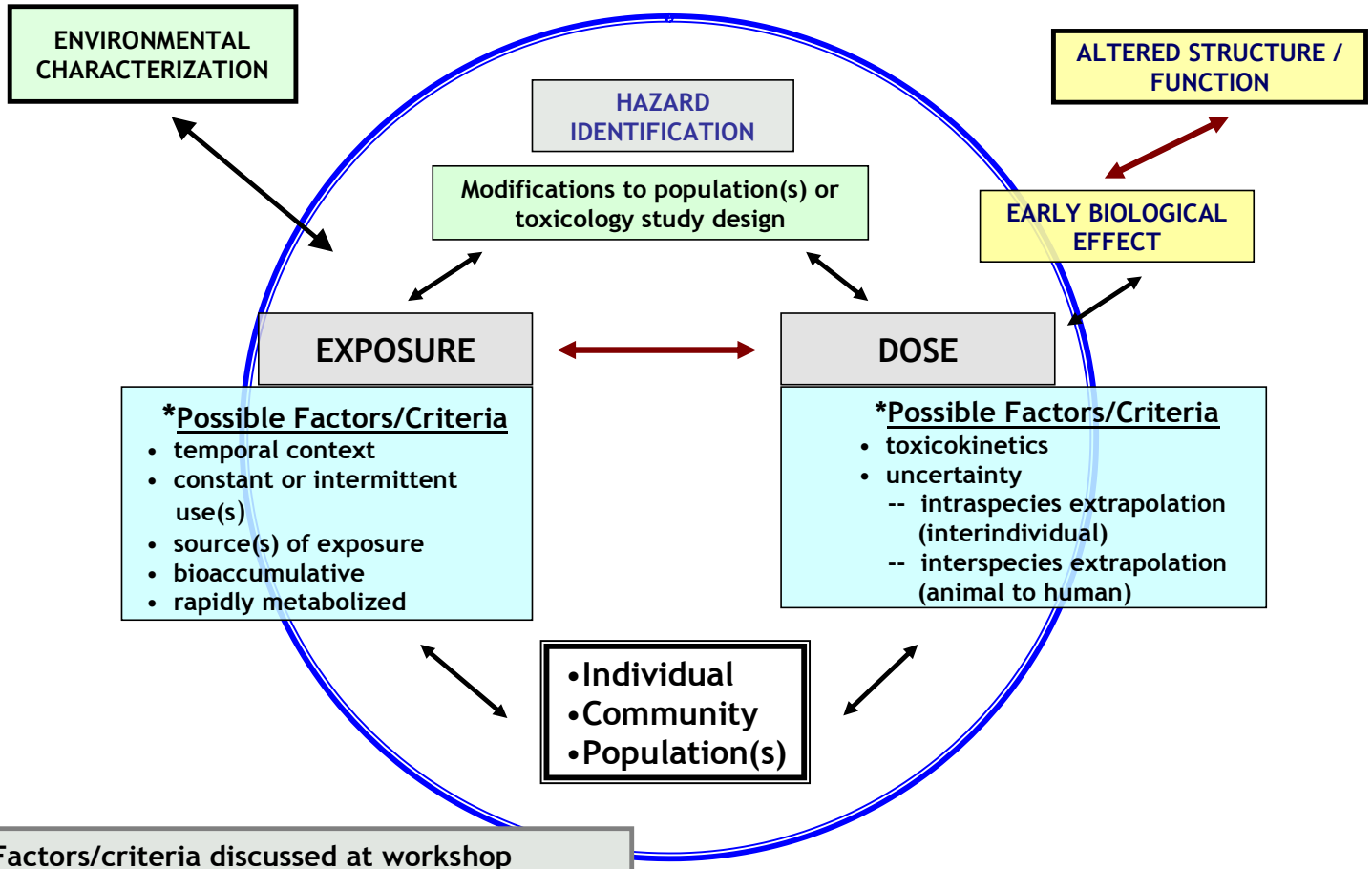
Environmental Public Health Paradigm



HESI
2004 International Workshop

- Case-studies designed to compare relatively data-rich with data-poor chemicals
- Also compared chemicals that are well metabolized versus chemicals that are not metabolized
  - Organophosphates and polybrominated fire retardants
  - Organophosphates and phthalates (DEP and DEHP)
  - Perfluorooctane sulfonate (PFOS) and polycyclic aromatic hydrocarbons (PAH)
  - PFOS and arsenic
  - Methyl eugenol and aflatoxin

WORKSHOP FOCUS AREA

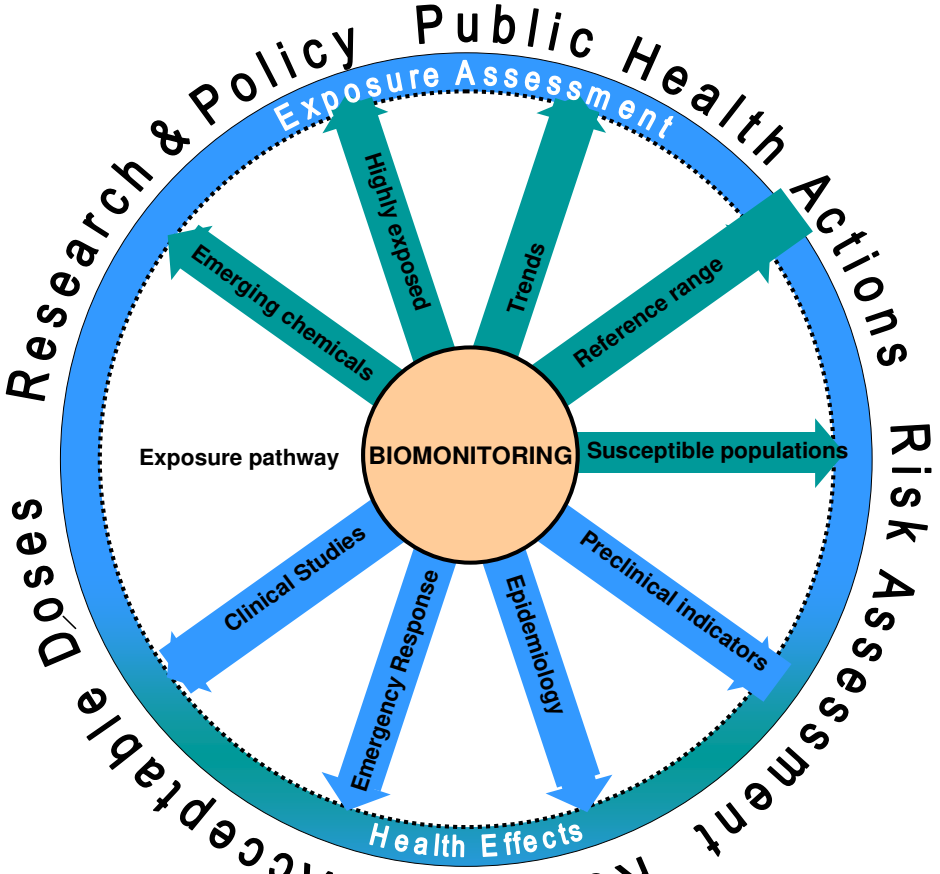


*Factors/criteria discussed at workshop

Biomonitoring: Common Criteria

- Analytical Methods for Biomarkers of Exposure
- Toxicology/Toxicokinetics
- Exposure
- Epidemiology
- Risk Assessment
- Risk Management

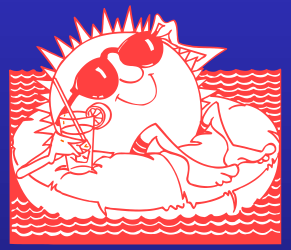
Different spokes for different biomonitoring questions



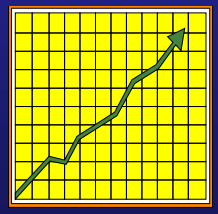
Risk Assessment Paradigm

H E S I

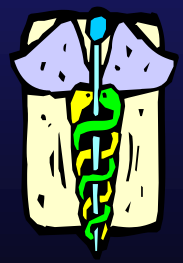
Hazard Identification



Exposure Assessment



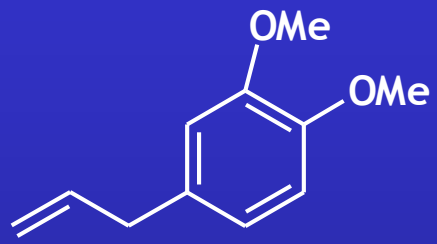
Dose-Response Assessment



Risk Characterization

Methyl Eugenol Hazard Identification

Methyl Eugenol
[4-allylveratrole, 1,2-dimethoxy-4-(2-propenyl)benzene]
CAS# 93-15-2



- Generally considered "non-genotoxic" although some compounds in this chemical class are positive in unscheduled DNA synthesis

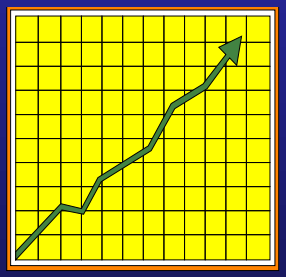
- Methyl eugenol induced liver tumors in mice and rats (NTP TR491) following gavage administration

Risk Assessment Paradigm

Hazard Identification

Exposure Assessment

Dose-Response Assessment



Risk Characterization

Biomonitoring: Common Criteria

Analytical Methods for Biomarkers of Exposure

- Were validated and standardized methods used?
- What are the specificity and sensitivity of the method being used?
- Is/are the biomarker(s) of exposure valid?
- Have inter- or intra-laboratory comparisons been conducted?
- Did the sampling strategy include considerations of toxicokinetics?
- Did the sampling strategy consider potential sources of error or sample contamination?

Analytical Contamination or Background

- ME use widespread -- foods, perfumes, soaps, etc
- Significant background concentration from air and water (5-20 pg/g)
- Eliminated perfumes in laboratory, restricted to nonperfumed soaps, eliminated other sources of contamination such a vacuum traps
- Reduced background to < 1 pg/g

Barr, D et al. 2000. Levels of methyl eugenol in a subset of adults in the general US population as determined by high resolution mass spectrometry. *Environ Health Perspect*. 108, 323-328.

Biomonitoring: Common Criteria

Exposure

- Have the primary sources of exposure been identified?
- Are pathways/routes of exposure understood?
- Can human exposure be related to animal toxicology studies?
- Is there an understanding of the exposure-dose relationship?
- What is understood about temporality and duration of exposure?

Exposure to Methyl Eugenol

- Common use – perfume/flavor raw material
- Also found in many perfume and flavor oils
- Found in orange juice and herbs such as tarragon and basil
- Naturally occurring in nutmeg, allspice and other common spices
- About 2,990 million pounds produced annually
- Nominated by FDA for NTP bioassay

Additional Sources of Methyl Eugenol Exposures

- **Methyl eugenol and cue-lure traps for suppression of male oriental fruit flies and melon flies (Diptera: Tephritidae) in Hawaii: effects of lure mixtures and weathering.**
  Vargas et al. 2000 *J Econ Entomol*., 93, 81-87.

- **Volatile compounds in a spanish red wine aged in barrels made of Spanish, French, and American oak wood.**
  De Simon BF, Cadahia E, Jalocha J. 2003. *J Agric Food Chem*. 51, 7671-7678.

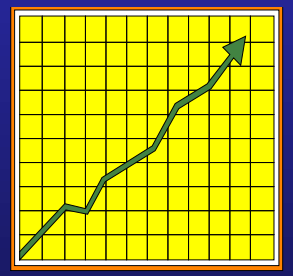
- **Changes in the chemical composition of basil caused by different drying procedures.**
  Di Cesare LF, Forni E, Viscardi D, Nani RC. 2003. *J Agric Food Chem*. 51, 3575-81.

- Contaminant in ambient air or municipal water? Barr et al. 2000. *Environ Health Perspect*. 108, 323-328.

Risk Assessment Paradigm

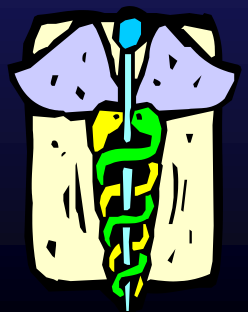
Hazard Identification

Exposure Assessment



Dose-Response Assessment

Risk Characterization



Biomonitoring: Common Criteria

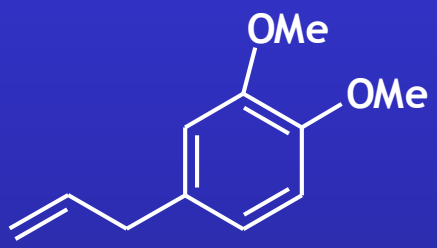
Toxicology/Toxicokinetics

- Are there sufficient toxicology data including longer term exposure?
- Are the human and toxicology study routes of exposure comparable?
- Are toxicokinetic data in animals and humans available?
- Are the animal data relevant for humans?

Methyl eugenol metabolism

- NTP has conducted single-dose and multi-dose toxicokinetic studies using the same doses/route as bioassay (NTP TR491)
- Duration of toxicokinetic study approximated bioassay – 6, 12 or 18 months (NTP TR 491)
- Covalent binding studies (NTP TR491)
- Some human data also available (Ginger-snap study)

Methyl Eugenol Metabolism



- O-demethylation
- Epoxide formation
- Carbonium ion

"It appears that the 1'-hydroxylation pathway is more prominent at higher levels of exposure (e.g., > 10 mg/kg bw). Certainly at low dose (100 ug or 1.5 ug/kg bw), human production of 1'-hydroxy metabolite is expected to be very low given that urinary excretion of the 1'-hydroxy metabolite is 0.5%."

Smith et al.. 2002. *Food Chem Toxicol*. 40, 851-870

Methyl Eugenol

- Serum levels from biomonitoring study were 0-390 pg/g

  (Barr et al., 2000)

- Based on consumption habits, the daily per capita intake is estimated to be ~5-6 μg/kg/day

  (Smith et al., 2002)

- Does consumption data relate to biomonitoring data?

Consumption Study

- Human study conducted to understand relationship between ingestion and serum concentration of methyl eugenol
- Temporal changes in methyl eugenol levels following ingestion of food (gingersnap cookies) containing 18 μg methyl eugenol/cookie, total methyl eugenol consumption was 216 μg or about 3.7 μg/kg
- The level of methyl eugenol in blood peaked at about 15 minutes after ingestion with an estimated half-life of approximately 100 minutes
- The mean level of methyl eugenol went from a peak value of 53.9 pg/g serum fell to a mean of 25.2 pg/g serum at 2 hours

(Schecter et al. 2004. *Environ Health Perspect*. 112, 678-680)

Methyl Eugenol

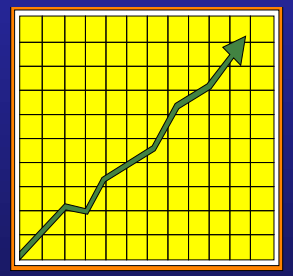
- Based on consumption habits, the daily per capita intake is estimated to be ~5-6 μg/kg/day
  (Smith et al., 2002)

- Ingestion of ginger snap cookies containing ~ 216 μg methyl eugenol (~3.7 μg/kg/day) resulted in peak serum concentration range of 25-100 pg/g
  (Schecter et al., 2004)

Risk Assessment Paradigm

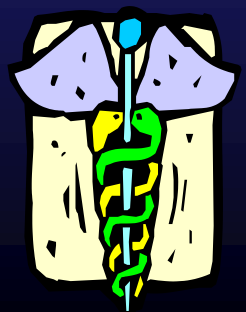
Hazard Identification

Exposure Assessment



Dose-Response Assessment

Risk Characterization



Biomonitoring – Common Criteria

Epidemiology

- Are the Bradford-Hill criteria supported?
- Is there an effect in humans?
- Is the effect observed in populations?
- Are there human polymorphisms?

Risk Assessment/Risk Management

- Are there sufficient and relevant toxicology data?
- Is there a relationship between the biomarker of exposure and a known human health effect?
- If applicable, is there evidence that remediation efforts are working?

Methyl Eugenol

- Human toxicity not known
- Human pharmacokinetics unknown
- Human mode of action not understood
- Limited data on exposure – biomarker relationship

Biomonitoring and Risk Assessment

Where to from here?

- What are the risks to individuals or populations?
- Are there other biomarkers of exposure that should be incorporated/used?
- Are there other tissue sources that would be more appropriate to biomonitor?
- Do we have biomonitoring data in experimental animals?
- Should we re-evaluate risk assessment methods?

Methyl Eugenol

Safety assessment of allylalkoxybenzene derivatives used as flavouring substances-methyl eugenol and estragole.

Smith, RL et al. 2002. *Food Chem Toxicol*. 40, 851-870.

Human consumption of methyl eugenol and its elimination from serum.

Schecter, A et al. 2004. *Environ Health Perspect*. 112, 678-680.

Biomonitoring Technical Committee Ongoing/Future Projects

Strawman Interpretive Framework (SIF) Work Group

- The Strawman Interpretive Framework (SIF) Work Group is developing a framework that identifies and links information sets, and identifies appropriate biomarkers of exposure. The prototype framework has been tested via a case study, and continues to be refined.
- During 2008, the SIF Work Group will develop additional guidance for interpreting criteria, reduce the subjectivity of the prototype tool, identify mechanisms for quantifying uncertainty, and test the framework against controlled case studies (including the Generic Criteria Work Group's case study).
- The SIF Work Group intends to develop a tool that can be tested by the Technical Committee and, ultimately, be made public for broad use.
- One or more publications are anticipated by the close of 2008.

SIF Work Group Members

- **Dr. Dana Barr**
  CDC
- **Dr. Linda Birnbaum**
  US EPA
- **Dr. Timothy Buckley**
  Ohio State University
- **Dr. John Butenhoff**
  3M Company
- **Dr. Monty Eberhart**
  Bayer CropScience
- **Prof. Peter Farmer**
  University of Leicester
- **Dr. Craig Farr**
  Arkema Inc.
- **Dr. Susan Metcalf**
  ATSDR
- **Dr. Michael Zelenka†**
  ExxonMobil Biomedical Sciences
- **Dr. Hal Zenick**
  US EPA

† SIF Work Group Chair

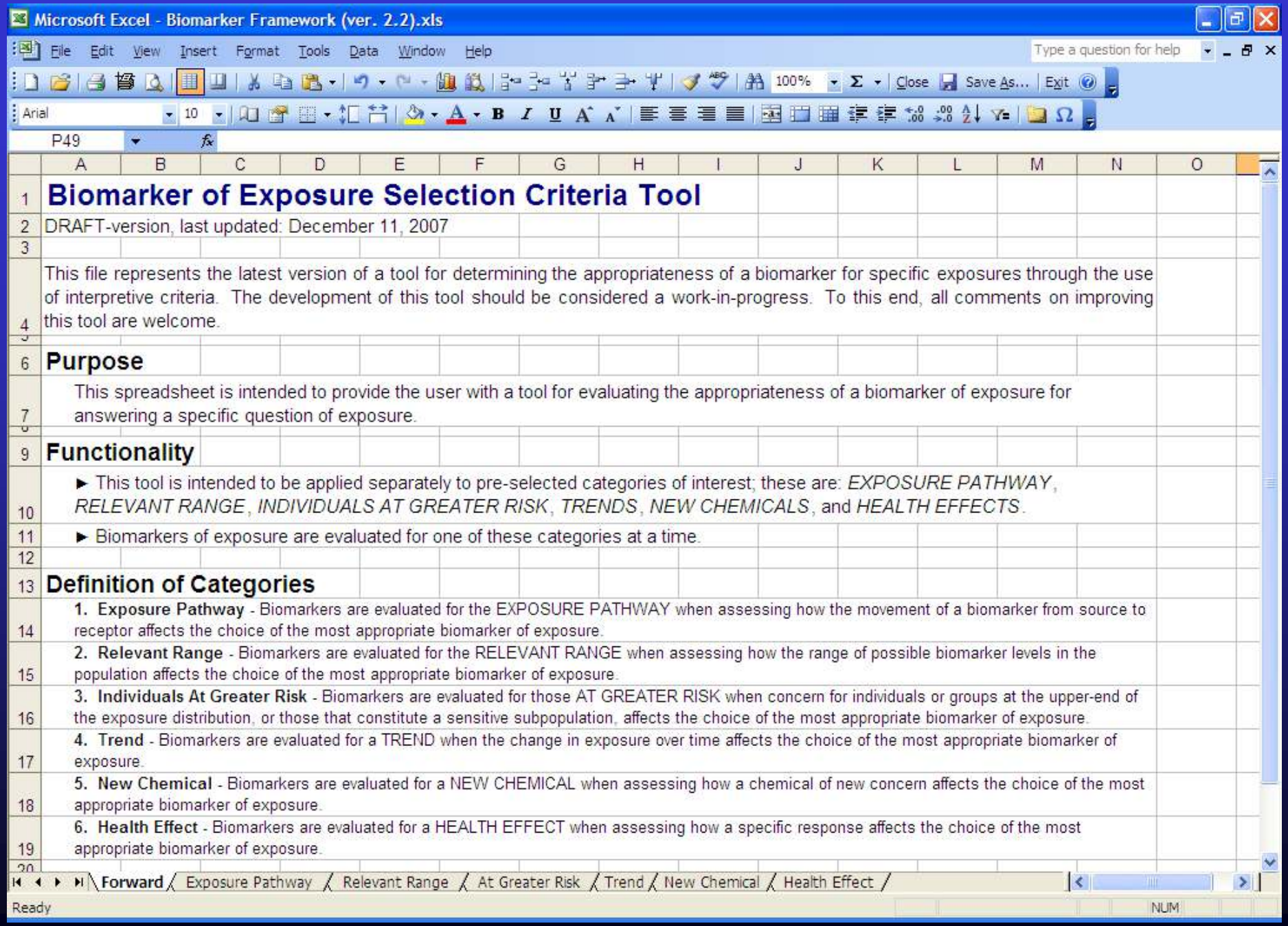
† With support from EMBSI scientists

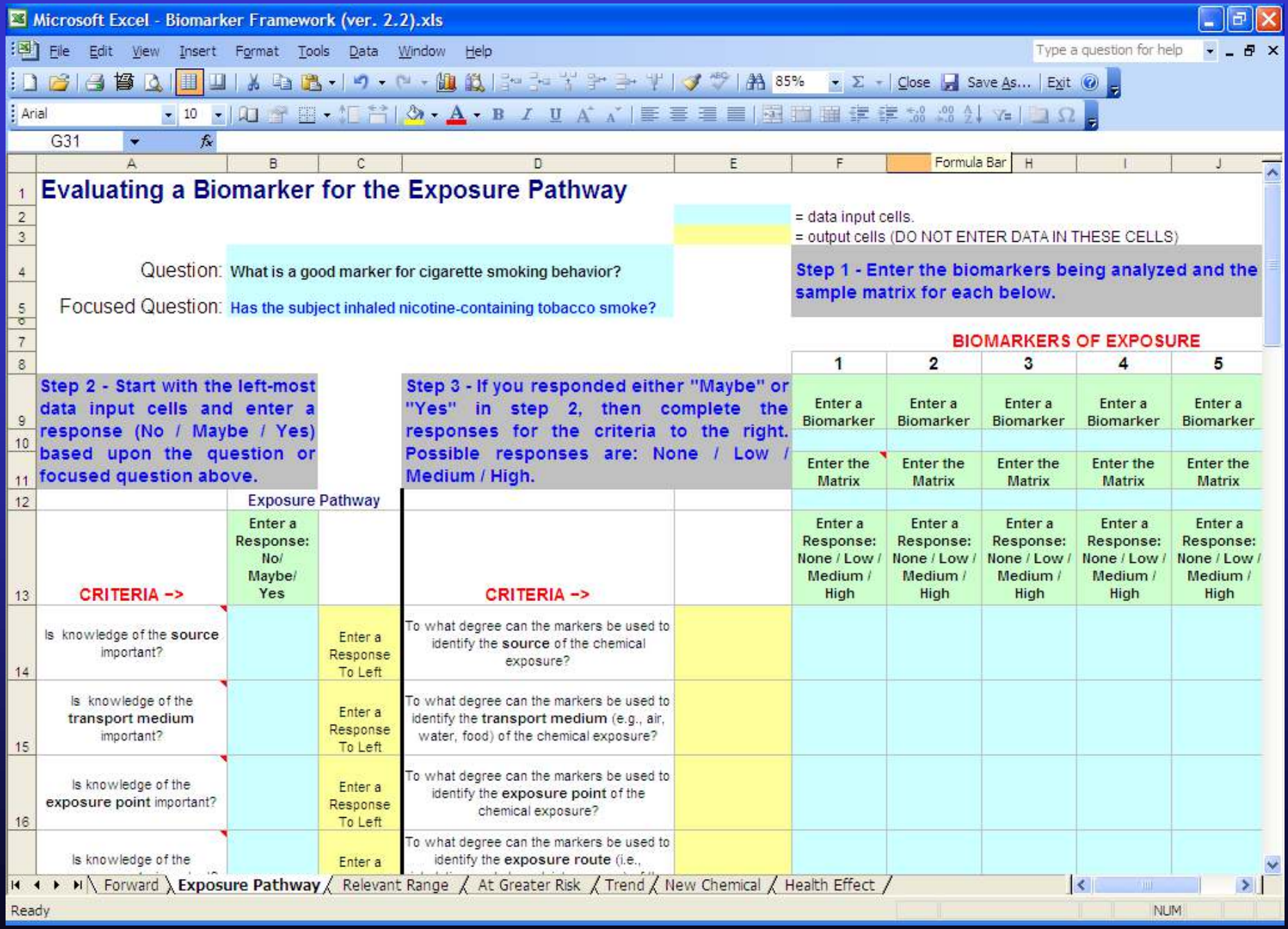
SIF WG MISSION STATEMENT:

The Strawman Interpretive Framework (SIF) Work Group is responsible for developing a practical method for determining the appropriateness of a biomarker for specific exposures through the use of interpretive criteria.

Status of SIF WG Activities

- Completed
  - Organized smaller working group
  - Agreed upon appropriate framework to fulfill WG mission
  - Identified and defined key interpretive criteria
  - Developed prototype tool for evaluating biomarkers of exposure for specific biomonitoring questions
- Ongoing
  - Developing additional guidance on interpreting criteria
  - Addressing subjectivity issue
    - Need to make tool more objective
    - Introduce probabilistic component
  - Quantifying uncertainty
  - Test framework using controlled case studies


Microsoft Excel - Biomarker Framework (ver. 2.2).xls
File Edit View Insert Format Tools Data Window Help
Type a question for help
Close Save As... Exit
Arial 10
P49
Biomarker of Exposure Selection Criteria Tool
DRAFT-version, last updated: December 11, 2007
This file represents the latest version of a tool for determining the appropriateness of a biomarker for specific exposures through the use of interpretive criteria. The development of this tool should be considered a work-in-progress. To this end, all comments on improving this tool are welcome.
Purpose
This spreadsheet is intended to provide the user with a tool for evaluating the appropriateness of a biomarker of exposure for answering a specific question of exposure.
Functionality
► This tool is intended to be applied separately to pre-selected categories of interest; these are: EXPOSURE PATHWAY, RELEVANT RANGE, INDIVIDUALS AT GREATER RISK, TRENDS, NEW CHEMICALS, and HEALTH EFFECTS.
► Biomarkers of exposure are evaluated for one of these categories at a time.
Definition of Categories
1. Exposure Pathway - Biomarkers are evaluated for the EXPOSURE PATHWAY when assessing how the movement of a biomarker from source to receptor affects the choice of the most appropriate biomarker of exposure.
2. Relevant Range - Biomarkers are evaluated for the RELEVANT RANGE when assessing how the range of possible biomarker levels in the population affects the choice of the most appropriate biomarker of exposure.
3. Individuals At Greater Risk - Biomarkers are evaluated for those AT GREATER RISK when concern for individuals or groups at the upper-end of the exposure distribution, or those that constitute a sensitive subpopulation, affects the choice of the most appropriate biomarker of exposure.
4. Trend - Biomarkers are evaluated for a TREND when the change in exposure over time affects the choice of the most appropriate biomarker of exposure.
5. New Chemical - Biomarkers are evaluated for a NEW CHEMICAL when assessing how a chemical of new concern affects the choice of the most appropriate biomarker of exposure.
6. Health Effect - Biomarkers are evaluated for a HEALTH EFFECT when assessing how a specific response affects the choice of the most appropriate biomarker of exposure.
Forward Exposure Pathway Relevant Range At Greater Risk Trend New Chemical Health Effect
Ready
NUM


Microsoft Excel - Biomarker Framework (ver. 2.2).xls
File Edit View Insert Format Tools Data Window Help
Type a question for help
Close Save As... Exit
Arial 10
G31
Formula Bar
Evaluating a Biomarker for the Exposure Pathway
= data input cells.
= output cells (DO NOT ENTER DATA IN THESE CELLS)
Question: What is a good marker for cigarette smoking behavior?
Focused Question: Has the subject inhaled nicotine-containing tobacco smoke?
Step 1 - Enter the biomarkers being analyzed and the sample matrix for each below.
BIOMARKERS OF EXPOSURE
1 2 3 4 5
Enter a Biomarker
Enter the Matrix
Step 2 - Start with the left-most data input cells and enter a response (No / Maybe / Yes) based upon the question or focused question above.
Step 3 - If you responded either "Maybe" or "Yes" in step 2, then complete the responses for the criteria to the right. Possible responses are: None / Low / Medium / High.
Exposure Pathway
Enter a Response: No/ Maybe/ Yes
Enter a Response: None / Low / Medium / High
CRITERIA ->
Is knowledge of the source important?
To what degree can the markers be used to identify the source of the chemical exposure?
Is knowledge of the transport medium important?
To what degree can the markers be used to identify the transport medium (e.g., air, water, food) of the chemical exposure?
Is knowledge of the exposure point important?
To what degree can the markers be used to identify the exposure point of the chemical exposure?
Is knowledge of the
To what degree can the markers be used to identify the exposure route (i.e.,
Enter a Response To Left
Forward Exposure Pathway Relevant Range At Greater Risk Trend New Chemical Health Effect
Ready
NUM

Sample Interpretive Criteria*

- **Exposure**
  - Marker appropriate for measuring source of the exposure?
  - Marker appropriate for measuring transport medium of the exposure?
  - Marker appropriate for measuring exposure point of the exposure?
  - Marker appropriate for measuring route of the exposure?
- **Pharmacokinetics**
  - Pharmacokinetics (human) – is PK well understood?
  - Inter-individual variation in pharmacokinetics
- **Temporality**
  - Temporality of marker
  - Temporality of exposure (episodic)
  - Temporality of exposure (chronic)

* Criteria developed by HESI

- **Association**
  - Strength of association – degree of relationship between intensity of exposure and level of biomarker
  - Degree to which the biomarker is representative of all sources of exposure (mass balance)
- **Marker Attributes**
  - Specificity of marker for exposure (e.g., hemoglobin adduct versus SCEs)
  - Contamination which may result in presence of biomarker in matrix
- **Analytical**
  - Multiple analytical lab capacity available
  - Stability of marker
  - Internal standards
  - Sensitivity
- **Others**
  - Cost per sample
  - Ease of acquiring body sample

Generic Criteria Work Group

The mission of the Generic Criteria Work Group is to formulate criteria for the use and interpretation of biomonitoring exposure data by comparing biological monitoring methodologies in occupational and environmental settings.

Generic Criteria Work Group Participants

- Dr. Scott Arnold (The Dow Chemical Company)
- †Dr. Craig Barrow (The Dow Chemical Company)
- Dr. Timothy Bingman (DuPont)
- Dr. Stuart Cagen (Shell Health)
- Dr. Antonia Calafat (CDC NCEH)
- Dr. Peter Farmer (University of Leicester)
- Dr. Andrew Goetz (BASF Corporation)
- Dr. Michael Hughes (US EPA)
- Dr. A. Michael Kaplan (DuPont Haskell Laboratory)
- Mr. Paul Price (The Dow Chemical Company)
- †Dr. Steven Robison (The Procter & Gamble Company)
- Many others

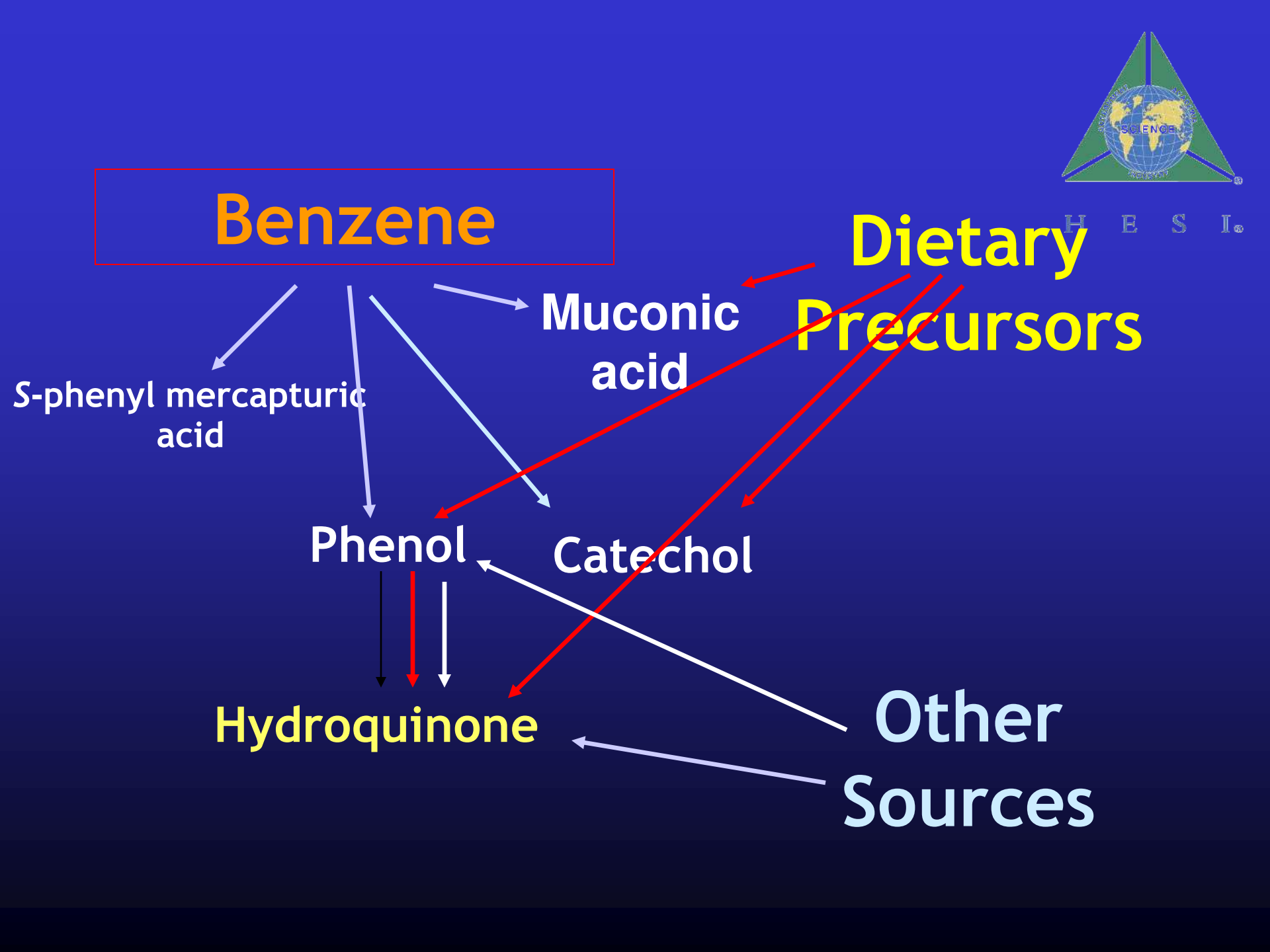
†Work Group Co-Chairs

Generic Criteria Work Group

- A case study is in preparation and will be presented in poster format at the March 2008 Annual Meeting of the Society of Toxicology (Seattle).
- A program is in development for a session at the July 2008 Toxicology Forum in Aspen, CO, on the Work Group's case study.
- The final work product of the Work Group will be one or more manuscripts submitted to peer-reviewed scientific journals.

Objective

- Determine the relationship between benzene exposure and risk
  - Many published data sets
  - NHANES
  - Epidemiology data
  - Toxicology data


Benzene
Muconic acid
S-phenyl mercapturic acid
Phenol
Catechol
Hydroquinone
Dietary Precursors
Other Sources

Benzene Case Study Initial Work

- Define the lower limits of occupational and environmental air benzene concentrations that can be reliably characterized via:

  -- urinary metabolites (SPMA, MA, phenol, catechol, hydroquinone),

  -- urinary benzene,

  -- and blood benzene.

Ongoing Work

- Determine the background sources of benzene, and determine the range of "typical" levels
- Determine the background sources of benzene metabolites and determine the range of "typical" levels
- Determine the formation and distribution of benzene metabolites in the body resulting from benzene exposure

Ongoing Work

- Identify the analytical issues (e.g., sample collection, storage, and analysis.)
- ACGIH Biological Exposure Index (BEI) and German MAK value for benzene
- Review literature to determine which metabolite(s) is (are) thought to cause benzene's effects.

TECHNICAL COMMITTEE PUBLICATIONS

• Albertini, R, Bird, MG, Doerrer, NG, Needham, L, Robison, S, Sheldon, L, and Zenick, H. 2006. The use of biomonitoring data in exposure and human health risk assessment. *Environ Health Perspect.* 114, 1755-1762.

• Angerer, J, Bird, MG, Burke, TA, Doerrer, NG, Needham, L, Robison, SH, Sheldon, L, and Zenick, H. 2006. Meeting Report. Strategic biomonitoring initiatives: moving the science forward. *Toxicol Sci.* 93, 3-10.

• Barr, DB, Angerer, J. 2006. Potential uses of biomonitoring data: a case study using the organophosphorus pesticides chlorpyrifos and malathion. *Environ Health Perspect.* 114, 1763-1769.

• Birnbaum, LS, Cohen Hubal, EA. 2006. Polybrominated diphenyl ethers: a case study for application of biomonitoring data to characterize exposure. *Environ Health Perspect*. 114, 1770-1775.

• Butenhoff, JL, Olsen, GW, Pfahles-Hutchens, A. 2006. The applicability of biomonitoring data for perfluorooctanesulfonate (PFOS) to the environmental public health continuum. *Environ Health Perspect.* 114, 1776-1782.

• Calafat, AM, McKee, RH. 2006. Integrating biomonitoring exposure data into the risk assessment process: phthalates (diethyl phthalate and di[2-ethylhexyl] phthalate) as a case study. *Environ Health Perspect* . 114, 1783-1789.

• Doerrer, NG. 2007. Integration of human biomonitoring exposure data into risk assessment: HESI initiatives and perspectives. *Int J Hyg Environ Health* 210, 247-251.

• Hughes, MF. 2006. Biomarkers of exposure: a case study with inorganic arsenic. *Environ Health Perspect*. 114, 1790-1796.

• Robison, SH, Barr, DB. 2006. Use of biomonitoring data to evaluate methyl eugenol exposure and its relationship to the environmental public health continuum. *Environ Health Perspect*. 114, 1797-1801.