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**Using Biomarkers in Human Health Risk Assessment:**
**A Workshop to Identify Research Priorities**

**June 21 & 22, 2000**
**Embassy Suites Raleigh Durham Airport Hotel**
**Cary, North Carolina**

**Objective.** The Chemical Manufacturers Association (CMA) Risk Assessment Methods Technical Implementation Panel is working with the National Institute of Environmental Health Sciences (NIEHS) and the Society of Toxicology (SOT) to host a workshop to identify research needs in the area of biomarkers in risk assessment. In addition, staff from the National Center for Environmental Assessment (NCEA) of the U.S. EPA and the Chemical Industry Institute of Toxicology (CIIT) are assisting in the planning of the workshop. CMA will use the workshop recommendations to prioritize a research agenda and generate requests for research proposals in this topic area. These requests for proposals (RFPs) are being developed for CMA's Long-Range Research Initiative (LRI).

The focus of this workshop is to identify key areas where research is needed to successfully incorporate biomarkers in risk assessment. Biomarkers were identified as a cross-cutting issue in almost all of the 1998 State of the Science Study (STOTS) White Papers. A balance of experts in toxicology, epidemiology (ecological, occupational and transitional), clinical studies, dosimetry, exposure assessment, and risk assessment/biostatistics drawn from industry, government, and academia will meet for one and a half days with the objective to identify and prioritize research needs. A format of discussions, rather than lectures, will facilitate the workshop objective. The committee envisions that 25 to 30 core workshop participants will be invited to attend the workshop. The interested public will be able to register and attend as observers.

**Schedule, Location, and Proceedings.** The workshop is scheduled for June 21 & 22, 2000. The workshop will be held at the Embassy Suites Raleigh Durham Airport Hotel in Cary, North Carolina. A report summarizing the workshop output will be developed and published on CMA's website.

**Background.** The identification, development, and validation of biomarkers for use in environmental and human health risk assessments have tremendous potential to improve the quality and reduce the uncertainty in risk estimates. Biologic markers are not new. Markers such as blood lead, mercury levels in hair, and exhaled or excreted metabolites or liver function assays after solvent exposures have long been used in health research and management to indicate exposure to or predict effects of these compounds. Currently, several areas of biomarker development are underway. These include: biomarkers of exposure, biomarkers of internal dose, biomarkers of susceptibility or individual variability, and biomarkers of effects. Significant advances in molecular biology and analytical chemistry have lead to the use of biomarkers in both molecular epidemiology and toxicology studies, providing the potential to integrate the results of these disciplines that typically evaluate health outcomes at different levels of analysis (e.g., population versus cellular). The findings of such studies are and will be incorporated increasingly into human health risk assessments and thus, ultimately, will be the basis of regulatory standard setting. However, biomarkers also have the potential to be over-interpreted. In fact, consensus among scientists and policy makers regarding the interpretation, acceptance, and use of biomarkers in risk assessment has not been reached. Additional scientific research is required to fill the substantial data gaps concerning the biological implications of the cellular changes manifested as biomarkers, and the effects of these changes on health risk.

The identification of the most relevant and immediately required information is essential in order to focus the research in those areas that will reduce uncertainty in risk assessment and support the appropriate scientific use of biomarker data. Research is needed to develop credible approaches for their use in all four phases of risk assessment (i.e., Hazard Characterization, Dose-response Assessment, Exposure Assessment and Risk Characterization). For example, the 1996 proposed EPA Cancer Risk Assessment Guidelines encourage the use of non-tumor data for dose-response assessment, as an adjunct or perhaps in lieu of, tumor data based on an understanding of an agent's mode of action (MOA). How biomarker data can be used to inform the understanding of mode of action and provide a platform for integration of diverse data should be explored. Methods are also being proposed to use inter-individual biomarker variability to estimate human variability with respect to risk and identify susceptible populations. NIEHS is gearing up to apply markers of genetic susceptibility to human population studies and search for gene-environment interactions, which translates into the ability to identify susceptible populations. The research required to use biomarkers in risk assessment needs to be outlined so that efforts can be focused in those areas most likely to improve the risk assessment process and to support the appropriate use of biomarker data.

**Definition and Identification of Biomarkers: The Exposure-Dose-Response Continuum.** As defined by the National Research Council Board on Environmental Studies and Toxicology in 1987, a biologic marker is any cellular or molecular indicator of toxic exposure, adverse health effects or susceptibility. The markers may represent measurable biological events in a continuum between a causal exposure and resultant disease.

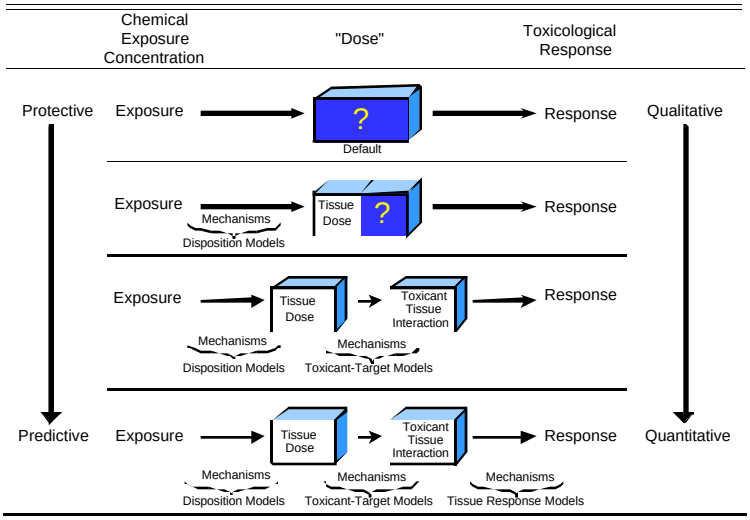
**Biomarkers of exposure** indicate whether exposure to an agent has taken place, and include measurement of chemicals, specific metabolites, or adducts formed by reaction of the compound or its metabolites with macromolecules.

**Biomarkers of effect** provide an indication of early events, and may indicate the development of toxicity, carcinogenesis, or disease.

**Biomarkers of susceptibility** may be used to identify specific individuals at greater risk than the general population as a result of a genetic or other predisposition to the effects of exposure.

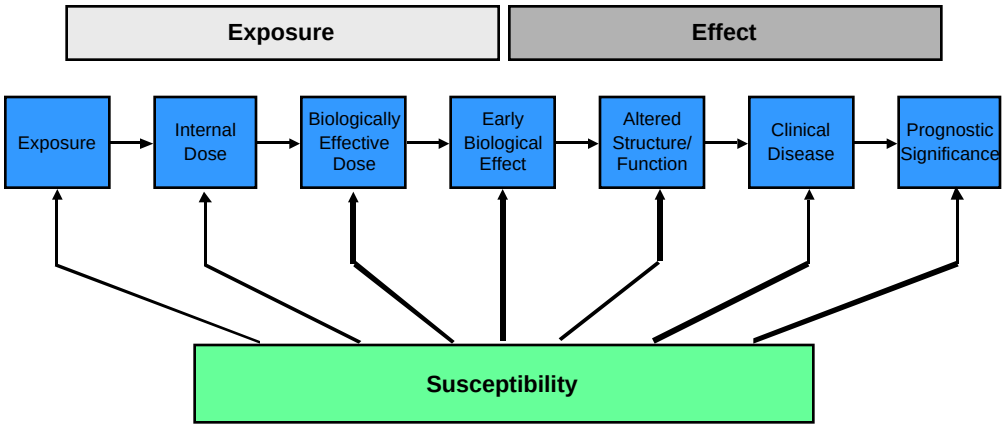
The incentives for the use of biomarkers in risk assessment and molecular epidemiology are based on the biological tenets that: (1) biomarkers may be early warning signs of disease; (2) early biologic effects from a toxic exposure are far more prevalent in the population at risk than the late events of disease (e.g., morbidity and mortality) that were historical outcome measures of interest to risk assessment; (3) the early events may be more reflective of the exposures than the end disease outcomes; and (4) technological advances allow xenobiotics to be directly or indirectly quantified by identification of some predictable, dose-related biological responses. Likewise, contemporary bioassays are more comprehensive in scope and include more mechanistic assays on dosimetry and toxic action than previous testing protocols only a decade ago. Recognition of this has motivated a new framework for the incorporation of mechanistic data into "exposure-dose-response assessment." Emphasis has been placed on characterizing the mode of action, defined as a chemical's influence on molecular, cellular, and physiological functions; and includes elucidation of the mechanistic determinants governing dosimetry (pharmacokinetics) and toxicant-target interactions (pharmacodynamics). Ultimately, it is desirable to have a comprehensive biologically-based dose response model for accurate risk assessment as shown in Figure 1. Due to the increase in accuracy of the characterization with each progressive level, estimates also progress from more conservative (presumably protective) to factually based (predictive). This scheme and that used for biological markers (Figure 2) bear remarkable similarity, so that it can readily be appreciated that the consideration and validation of biomarkers will directly inform how mechanistic data can be used to integrate diverse data at different levels of biological organization (e.g., population versus cellular) for risk assessment.

**Figure 1. Schematic Characterization of Comprehensive Exposure-Dose-Response Continuum and the Evolution of Protective to Predictive Dose-Response Estimates**




Source: US EPA (1994)

**Figure 2. Biological Marker Components in Sequential Progression Between Exposure and Disease**

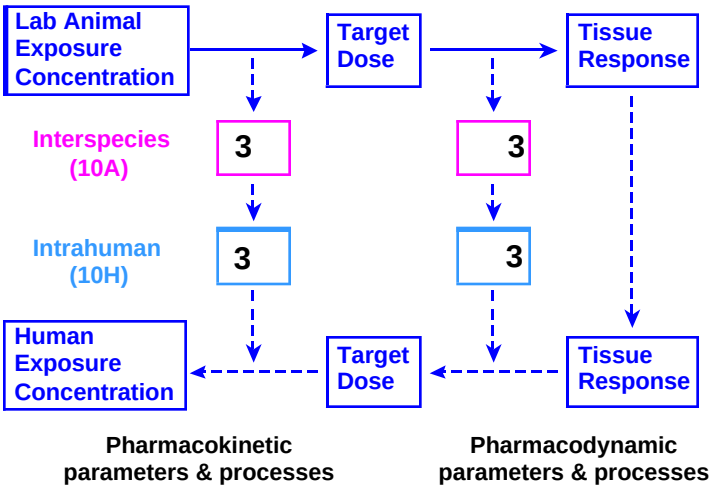



Source: Schulte (1989)

Pharmacokinetics and pharmacodynamics are also components of both the interspecies and intraspecies uncertainty factors (UFs) typically applied in the face of substantial data gaps when the mode of action and description of the exposure-dose-response continuum is at a rudimentary level

(Figure 3). The factors are applied for both uncertainty in the characterization of the process as well as potential variability in the governing parameters of the process. Comprehensive biologically-based models can replace these presumably protective factors with a more accurate and predictive description of the key events along the continuum.

**Figure 3. Schematic of UF Components Incorporated Into Exposure-Dose-Response Characterization**




Source: US EPA (1994)

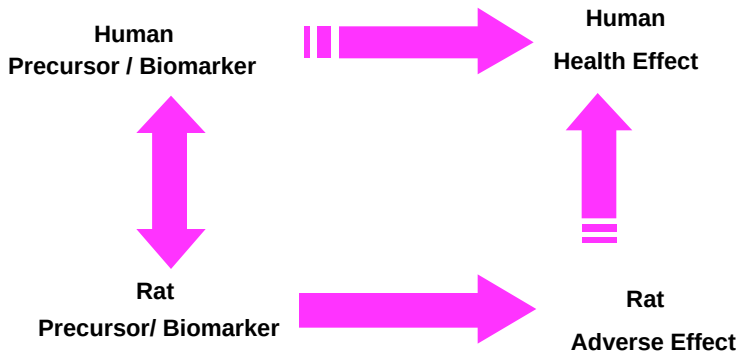
The benefits of biomarkers to risk assessment are likely to lie in their ability to inform an understanding of the mode of action, including a chemical's phamacokinetic (PK) determinants (e.g., uptake, distribution, metabolism, and elimination) and its pharmacodynamic (PD) attributes (e.g., repair, detoxication). Understanding the temporal aspects of these processes (e.g., whether the chemical or its damage accumulate) will provide insight on choice of an appropriate dose surrogate for the dose-response assessment. Using species-specific parameters for these dose and response measures will thereby improve both inter- and intraspecies extrapolations. Extending the laboratory animal data to humans with biomarker work in the PK and PD arenas will provide a means of validation of the extrapolations (Figure 4).

**Process.** The objective of the workshop will be met best by providing a framework with illustrations rather than focusing on individual case studies in order to establish a platform for breakout discussions. The advantage of the plenary framework is that it facilitates development of general principles and thereby avoids emphasis on the details for individual chemicals; especially since controversy remains for some chemicals and a number of case studies have already been developed which would be redundant with such an exercise.

The objectives of each group would then be to: (1) develop a mature understanding of what each disciplinary group currently does; (2) identify issues and what is required to improve extrapolations for risk assessment; and (3) brainstorm on how to address issues and then articulate them as research needs. Each group will be expected to produce a prioritized list of key issues and research needs related to the use of biomarkers in human health risk assessment.

The plenary discussion after the individual breakout sessions will afford the opportunity for cross-disciplinary interaction and refinement and integration of research needs.

**Figure 4. Use of Biomarker Data in Parallelogram Extrapolation to Human Homology**




Jarabek (In preparation)

**Tentative Agenda.** The following presents a tentative agenda for the two-day workshop.

***Day 1, June 21, 2000***

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| 7:00 – 8:30 AM | Registration |
| 7:45 – 8:15 AM | Breakfast |
| 8:30 – 8:45 AM | Welcome and Charge for the Workshop<br>*Steering Committee Member (tbd)* |
| 8:45 – 9:30 AM | Overview of Uncertainties in Human Health Risk Assessment and Examples of Risk Assessment with Biomarkers Data<br>*Risk Assessment Expert (Annie Jarabek, USEPA, NCEA)* |
| 9:30 – 10:00 AM | Charge for the Breakout Groups<br>*Facilitator (Joseph Rodricks, Life Sciences Consultancy)* |
| 10:00 – 10:30 AM | Q&A Session |
| 10:30 – 10:45 AM | Break |
| 10:45 – Noon | Breakout Group Discussions |
| Group 1 | What research can be done to expand the use of biomarkers to characterize uncertainty and variability associated with exposure-dose relationships? |
| Group 2 | What research can be done to expand the use of biomarkers to characterize uncertainty and variability associated with toxicant target interactions? |
| Group 3 | What research can be done to evaluate and validate biomarkers? |
| Noon – 1:15 PM | Lunch |
| 1:15 – 3:00 PM | Breakout Group Discussions (Continued) |
| 2:30 – 3:00 PM | Designated Time for Observers to Contribute to Discussion |
| 3:00 – 3:20 PM | Break |
| 3:20 – 5:00 PM | Breakout Group Discussions (Continued) |
| 4:30 – 5:00 PM | Designated Time for Observers to Contribute to Discussion |
| 5:00 – 5:30 PM | Breakout Group Discussions (Completed) |
| 6:30 – 8:30 PM | Dinner |

**Day 2, June 22, 2000**

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|---|---|
| 7:15 – 7:45 AM | Breakfast |
| 8:00 – 10:00 AM | Presentation of Breakout Group Recommendations<br>*Breakout Group Chairs and Rapporteurs* |
| 10:00 – 10:15 AM | Break |
| 10:15 – 11:00 AM | Plenary Discussion<br>*Moderated by Facilitator* |
| 11:00 – 11:30 AM | Designated Time for Observers to Contribute to Plenary Discussion<br>*Moderated by Facilitator* |
| 11:30 – Noon | Plenary Discussion Wrap Up<br>*Moderated by Facilitator* |
| Noon | Adjournment<br>*Steering Committee Member* |

**Registration Information**. To register please use the form located on page 2 of the registration document (http://ntp-server.niehs.nih/gov/htdocs/liaison/BiomarkersRegInfo.pdf) or visit the NTP homepage at URL: http://ntp-server.niehs.nih.gov.