Biomarkers - Key to Exposure Reconstruction

Yu-Mei Tan, Martin Phillips, Jon Sobus, Daniel Chang, Rocky Goldsmith
U.S. Environmental Protection Agency, National Exposure Research Laboratory

Corresponding author: Yu-Mei Tan
Mail Code: E205-01, 109 T.W. Alexander Drive, Research Triangle Park, NC 27711
Phone: 919-541-2542
Email: tan.cecilia@epa.gov

Key Words
Biomarker, Exposure Reconstruction, Computational Model, Exposure Pathways

Disclaimer: *The United States Environmental Protection Agency has provided administrative review and has approved for publication. The views expressed in this chapter are those of the authors and do not necessarily reflect the views or policies of the United States Environmental Protection Agency.*

The goal of environmental health science is to understand the interplay between environment and humans in order to evaluate the effects of human activities on the environment, as well as to evaluate the effects of various aspects of the environment on human health. When investigating the effects that exposures to environmental chemicals have on human health, the major challenge lies in establishing the causal relationship between the magnitude of exposure to environmental chemicals and the incidence of adverse outcomes at various biological endpoints (e.g., cancer, irritation). This causal relationship can only be established when each element on the source-exposure-dose-effect continuum are linked (Fig 1). For an adverse health outcome to occur from exposure to a chemical, the chemical has to be released from a source, transported through environmental media, reach a human receptor, enter the body, and accumulate within the target tissue to a sufficient degree to cause biological changes that ultimately overwhelm the adaptive mechanisms and result in adverse health outcomes. For example, it has been established that secondhand smoke leads to an increased risk of several diseases. In this scenario, cigarette smoke is released from a source, the burning cigarette. It is transported through the environmental media of air, and reaches a human receptor, perhaps a patron within a smoky restaurant as he inhales the smoke-laden air. Cigarette smoke then enters the body through absorption in the lungs and is distributed to various organs and tissues, leading to an increased risk of lung cancer, asthma, pneumonia, and heart disease. Thus, to verify a causal relationship between an observed health effect and exposures to the chemical(s) of interest, exposure reconstruction is a one of the necessary processes. The term ‘exposure reconstruction’ is defined here as a process for identifying the specific exposure sources and routes, as well as the frequency, duration and magnitude of the exposure.

Exposure may be quantitatively reconstructed using different approaches: (1) collecting personal monitoring data for similar exposure scenarios; (2) measuring environmental concentrations for similar exposure scenarios; (3) using computational models and available environmental measurement data to simulate plausible exposures; (4) reconstructing exposures based on biomarker data; or (5) combinations of different approaches above (Sahmel et al., 2010). As tens of thousands of biomarker measurements are now made each year as part of targeted cohort studies or recurring national surveys, there is a lot of interest in utilizing these data to characterize exposures over a specific period of time or to correlate them to health outcomes in epidemiological studies. In addition, biomarker data are combined with other quantitative approaches to reconstruct exposures (Fig 2) since most risk-based benchmark doses are external doses. Exposure reconstruction allows for better assessment of exposure sources and pathways, which not only supports better internal dose estimates for more informed human health risk assessment, but also guides and evaluates risk mitigation efforts.

Biomarkers of exposure

A biomarker is any substance that can be measured in a biological sample and is correlated to some other metric of interest, such as disease-related biomarkers, drug-related biomarkers, biomarkers of effect, and biomarkers of susceptibility. Our focus is on "biomarkers of exposure", which are markers that are measured in accessible biological media (e.g., blood, urine) for inferring exposures to exogenous chemicals. A biomarker of exposure can be the chemical itself, its metabolite, or an endogenous species that changes

in response to exposure. Since biomarkers of exposure provide direct evidence of human exposure to and uptake of a chemical, they have been used to reconstruct exposures in the workplace for decades. As analytical techniques for measuring biomarker concentrations continue to advance, allowing detection of an increasing number of chemicals at ever-lower concentrations, exposure biomarkers are now used to observe trends of exposures to environmental chemicals over time and between different populations. For example, the Centers for Disease Control and Prevention (CDC) were among the first to measure biomarkers for environmental exposures in the general population. CDC started to include exposure biomarkers in their National Health and Nutrition Examination Survey III (NHANES III; 1988-1994). To date, four National Reports have been published on biomarkers measured in blood, serum, or urine, including a total of more than 300 chemicals. Illustrative classes of chemicals in the latest Report include disinfection by-products, phenols, fungicides, herbicides, pesticides, metals, parabens, perfluorinated chemicals, phthalates, polycyclic aromatic hydrocarbons (PAHs), and volatile organic compounds (VOCs).

Biomarker data may be superior to conventional exposure data collected from environmental sampling, since biomarkers reflect the actual absorbed dose from all sources and routes. These data alone, however, cannot be used to reconstruct exposures. In addition to biomarker data, the process of exposure reconstruction also requires (1) knowledge of the design and sampling procedure of the biomonitoring study; (2) exposure-related information, such as relative contributions from different routes of exposure; and (3) chemical pharmacokinetics, which describes the temporal aspects of absorption into the

body, distribution to organs, tissues, and cells, metabolism to other compounds, and elimination from the body via urine, feces, etc. (ADME) (Tan et al., 2012).

Incorporating biomarkers in exposure reconstruction

At its foundation, exposure reconstruction from internal biomarker measurements is an inverse problem. In contrast to a forward problem that can be solved deterministically, exposure reconstruction does not, and will never have, a unique solution (regardless of future technological advances). Compounding these inherent challenges is that for the majority of biomarker data there are no matching exposure data. A wide range of exposure scenarios may result in the same biomarker measurement. In addition, the difficulty in properly reconstructing exposures increases as the biological half-life of a chemical decreases and/or the number of exposure sources increases. Especially when the available data are single spot measurements, biomarkers may reflect recent exposure, chronic exposure, or neither.

Despite these challenges, reconstructing a range of possible exposure scenarios is not an impossible task. The level of accuracy in exposure reconstruction is dependent upon the availability of additional information to constrain the solution of this inverse problem. First, knowledge of the design and sampling procedure of the biomonitoring study (e.g., time between exposure and biomarker sampling, sampled urine volume) allows one to select appropriate technique for exposure reconstruction (Georgopoulos et al., 2009). Next, exposure-related information (e.g., frequency of pesticide uses in a month, duration of bath time) ensures that the reconstructed exposure scenarios reflect reality. In addition,

information regarding the time-scale variability of exposure can be extremely valuable. For example, if intra-day and intra-week variability in exposure concentrations is low, it may be possible to reconstruct an average daily dose from biomarker measurements. Besides exposure pathways, the exposure-biomarker relationship over time is also determined by ADME processes, which can be nonlinear (e.g., saturable metabolism) and are dependent on both biology and chemistry.

Data from pharmacokinetic, exposure, and biomarker measurements are often integrated using computational models, enabling the prediction of biomarkers concentrations for various exposure scenarios at different time points. In general, computational models can be used in two ways to reconstruct exposures:

(1) Forward predictions: First, possible exposure scenarios are simulated based on environmental concentrations (e.g., chemical concentrations in vegetable), time-location human activities (e.g., time of meals), and other exposure factors (e.g., hand-to-mouth frequency, fraction of house treated with pesticides). The simulated exposure concentrations are then used as inputs for pharmacokinetic models to predict biomarker concentrations. The predicted biomarker concentrations are then compared to measured data for different exposure scenarios to determine the mostly likely scenario from a range of options.

(2) Reverse predictions: First, the mostly likely exposure scenario is selected for simulating the exposure doses and corresponding biomarker concentrations at different time points. Then, a statistical method such as Bayesian inference is used to reconstruct exposures based on these predicted exposure-biomarker relationships and measured biomarker concentrations.

In the next section, three model types that are often used to better understand the exposures that biomarker measures imply are described.

Examples of computational models

Exposure models simulate the interaction between chemical concentrations in a specific environment and the amount of time an individual spends in this environment. Simple models predict an exposure concentration or an intake concentration. More complicated models can predict a time profile of exposure, which include the magnitude, frequency, and duration of exposures over time.

Classical pharmacokinetic models use a limited number of empirically-determined parameters, such as volume of distribution and systemic clearance, to link an exposure/intake concentration with a biomarker concentration. These are parameters that are simple to calculate and can be applied to many chemicals without adjusting the underlying structure of the model, but are not necessarily correlated with any particular physical attribute of the system - it is instead an exercise in parameter fitting. For instance, the volume of distribution is calculated by taking the total amount of chemical that enters the body divided by the measured chemical concentration in blood (or plasma). The resulting value may be larger in magnitude than the entire volume of the human body, but because it has units of volume and gives a general sense of how concentrated/dilute the substance is, it still has a great deal of utility. When exposure-biomarker relationship is linear, a classical pharmacokinetic model is often sufficient to reconstruct an equivalent daily dose from a steady-state biomarker concentration in blood.

Physiologically based pharmacokinetic (PBPK) models incorporate anatomical (e.g., tissue volume), physiological (e.g., blood flow rates), and chemical-specific (e.g., partition between tissue and blood) data to predict ADME processes in the body. In the case where exposure-biomarker relationship is nonlinear because of biochemical processes (e.g., active transport), a classical pharmacokinetic model will be unable to model these accurately over a reasonable range of exposures and a PBPK model will be needed. In addition, Monte Carlo-PBPK simulations can account for uncertainty and inter-individual variability in exposure patterns and pharmacokinetics. Monte Carlo methods incorporate random sampling from a specified distribution for select PBPK model parameters with the goal of generating a distribution of model outputs, e.g., biomarker concentrations. Using other statistical methods to solve the inverse problem, a distribution of reconstructed exposure concentrations can be generated based on observed biomarker concentrations.

Conclusions

Much of the uncertainty in traditional exposure studies comes from the huge variation between people: where they spend their time, how they prepare their food, how frequently they wash their hands, whether they drink from the tap or buy bottled water, if they have children who play in the dirt or spend all their time indoors. To reconstruct exposure to a specific chemical by tracking chemical concentrations in all possible sources, from all possible activities requires tremendous amount of resources. Biomarkers of exposure are advantageous because they are correlated to actual biological dose, which necessarily incorporates an individual's behavioral patterns, the prevalence of the chemical in the

locations where the person spends their time, their own unique physiology, etc. However, the process of exposure reconstruction, going from biomarker concentration back to real-life exposure, is complicated by the fundamental lack of a one-to-one relationship between them.

Once a chemical has been chosen for study, the first step is to classify the exposure-biomarker relationship in general terms as either linear or nonlinear. This can be done by looking first at common sources of nonlinearity, such as active transport or saturable metabolism. If the relationship is linear, either a classic exposure model or a simple PK model may be sufficient to perform an accurate exposure reconstruction. If the relationship is nonlinear, a PBPK model may be required; however, if the range of exposures can be shown to be sufficiently narrow, it may still be possible to determine that the exposure-biomarker relationship is approximately linear over the range of interest.

The actual reconstruction of exposures requires a coordinated application of the models discussed above along with complementary statistical techniques such as Bayesian inference and a generous helping of common sense and appropriate simplifying assumptions. All these things notwithstanding, exposure reconstruction is done every day and has proven to be of great value in furthering our understanding of the complex interactions between individuals and their environments that take place every moment of their lives.

Bibliography

P. Georgopoulos et al., Reconstructing population exposures to environmental chemicals from biomarkers: challenges and opportunities. *J Expo Sci Environ Epidemiol*, 19(2):149-171, 2009.

J. Sahmel et al., The role of exposure reconstruction in occupational human health risk assessment: current methods and a recommended framework, *Critical Reviews in Toxicolog*y, 40(9):799-843, 2010.
Y. Tan et al., Reconstructing human exposures using biomarkers and other “clues”. *J Toxicol Environ Health B Crit Rev*, 15(1):22-38, 2012.

For more information see these additional references:

R. Albertini et al., The use of biomonitoring data in exposure and human health risk assessment. *Environ Health Persp*, 114(11):1755-1762, 2006.
H. Clewell et al., Quantitative interpretation of human biomonitoring data. *Toxicol Appl Pharmacol*, 231:122-133, 2008.
NRC (National Research Council). Human Biomonitoring for Environmental Chemicals. National Research Council Committee on Human Biomonitoring for Environmental Toxicants. National Academies Press, Washington DC, 2006.
NRC (National Research Council). Exposure Science in the 21st Century: A Vision and a Strategy. National Academies Press, Washington DC, 2012.
D. Paustenbach and D. Galbraith, Biomonitoring and biomarkers: exposure assessment will never be the same. *Environ Health Persp*, 114(8):1143-1149, 2006.
J. Sobus et al., A biomonitoring framework to support exposure and risk assessments. *Sci Total Environ*, 409(22):4875-4884, 2011.

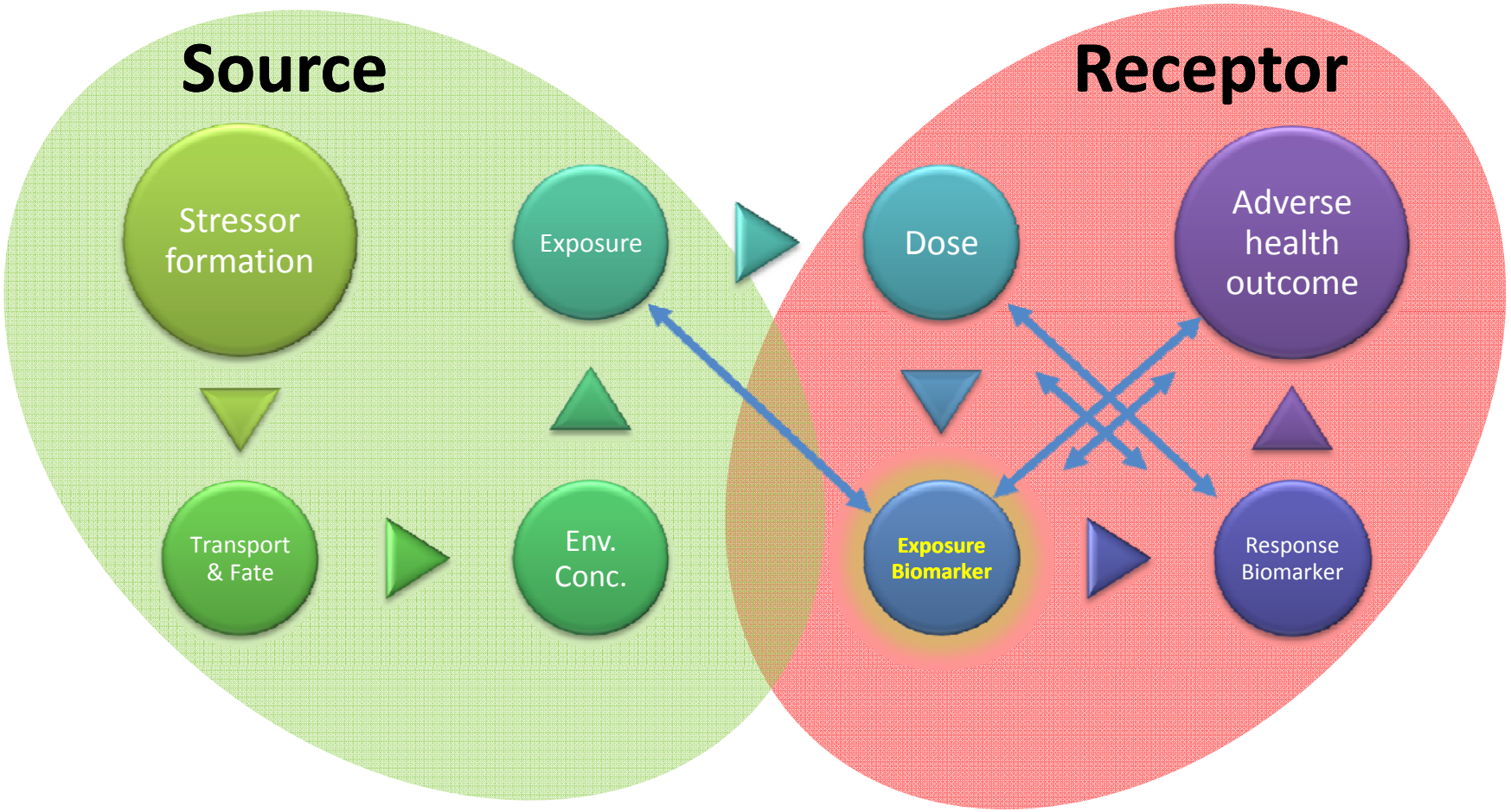

Fig 1. Source-exposure-dose-adverse outcome continuum

Fig 2. A visual analysis of 237 abstracts that contain “chemical AND exposure AND reconstruction” OR (“exposure biomarkers”) using IBM’s www.many-eyes.com Phrasenet analysis (searched on May 22, 2013).