PROcEED: Probabilistic reverse dosimetry approaches for estimating exposure distributions

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Abstract:
As increasing amounts of biomonitoring survey data become available, a new discipline focused on converting such data into estimates of chemical exposures has developed. Reverse dosimetry uses a pharmacokinetic model along with measured biomarker concentrations to determine the plausible exposure concentrations-- a critical step to incorporate ground-truthing experimental data into a distribution of probable exposures that reduces model uncertainty and variability. At the population level, probabilistic reverse dosimetry can utilize a distribution of measured biomarker concentrations to identify the most likely exposure concentrations (or intake doses) experienced by the study participants. PROcEED is software that provides access to probabilistic reverse dosimetry approaches for estimating exposure distributions via a simple user interface.

Availability: PROcEED along with installation instructions is freely available for download from http://www.epa.gov/heasd/products/proceed/proceed.html.

Key words: Reverse Dosimetry, PBPK Modeling, Exposure, Biomarkers.

Background:

The risk assessment of environmental chemicals has historically been conducted based on independently produced exposure and hazard data [1]. The disconnection between exposure and hazard information inherent to separate studies often leads to data gaps and scientific uncertainties. One promising tool for linking exposure and hazard information for improving the understanding of human and ecological health implications of chemical exposures is biomarker research. Biomarkers of exposure have been used to identify the presence of chemicals in workplaces for decades. However, using biomarkers to estimate the degree of health risk posed by environmental chemicals can be a great challenge for several reasons. In a population-based biomonitoring study, biomarkers are often measured as a snapshot of some internal or excreted concentrations. Also, biomarkers are only measured in accessible biological media (e.g., blood, urine), and they may or may not have a correlation with biologically effective dose, and

thus health effects [2]. Besides the difficulty of evaluating or bounding potential health risk, it is also difficult to relate biomarker data to sources and routes of exposure for developing effective risk mitigation or management strategies.

Biomarkers of exposure are not a direct measure of exposure or risk, nonetheless, regulatory bodies at the state, tribal, and federal level are being called upon to better utilize biomarker data for risk and exposure assessment [3] as the number of biomonitoring studies increases. One approach to place biomarker data in a risk context is to convert these measurements into exposure concentrations (i.e., exposure reconstruction). Exposure construction allows for the subsequent comparison to "safe or acceptable" exposure concentrations derived from a point of departure (e.g., no observable adverse effect level) in animal toxicity studies. One of the current state-of-the-science approaches for exposure reconstruction involves the use of pharmacokinetic models in

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two steps: (1) elucidating the time-course dose-biomarker relationship under the conditions of realistic exposure scenarios using available exposure data and pharmacokinetic modeling; and (2) conducting reverse dosimetry calculations from pharmacokinetic model simulations using statistical tools (e.g., Monte Carlo, Bayesian approach).

Reverse dosimetry does not equate to forward dosimetry (i.e., predicting biomarker concentrations at a given exposure concentration) in reverse; because of the complexity of forward dosimetry simulations and multiplicity of potential solutions, it is impossible to perform a deterministic simulation that calculates exposure from a biomarker concentration. Rather, it "reverses" forward dosimetry using statistical tools. Several reverse dosimetry approaches have been developed to reconstruct exposures from biomarker data including,

optimization **[4, 5]**, Exposure Conversion Factors **[6]**, Discretized Bayesian Approach **[7, 8]**, Markov Chain Monte Carlo **[9, 10]**. The reliability of the exposure/dose estimates from these reverse dosimetry approach depends on the accuracy of the dose-biomarker time-course relationship described by the PBPK model, the amount of information on exposure scenarios and their variability, and the capability to characterize biomarker samples and study design (e.g., urine outputs for urinary biomarkers, time of sampling).

PROcEED provides access to two of these approaches allowing risk assessors, exposure scientists, and toxicologists to readily (1) utilize biomarkers of exposures to assess exposure probabilities, (2) study the cause of exposures, and (3) compare the estimated distribution of exposure concentrations with an exposure guidance value to assess health risks.
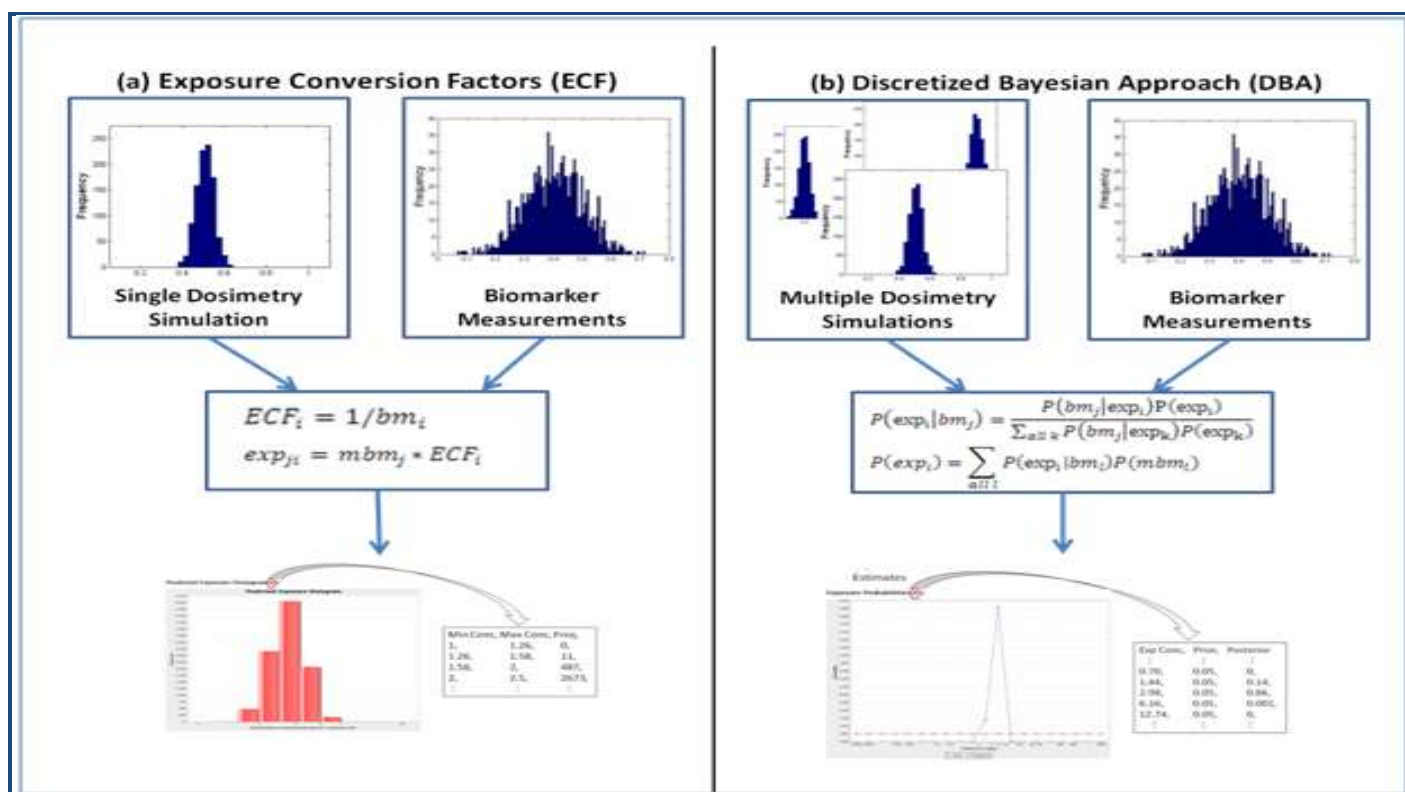
Figure 1: a) The ECF technique requires as input a single dosimetry simulation run at 1 unit of exposure. Assuming a linear relationship between exposure and biomarker concentrations, biomarkers concentrations (bm_i) resulting from the simulation are turned into conversion factors (ECF_i). The compendiums of conversion factors are then multiplied to the measured biomarker concentrations to estimate the distribution of possible exposures (exp_{ji}). **b)** DBA relies on binning the resultant biomarker concentrations from multiple dosimetry simulations run at varying exposure concentrations. Once binned, the probability of seeing a biomarker concentration given an exposure concentration can be evaluated ($P(bm_j|exp_i)$). Using Bayes theorem, these probabilities can be reversed to estimate the probability of seeing an exposure concentration given a biomarker concentration ($P(exp_i|bm_j)$). The probability resulting from this Bayes conversion can be multiplied with the probability of measuring a biomarker concentration ($P(mbml)$) to determine the probability of exposures in the measured population.

Methodology:

Exposure Conversion Factors (ECF)

ECF provides a simple method for converting biomarker concentration distributions into exposure distributions by assuming that the dose-biomarker relationship is linear in the range of the observed biomarker concentrations. To use the ECF approach, a forward dosimetry simulation at only a single exposure concentration is needed. The resultant distribution (due to modeled variation in a population-wide physiology) of

biomarker concentrations is used to extrapolate the exposure concentrations that would elicit the measured biomarker concentrations assuming a linear exposure-biomarker relationship. A simplified flowchart of the ECF technique for reverse dosimetry is displayed in **(Figure 1a)**.

Discretized Bayesian Approach (DBA)

DBA is a more robust reverse dosimetry approach which relies on the completion of a forward dosimetry simulation that

bounds the observed biomarker concentrations. Several potential exposure concentrations must be simulated so that a resultant probability distribution for exposure can be interpolated using Bayesian inference. A simplified flowchart of the DBA technique for reverse dosimetry is displayed in **(Figure 1b)**.

Implementation:
The graphical user interface for PROcEED has been developed using HTML, JSP, CSS, Java, Struts2, Javascript, and JQuery. Graphical representations of the results are created via JFreeChart. PROcEED is intended to be deployed to an Apache Tomcat 7.0 webserver and accessed using either Internet Explorer or Mozilla Firefox.

Software Input and Output:
The PROcEED interface takes in 3 forms of input: A forward dosimetry simulation file, a measured biomarker file, and a priors file (only needed for DBA). The dosimetry simulation file can either contain the predicted biomarker concentrations or for DBA, the pre-descretized counts of simulation runs for which a particular concentration was observed. The measured biomarker file can be comprised of a vector of measured biomarkers or the percentile information for the observed biomarker distribution. PROcEED provides both graphical visualization of the predicted exposure distribution as well as downloadable ".csv" formatted files. A detailed description and examples of the various input and output files are available in the software help documentation.

Caveat and Future Development:
PROcEED currently supports two methods of reverse dosimetry estimation greatly enhancing the accessibility of this key technique. However, other methods9 are documented in the literature. Unfortunately, many of these methods require sequential running of forward dosimetry simulations. It is our intention to develop a web-accessible forward dosimetry simulation platform and integrate that platform into PROcEED to enable the variety of reverse dosimetry techniques. The creation of a comprehensive reverse dosimetry calculator will enable thorough analysis of the ever increasing data resulting from biomonitoring surveys.

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