

permits the service to be dragged to the "Build Area." Clicking on the associated "Help" icon will provide information on the use of a component service.

The "Special Capabilities Menu" contains tools for drawing and other resources that are not within the scope of the other two menus. For example, arrowed lines to interconnect the component services are "pointed to, clicked on, and dragged to" the appropriate "Build Area" location.

Figure 4 is an example of a completed CWS as it appears on a build layout for the scenario of children waiting for a school bus. This CWS will periodically determine the location of the school bus, and when the bus is approaching the child's stop, an announcement will be made on the parents' wireless terminal.

For background information see DATA COMMUNICATIONS; MOBILE RADIO; TELEPHONE SERVICE; WIDE-AREA NETWORKS in the McGraw-Hill Encyclopedia of Science & Technology. Thaddeus J. A. Kobylarz

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Computational environmental toxicology

Hundreds of thousands of chemicals in current or past use are present in the environment, leaving human populations and ecosystems potentially at risk of exposure to them. The large number and various forms of chemicals preclude regulators from evaluating every chemical with the most rigorous testing strategies. Instead, standard toxicity tests have been limited to only a small number of chemicals, with the hope that the "worst" chemicals will receive specific attention. The chemicals that are tested may represent large classes of compounds, such as certain types of pesticides.

Today, advances in computational biology offer the possibility that scientists can develop a more detailed understanding of the risks posed by a larger number of chemicals. Computational toxicology is the application of computational biology, using mathematical and computer models, to the assessment of the risk chemicals pose to human health and the environment and to better understand the mechanism through which given chemicals induce harm.

Risk assessment. Early on, risk assessment was mostly a "blind" relationship between exposure levels and some observed response such as the occurrence of cancer, a neurological disorder, or a visible birth defect. The actual pathway between exposure and response, or disease, is better represented as a complex series of steps (**Fig. 1**). A chemical is absorbed (absorbed dose), distributed to internal target sites, and possibly metabolized to an active form

once within the body. This results in internal toxicologically relevant doses.

Computational toxicology is a systematic approach that can model a contaminant's effect on gene expression; that is, how the contaminant exposure will affect cellular behavior and signaling, including protein synthesis (proteomics) and metabolic changes as seen in concentrations of metabolites in tissues and biofluids (metabolomics). These advances would not have been possible without the emergence of bioinformatics and computational chemistry and the opportunities they offer for transforming data into information. In particular, computational toxicology will produce risk assessments based on specific molecular changes rather than just the number of tumors, deaths, and overt clinical changes observed in test animals. Future assessments will be based on the number of DNA molecules altered at a crucial site, the change in an allosteric membrane protein that acts as a receptor, or the change in a regulating protein inside the cell. This will lead to a better understanding of how those changes cause clinical disease.

Recent advances in computational toxicology focus on breaking down the traditional dichotomy between approaches to evaluating cancer versus other disease endpoints, on addressing sensitive life stages, and on addressing aggregate and cumulative exposure to pollutants. For example, a greater understanding is needed of why certain modes of action occur more rapidly when an organism is exposed to more than one chemical (synergism), but less rapidly when other chemicals are present (antagonism).

Advancements in genomics, proteomics, and metabolomics, coupled with the advances in analytic tools, such as microarray techniques, will enable us to predict changes and evaluate which changes can initiate and promote disease. Computational techniques will help estimate the necessary quantitative information related to those changes.

Physiologic models. Probably the greatest progress in the field of computational toxicology to date has been in characterizing and quantifying relevant internal doses. Physiologically based pharmacokinetic (PBPK) models describe the time course and mass balance of chemicals entering the body (**Fig. 2**). They mathematically account for both the physiologic and biochemical processes that affect the

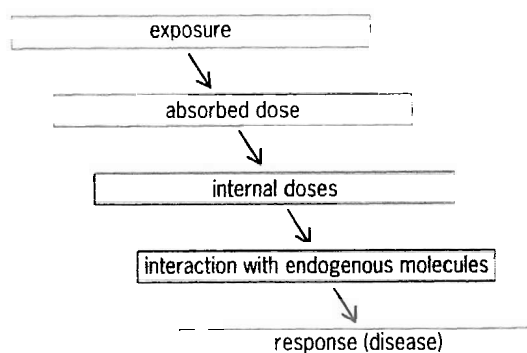


Fig. 1. Stepwise linkage of exposure to toxic response.

Example of types of parameters governing PBPK models

Parameter	Type
Partition coefficient	Thermodynamic
Organ and body volumes	Anatomic
Blood flows, ventilation rates, absorption rates, clearance	Physiologic
Metabolic transformation rates	Biochemical

disposition of these chemicals and their products of biotransformation. As a result, these models estimate the time course of the internal doses, especially at sites relevant to toxicity.

Physiologically based pharmacokinetic models are governed by parameters such as those shown in the table. These parameters may be chemical- and species-specific and are from values reported in published literature, determined experimentally, or extrapolated. They can be used to give estimates of doses within the body, resulting from actual or simulated exposure conditions, at or near the location of toxic action, including subcellular sites if the proper equations are included. The estimated dose is then used in dose-response functions to predict adverse reactions. In addition, these models can estimate the dose resulting from the different routes of entry into the body and the equivalence between different exposure routes. For example, the doses at a site of toxicity in an internal organ resulting from two different sources (such as food and inhaled air) can be easily calculated and compared. It is well known that many physiologic processes are nonlinear, and that the characteristics of these nonlinear processes may differ among dose levels and species. The physiologic models account for this in a quantitative fashion.

Figure 3 shows some typical output from a physiologically based pharmacokinetic model for an inhalation exposure of 4 h, where the exposure or parent chemical (chemical 1) is metabolized in the body to a second chemical (chemical 2). The concentration profile in the blood of the parent chemical and the product of metabolism or metabolite are quite different. Assuming these modeling results are being used to design a clinical or field study, it is apparent that capturing the peak concentration of the parent would require monitoring at different times than monitoring for the metabolite.

In Fig. 4, if the area under the concentration (AUC) is the endpoint of interest, the time at which monitoring should cease depends upon which chemical is monitored. The AUC of "chemical 1" shows negligible increase at around 90 h, so monitoring could stop then. The AUC of "chemical 2" is still increasing at 1000 h, so monitoring would have to continue for a considerable time longer.

Computational methods. The growth in the understanding of pharmacokinetics has called for new tools to predict how contaminants will behave after exposure. The focus on improved dose calculations and understanding the basis for outcomes within the

range of observation, and use of these to improve scientific judgment below the range of observation (into the range of extrapolation) will result in better environmental risk assessments. Computational toxicology information should allow the identification of hazards by providing data on measurable biochemical or cellular endpoints, which can serve as biomarkers of response for more complex adverse biological effects such as cancer or developmental disorders. Ideally, these measurable endpoints should be mechanistically linked to the biological effect, rather than simply being correlated with it. Identification of key events leading to toxicity can provide insights into the conditions necessary for response and the shape of the dose-response relationship as one goes from high to low doses. Developing the means for incorporating such "in silico" (computer-simulated) data should allow the extension of the dose-response relationship established by

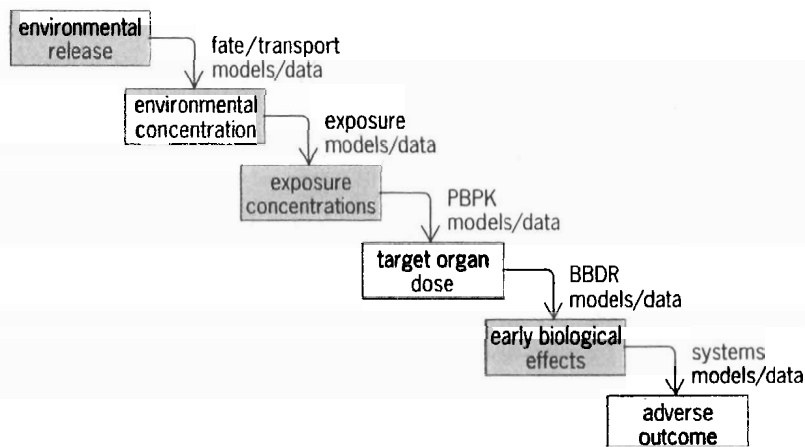


Fig. 2. Source-to-dose paradigm for studying environmental contaminants. PBPK = physiologically based pharmacokinetic; BBDR = biologically based dose response. (U.S. Environmental Protection Agency, *About Computational Toxicology*, <http://www.epa.gov/comptox/comptoxfactsheet.html>)

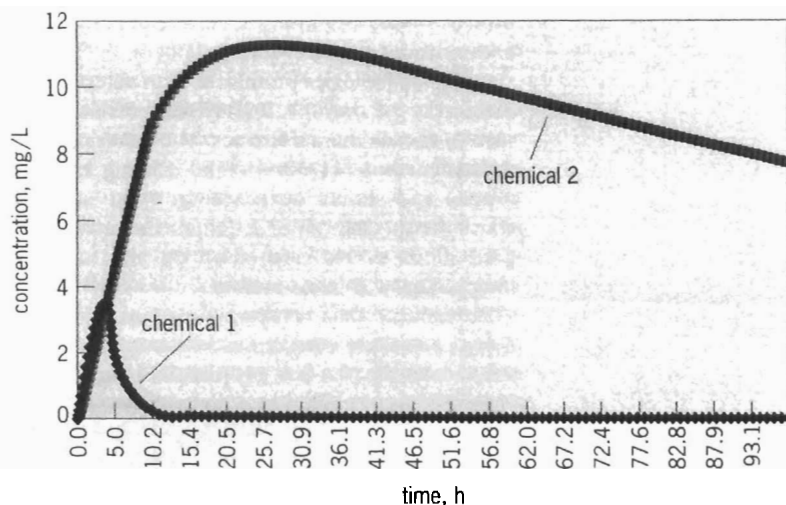


Fig. 3. Chemicals in blood. Output is from a prototypical physiologically based pharmacokinetic (PBPK) model. (PBPK simulations were performed using the U.S. EPA's Exposure Related Dose Estimating Mode, J. N. Blancato et al., 2002)

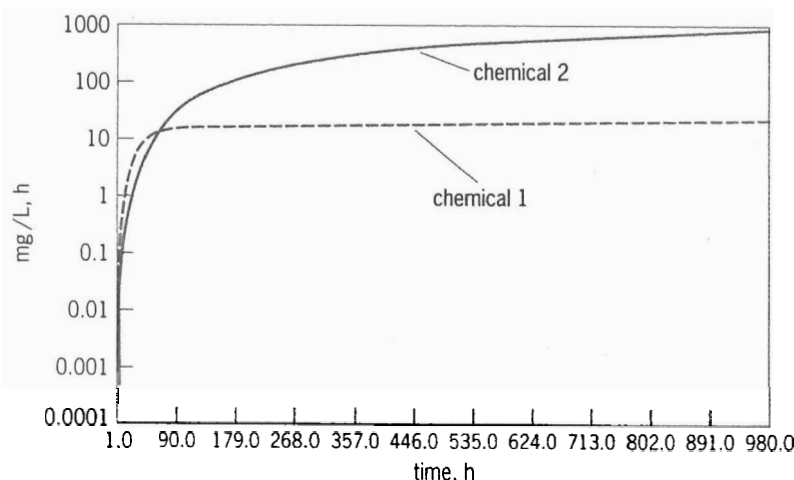


Fig. 4. Area under the concentration curve. Output is from an physiologically based pharmacokinetic (PBPK) model. (PBPK simulations were performed using the U.S. EPA's Exposure Related Dose Estimating Model, J. N. Blancato et al., 2002)

more traditional toxicology studies to lower levels using sensitive molecular biological and computational techniques. This approach should also save steps and reduce the need for animal testing, compared to traditional toxicology.

"Omics." In the area of computational biology, recent advances have allowed for the sequencing of whole genomes, which has enhanced the understanding of the complexity of cellular biology at the molecular level. Recent technological advances in these areas have led to the development of the new discipline of toxicogenomics in which the effects of chemicals on organisms and ecosystems can be examined using genomic, proteomic, and metabolomic methods.

Omics may also be used to identify those members of a population at greater risk. Disease is considered to result from endogenous predisposition and interaction with environmental stresses, with not all individuals in a population having the same clinical outcome given the same or similar exposures. However, the exact magnitude of the role of predisposing endogenous factors remains unknown.

Omic technologies promise to help determine the molecular pathways that lead to disease after exposure to environmental stresses. The selection of the proper measure of dose within a living system is crucial and should be based on what is known about the mechanism of action, so that quantitative predictions of risk are based on the molecular interactions within the system.

Bioinformatics. Data resulting from these omic technologies are very complex and voluminous. As a result, bioinformatics has evolved for managing and analyzing the data using advanced computational techniques. Powerful software enables us to study the pattern of gene and protein expression and relate those expressions to the structure of important chemical moieties. From such analyses, connections between exposure, genetic susceptibility, and adverse effect will be made. Omics may yield spe-

cific patterns, which may be markers of potential disease and exposure. These connections may be made without necessarily understanding the details of the pathways to disease. In the future, it is hoped that both in-vitro and in-silico methods will be used. With such rapid methods, various exposure scenarios could be studied, including those where exposures to a multitude of stressors occurs. At the very least, these techniques could help prioritize which stressors need further study and which may pose the greatest risk.

Structure activity relationships. Improved quantification, such as enhanced quantitative structure activity relationships (QSAR) techniques, are helping estimate the toxicity of poorly characterized substances based on comparisons to well-studied substances having similar chemical structures. Commercially available software is used to predict toxicity endpoints based on chemical structure to predict carcinogenicity in mammals, developmental toxicity, mutagenicity, acute toxicity such as 50% lethal dose (LD_{50}), chronic thresholds, and so on.

Outlook. It is easy to imagine how schemes far more complicated than this can be used to explain the complex biochemistry within a cell, the interaction of different cells within a tissue, or the interaction of the different types of cells in neurological tissue. Such models may, for example, predict changes in brain function resulting from exposure to chemicals which are biotransformed into chemicals that in turn change membrane potentials in the brain. In the future, models may be devised to help us understand how different regions of the brain respond to changes initiated in other regions.

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For background information see ENVIRONMENTAL ENGINEERING; ENVIRONMENTAL TOXICOLOGY; HAZARDOUS WASTE; HUMAN GENOME PROJECT; MATHEMATICAL BIOLOGY; MODEL THEORY; MUTAGENS AND CARCINOGENS; TOXICOLOGY in the McGraw-Hill Encyclopedia of Science & Technology.

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Conflict analysis and resolution

A strategic conflict is an interaction of two or more decision makers over issues such as rights or resources. Some conflicts, such as terrorist attacks, exhibit outright hostility, while others are highly cooperative situations in which disputants form coalitions or jointly act to achieve win/win solutions, that is, resolutions in which everyone gains. The key ingredients of any conflict model are the decision makers in disagreement, each decision maker's options or courses of action, how a scenario or state is determined by the decision makers' choices, and their objectives or preferences over states. Conflict analysis provides methodologies for studying these multiple participant-multiple objective decision situations systematically. By enhancing understanding and communication, it can lead to better decisions that produce resolutions that are more preferable, more stable, and more fair.

Strategic conflicts are ubiquitous; accordingly, research on conflict analysis and resolution has taken place in a wide range of disciplines including psychology, sociology, operations research, political science, and systems engineering. Many organizations—academic, governmental, or private—offer assistance with the theory and practice of conflict analysis and resolution.

Rigorous mathematical structures can provide considerable insight, which probably accounts for the success of the many game-theory-related methodologies for modeling and analyzing conflict. Techniques can be usefully classified according to the information required to calibrate a model. For example, a dinner-party host needs to know that the guest prefers red wine to white, but not how much more preferable red wine is than white. Quantitative preferences are represented on a continuous scale, and can express the extent of such differences. Usually measured in real numbers, they can also encode information about the decision maker's risk attitude: how the guest would feel if a coin toss determined red or white. Most game-theory models, including strategic form, extensive form, and characteristic function form, are quantitative techniques. Nonquantitative techniques, on the other hand, re-

quire only easier-to-obtain rankings of outcomes according to preference. Information about preference differences or preferences for randomly determined outcomes cannot be included. Nonquantitative methodologies, including metagame analysis, drama theory, conflict analysis, and the Graph Model for Conflict Resolution, are convenient for modeling societal disputes ranging from international trade to family arguments. These techniques can help resolve problems that arise in general approaches to negotiation, mediation, and arbitration. For example, nonquantitative methods are recommended for brainstorming sessions in interest-based negotiations, in part because they can be adjusted as more information becomes available or more options are recognized.

To illustrate how formal methods can be applied to actual disputes, the Graph Model for Conflict Resolution is employed here to analyze a simple sustainable development problem. This model is designed for application to both simple and complex real-world disputes, and is based on theoretical foundations formulated using the mathematics of relationships: set theory, logic, and graph theory. The decision support system GMCR II permits practitioners, researchers, teachers, and students to apply this unique decision technology conveniently to virtually any social conflict.

Decision support systems. A decision support system (DSS) is a user-friendly software package that encodes modeling and analysis capabilities for formal decision models. Decision support system technologies are an important subfield of information technology, which includes the development and application of computer software and hardware. The decision support system GMCR II allows users to readily model and analyze conflicts using the Graph Model for Conflict Resolution (Fig. 1). It has been applied in diverse domains including water resources, international trade, politics, and military science. GMCR II is appropriate for studying large complex disputes, but it can also be used for small models, such as the one examined below, which will provide context for a discussion of the modeling subsystem, the analysis engine, and the output interpretation subsystem.

Sustainable development conflict. Environmental conflicts can be very complex and hence require complex models. Nevertheless, in some situations it is possible to gain understanding of a conflict by studying a simple or rudimentary model. For instance, the sustainable development conflict represents a generic dispute occurring between environmentalists and developers. The developers typically wish to construct a new industrial facility, expand a residential area in a city, build a hydroelectric complex, sell genetically engineered seeds to farmers, or purchase public infrastructure. The environmentalists may include governmental agencies (often those that ensure compliance to environmental regulations), nongovernmental organizations representing specific environmental interests, and coalitions of concerned citizens. The environmentalists'